ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

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ABSTRACT

BACKGROUND

Dupilumab is a fully human anti–interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. We assessed its efficacy and safety in patients with uncontrolled asthma.

METHODS

We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and dupilumab safety were also assessed.

RESULTS

The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks. At week 12, the FEV_1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose. Among patients with a blood eosinophil count of 300 or more per cubic millimeter, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower-dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6); similar results were observed with the higher dose. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo.

CONCLUSIONS

In this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. Hypereosinophilia was observed in some patients. (Funded by Sanofi and Regeneron Pharmaceuticals; LIBERTY ASTHMA QUEST ClinicalTrials.gov number, NCT02414854.)

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A complete list of investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 20% of patients with asthma have uncontrolled, moderate-to-severe disease with recurrent exacerbations and persistent symptoms despite maximized standard-of-care controller therapy.[1-3] This population is at an increased risk for illness (especially exacerbations) and accounts for considerable health care resources.[4] Many of these patients have substantially reduced lung function, despite maximum treatment, and face a further loss of lung function over time.[5]

Type 2 inflammation, mediated by cytokines such as interleukin-4, interleukin-5, and interleukin-13, occurs in approximately 50% of patients with asthma.[6] Blood and sputum levels of eosinophils, the fraction of exhaled nitric oxide (F_{ENO}), and the serum IgE level have been linked to mechanisms involved in type 2 inflammation.[7,8] Levels of serum IgE and blood eosinophils can be used to guide the use of currently approved biologic agents in the treatment of severe asthma.

Dupilumab is a fully human VelocImmune-derived monoclonal antibody[9] that is directed against the alpha subunit of the interleukin-4 receptor, thereby blocking both interleukin-4 and interleukin-13 signaling and hence type 2 inflammation.[8] It has been approved for the treatment of moderate-to-severe atopic dermatitis.[10-12] This phase 3 trial, LIBERTY ASTHMA QUEST, was designed to confirm earlier findings in patients with severe asthma.[13] A companion article now published in the *Journal* describes the evaluation of dupilumab in patients with oral glucocorticoid–dependent severe asthma.[14]

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled, parallel-group trial assessed the efficacy of dupilumab in patients with uncontrolled moderate-to-severe asthma. Patients completed a screening period of 4 weeks (window, ±1 week), followed by randomization to subcutaneous injections of dupilumab or matched-volume placebo, a 52-week randomized intervention period, and a 12-week postintervention follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The protocol (available at NEJM.org) was developed by the sponsors (Sanofi and Regeneron Pharmaceuticals). Data were collected by the investigators and analyzed by the sponsors. The trial was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data (details on the committee are available in the Supplementary Appendix). The local institutional review board or ethics committee at each trial center oversaw trial conduct and documentation. All the patients provided written informed consent before participating in the trial. Those younger than 18 years of age provided assent according to the ethics committee–approved standard practice for pediatric patients at each participating center.

All the authors participated in the interpretation of the data; provided input into the drafting of the manuscript, critical feedback, and final approval for submission; and vouch for the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol. All the investigators had confidentiality agreements with the sponsors, Sanofi and Regeneron Pharmaceuticals. The manuscript drafts were prepared with the assistance of a medical writer paid by the sponsors.

Patients

Patients 12 years of age or older with physician-diagnosed persistent asthma for 12 months or more, according to the Global Initiative for Asthma 2014 guidelines,[15] were eligible to participate if they met the following key criteria: current treatment with a medium-to-high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of ≥500 μg or equipotent equivalent) plus up to two additional controllers (e.g., a long-acting β_2-agonist or leukotriene-receptor antagonist); a forced expiratory volume in 1 second (FEV_1) before bronchodilator use of 80% or less of the predicted normal value (or ≤90% of the predicted normal value in those 12 to 17 years of age); FEV_1 reversibility of at least 12% and 200 ml; a score on the 5-item Asthma Control Questionnaire (ACQ-5) of 1.5 or higher (on a scale from 0 [no impairment] to 6 [maximum impairment]; the minimal clinically im-

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portant difference is 0.5)[16,17]; and a worsening of asthma in the previous year that led to hospitalization, emergency medical care, or treatment with systemic glucocorticoids for 3 days or more. Patients were recruited irrespective of a minimum baseline blood eosinophil count or biomarkers of type 2 inflammation. Full inclusion and exclusion criteria are available in the Supplementary Appendix.

INTERVENTIONS AND PROCEDURES

Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose (supplied in prefilled syringes). Randomization was conducted by means of interactive voice–Web response technology and was stratified according to age (<18 years or ≥18 years), peripheral-blood eosinophil count (<300 or ≥300 per cubic millimeter) at screening, inhaled glucocorticoid dose (medium or high), and country. Background asthma-controller medicines were continued at a stable dose throughout the trial and recorded daily by patients in an electronic diary. Use of long-acting β_2-agonists, long-acting muscarinic antagonists, antileukotriene agents, and methylxanthines was permitted. Throughout the trial, patients were permitted to use a short-acting β_2-adrenergic–receptor agonist as necessary for symptom relief. Biomarkers of type 2 inflammation that were measured included blood eosinophils, $F_{E_{NO}}$, serum IgE, periostin, thymus and activation-regulated chemokine (TARC), eosinophil cationic protein, and plasma eotaxin-3. Full details are available in the protocol.

END POINTS

The primary efficacy end points were the annualized rate of severe exacerbation events (number of severe exacerbations per patient-year) during the 52-week intervention period and the absolute change from baseline in the FEV_1 before bronchodilator use at week 12 in the overall trial population. These end points were also included as secondary trial end points with control for multiplicity in those with a blood eosinophil count of 300 or more per cubic millimeter. Additional secondary trial end points, including the key secondary end point of percentage change from baseline in the FEV_1 before bronchodilator use, are summarized in Table S1 in the Supplementary Appendix. A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for 3 days or more with systemic glucocorticoids or hospitalization or an emergency department visit leading to treatment with systemic glucocorticoids.[18] The incidence of adverse events and serious adverse events that emerged during the trial period was reported, with the trial period defined as the time from the first administration of the trial regimen to the last administration of the trial regimen plus 98 days or until the patient enters the extension study.

STATISTICAL ANALYSIS

On the basis of the previous phase 2b study, we estimated that a sample of approximately 1638 patients would give the trial 99% power (with a two-tailed test at an alpha level of 0.05) to detect a 55% lower rate of severe asthma exacerbations with dupilumab than with placebo — that is, an annualized rate of 0.27 severe exacerbations in each dupilumab group as compared with 0.60 with placebo.[13] This sample was also expected to provide 98% power to detect a between-group difference of 0.15 liters in the change from baseline in the FEV_1 before bronchodilator use at week 12.

Efficacy analyses were performed in the intention-to-treat population, defined as all the patients who underwent randomization; data were analyzed according to the assigned intervention, whether an intervention was received or not. The annualized rate of severe exacerbations was analyzed with the use of a negative binomial regression model, including the four intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and number of exacerbations in the previous year as covariates. Patients who discontinued the assigned intervention were encouraged to return to the clinic for all remaining trial visits, and all severe exacerbations up to week 52 were included in the primary analysis, regardless of whether the patient was receiving an intervention. The change from baseline in continuous end points such as the FEV_1 and patient-reported

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outcomes were analyzed with the use of a mixed-effects model with repeated measures, including assigned intervention, age, baseline eosinophil strata, baseline inhaled glucocorticoid dose, visit, intervention-by-visit interaction, the corresponding baseline value, and baseline-by-visit interaction as covariates. Sex and baseline height were included as covariates only in the models for spirometric values. For patients who discontinued the assigned intervention and remained in the trial, measurements after the intervention was discontinued were included in the primary model.

In order to control the family-wise type I error for the primary analyses (two primary end points and two doses) and selected secondary end points, a hierarchical testing procedure was applied at a two-sided 5% significance level. A list of these end points with their testing order is provided in Table S1 in the Supplementary Appendix. The end points after the hierarchy break are presented with 95% confidence intervals. The other efficacy end points that were not listed in the hierarchical testing procedure were not controlled for multiplicity and are also presented with 95% confidence intervals. Full statistical methods are summarized in the Supplementary Appendix and the statistical analysis plan (available with the protocol).

RESULTS

TRIAL PATIENTS

From May 2015 through September 2016, a total of 1902 patients underwent randomization per protocol (intention-to-treat population) (Fig. S2 in the Supplementary Appendix); of these, 1897 received the assigned intervention. As planned, the database was locked for analysis once approximately 1638 patients had completed 52 weeks of the assigned intervention or had discontinued the trial. All 1902 randomly assigned patients were included in the final analysis: 1434 patients completed the 52-week intervention period, 235 had treatment ongoing, and 228 discontinued the intervention (Fig. S2 in the Supplementary Appendix). Baseline demographic and clinical characteristics of the intention-to-treat population were generally similar across the four intervention groups (Table 1, and Table S2 in the Supplementary Appendix).

PRIMARY OUTCOMES

Exacerbations

In the intention-to-treat population (1902 patients), during the 52-week intervention period, the adjusted annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks versus 0.87 (95% CI, 0.72 to 1.05) among those assigned to matched placebo (47.7% lower rate with dupilumab than with placebo, P<0.001). The rate was 0.52 (95% CI, 0.45 to 0.61) among patients assigned to 300 mg of dupilumab every 2 weeks versus 0.97 (95% CI, 0.81 to 1.16) among those assigned to matched placebo (46.0% lower rate with dupilumab than with placebo, P<0.001) (Fig. 1, and Table S3 in the Supplementary Appendix).

Prespecified subgroup analyses according to baseline blood eosinophil count showed significant differences in exacerbation rates with either dose of dupilumab as compared with matched placebo among patients with an eosinophil count of 300 or more per cubic millimeter. The rate was 0.37 (95% CI, 0.29 to 0.48) with lower-dose dupilumab versus 1.08 (95% CI, 0.85 to 1.38) with matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6), and 0.40 (95% CI, 0.32 to 0.51) with higher-dose dupilumab versus 1.24 (95% CI, 0.97 to 1.57) with matched placebo (67.4% lower rate with dupilumab than with placebo, P<0.001). Among patients with a baseline blood eosinophil count of 150 to less than 300 per cubic millimeter, the exacerbation rate was also lower with dupilumab than with placebo: 0.56 (95% CI, 0.42 to 0.75) with lower-dose dupilumab versus 0.87 (95% CI, 0.59 to 1.27) with matched placebo (35.6% lower rate with dupilumab than with placebo), and 0.47 (95% CI, 0.35 to 0.64) with higher-dose dupilumab versus 0.84 (95% CI, 0.58 to 1.23) with matched placebo (44.3% lower rate with dupilumab than with placebo) (Fig. 1, and Table S5 in the Supplementary Appendix).

Among patients with a baseline blood eosinophil count of less than 150 per cubic millimeter, the exacerbation rate was similar with dupilumab and with placebo: 0.47 (95% CI, 0.36 to 0.62) with lower-dose dupilumab and 0.51 (95% CI, 0.35 to 0.76) with matched placebo, and 0.74 (95% CI, 0.58 to 0.95) with higher-dose dupilu-

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Table 1. Selected Baseline Demographic and Clinical Characteristics of the Patients (Intention-to-Treat Population).*

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
F_{ENO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization, regardless of whether an intervention was received. Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. Further information on baseline demographic and clinical characteristics is provided in Table S2 in the Supplementary Appendix. F_{ENO} denotes fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, and ppb parts per billion.

† The 5-item Asthma Control Questionnaire (ACQ-5) is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Scores range from 0 to 6, with higher scores indicating less control. The minimal clinically important difference is 0.5.[17,18]

mab and 0.64 (95% CI, 0.44 to 0.93) with matched placebo (Fig. 1, and Table S5 in the Supplementary Appendix). Prespecified subgroup analyses according to the baseline F_{ENO} showed a greater benefit of dupilumab with respect to the exacerbation rate among patients with a higher F_{ENO} (≥25 to <50 parts per billion [ppb] or ≥50 ppb) than among those with a lower value (<25 ppb) (Fig. 1, and Table S5 in the Supplementary Appendix).

FEV_1 Outcomes

In the overall trial population, the change from baseline in the FEV_1 before bronchodilator use at week 12 was 0.32 liters with lower-dose dupilumab versus 0.18 liters with matched placebo (difference, 0.14 liters; P<0.001). The change was 0.34 liters with higher-dose dupilumab versus 0.21 liters with matched placebo (difference, 0.13 liters; P<0.001) (Fig. S3 and Table S3 in the Supplementary Appendix).

The benefit of dupilumab with respect to the FEV_1 was greatest among patients with a blood eosinophil count of 300 or more per cubic millimeter at baseline. The change at week 12 was 0.43 liters with lower-dose dupilumab versus 0.21 liters with matched placebo (difference, 0.21 liters; 95% CI, 0.13 to 0.29) and 0.47 liters with higher-dose dupilumab versus 0.22 liters with matched placebo (difference, 0.24 liters; 95% CI,

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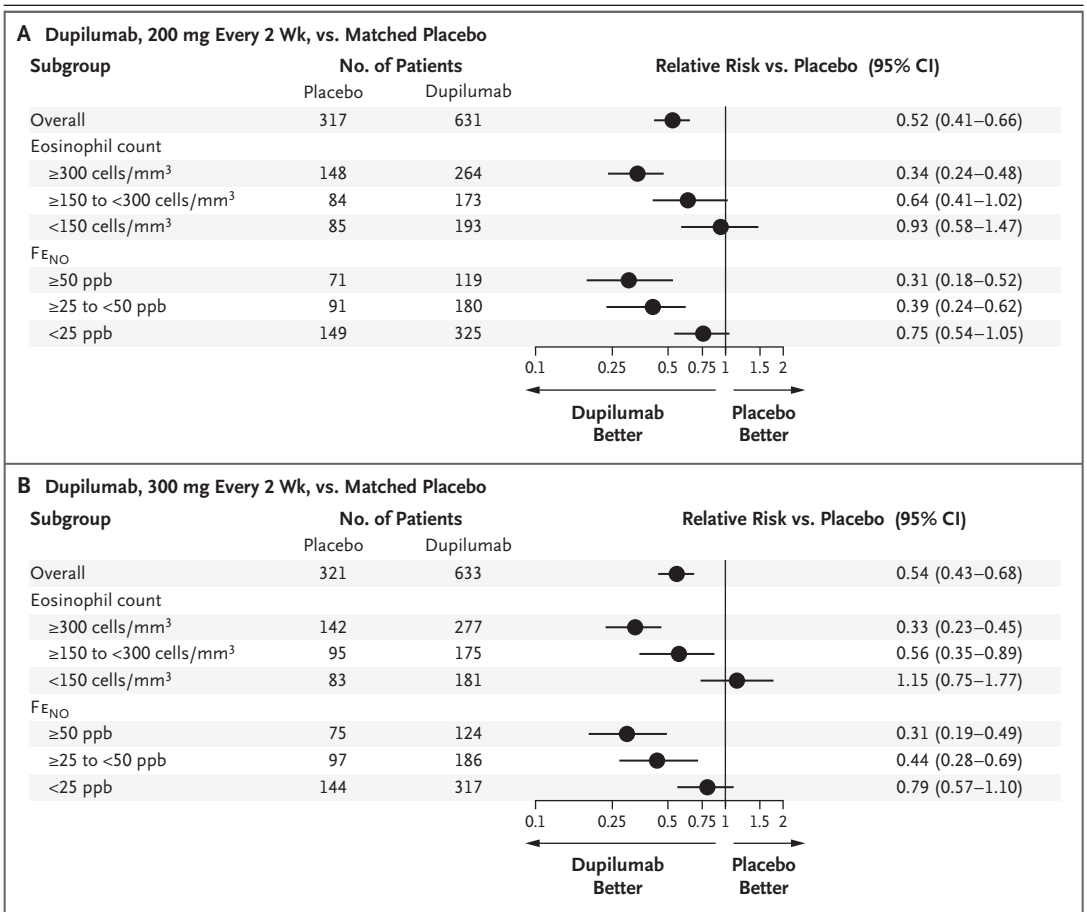


Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline F_{ENO}.

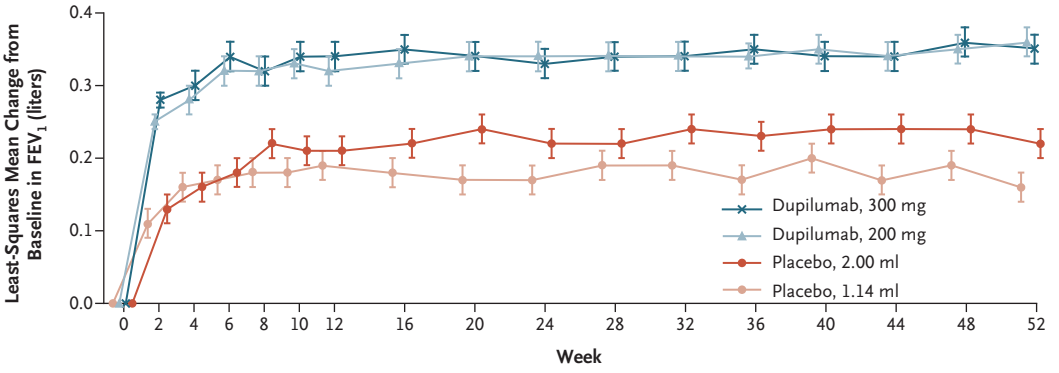
F_{ENO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

0.16 to 0.32; P<0.001) (Fig. S3 and Table S5 in the Supplementary Appendix). In patients with a blood eosinophil count of 150 to less than 300 per cubic millimeter at baseline, the change in the FEV_1 at week 12 was 0.28 liters with lower-dose dupilumab and 0.17 liters with matched placebo (difference, 0.11 liters; 95% CI, 0.01 to 0.21) and 0.25 liters with higher-dose dupilumab and 0.25 liters with matched placebo (difference, 0.00 liters; 95% CI, −0.10 to 0.10). In patients with a blood eosinophil count of less than 150 per cubic millimeter at baseline, the change in the FEV_1 at week 12 was 0.19 liters with lower-dose dupilumab and 0.13 liters with matched placebo (difference, 0.06 liters; 95% CI, −0.04 to 0.15) and 0.20 liters with higher-dose dupilumab and 0.11 liters with matched placebo (difference, 0.09 liters; 95% CI, −0.01 to 0.18).

A benefit of dupilumab over matched placebo with respect to the change in the FEV_1 from baseline was evident by the first evaluation at week 2 and was sustained throughout the 52-week intervention period (difference vs. matched placebo at 52 weeks, 0.20 liters [95% CI, 0.14 to 0.25] with the lower dose and 0.13 liters [95% CI, 0.08 to 0.19] with the higher dose) (Fig. 2). In addition, a prespecified analysis of the rate of change in the postbronchodilator FEV_1 (FEV_1 slope after week 4 to week 52) showed a loss of lung function of 40 ml per year with placebo and no loss with either dupilumab dose (Table S4 in the Supplementary Appendix).

Dupilumab had a greater benefit with respect to the change from baseline in the FEV_1 at week 12 among patients with a higher F_{ENO} (≥25 to <50 ppb or ≥50 ppb) than among those with a

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No. at Risk																	
Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.
Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

lower value (<25 ppb) (Fig. S3 and Table S5 in the Supplementary Appendix). In patients with a F_{ENO} of 25 to less than 50 ppb, the difference as compared with matched placebo was 0.19 liters (95% CI, 0.09 to 0.28) with lower-dose dupilumab and 0.12 liters (95% CI, 0.03 to 0.21) with higher-dose dupilumab. In patients with a F_{ENO} of 50 ppb or more, the difference as compared with matched placebo was 0.30 liters (95% CI, 0.17 to 0.44) with lower-dose dupilumab and 0.39 liters (95% CI, 0.26 to 0.52) with higher-dose dupilumab.

ADDITIONAL SECONDARY OUTCOMES

The percentage change from baseline to week 12 in the FEV_1 before bronchodilator use was greater with dupilumab than with placebo. The difference as compared with matched placebo was 9.2 percentage points (95% CI, 5.5 to 12.9) with lower-dose dupilumab and 9.4 percentage points (95% CI, 5.7 to 13.1) with higher-dose dupilumab (P<0.001 for higher-dose dupilumab vs. matched placebo) (Table S3 in the Supplementary Appendix).

ACQ-5 scores were lower (indicating better asthma control) with dupilumab than with placebo as early as week 2, and the effect was sustained over the 52-week intervention period (Table S6 in the Supplementary Appendix). Similarly, dupilumab showed benefits over matched placebo with respect to the global score on the Asthma Quality of Life Questionnaire (standardized),[17] morning and evening asthma symptom scores, and morning and evening peak expiratory flow at weeks 24 and 52 (Table S6 in the Supplementary Appendix).

The rate of severe exacerbation events resulting in hospitalization or an emergency department visit during the 52-week intervention period was 0.035 (95% CI, 0.025 to 0.048) in the combined dupilumab groups and 0.065 (95% CI, 0.047 to 0.090) in the combined placebo groups (Table S6 in the Supplementary Appendix). This produced a 46.8% lower rate with dupilumab than with placebo.

EXPLORATORY OUTCOMES

Patients who received dupilumab had greater reductions from baseline over the course of the intervention period in the F_{ENO} and levels of total IgE, periostin, eotaxin-3, and TARC than did patients who received matched placebo (Table S7 in the Supplementary Appendix). Transient elevations in blood eosinophil counts were observed in both dupilumab groups; the counts decreased to close to baseline levels by week 52

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Table 2. Adverse Events That Emerged during the Intervention Period (Safety Population).*

Event	Placebo, 1.14 ml (N=313)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=632)	Combined Placebo (N=634)	Combined Dupilumab (N=1263)
			number of patients (percent)			
Any adverse event	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious adverse event	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any adverse event leading to death†	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
Any adverse event leading to permanent discontinuation of the intervention	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
Adverse events occurring in ≥5% of patients in any group‡						
Viral upper respiratory tract infection	60 (19.2)	119 (18.9)	64 (19.9)	111 (17.6)	124 (19.6)	230 (18.2)
Upper respiratory tract infection	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	86 (13.6)	146 (11.6)
Bronchitis	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	89 (14.0)	144 (11.4)
Influenza	29 (9.3)	36 (5.7)	22 (6.9)	38 (6.0)	51 (8.0)	74 (5.9)
Sinusitis	27 (8.6)	36 (5.7)	29 (9.0)	26 (4.1)	56 (8.8)	62 (4.9)
Urinary tract infection	17 (5.4)	17 (2.7)	12 (3.7)	19 (3.0)	29 (4.6)	36 (2.9)
Headache	26 (8.3)	46 (7.3)	25 (7.8)	40 (6.3)	51 (8.0)	86 (6.8)
Rhinitis allergic	16 (5.1)	21 (3.3)	15 (4.7)	18 (2.8)	31 (4.9)	39 (3.1)
Back pain	16 (5.1)	30 (4.8)	7 (2.2)	25 (4.0)	23 (3.6)	55 (4.4)
Accidental overdose§	16 (5.1)	33 (5.2)	16 (5.0)	33 (5.2)	32 (5.0)	66 (5.2)
Injection-site reaction¶	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

* The safety population included all the patients who received at least one dose or part of a dose, and data were analyzed according to the intervention received. Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo.

† Causes of death in the dupilumab groups were pulmonary embolism, cardiopulmonary arrest in a patient with paraplegia due to spinal cord injury and multiple vertebral fractures due to osteoporosis, respiratory depression with cardiorespiratory arrest and ischemic encephalopathy, unwitnessed death attributed to myocardial infarction, and cardiac congestive failure with ventricular tachycardia in an obese patient with a history of obstructive sleep apnea. In the placebo groups, deaths were attributed to recurrence of thyroid cancer, postoperative pulmonary embolism after knee arthroplasty, and suicide.

‡ Adverse events in this category were reported according to the preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0, unless otherwise indicated.

§ Accidental overdose is coded in MedDRA as an overdose arising from a medication error (e.g., drug reconstitution error, incorrect dose, or incorrect dosing interval) and that was not associated with clinical symptoms.

¶ Injection-site reaction is a high-level term in MedDRA.

(Fig. S4 and Table S7 in the Supplementary Appendix). Transient increases were also observed in serum concentrations of eosinophil cationic protein in all intervention groups (Table S7 in the Supplementary Appendix). Eosinophilia is discussed further in the safety section below.

After a post hoc interaction analysis of biomarkers with the primary efficacy end points (Table S8 in the Supplementary Appendix), an analysis of the effect of dupilumab on exacerbations and the FEV_1 was conducted on the basis of both the baseline blood eosinophil count and the baseline $F_{E_{NO}}$ (Fig. S5 in the Supplementary Appendix). The greatest treatment benefit as compared with placebo was observed in patients with elevated type 2 biomarkers (both baseline blood eosinophil count of ≥150 per cubic millimeter and baseline $F_{E_{NO}}$ of ≥25 ppb).

SAFETY

The incidence of adverse events that emerged during the trial period was similar across intervention groups (81.0% in the combined dupilumab groups and 83.1% in the combined placebo

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groups) in the safety population (Table 2). The most frequent adverse event, occurring in 5% or more of the patients and at higher rates among patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo), reported as a high-level term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0. Eosinophilia was reported as an adverse event that emerged during the trial period in 52 patients (4.1%) who received dupilumab versus 4 patients (0.6%) who received placebo; in 0.2% of the total patient population, these adverse events were accompanied by clinical symptoms. Increased blood eosinophil levels (Fig. S4 and Table S7 in the Supplementary Appendix) were associated with symptoms in 4 patients who received dupilumab, and two of these events were reported as serious adverse events (worsening of hypereosinophilia and chronic eosinophilic pneumonia; patient narratives are provided in the Supplementary Appendix). A total of eight adverse events of eosinophilia (seven in patients who received dupilumab and one in a patient who received placebo) resulted in permanent discontinuation of the assigned intervention.

Per the trial protocol, all cases of an eosinophil count of more than 3000 per cubic millimeter during the 52-week intervention period were reported as adverse events. This event occurred in 1.2% of the patients in the combined dupilumab groups and 0.3% of those in the combined placebo groups.

The rate of persistent antidrug antibody responses was 4.2% with lower-dose dupilumab and 2.1% with higher-dose dupilumab, as compared with 1.1% in the combined placebo groups, and had no meaningful effect on efficacy or safety. A numerical imbalance in serious adverse events that were categorized as cardiac disorders in the MedDRA system organ class was noted. After assessment by an expert panel whose members were unaware of the intervention assignments, no imbalances in rates of major adverse cardiac events were observed (Table S9 in the Supplementary Appendix), and none of the events were associated with increased eosinophil levels (Table S10 in the Supplementary Appendix). During the 52-week intervention period, there were no meaningful between-group differences in adverse events of conjunctivitis, observed in 2.3% of the patients receiving dupilumab and 3.3% of those receiving placebo.

Serious adverse events that emerged during the trial period were reported in 104 patients (8.2%) who received dupilumab and 53 patients (8.4%) who received placebo (Table 2). The most frequent serious adverse event was pneumonia, observed in 4 patients (0.3%) who received dupilumab and 2 patients (0.3%) who received placebo. A total of 5 patients (0.4%) who received dupilumab (1 patient received the lower dose, and 4 received the higher dose) and 3 patients (0.5%) who received placebo (all 3 were in the 1.14-ml group) had an adverse event leading to death. All deaths were considered by the investigator to be unrelated to the intervention (detailed narratives are provided in the Supplementary Appendix).

DISCUSSION

The annualized rate of severe asthma exacerbations was significantly lower with either dose of dupilumab than with matched placebo in the intention-to-treat population, with greater treatment effects observed with increasing baseline levels of blood eosinophils and $F_{E_{NO}}$. The rate of the most severe asthma exacerbations, those leading to hospitalization or emergency department visits, was also significantly lower with dupilumab than with placebo. Assessment of the FEV_1 and asthma control over time showed that dupilumab efficacy was rapid, with significant differences versus placebo seen at the first evaluation at week 2 and maintained throughout the 52-week intervention period for both dose regimens. In the overall population, increases in the FEV_1 of 0.32 to 0.34 liters were observed at week 12, with even larger increases in patients with a baseline blood eosinophil count of 300 or more per cubic millimeter and in those with a baseline $F_{E_{NO}}$ of 25 ppb or more.

Furthermore, an analysis of the postbronchodilator FEV_1 slope showed a loss of lung function in patients who received placebo and no loss in those who received dupilumab, findings that suggest a potential effect of dupilumab on airway

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remodeling. The slope analysis showed that patients who received placebo lost, on average, approximately 40 ml annually, which is consistent with data from other cohorts of patients with asthma.[19]

The results of this trial confirm that interleukin-4 and interleukin-13 are key proximal drivers of type 2 inflammation in asthma. Dupilumab significantly reduced the $F_{E_{NO}}$, in addition to other biomarkers of systemic type 2 inflammation such as IgE, confirming its biologic activity on airway inflammation. A higher baseline $F_{E_{NO}}$ was also predictive of greater response to dupilumab with respect to both exacerbations and the FEV_1, findings that suggest the importance of other biomarkers of type 2 inflammation beyond blood eosinophils. The mechanism of action of dupilumab, with dual blockade of interleukin-4 and interleukin-13 signaling, may explain why dupilumab had a significant treatment effect in a broad patient population with a type 2 phenotype, as compared with the targeted use of anti–interleukin-5 agents in populations with eosinophilia. In the accompanying trial, LIBERTY ASTHMA VENTURE, add-on therapy with dupilumab significantly reduced the use of oral glucocorticoids, while simultaneously reducing severe exacerbations and improving lung function (FEV_1), in patients with glucocorticoid-dependent severe asthma, irrespective of baseline blood eosinophil count.[14]

In our trial, patients who received dupilumab had a greater mean transient increase from baseline in blood eosinophil counts than did patients who received placebo. Per trial protocol, all cases of eosinophil counts of more than 3000 per cubic millimeter during the intervention period were to be reported as adverse events in this trial. Most of the observed elevations in eosinophil counts were laboratory findings without clinical consequences or associated adverse events. The increase in blood eosinophil counts is consistent with the hypothesis that dupilumab blocks interleukin-4 and interleukin-13 function in eosinophil survival, activation, and recruitment to tissues but not egress from bone marrow, which is influenced by interleukin-5. As a result, it has been speculated that initial treatment with dupilumab may result in a transient increase in circulating blood eosinophil counts.[20] No meaningful differences in adverse events of conjunctivitis were observed between the dupilumab and placebo groups, in contrast to the findings of studies of dupilumab involving patients with atopic dermatitis.[10-12]

In conclusion, we found that dupilumab effectively treated patients with moderate-to-severe asthma, providing a significant reduction in the rate of severe exacerbations, rapid and sustained improvement in lung function and asthma control, and symptom relief. The most robust results were observed in patients with elevated type 2 immune characteristics, including eosinophil counts and $F_{E_{NO}}$.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

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Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. DOI: 10.1056/NEJMoa1804092

This Supplement Contains:

1. Original Protocol – p2
2. Final Protocol – p116
3. Summary of Protocol Amendments – p239
4. Original SAP – p241
5. Final SAP – p319
6. Summary of SAP Amendments – p331,332

CLINICAL TRIAL PROTOCOL

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

COMPOUND: Dupilumab

STUDY NUMBER: EFC13579

Version Number:	1	IND Number	105379
		EudraCT number	2014-004940-36
Date:	25-Feb-2015	Total number of pages:	149

WHO Universal Trial Number: U1111-1163-1293

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NAMES AND ADDRESSES OF

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MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Dupilumab	**STUDY No: EFC13579**
TITLE	A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary Objective** • To evaluate the efficacy of dupilumab in patients with persistent asthma **Secondary Objective(s)** • To evaluate the safety and tolerability of dupilumab • To evaluate the effect of dupilumab on improving patient reported outcomes (PROs) including health related quality of life (HRQoL) • To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies (ADA) **Exploratory Objective(s)** • To explore the association of biomarkers with treatment response • To explore the association of genetic profiles with treatment response • To explore the association of vaccine response with treatment
STUDY DESIGN	**General design** Multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. **Periods** The clinical trial consists of 3 periods: • Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization • Treatment Period (52 weeks): treat with dupilumab or placebo SC injection • Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study <u>Screening Period</u> Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring oral steroids as controller medication or biologics are excluded).

	The Screening Period will be 4±1 weeks (21-35 days) in duration. Randomized Treatment Period Patients will be randomized to either dupilumab or matching placebo administered SC for a treatment duration of 52 weeks. During the Randomized Treatment Period, patients will continue the stable dose(s) of controller medication used during the Screening Period. Patients who permanently discontinue the study medication will be asked and encouraged to return to the site for all remaining study visits and participate in follow-up assessments according to the visit schedule until the end of the study. Post-treatment Period After completing the treatment period, patients will be evaluated for 12 weeks in the post-treatment period. During this follow-up period, patients could continue treatment with their stable dose of controller medication or it can be modified based on their level of asthma control, as determined by the Investigator. During the post-treatment period, patients will continue to collect diary information that can be used to determine asthma control. Eligible patients who complete the treatment period with compliance for taking the investigational medicinal product (IMP) ≥80% will be offered the opportunity to participate in an open label extension (OLE) study with dupilumab. Patients subsequently enrolled in the OLE will not participate in the post-treatment period of this trial.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria: A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. - Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent. - Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. B) Pre-bronchodilator forced expiratory volume (FEV1) 40 to 80% of predicted normal at Visits 1 and 2, prior to randomization. C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization. D) Reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 mcg albuterol/salbutamol (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol, if considered as a standard office practice) before randomization.

	E) Must have experienced, within 1 year prior to Visit 1, any of the following events: - Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once. - Hospitalization or emergency medical care visit for worsening asthma. **Exclusion Criteria:** • Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age). • Weight is less than 30 kilograms. • Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function. • A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit). • Clinical evidence or imaging [eg, Chest X-ray, computed tomography (CT), Magnetic resonance imaging(MRI)] within 12 months of Visit 1 consistent with lung disease(s) other than asthma. • Current smoker or cessation of smoking within 6 months prior to Visit 1. • Previous smoker with a smoking history >10 pack-years. • Comorbid disease that might interfere with the evaluation of IMP.
Total expected number of patients	At least 1638 patients will be randomized to dupilumab or placebo with at least 690 patients with a baseline blood eosinophil count ≥300 cells/μL (0.3 giga/L) and with at least 84 adolescent patients.
STUDY TREATMENT(s) **Investigational medicinal product(s)** **Formulation**	Dupilumab (SAR231893/REGN668) or matching placebo Dupilumab: 150 mg/mL in a prefilled syringe to deliver 300 mg in 2 mL; 175 mg/mL in pre-filled syringe to deliver 200 mg in 1.14 mL Placebo: Prefilled syringe to deliver 2 mL and 1.14 mL respectively.
Route(s) of administration	Subcutaneous
Dose regimen	Randomized 2:2:1:1 to the following regimens: • dupilumab 300 mg SC q2w with a 600 mg loading dose • dupilumab 200 mg SC q2w with a 400 mg loading dose • placebo SC q2w in pre-filled syringe to deliver 2 mL with placebo loading dose • placebo SC q2w in pre-filled syringe to deliver 1.14 mL with placebo loading dose
Noninvestigational medicinal	**Inhaled corticosteroid in combination with other controllers**

product(s) (if applicable) **Formulation**	Screening Period Prior to and during the Screening Period, patients must be on a stable dose of medium to high dose ICS in combination with a second controller medication (eg, LABA, LTRA, theophylline, etc). Patients needing a third controller are elligible for this study. Randomized Treatment Period During this period, patients will continue taking their controller medication(s) at stable dose used during screening period. Post-treatment Period Upon completing the Randomized Treatment Period, patients not continuing with the OLE study, will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on the medical judgement of the Investigator of the patients' asthma control status. **Reliever Medication** Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.
Route(s) of administration	Oral inhalation, nebulizer: ICS, ICS combination, albuterol/salbutamol; For other background controllers: according to label
Dose regimen	ICS: medium to high dose Albuterol/salbutamol: as needed Other background controllers: referring to label
ENDPOINT(S)	**Primary Endpoints:** • Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 **Key Secondary Endpoint:** • Percent change from baseline in pre-bronchodilator FEV1 at week 12 **Secondary Endpoint(s):** **Efficacy** • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L • Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline

	blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52 • Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52 • Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52 • Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period • Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period • Time to first severe exacerbation event • Time to first loss of asthma control event (LOAC) • Change from baseline in Asthma Control Questionnaire (ACQ)-5 score (for adults) and ACQ-7 (for adolescents) at Weeks 2, 4, 8, 12, 24, 36, and 52 • Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in: - Morning/evening asthma symptom score and nocturnal awakenings (e-diary) - Use of daily puffs of rescue medication • Change from baseline in Health care resource utilization at Weeks 4, 8, 12, 24, 36, and 52 • Change from baseline in PROs at Week 12, 24, 36, and 52: - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years) - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) - Hospital Anxiety and Depression Scale (HADS) - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis **Safety and tolerability** • Adverse events (AEs) • Vital signs • Physical examination • Electrocardiogram (ECG)

	• Clinical laboratory tests **Systemic drug concentration and Anti-drug antibodies** • Serum functional dupilumab concentrations • ADA **Biomarkers and others** • Fractional exhaled nitric oxide (FENO) levels • Blood eosinophils • Total and antigen-specific IgE • Thymus and activation-regulated chemokine (TARC) • Periostin • Eosinophil cationic protein (ECP) • Eotaxin-3 • (Optional). Blood samples for exploratory genetic analysis of DNA and RNA to assess the i relationship of DNA variants and/or RNA expression with asthma and response to dupilumab treatment. • (Optional). Blood samples for exploratory analysis of vaccine IgG response during treatment. **Criteria for asthma exacerbations during the study** Two types of asthma exacerbation events are defined: • A severe exacerbation event during the study is defined as a deterioration of asthma requiring: - Use of systemic corticosteroids for ≥3 days; or - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids • A LOAC event during the study is defined as any of the following: - ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on 2 consecutive days; - ≥20% decrease in pre-bronchodilator FEV_1 compared with baseline; - Increase in ICS dose ≥4 times than the dose at Visit 2; - A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1(randomization). - Severe exacerbation event Two events will be considered as different if the start dates are separated by at least 4 weeks.
ASSESSMENT SCHEDULE	• Screening Period (4±1 weeks, 21-35 days) • Randomized Treatment Period (52 weeks) • Post-treatment Period (12 weeks)
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary

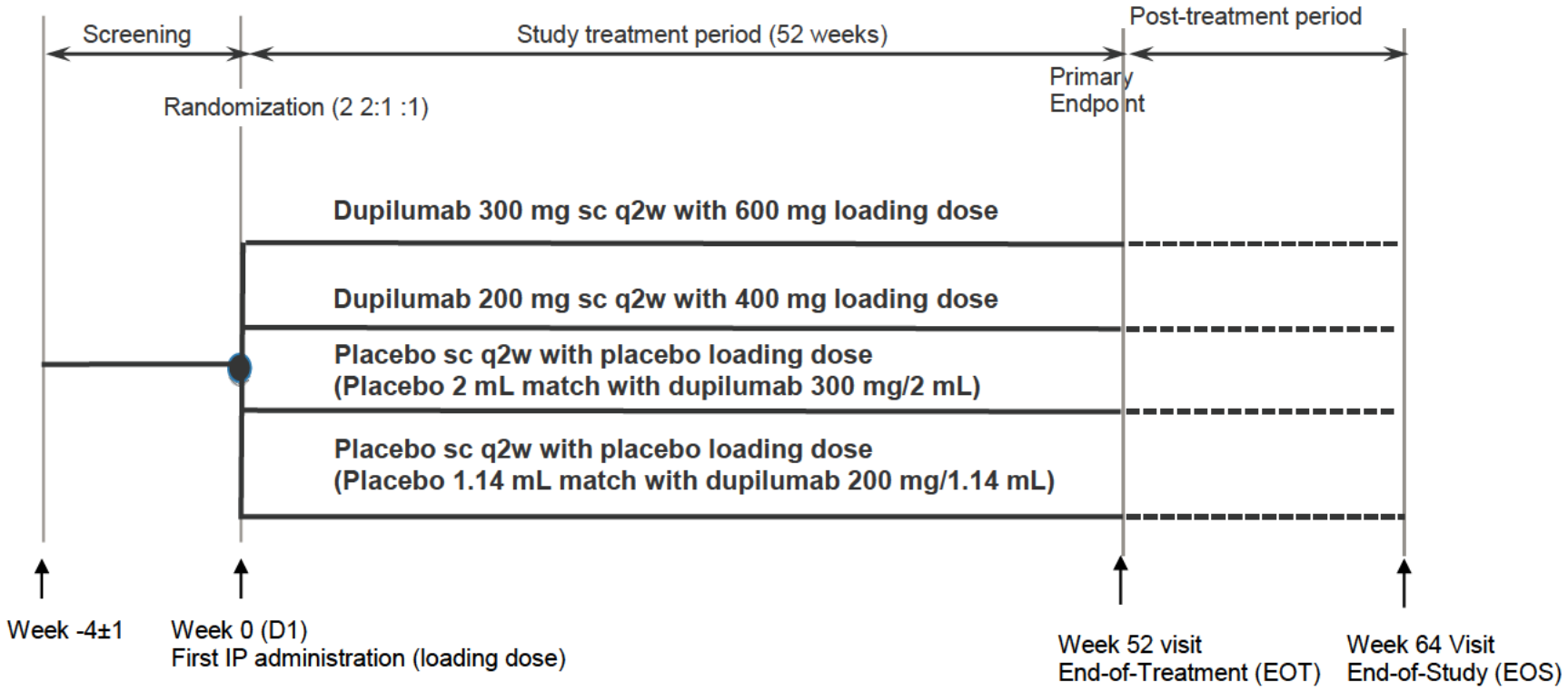
	endpoints: annualized rate of severe exacerbations and absolute change from baseline in FEV1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/μL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/mL (0.3 giga/L). The recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/μL (0.3 giga/L). In addition, approximately 84 adolescent patients will be randomized. Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/μL, 150 – 299 cells/μL, and ≥300 cells/μL) at screening and country. **Analysis populations:** The primary analysis population for the efficacy endpoints will be intent-to-treat (ITT) population defined as all randomized patients. The efficacy analyses will be conducted according to the treatment to which they are randomized. The secondary analysis population for the efficacy endpoints will be HEos (High Eosinophils) ITT defined as all randomized patients with baseline eosinophil count ≥300 cells/μL The analysis population for the safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received. **Analysis of the primary endpoints:** The two placebo groups will be compared for the two primary efficacy endpoints: annualized rate of severe exacerbation events during the 52 weeks, and absolute change from baseline in FEV1 at Week 12. If they are similar for both endpoints based on the predefined criteria, the two placebo groups will be pooled together and all efficacy analyses will be performed with the pooled placebo group. The criteria to determine if the two placebo groups are similar will be specified in the SAP prior to database lock.

	The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable. The change from baseline in FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline FEV1 values up to Week 12 as response variables, and factors for treatment, age, sex, height, region (pooled country), baseline eosinophil strata, visit, treatment by-visit interaction, baseline FEV1 value, and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12, off study-treatment FEV1 values measured up to Week 12 will be included in the primary analysis. Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /µL vs. <300 cells /µL and ≥150 cells /µL vs. <150 cells /µL). **Multiplicity considerations** To strongly control the type-I error rate for the primary family (2 primary endpoints and 2 doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300mg q2w versus placebo, 2) absolute change from baseline in FEV1 at Week 12 for 300mg q2w versus placebo, 3) annualized severe exacerbation rate for 200mg q2w versus placebo and 4) absolute change from baseline in FEV1 at Week 12 for 200mg q2w versus placebo. The secondary endpoints will be tested follow the predefined hierarchical order for the dose that meets the statistical significance for both primary endpoints: annualized event rate of severe exacerbation and absolute change from baseline in FEV1 at Week 12. The primary family error rate will be controlled at 2-sided 5% level for 2 primary endpoints and 2 doses. The family error rate will be controlled at 2-sided 5% level for primary and secondary endpoints within the dose group. The overall family error rate will be controlled at 1-sided 5% level for all endpoints across dose groups. **Handling of missing data** Sensitivity analyses excluding the additional off-treatment measurements will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses may be performed.

	Analysis of other secondary endpoints The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events. Time to severe exacerbation will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, region (pooled country), baseline eosinophil strata and number of asthma events prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an asthma exacerbation event at Weeks 12, 24, 36, and 52, specific to each treatment group. The change from baseline for continuous endpoints will be analyzed using a MMRM in the same fashion as for the endpoint of FEV_1. Sex and height will be included as covariates only in the models for spirometry parameters. . The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics. **Interim Analysis** There is no interim analysis planned for this study. The primary analysis is planned when the last patient completes Week 52 visit. **Planned database lock date**: The database lock will be planned based on the date when the last patient completes Week 52 Visit.
DURATION OF STUDY PERIOD (per patient)	The total duration of the study (per patient) is expected to be up to 69 weeks: • 4±1 weeks for screening • 52 weeks of treatment • 12 weeks of post-treatment follow-up

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Background therapy: medium to high dose ICS plus second controller (LABA, LTRA, etc)
Third controller is allowed

1.2 STUDY FLOW CHART

	SCR[a]	Randomized Treatment Period																												Post-treatment Period		
		RND[c]																											EOT[b]		EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Informed Consent	x																														
Incl/Excl Criteria	x	x																													
Patient Demography	x																														
Medical/Surgical History	x																														
Reversibility[d]	x		x	x		x		x						x						x								x			x
Spirometry[e]	x	x[f]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
CXR (if none within previous year)[g]	x																														
Prior & concomitant[h]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Physical Examination	x													x														x			x
Randomization		x																													
Call IVRS/IWRS	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x			x
Investigational Product Administration[i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	X	x				
Dispense or download e-diary/PEF meter	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Dispense/Review Home Dosing Diary[j]								x		x		x		x		x		x		x		x		x		X		x			
ACQ-7[k]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x

	SCR[a]	Randomized Treatment Period																											Post-treatment Period		
		RND[c]																										EOT[b]			EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
AQLQ(S)		x						x						x						x								x			X
Health Care Resource Utilisation		x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Exhaled NO[l]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Vital Signs[m]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
ECG	x		x	x				x						x						x								x			x
Pregnancy test[n]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x			x
Clinical lab testing[o]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Hepatitis B viral load[p]		x						x						x						x								x			
AE/SAE recording	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Urinalysis	x							x						x						x								x			x
Serum immunoglobulins (IgG, IgM, IgA)	X							x						x						x								x			x
Systemic drug concentration[q]		x	x	x		x		x		x				x						x								x	x	x	x
Anti-drug antibodies[q]		x	x	x				x						x						x								x			x
Biomarker [r]		x	x	x		x		x		x				x						x								x	x	x	x
Archival serum[s]		x						x						x						x								x			
Pharmacogenetics: blood samples for DNA and RNA[t]		x																													
EQ-5D-5L		x						x						x						x								x			x
HADS[u]		x						x						x						x								x			x
SNOT-22[v]		x						x						x						x								x			x

	SCR[a]	Randomized Treatment Period																												Post-treatment Period		
		RND[c]																											EOT[b]			EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
RQLQ(S) +12[w]		x						x						x						x								x			x
Vaccine IgG	x[x]	*y*	*y*	*y*	*y*	*y*	*y*	*y*		*y*		*y*		*y*		*y*		*y*		*y*		*y*		*y*		*y*		*y*	*y*	*y*	*y*

a The Screening Period is 4±1 weeks (21-35 days) in duration to collect baseline data on asthma control and assure eligibility criteria.

b Patients who permanently discontinue treatment early will continue the remaining visits for follow up assessment until end of study.

c Randomization Visit (Visit 2) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.

d Three attempts may be made during the Screening Period to meet the qualifying criteria for reversibility. During the treatment period, post-bronchodilator FEV1 will be determined at the designated treatment visits.

e Forced expiratory volume (FEV1), PEF, Forced vital capacity (FVC), Forced expiratory flow between 25% to 75% of vital capacity (FEF25%-75%) at all visits; pulmonary function tests should be performed in the morning. Spirometry after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and with the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs.

f Treatment Period stability limits will be established for FEV1 and PEF. Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2 ((Day1). There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

g Perform chest X-ray if no chest imaging (X-ray, CT, MRI) available within the previous year or if there is local requirement.

h Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1 (patients requiring oral steroids as controller medication or biologics are excluded).

i Every 2 week (q2w) investigational product administrations must be separated by at least 11 days. The randomized Treatment Period visits occur every 2 weeks up to Week 12 and then every 4 weeks, alternating with q2w home administration of IMP (patient, caregiver, or health care professional) without study visit up to the end of treatment period at Week 52. After Week 12, if the patient or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site by way of unscheduled visits. Patients will be monitored at the study site for a minimum of 30 minutes after injections in the first 12 weeks.

j Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, oral steroid requirements, nocturnal awakenings due to asthma symptoms, morning and evening asthma symptom NRS scores and AM and PM PEF. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days.

k ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in adolescents (12 years to less than 18 years) while ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in adults (≥ 18 years).

l Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

n Serum pregnancy test at Visit 1 and urine dipstick pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization.

o Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 includes hepatitis screen covering hepatitis B surface antigen (HBs Ag), Hepatitis B surface antibody(HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C antibodies (HC Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

p This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

q Systemic drug concentration and ADA samples are to be collected prior to dosing.

r Biomarker includes Eotaxin-3, eosinophil cationic protein (ECP), antigen-specific IgE, total IgE, Thymus and Activation-Regulated Chemokine (TARC),). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

s Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

t This is optional and a separate written consent form must be signed.

u HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

v For those patients with bilateral nasal polyposis/chronic rhinosinusitis.

w For those patients with comorbid allergic rhinitis.

x Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the patients age and local medical practice (Live attenuated vaccines are excluded) during the study. Subjects planning to receive any vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccination.

y Optional collection of blood for assay of vaccine IgG in serum for each vaccine: the first sample should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

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3 LIST OF ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire 5-question version
ACQ-7	Asthma Control Questionnaire 7-question version
AD	Atopic dermatitis
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ATS	American Thoracic Society
AQLQ(S)	Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥ 12 years)
BCG	Bacillus Calmette-Guérin
CDMS	Clinical Data Management System
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRFs	Case Report Forms
CPK	Creatine phosphokinase
CV	Curriculum Vitae
CV%	Coefficient of Variation
CYP	Cytochrome P450
CT	Computed Tomography
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Discrepancy Resolution Form
ECG	Electrocardiography
ECP	Eosinophil Cationic Protein
e-CRF	Electronic Case Report Form
ERS	European Respiratory Society
EQ-5D-5L	EuroQoL Working Group Health Status Measure 5 Dimensions, 5 Levels
EOS	End-of-Study

EOT	End-of-Treatment
FEF	Forced expiratory flow
FENO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSO	Global Safety Officer
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale- Depression subscale
HBs Ab	Hepatitis B Surface antibody
HBs Ag	Hepatitis B Surface Antigen
HC Ab	Hepatitis C Core Antibody
HEos	High Eosinophils
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HRQoL	Health related quality of life
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
ID	De-identification Code
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 Receptor Alpha Subunit
IL-13	Interleukin 13
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
IUD	Intrauterine Device
IUS	Intrauterine System

ITT	Intent-To-Treat
K-M	Kaplan-Meier
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Liver Function Test
LOAC	Loss Of Asthma Control
LTRA	Leukotriene receptor antagonist
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MID	Minimal Important Difference
MMR	Measles, Mumps, Rubella
MMRM	Mixed-effect Model with Repeated Measures
MMRV	Measles, Mumps, Rubella, Varicella
MRI	Magnetic Resonance Imaging
NIMP	Noninvestigational Medicinal Product
NRS	Numerical Rating Scale
OLE	Open label extension
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
Pop	Population
PROs	Patient-Reported Outcomes
PT	Preferred Term
RNA	Ribonucleic Acid
RQLQ(S)+12	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SC	Subcutaneously
SD	Standard Deviation
SNOT-22	Sinonasal Outcomes Test 22-item scale
SOC	System Organ Class

SUSARs	Suspected Unexpected Serious Adverse Reactions
TARC	Thymus and Activation-Regulated Chemokine
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 T-helper cell
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control. However, it is estimated that 5% to 10% of asthma patients have symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. These patients account for up to 50% of the total health cost through hospital admissions, use of emergency services, and unscheduled physician visits (1).

The long term adverse effects of systemic and inhaled corticosteroids on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Additionally, the consequences of unresponsiveness to therapy or lack of compliance with therapy is loss of asthma control and ultimately, asthma exacerbation. The poor response of some patients with asthma may reflect the number of cellular and molecular mechanisms operative in asthma. There is increasing interest in distinct phenotypes because targeted therapy is more likely to be successful in patients with similar underlying pathobiologic features (2). Recent therapeutic approaches in asthma have been focused on trying to control the type 2 T-helper cell (Th2) response. Up-regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) activity has been implicated as an important inflammatory component of asthma disease progression. Dupilumab is under development as a potential novel treatment for asthma. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor. The binding of dupilumab to IL-4Rα results in blockade of downstream signaling initiated by both IL-4 and IL-13. For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure.

4.2 RATIONALE

This is a phase 3, randomized, placebo-controlled efficacy and safety study to be conducted in patients with persistent asthma while on a medium to high dose ICS, in combination with a second controller. This study is designed to investigate the efficacy and safety profile of dupilumab over one year in a patients with asthma who are in need for an additional of another treatment added to their current management. The presence of a placebo arm is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

The proposed study design provides the opportunity to confirm the efficacy of dupilumab on multiple asthma domains including lung function, prevention of severe exacerbations and

symptom control. The effect on lung function and symptom control will be evaluated over short term and long terms.

4.2.1 Population rationale

In this study, dupilumab will be added-on to an inhaled corticosteroid in combination with one or two other controller medications in patients with persistent asthma. The population is comprised of patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines (3) and entry criteria described in Section 7. As described above, in addition to suffering the symptoms associated with a lack of asthma control, such patients utilize a disproportionate level of health care services, may suffer the long term adverse effects of systemic and inhaled corticosteroids, and ultimately, are at increased risk of a severe asthma exacerbation.

4.2.2 Design rationale

This study is a randomized, double blind, placebo-controlled, parallel group study. The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with one or two other controller medicines:

- Screening Period (4±1 weeks)
- Randomized Treatment Period (52 weeks)
- Post-treatment Period (12 weeks)

This study has two arms of placebo with different volume, which is to match the different dose regimens of dupilumab 300 mg q2w and 200 mg q2w respectively. Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

4.2.3 Endpoint rationale

There are two primary endpoints for this study. One primary endpoint is the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period, as this is one of the most clinically relevant endpoints to evaluate an asthma controller medication. The treatment period of 52 weeks is sufficient for assessing this type of event and avoiding the potential impact of seasonality. The other primary endpoint is the absolute change from baseline in pre-bronchodilator FEV1 at Week 12, as this is a well-accepted parameter to determine the effect of a drug on lung function. Safety endpoints are typical for investigational drugs at the current stage of clinical development.

Other endpoints including systemic drug concentration/ADA and biomarkers of drug action have been used previously to evaluate the exposure/effect relationship of dupilumab in asthma patients.

4.2.4 Rationale for dose and regimen selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg every 2 weeks (q2w) or 200 mg q2w. Patients randomized to 300 mg q2w will get an initial loading dose of 600 mg on Day 1 while patients randomized to 200 mg q2w will get an initial loading dose of 400 mg on Day 1, and q2w dosing will commence 2 weeks after the loading dose. The administration of the loading dose of dupilumab will allow systemic concentrations to reach target saturation, potentially reducing the time to onset of clinical effect.

Proof of concept has been established in the ACT11457 study at 300 mg weekly. One hundred and four patients with persistent, moderate-to-severe asthma and a blood eosinophil count of at least 300 cells per microliter or a sputum eosinophil level of at least 3%, partially controlled or uncontrolled by medium-to-high doses of ICS plus LABA (fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) were randomized to the study. The study showed significant efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function with mostly high doses of ICS in combination with a LABA.

In the ongoing dose ranging study (DRI12544 study), 776 patients with asthma uncontrolled by medium-to-high dose ICS plus LABA were randomized in the study. Four dose regimens (300 mg q2w with 600mg loading dose, 200 mg q2w with 400mg loading dose, 300mg q4w with 600 mg loading dose and 200mg q4w with 400 mg loading dose) were tested in the study. The results showed that 300 mg q2w and 200 mg q2w treatment with dupilumab provided a significant improvement on FEV1 at week 12 and a statistically significant reduction in the annualized rate of severe exacerbations when compared to placebo. Both dose regimens provided comparable efficacy on most of the efficacy endpoints regardless of the eosinophil count at baseline. Both doses were safe and well tolerated with a profile comparable to that seen with placebo except for an increased number of injection site reactions. To further characterize the optimal regimen for patients, both regimens will be assessed in the current trial.

The Pop PK model predictions demonstrated that exposure in adolescents at the highest proposed adult Phase 3 dose (300 mg q2w) is not expected to exceed the observed adult exposure at the dupilumab dose regimen of 300 mg once weekly, which was observed to be generally well tolerated in adults. Therefore, adolescent dosing at 300 mg q2w or 200 mg q2w regimen is expected to yield dupilumab exposure that is expected to result in efficacious exposures and unlikely to be associated with a heightened safety risk in this age population.

Dupilumab has been safe and well-tolerated in all clinical trials completed to date in healthy volunteers and patients with AD or asthma who were dosed for up to 16 weeks with a maximum dose of 300 mg administered every week. The phase 3 study will utilize less frequent dosing. No important identified risks have been established during the dupilumab clinical program. A low discontinuation rate has been observed across the completed clinical trials in dupilumab treated patients. The reported rate of suspected unexpected adverse drug reaction (SUSAR) has also been low. In addition, no imbalance in the frequency of TEAEs between patients treated with dupilumab versus placebo has been observed, with the exception of injection site reactions, nasopharyngitis and headache. In summary, the safety data observed so far in completed and currently ongoing studies in AD and asthma patients (at the same or even higher doses than that

proposed for this study) have demonstrated a positive benefit-risk profile for dupilumab in comparison to placebo.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of dupilumab in patients with persistent asthma

5.2 SECONDARY

To evaluate the safety and tolerability of dupilumab

To evaluate the effect of dupilumab on improving PROs including HRQoL

To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

5.3 EXPLORATORY

To explore the association of biomarkers with treatment response

To explore the association of genetic profiles with treatment response

To explore the association of vaccine response with treatment

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma with a medium to high dose of ICS in combination with a second controller medication (a third controller is allowed).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The clinical trial consists of three periods:

Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization.

Treatment Period (52 weeks): treat with dupilumab or placebo SC injection.

Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur at last patient who has completed 52 weeks treatment and elect to enter the long term extension study or at the end of a 12-week safety follow-up period for those patients who complete the treatment and elect not to enter extension study as well as for those who permanently discontinue medication and continue for all the remaining visits.

6.3 INTERIM ANALYSIS

Not applicable.

6.4 STUDY COMMITTEES

6.4.1 Steering committee

The Committee will have responsibilities that include, but are not limited to:

- Provide input on late stage clinical development strategy
- Assist in study designs and protocol development for upcoming studies
- Provide ongoing support and problem-solving during the execution of clinical trials

- Interact with study investigators (eg, to discuss and clarify the protocol, encourage enrollment, etc.)
- Aid in the development of study-specific sub-committees
- Review emerging non-clinical and clinical information relevant to the program and make recommendations for appropriate program adjustments
- Review study results and help develop key messages
- Assist in the creation of high quality publications and regulatory submissions
- Assist in other aspects of program development, as deemed necessary by Sanofi

The SC will be comprised of approximately seven members who are selected based on their keen interest in asthma research and on their specific and diverse expertise in areas relevant to the function of this committee. These areas of expertise include epidemiology, pathobiology, therapy of asthma, clinical trial design and outcome measure development, experience with developing biologics, large clinical trial management, clinical data analysis and reporting, regulatory strategy for respiratory drugs, etc.

6.4.2 Data monitoring committee

A data monitoring committee (DMC) is independent from sponsor and is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the course of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC are described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

6.4.3 Clinical advisory committee

A clinical advisory committee is commissioned for the dupilumab clinical development program. The clinical advisory committee would be made up of 5-7 key academic clinicians, with selection criteria including a key opinion leader in strategic regions including Japan, US, Europe and Latin America. These clinicians have been selected based on their publications, experience in conducting clinical asthma/nasal polyps studies, and their ability to both challenge and provide input during the protocol review process, speak to heath authority/ethics committee for operational issues/challenges/unexpected safety issues. Furthermore, they can speak with credibility to feasibility issues and impact the recruitment. These clinicians will provide invaluable insight and direction to ensure a successful clinical program.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria:

A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1.

- Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent.
- Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1.

B) Pre-bronchodilator forced expiratory volume (FEV1) 40 to 80% of predicted normal at Visits 1 and 2, prior to randomization.

C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization.

D) Reversibility of at least 12% and 200 mL in FEV1 after the administration of 200 to 400 mcg albuterol/salbutamol (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol, if considered as a standard office practice) before randomization.

E) Must have experienced, within 1 year prior to Visit 1, any of the following events:

- Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once.
- Hospitalization or emergency medical care visit for worsening asthma.

I 02. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age).

E 02. Weight is less than 30 kilograms.

E 03. Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function.

E 04. A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit).

E 05. Clinical evidence or imaging (Chest X-ray, CT, MRI) within 12 months of Visit 1 or at the screening visit with clinically significant findings of lung disease(s) other than asthma.

E 06. A subject who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1.

E 07. Current smoker or cessation of smoking within 6 months prior to Visit 1.

E 08. Previous smoker with a smoking history >10 pack-years.

E 09. Comorbid disease that might interfere with the evaluation of IMP.

E 10. Known or suspected alcohol and/or drug abuse.

E 11. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).

E 12. Patients requiring non-selective beta-1 adrenergic receptor blockers for any reason

E 13. Anti-immunoglobulin E (IgE) therapy (omalizumab) or any other biologic therapy to treat inflammatory disease autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) within 6 months of Visit 1.

E 14. Patients on allergen immunotherapy or initiation of allergen immunotherapy within 3 months prior to Visit 1 or plan to begin therapy during the Screening Period or the Randomized Treatment Period.

E 15. Patients on or initiation of Bronchial thermoplasty prior to Visit 1 or plan to begin therapy during the Screening Period or the Randomized Treatment Period.

E 16. Exposure to another investigative antibody within a time period prior to Visit 1 that is less than 5 half-lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.

E 17. Patients receiving medications or therapy that are prohibited as concomitant medications (See Section 8.8).

E 18. Patients who have previously been treated in any clinical trial of dupilumab.

E 19. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 20. Non-compliance with use of the mandatory background therapy, eg, ICS/LABA combination, during the screening period, as defined as:

- <80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.

E 21. A subject with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to insulin-dependent diabetes, uncontrolled hypertension, active hepatitis, active or latent untreated tuberculosis, bronchiectasis. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the investigator's judgment.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 22. Pregnant or breast-feeding women.

E 23. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:

- Do not have a confirmed negative serum beta-hCG test at Visit 1.
- Who are not protected by one of the following acceptable forms of effective contraception during the study:
  - Established use of oral, injected or implanted hormonal contraceptive.
  - Intrauterine device (IUD) with or intrauterine system (IUS) with progestogen

- Barrier contraceptive (condom, diaphragm or cervical/vault caps) used with spermicide (foam, gel, film, cream or suppository)
- Female sterilization (eg tubal occlusion, hysterectomy or bilateral salpingectomy)
- Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients the study, the vasectomized male partner should be the sole partner for that patient
- True abstinence; periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception
- Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception

E 24. Male participant with a female partner of childbearing potential not protected by highly-effective method(s) of birth control (as defined in a local protocol amendment in case of specific local requirement).

E 25. Diagnosed active parasitic infection (helminthes), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 26. History of HIV infection or positive HIV serology at Visit 1.

E 27. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, tuberculosis, histoplasmosis, listeriosis, coccidioidomycosis, penumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per investigator's judgment. Tuberculosis testing would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethic committees.

E 28. Evidence of acute or chronic infection requiring treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1, significant viral infections within 4 weeks before Visit 1 that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 29. Live attenuated vaccinations within 12 weeks prior to Visit 1 or planned live attenuated vaccinations during the study; see Appendix A for list of prohibited live attenuated vaccines.

E 30. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.)

E 31. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 32. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 33. Active hepatitis or patients with positive or indeterminate hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab) or positive hepatitis C antibody at Visit 1.

E 34. Drug induced liver injury related criteria:

- Underlying hepatobiliary disease
- Alanine Aminotransferase (ALT) >3 Upper Limit of Normal (ULN)

E 35. Abnormal lab values at Screening:

- Creatine phosphokinase (CPK) >10 ULN
- Platelets <100.000 cells/mm3
- Eosinophils >1500 cells/mm3

7.2.4 Additional exclusion criteria during or at the end of screening

E 36. Patient who has withdrawn consent before enrollment/randomization (starting from signed informed consent form)

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

Sterile dupilumab of various concentrations will be provided in 150 mg/mL in glass pre-filled syringe to deliver 300 mg in 2 mL and 175 mg/mL in glass pre-filled syringe to deliver 200 mg in 1.14 mL.

8.1.2 Placebo

Sterile placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL or 1.14 mL, which will match dupilumab 300 mg (2 mL) and 200 mg (1.14 mL) respectively.

8.1.3 Preparation of investigational product

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients.

8.1.4 Dosing schedule

The IMP is administered every 14 ± 3 days (q2w). The doses of investigational product must be separated by ≥11 days to avoid an overdose.

The Investigator or delegate will train the patient (or caregiver(s)) how to prepare and inject IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver(s)) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the patient's study file. At subsequent study visits, patients are trained to self-inject IMP, and the patients are allowed to self-inject IMP at home after 6 injections at investigational site.

When the patient has a study visit, the IMP will be administered following clinic procedures and blood collection. Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

For doses not given at the study site, diaries will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file.

If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

If the study visit is not performed at the site as scheduled, the dose will be administered by the patient and/or their caregiver/health care professional, or arrangements must be made for an unscheduled visit at the site to administer the IMP. When IMP is administered at home, the patients must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration.

If the patient, or caregiver(s) do not develop the comfort to inject the investigational drug at home, or the Investigator determines that patient (or caregiver) injection at home is not appropriate, injections can be performed at the site by way of unscheduled visits.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected twice consecutively. Injection in the upper arms could be done only by a trained person (Parent/ caregiver trained by Investigator or Delegate) or health care professional but not the patient themselves. This instruction pertains to the day that the loading dose is injected as well as the administration of q2w injections. For each injection, the anatomic site of administration will be recorded in the electronic case report form (e-CRF) and, as applicable, the home diary.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient. Patients will complete a dosing diary to document compliance with self-injection (or caregiver) injection of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor as an IMP.

8.2.1.1 Screening period

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring oral steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix B. Please note that the dose of ICS means the delivered dose from inhaler. For example, 110 mcg of fluticasone

propionate MDI could deliver 125 mcg of fluticasone propionate, and 125 mcg will be used to calculate the ICS dose for eligibility.

8.2.1.2 Randomized treatment period

During this period, patients will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed.

8.2.1.3 Post-treatment period

Upon completing the randomized treatment period, patients not continuing with the open label extension will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the investigator of the patients' asthma control status.

8.2.2 Albuterol or levalbuterol reliever medication

The reliever medication will not be dispensed or supplied by the sponsor as an IMP.

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

The description of the criterion for qualifying an asthma exacerbation event based on nebulizer using, will use the nebulizer-to-puff conversion factor for application to loss of asthma control (LOAC) definition.

Study personnel should convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown on the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16
*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs	

- Example of salbutamol/albuterol Nebulizer-to-Puff Conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg ->12 puffs

Levsalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4

2.5	8
3.75	12
5	16
*Conversion factor: levsalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs	

- Example of levsalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levsalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg ->12 puffs.

Criterion used to specify an asthma exacerbation event in eCRF based on nebulizer use:

After conversion of nebulizer-to-puff, in every instance that the number of puffs is ≥6 additional puffs of salbutamol/albuterol or levsalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days, tick the "Qualifying criteria box" on the asthma exacerbation event.

All other reliever medications rather than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL or 1.14 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) or 1.14 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

Study patients, Investigators, and study site personnel will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) and/or by calling any other

phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking.

Subject withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the investigator (ie, at the site level), then the subject will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the subject will not be withdrawn from treatment.

At the facilities where the systemic drug concentration measurements, anti-drug antibodies and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

Patients, investigators and site personnel will not have access to assay results for eotaxin-3, antigen-specific IgE, total IgE, Eosinophil Cationic Protein (ECP), TARC and periostin while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled strictly confidentially. None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by Sanofi. The investigational product (dupilumab or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients.

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo.

Patients who meet exclusion criteria may be re-screened once during the open screening period of the study; a different patient identification will be issued. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will

be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/µL, 150 – 299 cells/µL, and ≥300 cells/µL) at screening and country.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All investigational products should be stored at a temperature between 2°C and 8°C in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures.

Control of investigational product storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, to allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number as required on appropriate e-CRF page for accounting purposes;
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
  - The completed patient injection diary (returned to the site at each visit), returned treatment kit boxes and any unused prefilled syringes will be used for drug accountability purposes.
- The Investigator or designee tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. All used prefilled syringes should be kept in a sharp container by the patients and be returned to sites for destroy. A detailed treatment log of the returned IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

For noninvestigational medicinal product not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator according to the system proposed by the Sponsor.

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Prohibited Concomitant Medication

The following concomitant treatments are not permitted during the Screening Period or the Randomized Treatment Period:

- Systemic steroids (steroids can only be used to treat an asthma exacerbation)
- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab)
- Biologic therapy
- Immunosupressant

- Allergen immunotherapy
- Bronchial thermoplasty
- Intravenous immunoglobulin (IVIG) therapy
- Live Attenuated Vaccines: refer to Appendix A

8.8.2 Permitted concomitant medication

- Antihistamines are permitted as concomitant medication.
- Topical, ocular or intranasal corticosteroids are permitted during the study.

CYP substrates:

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, interleukin-4 (IL-4) was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (4), (5). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (6). Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs which are metabolized via these CYP isoforms and which have a narrow therapeutic index. This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed (4), (5), (6). Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix C.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary endpoints

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV1 at week 12.

9.1.1.1 *Asthma exacerbation events*

Two types of asthma exacerbation events are defined:

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

A loss of asthma control (LOAC) event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days;
- ≥20% decrease in pre-bronchodilator FEV1 compared to baseline or
- Increase in ICS dose ≥4 times than the dose at Visit 2 or
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1);
- Severe exacerbation event

Two events will be considered as different if the start dates are separated by at least 4 weeks.

The reasons (ex, infections including viral and bacterial, allergen exposure, exercise and others) of the exacerbation events will be collected in eCRF**.**

9.2 SECONDARY ENDPOINT(S)

Key secondary Endpoints:

- Percent change from baseline in pre-bronchodilator FEV1 at Week 12

9.2.1 Efficacy endpoints

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF]25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period
- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score (for adults) and ACQ-7 (for adolescents) at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 4, 8, 12, 24, 36, and 52.
- Change from baseline in PROs at Week 12, 24, 36, and 52:
  - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
  - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
  - Hospital Anxiety and Depression Scale (HADS)

- 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis
- Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

9.2.1.1 Disease-specific efficacy measures

9.2.1.1.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (7). For pre-bronchodilator measured parameters, including FEV1, PEF, FVC and FEV 25-75%, spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours.

For post-bronchodilator FEV1, the measure should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry should be performed in the AM. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Pulmonary function tests will be measured in the sitting position; however, if necessary to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable maneuvers, an explanation should be recorded in the eCRF. At least two acceptable curves must be obtained.

The largest FEV1 and largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

Automated best efforts, which combine FEV1 and FVC are not acceptable.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study subject is seen and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

Further details on spirometry will be available in a separate operational manual provided to the sites.

9.2.1.1.2 Reversibility

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV1 of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the subject does not meet the reversibility at Visit 1, up to 3 repeat assessments can be performed at any time (ie, unscheduled visits) prior to the Baseline Visit (Visit 2) .

9.2.1.1.3 ACQ (Asthma Control Questionnaire)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

9.2.1.1.3.1 ACQ-7 (Asthma Control Questionnaire, 7-question version)

The ACQ-7 has 7 questions- the first 5 items assess the most common asthma symptoms:
1. frequency in past week awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma and 5. wheeze, plus 6. short-acting bronchodilator use and 7. FEV1 (pre-bronchodilator use, % and % predicted use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see Appendix D).

Clinic staff scores the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-7, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (8).

The ACQ-7 questionnaire will be put into eDiary to be completed by all patients regardless of adults or adolescents. Patients should complete ACQ-7 before spirometry test.

9.2.1.1.3.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (9).

9.2.1.2 Disease-specific, daily efficacy assessments

9.2.1.2.1 Electronic diary/ PEF meter

On a daily basis throughout the study, the patient uses an electronic diary / PEF meter to:

- Measure morning and evening PEF
- Respond to the morning and evening asthma symptom scale questions
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the number of inhalations/day of background product used
- Record the number of nocturnal awakenings due to asthma symptoms
- Record oral steroids use for exacerbation event

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 10 AM) prior to taking any albuterol or levalbuterol
- PM PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any albuterol or levalbuterol
- Patients should try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of investigational product, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

Information derived from the electronic PEF meter will be evaluated by the Investigator at study visits.

9.2.1.2.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary/PEF meter twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. There is no global score, just an AM score and a PM score. An MCID of 0.35 is being used (10) (see Appendix E).

9.2.1.2.3 Use of rescue medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in an electronic diary/PEF meter. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

9.2.1.3 Health care resource utilization

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days' loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

9.2.1.4 Patient-reported outcomes

Patients should complete the following PROs before spirometry test.

9.2.1.4.1 Asthma Quality of Life Questionnaire) Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)

The AQLQ (S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to adolescents and adults≥12 years of age as a result of their asthma (see Appendix F). The instrument is comprised of 32 items, each rated on a

7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (11).

9.2.1.4.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on health-related quality of life (see Appendix G). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30) with MID of -2.5, Ear (range 0-15) with MID of -1.25, Sleep (0-20) with MID of -1.67, General and Practical (0-30) with MID of -2.50, and Emotional (0-15) with MID of -1.25. The range of the global score is 0-110 and an MID (the smallest difference between clinical trial arms mean change from baseline [point estimates] that will be interpreted as important) of 8.9 (12). Lower scores indicate less impact and the recall period is past 2 weeks.

9.2.1.4.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix H). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3; one can score between 0 and 21 for either anxiety or depression.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (13). The MID for the HADS-A (anxiety) has been reported to be in the range of 0.41 (anxious and depressed subjects in active treatment controlled studies) to 1.32 (COPD patients), in the range of 0.50 (anxious and depressed subjects in active treatment controlled studies) to 1.40 (COPD patients) for HADS-D (depression) and approximately 1.5 (COPD patients) for the HADS Total score (14, 15)

Alternatively, a significant improvement in treatment versus placebo group was defined as the % of subjects who moved from a defined category of moderate to severe depression or anxiety (≥8 to not having the disease (<8) (16). Using this methodology Stelara (Ustekinumab) was able to make the claim in summary of product characteristics that “HADS was significantly improved in the treatment group compared with placebo” (17).

9.2.1.4.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (18). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (see Appendix I). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. The MCID for the EQ-5D in asthma patients has been reported to be in the range of .001 to 0.074 (19, 20)

9.2.1.4.5 Standardized Rhinoconjunctivitis Quality Of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix J) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-Hay Fever Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 5. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (21).

9.2.2 Safety and tolerability endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.

- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2.2.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the subject gives informed consent at Visit 1 until the End-of Study Visit or till the rollover to the extension study, except for:

- SAEs
- AEs that are ongoing at database lock.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in Section 10.4.

9.2.2.2 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) only. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits. Refer to Section 1.2 Study Flow Chart for the schedule of vital signs performed throughout this study.

9.2.2.3 Physical examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease. Refer to Section 1.2 Study Flow Chart for the schedule of physical examination performed throughout this study.

9.2.2.4 ECG

One recording of a standard 12-lead ECG will be performed centrally. Refer to Section 1.2 Study Flow Chart for the schedule of ECG performed throughout this study. At the post-randomization visits, ECGs will be performed prior to investigational product administration. All ECGs will be performed with the subject in a reclined position. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG.

All measurements will be made from a single lead: Lead II, or Lead I if Lead II is not possible or lead V5 if Lead II and Lead I are not possible.

9.2.2.5 Clinical laboratory tests

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Abnormal laboratory values that are considered to be clinically significant by the Investigator must be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

Refer to Section 1.2 Study Flow Chart for the description of the clinical laboratory evaluations and the schedule of laboratory evaluations performed throughout this study.

The clinical laboratory parameters that will be measured in safety hematology and chemistry blood samples are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, differential count, and total red blood cell count.
- Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. The blood sample must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours.
- Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.
- Clinical laboratory testing at Visit 1 adds hepatitis screen including hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab) and hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

9.2.2.6 Hepatitis B viral load

Hepatitis B viral load will be tested at Visit 2, then every 12 weeks and end of treatment period for patients in Japan or other countries/regions if there is local regulatory requirement who are HBsAg negative and HBs Ab positive at screening.

9.2.2.7 Pregnancy test

A serum pregnancy test (β-human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine dipstick pregnancy test will be performed at Visit 2 prior to randomization and other visits. A negative result must be obtained at Visit 1 and 2 prior to randomization. Refer to Section 1.2 Study Flow Chart for the schedule of pregnancy test performed throughout this study.

9.3 OTHER ENDPOINTS

9.3.1 Systemic drug concentration and anti-drug antibodies

9.3.1.1 Sampling time

Predose blood samples will be collected for determination of serum functional dupilumab and anti-dupilumab antibodies as designated in the study flow chart (see Section 1.2). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory.

If an SAE occurs in a patient, blood samples should be collected for determination of functional dupilumab concentration, and anti-dupilumab antibody assessment at or near the onset and completion of the occurrence of the event, if possible. The exact date and time of sample collection must be recorded and entered into the database by the central laboratory. An unscheduled systemic drug concentration page in the e-CRF must be completed as well.

9.3.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure for samples used in the determination of systemic drug concentration and anti-drug antibodies is provided in Table 1.

Table 1 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	Two aliquots	Two aliquots
Storage conditions	< 6 months: below -20°C	< 6 months: below -20°C
	<24 months: below -80°C (preferred)	<24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

9.3.1.3 Bioanalytic method

Serum samples will be assayed using validated methods as described in Table 2.

Table 2 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Site of bioanalysis	Regeneron	Regeneron

9.3.1.4 Systemic drug concentrations and Anti-drug antibody measurement and samples

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52 and follow-up serum dupilumab at Week 56, Week 60, Week 64 will be provided.

Anti-dupilumab antibody status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 2, Week 4, Week 12, Week 24, Week 36, Week 52 and follow up at Week 64 will be provided.

Unused samples collected for drug concentration or ADA analyses may be used for exploratory analyses.

Further follow-up will be considered based on the overall assessment of antibody titers and clinical presentation.

9.3.2 Pharmacodynamics

Several biomarkers related to asthmatic inflammation and Th2 polarization will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response. In a prior asthma trial (ACT11457), treatment with dupilumab significantly suppressed systemic levels of serum TARC (CCL17; a ligand of CCR4 receptors that attracts Th2 cells), plasma eotaxin-3 (CCL26; a ligand of CCR3 receptors that attracts eosinophils and lung mast cells), and serum total IgE (a product of immunoglobulin class switching driven by IL-4), as well as reduced the concentrations of fractional exhaled nitric oxide (a marker of airway inflammation). Now added to these are the following serum biomarkers: eosinophil cationic protein (ECP; a stored protein released from activated eosinophils) and periostin, a protein reported to be elevated at baseline in patients responsive to treatment with anti-IL-13 antibodies.

Assay methodologies are briefly summarized below. More detailed information on the collection, handling, transport and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

9.3.2.1 Whole blood biomarkers

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

9.3.2.2 Plasma biomarkers

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay (Human Eotaxin-3 Quantikine ELISA kit; R&D Systems).

9.3.2.3 Serum biomarkers

Concentrations of eosinophil cationic protein (ECP) will be measured using a quantitative ImmunoCAP assay (Phadia).

Antigen-specific IgE will be detected using panels of antigens appropriate to the location of the clinical site (ImmunoCAP test; Phadia).

Total IgE will be measured with a quantitative method (eg, ImmunoCAP) approved for diagnostic testing.

TARC and periostin will be assayed with validated immunoassays.

9.3.2.4 Exhaled nitric oxide

Exhaled nitric oxide will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. Further

details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.3.3 Pharmacogenetics

9.3.3.1 Optional stored DNA and RNA samples

Pharmacogenetic testing is optional and voluntary.

For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the study flow chart and these samples will be stored for future analysis. Specific procedures for collection, storage and shipping of pharmacogenetic samples will be provided in a lab manual.

DNA or RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab, possible adverse reactions to dupilumab, and to study the genetics of asthma. The DNA may be subjected to a genome-wide association study by microarray analysis and/or to whole exome sequencing or whole genome analysis in order to thoroughly explore genetic associations with disease progression or treatment response. The RNA may be subjected to discrete panels of PCR analyses, microarray analyses or RNA sequencing analyses.

The blood DNA sample, and the DNA or RNA that is extracted, will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This "double coding" is performed to separate a subject's medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

The aliquots of DNA and RNA sent to the bioanalytical laboratories for specific genetic testing will be destroyed after completion of that specific analysis and issuance of the related analytical data.

9.3.4 Vaccine response

Patients will be encouraged to provide vaccination plans for any vaccines which are in line with the patients age and local medical practice (live attenuated vaccines are excluded) during the study. Subjects planning to receive any vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should

be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are archived, unused or left over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per Section 9.3.3). For subjects who have consented to it, archival blood samples will be collected at the visit specified in the study flow chart, 15 mL each, will be collected into a dry, red topped tube (or into smaller tubes of equivalent total volume) kept at room temperature for 30 minutes and then centrifuged at approximately 1500 g for 10 minutes at room temperature. The serum will then be transferred, in equal portions, into 3 storage tubes, which will be immediately capped and frozen in an upright position at -20°C or colder.

These archived serum samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to asthma (eg, exploratory biomarkers of disease or drug effect), additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, subject ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with asthma.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with one or two other controller medications:

- Screening Period (4±1 weeks; Visit 1)
- Randomized Treatment Period (52 weeks; Visits 2-18)
- Post-treatment Period (12 weeks; Visits 19-21)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 3 day visit window.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and participate in follow-up assessments according to the visit schedule.

Patients should be reminded that sexually active female patients of reproductive potential are required to practice effective contraception during the entire study duration, while taking dupilumab and for 12 weeks post last IMP dose.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in pharmacogenetic testing/future use of blood samples/vaccination testing) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as long as the screening visit window prior to randomization (Day 1) is respected. If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the investigator, if it is judged to be likely to return to acceptable range for study inclusion within the screening visit window (35 days) prior to Day1. These patients do not need to sign a new ICF and be allocated a new patient number within this same screening window.

Patients that fail the initial screening for exclusion criteria, eg, concomitant medications, may be rescreened for study eligibility 1 additional time. Patients that are re-screened must sign a new consent form and all of the Visit 1 procedures must be repeated (refer to Section 8.4 for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry.

When approaching the season appropriate for influenza vaccination, patients will be reminded to inform the clinic staff about vaccination plans. Similarly, when approaching the planned date of any vaccination, patients will be reminded about the related pre- and post-vaccination blood

sampling for vaccine IgG testing. Those who have not yet signed the separate consent for collection of blood pre-vaccination (eg, those who make mid-study decisions about vaccinations) may do so just prior to blood collection.

10.1.1 Visit 1 (Week -4 ± 1, -35 days to -21 days)

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study procedures.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit
- Interview to collect patient demographic information, asthma history (including smoking habits), other medical history and surgical history, and prior and concomitant medications
- Interview to collect vaccination information and vaccination plan during the treatment period for patient who agree to participate to the vaccine response assessment.
- Review entry criteria to assess eligibility, with special attention to verify the following:
  - Prescribed treatment dosage meets the pre-protocol definition of medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. In addition, patients requiring a third controller for their asthma are considered eligible for this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring oral steroids as controller medication or biologics are excluded).
  - Patient has experienced, within 1 year prior to Visit 1: 1) Treatment with ≥1 systemic (oral or parenteral) steroids bursts for worsening asthma and/or 2) Hospitalization or an emergency/urgent medical care visit for worsening asthma.
- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)]
- Perform physical examination
- Administer ACQ-7
  - Verify ACQ-5 score is ≥1.5
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry

- Entry criteria at Visit 1 include the requirement of a specific FEV_1 and demonstration of reversibility as specified in Section 7.1. See below for additional directions.
- Spirometry will be performed in the morning, after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours.
- Pre-bronchodilator Forced expiratory volume (FEV_1) must be 40 to 80% predicted normal.
- Three attempts may be made during the Screening Period to meet the qualifying criteria for spirometry.

- Establish reversibility
  - Reversibility must be at least 12% and 200 mL in FEV_1 after 200 mcg to 400 mcg (2 to 4 inhalations of albuterol/salbutamol or of a nebulized solution of albuterol/salbutamol, if considered as a standard office practice.
- Perform 12-lead electrocardiography (ECG)
- Perform chest X-ray if no chest imaging (X-ray, CT, MRI) available within the previous year or if there is local requirement.
- Obtain (fasting) blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 9.2.2.5 for details)
  - Serum chemistry (see Section 9.2.2.5 for details)
- Obtain blood samples for hepatitis screen (hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C antibodies (HC Ab), HIV screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA) .
- Obtain blood sample for serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA)
- Obtain serum β-HCG pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick)
- Dispense electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at

least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.

- Schedule a site visit within a maximum of 35 days (Visit 2, Week 0) and request patient to come in fasting.

10.1.2 Visit 2 (Week 0, Day1)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Review entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria.
- Administer ACQ-7
  - Verify ACQ-5 score is ≥1.5
- Compliance with use of the mandatory background therapy, ICS in combination with one or two other controller product as used just prior to screening, as defined as:
  - ≥80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform spirometry

Entry criteria at Visit 1 include the requirement of a specific FEV_1 and demonstration of reversibility as specified in Section 7.1. See below for additional directions.

- Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Pre-bronchodilator forced expiratory volume (FEV_1) must be 40 to 80% predicted normal.
- Patients must also meet the criteria for spirometry at Visit 2 prior to randomization. If a patient's FEV_1 does not qualify, then the patient will not be randomized on that day. The patient may return to the site on a subsequent day to attempt to meet the spirometry criteria (3 pre-randomization attempts maximum) without the need to re-perform other Visit 2 procedures.
- Treatment Period stability limits will be established for FEV1 and PEF (The Treatment Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1).

If the patient meets all inclusion and does not meet any exclusion criteria:

- Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first assignment for 2 treatment kit numbers.
  - Note: Please screen-fail the patient if entry criteria are not met.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
  - Clinical lab testing: hematology/biochemistry (refer to Section 9.2.2.5)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
  - Systemic drug concentration and ADA (refer to Section 9.3.1)
  - Biomarkers (refer to Section 9.3.2)
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4)
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - For those patients who have signed a specific pharmacogenetic informed consent form, collect blood samples for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period), please refer to Section 9.3.3.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and administer IMP
  - For those patients willing to perform self-injection: The Investigator or delegate will train the patient (or caregiver) regarding preparation and injection of IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver) will perform the second injection under the supervision of the Investigator or delegate. Document the training for IMP self-injection in the patient's study file.
  - Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 2 ± 3 days).

10.1.3 Visit 3 (Week 2)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Perform blood sampling (prior to administration of IMP) for the following tests:
  - Systemic drug concentration, anti-drug antibodies and biomarkers.
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4).
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain next treatment kit number
- Dispense and administer IMP.
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection under the supervision of the Investigator or delegate.

- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 4 ± 3 days) and ask patient to come in fasting.

10.1.4 Visit 4 (Week 4)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
  - Clinical laboratories, systemic drug concentration, anti-drug antibodies and biomarkers.
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4).
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain treatment kit number

- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit two weeks later (Week 6 ± 3 days).

10.1.5 Visit 5 (Week 6)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Perform blood sampling for the following tests:
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)

- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit
- Schedule a site visit 2 weeks later (Week 8 ± 3 days) and ask patient to come in fasting.

10.1.6 Visit 6 (Week 8)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (prior to administration of IMP) for the following tests:

  - Clinical laboratories, systemic drug concentration and biomarkers
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit
- Schedule a site visit 2 weeks later (Week 10 ± 3 days).

10.1.7 Visit 7 (Week 10)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry

  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.

- Perform blood sampling for the following tests:
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit
- Schedule a site visit 2 weeks later (Week 12 ± 3 days) and ask patient to come in fasting.

10.1.8 Visit 8 (Week 12)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide

  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick)
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting, prior to administration of IMP) for the following tests:
  - Clinical laboratories,
  - Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
  - Systemic drug concentration,
  - Anti-drug antibodies,
  - Biomarkers
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4)
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who were HBs Ag negative and HBs Ab positive at screening.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.

- For patients (or caregivers) willing to self-administer IMP:
  - Provide instructions on preparation, self-injection and dose. Allow the patient (or caregiver) to perform the injection under the supervision of the Investigator or delegate, and provide feedback on technique. Verify that the training for IMP self-injection is documented in the patient's study file. Instruct patients to administer IMP at q2w intervals.
- For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.

- Dispense patient (self-injection) Home Dosing Diary
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (Week 16 ± 3 days) and ask patient to come in fasting.

10.1.9 Visit 9 (Week 16)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Perform urine dipstick pregnancy test (for women of childbearing potential)

- Perform blood sampling (fasting, prior to IMP administration) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
  - Biomarkers.
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
- Administer health care resource utilization questionnaire.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (Week 20 ± 3 days) and ask patient to come in fasting.

10.1.10 Visit 10, 12, 13, 15, 16, 17 (Week 20, 28, 32, 40, 44, 48)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Administer health care resource utilization questionnaire.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting, prior to IMP administration) for the following tests:
  - Clinical laboratories.
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.

- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in fasting.

10.1.11 Visit 11, 14, 18 (Week 24, 36, 52 / End-of-Treatment Visit)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform physical examination (only applicable for Visit 11 and EOT visit)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick)
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling(fasting, prior to administration of IMP) for the following tests:
  - Clinical laboratories,
  - Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),

- Systemic drug concentration,
- Anti-drug antibodies,
- Biomarkers
- Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4)
- Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
- Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4)
- Blood sampling for hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.

- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number (applicable for Visit 11 and Visit 14)
- Dispense and administer IMP (only applicable for Visit 11 and Visit 14)
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period (only applicable for Visit 11, Visit 14 and EOT visit after which patients continue to participate the open label extension trial) and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks (±3 days) and ask patient to come in fasting (fasting reminder only applicable for Visit 11 and Visit 14).

- Call IVRS/IWRS to register the EOT date (only applicable for EOT visit)

At Visit 18 (EOT visit), patients who will not continue with the open label extension, the controller medication regimen and dose used during the randomized period could be adjusted based on medical judgment of the patients' asthma control status.

10.1.12 Visit 19 and Visit 20 (Week 56 and Week 60, Post-Treatment Period)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Administer ACQ-7
- Administer health care resource utilization questionnaire
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
- Perform blood sampling (fasting) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
  - Biomarkers
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4).
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Dispense and resupply salbutamol/albuterol or levosalbutamol/levalbuterol for use as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue the stable dose of ICS in combination with one or two other controller which was maintained over the randomized treatment period (unless treatment modified based on medical judgment) and record daily usage in the electronic diary.
- Remind patient to withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at

least 12 hours and withholding the last dose of LAMA for at least 24 hours prior to next visit.

- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in fasting.

10.1.13 Visit 21 (Week 64, End-of-Study Visit)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight)
- Perform physical examination
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed in the morning after withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product.
  - Post-bronchodilator FEV1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis), RQLQ(S)+12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick)
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting) for the following tests:
  - clinical laboratories,
  - serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
  - Systemic drug concentration,
  - Anti-drug antibodies
  - Biomarkers.
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) and had a pre-vaccine IgG sample drawn (refer to Section 9.3.4).
- Download electronic diary/PEF meter and take back the device

- Call IVRS/IWRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, spirometry, nitric oxide measurement, ECG, and patient electronic diary / PEF meter will be considered source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of suspected AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer to Section 7.1 and Section 7.2).

For all temporary treatment discontinuations, duration should be recorded by the Investigator in the appropriate pages of the CRF.

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the CRF or e-CRF.

Patients must be withdrawn from the study (ie, from any further investigational product or study procedure) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the Sponsor
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
- Pregnancy.

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a systemic drug concentration sample, if appropriate, and three Post-treatment Period Visits.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient's family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status.

Attempts to contact such patients must be documented in the patient's records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered. Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Anaphylaxis (refer to Appendix M for Definition of Anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
  - Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the Investigators in oncology studies)
- Chronic neurodegenerative diseases (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the Investigators in studies assessing specifically the effect of a study drug on these diseases).

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.3, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

- Anaphylactic reactions, acute systemic allergic reactions or acute allergic reactions that require immediate treatment (refer to Appendix M for Definition of Anaphylaxis)
- Severe injection site reactions that last longer than 24 hours

Severe infections, any serious infection, any bacterial infection requiring treatment with parenteral antibiotics for longer than 2 weeks, any parasitic infection, any systemic opportunistic infection (see Appendix N), any viral infection requiring antiviral treatment, or any uncommon, atypical, or unusually frequent or persistent infection and Tuberculosis that requires anti-tuberculosis medication. For details, refer to Section 10.6.3.

Note: Candidiasis – all cases should be collected as AEs (or SAEs if requirements met), however, only cases which are NOT cutaneous (systemic or mucous membranes involved) unless involvement is extensive, will be considered as AESI.

- Significant ALT elevation
  - ALT >5 x the upper limit of normal (ULN) in patients with baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/Noninvestigational medicinal product (NIMP);

Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).

- In the event of pregnancy in a female participant, IMP should be discontinued.
- Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.

- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

  Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them.
- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to

IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). In studies that require the use of combined/multiple IMPs/NIMPs, the Global Safety Officer (GSO) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.

- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI with immediate notification, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

The following table summarizes the reporting timelines:

Adverse event / laboratory abnormality		Reporting timeline
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation		
	ALT > 5 ULN if baseline ALT is ≤ 2 ULN	Within 24 hours
	ALT > 8 ULN if baseline ALT is > 2 ULN	Within 24 hours
	ALT > 3 ULN plus total bilirubin > 2 ULN	Within 24 hours
Anaphylactic reactions or acute allergic reactions that require immediate treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Severe infections including parasitic infections		Within 24 hours

10.4.3 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.4 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia
- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

In addition, on treatment eosinophil counts >3000 cells/µL (3.0 giga/L) are to be reported as AEs.

NOTE: In some clinical trials these laboratory abnormalities can be considered as AESIs (see Section 10.4.1.3)

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [eg, wheezing related to asthma].

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

For safety, the treatment code will be unblinded by the Sponsor for reporting to the Health Authority of any suspected unexpected adverse drug reaction (SUSAR) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibodies.

Acute allergic reactions may be defined as allergic reaction-mediated signs and symptoms experienced by patients during or shortly after the pharmacologic or biologic agent given. These reactions may present in a variety of ways, including dizziness, headache, anxiety, dyspnea, hypotension, tachycardia, pruritus, rash, urticaria/angioedema, flushing, nausea, or vomiting. Anaphylaxis may represent the most severe form of infusion reaction, but these events may also occur via non-IgE mediated mechanisms (eg, anaphylactoid reactions), or may occur via other immune-mediated mechanisms (eg, cytokine-mediated). Allergic reactions may begin within a few hours and persist up to 24 hours post dosing. Refer to Appendix M "Definition of Anaphylaxis", which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction in the first 12 weeks. Any instance of allergic reaction should be reported as an adverse event of special interest (AESI). Any anaphylactic reactions, acute systemic allergic reactions or acute allergic reactions that require immediate treatment will be AESI with immediate reporting (within

24 hours) and study medication should be permanently discontinued. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration.

10.6.2 Severe injection site reactions

Based on the subcutaneous mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly), severe injection site reactions, are considered as a potential risk. Patients who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection. Any severe injection reaction that lasts over 24 hours will be reported as an AESI with immediate notification.

If there is any consideration being given to premedicating before the next dose (for preceding systemic or local allergic symptoms of any type/severity), please contact sponsor prior to dosing patients.

10.6.3 Infections, including parasitic infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

Any opportunistic infection requiring parenteral or prolonged (>14 days) antibiotics or antituberculosis medication should be considered serious and be reported as AESI with immediate notification. The study medication should be discontinued in case of suspicion of serious infection and a complete diagnostic work-up should be performed (ie, cultures for fungi and/or mycobacteria other than tuberculosis, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 activation of their respective receptors, it inhibits the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL-4, IL-13 and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with dupilumab may potentially have an increased risk of parasitic infection.

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of

parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/ or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (eg, stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification and will be permanently discontinued from the study.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data has suggested any hepatic toxicity of dupilumab; however, as a general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

In order to closely follow liver function tests (LFT), assessment of total protein, albumin, total bilirubin, alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing. Clinical laboratory testing at Visit 1 adds hepatitis screen (hepatitis B surface antigen (HBs Ag), Hepatitis surface antibody (HBs Ab), hepatitis B core antibody (HBc AB), hepatitis C antibodies (HC Ab). Active hepatitis or patients with positive or indeterminate hepatitis B surface antigen (HBs Ag), hepatitis B core antibody (HBc Ab) or positive hepatitis C antibody at Visit 1 are excluded from the study.

Guidance for the investigation of elevated LFTs is provided in Appendix K.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations and absolute change from baseline in FEV1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/μL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/ /μL (0.3 giga/L). The recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/ /μL (0.3 giga/L). In addition, approximately 84 adolescent patients will be randomized.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w and dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL respectively.

Randomization will be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/μL, 150 – 299 cells/μL, ≥300 cells/μL) at screening and country.

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population.

The safety experience of patients treated and not randomized will be reported separately, and these patients will not be in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The analysis population for the efficacy endpoints will be intent-to-treat (ITT) population. The two primary endpoints will also be analyzed in the HEos ITT population.

ITT population: all randomized population analyzed according to the treatment group allocated by randomization regardless of whether treatment kit is used or not.

HEos ITT population: ITT population with baseline eosinophils ≥300 cells/μL.

11.3.2 Safety population

The analysis population for the safety endpoints will be safety population defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time between the first administration of study medication to the end of the Post-treatment Period or till the rollover to the extension study.

In addition:

- Nonrandomized but treated patients will not be part of the safety population, but their safety data will be presented separately.
- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

11.3.3 Systemic drug concentration population

The systemic drug concentration population will consist of all patients in the safety population with at least one evaluable functional dupilumab concentration result. Patients will be analyzed according to the treatment actually received.

11.3.4 Anti-drug antibody population

The anti-drug antibody population will consist of all patients in the safety population with at least one qualified ADA result in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

An administration is considered compliant if an injection is performed, regardless the actual amount of solution injected. The loading dose will be considered as two administrations. No imputation will be made for patients with missing or incomplete data.

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

The two placebo groups will be compared for the two primary efficacy endpoints: annualized rate of severe exacerbation events during the 52 weeks, and absolute change from baseline in FEV1 at Week 12. If they are similar for both endpoints based on the predefined criteria, the two placebo groups will be pooled together and all efficacy analyses will be performed with the pooled placebo group. The criteria to determine if the two placebo groups are similar will be specified in the SAP prior to database lock.

11.4.2.1 Analysis of primary efficacy endpoints

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable.

The absolute change from baseline in FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in FEV1 values up to Week 12 as response variables, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, visit, treatment by-visit interaction, baseline FEV1

value and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12, off study-treatment FEV1 values measured up to Week 12 will be included in the primary analysis.

Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /μL vs <300 cells /μL and ≥150 cells /μL vs <150 cells /μL).

11.4.2.1.1 Analysis of annualized event rate

The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events.

11.4.2.1.2 Analysis of Time to event variables

Time to event (eg, LOAC, severe exacerbation) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, number of asthma exacerbation events within 1 year prior to the study, region (pooled country) and baseline eosinophil strata as covariates. The Kaplan-Meier method will be used to respectively estimate the probabilities that a patient would experience events at Week 12, 24, 36 and 52 per each treatment group.

11.4.2.1.3 Analysis of change from baseline for other continuous variables

The change from baseline for other continuous endpoints will be analyzed using MMRM in the same fashion as for the endpoint of FEV1. The covariates to be included are treatment, age, region (pooled country), baseline eosinophil strata, visit, treatment-by-visit interaction, corresponding baseline value and baseline-by-visit interaction. Sex and height will be included as covariates only in the models for spirometry parameters.

Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 95% CI and the p-value will be derived from the MMRM model for comparison of dupilumab against placebo.

Change from baseline at other time points will be analyzed in the same way.

11.4.2.1.4 Subgroup analysis

To assess the consistency in treatment effects across the subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to baseline eosinophil level (≥300 cells /μL vs. <300 cells /μL and ≥150 cells /μL vs. < 150 cells /μL), age group, gender, region, race, background ICS dose levels, background controller medication type, baseline FEV1, predicted FEV_1 %, ACQ-5, weight, BMI, smoking history, atopic medical history, age of onset of asthma and number of asthma exacerbation events within 1 year prior to the study.

11.4.2.2 Multiplicity considerations

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo.

The secondary endpoints will be tested follow the hierarchical order defined below for the dose meets the significance for both primary endpoints: severe exacerbation and absolute change from baseline in FEV_1 at Week 12.

The primary family error rate will be controlled at 2-sided 5% level for 2 primary endpoints and 2 doses. The family error rate will be controlled at 2-sided 5% level for primary and secondary endpoints within the dose group. The overall family error rate will be controlled at 1-sided 5% level for all endpoints across dose groups.

- Percent change from baseline in pre-bronchodilator FEV1 at week 12
- Annualized rate of severe exacerbations events during the 52 weeks for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52 weeks for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 52
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 52
- Time to first severe exacerbation event
- Change from baseline in Asthma Control Questionnaire at Weeks 12
- Change from baseline in AQLQ(S) at week 12
- Change from baseline in morning asthma symptom score at Week 12
- Change from baseline in evening asthma symptom score at Week 12
- Nocturnal awakenings due to asthma symptoms (e-diary) at Week 12
- Change from baseline in daily puffs of rescue medication at Week 12
- Change from baseline in 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis at Week 12

- Change from baseline in European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) at Week 12
- Change from baseline in Hospital Anxiety and Depression Scale (HADS) at Week 12
- Annualized rate of loss of asthma control (LOAC) event during the 52 weeks.
- Time to first loss of asthma control event (LOAC)
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF]25-75%, post-bronchodilator FEV1 at Week 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period.
- Change from baseline in Health care resource utilization at Week 4, 8, 12, 24, 36, and 52
- Change from baseline in Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis at Week 12, 24, 36, and 52

11.4.2.3 Handling of missing data

Sensitivity analyses excluding the additional off-treatment measurements up to Week 52 will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analysis and additional sensitivity analyses may be performed. The details will be specified in the SAP.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. The results of the two placebo groups will be presented separately. All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before the first dose of IMP.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Proportion of patients with at least one treatment emergent adverse event (TEAE), serious TEAE and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study drug. None treatment emergent serious AE, None treatment emergent AE leading to study discontinuation will be summarized separately.

11.4.3.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.
- An overview summary of the number (%) of patients with
  - any TEAE
  - any serious AE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome
  - cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks, 24 weeks and 52 weeks)

AESI definitions and the method to identify AESIs will be specified in the SAP.

11.4.3.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received

- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.3.1.3 Clinical Laboratory Evaluation, Vital Signs and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

11.4.3.2 Vaccine response

For patients who receive vaccination, vaccine response parameters will be summarized by treatment groups with descriptive statistics.

11.4.4 Analyses of systemic drug concentration, anti-drug antibodies and pharmacodynamic variables

11.4.4.1 Drug concentration analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Concentrations of functional dupilumab in serum will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.4.2 Anti-drug antibodies analysis

Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by study cohorts. Listing of all ADA titer levels will be provided for

patients positive in the ADA assay. All samples that are positive in the ADA assay will be further tested for the presence of anti-dupilumab neutralizing antibodies.

Plots of concentrations of functional dupilumab will be examined and the potential influence of ADA on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

ADA at baseline will be summarized by:

- Number (%) of patients with a baseline sample negative in the ADA assay.
- Number (%) of patients with a baseline sample positive in the ADA assay.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for patients positive in the ADA assay at baseline.

ADA incidence and titer will be provided for the following:

- Number (%) of patients negative in ADA assay at all times
- Number (%) of patients positive in ADA assay at any time
- Number (%) of patients with treatment-emergent positive response in the ADA assay.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for treatment-emergent positive patients
- Number (%) of transient treatment-emergent positive patients
- Number (%) of persistent treatment-emergent positive patients

Titer values (Titer value category)

The minimum titer for samples positive in the ADA assay is based on the minimum required dilution of the assay.

Low (Titer < 1000)
Moderate (1,000 ≤ Titer ≤ 10,000)
High (Titer > 10,000)

Definitions:
Pre-existing immunoreactivity – defined as either a positive response in the ADA assay at baseline with all post-treatment samples negative in the ADA assay, OR a positive response at baseline in the ADA assay, with all post-treatment samples with titer levels less than 4-fold over baseline titer levels.

Treatment emergent - defined as either a post treatment positive response in the ADA assay when baseline results are negative, OR if any post treatment response is positive in the ADA assay with titer levels greater-than or equal to 4-fold over baseline titer levels. The treatment emergent responses will be further characterized into Persistent and Transient responses.

Persistent Response- Treatment-emergent positive assay response with two or more consecutive ADA positive sampling time points separated by at least a 12-week period OR the last collected sample is positive in the ADA assay.

Transient Response - Any ADA positive response that is not considered persistent.

11.4.4.3 Pharmacodynamics

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables

Change from baseline in the following variables: global measure of AQLQ(S) and the four domains, the quantitative variables of EQ-5D-5L (single index utility), the anxiety and depression scores of HADS will be analyzed with an MMRM approach described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI's and the p-values will be provided for comparison between dupilumab and placebo.

SNOT-22 (only for those patients with bilateral nasal polyposis) and RQLQ(S)+12 (only for those patients with comorbid allergic rhinitis) will be analyzed using the similar approach.

11.5 INTERIM ANALYSIS

There is no interim analysis planned for this study. The primary analysis is planned when the last patient completes Week 52 visit. The database lock will be planned based on the date when the last patient completes Week 52 Visit.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s] for pediatric patients) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the Institutional Review Board / Institutional Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patients (for adult patients) or patient's parent(s) for pediatric patients or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient (for adult patients) or patient's parent(s) for pediatric patients. Local law must be observed in deciding whether 1 or both parents/guardians consent is required for pediatric patients. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

Pediatric participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Pediatric participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Pediatric participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the Investigator for obtaining the pediatric patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial, ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for evaluation of vaccine response, the optional vaccine response informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for archiving of serum, the optional Future Use of Specimens informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The main study informed consent form, the optional Pharmacogenetic informed consent form, optional Vaccine Response informed consent form and the Future Use of Specimens informed consent form to be used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purpose of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;
- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;

- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor's written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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AMENDED CLINICAL TRIAL PROTOCOL 04

COMPOUND: dupilumab (SAR231893)

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

STUDY NUMBER: EFC13579

VERSION DATE / STATUS: 26-May-2017 / Approved

CLINICAL STUDY DIRECTOR: [redacted]

STUDY NAME: LIBERTY ASTHMA QUEST

Protocol Amendment 08 – Global	Version number 1: (electronic 2.0)	Date: 26-May-2017
Protocol Amendment 07 - Global	Version number 1: (electronic 1.0)	Date: 9-Aug-2016
Amended Clinical Trial Protocol 03-France	Version number 1: (electronic 1.0)	Date: 15-Dec-2015
Protocol Amendment 06-France	Version number 1: (electronic 1.0)	Date: 15-Dec-2015
Amended Clinical Trial Protocol 05-Germany	Version number 1: (electronic 4.0)	Date:09-Nov-2015
Amended Clinical Trial Protocol 04-Germany	Version number 1: (electronic 2.0)	Date: 23-Oct-2015
Protocol Amendment05-Local for Germany	Version number 1: (electronic 1.0)	Date: 23-Oct-2015
Amended Clinical Trial Protocol 2	Version number 1: (electronic 1.0)	Date: 21-Sep-2015
Protocol Amendment 4 - Global	Version number: 1 (electronic 1.0)	Date: 21-Sep-2015
Amended Clinical Trial Protocol 1-Germany	Version number: 1 (electronic 1.0)	Date: 28-Jul-2015
Protocol Amendment 3 - Local for Germany	Version number: 1 (electronic 1.0)	Date: 28-Jul-2015
Amended Clinical Trial Protocol 1	Version number: 1 (electronic 1.0)	Date: 21-May-2015
Protocol Amendment 2 - Global	Version number: 1 (electronic 1.0)	Date: 21-May-2015
Amended Clinical Trial Protocol 1 - Japan	Version number: 1 (electronic 1.0)	Date: 10-Apr-2015
Protocol Amendment 1 - Local for Japan	Version number: 1 (electronic 1.0)	Date: 10-Apr-2015
Clinical Trial Protocol	Version number: 1 (electronic 1.0)	Date : 25-Feb-2015

Version Number: 1	EudraCT : IND Number: WHO universal trial number:	**2014-004940-36** **105379** U1111-1163-1293
Date: 26-May-2017	Total number of pages:	161

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NAMES AND ADDRESSES OF

COORDINATING INVESTIGATOR	Name: Address: Tel: Fax: E-mail:	
MONITORING TEAM'S REPRESENTATIVE	Name: Address: Tel: Fax: E-mail:	
SPONSOR	Company: Address:	
OTHER EMERGENCY TELEPHONE NUMBERS		

CLINICAL TRIAL SUMMARY

COMPOUND: Dupilumab	**STUDY No: EFC13579**
TITLE	A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma
INVESTIGATOR/TRIAL LOCATION	Worldwide
PHASE OF DEVELOPMENT	3
STUDY OBJECTIVE(S)	**Primary Objective** • To evaluate the efficacy of dupilumab in patients with persistent asthma **Secondary Objective(s)** • To evaluate the safety and tolerability of dupilumab • To evaluate the effect of dupilumab on improving patient reported outcomes (PROs) including health related quality of life (HRQoL) • To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies (ADA) **Exploratory Objective(s)** • To explore the association of biomarkers with treatment response • To explore the association of genetic profiles with treatment response • To explore the association of vaccine response with treatment
STUDY DESIGN	**General design** Multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. Periods The clinical trial consists of 3 periods: • Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization • Treatment Period (52 weeks): treat with dupilumab or placebo SC injection • Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study <u>Screening Period</u> Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthines, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are

	excluded). The Screening Period will be 4±1 weeks (21-35 days) in duration. <u>Randomized Treatment Period</u> Patients will be randomized to either dupilumab or matching placebo administered SC for a treatment duration of 52 weeks. During the Randomized Treatment Period, patients will continue the stable dose(s) of controller medication used during the Screening Period. Patients who permanently discontinue the study medication will be asked and encouraged to return to the site for study visits and participate in assessments according to the visit schedule until the end of the study with a +/-5 day window (See study flowchart for patients after permanent treatment discontinuation in Section 1.3). At the time of permanent treatment discontinuation, patients will perform early treatment discontinuation visit (ETD) with all the assessments defined for Visit 18 (EOT). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected. In addition, patients who discontinue early from treatment or patients who choose not to participate in the open label extension (OLE) study may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and/or clinical presentation at the time of discontinuation or at the time of last study visit. <u>Post-treatment Period</u> After completing the treatment period, patients will be evaluated for 12 weeks in the post-treatment period. During this follow-up period, patients could continue treatment with their stable dose of controller medication or it can be modified based on their level of asthma control, as determined by the Investigator. During the post-treatment period, patients will continue to collect diary information that can be used to determine asthma control. Eligible patients who complete the treatment period will be offered the opportunity to participate in the OLE study with dupilumab. Patients subsequently enrolled in the OLE study will not participate in the post-treatment period of this trial.
STUDY POPULATION **Main selection criteria**	**Inclusion criteria:** Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria: A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. - Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent.

	- Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1. B) Pre-bronchodilator forced expiratory volume (FEV_1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization. C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization. D) Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization. E) Must have experienced, within 1 year prior to Visit 1, any of the following events: - Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once. - Hospitalization or emergency medical care visit for worsening asthma. **Exclusion Criteria:** • Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age). • Weight is less than 30 kilograms. • Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function. • A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit). • Evidence of lung disease(s) other than asthma, either clinical evidence or imaging [eg, Chest X-ray, computed tomography (CT), Magnetic resonance imaging(MRI)] within 12 months of Visit 1 as per local standard of care. • Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis. • Current smoker or cessation of smoking within 6 months prior to Visit 1. • Previous smoker with a smoking history >10 pack-years. • Comorbid disease that might interfere with the evaluation of IMP.

Total expected number of patients	At least 1638 patients will be randomized to dupilumab or placebo with at least 690 patients with a baseline blood eosinophil count $\geqslant 300$ cells/L (0.3 giga/L) and with approximately 84 adolescent patients. In addition, recruitment for patients on medium dose of ICS will be stopped at approximately 819 to ensure at least 50% patients are on high dose of ICS. In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638).
STUDY TREATMENT(s)	
Investigational medicinal product(s) **Formulation**	Dupilumab (SAR231893/REGN668) or matching placebo Dupilumab: 150 mg/mL in a prefilled syringe to deliver 300 mg in 2 mL; 175 mg/mL in pre-filled syringe to deliver 200 mg in 1.14 mL Placebo: Prefilled syringe to deliver 2 mL and 1.14 mL respectively.
Route(s) of administration	Subcutaneous
Dose regimen	Randomized 2:2:1:1 to the following regimens: • dupilumab 300 mg SC q2w with a 600 mg loading dose • dupilumab 200 mg SC q2w with a 400 mg loading dose • placebo SC q2w in pre-filled syringe to deliver 2 mL with placebo loading dose • placebo SC q2w in pre-filled syringe to deliver 1.14 mL with placebo loading dose
Noninvestigational medicinal product(s) (if applicable) **Formulation**	Inhaled corticosteroid in combination with other controllers Screening Period Prior to and during the Screening Period, patients must be on a stable dose of medium to high dose ICS in combination with a second controller medication (eg, LABA, LTRA, methylxanthines, etc). Patients needing a third controller are elligible for this study. Randomized Treatment Period During this period, patients will continue taking their controller medication(s) at stable dose used during screening period. Post-treatment Period Upon completing the Randomized Treatment Period, patients not continuing with the OLE study, will continue treatment with the controller medication regimen and dose used during the randomized period, which could be adjusted based on the medical judgement of the Investigator of the patients' asthma control status. Reliever Medication Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol metered dose inhaler (MDI) as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Route(s) of administration	Oral inhalation, nebulizer: ICS, ICS combination, albuterol/salbutamol or levalbuterol/levosalbutamol; for other background controllers: according to label
Dose regimen	ICS: medium to high dose Albuterol/salbutamol or levalbuterol/levosalbutamol: as needed Other background controllers: referring to label
ENDPOINT(S)	**Primary Endpoints:** • Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 **Key Secondary Endpoint:** • Percent change from baseline in pre-bronchodilator FEV_1 at week 12 **Secondary Endpoint(s):** Efficacy • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS • Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L • Absolute change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52 • Percent change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52 • Change from baseline in other lung function measurements (% predicted FEV_1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52

	• Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period • Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period • Time to first severe exacerbation event • Time to first loss of asthma control event (LOAC) • Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52 • Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in: - Morning/evening asthma symptom score and nocturnal awakenings (e-diary) - Use of daily puffs of rescue medication • Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52 • Change from baseline in PROs at Week 12, 24, 36, and 52: - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years) - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L) - Hospital Anxiety and Depression Scale (HADS) - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis Safety and tolerability • Adverse events (AEs) • Vital signs • Physical examination • Electrocardiogram (ECG) • Clinical laboratory tests Systemic drug concentration and Anti-drug antibodies • Serum functional dupilumab concentrations • ADA Biomarkers and others • Fractional exhaled nitric oxide (FENO) levels • Blood eosinophils • Total and antigen-specific IgE • Thymus and activation-regulated chemokine (TARC) • Periostin • Eosinophil cationic protein (ECP) • Eotaxin-3 • (Optional). Blood samples for exploratory genetic analysis of DNA and RNA to assess the relationship of DNA variants and/or RNA expression with asthma and response to dupilumab treatment. • (Optional). Blood samples for exploratory analysis of vaccine IgG response during treatment.

	Criteria for asthma exacerbations during the study Two types of asthma exacerbation events are defined: • A severe exacerbation event during the study is defined as a deterioration of asthma requiring: - Use of systemic corticosteroids for ≥3 days; or - Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids • A LOAC event during the study is defined as any of the following: - ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared with baseline) on 2 consecutive days; - ≥20% decrease in pre-bronchodilator FEV1 compared with baseline; - Increase in ICS dose ≥4 times than the dose at Visit 2; - A decrease in AM or PM PEF of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1(randomization). - Severe exacerbation event Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.
ASSESSMENT SCHEDULE	• Screening Period (4±1 weeks, 21-35 days) • Randomized Treatment Period (52 weeks) • Post-treatment Period (12 weeks)
STATISTICAL CONSIDERATIONS	**Sample size determination:** The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations during the 52-week treatment period and absolute change from baseline in FEV_1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/µL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/µL (0.3 giga/L). The overall study recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/µL (0.3 giga/L) are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84

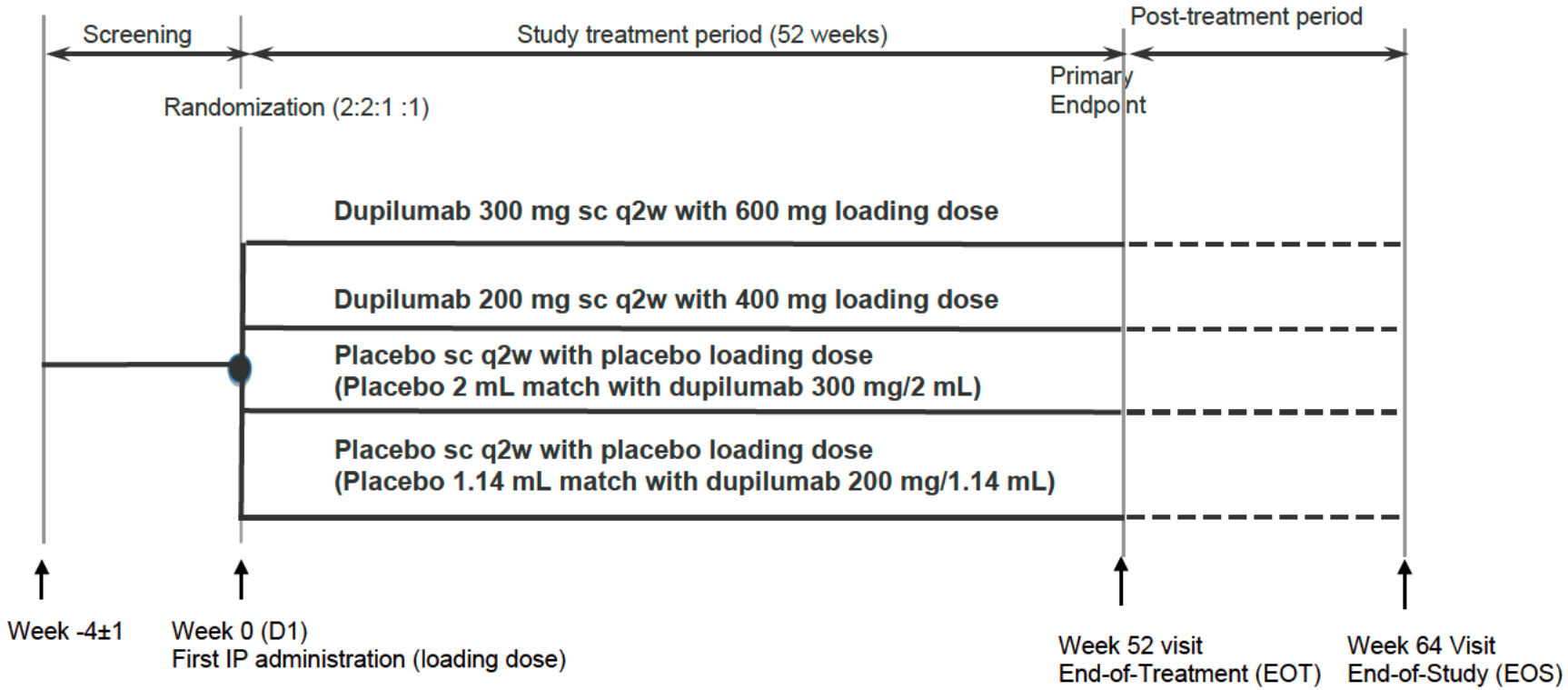
	adolescent patients will be randomized. Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/μL, ≥300 cells/μL) at screening, ICS dose level (medium, high) and country. In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638). **Analysis populations:** The primary analysis population for the efficacy endpoints will be intent-to-treat (ITT) population defined as all randomized patients. The efficacy analyses will be conducted according to the treatment to which they are randomized. The secondary analysis population for the efficacy endpoints will be HEos (High Eosinophils) ITT defined as all randomized patients with baseline eosinophil count ≥300 cells/μL The analysis population for the safety endpoints will be the safety population, defined as all patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received. **Analysis of the primary endpoints:** The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable. The change from baseline in FEV_1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline FEV_1 values up to Week 12 as response variables, and factors for treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV_1 value, and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method using the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV_1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12,

	off study-treatment FEV_1 values measured up to Week 12 will be included in the primary analysis. Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /µL vs. <300 cells /µL and ≥150 cells /µL vs. <150 cells /µL). **Multiplicity considerations** To strongly control the type-I error rate for the primary family (2 primary endpoints and 2 doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300mg q2w versus placebo, 2) absolute change from baseline in FEV_1 at Week 12 for 300mg q2w versus placebo, 3) annualized severe exacerbation rate for 200mg q2w versus placebo and 4) absolute change from baseline in FEV_1 at Week 12 for 200mg q2w versus placebo. If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The first four tests will be 1) % change from baseline in FEV_1 at Week 12 for 300 mg q2w versus placebo 2) absolute change from baseline in AQLQ global score at Week 12 for 300 mg q2w versus placebo 3) % change from baseline in FEV_1 at Week 12 for 200 mg q2w versus placebo, 4) absolute change from baseline in AQLQ global score at Week 12 for 200 mg q2w versus placebo. The remaining list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups. **Handling of missing data** Sensitivity analyses excluding the additional off-treatment measurements will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analyses and other sensitivity analyses may be performed. **Analysis of other secondary endpoints** The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events. Time to severe exacerbation will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of asthma events prior to the study as covariates. The Kaplan-Meier method will be used to derive the proportion of patients with an asthma exacerbation event at Weeks 12, 24, 36, and 52, specific to each treatment group. The change from baseline for continuous endpoints will be analyzed using a MMRM in the same fashion as for the endpoint of FEV_1. Sex and height will be included as covariates only in the models for spirometry parameters. . The safety variables, including AEs, laboratory parameters, vital signs, ECG, and physical examinations will be summarized using descriptive statistics. **Interim Analysis** There is no interim analysis planned for this study.

	Planned database lock date: The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete week 52 visit or discontinue from the study before week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR (Clinical Study Report). Additional data between database lock and last patient completing last visit will be summarized in a CSR addendum.
DURATION OF STUDY PERIOD (per patient)	The total duration of the study (per patient) is expected to be up to 69 weeks: • 4±1 weeks for screening • 52 weeks of treatment • 12 weeks of post-treatment follow-up

1 FLOW CHARTS

1.1 GRAPHICAL STUDY DESIGN



Background therapy: medium to high dose ICS plus second controller (LABA, LTRA, etc)
Third controller is allowed

1.2 STUDY FLOW CHART FOR PATIENTS WHO WILL COMPLETE TREATMENT

	SCR[a]	Randomized Treatment Period																											Post-treatment Period		
		RND[c]																										EOT[b]			EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Informed Consent	x																														
Incl/Excl Criteria	x	x																													
Patient Demography	x																														
Medical/Surgical History	x																														
Reversibility[d]	x																														
Post-bronchodilator FEV_1[d]		x	x	x		x		x						x						x								x			x
Spirometry[e]	x	x[f]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
CXR or MRI (if none within previous 12 months, MRI is only for Germany) [g]	x																									X					
Prior & concomitant medication[h]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Physical Examination	x													x														x			x
Randomization		x																													
Call IVRS/IWRS	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x			x
Investigational Product Administration[i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	X	x	x	x	x	x	x	X	x				
Dispense or download e-diary/PEF meter[j]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x

	SCR[a]	Randomized Treatment Period																												Post-treatment Period		
		RND[c]																										EOT[b]			EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Dispense/Review Home Dosing Diary								x		x		x		x		x		x		x		x		x		X		x			
ACQ-7[k]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
AQLQ(S)		x						x						x						x								x			X
Health Care Resource Utilisation		x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Exhaled NO[l]	x	x	x	x				x		x		x		x						x						X		x	x	x	x
Vital Signs[m]	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
ECG	x		x	x				x						x						x								x			x
Pregnancy test[n]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x			x
Clinical lab testing[o]	x	x		x		x		x		x		x		x		x		x		x		x		x		X		x	x	x	x
Hepatitis B viral load[p]		x						x						x						x								x			
AE/SAE recording	x	x	x	x	x	x	x	x		x		x		x		x		x		x		x		x		X		x	x	x	x
Urinalysis[q]	x							x						x						x								x			x
Serum immunoglobulins (IgG, IgM, IgA)	X							x						x						x								x			x
Systemic drug concentration (functional dupilumab) [r]		x	x	x		x		x		x				x						x								x	x	x	x
Anti-drug antibodies[r]		x						x						x														x			x
Biomarker set [s]		x						x						x						x								x			
Periostin		x		x				x																				x			
Antigen-specific IgE		x						x						x														x			

	SCR[a]	Randomized Treatment Period																											Post-treatment Period		
		RND[c]																										EOT[b]			EOS
Week	-4± 1	0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	56	60	64
Visit	1	2	3	4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	19	20	21
Archival serum[t]		X						X						X						X								X			
Pharmacogenetics: blood samples for DNA and RNA[u]		X																													
EQ-5D-5L		X						X						X						X								X			X
HADS[v]		X						X						X						X								X			X
SNOT-22[w]		X						X						X						X								X			X
RQLQ(S) +12[x]		X						X						X						X								X			X
Vaccine IgG	X[y]				*z*	*z*	*z*	*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*		*z*			

a The Screening Period is 4±1 weeks (21-35 days) in duration to collect baseline data on asthma control and assure eligibility criteria.

b Patients who permanently discontinue treatment early will continue the remaining visits per protocol schedule with a +/-5 day window until end of study (See section 1.3). At the time of permanent treatment discontinuation the patients will perform early treatment discontinuation (ETD) visit with all the assessments defined for Visit 18 (EOT).

c Randomization Visit (Visit 2) is defined as Day 1. Visit windows for subsequent visits are +/- 3 days.

d Three attempts may be made during the Screening Period until the Baseline visit to meet the qualifying criteria for reversibility. During the treatment period, post-bronchodilator FEV_1 will be determined at the designated treatment visits. If other attempt for reversibility test was performed at Baseline visit, then the post-bronchodilator FEV_1 will come from the result of this reversibility test.

e Forced expiratory volume (FEV_1), PEF, Forced vital capacity (FVC), Forced expiratory flow between 25% to 75% of vital capacity (FEF25%-75%) at all visits; pulmonary function tests should be performed in the morning if possible, but if it could only be done at a different time of the day, the spirometry should be done at approximately the same time of the day at each visit throughout the study. Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs. This will be verified before performing the measurements.

f Treatment Period stability limits will be established for FEV_1 and PEF. Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Visit 2 ((Day1). There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

g Perform chest X-ray or MRI (MRI is for Germany only) if no chest imaging (X-ray, CT, MRI) available within the previous 12 months as per local standard of care or if there is local requirement.. At Visit 17, it is only applicable for patients who plan to participate in the OLE study and available chest imaging is over 12 months from entry into the OLE study.

Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.

h Prior to screening, patients must be on a stable background therapy of a medium to high dose of inhaled corticosteroid (ICS) in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], methylxanthine , etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1 (patients requiring systemic steroids as controller medication or biologics are excluded).

i Every 2 week (q2w) investigational product administrations must be separated by at least 11 days. The randomized Treatment Period visits occur every 2 weeks up to Week 12 and then every 4 weeks, alternating with q2w home administration of IMP (patient, caregiver, or health care professional) without study visit up to the end of treatment period at Week 52. After Week 12, if the patient or Investigator decides not to administer IMP at home, the IMP injections can be performed at the site by way of unscheduled visits. Patients will be monitored at the study site for a minimum of 30 minutes after injections in the first 12 weeks.

j Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, oral steroid requirements, nocturnal awakenings due to asthma symptoms, morning and evening asthma symptom NRS scores and AM and PM PEF. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days.

k ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in all patients. ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in all patients.

l Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

m Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured only at screening (Visit 1) for adults, and be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit for adolescents. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

n Serum pregnancy test at Visit 1 and urine dipstick pregnancy tests at other visits. A negative result must be obtained at Visits 1 and 2 prior to randomization.

o Hematology: hemoglobin, hematocrit, platelet count, total white blood cell (WBC) count with five-part differential count, differential count, and total red blood cell count. Serum chemistry: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. Clinical laboratory testing at Visit 1 and Visit 17 (only applicable for patients who plan to participate in the OLE study) include hepatitis screen covering hepatitis B surface antigen (HBs Ag), hepatitis B surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab) including HBcAb IgM and total, hepatitis C virus antibodies (HCV Ab), Human Immunodeficiency Virus (HIV) screen (Anti-HIV-1 and HIV-2 antibodies) and anti-nuclear antibody (ANA). In case of results showing HBs Ag (negative), and HBc Ab total (positive), a hepatitis B virus DNA (HBV DNA) testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV virus RNA (HCV RNA) testing must be performed prior to randomization to determine eligibility. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer). The blood sample for serum chemistry must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours (if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).

p This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

q Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

r Systemic drug concentration and ADA samples are to be collected prior to dosing. In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes.. See Section 9.3.1 for more details.

s Biomarker set includes Eotaxin-3, eosinophil cationic protein (ECP), total IgE, Thymus and Activation-Regulated Chemokine (TARC). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

t Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

u This is optional and a separate written consent form must be signed before sampling. For those who consented, the sample should be drawn at Week 0, before IMP administration.

v HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

w For those patients with bilateral nasal polyposis and/or chronic rhinosinusitis.

x For those patients with comorbid allergic rhinitis.

y Patients will be encouraged to provide vaccination plans for the following vaccines, tetanus (alone or combined), any injectable influenza, any pneumococcal and any meningococcal, which are in line with the patients age and local medical practice (live attenuated vaccines are excluded) during the study. Subjects planning to receive any of the above listed vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccination.

z Optional collection of blood for assay of vaccine IgG in serum for each vaccine of interest: the first sample should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Pre-vaccine blood sample collection will not take place until patient is on treatment of IMP for at least 6 weeks. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits.

1.3 STUDY FLOW CHART FOR PATIENTS AFTER EARLY PERMANENT TREATMENT DISCONTINUATION

VISIT	ETD[a]																										EOS
Week[a]		4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	64
Visit[a]		4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	21
Post-bronchodilator FEV_1	x	x		x		x						x						x								x	x
Spirometry[b]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
Prior & concomitant medication	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
Physical Examination	x											x														x	
Call IVRS/IWRS	x																										x
Dispense or download e-diary/PEF meter[c]	x																										
Dispense/Review Home Dosing Diary	x																										
ACQ-7[d]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
AQLQ(S)	x					x						x						x								x	X
Health Care Resource Utilization	x																										
Exhaled NO[e]	x																										
Vital Signs[f]	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x
ECG	x	x				x						x						x								x	
Urine Pregnancy dipstick test	x																										
Clinical lab testing[g]	x					x						x						x								X	
Hepatitis B viral load[h]	x					x						x						x								x	
AE/SAE recording	x	x	x	x	x	x		x		x		x		x		x		x		x		x		x		x	x

VISIT	ETD[a]																										EOS
Week[a]		4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46	48	50	52	64
Visit[a]		4	5	6	7	8		9		10		11		12		13		14		15		16		17		18	21
Urinalysis[i]	x																										
Serum immunoglobulins (IgG, IgM, IgA)	x																										
Systemic drug concentration (functional dupilumab) [j]	x	x		x		x		x				x						x								x	x
Anti-drug antibodies[j]	x					x						x														x	x
Biomarker set [k]	x																										
Periostin	x																										
Antigen-specific IgE	x																										
Archival serum[l]	x																										
EQ-5D-5L	x																										
HADS[m]	x																										
SNOT-22[n]	x																										
RQLQ(S) +12[o]	x																										
Vaccine IgG [p]	x																										

a Patients who permanently discontinue treatment early will continue the remaining visits per protocol schedule with a +/-5 day window until end of study. At the time of permanent treatment discontinuation, patients will perform early treatment discontinuation (ETD) visit with all the assessments defined for Visit 18 (EOT). Visit 19 (Week 56) and Visit 20 (Week 60) will not be performed.

b Forced expiratory volume (FEV_1), PEF, Forced vital capacity (FVC), Forced expiratory flow between 25% to 75% of vital capacity (FEF25%-75%) at all visits; pulmonary function tests should be performed in the morning if possible, but if it could only be done at a different time of the day, the spirometry should be done at approximately the same time of the day at each visit throughout the study. Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of Long-Acting Muscarinic Antagonist (LAMA) for at least 24 hrs. This will be verified before performing the measurements.

c Electronic diary/PEF meter is used for daily recording of salbutamol/albuterol or levosalbutamol/levalbuterol use, asthma controller drug use, oral steroid requirements, nocturnal awakenings due to asthma symptoms, morning and evening asthma symptom NRS scores and AM and PM PEF. This device is dispensed at Visit 1 and information is downloaded from this device on the other indicated days.

d ACQ-7 is completed in the patient's electronic diary during clinic visits. ACQ-7 (Asthma Control Questionnaire 7-question version) score will be used to follow up evaluations in all patients. ACQ-5 (the first 5 items of the ACQ-7) score is used for eligibility evaluation at visit 1 and visit 2 for all patients and follow up evaluations in all patients.

e Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.

f Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), body weight (kg) and height (cm). Height (cm) will be measured only for adolescents. Vital signs will be measured in the sitting position using the same arm at each visit.

g Only hematology and serum chemistry tests will be done, see Section 9.2.2.5 for details.

h This is only applicable for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at the screening visit.

i Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood protein, nitrite, leukocyte esterase, urobilinogen and bilirubin. If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis will be performed by central laboratory.

j In the event of any SAE, or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. See Section 9.3.1 for more details.

k Biomarker set includes Eotaxin-3, eosinophil cationic protein (ECP), total IgE, Thymus and Activation-Regulated Chemokine (TARC). Blood eosinophil count will be measured as part of hematology test. Exhaled nitric oxide assessment is described separately in the flowchart.

l Archival serum in case needed for retrospective safety follow-up or additional biomarker analysis, and this is optional and a separate written consent form must be signed.

m HADS includes Hospital Anxiety and Depression Scale- Anxiety subscale (HADS-A) and Hospital Anxiety and Depression Scale- Depression subscale.

n For those patients with bilateral nasal polyposis and/or chronic rhinosinusitis.

o For those patients with comorbid allergic rhinitis.

p It indicates the sampling of post vaccination and if it is within 6 weeks after vaccination as applicable.

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3 LIST OF ABBREVIATIONS

ACQ-5	Asthma Control Questionnaire 5-question version
ACQ-7	Asthma Control Questionnaire 7-question version
AD	Atopic dermatitis
ADA	Anti-drug Antibodies
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Anti-nuclear Antibodies
ATS	American Thoracic Society
AQLQ(S)	Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥ 12 years)
BCG	Bacillus Calmette-Guérin
CDMS	Clinical Data Management System
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRFs	Case Report Forms
CPK	Creatine phosphokinase
CSR	Clinical Study Report
CV	Curriculum Vitae
CV%	Coefficient of Variation
CYP	Cytochrome P450
CT	Computed Tomography
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DRF	Discrepancy Resolution Form
ECG	Electrocardiography
ECP	Eosinophil Cationic Protein
e-CRF	Electronic Case Report Form
ERS	European Respiratory Society
EQ-5D-5L	EuroQoL Working Group Health Status Measure 5 Dimensions, 5 Levels

EOS	End-of-Study
EOT	End-of-Treatment
ETD	Early Treatment Discontinuation
FEF	Forced expiratory flow
FENO	Fractional Exhaled Nitric Oxide
FEV_1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSO	Global Safety Officer
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale- Depression subscale
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface Antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HEos	High Eosinophils
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HRQoL	Health related quality of life
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
ID	De-identification Code
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4	Interleukin 4
IL-4Rα	Interleukin 4 Receptor Alpha Subunit
IL-13	Interleukin 13

IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
IUD	Intrauterine Device
IUS	Intrauterine System
ITT	Intent-To-Treat
K-M	Kaplan-Meier
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Liver Function Test
LOAC	Loss Of Asthma Control
LTRA	Leukotriene receptor antagonist
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MID	Minimal Important Difference
MMR	Measles, Mumps, Rubella
MMRM	Mixed-effect Model with Repeated Measures
MMRV	Measles, Mumps, Rubella, Varicella
MRI	Magnetic Resonance Imaging
NIMP	Noninvestigational Medicinal Product
NRS	Numerical Rating Scale
OLE	Open label extension
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetics
Pop	Population
PROs	Patient-Reported Outcomes
PT	Preferred Term
RNA	Ribonucleic Acid
RQLQ(S)+12	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SAP	Statistical Analysis Plan

SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SC	Subcutaneously
SD	Standard Deviation
SNOT-22	Sinonasal Outcomes Test 22-item scale
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
TARC	Thymus and Activation-Regulated Chemokine
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 T-helper cell
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell

4 INTRODUCTION AND RATIONALE

4.1 INTRODUCTION

Asthma is a chronic inflammatory disease of the airways characterized by airway hyperresponsiveness, acute and chronic bronchoconstriction, airway edema, and mucus plugging. The inflammatory component of asthma involves many cell types, including mast cells, eosinophils, T-lymphocytes, neutrophils, and epithelial cells and their biological products. For most asthma patients, a regimen of controller therapy and reliever therapy provides adequate long-term control. However, it is estimated that 5% to 10% of asthma patients have symptomatic disease despite maximum recommended treatment with combinations of anti-inflammatory and bronchodilator drugs. These patients account for up to 50% of the total health cost through hospital admissions, use of emergency services, and unscheduled physician visits (1).

The long term adverse effects of systemic and inhaled corticosteroids on bone metabolism, adrenal function, and growth in children lead to attempts to minimize the amount of corticosteroid usage. Additionally, the consequences of unresponsiveness to therapy or lack of compliance with therapy is loss of asthma control and ultimately, asthma exacerbation. The poor response of some patients with asthma may reflect the number of cellular and molecular mechanisms operative in asthma. There is increasing interest in distinct phenotypes because targeted therapy is more likely to be successful in patients with similar underlying pathobiologic features (2). Recent therapeutic approaches in asthma have been focused on trying to control the type 2 T-helper cell (Th2) response. Up-regulation of interleukin-4 (IL-4) and interleukin-13 (IL-13) activity has been implicated as an important inflammatory component of asthma disease progression. Dupilumab is under development as a potential novel treatment for asthma. Dupilumab, a fully human monoclonal antibody, is directed against the IL-4 receptor alpha subunit (IL-4Rα), which is a component of IL-4 receptors Type I and Type II, as well as the IL-13 receptor. The binding of dupilumab to IL-4Rα results in blockade of downstream signaling initiated by both IL-4 and IL-13. For complete information regarding the preclinical and clinical evaluation of dupilumab to date, see the Investigator's Brochure.

4.2 RATIONALE

This is a phase 3, randomized, placebo-controlled efficacy and safety study to be conducted in patients with persistent asthma while on a medium to high dose ICS, in combination with a second controller. This study is designed to investigate the efficacy and safety profile of dupilumab over one year in a patients with asthma who are in need for an additional of another treatment added to their current management. The presence of a placebo arm is appropriate for the objectives of this study, since it will provide the most robust assessment of the efficacy and safety of dupilumab.

The proposed study design provides the opportunity to confirm the efficacy of dupilumab on multiple asthma domains including lung function, prevention of severe exacerbations and

symptom control. The effect on lung function and symptom control will be evaluated over short term and long terms.

4.2.1 Population rationale

In this study, dupilumab will be added-on to an inhaled corticosteroid in combination with one or two other controller medications in patients with persistent asthma. The population is comprised of patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines (3) and entry criteria described in Section 7. As described above, in addition to suffering the symptoms associated with a lack of asthma control, such patients utilize a disproportionate level of health care services, may suffer the long term adverse effects of systemic and inhaled corticosteroids, and ultimately, are at increased risk of a severe asthma exacerbation.

4.2.2 Design rationale

This study is a randomized, double blind, placebo-controlled, parallel group study. The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with one or two other controller medicines:

- Screening Period (4±1 weeks)
- Randomized Treatment Period (52 weeks)
- Post-treatment Period (12 weeks)

This study has two arms of placebo with different volume, which is to match the different dose regimens of dupilumab 300 mg q2w and 200 mg q2w respectively. Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

4.2.3 Endpoint rationale

There are two primary endpoints for this study. One primary endpoint is the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period, as this is one of the most clinically relevant endpoints to evaluate an asthma controller medication. The treatment period of 52 weeks is sufficient for assessing this type of event and avoiding the potential impact of seasonality. The other primary endpoint is the absolute change from baseline in pre-bronchodilator FEV_1 at Week 12, as this is a well-accepted parameter to determine the effect of a drug on lung function. Safety endpoints are typical for investigational drugs at the current stage of clinical development.

Other endpoints including systemic drug concentration/ADA and biomarkers of drug action have been used previously to evaluate the exposure/effect relationship of dupilumab in asthma patients.

4.2.4 Rationale for dose and regimen selection

The dose regimens of subcutaneous (SC) dupilumab selected for this study are 300 mg every 2 weeks (q2w) or 200 mg q2w. Patients randomized to 300 mg q2w will get an initial loading dose of 600 mg on Day 1 while patients randomized to 200 mg q2w will get an initial loading dose of 400 mg on Day 1, and q2w dosing will commence 2 weeks after the loading dose. The administration of the loading dose of dupilumab will allow systemic concentrations to reach target saturation, potentially reducing the time to onset of clinical effect.

Proof of concept has been established in the ACT11457 study at 300 mg weekly. One hundred and four patients with persistent, moderate-to-severe asthma and a blood eosinophil count of at least 300 cells per microliter or a sputum eosinophil level of at least 3%, partially controlled or uncontrolled by medium-to-high doses of ICS plus LABA (fluticasone/salmeterol, budesonide/formoterol, or mometasone/formoterol) were randomized to the study. The study showed significant efficacy in a population of mostly severe asthmatics with poor asthma control and decreased lung function with mostly high doses of ICS in combination with a LABA.

In the dose ranging study (DRI12544 study), 776 patients with asthma uncontrolled by medium-to-high dose ICS plus LABA were randomized in the study. Four dose regimens (300 mg q2w with 600mg loading dose, 200 mg q2w with 400mg loading dose, 300mg q4w with 600 mg loading dose and 200mg q4w with 400 mg loading dose) were tested in the study. The results showed that 300 mg q2w and 200 mg q2w treatment with dupilumab provided a significant improvement on FEV_1 at week 12 and a statistically significant reduction in the annualized rate of severe exacerbations when compared to placebo. Both dose regimens provided comparable efficacy on most of the efficacy endpoints regardless of the eosinophil count at baseline. Both doses were safe and well tolerated with a profile comparable to that seen with placebo except for an increased number of injection site reactions. To further characterize the optimal regimen for patients, both regimens will be assessed in the current trial.

The Pop PK model predictions demonstrated that exposure in adolescents at the highest proposed adult Phase 3 dose (300 mg q2w) is not expected to exceed the observed adult exposure at the dupilumab dose regimen of 300 mg once weekly, which was observed to be generally well tolerated in adults. Therefore, adolescent dosing at 300 mg q2w or 200 mg q2w regimen is expected to yield dupilumab exposure that is expected to result in efficacious exposures and unlikely to be associated with a heightened safety risk in this age population.

Dupilumab has been safe and well-tolerated in all clinical trials completed to date in healthy volunteers and patients with Atopic dermatitis (AD) or asthma who were dosed for up to 16 weeks with a maximum dose of 300 mg administered every week. The phase 3 study will utilize less frequent dosing. No important identified risks have been established during the dupilumab clinical program. A low discontinuation rate has been observed across the completed clinical trials in dupilumab treated patients. The reported rate of suspected unexpected serious adverse reaction (SUSAR) has also been low. In addition, no imbalance in the frequency of TEAEs between patients treated with dupilumab versus placebo has been observed, with the exception of injection site reactions, nasopharyngitis and headache. In summary, the safety data observed so far in completed and currently ongoing studies in AD and asthma patients (at the same or even higher

doses than that proposed for this study) have demonstrated a positive benefit-risk profile for dupilumab in comparison to placebo.

5 STUDY OBJECTIVES

5.1 PRIMARY

To evaluate the efficacy of dupilumab in patients with persistent asthma

5.2 SECONDARY

To evaluate the safety and tolerability of dupilumab

To evaluate the effect of dupilumab on improving PROs including HRQoL

To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

5.3 EXPLORATORY

To explore the association of biomarkers with treatment response

To explore the association of genetic profiles with treatment response

To explore the association of vaccine response with treatment

6 STUDY DESIGN

6.1 DESCRIPTION OF THE PROTOCOL

This study is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma with a medium to high dose of ICS in combination with a second controller medication (a third controller is allowed).

6.2 DURATION OF STUDY PARTICIPATION

6.2.1 Duration of study participation for each patient

The clinical trial consists of three periods:

Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization.

Treatment Period (52 weeks): treat with dupilumab or placebo SC injection.

Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study.

6.2.2 Determination of end of clinical trial (all patients)

The last patient last visit will occur at last patient who has completed 52 weeks treatment and elect to enter the long term extension study or at the end of a 12-week safety follow-up period for those patients who complete the treatment and elect not to enter extension study as well as for those who permanently discontinue medication and continue for all the remaining visits.

6.3 INTERIM ANALYSIS

Not applicable.

6.4 STUDY COMMITTEES

6.4.1 Data monitoring committee

A data monitoring committee (DMC) is independent from sponsor and is commissioned for the dupilumab clinical development program. This committee is comprised of externally-based individuals with expertise in the diseases under study, biostatistics, or clinical research. The primary responsibilities of the DMC are to review and evaluate the safety data during the course

of the trial and make appropriate recommendations regarding the conduct of the clinical trial to the Sponsor.

The DMC procedures and safety data to be reviewed by the DMC are described in the DMC charter. In the above capacities, the DMC is advisory to the Sponsor. The Sponsor is responsible for promptly reviewing and for taking into account in a timely manner the recommendations of the DMC in terms of trial continuation with or without alterations or of potential trial termination.

6.4.2 Executive advisory committee

An executive advisory committee is commissioned for the dupilumab clinical development program. The executive advisory committee is made up of 5-7 key academic clinicians, with selection criteria including a key opinion leader in strategic regions including Japan, US, Europe and Latin America. These clinicians have been selected based on their publications, experience in conducting clinical asthma/nasal polyps studies, and their ability to both challenge and provide input during the protocol review process, speak to heath authority/ethics committee for operational issues/challenges/unexpected safety issues. Furthermore, they can speak with credibility to feasibility issues and impact the recruitment. These clinicians will provide invaluable insight and direction to ensure a successful clinical program.

7 SELECTION OF PATIENTS

7.1 INCLUSION CRITERIA

I 01. Adults and adolescent patients with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines and the following criteria:

A) Existing treatment with medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1.

- Note for Japan: for subjects aged 18 years and older, ICS must be on ≥200 mcg of fluticasone propionate twice daily or equivalent; for subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent.
- Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1.

B) Pre-bronchodilator forced expiratory volume (FEV_1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization.

C) Asthma Control Questionnaire 5-question version (ACQ-5) score ≥1.5 at Visits 1 and 2, prior to randomization.

D) Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization.

E) Must have experienced, within 1 year prior to Visit 1, any of the following events:

- Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once.
- Hospitalization or emergency medical care visit for worsening asthma.

I 02. Signed written informed consent.

7.2 EXCLUSION CRITERIA

Patients who have met all the above inclusion criteria listed in Section 7.1 will be screened for the following exclusion criteria which are sorted and numbered in the following 4 subsections:

7.2.1 Exclusion criteria related to study methodology

E 01. Patients <12 years of age or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (For those countries where local regulations permit enrollment of adults only, subject recruitment will be restricted to those who are ≥18 years of age).

E 02. Weight is less than 30 kilograms.

E 03. Chronic obstructive pulmonary disease (COPD) or other lung diseases (eg, idiopathic pulmonary fibrosis, Churg-Strauss Syndrome, etc) which may impair lung function.

E 04. A subject who experiences a severe asthma exacerbation (defined as a deterioration of asthma that results in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the Screening Visit up to and including the Baseline Visit).

E 05. Evidence of lung disease(s) other than asthma, either clinical evidence or imaging (Chest X-ray, CT, MRI) within 12 months of Visit 1 or at the screening visit, as per local standard of care.

Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.

E 06. A subject who has experienced an upper or lower respiratory tract infection within the 4 weeks prior to Visit 1 or during the screening period.

E 07. Current smoker or cessation of smoking within 6 months prior to Visit 1.

E 08. Previous smoker with a smoking history >10 pack-years.

E 09. Comorbid disease that might interfere with the evaluation of IMP.

E 10. Known or suspected alcohol and/or drug abuse.

E 11. Inability to follow the procedures of the study (eg, due to language problems or psychological disorders).

E 12. Patients requiring non-selective beta-1 adrenergic receptor blockers for any reason, or initiation or change in dose of a selective beta-1 adrenergic receptor blocker within 1 month prior to Visit 1 or plan to initiate or change in dose of a selective beta-1 adrenergic receptor blocker during the screening period or the randomized treatment period.

E 13. Anti-immunoglobulin E (IgE) therapy (omalizumab) within 130 days prior to Visit 1 or any other biologic therapy/immunosuppressant to treat inflammatory disease or autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary

cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) as well as other diseases within 2 months or 5 half-lives prior to Visit 1, whichever is longer.

E 14. Initiation of allergen immunotherapy within 3 months prior to Visit 1 or dose change from 1 month prior to Visit 1 or a plan to begin allergen immunotherapy or to change its dose during the Screening Period or the Randomized Treatment Period.

E 15. Patients on or initiation of Bronchial thermoplasty within 3 years prior to Visit 1 or plan to begin therapy during the Screening Period or the Randomized Treatment Period.

E 16. Exposure to another investigative antibody within a time period prior to Visit 1 that is less than 5 half-lives of the antibody. In case the half-life is not known, then the minimum interval since exposure to the prior investigative antibody is 6 months. The minimum interval since exposure to any other (non-antibody) investigative study medication is 30 days prior to Visit 1.

E 17. Patients receiving medications or therapy that are prohibited as concomitant medications (See Section 8.8).

E 18. Patients who have previously been treated in any clinical trial of dupilumab.

E 19. Patient is the Investigator or any Sub-Investigator, research assistant, pharmacist, study coordinator, other staff or relative thereof directly involved in the conduct of the study.

7.2.2 Exclusion criteria related to the active comparator and/or mandatory background therapies

E 20. Non-compliance with use of the mandatory background therapy, eg, ICS/LABA combination, during the screening period, as defined as:

- <80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.

E 21. A subject with a history of clinically significant renal, hepatic, cardiovascular, metabolic, neurologic, hematologic, ophthalmologic, respiratory, gastrointestinal, cerebrovascular or other significant medical illness or disorder which, in the judgment of the investigator, could interfere with the study or require treatment that might interfere with the study. Specific examples include but are not limited to uncontrolled diabetes, uncontrolled hypertension, bronchiectasis. Active tuberculosis or non-tuberculous mycobacterial infection, latent untreated tuberculosis or a history of incompletely treated tuberculosis will be excluded from the study unless it is well documented by a specialist that the patient has been adequately treated and can now start treatment with a biologic agent, in the medical judgment of the investigator and/or infectious disease specialist. Tuberculosis testing would be performed on a country by country basis according to local guidelines if required by regulatory authorities or ethic committees. Other conditions that are well controlled and stable will not prohibit participation if deemed appropriate per the investigator’s judgment.

7.2.3 Exclusion criteria related to the current knowledge of Sanofi compound

E 22. Pregnant or breast-feeding women.

E 23. Women of childbearing potential (pre-menopausal female biologically capable of becoming pregnant) who:

- Do not have a confirmed negative serum beta-hCG test at Visit 1.
- Who are not protected by one of the following acceptable forms of effective contraception during the study:
  - Established use of oral, injected, implanted or inserted hormonal contraceptive.
  - Intrauterine device (IUD) with copper or intrauterine system (IUS) with progestogen
  - Barrier contraceptive (condom, diaphragm or cervical/vault caps) used with spermicide (foam, gel, film, cream or suppository), if allowed by local regulation
  - Female sterilization (eg tubal occlusion, hysterectomy or bilateral salpingectomy),
  - Male sterilization with post-vasectomy documentation of the absence of sperm in the ejaculate; for female patients the study, the vasectomized male partner should be the sole partner for that patient
  - True abstinence in keeping with the preferred and usual lifestyle and if allowed by local regulation; periodic abstinence (eg calendar, ovulation, symptothermal, post-ovulation methods) is not an acceptable method of contraception
  - Postmenopausal women (defined as at least 12 consecutive months without menses) are not required to use additional contraception

E 24. Deleted.

E 25. Diagnosed active parasitic infection (helminthes), suspected or high risk of parasitic infection, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization.

E 26. History of HIV infection or positive HIV serology at Visit 1.

E 27. Known or suspected history of immunosuppression, including history of invasive opportunistic infections (eg, histoplasmosis, listeriosis, coccidioidomycosis, penumocystosis, aspergillosis), despite infection resolution; or unusually frequent, recurrent or prolonged infections, per investigator's judgment.

E 28. Evidence of acute or chronic infection requiring systemic treatment with antibacterials, antivirals, antifungals, antiparasitics, or antiprotozoals within 4 weeks before Visit 1 or during the screening period, significant viral infections within 4 weeks before Visit 1 or during the screening period that may not have received antiviral treatment (eg, influenza receiving only symptomatic treatment).

E 29. Live attenuated vaccinations within 4 weeks prior to Visit 1 or planned live attenuated vaccinations during the study; see Appendix A for list of prohibited live attenuated vaccines.

E 30. Patients with active autoimmune disease or patients using immunosuppressive therapy for autoimmune disease (eg, rheumatoid arthritis, inflammatory bowel disease, primary biliary cirrhosis, systemic lupus erythematosus, multiple sclerosis, etc.) or patients with high titer autoantibodies at screening who are suspected of having high risk for developing autoimmune disease at the discretion of the Investigator or the Sponsor.

E 31. History of malignancy within 5 years before the screening visit, except completely treated in situ carcinoma of the cervix, completely treated and resolved nonmetastatic squamous or basal cell carcinoma of the skin.

E 32. Patients with a history of a systemic hypersensitivity reaction, other than localized injection site reaction, to any biologic drug.

E 33. Patients with any of the following result at screening:

- Positive (or indeterminate) HBs Ag or,
- Positive IgM HBc Ab or
- Positive total HBc Ab confirmed by positive HBV DNA or
- Positive HCV Ab confirmed by positive HCV RNA

E 34. Liver injury related criteria:

- Clinically significant/active hepatobiliary disease or
- Alanine Aminotransferase (ALT) >3 Upper Limit of Normal (ULN)

E 35. Abnormal lab values at Screening:

- Creatine phosphokinase (CPK) >10 ULN or
- Platelets <100,000 cells/mm3 or
- Eosinophils >1500 cells/mm3

7.2.4 Additional exclusion criteria during or at the end of screening

E 36. Patient who has withdrawn consent before enrollment/randomization.

8 STUDY TREATMENTS

8.1 INVESTIGATIONAL MEDICINAL PRODUCT(S)

8.1.1 Dupilumab

Sterile dupilumab of various concentrations will be provided in 150 mg/mL in glass pre-filled syringe to deliver 300 mg in 2 mL and 175 mg/mL in glass pre-filled syringe to deliver 200 mg in 1.14 mL.

8.1.2 Placebo

Sterile placebo for dupilumab will be provided in identically matched glass pre-filled syringe to deliver 2 mL or 1.14 mL, which will match dupilumab 300 mg (2 mL) and 200 mg (1.14 mL) respectively.

8.1.3 Preparation of investigational product

Dupilumab or matching placebo in glass pre-filled syringes will be dispensed to the patients.

8.1.4 Dosing schedule

Two injections of IMP will be administered on Day 1 at Visit 2 as a loading dose. Subsequently one injection of IMP will be given every 14 ± 3 days (q2w). The doses of investigational product must be separated by ≥11 days to avoid an overdose.

The Investigator or delegate will train the patient (or caregiver(s)) how to prepare and inject IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver(s)) will perform the second injection under the supervision of the Investigator or delegate. This training must be documented in the patient's study file. At subsequent study visits, patients are trained to self-inject IMP, and the patients are allowed to self-inject IMP at home after 6 injections at investigational site, counting from Visit 3.

Patients should be instructed to avoid missing any doses of medication during the study. Any patient who misses one dose should be reminded to be diligent, in order to avoid further missing doses thereafter. In case of missed dose(s) no loading dose of 2 injections will be administered when restarting the treatment, whatever the number of missed doses. The patients should continue on their scheduled IMP treatment and visit, even if more than 2 consecutive doses are missed.

When the patient has a study visit, the IMP will be administered following clinic procedures and blood collection. Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.

For doses not given at the study site, diaries will be provided to record information related to the injections. The diary will be kept as source data in the patient's study file.

If the patient (or caregiver) is unable or unwilling to administer IMP, arrangements must be made for qualified site personnel and/or health care professionals (eg, visiting nurse service) to administer IMP for the doses that are not scheduled to be given at the study site.

If the study visit is not performed at the site as scheduled, the dose will be administered by the patient and/or their caregiver/health care professional, or arrangements must be made for an unscheduled visit at the site to administer the IMP. When IMP is administered at home, the patients must be advised by the site staff to self-monitor for potential signs and symptoms that may suggest a hypersensitivity reaction for at least 30 minutes after administration.

If the patient, or caregiver(s) do not develop the comfort to inject the investigational drug at home, or the Investigator determines that patient (or caregiver) injection at home is not appropriate, injections can be performed at the site by way of unscheduled visits.

Subcutaneous injection sites should be alternated among the 4 quadrants of the abdomen (avoiding navel and waist areas), the upper thighs or the upper arms, so that the same site is not injected twice consecutively. Injection in the upper arms could be done only by a trained person (Parent/ caregiver trained by Investigator or Delegate) or health care professional but not the patient themselves. This instruction pertains to the day that the loading dose is injected as well as the administration of q2w injections. For each injection, the anatomic site of administration will be recorded in the electronic case report form (e-CRF) and, as applicable, the home diary.

Detailed instructions for transport, storage, preparation, and administration of IMP are provided to the patient. Patients will complete a dosing diary to document compliance with self-injection (or caregiver) injection of IMP.

8.2 NONINVESTIGATIONAL MEDICINAL PRODUCT(S)

8.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor.

The recognized asthma controllers for the study will include the following 5 classes: ICS, LABA, LAMA, Anti-leukotrienes and methylxanthines. Please refer to Appendix O for a list of commonly used asthma controller medication.

8.2.1.1 Screening period

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects

aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (Refer to Appendix O on the recognized controller medication class) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix B. The minimum daily dose of flucticasone propionate is 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equal to the upper limit of medium daily dose for fluticasone propionate as instructed in Appendix B. For ICS other than fluticasone propionate, please refer to the table in Appendix B which indicates the upper limit of the medium daily dose for each ICS which is equivalent to 500 mcg/day of fluticasone propionate.

If the Study Investigator based on his/her medical judgment, decides to optimize use of asthma medications prior to Visit 1 irrespective of potential participation in the study, note that changes in ongoing asthma medications must occur at least 1 month prior to Visit 1. The introduction of new controller medications must occur at least 3 months prior to Visit 1 with a stable dose for at least 1 month prior to Visit 1.

8.2.1.2 Randomized treatment period

During this period, patients will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed. Only a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance. This will be recorded in the eDiary.

8.2.1.3 Post-treatment period

Upon completing the randomized treatment period, patients not continuing with the open label extension study will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the investigator of the patients' asthma control status.

8.2.2 Reliever medication

The reliever medication will not be dispensed or supplied by the sponsor.

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

The description of the criterion for qualifying an asthma exacerbation event based on nebulizer using, will use the nebulizer-to-puff conversion factor for application to loss of asthma control (LOAC) definition.

Study personnel should convert salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use as shown on the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16
*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs	

- Example of salbutamol/albuterol Nebulizer-to-Puff Conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg ->12 puffs

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4
2.5	8
3.75	12
5	16
*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs	

- Example of levosalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg ->12 puffs.

Criterion used to specify an asthma exacerbation event in eCRF based on nebulizer use:

After conversion of nebulizer-to-puff, in every instance that the number of puffs is ≥6 additional puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24-hour period (compared to baseline) on 2 consecutive days, tick the "Qualifying criteria box" on the asthma exacerbation event.

All other reliever medications rather than albuterol/salbutamol or levalbuterol/levosalbutamol should be avoided.

8.3 BLINDING PROCEDURES

8.3.1 Methods of blinding

Dupilumab and placebo will be provided in identically matched 2 mL or 1.14 mL pre-filled syringes. To protect the blind, each treatment kit of 2 mL (dupilumab / placebo) or 1.14 mL (dupilumab / placebo) glass pre-filled syringes will be prepared such that the treatments (dupilumab and its matching placebo according to its dose) are identical and indistinguishable and will be labeled with a treatment kit number. The randomized treatment kit number list will be generated by Sanofi.

Both the patient and investigator will be blinded to assigned active drug or placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

Study patients, Investigators, and study site personnel will not have access to the randomization (treatment codes) except under circumstances described in Section 8.3.2.

8.3.2 Randomization code breaking during the study

In case of an adverse event (AE), the code should only be broken in circumstances when knowledge of the IMP is required for treating the patient.

Code breaking can be performed at any time by using the proper module of the interactive voice response system (IVRS)/interactive web response system (IWRS) and/or by calling any other phone number provided by the Sponsor for that purpose. If the blind is broken, the Investigator should document the date, time of day and reason for code breaking.

Subject withdrawal will only occur when the code break call is made at the site level, not the study level. This means that if the Emergency Unblinding transaction is performed by the investigator (ie, at the site level), then the subject will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Global Safety Officer (GSO) (ie, at the study level, as the GSO is not site based), then the subject will not be withdrawn from treatment.

At the facilities where the systemic drug concentration measurements, anti-drug antibodies and selected biomarkers are determined, the samples will be analyzed prior to data base lock leading to unblinding of responsible bioanalysts. Bioanalysts are excluded from the clinical trial team.

Patients, investigators and site personnel will not have access to assay results for immunoglobulins (IgG, IgG subclasses, IgA and IgM) after the first administration of study medication because these values have the potential for unblinding. Furthermore, neither patients, investigators nor site personnel will have access to eotaxin-3, antigen-specific IgE, total IgE, Eosinophil Cationic Protein (ECP), TARC or periostin while the study is ongoing, as the related data are not essential for patient care and have the potential for unblinding.

The Data Monitoring Committee will receive blinded by treatment group or unblinded (if necessary) confidential reports from an independent statistician for review, which have to be handled [redacted] None of these reports can be delivered to unauthorized persons.

8.4 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUP

A randomized treatment kit number list will be generated centrally by Sanofi. The investigational product (dupilumab or placebo) will be packaged in accordance with this list.

The Sanofi Clinical Supplies team will provide the randomized treatment kit number list and the Study Biostatistician will provide the randomization scheme to the centralized treatment allocation system. This centralized treatment allocation system will generate the patient randomization list according to which it will allocate the treatments to the patients.

Patients who meet the entry criteria will be randomized to receive either dupilumab or placebo.

Patients who meet exclusion criteria may be re-screened once during the open screening period of the study; a different patient identification will be issued. Re-screening is not permitted if the patient fails to meet inclusion criteria. There is no requirement for a waiting period between the screen-failure date and the re-screening date. The IVRS/IWRS report will flag re-screened patients. Patients that are re-screened must sign a new consent form and all Visit 1 procedures must be repeated.

The Investigator obtains treatment kit numbers at randomization and subsequent scheduled visits via an Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) that will be available 24 hours a day.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/µL, ≥300 cells/µL) at screening, ICS dose level (medium, high) and country.

A randomized patient is defined as a patient who is registered and assigned with a treatment kit number from the centralized treatment allocation system, as documented from its log file. A patient cannot be randomized more than once in the study.

8.5 PACKAGING AND LABELING

Dupilumab and placebo will be supplied as one glass pre-filled syringe packed in a patient kit box. Both glass pre-filled syringe and box will be labeled.

Packaging is in accordance with the administration schedule. The content of the labeling is in accordance with the local regulatory specifications and requirements.

8.6 STORAGE CONDITIONS AND SHELF LIFE

All investigational products should be stored at a temperature between 2°C and 8°C in an appropriate, locked room under the responsibility of the Investigator or other authorized persons (eg, pharmacists) in accordance with local regulations, policies and procedures.

Control of investigational product storage conditions, especially control of temperature (eg, refrigerated storage) and information on in-use stability and instructions for handling the Sanofi compound should be managed according to the rules provided by the Sponsor.

8.7 RESPONSIBILITIES

The Investigator, the hospital pharmacist, or other personnel allowed to store and dispense the IMP will be responsible for ensuring that the IMP used in the clinical trial is securely maintained as specified by the Sponsor and in accordance with applicable regulatory requirements.

All IMPs will be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of IMP issued and returned is maintained.

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party, to allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

8.7.1 Treatment accountability and compliance

Measures taken to ensure and document treatment compliance and IMP accountability include:

- Proper recording of treatment kit number as required on appropriate e-CRF page for accounting purposes;
- All medication treatment kits (whether empty or unused) are returned by the patient at each visit when a treatment dispensing is planned.
    - The completed patient injection diary (returned to the site at each visit), returned treatment kit boxes and any unused prefilled syringes will be used for drug accountability purposes.
- The Investigator or designee tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits and fills in the appropriate page of the patient treatment log.

The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the patient treatment log form.

8.7.2 Return and/or destruction of treatments

All partially used or unused treatment kits will be retrieved by the Sponsor or destroyed at study site. All used prefilled syringes should be kept in a sharp container by the patients and be returned to sites for destroy. The Investigator will not destroy any unused IMP unless the Sponsor provides written authorization.

A detailed treatment log of the destroyed IMP will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the monitoring team. The Investigator will not destroy the unused IMP unless the Sponsor provides written authorization.

For non-investigational medicinal product not provided by the Sponsor, tracking and reconciliation has to be achieved by the Investigator and need to be captured in standard site documents and records (eg, medical notes).

8.8 CONCOMITANT MEDICATION

A concomitant medication is any treatment received by the patient concomitantly to any IMP(s).

8.8.1 Prohibited Concomitant Medication

The following concomitant treatments are not permitted during the Screening Period or the Randomized Treatment Period:

- Systemic steroids (systemic steroids can only be used to treat an asthma exacerbation, and are not allowed to be used for other conditions from 1 month or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period. Intra-articular steroids are considered as systemic steroids and are not allowed to be used in the above mentioned period.)
- Anti-immunoglobulin E (IgE) therapy (eg, omalizumab, is not allowed to be used from 130 days prior to Visit 1, or during the screening period or the randomized treatment period)
- Biologic therapy (Biologic therapy is not allowed to be used from 2 months or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period).
- Systemic immunosuppressant (immunosuppressants are not allowed to be used from 2 months or at least 5 half-lives prior to Visit 1, whichever is longer, or during the screening period or the randomized treatment period)
- Allergen immunotherapy (except if initiated more than 3 months prior to Visit 1 and dose stabled 1 month prior to Visit 1)
- Bronchial thermoplasty

- Intravenous immunoglobulin (IVIG) therapy
- Live Attenuated Vaccines: refer to Appendix A
- Beta-adrenergic receptor blockers (except for a selective beta-1 adrenergic receptor blocker used with dose stabled 1 month prior to Visit 1)
- Asthma relievers other than salbutamol/albuterol or levosalbutamol/levalbuterol: their use is not recommended during the study period. In case of use in exceptional circumstances (eg, prescribed by a physician not participating in the study), their use will be documented in the patient's file and reported in the eCRF.
- Other investigational drugs

8.8.2 Permitted concomitant medication

- Antihistamines are permitted as concomitant medication.
- Topical, ocular or intranasal corticosteroids are permitted during the study.

CYP substrates:

The impact of dupilumab on cytochrome P450 (CYP) enzyme activity has not been studied and the effect of dupilumab on levels of IL-4 and IL-13 has not been fully characterized. However, interleukin-4 (IL-4) was reported to upregulate CYP2E1, 2B6, 3A4 mRNA expression or downregulate CYP1A2 mRNA (4), (5). Human peripheral blood mononuclear cells (PBMC) incubated with various Th2 cytokines showed that IL-4 and IL-13 increased mRNA expression of CYP2B6 and CYP3A4 (6). Since the clinical significance of the limited in vitro findings for IL-4 and IL-13 involvement in CYP regulation and the impact of dupilumab on CYP enzymes is not fully understood, during the study treatment and at least up to the end of follow-up, caution should be used for drugs which are metabolized via these CYP isoforms and which have a narrow therapeutic index. This means that close clinical observation and/or laboratory monitoring as applicable are required in order to enable early detection of toxic manifestations or lack of activity/efficacy of these drugs, followed by dose adjustment or their withdrawal if needed (4), (5), (6). Some examples of CYP450 substrates with narrow therapeutic index are provided in Appendix C.

9 ASSESSMENT OF INVESTIGATIONAL MEDICINAL PRODUCT

9.1 PRIMARY ENDPOINT

9.1.1 Primary endpoints

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV_1 at week 12.

9.1.1.1 *Asthma exacerbation events*

Two types of asthma exacerbation events are defined:

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

A loss of asthma control (LOAC) event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days;
- ≥20% decrease in pre-bronchodilator FEV1 compared with baseline;
- Increase in ICS dose ≥4 times than the dose at Visit 2;
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1);
- Severe exacerbation event

Two events will be considered as different if the interval between their start dates is equal or greater than 28 days.

The reasons (ex, infections including viral and bacterial, allergen exposure, exercise and others) of the exacerbation events will be collected in eCRF**.**

9.2 SECONDARY ENDPOINT(S)

Key secondary Endpoints:

- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12

9.2.1 Efficacy endpoints

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients on high dose of ICS
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV_1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV_1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV_1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF]25-75%, post-bronchodilator FEV_1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period
- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52.
- Change from baseline in PROs at Week 12, 24, 36, and 52:

- Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
- European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
- Hospital Anxiety and Depression Scale (HADS)
- 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis
- Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

9.2.1.1 Disease-specific efficacy measures

9.2.1.1.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (7). For pre-bronchodilator measured parameters, including FEV_1, PEF, FVC and FEF 25-75%, spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

For post-bronchodilator FEV_1, the measure should follow the steps as that at screening test for reversibility validation.

At all visits, spirometry should be performed in the morning if possible, but if it could only be done at a different time of the day, the spirometry should be done at approximately the same time of the day at each visit throughout the study. The same spirometer and standard spirometric techniques, including calibration, will be used to perform spirometry at all visits and, whenever possible, the same person should perform the measurements.

Pulmonary function tests will be measured in the sitting position; however, if necessary to undertake the testing with the subject standing or in another position, this should be noted on the spirometry report. For any subject, the position should be consistent throughout the study.

Three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded.

The largest FEV_1 and largest FVC should be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be

obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV_1 (best test).

Automated best efforts, which combine FEV_1 and FVC are not acceptable.

The spirometer must be calibrated following the principles of the ATS/ERS guidelines every day that a study subject is seen and spirometry is carried out. The calibration records should be kept in a reviewable log. It is preferred that the calibration equipment (ie, 3-liter syringe) that is used to calibrate the spirometer be subjected to a validated calibration according to the manufacturer's specifications.

Spirometry will be performed centrally and all recordings will be centrally read by independent experts. Further details on spirometry will be available in a separate operational manual provided to the sites.

9.2.1.1.2 Reversibility/Post-bronchodilator FEV_1

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. Reversibility, which is defined as an increase in absolute FEV_1 of 12% over the baseline value, with an absolute increase of at least 200 mL, must be demonstrated within 30 minutes of bronchodilator administration. If the subject does not meet the reversibility at Visit 1, up to 3 assessments can be performed at any time during the screening period until the Baseline Visit (Visit 2).Whenever the reversibility was repeated, the pre-bronchodilator FEV_1 should again meet the inclusion criteria of $\leq$ 80% of predicted normal for adults and $\leq$ 90% of predicted normal for adolescents.

For post-bronchodilator FEV_1, the measure should follow the steps as that at screening test for reversibility validation. If other attempt for reversibility test was performed at Baseline visit, then the post-bronchodilator FEV_1 will come from the result of this reversibility test.

9.2.1.1.3 ACQ (Asthma Control Questionnaire)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

9.2.1.1.3.1 ACQ-7 (Asthma Control Questionnaire, 7-question version)

The ACQ-7 has 7 questions- the first 5 items assess the most common asthma symptoms:
1. frequency in past week awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma and 5. wheeze, plus 6. short-acting bronchodilator use and 7. FEV_1 (pre-bronchodilator use, %

and % predicted use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6= maximum impairment) (see Appendix D).

Clinic staff scores the FEV_1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-7, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (8).

The ACQ-7 questionnaire will be put into eDiary to be completed by all patients regardless of adults or adolescents. Patients should complete ACQ-7 before spirometry test.

9.2.1.1.3.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Measurement properties such as reliability and ability to detect change have been documented in the literature (9).

9.2.1.2 Disease-specific, daily efficacy assessments

9.2.1.2.1 Electronic diary/ PEF meter

On a daily basis throughout the study, the patient uses an electronic diary / PEF meter to:

- Measure morning and evening PEF
- Respond to the morning and evening asthma symptom scale questions
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the number of inhalations/day of background product used

- Record the number of nocturnal awakenings due to asthma symptoms
- Record oral steroids use for exacerbation event

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 12:00 PM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol
- PM PEF performed in the evening (between 5:30 PM and 12 AM) prior to taking any albuterol/salbutamol or levalbuterol/levosalbutamol
- Patients should try to withhold albuterol/salbutamol or levalbuterol/levosalbutamol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM PEF will be the mean AM measurement recorded for the 7 days prior to the first dose of investigational product, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the first dose of investigational product. Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day1. There should be at least 4 days' measurement for setting up the stability limit, and the first dosing visit should be rescheduled until data for 4 days are available.

Information derived from the electronic PEF meter will be evaluated by the Investigator at study visits.

9.2.1.2.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary/PEF meter twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Baseline symptom scores will be the mean AM and mean PM scores recorded for the 7 days prior to randomization. The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. There is no global score, just an AM score and a PM score. An MCID of 0.35 is being used (10) (see Appendix E).

9.2.1.2.3 Use of rescue medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in an electronic diary/PEF meter. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or

levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

9.2.1.3 Health care resource utilization

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days' loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

9.2.1.4 Patient-reported outcomes

Patients should complete the following PROs before spirometry test.

9.2.1.4.1 Asthma Quality of Life Questionnaire (AQLQ (S)

The AQLQ (S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to patients as a result of their asthma (see Appendix F). The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

A global score is calculated ranging from 1 to 7 and a score by domain. Higher scores indicate better quality of life.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The MCID for AQLQ(S) is 0.5 (11).

9.2.1.4.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis and/or chronic rhinosinusitis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis on health-related quality of life (see Appendix G). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30) with MID of -2.5, Ear (range 0-15) with MID of -1.25, Sleep (0-20) with MID of -1.67, General and Practical (0-30) with MID of -2.50, and Emotional (0-15) with MID of -1.25. The range of the global score is 0-110 and an MID (the smallest difference between clinical trial arms mean change from baseline [point estimates] that will be interpreted as important) of 8.9 (12). Lower scores indicate less impact and the recall period is past 2 weeks.

9.2.1.4.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix H). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3; one can score between 0 and 21 for either anxiety or depression.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (13). The MID for the HADS-A (anxiety) has been reported to be in the range of 0.41 (anxious and depressed subjects in active treatment controlled studies) to 1.32 (COPD patients), in the range of 0.50 (anxious and depressed subjects in active treatment controlled studies) to 1.40 (COPD patients) for HADS-D (depression) and approximately 1.5 (COPD patients) for the HADS Total score (14, 15)

Alternatively, a significant improvement in treatment versus placebo group was defined as the % of subjects who moved from a defined category of moderate to severe depression or anxiety (≥8 to not having the disease (<8) (16). Using this methodology Stelara (Ustekinumab) was able to make the claim in summary of product characteristics that "HADS was significantly improved in the treatment group compared with placebo" (17).

9.2.1.4.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (18). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages – the EQ-5D descriptive system and the EQ VAS (see Appendix I). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom. The MCID for the EQ-5D in asthma patients has been reported to be in the range of .001 to 0.074 (19, 20)

9.2.1.4.5 Standardized Rhinoconjunctivitis Quality Of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix J) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-Hay Fever Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 5. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument

takes approximately 7 minutes to complete. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (21).

9.2.2 Safety and tolerability endpoints

The same safety assessments will be applied across all arms. Adverse events, including serious adverse events (SAEs) and adverse events of special interest (AESI), will be collected at every visit. The Investigator will ask the patient how he/she has felt since the last study visit. The study specific and general safety criteria are detailed in Section 10.4.1. To assure the continuing safety of patients in this study, an independent DMC will be responsible for reviewing the safety data on a periodic basis throughout the course of the study as outlined in Section 6.4.

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients. Notably, he/she should follow up the outcome of SAEs /AESI until clinical recovery is complete and laboratory results have returned to normal or until progression has been stabilized or death. In all cases, this may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the Sponsor.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- In case of any SAE/AESI with immediate notification brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the investigational product with a reasonable possibility, this should be reported to the Sponsor.

9.2.2.1 Adverse events

Adverse events for each patient will be monitored and documented from the time the subject gives informed consent at Visit 1 until the End-of Study Visit or till the rollover to the extension study, except for:

- SAEs
- AEs that are ongoing at database lock.

Adverse events, adverse events with special interest (AESI) and serious adverse events (SAEs) will be reported as described in Section 10.4.

9.2.2.2 Vital signs

Vital signs, including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius), body weight (kg) and height (cm) will be measured. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits if applicable.

9.2.2.3 Physical examination

Physical examinations will include an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease.

9.2.2.4 ECG

One recording of a standard 12-lead ECG will be performed centrally. At the post-randomization visits, ECGs will be performed prior to investigational product administration if applicable. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts. Refer to central ECG reading manual for more details.

9.2.2.5 Clinical laboratory tests

The clinical laboratory tests will be conducted by an accredited (College of American Pathologists or equivalent) central laboratory with national and regional clinical licenses as required for diagnostic testing and must provide evidence of participation in proficiency testing, as appropriate. After reviewing the laboratory report and evaluating any results that are outside the normal range, the Investigator must sign and date the laboratory report. Abnormal laboratory values that are considered to be clinically significant by the Investigator should be repeated as soon as possible after receiving the laboratory report to rule out laboratory error. Persistent abnormal laboratory values should be repeated until they return to normal or until an etiology of the persistent abnormality is determined.

The clinical laboratory parameters that will be measured are:

- Hematology: To include hemoglobin, hematocrit, platelet count, total white blood cell count with five-part differential count, differential count, and total red blood cell count.
- Serum chemistry: To include: creatinine, blood urea nitrogen, glucose, uric acid, total cholesterol, total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, electrolytes (sodium, potassium, chloride), bicarbonate, and creatine phosphokinase. The blood sample must be taken with the patient in fasting state which means no intake of any food or drink except for water for at least 8 hours (If the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to eat light food and the site should document that serum chemistry was not obtained under fasting conditions).
- Urine dipstick analysis including specific gravity, pH, glucose, ketones, blood, protein, nitrite, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.

- Serum immunoglobulins: quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.
- Hepatitis screening: HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, HCV Ab. In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to randomization to determine eligibility.
- HIV screening (Anti-HIV-1 and HIV-2 antibodies)
- Anti-nuclear antibody (ANA). Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

9.2.2.6 Hepatitis B viral load

Hepatitis B viral load (HBV DNA) must be tested at Visit 1 and Visit 17 (only applicable for patients who plan to participate in the OLE study) in case of results showing HBs Ag (negative), HBs Ab (negative or positive) and HBc Ab total (positive), refer to Section 9.2.2.5 for details.

In Japan or other countries/regions if there is local regulatory requirement, hepatitis B viral load (HBV DNA) will be tested at Visit 2, then every 12 weeks until Visit 14 and at end of treatment visit for patients who are HBs Ag negative and HBs Ab positive at screening.

9.2.2.7 Pregnancy test

A serum pregnancy test (β-human chorionic gonadotrophin) will be performed at screening (Visit 1) in women of childbearing potential, and a urine dipstick pregnancy test will be performed at Visit 2 prior to randomization and other visits. A negative result must be obtained at Visit 1 and 2 prior to randomization.

9.3 OTHER ENDPOINTS

9.3.1 Systemic drug concentration and anti-drug antibodies

9.3.1.1 Sampling time

Serum samples for determination of functional dupilumab and anti-dupilumab antibodies (also known as anti-drug antibodies (ADA)) will be collected as per study flow chart (see Section 1.2 and Section 1.3). The date of collection should be recorded in the patient e-CRF. The date and time also will be collected on the central laboratory requisition form and entered into the database through data transfers from the central laboratory. Patients who discontinue early from treatment or patients who choose not to participate in the long term extension study may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall

assessment of antibody titers and/or clinical presentation at the time of discontinuation or at the time of last study visit.

In the event of any SAE or any AESI of anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment, or severe injection site reaction lasting longer than 24 hours, samples will be collected near the onset and resolution of the event for any additional analysis if required or for archival purposes. An unscheduled systemic drug concentration page in the e-CRF must be completed as well.

Pre-existing anti-drug antibodies are defined as:

- An ADA positive response in the assay at baseline with all post treatment ADA results negative, OR

- An ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent anti-drug antibodies are defined as:

- An ADA positive response in the assay post first dose, when baseline results are negative or missing.

Treatment-boosted anti-drug antibodies are defined as:

- An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Treatment-emergent (TE) ADA responses are further classified as Transient, Persistent or Indeterminate

a) Persistent Response- defined as a treatment-emergent response with two or more consecutive ADA positive sampling time points, separated by more than 12-week period (with no ADA negative samples in between).

b) Indeterminate Response- defined as a treatment-emergent response with only the last collected sample positive in the ADA assay

c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Unused samples collected for drug concentration or ADA analyses may be used for research purpose.

9.3.1.2 Handling procedures

Special procedures for collection, storage, and shipping of serum are described in separate operational manuals. An overview of handling procedure of samples used in the determination of functional dupilumab concentration and ADA is provided in Table 1.

Table 1 - Summary of handling procedures for dupilumab

Sample type	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Blood sample volume	5 mL	5 mL
Anticoagulant	None	None
Blood handling procedures	See Operational Manual	See Operational Manual
Serum aliquot split	2 aliquots	2 aliquots
Storage conditions	<6 months: below -20°C <24 months: below -80°C (preferred)	<6 months: below -20°C <24 months: below -80°C (preferred)
Serum shipment condition	In dry ice	In dry ice

9.3.1.3 Bioanalytic method

Serum PK and ADA samples will be assayed using validated methods as described in Table 2.

Table 2 - Summary of bioanalytical methods for dupilumab and anti-dupilumab antibody

Analyte	Functional dupilumab	Anti-dupilumab antibody
Matrix	Serum	Serum
Analytical technique	ELISA	Electrochemiluminescence
Lower limit of quantification	0.078 mg/L	Not applicable
Site of bioanalysis	Regeneron	Regeneron

ELISA=enzyme-linked immunosorbent assay.

9.3.2 Pharmacodynamics

Several biomarkers related to asthmatic inflammation and Th2 polarization will be assessed for their value in predicting therapeutic response and/or in documenting the time course of drug response. In a prior asthma trial (ACT11457), treatment with dupilumab significantly suppressed systemic levels of serum TARC (CCL17; a ligand of CCR4 receptors that attracts Th2 cells), plasma eotaxin-3 (CCL26; a ligand of CCR3 receptors that attracts eosinophils and lung mast cells), and serum total IgE (a product of immunoglobulin class switching driven by IL-4), as well as reduced the concentrations of fractional exhaled nitric oxide (a marker of airway inflammation). Now added to these are the following serum biomarkers: eosinophil cationic protein (ECP; a stored protein released from activated eosinophils) and periostin, a protein reported to be elevated at baseline in patients responsive to treatment with anti-IL-13 antibodies.

Assay methodologies are briefly summarized below. More detailed information on the collection, handling, transport and preservation of samples (eg, minimum volumes required for blood collection and for aliquots for each biomarker assay) will be provided in a separate laboratory manual.

Eotaxin-3, eosinophil cationic protein (ECP), total IgE and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at the same time points as a biomarker set and as indicated in the study flow chart. Periostin and antigen-specific IgE panels will be collected individually per the study flow chart.

9.3.2.1 Whole blood biomarkers

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

9.3.2.2 Plasma biomarkers

Eotaxin-3 will be measured in heparinized plasma with a validated enzyme immunoassay (Human Eotaxin-3 Quantikine ELISA kit; R&D Systems).

9.3.2.3 Serum biomarkers

Concentrations of eosinophil cationic protein (ECP) will be measured using a quantitative ImmunoCAP assay (Phadia).

Antigen-specific IgE will be detected using panels of antigens appropriate to the location of the clinical site (ImmunoCAP test; Phadia).

Total IgE will be measured with a quantitative method (eg, ImmunoCAP) approved for diagnostic testing.

TARC and periostin will be assayed with validated immunoassays.

9.3.2.4 Exhaled nitric oxide

Exhaled nitric oxide will be performed centrally and analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour. All exhaled nitric oxide recordings will be centrally read by independent experts. Further details on the procedure for measuring exhaled nitric oxide with NIOX will be provided in a separate instruction manual.

9.3.3 Pharmacogenetics

9.3.3.1 Optional stored DNA and RNA samples

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling.

For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as

specified in the study flow chart, and these samples will be stored for up to 15 years after completion of the final report of the main clinical trial or for a shorter time if there is local requirement. Specific procedures for collection, storage and shipping of pharmacogenetic samples will be provided in a lab manual.

DNA or RNA samples may be used to determine a possible relationship between genes and response to treatment with dupilumab, possible adverse reactions to dupilumab, and to study the genetics of asthma. The DNA may be subjected to a genome-wide association study by microarray analysis and/or to whole exome sequencing or whole genome analysis in order to thoroughly explore genetic associations with disease progression or treatment response. The RNA may be subjected to discrete panels of PCR analyses, microarray analyses or RNA sequencing analyses.

The blood DNA sample, and the DNA or RNA that is extracted, will be assigned a second number, a Genetic ID (de-identification code) that is different from the Subject ID. This “double coding” is performed to separate a subject’s medical information and DNA data.

The clinical study data (coded by Subject ID) will be stored in the clinical data management system (CDMS), which is a distinct database in a separate environment from the database containing the pharmacogenetic data (coded by Genetic ID). The key linking Subject ID and Genetic ID will be maintained by a third party, under appropriate access control. The matching of clinical data and pharmacogenetic data, for the purpose of data analysis, will be possible only by using this key, which will be under strict access control. All data will be reported only in coded form in order to maintain confidentiality.

9.3.4 Vaccine response

Patients will be encouraged to provide vaccination plans for the following vaccines, tetanus (alone or combined), any injectable influenza, any pneumococcal and any meningococcal, which are in line with the patients age and local medical practice (live attenuated vaccines are excluded) during the study. Subjects planning to receive any of the above listed vaccines during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient’s recommended immunization schedule. Pre-vaccine blood sample collection will not take place until patient is on treatment of IMP for at least 6 weeks. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

9.4 FUTURE USE OF SAMPLES

Not all of the samples collected during this study may be required for the tests planned in this clinical trial. For subjects who have consented to it, the samples that are archived, unused or left

over after planned testing may be used for additional research purposes (any genetic analysis subject to additional consent per Section 9.3.3). For subjects who have consented to it, archival blood samples will be collected at the visit specified in the study flow chart, 15 mL each, will be collected into a dry, red topped tube (or into smaller tubes of equivalent total volume) kept at room temperature for 30 minutes and then centrifuged at approximately 1500 g for 10 minutes at room temperature. The serum will then be transferred, in equal portions, into 3 storage tubes, which will be immediately capped and frozen in an upright position at -20°C or colder.

These archived serum samples, and any residual or leftover serum, plasma or blood remaining from planned laboratory work, may be used for research purposes related to asthma (eg, exploratory biomarkers of disease or drug effect), additional drug safety assessments or development and validation of bioassay methods beyond those defined in the present protocol. These samples will remain labelled with the same identifiers as the ones used during the study (ie, subject ID, sample ID). They will be transferred to a Sanofi site (or a subcontractor site) which can be located outside of the country where the study is conducted. The Sponsor has included safeguards for protecting subject confidentiality and personal data (see Section 14.3 and Section 14.5).

9.5 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments used in this study are standard for the evaluation of therapy in patients with asthma.

10 STUDY PROCEDURES

10.1 VISIT SCHEDULE

The clinical trial consists of three periods, using an add-on therapy approach to inhaled corticosteroid in combination with one or two other controller medications:

- Screening Period (4±1 weeks; Visit 1)
- Randomized Treatment Period (52 weeks; Visits 2-18)
- Post-treatment Period (12 weeks; Visits 19-21)

The study visits occur on the planned dates (relative to the first injection), as scheduled. The visit schedule should be adhered to within the ± 3 day visit window.

All the study visits should be scheduled in the morning, to have the spirometry performed and the patient should be fasting for serum chemistry tests. However, if the visit can only be done at a different time of the day and the patient is not fasting, then he/she should be advised to have a light meal and the site should document that serum chemistry was not obtained under fasting conditions. For spirometry, it should be performed at approximately the same time of the day at each visit throughout the study.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the end of the study with a +/-5 day window (See Section 1.3). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected.

Patients who discontinue early from treatment or patients who choose not to participate in the OLE study may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and/or clinical presentation at the time of discontinuation or at the time of last study visit.

Reminder: sexually active female patients of reproductive potential are required to practice an effective contraception throughout the participation in the study including a 12-week period after last IMP dose. Sites should counsel these patients, with special attention towards adolescent patients regarding the importance of practicing responsible and effective contraception throughout the participation in the study including a 12-week period after last IMP dose.

Prior to all screening assessments, after discussion of participation in the study, the written consent form (including voluntary participation in pharmacogenetic testing/future use of blood samples/vaccination testing) must be signed and dated.

Although the screening assessments for this study are grouped under the heading of a single visit in this protocol, it is possible for them to be performed over more than 1 site visit if necessary, as

long as the screening visit window prior to randomization (Day 1) is respected. If certain dynamic laboratory tests do not meet the eligibility criteria, these laboratory assessments may be repeated, at the discretion of the investigator, if it is judged to be likely to return to acceptable range for study inclusion within the screening visit window (35 days) prior to Day1. These patients do not need to sign a new ICF and be allocated a new patient number within this same screening window.

Patients that fail the initial screening for exclusion criteria, eg, concomitant medications, may be rescreened for study eligibility 1 additional time. Patients that are re-screened must sign a new consent form and will be allocated a new patient number; all of the Visit 1 procedures must be repeated (refer to Section 8.4 for further instructions related to rescreening) unless a prior assessment is performed within the time frame permitted prior to study entry.

Patients that fail the Screening Visit (Visit 1) or Randomization Visit (Visit 2) because of eDiary /spirometry equipment malfunction, or patient-related / site personnel-related unintentional errors may be rescreened one time after approval is granted by the Sponsor's clinical study director. In every case of rescreen allowance due to technical equipment malfunction and/or unintentional human error(s), the Study Investigator must document receipt of Sponsor approval and when applicable, document the site's corrective action plan to prevent future occurrences.

When approaching the season appropriate for influenza vaccination, patients will be reminded to inform the clinic staff about vaccination plans. Similarly, when approaching the planned date of tetanus (alone or combined), any pneumococcal and any meningococcal vaccination, patients will be reminded about the related pre- and post-vaccination blood sampling for vaccine IgG testing. Those who have not yet signed the separate consent for collection of blood pre-vaccination (eg, those who make mid-study decisions about vaccinations) may do so just prior to blood collection.

It is recommended that assessments/procedures at a site visit are performed in the following order if applicable, and these assessments/procedures should be done prior to IMP administration:

1. Patient-reported outcomes and other questionnaires
2. Procedures:
    a) ECG
    b) FENO
    c) Spirometry
    d) Reversibility/Post-bronchodilator FEV_1
    e) eDiary download
3. Safety and laboratory assessments
4. IMP administration

10.1.1 Visit 1 (Week -4 ± 1, -35 days to -21 days)

Following a discussion of participation in the clinical trial, informed consent must be obtained and documented. These steps precede any study procedures.

The following procedures will then be performed:

- Call IVRS/IWRS to assign patient number and register screening visit
- Interview to collect patient demographic information, asthma history (including smoking habits), other medical history and surgical history, and prior and concomitant medications
- Interview to collect vaccination information and vaccination plan during the treatment period for patient who agree to participate to the vaccine response assessment.
- Review entry criteria to assess eligibility, with special attention to verify the following:
  - Prescribed treatment dosage meets the pre-protocol definition of medium to high dose ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller (eg, LABA, LTRA) for at least 3 months with a stable dose ≥1 month prior to Visit 1. In addition, patients requiring a third controller for their asthma are considered eligible for this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded).
  - Patient has experienced, within 1 year prior to Visit 1: 1) Treatment with ≥1 systemic (oral or parenteral) steroids bursts for worsening asthma and/or 2) Hospitalization or an emergency/urgent medical care visit for worsening asthma.
- Measure vital signs [blood pressure, heart rate, respiration rate, body temperature, weight (kg), height (cm)]
- Perform physical examination
- Administer ACQ-7
  - Verify ACQ-5 score is ≥1.5
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Entry criteria at Visit 1 include the requirement of a specific FEV_1 and demonstration of reversibility as specified in Section 7.1. See below for additional directions.
  - Spirometry will be performed after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

  - Pre-bronchodilator Forced expiratory volume (FEV_1) must be ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents.

- Establish reversibility
  - Reversibility must be at least 12% and 200 mL in FEV_1 after 200 mcg to 400 mcg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice.
- Perform 12-lead electrocardiography (ECG)
- Perform chest X-ray or MRI (MRI is for Germany only) if no chest imaging (X-ray, CT, MRI) available within the previous 12 months as per local standard of care or if there is local requirement.
- Note for Japan: According to the request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (Chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis.
- Obtain (fasting if morning visit) blood samples for screening clinical laboratory determinations:
  - Hematology (see Section 9.2.2.5 for details)
  - Serum chemistry (see Section 9.2.2.5 for details)
- Obtain blood samples for hepatitis screen (HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, and HCV Ab). In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to randomization to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to randomization to determine eligibility.
- Obtain blood sample for HIV screen (Anti-HIV-1 and HIV-2 antibodies)
- Obtain blood sample for ANA test. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Obtain blood sample for serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA)
- Obtain serum β-HCG pregnancy test if female of childbearing potential
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Dispense electronic diary/PEF meter, provide instructions for daily use, and remind patient to bring the device to the next visit.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit within 21 to 35 days (Visit 2, Week 0) and request patient to come at approximately the same time of this visit (fasting if morning visit).

10.1.2 Visit 2 (Week 0, Day1)

- Record all medication use with start date and dose in eCRF; inquire about AEs/SAEs and background asthma therapy tolerability.
- Review entry criteria and reconfirm eligibility based on review of Inclusion/Exclusion Criteria.
- Administer ACQ-7 and all other scales (AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales)). Verify ACQ-5 score is $\geq$ 1.5.
- Compliance with use of the mandatory background therapy, ICS in combination with one or two other controller product as used just prior to screening, as defined as:
  - $\geq$80% of total number of prescribed doses of background medication taken during the screening period. Compliance is verified based on background medication use recorded on the patient electronic diary during the screening period.
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of $\geq$1 hour.
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform spirometry

Entry criteria at Visit 2 include the requirement of a specific FEV_1 and demonstration of reversibility as specified in Section 7.1. See below for additional directions.

- Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.

- Pre-bronchodilator Forced expiratory volume (FEV_1) must be ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents.
- Post-bronchodilator FEV_1 should be determined
- Treatment Period stability limits will be established for FEV_1 and PEF (The Treatment Period stability limit for PEF is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to Day 1).

If the patient meets all inclusion and does not meet any exclusion criteria:

- Call IVRS/IWRS to register visit, randomize the patient if entry criteria are met, and receive the first assignment for 2 treatment kit numbers.
  - Note: Please screen-fail the patient if entry criteria are not met.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical lab testing: hematology/biochemistry (refer to Section 9.2.2.5)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
  - Systemic drug concentration and ADA (refer to Section 9.3.1)
  - Biomarker set, Periostin and Antigen-specific IgE (refer to Section 9.3.2)
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer Section 9.4).
  - For those patients who have signed a specific pharmacogenetic informed consent form, collect blood samples for DNA and RNA sampling (prior to administration of investigational product during the Randomized Treatment Period), please refer to Section 9.3.3.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Dispense and administer IMP
  - For those patients willing to perform self-injection: The Investigator or delegate will train the patient (or caregiver) regarding preparation and injection of IMP at Visit 2 and will inject the first of the 2 injections. The patient (or caregiver) will perform the second injection under the supervision of the Investigator or delegate. Document the training for IMP self-injection in the patient's study file.
  - Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 2 ± 3 days) at approximately the same time of this visit.

10.1.3 Visit 3 (Week 2)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following test:
  - Systemic drug concentration.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain next treatment kit number
- Dispense and administer IMP.
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.

- For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection under the supervision of the Investigator or delegate.

- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 4 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.4 Visit 4 (Week 4)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined
- Perform 12-lead electrocardiography (ECG)
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:

  - Clinical laboratories, systemic drug concentration and Periostin (refer to Section 9.3.2).

- Download electronic diary/PEF meter and remind patient to bring the device to the next visit.
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit two weeks later (Week 6 ± 3 days) at approximately the same time of this visit.

10.1.5 Visit 5 (Week 6)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for the following test:

  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)

- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 8 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.6 Visit 6 (Week 8)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.

  - Post-bronchodilator FEV_1 should be determined
- Administer health care resource utilization questionnaire
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories and systemic drug concentration
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 10 ± 3 days) at approximately the same time of this visit.

10.1.7 Visit 7 (Week 10)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)

- Administer ACQ-7
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling for the following tests:
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP under the supervision of the Investigator or delegate.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 2 weeks later (Week 12 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.8 Visit 8 (Week 12)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories,
  - Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
  - Systemic drug concentration,
  - Anti-drug antibodies,
  - Biomarker set, Periostin and Antigen-specific IgE (refer to Section 9.3.2)
  - Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4).

  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
  - Hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who were HBs Ag negative and HBs Ab positive at screening.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Dispense and administer IMP
  - Patients will be monitored at the study site for a minimum of 30 minutes after the injection.
  - For patients (or caregivers) willing to self-administer IMP:
    - Provide instructions on preparation, self-injection and dose. Allow the patient (or caregiver) to perform the injection under the supervision of the Investigator or delegate, and provide feedback on technique. Verify that the training for IMP self-injection is documented in the patient's study file. Instruct patients to administer IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Dispense patient (self-injection) Home Dosing Diary
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (Week 16 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.9 Visit 9 (Week 16)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to IMP administration) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
  - Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
  - Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Administer health care resource utilization questionnaire.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.

- For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.

- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (Week 20 ± 3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.10 Visit 10, 12, 13, 15, 16, 17 (Week 20, 28, 32, 40, 44, 48)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Measure exhaled nitric oxide (only applicable for Visit 10 and Visit 17)
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Administer health care resource utilization questionnaire.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit, prior to IMP administration) for the following tests:

- Clinical laboratories include hematology and serum chemistry (see Section 9.2.2.5 for details)
- At Visit 17, for patients who will continue in the OLE study, obtain blood samples for hepatitis screen (HBs Ag, HBs Ab, HBc Ab including HBcAb IgM and total, and HCV Ab). In case of results showing HBs Ag (negative) and HBc Ab total (positive), a HBV DNA testing must be performed prior to inclusion to OLE in order to determine eligibility. In case of results showing HCV Ab (positive), a HCV RNA testing must be performed prior to inclusion to OLE in order to determine eligibility.
- At Visit 17, for patients who will continue in the OLE study, obtain blood sample for HIV screen (Anti-HIV-1 and HIV-2 antibodies)
- At Visit 17, for patients who will continue in the OLE study, obtain blood sample for ANA test. Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).
- Obtain blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4).
- Obtain blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)

- At Visit 17, for patients who plan to participate in the OLE study, perform chest X-ray or MRI (MRI is for Germany only) if available chest imaging (X-ray, CT, MRI) is over 12 months from entry into the OLE study.
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number
- Review instructions on self-injection and dosing and dispense patient (self-injection) Home Dosing Diary
- Dispense and administer IMP
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period and instruct patient to record daily usage in the electronic diary.

- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.11 Visit 11, 14, 18 (Week 24, 36, 52 / End-of-Treatment Visit)

- Check compliance to IMP; record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Review patient Home Dosing Diary for content and completeness
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform physical examination (only applicable for Visit 11 and EOT visit)
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S) +12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling(fasting if morning visit, prior to administration of IMP) for the following tests:
  - Clinical laboratories,

- Serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
- Systemic drug concentration,
- Anti-drug antibodies (only applicable for Visit 11 and Visit 18),
- Biomarker set, Periostin (Only applicable for Visit 18, refer to Section 9.3.2) and Antigen-specific IgE (only applicable for Visit 11 and Visit 18, refer to Section 9.3.2)
- Archival serum for those patients who have signed a specific Future Use of Specimens informed consent (refer to Section 9.4)
- Blood sample for pre-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who plan to receive a vaccine in the coming 6 weeks (refer to Section 9.3.4)
- Blood sample for post-vaccine IgG for patients who have signed a specific informed consent for vaccine assessment and who have received a vaccine in the past 3 to 4 weeks (preferred but up to 6 weeks allowed) (refer to Section 9.3.4)
- Blood sampling for hepatitis B viral load for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.

- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Call IVRS/IWRS to register visit and obtain treatment kit number (applicable for Visit 11 and Visit 14)
- Dispense and administer IMP (only applicable for Visit 11 and Visit 14)
  - For those patients willing and trained to perform self-injection: The patient (or caregiver) will perform the injection of IMP at q2w intervals.
  - For patients (or caregivers) unable or unwilling to self-administer IMP: Arrangements must be made for the patient to receive IMP injections at the study site as unscheduled visits, or for qualified site personnel and/or a professional caregiver to administer IMP at home at q2w intervals.
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.
- Remind patient to continue their stable dose of ICS in combination with one or two other controllers as used during the screening period (only applicable for Visit 11, Visit 14 and EOT visit after which patients continue to participate the open label extension trial) and instruct patient to record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.

- Schedule a site visit 4 weeks (±3 days) and ask patient to come at approximately the same time of this visit (only for Visit 11 and Visit 14: fasting if morning visit).
- Call IVRS/IWRS to register the EOT date (only applicable for EOT visit)

At Visit 18 (EOT visit), for patients who will not continue with the open label extension, the controller medication regimen and dose used during the randomized period could be adjusted based on medical judgment of the patients' asthma control status.

Patients who permanently discontinue the study treatment will perform early treatment discontinuation visit (ETD) at the time of permanent treatment discontinuation as well as EOT visit (visit 18) at planned Week 52. See section 1.3 for assessments to be performed at ETD and EOT visits and Section 10.3.4 for additional details.

10.1.12 Visit 19 and Visit 20 (Week 56 and Week 60, Post-Treatment Period)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Administer ACQ-7
- Administer health care resource utilization questionnaire
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
- Perform blood sampling (fasting if morning visit) for the following tests:
  - Clinical laboratories,
  - Systemic drug concentration
- Download electronic diary/PEF meter and remind patient to bring the device to the next visit
- Remind patients to use salbutamol/albuterol or levosalbutamol/levalbuterol as reliever medication throughout the study. Instruct patient to record usage in the electronic diary.

- Remind patient to continue the stable dose of ICS in combination with one or two other controller which was maintained over the randomized treatment period (unless treatment modified based on medical judgment) and record daily usage in the electronic diary.
- Remind patient to withhold bronchodilators according to their action duration, for example, withhold last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withhold last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withhold the last dose of LAMA for at least 24 hours prior to next visit.
- Schedule a site visit 4 weeks later (±3 days) and ask patient to come in at approximately the same time of this visit (fasting if morning visit).

10.1.13 Visit 21 (Week 64, End-of-Study Visit)

- Record all concomitant medication use; inquire about AEs/SAEs and background asthma therapy tolerability
- Measure vital signs (blood pressure, heart rate, respiration rate, body temperature, weight for all patients and height for adolescents only)
- Perform physical examination
- Administer ACQ-7
- Measure exhaled nitric oxide
  - Exhaled nitric oxide assessment is conducted prior to spirometry and following a fast of ≥1 hour.
- Perform spirometry
  - Spirometry will be performed at approximately the same time of last visit after a wash out period of bronchodilators according to their action duration, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours and prior to administration of investigational product. This will be verified before performing the measurements.
  - Post-bronchodilator FEV_1 should be determined.
- Administer AQLQ(S), health care resource utilization questionnaire, EQ-5D-5L, SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis), RQLQ(S)+12 in those patients with allergic rhinitis and HADS (HADS-A and HADS-D subscales).
- Perform 12-lead electrocardiography (ECG)
- Obtain urine for urinalysis (dipstick) If any assessment on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing.
- Perform urine dipstick pregnancy test (for women of childbearing potential)
- Perform blood sampling (fasting if morning visit) for the following tests:

- clinical laboratories,
- serum immunoglobulins (total IgG, IgG subclasses1-4, IgM and IgA),
- Systemic drug concentration,
- Anti-drug antibodies

- Download electronic diary/PEF meter and take back the device
- Call IVRS/IWRS to register the EOS date

10.2 DEFINITION OF SOURCE DATA

Source data is all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Source documents are original documents, data and records such as hospital records, clinic and office charts, laboratory notes, memoranda, pharmacy dispensing records, recorded data from automated instruments, etc.

All the data collected in the e-CRF should be transcribed directly from source documents. Data downloaded from the study-associated central laboratories, spirometry, nitric oxide measurement, ECG, and patient electronic diary / PEF meter will be considered source data.

10.3 HANDLING OF PATIENT TEMPORARY OR PERMANENT TREATMENT DISCONTINUATION AND OF PATIENT STUDY DISCONTINUATION

The IMP should be continued whenever possible. In case the IMP is stopped, it should be determined whether the stop can be made temporarily; permanent IMP discontinuation should be a last resort. Any IMP discontinuation should be fully documented in the CRF. In any case, the patient should remain in the study as long as possible.

10.3.1 Temporary treatment discontinuation with investigational medicinal product(s)

Temporary treatment discontinuation may be considered by the Investigator because of AEs. Reinitiation of treatment with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that AE is sufficiently resolved and unlikely to recur after resuming therapy with IMP.

In addition, the following conditions(s) will be causes for temporary treatment discontinuation:

- Infections or infestations that do not respond to medical treatment
- Any laboratory abnormality that meets temporary treatment discontinuation criteria as per Appendix K

10.3.2 Permanent treatment discontinuation with investigational medicinal product(s)

Permanent treatment discontinuation is any treatment discontinuation associated with the definitive decision from the Investigator or the patient not to re-expose the patient to the IMP at any time.

10.3.3 List of criteria for permanent treatment discontinuation

The patients may withdraw from treatment with the IMP if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation and this should be documented in the CRF or e-CRF.

Patients must be withdrawn from the treatment (ie, from any further investigational product administration) for the following reasons:

- At their own request or at the request of their legally authorized representative (Legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective patient to the patient's participation in the procedure(s) involved in the research).
- If, in the Investigator's opinion, continuation in the study would be detrimental to the patient's well-being
- At the specific request of the Sponsor
- In the event of a protocol deviation, at the discretion of the Investigator or the Sponsor
- Any code broken requested by the Investigator will lead to permanent treatment discontinuation.
- Pregnancy
- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment.
- Diagnosis of a malignancy during study, excluding carcinoma in situ of the cervix, or squamous or basal cell carcinoma of the skin.
- Any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Appendix N).
- Serum ALT >3 ULN and Total Bilirubin > 2ULN (See Appendix K).
- Serum ALT > 5 ULN if baseline ALT < 2 ULN or ALT >8 ULN if baseline ALT > 2 ULN (Appendix K).

Any abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of permanent discontinuation of the IMP for the concerned patient.

10.3.4 Handling of patients after permanent treatment discontinuation

Patients will be followed-up according to the study procedures as specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for study visits and participate in assessments according to the visit schedule until the end of the study with a +/-5 day window (See Section 1.3). Under exceptional circumstances when a patient cannot come to the site for the scheduled visit, a phone contact can be made after sponsor approval is given. During the phone contact, at least information about AEs, concomitant medication and asthma exacerbation events should be collected.

Patients who discontinue early from treatment may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall assessment of antibody titers and/or clinical presentation at the time of discontinuation.

All cases of permanent treatment discontinuation should be recorded by the Investigator in the appropriate pages of the CRF when considered as confirmed.

10.3.5 Procedure and consequence for patient withdrawal from study

The patients may withdraw from the study before study completion if they decide to do so, at any time and irrespective of the reason.

Withdrawal of consent for follow-up should be accompanied by documentation of the reason for withdrawal. Withdrawal of consent for treatment should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for non-patient contact follow-up, eg, medical records checks. Patients requesting withdrawal should be informed that withdrawal of consent for follow-up will jeopardize the public health value of the study.

Patients who withdraw should be explicitly asked about the contribution of possible adverse events to their decision to withdraw consent, and any adverse event information elicited should be documented.

Patients may withdraw consent verbally or in writing and, if verbal, then the site needs to document in source records that patient withdrew consent verbally.

If possible, the patients are assessed using the procedure normally planned for the end-of-study visit including a systemic drug concentration sample, if appropriate, and three Post-treatment Period Visits.

For patients who fail to return to the site, the Investigator should make the best effort to re-contact the patient (eg, contacting patient’s family or private physician, reviewing available registries or health care databases), and to determine his/her health status, including at least his/her vital status. Attempts to contact such patients must be documented in the patient’s records (eg, times and dates of attempted telephone contact, receipt for sending a registered letter).

A subject should only be designated as lost to follow-up if the site is unable to establish contact with the subject after 3 documented attempts via 2 different methods (phone, text, e-mail, certified letter, etc).

The statistical analysis plan (SAP) will specify how these patients lost to follow-up for their primary endpoints will be considered. Patients who have withdrawn from the study cannot be rerandomized (treated) in the study. Their inclusion and treatment numbers must not be reused.

10.4 OBLIGATION OF THE INVESTIGATOR REGARDING SAFETY REPORTING

10.4.1 Definitions of adverse events

10.4.1.1 Adverse event

An **adverse event** (AE) is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

Protocol defined asthma exacerbation events are collected as efficacy endpoints via the “Asthma Exacerbation Events” form. These events should not be reported as AEs unless they fulfill a seriousness criterion.

For this study, asthma exacerbations should be managed by the Investigators based on their medical judgment and applicable national / international asthma management guidelines.

10.4.1.2 Serious adverse event

A **serious adverse event** (SAE) is any untoward medical occurrence that at any dose:

- Results in death, or
- Is life-threatening, or
  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization, or
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is a medically important event
  Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention (ie, specific measures or corrective treatment) to prevent one of the other outcomes listed in the definition above.

Note: The following list of medically important events is intended to serve as a guideline for determining which condition has to be considered as a medically important event. The list is not intended to be exhaustive:

- Intensive treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Anaphylaxis (refer to Appendix M for Definition of Anaphylaxis)
  - Blood dyscrasias (ie, agranulocytosis, aplastic anemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc),
- Convulsions (seizures, epilepsy, epileptic fit, absence, etc).
- Development of drug dependence or drug abuse
- ALT >3 x ULN + total bilirubin >2 x ULN or ALT increase > 10 x ULN
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (except if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions
- Cancers diagnosed during the study
- Chronic neurodegenerative diseases (newly diagnosed)

10.4.1.3 Adverse event of special interest

An adverse event of special interest (AESI) is an AE (serious or non-serious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added or removed during a study by protocol amendment.

For these AESIs, the Sponsor will be informed immediately (ie, within 24 hours), per SAE notification described Section 10.4.4, even if not fulfilling a seriousness criterion, using the corresponding pages in the CRF (to be sent) or screens in the e-CRF.

- Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment (refer to Appendix M for Definition of Anaphylaxis)
- Severe injection site reactions that last longer than 24 hours
- Any infection meeting at least one of the following criteria:
  - Any serious infection (SAE)
  - Requires parenteral (intravenous, intramuscular, subcutaneous) antimicrobial therapy
  - Requires oral antimicrobial therapy for longer than 2 weeks
  - Is a parasitic infection
  - Is an opportunistic infection (see Appendix N)

Note: antimicrobial therapy refers to antibiotic, antiviral, and antifungal agents

- Significant ALT elevation
  - ALT >5 x the upper limit of normal (ULN) in patients with baseline ALT ≤2 x ULN; or
  - ALT >8 x ULN if baseline ALT >2 x ULN
- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/Noninvestigational medicinal product (NIMP);
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Section 10.4.1.2).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.

Of note, asymptomatic overdose has to be reported as a standard AE.

10.4.2 Serious adverse events waived from expedited regulatory reporting to regulatory authorities

Not applicable.

10.4.3 General guidelines for reporting adverse events

- All AEs, regardless of seriousness or relationship to IMP/NIMP, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for that patient, are to be recorded on the corresponding page(s) or screen(s) of the CRF.
- When a safety event is categorized as a primary outcome, the event will be reported as an AE but will be waived from reporting to health authorities providing an agreement has been reached with them.

- Whenever possible, diagnosis or single syndrome should be reported instead of symptoms. The Investigator should specify the date of onset, intensity, action taken with respect to IMP, corrective treatment/therapy given, additional investigations performed, outcome, and his/her opinion as to whether there is a reasonable possibility that the AE was caused by the IMP or by the study procedure(s). In studies that require the use of combined/multiple IMPs/NIMPs, the Global Safety Officer (GSO) with input from other appropriate study team members must determine if the causal relationship will either be assessed for the combined product as a regimen or as distinct entities. The GSO must communicate this decision to the study team for inclusion in the protocol and AE CRF.
- The Investigator should take appropriate measures to follow all AEs until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized, or until death, in order to ensure the safety of the patients. This may imply that observations will continue beyond the last planned visit per protocol, and that additional investigations may be requested by the monitoring team up to as noticed by the Sponsor. Patients who experience an ongoing SAE or an AESI with immediate notification, at the prespecified study end-date, should be followed until resolution, stabilization, or death and related data will be collected.
- When treatment is prematurely discontinued, the patient's observations will continue until the end of the study as defined by the protocol for that patient.
- Laboratory, vital signs or ECG abnormalities are to be recorded as AEs only if:
  - Symptomatic and/or
  - Requiring either corrective treatment or consultation, and/or
  - Leading to IMP discontinuation or modification of dosing, and/or
  - Fulfilling a seriousness criterion, and/or
  - Defined as an AESI

The following table summarizes the reporting timelines:

Adverse event / laboratory abnormality		Reporting timeline
Serious adverse event		Within 24 hours
Pregnancy		Within 24 hours
Overdose	Symptomatic	Within 24 hours
	Asymptomatic	Routine
ALT elevation	ALT > 5 ULN if baseline ALT is ≤ 2 ULN	Within 24 hours
	ALT > 8 ULN if baseline ALT is > 2 ULN	
Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment		Within 24 hours
Severe injection site reactions that last longer than 24 hours		Within 24 hours
Infections as defined in Section 10.4.1.3.		Within 24 hours

10.4.4 Instructions for reporting serious adverse events

In the case of occurrence of an SAE, the Investigator must immediately:

- ENTER (within 24 hours) the information related to the SAE in the appropriate screens of the e-CRF; the system will automatically send a notification to the monitoring team after approval of the Investigator within the e-CRF or after a standard delay.
- SEND (preferably by fax or e-mail) a photocopy of all examinations carried out and the dates on which these examinations were performed, to the representative of the monitoring team whose name, fax number, and email address appear on the clinical trial protocol. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the clinical trial are properly mentioned on any copy of a source document provided to the Sponsor. For laboratory results, include the laboratory normal ranges.
- All further data updates should be recorded in the e-CRF as appropriate, and further documentation as well as additional information (for laboratory data, concomitant medications, patient status, etc) should be sent (by fax or e-mail) to the monitoring team within 24 hours of knowledge of the SAE. In addition, every effort should be made to further document any SAE that is fatal or life threatening within a week (7 days) of the initial notification.
- A back-up plan (using a paper CRF process) is available and should be used when the e-CRF system does not work.

Any SAE brought to the attention of the Investigator at any time after the end of the study for the patient and considered by him/her to be caused by the IMP with a reasonable possibility, should be reported to the monitoring team.

10.4.5 Guidelines for management of specific laboratory abnormalities

Decision trees for the management of certain laboratory abnormalities by Sanofi are provided in Appendix K.

The following laboratory abnormalities should be monitored, documented, and managed according to the related flow chart in protocol appendices.

- Neutropenia

- Thrombocytopenia
- Increase in ALT
- Acute renal insufficiency
- Suspicion of rhabdomyolysis

Note: In some clinical trials these laboratory abnormalities can be considered as AESIs. For this study, only significant ALT increase will be considered as AESIs (see Section 10.4.1.3)

In addition, on treatment eosinophil counts >3000 cells/µL (3.0 giga/L) are to be reported as AEs.

10.5 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor will report in an expedited manner:

- All SAEs that are both unexpected and at least reasonably related to the IMP (SUSAR), to the regulatory authorities, IECs/IRBs as appropriate and to the Investigators.
- All SAEs that are expected and at least reasonably related to the IMPs to the regulatory authorities, according to local regulations.

In this study, some AEs are considered related to the underlying condition and thus will not be considered unexpected [eg, wheezing related to asthma].

Any other AE not listed as an expected event in the Investigator's Brochure or in this protocol will be considered unexpected.

For safety, the treatment code will be unblinded by the Sponsor for reporting to the Health Authority of any suspected unexpected serious adverse drug reaction (SUSAR) and reasonably associated with the use of the IMP according to either the judgment of the Investigator and/or the Sponsor.

In case of a SUSAR, Sanofi Global Pharmacovigilance and Epidemiology will utilize XGRID to reveal medication assignment for regulatory reporting requirements for the particular case.

The Sponsor will report all safety observations made during the conduct of the trial in the clinical study report.

10.6 SAFETY INSTRUCTIONS

10.6.1 Hypersensitivity

Allergic reaction is a potential risk associated with the administration of most therapeutic monoclonal antibodies.

Allergic reactions may be defined as an immunologically mediated response to a pharmaceutical and/or formulation agent in a sensitized person. Signs and symptoms are often experienced during

or shortly after therapeutic administration. Anaphylaxis may represent the most severe form of allergic reactions, refer to Appendix M “Definition of Anaphylaxis”, which describes the clinical criteria for the diagnosis of anaphylaxis.

Patients should be monitored for at least 30 minutes after each study-site administered investigational product administration for any signs or symptoms of a hypersensitivity reaction. Trained personnel and medications should be available to treat anaphylaxis or any severe allergic reaction if it occurs. Furthermore, the patients will be advised, when the IMP is administered at home, to self-monitor for potential signs and symptoms that may suggest a hypersensitive reaction for 30 minutes after administration.

Anaphylactic reactions or systemic allergic reactions that are related to IMP and require treatment must-be reported as an adverse event of special interest (AESI) (within 24 hours, for further details, see AESI definition in Section 10.4.1.3 and Appendix M) and study medication must be permanently discontinued. ADA and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

10.6.2 Severe injection site reactions

Based on the subcutaneous mode of administration of high doses of protein and on a higher incidence of local injection site reactions observed at the highest dose level (300 mg weekly), severe injection site reactions, are considered as a potential risk. Patients who experience an injection site reaction must be closely monitored for the possibility of a more intense injection site reaction with a future injection. Any severe injection reaction that lasts over 24 hours will be reported as an AESI with immediate notification. ADA and PK samples will be collected near the onset and resolution of the AESI for any additional analysis.

Prophylactic treatment/premedication for an Injection Site Reaction is not permitted.

10.6.3 Infections

Some biologic therapies have been associated with an increased risk of infection, including opportunistic infection. As a precautionary measure, the Investigator is required to carefully monitor for any signs or symptoms of infection such as, but not limited to, increased body temperature, malaise, weight loss, sweats, cough, dyspnea, pulmonary infiltrates, or serious febrile systemic illness.

Since dupilumab binds to IL-4Rα, preventing IL-4 and IL-13 activation of their respective receptors, it inhibits the T-helper 2 (Th2) cytokines production. Infections with a diversity of helminthic parasites elicit eosinophilia via stimulation of Th2-like lymphocyte responses. The Th2 response is characterized by production of IL-4, IL-13 and IL-5, subsequently generating IgG1 and IgE-secreting cells, and eliciting eosinophilia. Eosinophilia is prominent in a number of helminthic parasitic diseases. The eosinophilic response to helminths is determined both by the host's immune response and by the parasite, including its distribution, migration, and development within the infected host. Therefore, patients treated with dupilumab may potentially have an increased risk of parasitic infection.

In order to minimize this risk, any patient with an active parasitic infection should be excluded from the study. Similarly, patients with suspected parasitic infection, or those at high risk of parasitic infection are also excluded, unless clinical and (if necessary) laboratory assessments have ruled out active infection before randomization. During the study, appearance of signs or symptoms (such as abdominal pain, cough, diarrhea, fever, fatigue hepatosplenomegaly) that could be associated with a parasitic infection should be carefully evaluated, especially if there is a history of parasitic exposure through recent travel to/ or residence in endemic areas, especially when conditions are conducive to infection (eg, extended stay, rural or slum areas, lack of running water, consumption of uncooked, undercooked, or otherwise potentially contaminated food, close contact with carriers and vectors, etc.). Subsequent medical assessments (eg, stool exam, blood tests, etc.) must be performed in order to rule out parasitic infection/infestation. Patients with confirmed parasitic infections during the study should be reported as AESI with immediate notification.

Infections defined in Section 10.4.1.3 should be reported as AESIs within 24 hours.

A complete diagnostic work-up should be performed (i.e., cultures, histopathological or cytological evaluation, antigen detection and serum antibody titers). Patients should be referred to an infectious disease specialist if deemed necessary for diagnostic work up and appropriate treatment.

Infections or infestations that do not respond to medical treatment should have study drug discontinued until the infection is resolved.

For any opportunistic infection, such as TB or other infections whose nature or course may suggest an immunocompromised status (See Appendix N), patients must be permanently discontinued from study medication.

10.6.4 Elevated liver function tests

No pre-clinical and clinical data has suggested any hepatic toxicity of dupilumab; however, as a general consideration of clinical development, the administration of immunosuppressant or immunomodulating agents may represent an additional risk factor for hepatotoxicity.

Hepatitis virus tests and liver function tests (LFT) will be performed at Visit 1, prior to randomization to exclude those patients with high risk of hepatitis infection or severe liver injury from this study (Refer to Section 7.2 and Section 9.2.2.5).

In order to closely follow potential liver abnormalities, assessment of total protein, albumin, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), alanine aminotransferase, aspartate aminotransferase, and alkaline phosphatase are measured as part of the clinical laboratory testing (Refer to Section 9.2.2.5).

Guidance for the investigation of elevated ALT as well as concurrent management of IMP is provided in Appendix K.

10.7 ADVERSE EVENTS MONITORING

All events will be managed and reported in compliance with all applicable regulations, and included in the final clinical study report.

11 STATISTICAL CONSIDERATIONS

11.1 DETERMINATION OF SAMPLE SIZE

The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations during the 52-week treatment period and absolute change from baseline in FEV_1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/µL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for the subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV_1 from baseline at Week 12 for the overall population, and 690 patients will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/ /µL (0.3 giga/L). The overall study recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/µL (0.3 giga/L) are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84 adolescent patients will be randomized.

Patients will be randomized using a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w and dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL respectively.

Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/µL, ≥300 cells/µL) at screening, ICS dose level (medium, high) and country.

In addition, in order to have additional patients treated with drug manufactured using the intended commercial process, approximately 220 patients will be randomized in addition to the originally planned sample size (1638).

11.2 DISPOSITION OF PATIENTS

Screened patients are defined as any patient who met the inclusion criteria and signed the informed consent.

Randomized patients consist of all patients with a treatment kit number allocated and recorded in IVRS database, and regardless of whether the treatment kit was used or not.

Patients treated without being randomized will not be considered as randomized and will not be included in any efficacy population, but will be included in the safety population.

11.3 ANALYSIS POPULATIONS

11.3.1 Efficacy populations

The analysis population for the efficacy endpoints will be intent-to-treat (ITT) population. The two primary endpoints will also be analyzed in the HEos ITT population.

ITT population: all randomized population analyzed according to the treatment group allocated by randomization regardless of whether treatment kit is used or not.

HEos ITT population: ITT population with baseline eosinophils ≥300 cells/μL.

11.3.2 Safety population

The analysis population for the safety endpoints will be safety population defined as all patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment patients actually received.

Treatment emergent period for safety population is defined as the time between the first administration of study medication to the end of the Post-treatment Period or till the rollover to the extension study.

In addition:

- Randomized patients for whom it is unclear whether they took the study medication will be included in the safety population as randomized.

11.3.3 Systemic drug concentration population

The systemic drug concentration population will consist of all patients in the safety population with at least one evaluable functional dupilumab concentration result. Patients will be analyzed according to the treatment actually received.

11.3.4 Anti-drug antibody population

The anti-drug antibody population will consist of all patients in the safety population with at least one qualified ADA result in the ADA assay following the first dose of the study medication. Patients will be analyzed according to the treatment actually received.

11.4 STATISTICAL METHODS

11.4.1 Extent of study treatment exposure and compliance

The extent of study treatment exposure and compliance will be assessed and summarized by actual treatment received within the safety population.

11.4.1.1 Extent of investigational medicinal product exposure

Duration of IMP exposure is defined as: last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations.

11.4.1.2 Compliance

An administration is considered compliant if an injection is performed, regardless the actual amount of solution injected. The loading dose will be considered as two administrations. No imputation will be made for patients with missing or incomplete data.

Treatment compliance will be summarized descriptively (N, Mean, SD, Median, Min, and Max). The percentage of patients with compliance is <80% will be summarized.

11.4.2 Analyses of efficacy endpoints

11.4.2.1 Analysis of primary efficacy endpoints

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed treatment duration will be the offset variable. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and the additional off-treatment severe exacerbation events up to Week 52 will be included in the analysis and the last contact date at Week 52 will be used to calculate the offset variable.

The absolute change from baseline in FEV_1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in FEV_1 values up to Week 12 as response variables, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline FEV_1 value and baseline-by-visit interaction as covariates. An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in FEV_1 at Week 12 will be derived from the mixed-effect model. For patients discontinuing the treatment before Week 12, off study-treatment FEV_1 values measured up to Week 12 will be included in the primary analysis.

Subgroup analyses will be performed for the two primary endpoints using the same methods by baseline eosinophil levels (≥300 cells /μL vs <300 cells /μL and ≥150 cells /μL vs <150 cells /μL).

11.4.2.1.1 Analysis of annualized event rate

The annualized rate of exacerbation events, including severe exacerbation events resulting in hospitalization or emergency room visit and LOAC events, will be analyzed using the same way as for severe exacerbation events.

11.4.2.1.2 Analysis of Time to event variables

Time to event (eg, LOAC, severe exacerbation) will be analyzed using a Cox regression model with time to event as the dependent variable, and treatment, age, number of asthma exacerbation events within 1 year prior to the study, region (pooled country), baseline eosinophil strata and baseline ICS dose level as covariates. The Kaplan-Meier method will be used to respectively estimate the probabilities that a patient would experience events at Week 12, 24, 36 and 52 per each treatment group.

11.4.2.1.3 Analysis of change from baseline for other continuous variables

The change from baseline for other continuous endpoints will be analyzed using MMRM in the same fashion as for the endpoint of FEV_1. The covariates to be included are treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, corresponding baseline value and baseline-by-visit interaction. Sex and height will be included as covariates only in the models for spirometry parameters.

Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, differences in LS means, the corresponding 95% CI and the p-value will be derived from the MMRM model for comparison of dupilumab against placebo.

Change from baseline at other time points will be analyzed in the same way.

11.4.2.1.4 Subgroup analysis

To assess the consistency in treatment effects across the subgroup levels, subgroup analyses will be performed for the primary efficacy endpoints with respect to baseline eosinophil level (≥300 cells /μL vs. <300 cells /μL and ≥150 cells /μL vs. < 150 cells /μL), age group, gender, region, race, background ICS dose levels, background controller medication type, baseline FEV_1, predicted FEV_1 %, ACQ-5, weight, BMI, smoking history, atopic medical history, age of onset of asthma and number of asthma exacerbation events within 1 year prior to the study.

11.4.2.2 Multiplicity considerations

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The

hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV_1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV_1 at Week 12 for 200 mg q2w versus placebo.

If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups.

11.4.2.3 Handling of missing data

Sensitivity analyses excluding the additional off-treatment measurements up to Week 52 will be performed to corroborate the primary analyses. The reason and pattern of missing data will be carefully examined and tipping point analysis and additional sensitivity analyses may be performed. The details will be specified in the SAP.

11.4.2.4 Loading dose evaluation

To examine if inclusion of the loading dose may impact demonstration sustained efficacy regard to exacerbations, additional sensitivity analyses of the annualized rate of severe exacerbation will be performed by excluding severe exacerbation events occurring during the first four weeks and 12 weeks, respectively. The analyses will be performed the same way as the primary analysis. To avoid possible confounding effect due to off-treatment data, only on-treatment events will be included. Due to potential insufficient number of events after excluding data from the first 12 weeks, two dupilumab groups will be combined and two placebo groups will be combined.

11.4.3 Analyses of safety data

The summary of safety results will be presented by treatment group. The results of the two placebo groups will be presented separately. All safety analyses will be performed on the safety population using the following common rules:

The baseline value is defined generally as the last available value before the first dose of IMP.

The following definitions will be applied to laboratory parameters, vital signs and ECG.

- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs and ECG.
- PCSA criteria will determine which patients had at least 1 PCSA during the on-treatment period, taking into account all evaluations performed during the on-treatment period, including unscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.

11.4.3.1 Adverse events

Adverse event incidence tables will present by system organ class (SOC) (sorted by internationally agreed order), high-level group term (HLGT), high level term (HLT) and preferred term (PT) sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an AE. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group.

Proportion of patients with at least one treatment emergent adverse event (TEAE), serious TEAE and TEAE leading to discontinuation of the study will be tabulated by treatment group. In addition TEAEs will be described according to maximum intensity and relation to the study drug. None treatment emergent serious AE, None treatment emergent AE leading to study discontinuation will be summarized separately.

11.4.3.1.1 AESI

The following summaries will be generated:

- Incidence of each AESI will be tabulated by treatment group.
- The time-to-first event analyzed using K-M methods and displayed as K-M plots (cumulative incidence (%) versus time based on K-M estimates) will be provided to depict the course of onset over time. When TEAE start date or worsening date is partially available, the maximum of the earliest possible TEAE start date and the treatment start date will be used. When TEAE start date or worsening date is completely missing, the treatment start date will be used.
- An overview summary of the number (%) of patients with
  - any TEAE
  - any serious AE (regardless of treatment-emergent status)
  - any treatment-emergent SAE
  - any AE leading to death
  - any TEAE leading to permanent study drug discontinuation
  - any TEAE by maximum intensity, corrective treatment, and final outcome
  - cumulative incidence at specified time points (K-M estimates at 1 week, 4 weeks, 12 weeks, 24 weeks and 52 weeks)

AESI definitions and the method to identify AESIs will be specified in the SAP.

11.4.3.1.2 Death

The following deaths summaries will be generated:

- Number (%) of patients who died by study period (TEAE, on-study) and reasons for death summarized on the safety population by treatment received

- Death in nonrandomized patients or randomized and not treated patients
- TEAE leading to death (death as an outcome on the AE CRF page as reported by the Investigator) by primary SOC , HLGT, HLT and PT showing number (%) of patients sorted by internationally agreed order of SOC and alphabetic order of HLGT, HLT, and PT.

Patient data listings will be provided for all AEs, TEAEs, SAE, AEs leading to study discontinuation, AESIs and deaths.

11.4.3.1.3 Clinical Laboratory Evaluation, Vital Signs and electrocardiogram data

Results and change from baseline for the parameters will be summarized by treatment group for baseline and each post baseline time point, endpoint, minimum and maximum value. Summary statistics will include number of patients, mean, standard deviation, median, Q1, Q3, minimum and maximum.

The proportion of patients who had at least one incidence of PCSA at any time during the TEAE period will be summarized by treatment group. Shift tables showing changes with respect to the baseline status will be provided.

Listings will be provided with flags indicating clinically out-of range values, as well as PCSA values.

11.4.3.2 Vaccine response

For patients who receive vaccination, vaccine response parameters will be summarized by treatment groups with descriptive statistics.

11.4.4 Analyses of systemic drug concentration, anti-drug antibodies and pharmacodynamic variables

11.4.4.1 Drug concentration analysis

Concentrations of functional dupilumab in serum will be summarized using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV%), minimum, median, and maximum by treatment per visit.

Concentrations of functional dupilumab in serum will be used for population PK analysis by non-linear mixed effects modeling if warranted. Additional details of the analysis plan and the results will be provided in a separate document.

11.4.4.2 Anti-drug antibodies analysis

Incidence of positivity in the ADA assay will be assessed as absolute occurrence (n) and percent of patients (%), presented by study cohorts. Listing of all ADA titer levels will be provided for

patients positive in the ADA assay. All samples that are positive in the ADA assay will be further tested for the presence of anti-dupilumab neutralizing antibodies.

Plots of concentrations of functional dupilumab will be examined and the potential influence of ADA on individual concentration-time profiles will be evaluated. Assessment of the potential impact of ADA on safety and efficacy may be provided.

ADA at baseline will be summarized by:

- Number (%) of patients with a baseline sample negative in the ADA assay.
- Number (%) of patients with a baseline sample positive in the ADA assay.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the titer for patients positive in the ADA assay at baseline.

ADA incidence and titer will be provided for the following:

- Number (%) of patients negative in ADA assay at all times
- Number (%) of patients positive in ADA assay at any time
- Number (%) of patients with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA
- Number (%) of patients with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA

Titer values (Titer value category)

The minimum titer for samples positive in the ADA assay is based on the minimum required dilution of the assay.

Low (Titer < 1000)
Moderate (1,000 ≤ Titer ≤ 10,000)
High (Titer > 10,000)

More details will be specified in SAP.

11.4.4.3 Pharmacodynamics

The values to be used as baselines will be those collected on Day 1 (predose assessments). If any of the scheduled assessments on Day 1 are technically disqualified (eg, insufficient sample), then values determined at Screening can be used as baseline.

For all parameters, raw data, absolute changes from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point.

Summary plots (mean +/- standard error of the mean) on raw data, absolute changes from baseline and percent changes from baseline will be provided by treatment group.

11.4.5 Analyses of Patient Reported Outcomes (Health-related Quality of Life/health economics variables

Change from baseline in the following variables: global measure of AQLQ(S) and the four domains, the quantitative variables of EQ-5D-5L (single index utility), the anxiety and depression scores of HADS will be analyzed with an MMRM approach described previously for the continuous efficacy variables. Descriptive statistics including number of patients, mean, standard error and LS means will be provided. In addition, difference in LS means, the corresponding 95% CI's and the p-values will be provided for comparison between dupilumab and placebo.

SNOT-22 (only for those patients with bilateral nasal polyposis and/or chronic rhinosinusitis) and RQLQ(S)+12 (only for those patients with comorbid allergic rhinitis) will be analyzed using the similar approach.

11.5 INTERIM ANALYSIS

There is no interim analysis planned for this study.

12 ETHICAL AND REGULATORY CONSIDERATIONS

12.1 ETHICAL AND REGULATORY STANDARDS

This clinical trial will be conducted by the Sponsor, the Investigator, delegated Investigator staff and Subinvestigator, in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments laid down by the World Medical Assemblies, and the ICH guidelines for good clinical practice (GCP), all applicable laws, rules and regulations.

This clinical trial will be recorded in a free, publicly accessible, internet-based registry, no later than 21 days after the first patient enrollment, in compliance with applicable regulatory requirements and with Sanofi public disclosure commitments.

12.2 INFORMED CONSENT

The Investigator (according to applicable regulatory requirements), or a person designated by the Investigator, should fully inform the patient (and the parent[s] or guardian[s] for pediatric patients) of all pertinent aspects of the clinical trial including the written information given approval/favorable opinion by the Institutional Review Board / Institutional Ethics Committee (IRB/IEC). All participants should be informed to the fullest extent possible about the study in language and terms they are able to understand.

Prior to a patient's participation in the clinical trial, the informed consent form should be signed, name filled in and personally dated by the patients (for adult patients) or patient's parent(s) for pediatric patients or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written informed consent form will be provided to the patient (for adult patients) or patient's parent(s) for pediatric patients. Local law must be observed in deciding whether 1 or both parents/guardians consent is required for pediatric patients. If only 1 parent or guardian signs the consent form, the Investigator must document the reason for only 1 parent or guardian's signature.

In addition, participants will assent as detailed below or will follow the Ethics Committee (IRB/IEC) approved standard practice for pediatric participants at each participating center (age of assent to be determined by the IRB's/IEC's or be consistent with the local requirements):

Pediatric participants who can read the assent form will do so before writing their name and dating or signing and dating the form.

Pediatric participants who can write but cannot read will have the assent form read to them before writing their name on the form.

Pediatric participants who can understand but who can neither write nor read will have the assent form read to them in presence of an impartial witness, who will sign and date the assent form to confirm that assent was given.

The informed consent form and the assent form used by the Investigator for obtaining the pediatric patient's Informed Consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

In relation with the population of patients exposed in the trial, ie, pediatric/minor patients, the IRB/IEC should ensure proper advice from specialist with pediatrics expertise (competent in the area of clinical, ethical and psychosocial problems in the field of pediatrics) according to national regulations. This should be documented.

Prior to collection of blood for pharmacogenetics, the optional pharmacogenetic informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for evaluation of vaccine response, the optional vaccine response informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

Prior to collection of blood for archiving of serum, the optional Future Use of Specimens informed consent form (written) should be signed, name filled in, and personally dated by the patient or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written optional informed consent form will be provided to the subject.

The main study informed consent form, the optional Pharmacogenetic informed consent form, optional Vaccine Response informed consent form and the Future Use of Specimens informed consent form to be used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval/favorable opinion.

If the race/ethnic origin of the patients will be collected in the clinical trial, the scientific justification should be specified.

12.3 INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

As required by local regulation, the Investigator or the Sponsor must submit this clinical trial protocol to the appropriate IRB/IEC, and is required to forward to the respective other party a copy of the written and dated approval/favorable opinion signed by the Chairman with IRB/IEC composition.

The clinical trial (study number, clinical trial protocol title and version number), the documents reviewed (clinical trial protocol, informed consent form, Investigator's Brochure, Investigator's curriculum vitae [CV], etc) and the date of the review should be clearly stated on the written (IRB/IEC) approval/favorable opinion.

IMP will not be released at the study site and the Investigator will not start the study before the written and dated approval/favorable opinion is received by the Investigator and the Sponsor.

During the clinical trial, any amendment or modification to the clinical trial protocol should be submitted to the IRB/IEC before implementation, unless the change is necessary to eliminate an immediate hazard to the patients, in which case the IRB/IEC should be informed as soon as possible. It should also be informed of any event likely to affect the safety of patients or the continued conduct of the clinical trial, in particular any change in safety. All updates to the Investigator's Brochure will be sent to the IRB/IEC.

A progress report is sent to the IRB/IEC at least annually and a summary of the clinical trial's outcome at the end of the clinical trial.

13 STUDY MONITORING

13.1 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator is required to ensure compliance with all procedures required by the clinical trial protocol and with all study procedures provided by the Sponsor (including security rules). The Investigator agrees to provide reliable data and all information requested by the clinical trial protocol (with the help of the CRF, Discrepancy Resolution Form [DRF] or other appropriate instrument) in an accurate and legible manner according to the instructions provided and to ensure direct access to source documents by Sponsor representatives.

If any circuit includes transfer of data particular attention should be paid to the confidentiality of the patient's data to be transferred.

The Investigator may appoint such other individuals as he/she may deem appropriate as Subinvestigators to assist in the conduct of the clinical trial in accordance with the clinical trial protocol. All Subinvestigators shall be appointed and listed in a timely manner. The Subinvestigators will be supervised by and work under the responsibility of the Investigator. The Investigator will provide them with a copy of the clinical trial protocol and all necessary information.

13.2 RESPONSIBILITIES OF THE SPONSOR

The Sponsor of this clinical trial is responsible to regulatory authorities for taking all reasonable steps to ensure the proper conduct of the clinical trial as regards ethics, clinical trial protocol compliance, and integrity and validity of the data recorded on the CRFs. Thus, the main duty of the monitoring team is to help the Investigator and the Sponsor maintain a high level of ethical, scientific, technical and regulatory quality in all aspects of the clinical trial.

At regular intervals during the clinical trial, the site will be contacted, through monitoring visits, letters or telephone calls, by a representative of the monitoring team to review study progress, Investigator and patient compliance with clinical trial protocol requirements and any emergent problems. These monitoring visits will include but not be limited to review of the following aspects: patient informed consent, patient recruitment and follow-up, SAE documentation and reporting, AESI documentation and reporting, AE documentation, IMP allocation, patient compliance with the IMP regimen, IMP accountability, concomitant therapy use and quality of data.

13.3 SOURCE DOCUMENT REQUIREMENTS

According to the ICH GCP, the monitoring team must check the CRF entries against the source documents, except for the pre-identified source data directly recorded in the CRF. The informed consent form will include a statement by which the patient allows the Sponsor’s duly authorized

personnel, the Ethics Committee (IRB/IEC), and the regulatory authorities to have direct access to original medical records which support the data on the CRFs (eg, patient's medical file, appointment books, original laboratory records, etc). These personnel, bound by professional secrecy, must maintain the confidentiality of all personal identity or personal medical information (according to confidentiality and personal data protection rules).

13.4 USE AND COMPLETION OF CASE REPORT FORMS (CRFS) AND ADDITIONAL REQUEST

It is the responsibility of the Investigator to maintain adequate and accurate CRFs (according to the technology used) designed by the Sponsor to record (according to Sponsor instructions) all observations and other data pertinent to the clinical investigation in a timely manner. All CRFs should be completed in their entirety in a neat, legible manner to ensure accurate interpretation of data.

Should a correction be made, the corrected information will be entered in the e-CRF overwriting the initial information. An audit trail allows identifying the modification.

Data are available within the system to the Sponsor as soon as they are entered in the e-CRF.

The computerized handling of the data by the Sponsor may generate additional requests (DRF) to which the Investigator is obliged to respond by confirming or modifying the data questioned. The requests with their responses will be managed through the e-CRF.

13.5 USE OF COMPUTERIZED SYSTEMS

The complete list of computerized systems used for the study is provided in a separate document which is maintained in the Sponsor and Investigator study files.

14 ADDITIONAL REQUIREMENTS

14.1 CURRICULUM VITAE

A current copy of the curriculum vitae describing the experience, qualification and training of each Investigator and Subinvestigator will be signed, dated and provided to the Sponsor prior to the beginning of the clinical trial.

14.2 RECORD RETENTION IN STUDY SITES

The Investigator must maintain confidential all study documentation, and take measures to prevent accidental or premature destruction of these documents.

The Investigator should retain the study documents at least 15 years after the completion or discontinuation of the clinical trial.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

The Investigator must notify the Sponsor prior to destroying any study essential documents following the clinical trial completion or discontinuation.

If the Investigator's personal situation is such that archiving can no longer be ensured by him/her, the Investigator shall inform the Sponsor and the relevant records shall be transferred to a mutually agreed upon designee.

14.3 CONFIDENTIALITY

All information disclosed or provided by the Sponsor (or any company/institution acting on their behalf), or produced during the clinical trial, including, but not limited to, the clinical trial protocol, personal data in relation to the patients, the CRFs, the Investigator's Brochure and the results obtained during the course of the clinical trial, is confidential, prior to the publication of results. The Investigator and any person under his/her authority agree to undertake to keep confidential and not to disclose the information to any third party without the prior written approval of the Sponsor.

However, the submission of this clinical trial protocol and other necessary documentation to the Ethics committee (IRB/IEC) is expressly permitted, the IRB/IEC members having the same obligation of confidentiality.

The Subinvestigators shall be bound by the same obligation as the Investigator. The Investigator shall inform the Subinvestigators of the confidential nature of the clinical trial.

The Investigator and the Subinvestigators shall use the information solely for the purposes of the clinical trial, to the exclusion of any use for their own or for a third party's account.

14.4 PROPERTY RIGHTS

All information, documents and IMP provided by the Sponsor or its designee are and remain the sole property of the Sponsor.

The Investigator shall not and shall cause the delegated Investigator staff /Subinvestigator not to mention any information or the Product in any application for a patent or for any other intellectual property rights.

All the results, data, documents and inventions, which arise directly or indirectly from the clinical trial in any form, shall be the immediate and exclusive property of the Sponsor.

The Sponsor may use or exploit all the results at its own discretion, without any limitation to its property right (territory, field, continuance). The Sponsor shall be under no obligation to patent, develop, market or otherwise use the results of the clinical trial.

As the case may be, the Investigator and/or the Subinvestigators shall provide all assistance required by the Sponsor, at the Sponsor's expense, for obtaining and defending any patent, including signature of legal documents.

14.5 DATA PROTECTION

- The patient's personal data, which are included in the Sponsor database shall be treated in compliance with all applicable laws and regulations;
- When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.
- The Sponsor also collects specific data regarding Investigator as well as personal data from any person involved in the study which may be included in the Sponsor’s databases, shall be treated by both the Sponsor and the Investigator in compliance with all applicable laws and regulations.

Subject race or ethnicity will be collected in this study because these data are required by several regulatory authorities (eg, on Afro-American population for FDA, on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China).

Analyses of subject genetic data will be conducted as described in the protocol as this is needed for pharmacogenetics analyses required for the purpose of the study or by regulatory authorities.

The data collected in this study will only be used for the purpose(s) of the study and to document the evaluation of the benefit/ risk ratio, efficacy and safety of the product(s). They may be further processed if they have been anonymized.

14.6 INSURANCE COMPENSATION

The Sponsor certifies that it has taken out a liability insurance policy covering all clinical trials under its sponsorship. This insurance policy is in accordance with local laws and requirements. The insurance of the Sponsor does not relieve the Investigator and the collaborators from any obligation to maintain their own liability insurance policy. An insurance certificate will be provided to the IECs/IRBs or regulatory authorities in countries requiring this document.

14.7 SPONSOR AUDITS AND INSPECTIONS BY REGULATORY AGENCIES

For the purpose of ensuring compliance with the clinical trial protocol, Good Clinical Practice and applicable regulatory requirements, the Investigator should permit auditing by or on the behalf of the Sponsor and inspection by regulatory authorities.

The Investigator agrees to allow the auditors/inspectors to have direct access to his/her study records for review, being understood that these personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The Investigator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

As soon as the Investigator is notified of a planned inspection by the authorities, he will inform the Sponsor and authorize the Sponsor to participate in this inspection.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the regulatory authorities will be immediately communicated by the Investigator to the Sponsor.

The Investigator shall take appropriate measures required by the Sponsor to take corrective actions for all problems found during the audit or inspections.

14.8 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

14.8.1 By the Sponsor

The Sponsor has the right to terminate the participation of either an individual site or the study at any time, for any reason, including but not limited to the following:

- The information on the product leads to doubt as to the benefit/risk ratio;
- Patient enrollment is unsatisfactory;

- The Investigator has received from the Sponsor all IMP, means and information necessary to perform the clinical trial and has not included any patient after a reasonable period of time mutually agreed upon;
- Non-compliance of the Investigator or Subinvestigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP;
- The total number of patients are included earlier than expected;

In any case the Sponsor will notify the Investigator of its decision by written notice.

14.8.2 By the Investigator

The Investigator may terminate his/her participation upon thirty (30) days' prior written notice if the study site or the Investigator for any reason becomes unable to perform or complete the clinical trial.

In the event of premature discontinuation of the study or premature close-out of a site, for any reason whatsoever, the appropriate IRB/IEC and regulatory authorities should be informed according to applicable regulatory requirements.

14.9 CLINICAL TRIAL RESULTS

The Sponsor will be responsible for preparing a clinical study report and to provide a summary of study results to the Investigator.

14.10 PUBLICATIONS AND COMMUNICATIONS

The Investigator undertakes not to make any publication or release pertaining to the study and/or results of the study prior to the Sponsor’s written consent, being understood that the Sponsor will not unreasonably withhold its approval.

As the study is being conducted at multiple sites, the Sponsor agrees that, consistent with scientific standards, a primary presentation or publication of the study results based on global study outcomes shall be sought. However, if no multicenter publication is submitted, underway or planned within twelve (12) months of the completion of this study at all sites, the Investigator shall have the right to publish or present independently the results of this study in agreement with other Investigators and stakeholders. The Investigator shall provide the Sponsor with a copy of any such presentation or publication for review and comment at least 30 days in advance of any presentation or submission for publication. In addition, if requested by the Sponsor, any presentation or submission for publication shall be delayed for a limited time, not to exceed 90 days, to allow for filing of a patent application or such other justified measures as the Sponsor deems appropriate to establish and preserve its proprietary rights.

The Investigator shall not use the name(s) of the Sponsor and/or its employees in advertising or promotional material or publication without the prior written consent of the Sponsor. The Sponsor

shall not use the name(s) of the Investigator and/or the collaborators in advertising or promotional material or publication without having received his/her and/or their prior written consent(s).

The Sponsor has the right at any time to publish the results of the study.

15 CLINICAL TRIAL PROTOCOL AMENDMENTS

All appendices attached hereto and referred to herein are made part of this clinical trial protocol.

The Investigator should not implement any deviation from, or changes of the clinical trial protocol without agreement by the Sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to clinical trial patients, or when the change(s) involves only logistical or administrative aspects of the trial. Any change agreed upon will be recorded in writing, the written amendment will be signed by the Investigator and by the Sponsor and the signed amendment will be filed with this clinical trial protocol.

Any amendment to the clinical trial protocol requires written approval/favorable opinion by the IRB/IEC prior to its implementation, unless there are overriding safety reasons.

In some instances, an amendment may require a change to the informed consent form. The Investigator must receive an IRB/IEC approval/favorable opinion concerning the revised informed consent form prior to implementation of the change and patient signature should be re-collected if necessary.

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QUEST - Summary of protocol amendments

No.	Date	Purpose of Amendments	Comment
1	10 April 2015	• Change to timing of chest imaging (Chest X-ray, CT, MRI) prior to screening for excluding patients with suspected active or untreated latent tuberculosis	Local-Japan
2	21 May 2015	• Added stratification on ICS dose (medium/high) • Reduced number of randomization strata for age, eosinophil count	Global
3	28 July 2015	• Added anaphylactic, acute systemic or acute allergic reaction requiring immediate treatment, diagnosis of malignancy during study, and selected laboratory abnormalities to criteria for permanent discontinuation of IMP • Removed irrelevant language for SAEs pertaining to cancer, chronic neurodegenerative disease • Clarified management of significant ALT increase as an AESI • Clarified AESI reporting requirements for anaphylactic, acute systemic or acute allergic reaction that require immediate treatment	Local-Germany
4	21 Sep 2015	• Changes to statistical analyses (see Table 5) • Split the biomarkers into 3 subgroups • Limited the vaccine category considered for evaluation • Clarified clinical handling of patients with missed dose(s) of IMP • Added hepatitis/HIV/ANA test at Visit 17 for patients who plan to participate in the open label extension (OLE) study; Added HBV DNA test for patients believed to be false positive for HBc Ab or if the HBV serological status is unclear and HCV RNA for patients believed to be false positive for HCV Ab at Visits 1 & 17 • Deleted the eligibility criteria regarding IMP compliance for OLE study • Modified exclusion criteria regarding hepatitis and tuberculosis • Modified exclusion criteria regarding washout period of live attenuated vaccinations • Deleted exclusion criteria on birth control for male subjects with a female partner of childbearing potential • Added lactate dehydrogenase & differentiation in conjugated and non-conjugated bilirubin in case of total bilirubin above normal into serum chemistry panel • Added post-bronchodilator FEV1 at Visit 2 • Clarified spirometry operation requirement • Removed table of handling procedures for dupilumab and ADA	Global

		• Clarified difference between withdrawal from IMP and withdrawal from the study and how this should be documented • Incorporated local amendments 1 and 3 into global protocol • Additional minor changes to grammar, vocabulary, spelling, etc. • Removed lower limit of pre-bronchodilator FEV1 in inclusion criteria for all patients and revise the upper limit of pre-bronchodilator FEV1 in inclusion criteria for adolescents to decrease screening failure rate and to adapt the criterion to adolescent values of pre-bronchodilator FEV1	
5	23 Oct 2015	• Allowed German sites to do chest MRI in lieu of the chest X-ray for those patients who do not have a chest imaging within the previous year from Visit 1	Local-Germany
6	15 Dec 2015	• Detailed required duration of contraception	Local-France
7	9 Aug 2016	• Changed criteria for AESI • Simplification of study procedures for patients who permanently discontinued the study • Changed sampling times of ADA, added ADA response definitions • Modification of sample size and planned database lock date (see also Table 5) • Addition of loading dose analysis (see also Table 5) • Clarification of the recognized controller classes • Clarification to temporary and permanent treatment discontinuation criteria • Clarification of hepatitis serology testing and interpretation of the results in context of eligibility criteria • Introduction of chest X-Ray or MRI (MRI for Germany only) at Visit 17 for patients who plan to participate in the OLE study and if available chest imaging is over 12 months from entry into the open label extension study • Addition of height measurement for adolescents at each site visit for accurate calculation of spirometry parameters when doing spirometry • Incorporation of local amendments 5 and 6 into global protocol • To fix error regarding study committees implemented at project and study level which include data monitoring committee and executive advisory committee • Additional minor changes to grammar, vocabulary, spelling, etc	Global
8	26 May 2017	• Modification of wording referring to the sample size	Global

STATISTICAL ANALYSIS PLAN

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5	Asthma Control Questionnaire 5-question version
ACQ-7	Asthma Control Questionnaire 7-question version
AD	Atopic dermatitis
ADA	Anti-drug Antibodies
AE	Adverse Event
AEPM	Adverse Event with Prespecified Monitoring
AESI	Adverse Event of Special Interest
ALT	Alanine Aminotransferase
ANA	Antinuclear Antibodies
ATS	American Thoracic Society
AQLQ(S)	Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥ 12 years)
BCG	Bacillus Calmette-Guérin
CDMS	Clinical Data Management System
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRFs	Case Report Forms
CPK	Creatine phosphokinase
CV	Curriculum Vitae
CV%	Coefficient of Variation
CYP	Cytochrome P450
CT	Computed Tomography
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DPI	Dry Powder Inhaler
DRF	Discrepancy Resolution Form
ECG	Electrocardiography
ECP	Eosinophil Cationic Protein
e-CRF	Electronic Case Report Form

(electronic 1.0)

ERS	European Respiratory Society
EQ-5D-5L	EuroQoL Working Group Health Status Measure 5 Dimensions, 5 Levels
EOS	End-of-Study
EOT	End-of-Treatment
FEF	Forced expiratory flow
FENO	Fractional Exhaled Nitric Oxide
FEV1	Forced Expiratory Volume in one second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GINA	Global Initiative for Asthma
GSO	Global Safety Officer
HADS	Hospital Anxiety and Depression Scale
HADS-A	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D	Hospital Anxiety and Depression Scale- Depression subscale
HBc Ab	Hepatitis B Core Antibody
HBs Ab	Hepatitis B Surface antibody
HBs Ag	Hepatitis B Surface Antigen
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HCV Ab	Hepatitis C Virus Antibody
HFA	Hydrofluoroalkane
HLGT	High-Level Group Term
HLT	High Level Term
HIV	Human Immunodeficiency Virus
HRQoL	Health related quality of life
ICH	International Conference on Harmonization
ICS	Inhaled Corticosteroid
ID	De-identification Code
IgE	Immunoglobulin E
IgG	Immunoglobulin G
IL-4	Interleukin 4

IL-4Rα	Interleukin 4 Receptor Alpha Subunit
IL-13	Interleukin 13
IMP	Investigational Medicinal Product
IRB/IEC	Institutional Review Board / Institutional Ethics Committee
IRT	Interactive Response Technologies
IVRS/IWRS	Interactive Voice Response System/Interactive Web Response System
IUD	Intrauterine Device
IUS	Intrauterine System
ITT	Intent-To-Treat
K-M	Kaplan-Meier
LABA	Long-Acting Beta Agonist
LAMA	Long-Acting Muscarinic Antagonist
LFT	Liver Function Test
LLQ	Lower limit of quantitation
LOAC	Loss Of Asthma Control
LTRA	Leukotriene receptor antagonist
MCID	Minimal Clinically Important Difference
MDI	Metered Dose Inhaler
MID	Minimal Important Difference
MMR	Measles, Mumps, Rubella
MMRM	Mixed-effect Model with Repeated Measures
MMRV	Measles, Mumps, Rubella, Varicella
MRI	Magnetic Resonance Imaging
NSAID	Nonsteroidal Anti-inflammatory Drug
NIMP	Noninvestigational Medicinal Product
NRS	Numerical Rating Scale
OLE	Open label extension
PCSA	Potentially Clinically Significant Abnormalities
PD	Pharmacodynamics
PEF	Peak Expiratory Flow
PK	Pharmacokinetics

Pop	Population
PROs	Patient-Reported Outcomes
PT	Preferred Term
Pre-bronchodilator	Pre-BD
RNA	Ribonucleic Acid
RQLQ(S)+12	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SAE	Serious Adverse Event
SEM	Standard Error of the Mean
SC	Subcutaneously
SD	Standard Deviation
SNOT-22	Sinonasal Outcomes Test 22-item scale
SOC	System Organ Class
SUSARs	Suspected Unexpected Serious Adverse Reactions
TARC	Thymus and Activation-Regulated Chemokine
TE	Treatment-Emergent
TEAE	Treatment-Emergent Adverse Event
Th2	Type 2 T-helper cell
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WBC	White Blood Cell

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

EFC13579 is a Multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. Both the patient and investigator will be blinded to assigned active drug or matching placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

After a screening phase of 4±1 weeks, patients will be centrally randomized using permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 2:2:1:1 randomization ratio for dupilumab 300 mg q2w, dupilumab 200 mg q2w, placebo q2w in 2 mL and placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, central eosinophil count (<300 cells/μL, ≥300 cells/μL) at screening, ICS dose level (medium, high) and country.

At least 1638 patients, including approximately 84 adolescent patients, will be randomized to dupilumab or placebo, with at least 690 patients with a baseline blood eosinophil count ≥300 cells/μL (0.3 giga/L). Recruitment for patients on medium dose of ICS will be stopped at approximately 819 to ensure at least 50% patients are on high dose of ICS.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy of dupilumab in patients with persistent asthma.

1.2.2 Secondary objectives

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab on improving PROs including HRQoL
- To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

1.2.3 Exploratory objectives

- To explore the association of biomarkers with treatment response
- To explore the association of genetic profiles with treatment response
- To explore the association of vaccine response with treatment

1.3 DETERMINATION OF SAMPLE SIZE

The sample size calculation of this study was based on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe exacerbations during the 52-week treatment period, and absolute change from baseline in FEV1 at Week 12. Assuming the number of severe exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline eosinophil count ≥300 cells/μL (0.3 giga/L), approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for this subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients (546 for each dupilumab dose and 273 for each matching placebo group) will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline eosinophil count ≥300 cells/ /μL (0.3 giga/L). The overall study recruitment will continue until at least 1638 patients in total and 690 patients with eosinophils ≥300 cells/μL (0.3 giga/L) are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84 adolescent patients will be randomized.

1.4 STUDY PLAN

The clinical trial consists of three periods:

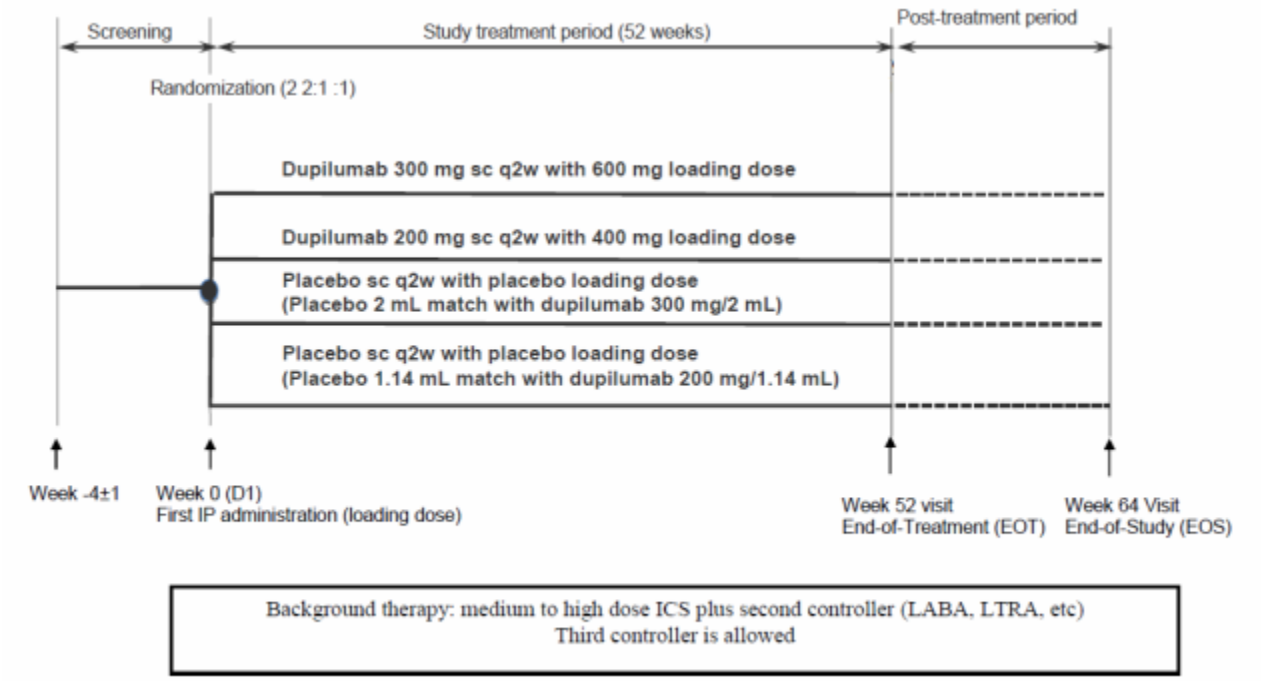
Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization.

Treatment Period (52 weeks): treat with dupilumab or placebo SC injection.

Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study.

1.4.1 Graphic study design

Please refer of Section 1.2 of the study protocol for the detailed study flow chart.



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled). These changes are not based on any unblinded study data.

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section. "Principal features of the analysis" encompass the confirmatory aspects of the trial, including the primary and key secondary endpoints/analyses, and the analysis populations associated with these analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	21-May-2015	To address the feedback from European health authority (EMA) on stratification for patients on medium and high doses of ICS to ensure that the benefit/risk is positive for both asthma populations.	The following text: Randomization will be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/μL, 150 – 299 cells/μL, and ≥300 cells/μL) at screening and country. Was replaced with:

Amendment Number	Date Approved	Rationale	Description of statistical changes
			Randomization will be stratified by age (<18 years, ~~18-64 years, ≥65 years~~≥18 years), central eosinophil count (~~<150 cells/ µL, 150 – 299 cells/ µL, and~~ <300 cells/µL, ≥300 cells/ µL) at screening, ICS dose level (medium, high) and country.
4	21-Sep-2015	To address the feedback from European health authority (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) not to pool the placebo arms	The following text was deleted: ~~The two placebo groups will be compared for the two primary efficacy endpoints: annualized rate of severe exacerbation events during the 52 weeks, and absolute change from baseline in FEV1 at Week 12. If they are similar for both endpoints based on the predefined criteria, the two placebo groups will be pooled together and all efficacy analyses will be performed with the pooled placebo group. The criteria to determine if the two placebo groups are similar will be specified in the SAP prior to database lock.~~
4	21-Sep-2015	To further meet the recommendation from EMA on stratification for patients on medium and high dose ICS to ensure that the benefit/risk is positive for both asthma populations, in addition to the added stratification factor of ICS dose level (medium, high).	The following text was added: The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to control overall type I error rate at a 2-sided alpha of 0.05.	The following text was deleted: ~~The secondary endpoints will be tested follow the predefined hierarchical order for the dose that meets the statistical significance for both primary endpoints: annualized event rate of severe exacerbation and absolute change from baseline in FEV1 at Week 12.~~ ~~The primary family error rate will be controlled at 2-sided 5% level for 2 primary endpoints and 2 doses. The family error rate will be controlled at 2-sided 5% level for primary and secondary endpoints within the dose group. The overall family error rate will be controlled at 1-sided 5% level for all endpoints across dose groups.~~ The following text was added: If both doses are significant for both primary

(electronic 1.0)

Amendment Number	Date Approved	Rationale	Description of statistical changes
			endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The first four tests will be 1) % change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo 2) absolute change from baseline in AQLQ global score at Week 12 for 300 mg q2w versus placebo 3) % change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo, 4) absolute change from baseline in AQLQ global score at Week 12 for 200 mg q2w versus placebo. The remaining list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to include treated but not randomized patients in the safety population	The following text: The analysis population for the safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received. Was replaced with: The analysis population for the safety endpoints will be the safety population, defined as all ~~randomized~~ patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarizes major changes in statistical analysis features made in approved SAP versions from statistical considerations in protocol or previous SAP versions, with emphasis on

changes after study start (after the first patient was enrolled). These changes are not based on any unblinded study data.

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	This version	Expand the multiplicity control procedure for additional secondary endpoints, sub-populations.	The testing order of secondary endpoints was expanded from protocol, and the complete list of endpoints to be tested in the hierarchical order was specified in Table 5
1	This version	To be aligned with ongoing protocol amendment 07	Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided.
1	This version	To meet the request from FDA to assess any potential confounding effects of the loading dose on efficacy.	Sensitivity analyses were added to examine if the treatment effect of dupilumab is sustained throughout the 52-week treatment period or if there is any confounding effect of the use of the loading dose resulting in a larger treatment effect in the early part of the study. Annualized rates of severe exacerbation will also be analyzed versus placebo excluding efficacy data obtained during the first 4 weeks and 12 weeks of treatment of dupilumab/placebo respectively.
1	This version	To meet the request from FDA to compare patients who receive only [redacted]-derived dupilumab to those who receive only [redacted]-derived dupilumab, and to include a reasonable number of patients treated with only the [redacted] derived dupilumab	In order to have a reasonable number of patients treated with only the [redacted] derived dupilumab, additional patients may be randomized in addition to the originally planned samples size (1638). The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.

(electronic 1.0)

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value of efficacy parameters is defined as the last available value up to randomization but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP). The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the patient is treated, or the last available value up to randomization if the patient is not exposed to IMP.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the post-baseline summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are

Gender (Male, Female),

Race (Caucasian/white, Black/of African descent, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)

Age in years (quantitative and qualitative variable : <18, 18-64, 65–74, 75-84, and ≥85 years)

Ethnicity (Hispanic, non-Hispanic)

Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia, Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)

Weight in kg (quantitative and qualitative variable : <50, 50-<100 and ≥100 kg)

BMI in kg/m^2 (quantitative and qualitative variable: <30, ≥30 kg/m^2)

Medical or surgical history
Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the patient.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Comorbidity history will be summarized separately. The following comorbid diseases will be summarized.

Atopic dermatitis history (Yes, Ongoing condition)

Allergic conjunctivitis history (Yes, Ongoing condition)

Allergic rhinitis history (Yes, Ongoing condition)

Allergic conjunctivitis and/or rhinitis history (Yes, Ongoing condition)

Chronic rhinosinusitis history (Yes, Ongoing condition)

Nasal polyposis history (Yes, Ongoing condition)

Eosinophillic esophagitis history (Yes, Ongoing condition)

Food allergy history (Yes, Ongoing condition)

Hives history (Yes, Ongoing condition)

A patient is considered to have atopic medical condition if he/she has any of the following: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least one aeroantigen specific IgE is positive (≥0.35 IU/mL) at baseline.

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by treatment group separately:

- ICS dose level (medium, high as defined in Appendix C)
- Age of asthma onset
- Time since first diagnosis of asthma (years)
- Smoking history (Never, Former*), time since cessation of smoking (months) and smoking quantity in pack-years for former smokers

  * *Current smokers are excluded from this study.*
- Alcohol drinking frequency (Never, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 OR 2, >2)
- Time since last severe asthma exacerbation (months)
- Number of severe asthma exacerbation experienced within1 year before Visit 1 (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Eosinophil stratum at randomization (<0.3, ≥0.3 Giga/L)
- Baseline spirometry data including pre-bronchodilator FEV1 (L), percent predicted FEV1, post-bronchodilator FEV1 (L) and FEV1 reversibility (%).
- AM and PM PEF (L/min)
- AM and PM symptom scores

- Number of nocturnal awakenings/day
- ACQ-5 score
- ACQ-7 score
- AQLQ global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin (Yes, Ongoing condition)
- Hypersensitivity to NSAID (Yes, Ongoing condition)

Severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma. Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 30 days before screening and until the end of the study, including asthma controller medications, systemic corticosteroids are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 98 days or till rollover to the LTS12551 study. A given medication can be classified as a prior medication, concomitant medication and posttreatment medication at the same time.
- Posttreatment medications are those the patient took in the period from the last administration of IMP + 99 days to the end of the study

2.1.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination or concurrently with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor, but the sponsor will reimburse investigators for patients' use of controller drugs in the study to ensure all patients have access to their controllers.

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged

18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months with a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months with a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix C. The minimum daily dose of fluticasone propionate is 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equal to the upper limit of medium daily dose for fluticasone propionate as instructed in Appendix C. For ICS other than fluticasone propionate, please refer to the table in Appendix C which indicates the upper limit of the medium daily dose for each ICS which is equivalent to 500 mcg/day of fluticasone propionate. A list of recognized controller medications is provided in Appendix B. Number of controllers taken by each patient will be counted by therapeutic drug class. All drugs in a therapeutic class will be only counted once.

During the randomized treatment period, patient will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed. Only a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance.

Upon completing the randomized treatment period or 52-week observation period, patients not continuing with the open label extension will proceed to be treated with the controller medication regimen and dose used during the randomized treatment period, which could be adjusted based on the medical judgment of the investigator of the patients' asthma control status.

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to number of puffs as shown on the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs

Example of salbutamol/albuterol Nebulizer-to-Puff Conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg ->12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4
2.5	8
3.75	12
5	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs

Example of levosalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg ->12 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints is defined as the last non-missing value up to randomization but prior to the administration of the first IMP unless otherwise specified.

2.1.3.1 Primary efficacy endpoint(s)

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV1 at week 12.

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

Two events are considered as different if the start dates are separated by at least 4 weeks.

The annualized rate of severe exacerbation events during the 52-week treatment period is defined as the number of severe exacerbation events with onset during the 52-week treatment period per patient-year. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment severe exacerbation events up to Visit 18(Week 52) will be included.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary endpoint

The key secondary endpoint of this study is percent change from baseline in pre-bronchodilator FEV1 at Week 12.

2.1.3.2.2 Other secondary efficacy endpoints

The other secondary efficacy endpoints include:

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced

expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52

- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period
- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 4, 8, 12, 24, 36, and 52
- Change from baseline in PROs at Week 12, 24, 36, and 52:
  - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
  - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
  - Hospital Anxiety and Depression Scale (HADS)
  - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis
  - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

Endpoints to be formally tested with multiplicity adjustments are listed in the testing order in Section 2.4.4.3 and Table 5.

2.1.3.2.2.1 Annualized rate of loss of asthma control (LOAC) event

LOAC event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days or
- ≥20% decrease in pre-bronchodilator FEV_1 compared to baseline or
- Increase in ICS dose ≥4 times than the dose at Visit 2 or

- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1); or
- Severe exacerbation event

The annualized rate of LOAC events during the 52-week treatment period is defined as the number of LOAC events with onset during the 52-week treatment period per patient-year.

2.1.3.2.2.2 Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit

Annualized rate of severe exacerbation event requiring hospitalization or emergency room visit (requiring systemic corticosteroids) during the 52-week treatment period will also be analyzed.

2.1.3.2.2.3 Time to first severe exacerbation event/first LOAC event

If a patient has an event during the 52-week treatment period, regardless the patient is on the study treatment or discontinues the study treatment but remains in the study, the time to first severe exacerbation event/first LOAC event is defined as (onset date of the first severe exacerbation/LOAC event – randomization date +1).

If a patient has no severe exacerbation event/LOAC event during the study up to Visit 18/Week 52, then the patient will be considered as free of event till the date of visit at Visit 18 or the last contact date, whichever happens earlier.

2.1.3.2.2.4 Disease-specific efficacy measures

2.1.3.2.2.4.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (1). For pre-bronchodilator measured parameters, including FEV1, PEF, FVC and FEF 25-75%, spirometry will be performed after a wash out period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

At least three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded. The largest FEV1 and largest FVC will be recorded after the data are

examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

Japanese Respiratory Society predicted set are used for Japanese patients to calculated percent predicted FEV1 and NHANES III predicted set for all other patients.

2.1.3.2.2.4.2 Reversibility

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. FEV1 reversibility is calculated as Post-BD FEV1 - Pre-BD FEV1 and percent FEV1 reversibility is calculated as (Post-BD FEV1 - Pre-BD FEV1) / Pre-BD FEV1 * 100.

2.1.3.2.2.4.3 Post-bronchodilator FEV1

Post-bronchodialtor FEV1 is obtained from the spirometry performed after administration of reliever medications for reversibility test. The largest FEV1 will be recorded after the data are examined from all of the acceptable curves.

2.1.3.2.2.4.4 ACQ (Asthma Control Questionnaire)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

2.1.3.2.2.4.4.1 ACQ-7 (Asthma Control Questionnaire, 7-question version)

The ACQ-7 has 7 questions- the first 5 items assess the most common asthma symptoms: 1. frequency in past week awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma and 5. wheeze, plus 6. short-acting bronchodilator use and 7. FEV1 (pre-bronchodilator use, % and % predicted use). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment) (see Appendix E).

Clinic staff scores the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

A global score is calculated: the questions are equally weighted and the ACQ-7 score is the mean of the 7 questions and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled).

Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-7, a change or difference in score of 0.5 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ (2), any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be interpolated (pro-rated) using the completed questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 2, and all questions are completed at Visit 1. Then the question 5 score at Visit 2 is interpolated as: (sum of score at Visit 2/sum of scores excluding question 5 at Visit 1) × score of question 5 at Visit 1. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

2.1.3.2.2.4.4.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions of ACQ-7 and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). The last two questions assessing lung functions are not included in ACQ-5. Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Missing scores will be handled in the same way as for ACQ-7 score.

2.1.3.2.2.5 Disease-specific, daily efficacy assessment

On a daily basis throughout the study, the patient uses an electronic diary / PEF meter to:

- Measure morning and evening PEF
- Respond to the morning and evening asthma symptom scale questions
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the number of nocturnal awakenings due to asthma symptoms

2.1.3.2.2.5.1 Morning (AM) and Evening (PM) Peak expiratory flow (PEF)

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be

provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 10 AM) prior to taking any albuterol or levalbuterol
- PM PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any albuterol or levalbuterol
- Patients should try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM PEF will be the mean AM measurement recorded in the 7 days prior to randomization including the morning diary completed on the randomization day prior to the first administration of IMP, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the randomization. There should be at least 4 days' measurement out of the 7 days for setting up the period stability limit/baseline, and the first dosing visit should be rescheduled until data for 4 days are available. In case less than 4 days' measurement is available during the 7 days prior to randomization, the baseline AM/PM PEF is the mean of the 4 AM/PM PEF prior to and closest to randomization during the whole screening period. Calculation of periodical average of post-baseline AM/PM PEF is specified in Section 2.5.2.

2.1.3.2.2.5.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Symptoms experienced during the night will be recorded upon arising (AM symptom score). The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. Calculation of periodical average of post-baseline AM/PM symptom score is specified in Section 2.5.2.

2.1.3.2.2.5.3 Use of rescue/reliever medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in an electronic diary/PEF meter. In the case that Nebulizer solutions are used as an alternative delivery method, the nebulizer dose will be converted to number of puffs according to Section 2.1.2.2. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The baseline reliever med use will be calculated as follows: The mean of reliever puffs taken in each of the 7 diary days (minimum 4 diary days) prior to

randomization, including the diary day that ends with the morning diary completed on the randomization day. A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing for that diary day. Out of the 7 diary days, if less than 4 are incomplete, the baseline reliever use is the mean of reliever puffs in each of the complete dairy days. If 4 or more diary days are incomplete, the baseline reliever use is the mean of reliever puffs taken in the closest 4 diary days with complete reliever use information prior to randomization. Calculation of periodical average of post-baseline use of reliever puffs is specified in Section 2.5.2.

2.1.3.2.2.6 Patient-reported outcomes

2.1.3.2.2.6.1 Asthma Quality of Life Questionnaire) Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)

The AQLQ (S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to adolescents and adults ≥12 years of age as a result of their asthma (see Appendix G). The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

Individual items are equally weighted. The overall score is the mean of response to each of the 32 questions. The score of each domain is the mean of response to each of the questions in that domain. The overall score and domain scores ranges from 1 to 7. Higher scores indicate better quality of life.

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms and activity limitation domain score, only one missing value per domain is acceptable. For the emotional function and environmental stimuli domain scores, no missing value is acceptable. For responses with more than acceptable amount of missing value(s), the overall or the domain score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The patient level MCID for AQLQ(S) is 0.5 (3).

2.1.3.2.2.6.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis and/or chronic rhinosinusitis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis with or without nasal polyposis on health-related quality of life (see Appendix H). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30), Ear (range 0-15), Sleep (0-20), General and Practical (0-30), and Emotional (0-15). The range of the global score is 0-110. Lower scores indicate less impact and the recall period is past 2 weeks. The domains and the items in each domain are as follows:

- Nasal: item 2, 3, 4, 6, 7, 12
- Ear: item 8, 9, 10
- Sleep: item 13, 14, 15, 16
- General and Practical: item 1, 5, 11, 17, 18, 19
- Emotional: item 20, 21, 22

The global score is the sum of response to each of the 22 questions. For responses with some item scores are missing, the global score will be imputed as mean of the completed scores× 22, providing at least 50% of items have been completed. If more than 50% of items are missing, the global score is set to missing. The score for each domain is the sum of response to each question in that domain. Missing score will be imputed as mean of the completed items in that domain× total number of items in that domain, providing at least 50% of items in that domain have been completed. If more than 50% of items in a domain are missing, the score for that domain is set to missing.

2.1.3.2.2.6.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix I). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3. The anxiety/depression score is the sum of the scores of the 7 related items; one can score between 0 and 21 for either anxiety or depression. And the total score is the sum of the scores of the 14 items ranging from 0-42.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (4).

2.1.3.2.2.6.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (5). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system and the EQ VAS (see Appendix J). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L health status will be converted into a single index value by using EQ-5D-5L value sets based on UK population. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

2.1.3.2.2.6.5 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix K) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-nose/eye Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 6. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within the RQLQ(S)+12 are equally weighted. The overall score is calculated as the mean score of all items. And the score for each domain is calculated as the mean score of the items in each of the domains. No interpolation will be performed for missing scores. Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (6).

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG and physical examination.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the time prior to first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days or till rollover to the LTS12551 study.

- The **residual treatment** epoch is defined as the time from the last administration of the IMP +15 days to the last administration of the IMP + 98 days or till rollover to the LTS12551 study.
- The treatment-emergent adverse event period will include both **treatment** and **residual treatment** epochs.
- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

All adverse events (including serious adverse events and adverse events with pre-specified monitoring/of special interests) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events with pre-specified monitoring/of special interests include the following terms:

AESIs reported by the investigator in CRF based on the protocol instruction

- Anaphylactic reactions, acute systemic allergic reactions or acute allergic reactions that require immediate treatment (refer to Appendix M for Definition of Anaphylaxis)
- Severe injection site reactions that last longer than 24 hours
- Severe infections, any serious infection, any bacterial infection requiring treatment with parenteral antibiotics for longer than 2 weeks, any parasitic infection, any systemic opportunistic infection (see Appendix N) , any viral infection requiring antiviral treatment (except when medications are only administered topically), or any uncommon, atypical, or unusually frequent or persistent infection and Tuberculosis that requires anti-tuberculosis medication.

Note: Candidiasis - all cases should be collected as AEs (or SAEs if requirements met), however, only cases which are systemic or diffuse/non-localized, will be considered as AESI.

- Significant ALT elevation

  - ALT >5 x the upper limit of normal (ULN) in patients with baseline ALT ≤ 2 x ULN;

  Or

  - ALT >8 x ULN if baseline ALT >2 x ULN

- Pregnancy of a female subject entered in a study as well as pregnancy occurring in a female partner of a male subject entered in a study with IMP/Non-investigational medicinal product (NIMP);
  - Pregnancy occurring in a female patient entered in the clinical trial or in a female partner of a male patient entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria.
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined.
- Symptomatic overdose (serious or non-serious) with IMP/NIMP
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice the intended dose during an interval of less than 11 days. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate adverse event forms.
  - An overdose (accidental or intentional) with any NIMP is an event suspected by the Investigator or spontaneously notified by the patient and defined as at least twice of the intended dose within the intended therapeutic interval. The circumstances (ie, accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
- Of note, asymptomatic overdose has to be reported as a standard AE.

In addition,

- Anaphylactic reactions will also be identified as
  - SMQ anaphylactic reaction (20000021) narrow search
- Hypersensitivity reactions will be identified as
  - SMQ hypersensitivity (20000214) narrow search, and confirmed by blinded medical review.
- Injection site reactions will be identified as AE with HLT as injection site reaction
- Serious injection site reactions or severe injection site reactions that last longer than 24 hours will be identified as AE with HLT as injection site reaction and

  - with serious status or
  - with severe status and (AE end date –AE start date) ≥1 or ongoing
- Severe or serious infections will also be identified as
  - AE with Primary SOC as infections and infestations and severe or serious status
- Parasitic infections will also be identified as AE with following primary HLGTs,
  - Helminthic disorders
  - Protozoal infectious disorders

  And also as AE with following PTs:
  - Amoeba test positive
  - Giardia test positive
  - Infection parasitic
  - Malaria antibody test positive
  - Parasitic oesophagitis
  - Parasitic encephalitis
  - Parasitic gastroenteritis
  - Parasitic test positive
  - Parasite DNA test positive
  - Parasite stool test positive
  - Parasite urine test positive
  - Parasite blood test positive
  - Parasite tissue specimen test positive
  - Parasite cervical specimen test positive
  - Schistosoma test positive
  - Toxoplasma serology positive
  - Trypanosoma serology positive
- Pregnancy will be also identified as AE with PT in Appendix O
- Suicidal behaviors will be identified as AE with PT:
  - Suicidal ideation
  - Suicide attempt
  - Completed suicide
  - Depression suicidal
  - Suicidal behavior

- Hepatic disorders will be identified as SMQ drug-related hepatic disorders – comprehensive search (20000006) narrow search

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death poststudy: deaths occurring after the end of the study

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in listings and tables. The same set of analysis will also be prepared in US units.

Blood samples for clinical laboratories will be taken at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64) and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, blood urea nitrogen, uric acid
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin
  - **Pregnancy test**: serum β-human chorionic gonadotropin (all female patients) will be performed at screening (Visit 1) in women of childbearing potential

- **Hepatitis screen**: clinical laboratory testing at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study) add hepatitis screen including hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.
- **Hepatitis B viral load** will be tested at Visit 2, then every 12 weeks until Visit 14 and end of treatment period for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
- **HIV screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)
- **Anti-nuclear antibody (ANA)** will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)

  Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

- Serum immunoglobulins (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.

Urine samples will be collected as follows:

- **Urinalysis** (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): Urine dipstick analysis specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- A **urine dipstick pregnancy test** will be performed at Visit 2 prior to randomization and Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52),Visit 21(Week 64)

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) for all patients and will be measured

throughout the study for adolescent patients. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

2.1.4.5 Electrocardiogram variables

One recording of a standard 12-lead ECG will be performed centrally at Visit 1(Week -4±1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64). At the post-randomization visits, ECGs will be performed prior to investigational product administration. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visit 1(Week -4±1), Visit 11 (Week 24), Visit 18(Week 52), and Visit 21 (Week 64) including an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease.

Refer to Section 1.2 Study Flow Chart for the schedule of physical examination performed throughout this study.

2.1.5 Pharmacokinetic variables

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52 and follow-up serum dupilumab at Week 56, Week 60, Week 64 will be provided.

Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided. Patients who discontinue early from treatment or patients who choose not to participate in the OLE study visit may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

ADA incidence will be classified as the following:

Pre-existing anti-drug antibodies are defined as:

An ADA positive response in the assay at baseline with all post treatment ADA results negative, OR an ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

Treatment-emergent anti-drug antibodies are defined as:

A positive response in the ADA assay post first dose, when baseline results are negative or missing.

Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient

a) Persistent Response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.

b) Indeterminate Response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay

c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

Treatment-boosted anti-drug antibodies are defined as:

A positive response in the ADA assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Titer values (Titer value category)

- Low (Titer < 1000)
- Moderate (1,000 ≤ Titer ≤ 10,000)
- High (Titer > 10,000)

2.1.6 Pharmacodynamics/genomics endpoints

Eotaxin-3, eosinophil cationic protein (ECP), total IgE and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at Visit 2(Week 0), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36) and Visit 18(Week 52).

Periostin will be assayed at Visit 2(Week 0), Visit 4 (Week 4), Visit 8 (Week 12) and Visit 18(Week 52). And antigen-specific IgE panels will be collected at Visit 2(Week 0), Visit 8 (Week 12), Visit 14 (Week 36) and Visit 18(Week 52).

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

Exhaled nitric oxide will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 3 (Week 2),Visit 4 (Week 4), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 14 (Week 36), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64)

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling. For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the study flow chart, and these samples will be stored for future analysis.

2.1.7 Vaccine response

Subjects planning to receive vaccinations for tetanus (alone or combined), influenza, pneumococcus or meningococcus during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

2.1.8 Health economic endpoints

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients

- Randomized and treated patients
- Patients who did not complete the 52-week treatment as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study prior to Week 52
- Patients who withdraw from study prior to Week 52 by main reason for study discontinuation.
- Patients who withdraw from study
- Patients who withdraw from study by main reason for study discontinuation
- Status at last study contact

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. This summary will be provided by treatment group and may also be further subgrouped by region/stratum as applicable.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, efficacy populations will be summarized by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population

The analysis populations for safety, pharmacokinetics/pharmacodynamics will be summarized by number of patents on the safety population.

- Safety population
- PK population
- ADA population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

1. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

2. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available
Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined in Section 2.3.1.1

2.3.1.1 Intent–to-treat population

The intent-to-treat population is the randomized population analyzed according to the treatment group allocated by randomization.

Patients will be analyzed in the treatment group to which they are randomized.

2.3.2 Safety population

The safety population is defined as:

- All patients who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment patients actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.
- For patients on placebo but accidentally exposed to the other placebo dose, the treatment group allocation for as-treated analysis will be the treatment as randomized.
- For patients on dupilumab but accidentally receive different treatment from the planned, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.

2.3.3 Population for pharmacokinetics/pharmacodynamics analyses

The **PK population** will consist of all patients in the safety population with at least one evaluable serum concentration data. Patients will be analyzed according to the treatment actually received.

ADA population will consist of all patients in the safety population who had at least one reportable ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment.

Biomarkers will be analyzed in the **exposed population**, consisting of patients in the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each treatment group. Categorical and

ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by treatment group and by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall incidence across treatment groups. Atopic medical history will be summarized separately.

No statistical testing on demographic and baseline characteristic data will be performed.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received during first IMP to last IMP +14 days and concomitant medication received during first IMP to last IMP +98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab 300 q2w group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, inhaled corticosteroid in combination with other controllers and reliever medications will be summarized separately.

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor.

2.4.2.1 ICS in combination with other controllers

ICS and other asthma controller medications will be identified as the medications reported on the 'Prescribed Asthma Controller Medications' eCRF page.

Prior asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

Concomitant asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the dupilumab 300 q2w group.

The total daily dose of ICS in asthma controller medication at randomization will be classified as medium-dose or high-dose according to Appendix C. If a patient takes more than one medication containing ICS, the ICS dose of different products will be standardized according to equivalent dose specified in Table 3 and Table 4. The equivalent dose is determined based on the thresholds in Appendix C. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as medium or high dose.

Table 3 – Equivalent dose for inhaled corticosteroids for adults and adolescents (≥ 12 years)

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
BECLOMETASONE DIPROPIONATE (CFC)	1000
BECLOMETASONE DIPROPIONATE (HFA)	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler
Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

Table 4 – Equivalent dose of inhaled corticosteroid for adults and children (Japan)

Inhaled corticosteroid	Equivalent dose (mcg) to 400 Fluticasone propionate (DPI or HFA)
BECLOMETHASONE DIPROPIONATE -HFA	400
CICLESONIDE -HFA	400

Inhaled corticosteroid	Equivalent dose (mcg) to 400 Fluticasone propionate (DPI or HFA)
BUDESONIDE-DPI	800
BUDESONIDE INHALATION SUSPENSION	1.0 mg
BUDESONIDE INHALATION SOLUTION	1000
MOMETASONE FUROATE-DPI	400

Example: A patient received 400 mcg Beclomethasone dipropionate -HFA and 400 mcg Ciclesonide-HFA. They are both equivalent to 400 fluticasone propionate. The combined total daily dose is equivalent to 800 fluticasone propionate.

Number and percentage of patients on high-dose ICS, medium-dose ICS, any non-ICS controller medication, LABA, LAMA and LTRA at baseline will also be summarized.

2.4.2.1.1 Compliance

During the study, the daily intake of each prescribed asthma controller medication will be recorded on the electronic diary every evening. Compliance for the controller medications with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient. For each day, a patient is considered as compliant to the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. Similarly, a patient is considered as compliant to all controller medication if the actual dose of each controller medication is same as or greater than the prescribed dose.

Compliance for controller medication(s) with ICS component is defined as the number of days when the patient is compliant to the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from first dose to last dose + 14 days). **Overall controller medication(s) compliance** is defined as the number of days when the patient is compliant to all prescribed controller medication divided by the number of days the patient stays in the treatment period.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

>0 and ≤2 weeks

>2 and ≤4 weeks

>4 and ≤8 weeks

>8 and ≤12 weeks

>12 and ≤16 weeks

…

….

>48 and ≤52 weeks

>52 weeks

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Above-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% under-planned dose administrations.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 11 days) will constitute serious adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period is to assess the efficacy of dupilumab in an intention to treat setting. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment will be included for the analysis. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits. If a patient stays in study till the end of 52-week treatment period, all severe exacerbation events that happen up to Visit 18 will be included in the primary analysis, regardless if the patient is on-treatment or not. And the observation duration is defined as from randomization to Visit 18. If a patient withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. This estimand compares the rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the observation period defined above as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Treatment groups, region, baseline eosinophil strata and baseline ICS dose level will be treated as categorical variable. Age and number of severe exacerbation events within 1 year prior to the study will be treated as continuous variable. Severe asthma exacerbation event prior to the study is defined as treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once or hospitalization or

emergency medical care visit for worsening asthma (as defined in section Section 2.1.1). Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived from the negative binominal model. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence interval of the rate ratio based on the negative binomial model and its p-value will be provided.

Based on EMEA feedback, the rate difference between each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Sample SAS code can be found below:

```
proc glimmix data=event;
  class subjid eosblgpn ics trt01pn cntygr1n;
  model numevents=trt01pn age eosblgpn ics cntygr1n asmanum
                  /offset=logdur dist=negbin link=log solution;
run;
```

The gross estimated of annualized events rate will also be presented by each treatment group. Mean cumulative function plot will be provided for descriptive purpose.

Estimand of clinical efficacy of dupilumab versus placebo

An analysis to assess the efficacy of dupilumab if patients adhere to the treatment as directed is also specified. In this approach, off-treatment measurements of patients who prematurely discontinue treatment will be excluded from the analysis. A negative binomial model with the same set of covariates as specified in the primary analysis will be used. This model will include severe exacerbation events occurring during the treatment epoch as the response variable and the log transformed duration of the treatment epoch will be the offset variable. This approach defines the estimand to be the efficacy of dupilumab with treatment adherence (7).

Handling of missing data

If patients withdraw from the study before Visit 18 (Week 52), severe exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data on severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. Graphical summaries of the dropout patterns such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if there is any different missing pattern between treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model:

- *Pattern mixture model (PMM)*

For each patient with partial missing data of severe exacerbation events, the number of events that would be observed after study discontinuation up to Week 52 will be imputed on monthly basis as the mean number of the observed events that occur in patients who are on study during the missing observation period with adjustment of treatment discontinuation reasons, missing observation duration and treatment group.

- *Control-based PMM*

For each patient with partial missing data of severe exacerbation events, the number of events that would be observed after study discontinuation up to Week 52 will be imputed on monthly basis as the mean number of the observed events that occur among on-study patients in the matching placebo group during the missing observation period with adjustment of discontinuation reasons and missing observation duration.

- *Tipping point analysis*

For each patient with missing data of severe exacerbation events, the rate of event will be predicted using the main negative binomial model built with all observed data. If the patient is on dupilumab, the predicted rate will be increased; if the patient is on Placebo, the predicted rate will be decreased. The adjusted rate will then be used to impute the number of events would occur during the missing observation period. A sequence of increasing/decreasing ratio will be used to generate different imputed datasets.

For each of the above methods, a negative binomial model will be fitted using the complete dataset composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 18 (Week 52).

More details of the imputation and analyses methods are provided in Appendix D.

Subgroup analyses

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be performed for the annualized rate of severe exacerbation event during the 52-week treatment period by:

- Age group: < 18, 18-64, ≥ 65 years; < 18 , ≥ 18 years
- Gender (Male, Female)
- Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)

- Baseline blood eosinophil level (≥ 300 cells /μL, <300 cells /μL; ≥ 150 cells /μL, < 150 cells /μL)
- Background ICS dose levels at randomization (medium, high)
- Background controller type at randomization (patients who use LAMA, patients who do not use LAMA)
- Baseline FEV1 (≤ 1.75, > 1.75 L)
- ACQ-5 (≤ 2, >2)
- Number of severe asthma exacerbation prior to the study as defined in Section 2.1.1 (1,>1)
- Baseline weight (< 70, ≥ 70 - < 90, ≥ 90 kg)
- BMI (< 30, ≥ 30 kg/m^2)
- Smoking history (Former, Never)
- Atopic medical condition (Yes, No)
- Age of onset of asthma (<18, 18-40, >40 years)
- Baseline predicted FEV1% (<60%, 60%-90%)
- Baseline periostin(NG/ML) (< median, ≥ median)
- Baseline FeNO (< 25, ≥25- < 50, ≥50 ppb)

Treatment by subgroup interaction and its p-value will be derived from a negative binomial model. This model will include the total number of events occurring during the observation period as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to the study, subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. Log transformed observation duration will be the offset variable. If quantitative treatment by subgroup interaction is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be performed to evaluate possible qualitative interaction. Summary statistics of severe exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

For local submission, efficacy analyses may be performed in specific countries/regions, eg, Japan.

Loading dose evaluation

To examine if the treatment effect of dupilumab in reducing the annualized rate of exacerbation is sustained throughout the 52-week treatment period and if there is any confounding effect of the use of the loading dose on a sustained effect on exacerbations, a sensitivity analysis of the annualized rate of severe exacerbation will be performed. It will include severe exacerbation events occurring after the first four weeks and 12 weeks, respectively, and only on-treatment events will be included to avoid possible confounding effect due to off-treatment data. Due to

potential insufficient number of events after excluding data from the first 12 week, two dupilumab groups will be combined and two placebo groups will be combined. Results of the sensitivity analysis will be compared to the result of on-treatment analysis including all on-treatment severe exacerbation events during the study.

2.4.4.1.2 Absolute change from baseline in pre-bronchodilator (pre-BD) FEV_1 at Week 12

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of change from baseline in pre-BD FEV1 at Week 12 is to assess the efficacy of dupilumab in a real-world setting. The absolute change from baseline in FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction as covariates. Treatment groups, sex, region, baseline eosinophil strata, baseline ICS dose level, and visit will be treated as categorical variables. Age and height will be treated as continuous variable. For patients who discontinue the treatment before Week 12, they will be asked and encouraged to return to the clinic for all remaining study visit and the additional off study-treatment pre-BD FEV1 values measured up to Week 12 will be included in the primary analysis. For patients who withdraw from the study before Week 12, pre-BD FEV1 values will be missing after study discontinuation. No imputation will be performed for missing values in the primary analysis. This estimand compares the change from baseline in pre-BD FEV1 for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in pre-BD FEV1 at Week 12 will be derived from the mixed-effect model. Difference in LS mean change from baseline, the corresponding 95% CI and the p-value with Kenward-Roger adjustment will be provided for comparison for each dupilumab group against its matching placebo. In addition, descriptive statistics including number of patients, mean, standard error and LS mean of change from baseline will be provided.

A sample SAS code can be found below:

```
proc mixed data=adsd.adre method=reml;
      where paramcd='FEV1' and avisitn ge 3 and avisitn le 8 and ittfl='Y';
      class subjid sex eosblgpn ics trt01pn avisitn cntygr1n;
      model chg = trt01pn sex age height ics eosblgpn cntygr1n avisitn
trt01p*avisitn base base*avisitn/ddfm=kr residual;
      repeated avisitn/type=un subject=subjid;
      lsmeans trt01pn*avisitn /pdiff cl ;
     estimate '300 mg q2w vs Placebo 2ml q2w at Week 12 Visit 8'
     trt01pn 0 -1 0 1  trt01pn*avisitn   0 0 0  0
                                         0 0 0 -1
```

```
                                    0 0 0  0
                                    0 0 0  1/ cl;
run;
```

Estimand of clinical efficacy of dupilumab versus placebo

To assess the treatment effect when the patients adhere to the study treatment as directed, on-treatment pre-BD FEV1 measurements will be analyzed using the similar MMRM model as for the primary analyses, including same set of covariates and estimation algorithm. The model will include on-treatment change from baseline in pre-BD FEV1 values up to Visit 8 (Week 12) as response variables. A pre-BD FEV1 value is considered as on-treatment if it's measured before or on the last dose date + 14 days.

Sensitivity analyses with different censoring methods for pre-BD FEV1 potentially confounded by systemic corticosteroid use

In addition, two sets of sensitivity analyses with different methods of handling pre-BD FEV1 measurements confounded by the systemic corticosteroid use will be performed:

- Censoring method 1: pre-BD FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 14 days will be excluded in order to reduce the confounding effect of systemic corticosteroids
- Censoring method 2: All pre-BD FEV_1 measurements collected on and after first day of systemic corticosteroid use will be excluded.

The above two censoring methods will be applied to both primary analyses and on-treatment analysis. On-treatment analysis with data censoring method 1 will be used to provide treatment effect size estimates without confounding effect of systemic corticosteroid use.

Handling of missing data

If a patient misses scheduled pre-BD FEV1 measurement during the first 12-week treatment, or withdraws from the study before Visit 8 (Week 12), he/she will have missing pre-BD FEV1 data at some time points up to Week 12. Descriptive statistics of pre-BD FEV1 by visit up to Week 12 will be summarized for patients with some missing data and patients with complete data up to Week 12 separately. Number of patients with missing pre-BD FEV1, reasons and timing for missing pre-BD FEV1 will be summarized by treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model:

- *Pattern mixture model-multiple imputation (PMM-MI)*

  Missing pre-BD FEV1 values will be imputed multiple times with adjustment for covariates including treatment groups, baseline eosinophil groups, age, sex, height, region, baseline ICS dose level and reason of treatment discontinuation. Each of the complete datasets will be analyzed using the ANCOVA model with change from baseline in pre-BD FEV1 at Week 12 as the response variable, treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline pre-BD FEV1 value as covariates.

Then the SAS MIANALYZE procedure will be used to generate statistical inference by combining results using Rubin's formula.

- *Control based PMM-MI*

The analysis is similar as the standard PMM-MI described above, except that it assumes that after withdrawal from the study, patients from the dupilumab groups would exhibit the same future evolution of pre-BD FEV1 as patients on the placebo who were not exposed to dupilumab.

- *Tipping point analysis*

First, missing values will be imputed by PMM-MI as illustrated above. The imputed values in placebo group will then be shifted by adding a sequence of positive values and the imputed values in dupilumab group will be shifted by subtracting a sequence of positive values. For each combination of the shift parameters, each of the imputed and shifted datasets will be analyzed with the ANCOVA model and their results will be combined using Rubin's formula to generate statistical inference. LS mean difference between dupilumab and placebo in change from baseline in pre-BD FEV1 at week 12 and the corresponding p-values will be provided for each combination of shift parameters.

More details of the imputation and analyses methods are included in Appendix D.

Subgroup analysis

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in pre-BD FEV1 at Week 12 with the same set of subgroups as defined for the annualized rate of severe exacerbation events. Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from a MMRM model. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value, baseline-by-visit interaction, subgroup (if different than the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction as covariates. If quantitative treatment by subgroup interaction at Week 12 is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be used to test the qualitative interaction. Summary statistics of change from baseline in pre-bronchodilator FEV1 will be provided within each subgroup. Forest plot of LS mean difference and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

Distribution of change from baseline in pre-BD FEV1

Cumulative distribution function of change from baseline in pre-BD FEV1 at Week 12 and Week 52 will be presented.

Comparison between [redacted]-derived dupilumab treated patients and [redacted]-derived dupilumab treated patients

To compare the treatment effect of [redacted]-derived dupilumab and [redacted]-derived dupilumab, subgroup analyses of absolute change from baseline in pre-BD FEV1 at week 12 will be conducted by the subgroups defined below:

- Patients who are treated with [redacted]-derived dupilumab or its matching placebo only before Week 12
- Patients who are treated with [redacted]-derived dupilumab or its matching placebo only before Week 12

Matching placebo for [redacted]-derived dupilumab is defined as placebo in the same IMP batch of [redacted]-derived dupilumab, and matching placebo for [redacted]-derived dupilumab is defined as placebo in the same IMP batch of [redacted]-derived dupilumab.

For each subgroup, a MMRM model will be used to analyze change from baseline in pre-BD FEV1 at Week 12. Change from baseline in pre-BD FEV1 up to Week 12 will be included as response variable. Treatment groups, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction will be included as covariates. LS mean change from baseline in pre-BD FEV1 at Week 12 for each treatment group and LS mean difference in change from baseline in pre-BD FEV1 at Week 12 for each dupilumab treatment group compared to placebo will be derived from the MMRM model for each subgroup.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Absolute/percent change from baseline for continuous endpoints

The key secondary endpoint, percent change from baseline in pre-bronchodilator FEV1 at Week 12, will be analyzed in the same way as for change from baseline in FEV1 at Week 12, with the only difference that percent changes, instead of absolute changes, from baseline in FEV1 up to Week 12 will be included as the response variables. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in ACQ-5 and AQLQ at Week 24 will be analyzed using MMRM including change from baseline up to Week 24 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value, and baseline-by-visit interaction as covariates. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in other continuous endpoint at all time-points will be analyzed using MMRM model including measurements up to Week 52. The model will include change from baseline in the endpoint values from Week 2 to Week 52 as response variables, regardless if the patient is on treatment or not when the endpoint is measured, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value and baseline-by-visit interaction as covariates. Sex and baseline height will be included as covariates only in the models for spirometry parameters. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

For post-bronchodilator FEV1, the rate of change in FEV1 (termed as FEV1 slope) will be compared between each dupilumab dose against its matching placebo. Change from baseline in post-bronchodilator FEV1 after Week 4 and after Week 8 will be analyzed correspondingly using linear mixed-effects model with treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization, and treatment-by-time interaction, baseline post-bronchodilator FEV1 and baseline-by-time interaction as covariates.

In addition to the MMRM analyses for change from baseline in ACQ-5, ACQ-7 and AQLQ total score a responder analysis will also be performed for these endpoints at Week 12, 24, 36 and 52. For ACQ-5 score, a logistic regression model will be used to compare percentage of patients who reached MCID (responders) in each dupilumab dose group against its matching placebo at the time points aforementioned correspondingly. Patients with change from baseline in ACQ-5 $\leq$ -0.5 will be considered as responders. Patients with change from baseline in ACQ-5 >-0.5 or with missing value will be considered as non-responders. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline ACQ-5 score as covariates. Odds ratio of being a responder comparing each dupilumab dose group to its matching placebo group will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided. Responder analysis for ACQ-7 and AQLQ global score will be performed in the same way. For ACQ-7, a patient is considered as a responder if change from baseline in ACQ-7 score $\leq$ -0.5, or as a non-responder if change from baseline in ACQ-7 score > -0.5 or missing. For AQLQ global score, a patient is considered as a responder if change from baseline in AQLQ global score $\geq$0.5, or as a non-responder if change from baseline < 0.5 or missing. ACQ-7 score will also be analyzed in adolescent patient population separately.

2.4.4.2.2 Annualized event rate

Annualized rate of loss of asthma control (LOAC) event and annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period will be analyzed in the similar method as for the annualized rate of severe exacerbation events using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated event rate for each treatment group and its two-sided 95% confidence intervals will be provided. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate ratio and its p-value will also be provided.

2.4.4.2.3 Time to event variables

A Cox regression model will be used to assess treatment differences in time to events defined in Section 2.1.3.2.2.3

The model will include the time to the first event as the dependent variable, and four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Hazard ratio will be estimated for pairwise comparison between each dose of dupilumab and its matching placebo. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience events up to Week 12, 24, 36 and 52 per each treatment group. Kaplan-Meier curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

Sample SAS codes can be found as below:

```
proc phreg data=timeto;
      class subjid eosblgpn ics trt01pn cntygr1n /param=GLM;
      model aval*CNSR(1) =trt01pn age eosblgpn ics cntygr1n asmanum;
      contrast '200 mg q2w vs Placebo rate ratio' trt01pn -1 0 1 0
      0/estimate=exp;
      contrast '300 mg q2w vs Placebo rate ratio' trt01pn 0 -1 0 1
      1/estimate=exp;
run;
```

2.4.4.3 Multiplicity issues

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo.

If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The complete list of the endpoints with their testing order is specified in Table 5.

Annualized rate of severe exacerbation events requiring hospitalization or emergency room visit (requiring systemic corticosteroids) will be analyzed combining data from DRI12544 study and

this study due to small number of events. The multiplicity control will be specified in the SAP of ISE before database lock of this study.

Table 5 – Hierarchical testing order

	Endpoints	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Primary endpoints	Annualized rate of severe exacerbation events during the treatment period - ITT population	3	1
	Change from baseline in FEV_1 at Week 12 - ITT population	4	2
Secondary endpoints	Percent change from baseline in FEV1 at Week 12 - ITT population	11	5
	Annualized rate of severe exacerbation events during the treatment period - ITT population with baseline eosinophil >=0.15 Giga/L	12	6
	Change from baseline in FEV_1 at Week 12 - ITT population with baseline eosinophil >=0.15 Giga/L	13	7
	Annualized rate of severe exacerbation events during the treatment period - ITT population with baseline eosinophil >= 0.3 Giga/L	14	8
	Change from baseline in FEV_1 at Week 12 - ITT population with baseline eosinophil >= 0.3 Giga/L	15	9
	Annualized rate of severe exacerbation events during the treatment period - ITT population with baseline eosinophil <0.3Giga/L	16	10
	Annualized rate of severe exacerbation events during the treatment period - ITT population with high dose ICS/LABA at baseline	22	17
	Change from baseline in FEV_1 at Week 12 - ITT population with high dose ICS/LABA at baseline	23	18
	Change from baseline in AQLQ global score at Week 24 - ITT population	24	19
	Change from baseline in AQLQ global score at Week 24 - ITT population with baseline eosinophil >= 0.3 Giga/L	25	20
	Change from baseline in ACQ-5 score at Week 24 - ITT population	26	21
	Change from baseline in FEV_1 at Week 12 - ITT population with baseline blood eosinophil <0.3 Giga/L	28	27

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available value before the first dose of IMP.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (PCSA version dated May 2014 [Appendix A])
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population. Number (%) of patients with at least 1 PCSA will be summarized regardless of baseline PCSA status and also by baseline PCSA status.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the end of treatment. If this value is missing, this endpoint value will be the closest value prior to the end of treatment epoch. The worst value is defined as the nadir and /or the peak post-baseline (up to the end of treatment epoch or EOT) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.3.

2.4.5.1 Analyses of adverse events

General information

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the dupilumab 300 mg q2w group.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary system organ class, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- A listing of all treatment-emergent adverse events will be presented

Analysis of all treatment-emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- A listing of all treatment-emergent serious adverse events will be presented

Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption

- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.

Analysis of adverse events with pre-specified monitoring (AEPM)/ of special interests (AESI)

- All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of patients with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ
- For each AEPM/AESI,
  - Number (%) of patients with any specific treatment emergent AEPM/AESI
  - Number (%) of patients with any specific serious AEPM/AESI (regardless of treatment emergent status)
  - Number (%) of patients with any specific treatment emergent serious AEPM/AESI
  - Number (%) of patients with any specific AEPM/AESI leading to death
  - Number (%) of patients with any specific treatment emergent AEPM/AESI leading to permanent study drug discontinuation

- Number (%) of patients with any specific AEPM/TEAE by maximum intensity, corrective treatment, and final outcome
- Number of any specific treatment emergent AEPM/AESI adjusted by the exposure duration

- Number of patients with any specific treatment emergent AEPM/AESI adjusted by the exposure duration at risk. For each AEPM/AESI, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough.
- Number (%) of patients with injection site reactions by the related injection.
- Number (%) of patients with different number of injection site reactions.

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All serious pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

If only a few patients have pretreatment adverse events leading to permanent treatment discontinuation, a listing will be presented instead of the summary table above.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients
- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC .
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

A listing of deaths will be provided.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of PCSAs will be provided.

Drug-induced liver injury

If there is any imbalance in the incidence of liver-related adverse events across the treatment groups, analysis of liver-related adverse events will be performed.

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT > 3 x ULN or total bilirubin > 2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented.

Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and creatine phosphokinase, serum creatinine, complete blood count, HCV RNA.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

Change in Blood Eosinophil

Mean changes from baseline in eosinophil with the corresponding standard error will be plotted over time in each treatment group for patients with baseline blood eosinophil < 0.5 Giga/L and patients with baseline blood eosinophil >=0.5 Giga/L. Number (%) of patients with post-baseline peak blood eosinophil >= 1 Giga/L, >=3 Giga/L and >=5 Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, <0.5 Giga/L,>=0.5 Giga/L).

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at the same time points) in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.6 Analyses of pharmacokinetic and pharmacodynamics variables

2.4.6.1 Pharmacokinetic analyses

2.4.6.1.1 Analyses of serum concentrations of SAR231893 (REGN668)

Serum concentrations of SAR231893 (REGN668) will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For drug-treated patients, where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For patients in the placebo group, concentration values are below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

Assessment of [redacted]-derived dupilumab treated patients and [redacted]-derived dupilumab treated patients

Serum concentration of SAR231893 (REGN668) up to Week 12 will be summarized separately in the following two subgroups.

- Patients who are treated with [redacted]-derived dupilumab only before Week 12
- Patients who are treated with [redacted]-derived dupilumab only before Week 12

2.4.6.1.2 Analyses of ADA variables

The following summary will be provided based on ADA population:

- Number (%) of patients negative in ADA assay at all times
- Number (%) of patients positive in ADA assay at any time

(electronic 1.0)

- Number (%) of patients with pre-existing ADA
- Number (%) of patients with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA, and patients with persistent, indeterminate and transient ADA response
- Number (%) of patient with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA
- Number (%) of patients with indeterminate treatment-emergent ADA
- Number (%) of patients with treatment-boosted ADA.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-boosted ADA
- The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer for patients with treatment-boosted ADA
- Listing of ADA peak titer levels and neutralizing antibody status
- Number(%) of patients with neutralizing antibody status

Kinetics of treatment-emergent ADA response

Number (%) of patients with ADA treatment-emergent ADA positive response at each visit will be summarized by each dose regimen group.

Plot of percentage of patients with ADA treatment-emergent ADA positive response at each visit will be provided by each dose regimen group.

Impact of ADA on PK

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and serum concentration of dupilumab may be explored for each dupilumab dose group. Plot of serum concentration of functional SAR231893 (REGN668) versus visit will be provided by ADA classifications for each dupilumab dose group.

Impact of ADA on clinical efficacy

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and following efficacy endpoints may be explored for each dupilumab dose group:

- Annualized rate of severe exacerbation events
- Change from baseline in Pre-BD FEV1

Impact of ADA on clinical safety

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review)
- Anaphylactic reactions (SMQ anaphylactic reaction narrow search)

In response to AESI like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent and treatment-boosted) and safety may be explored.

2.4.6.2 Pharmacodynamics/genomics analyses

All biomarkers listed in Section 2.1.6 will be summarized in the Exposed population defined as patients who actually received at least 1 dose or part of a dose of the IMP. Baseline values will be the last value collected prior to the first IMP. For randomized but not treated patients, baseline value will be the last value collected prior to the randomization. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized.

For all parameters including antigen-specific IgEs with a positive (≥0.35 IU/mL) incidence of greater than 25% at baseline, values at each visit, absolute change from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Values reported as below the LLQ (lower limit of quantitation) will be imputed as a value one half of the LLQ.

Number and percentage of patients with no positive (≥0.35 IU/mL) antigen-specific IgE result, with positive (≥0.35 IU/mL) result for only one antigen, and with positive (≥0.35 IU/mL) results for at least two antigens will be summarized by treatment group and time point. Same analysis will also be performed using LLQ as the threshold.

Summary plots (mean +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for each biomarker by treatment group.

Exploratory analysis of DNA/RNA will be addressed in a separate document.

2.4.7 Analyses of vaccine response

For patients who receive vaccination, vaccine IgG in serum prior and after vaccination will be summarized by treatment groups with descriptive statistics.

2.4.8 Analyses of health economics variables

Analyses of health care resource utilization will be performed under the responsibility of the Health Economics and Reimbursement Argumentation department of Sanofi. Methods and results will be made available in a separate report.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as:

Integer part of (informed consent date -birth date)/365.25

Age of onset of asthma is calculated as:

Integer part of (asthma onset date - birth date)/365.25

Time since first diagnosis of asthma (years) is calculated as:

(Year of randomization -Year of first diagnosis of asthma) + (month of randomization - month of first diagnosis of asthma)/12

Time since cessation of smoking is calculated as:

(Year of randomization - Year of cessation)×12 + (month of randomization -month of cessation)

Time since last asthma exacerbation (months) is calculated as:

(Year of randomization – Year of last asthma exacerbation)×12 + (month of randomization – month of last asthma exacerbation)

BMI is calculated as:

Weight in kg / (height^2 in meters)

Smoking quantity (pack-year) is calculated as following:

Number of pack-year= (packs smoked per day) × (years as a smoker)

Renal function formulas

For patients ≥ 18 years old, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 - age) × weight (kg) × (1 - 0.15 × sex (0-M, 1-F))/ (0.814 × creatinine

(μmol/l))

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement and age at the lab sampling date. Here age is calculated as following:

Age = integer part of (lab sampling date - birth date)/365.25

For patients < 18 years old, CLcr value will be derived using the equation of GFR Bedside Schwartz

GFR (mL/min/1.73 m2) = k × height (cm) / sCr (mg/dL)] ,

Where the coefficient k=0.65 for adolescent male patients, or k=0.55 for adolescent female patients.

2.5.2 Data handling conventions for secondary efficacy variables

Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

Periodical average of daily efficacy endpoints at designated study days

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in Table 6. Randomization day is used as the reference day (Day 1).

Table 6 - Periodical average of daily efficacy assessment

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 15	2-15	1-14	Diary day 1-14
Day 29	16-29	15-28	Diary day 15-28
Day 43	30-43	29-42	Diary day 29-42
Day 57	44-57	43-56	Diary day 43-56
Day 71	58-71	57-70	Diary day 57-70
Day 85	72-85	71-84	Diary day 71-84
Day 113	86-113	85-112	Diary day 85-112

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 141	114-141	113-140	Diary day 113-140
Day 169	142-169	141-168	Diary day 141-168
Day 197	170-197	169-196	Diary day 169-196
Day 225	198-225	197-224	Diary day 197-224
Day 253	226-253	225-252	Diary day 225-252
Day 281	254-281	253-280	Diary day 253-280
Day 309	282-309	281-308	Diary day 281-308
Day 337	310-337	309-336	Diary day 309-336
Day 365	338-365	337-364	Diary day 337-364
Day 393	366-393	365-392	Diary day 365-392
Day 421	394-421	393-420	Diary day 393-420
Day 449	422-449	421-448	Diary day 421-448

Note: A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary day 14 includes the evening dairy on day 14 and the morning dairy on day 15.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the Investigational Product Administration report form page. If this date is missing, the exposure duration should be left as missing.

The last dose injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a "missing" category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window define in Table 7 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 7 – Time window for safety endpoints

		Time windows for							
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Urinalysis, Serum immunoglobulins**	**Hepatitis B viral load**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 1 (Week -4±1)	-28±7	<-14	1-	<-14	1-		1-		1-
Visit 2 (Week 0)	1	-14-1-		-14-1-		1-		1-	
Visit 3 (Week 2)	15	1+-21	1+-21						
Visit 4 (Week 4)	29	22-35	22-56	1+-42		1+-42			
Visit 5 (Week 6)	43	36-49							
Visit 6 (Week 8)	57	50-63		43-70		43-70			
Visit 7 (Week 10)	71	64-77							
Visit 8 (Week 12)	85	78-98	57-126	71-98		71-98	1-126	1-126	

		Time windows for							
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Urinalysis, Serum immunoglobulins**	**Hepatitis B viral load**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 9 (Week 16)	113	99-126		99-126		99-126			
Visit 10 (Week 20)	141	127-154		127-154		127-154			
Visit 11 (Week 24)	169	155-182	127-210	155-182		155-182	127-210	127-210	
Visit 12 (Week 28)	197	183-210		183-210		183-210			
Visit 13 (Week 32)	225	211-238		211-238		211-238			
Visit 14 (Week 36)	253	239-266	211-308	239-266		239-266	211-308	211-308	
Visit 15 (Week 40)	281	267-294		267-294		267-294			
Visit 16 (Week 44)	309	295-322		295-322		295-322			
Visit 17 (Week 48)	337	323-350		323-350		323-350			1+
Visit 18 (Week 52)	365	351-378	309-406	351-378		351-406	309-406	309-406	

(electronic 1.0)

		Time windows for							
Visit	Target Day	Vital signs	ECG endpoints	Clinical lab testing	Serum Pregnancy test	Urine Pregnancy test	Urinalysis, Serum immunoglobulins	Hepatitis B viral load	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy
Visit 19 (Week 56)	393	379-406		379-406					
Visit 20 (Week 60)	421	407-434		407-434					
Visit 21 (Week 64)	449	>434	>406			>406	>406	>406	

1⁻: up to 1st dose date/time; 1⁺: after 1st dose date/time;

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a patient receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that patient. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 8. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For the on-treatment sensitivity analyses, only scheduled measurements collected during the treatment epoch will be assigned to a time window.

Table 8 – Time window for efficacy variables

		Time windows for		
Visit	Target Day	Pre-bronchodilator Spirometry, ACQ-5, ACQ-7	Post-bronchodilator spirometry, reversibility	AQLQ(S), EQ-5D-5L, HADS, SNOT-22, RQLQ(S)+12
Visit 1 (Week -4±1)	-28±7	<-14		
Visit 2 (Week 0)	1	-14-1⁻	1⁻	1⁻
Visit 3 (Week 2)	15	1⁺-21	1⁺-21	
Visit 4 (Week 4)	29	22-35	22-42	
Visit 5 (Week 6)	43	36-49		

Visit	Target Day	Time windows for		
		Pre-bronchodilator Spirometry, ACQ-5, ACQ-7	Post-bronchodilator spirometry, reversibility	AQLQ(S), EQ-5D-5L, HADS, SNOT-22, RQLQ(S)+12
Visit 6 (Week 8)	57	50-63	43-70	
Visit 7 (Week 10)	71	64-77		
Visit 8 (Week 12)	85	78-98	71-126	1-126
Visit 9 (Week 16)	113	99-126		
Visit 10 (Week 20)	141	127-154		
Visit 11 (Week 24)	169	155-182	127-210	127-210
Visit 12 (Week 28)	197	183-210		
Visit 13 (Week 32)	225	211-238		
Visit 14 (Week 36)	253	239-266	211-308	211-308
Visit 15 (Week 40)	281	267-294		
Visit 16 (Week 44)	309	295-322		
Visit 17 (Week 48)	337	323-350		
Visit 18 (Week 52)	365	351-378	309-406	309-406
Visit 19 (Week 56)	393	379-406		
Visit 20 (Week 60)	421	407-434		
Visit 21 (Week 64)	449	>434	>406	>406

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the patient is treated with study treatment, or the randomization date if the patient is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 9 for the by visit descriptive analyses. All available values of measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 9 – Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin
Visit 1 (Week -4±1)	-28±7						

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin
Visit 2 (Week 0)	1	1-	1-	1-	1-	1-	1-
Visit 3 (Week 2)	15		1+-21	1+-21			
Visit 4 (Week 4)	29		22-56	22-42			1+-56
Visit 5 (Week 6)	43						
Visit 6 (Week 8)	57			43-70			
Visit 7 (Week 10)	71						
Visit 8 (Week 12)	85	1+-126	57-98	71-98	1-126	1-126	57-224
Visit 9 (Week 16)	113		99-126	99-140			
Visit 10 (Week 20)	141		127-154				
Visit 11 (Week 24)	169	127-210	155-210	141-210	127-266	127-266	
Visit 12 (Week 28)	197						
Visit 13 (Week 32)	225						
Visit 14 (Week 36)	253	211-308	211-294	211-308			
Visit 15 (Week 40)	281						
Visit 16 (Week 44)	309						
Visit 17 (Week 48)	337		295-350				
Visit 18 (Week 52)	365	309-406	351-378	309-378	267-406	>267	>224
Visit 19 (Week 56)	393		379-406	379-406			
Visit 20 (Week 60)	421		407-434	407-434			
Visit 21 (Week 64)	449	>406	>434	>434	>406		

1-: up to 1st dose date/time or randomization if patient is not treated; 1+: after 1st dose date/time or randomization date if patient is not treated;

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries, computation of baseline, worst values, and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Due to the large number of centers, the randomization is stratified by country. Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Hungary, Poland, Russia, Turkey and Ukraine
- Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA
- Asia: Japan, South Korea and Taiwan;
- Latin America: Argentina, Brazil, Colombia, Chile and Mexico

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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7 LIST OF APPENDICES

Appendix A: Potentially clinically significant abnormalities (PCSA) criteria

Appendix B: List of recognized controller medications

Appendix C: Low, medium and high dose inhaled corticosteroids – Adults and adolescents (≥ 12 years)

Appendix D: Handling of missing data

Appendix E: Asthma Control Questionnaire (ACQ)

Appendix F: Asthma Symptom Score Numerical Rating Scale (NRS)

Appendix G: Asthma Quality of Life Questionnaire

Appendix H: 22-item Sinonasal Outcome Test (SNOT-22)

Appendix I: Hospital Anxiety and Depression Scale

Appendix J: EuroQual Questionnaire (EQ-5D-5L)

Appendix K : Standardized Rhinoconjunctivitis Quality of Life Questionnaire RQLQ(S)+12

Appendix L : Vaccination record form

Appendix M : Definition of Anaphylaxis

Appendix N : List of opportunistic infections

Appendix O : PT related to pregnancy

STATISTICAL ANALYSIS PLAN

A randomized, double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACQ-5:	Asthma Control Questionnaire 5-question version
ACQ-7:	Asthma Control Questionnaire 7-question version
ADA:	Anti-drug antibody
AE:	Adverse Event
AESI:	Adverse Event of Special Interest
ALT:	Alanine Aminotransferase
ANA:	Antinuclear Antibodies
AQLQ(S):	Asthma Quality Of Life Questionnaire with Standardized Activities
ATS:	American Thoracic Society
CI:	Confidence Interval
CRF:	Case Report Form
CV:	Coefficient of Variation
DNA:	Deoxyribonucleic acid
DPI:	Dry Powder Inhaler
ECG:	Electrocardiography
ECP:	Eosinophil Cationic Protein
eCRF:	electronic Case Report Form
EOT:	End of Treatment
EQ-5D-5L:	European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels
ERS:	European Respiratory Society
FeF:	Forced Expiratory Flow
FeNO:	Fractional Exhaled Nitric Oxide
FEV1:	Forced Expiratory Volume in One Second
FVC:	Forced Vital Capacity
GINA:	Global Initiative for Asthma
HADS:	Hospital Anxiety and Depression Scale
HADS-A:	Hospital Anxiety and Depression Scale- Anxiety subscale
HADS-D:	Hospital Anxiety and Depression Scale- Depression subscale
HBc Ab:	Hepatitis B Core Antibody
HBs Ab:	Hepatitis B Surface antibody
HBs Ag:	Hepatitis B Surface Antigen
HBV:	Hepatitis B Virus
HCV:	Hepatitis C Virus
HCV Ab:	Hepatitis C Virus Antibody
HFA:	Hydrofluoroalkane
HIV:	Human Immunodeficiency Virus
HLGT:	High-Level Group Term
HLT:	High Level Term
HRQoL:	Health related quality of life

ICS:	Inhaled Corticosteroid
IgA:	Immunoglobulin A
IgE:	Immunoglobulin E
IgG:	Immunoglobulin G
IgM:	Immunoglobulin M
IMP:	Investigational Medicinal Product
IRT:	Interactive Response Technologies
ITT:	Intent-To-Treat
IVRS/IWRS:	Interactive Voice Response System/Interactive Web Response System
K-M:	Kaplan-Meier
LABA:	Long-Acting Beta Agonist
LAMA:	Long-Acting Muscarinic Antagonist
LLQ:	Lower Limit of Quantitation
LLT:	Lower-Level Term
LOAC:	Loss Of Asthma Control
LTRA:	Leukotriene Receptor Antagonist
MCID:	Minimal Clinically Important Difference
MDI:	Metered Dose Inhaler
MedDRA:	Medical Dictionary for Regulatory Activities
MID:	Minimal Important Difference
MMRM:	Mixed-effect Model with Repeated Measures
NRS:	Numerical Rating Scale
NSAID:	Nonsteroidal Anti-inflammatory Drug
OLE:	Open Label Extension
PCSA:	Potentially Clinically Significant Abnormalities
PEF:	Peak Expiratory Flow
PK:	Pharmacokinetics
Post-BD:	Post-bronchodilator
Pre-BD:	Pre-bronchodilator
PROs:	Patient-Reported Outcomes
PT:	Preferred Term
RBC:	Red Blood Cell
RNA:	Ribonucleic Acid
RQLQ(S)+12:	Standardized Rhinoconjunctivitis Quality Of Life Questionnaire , ages 12+
SC:	subcutaneously
SD:	Standard Deviation
SEM:	Standard Error of the Mean
SNOT-22:	22-item Sino Nasal Outcome Test
SOC:	System Organ Class
TARC:	Thymus and Activation-Regulated Chemokine
TEAE:	Treatment-Emergent Adverse Event
ULN:	Upper Limit of Normal
VAS:	Visual Analogue Scale
WBC:	White Blood Cell

1 OVERVIEW AND INVESTIGATIONAL PLAN

1.1 STUDY DESIGN AND RANDOMIZATION

EFC13579 is a multinational, multicenter, randomized, double blind, placebo-controlled, parallel group study assessing the effect of dupilumab administered subcutaneously (SC) for 52 weeks in patients with persistent asthma. Both the patient and investigator will be blinded to assigned active drug or matching placebo, but will not be blinded to the dose level of dupilumab 300 mg/matching placebo or dupilumab 200 mg/matching placebo due to different volume size (2 mL vs 1.14 mL).

After a screening phase of 4±1 weeks, patients will be centrally randomized using permuted block randomization schedule via Interactive Voice Response System/Interactive Web Response System (IVRS/IWRS) in a 2:2:1:1 randomization ratio to dupilumab 300 mg q2w in 2mL, dupilumab 200 mg q2w in 1.14 mL, placebo q2w in 2 mL or placebo q2w in 1.14 mL. Randomization will be stratified by age (<18 years, ≥18 years) at screening, blood eosinophil count (<0.3 Giga/L, ≥0.3 Giga/L) done at the central laboratory at screening, ICS dose level (medium, high) and country.

At least 1638 patients, including approximately 84 adolescent patients, will be randomized to dupilumab or placebo, with at least 690 patients with a baseline blood eosinophil count ≥0.3 Giga/L. Recruitment for patients on medium dose of ICS will be stopped at approximately 819 to ensure at least 50% patients are on high dose of ICS.

1.2 OBJECTIVES

1.2.1 Primary objectives

- To evaluate the efficacy of dupilumab in patients with persistent asthma.

1.2.2 Secondary objectives

- To evaluate the safety and tolerability of dupilumab
- To evaluate the effect of dupilumab on improving PROs including HRQoL
- To evaluate dupilumab systemic exposure and incidence of anti-drug antibodies

1.2.3 Exploratory objectives

- To explore the association of biomarkers with treatment response
- To explore the association of genetic profiles with treatment response
- To explore the association of vaccine response with treatment

1.3 DETERMINATION OF SAMPLE SIZE

The sample size was calculated on a comparison between dupilumab 300 mg q2w versus placebo with regard to the 2 primary endpoints: annualized rate of severe asthma exacerbations during the 52-week treatment period, and absolute change from baseline in FEV1(L) at Week 12. Assuming the number of severe asthma exacerbations follows a negative binomial distribution with a dispersion parameter of 2, a placebo annualized rate of exacerbations being 0.6, a randomization ratio of 2:2:1:1, with 1638 randomized patients (546 for each dupilumab dose and 273 for each matching placebo group), the study will have 99% power to detect a 55% relative risk reduction (ie, annualized rate of 0.27 for the dupilumab group) in the annualized rate of severe asthma exacerbations at the 2-tailed significance level of α=0.05. Assuming 42% patients with a baseline blood eosinophil count ≥0.3 Giga/L, approximately 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 91% power to detect a 55% relative risk reduction for this subgroup. Assuming a common standard deviation of 0.5 L, 1638 patients (546 for each dupilumab dose and 273 for each matching placebo group) will provide 98% power to detect a treatment difference of 0.15 L in the change of FEV1 from baseline at Week 12 for the overall population, and 690 patients (230 for dupilumab 300mg q2w and 115 for the matching placebo) will provide 88% power to detect a treatment difference of 0.18 L for patients with a baseline blood eosinophil count ≥0.3 Giga/L. The overall study recruitment will continue until at least 1638 patients in total and 690 patients with blood eosinophils ≥0.3 Giga/L are randomized. The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized into the study. In addition, approximately 84 adolescent patients will be randomized.

In addition to the originally planned sample size of 1638 patients, approximately 220 patients will be randomized in order to have additional patients treated with the drug product manufactured using the intended commercial process.

1.4 STUDY PLAN

The clinical trial consists of three periods:

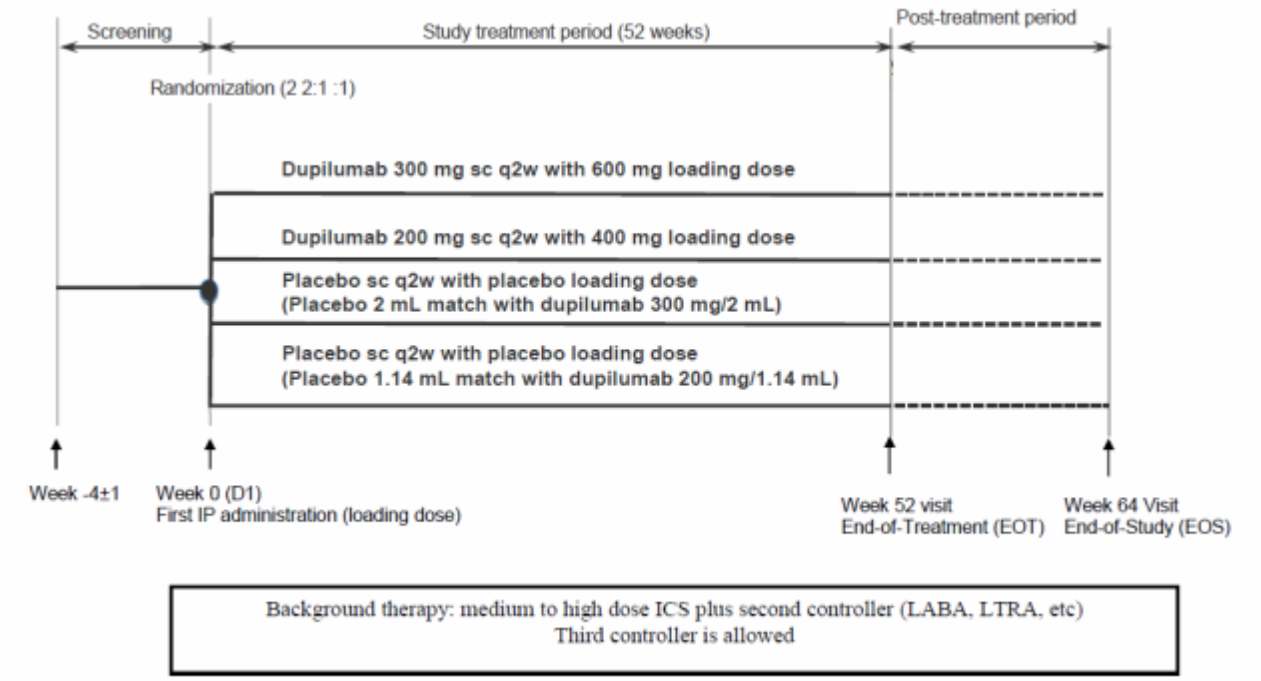
Screening Period (4±1 weeks): to determine a patient's eligibility status and establish level of asthma control before randomization.

Treatment Period (52 weeks): treat with dupilumab or placebo SC injection.

Post-treatment Period (12 weeks): to monitor a patient's status when off study drug treatment for patients not participating in the long term extension study.

1.4.1 Graphic study design

Please refer of Section 1.2 of the study protocol for the detailed study flow chart.



1.5 MODIFICATIONS TO THE STATISTICAL SECTION OF THE PROTOCOL

This section summarizes major changes to the protocol statistical section with emphasis on changes after study start (after the first patient was enrolled). These changes are not based on any unblinded study data.

The protocol history table below gives the timing, rationale, and key details of major changes to the protocol statistical section. "Principal features of the analysis" encompass the confirmatory aspects of the trial, including the primary and key secondary endpoints/analyses, and the analysis populations associated with these analyses.

Table 1 - Protocol amendment statistical changes

Amendment Number	Date Approved	Rationale	Description of statistical changes
2	21-May-2015	To address the feedback from European health authority (EMA) on stratification for patients on medium and high doses of ICS to ensure that the benefit/risk is positive for both asthma populations.	The following text: Randomization will be stratified by age (<18 years, 18-64 years, ≥65 years), central eosinophil count (<150 cells/μL, 150 – 299 cells/μL, and ≥300 cells/μL) at screening and country. Was replaced with: Randomization will be stratified by age (<18 years, ~~18-64 years, ≥65 years~~≥18 years),

Amendment Number	Date Approved	Rationale	Description of statistical changes
			central eosinophil count (~~<150 cells/ µL, 150 – 299 cells/ µL, and~~ <300 cells/µL, ≥300 cells/ µL) at screening, ICS dose level (medium, high) and country.
4	21-Sep-2015	To address the feedback from European health authority (EMA) and Pharmaceuticals and Medical Devices Agency (PMDA) not to pool the placebo arms	The following text was deleted: ~~The two placebo groups will be compared for the two primary efficacy endpoints: annualized rate of severe exacerbation events during the 52 weeks, and absolute change from baseline in FEV1 at Week 12. If they are similar for both endpoints based on the predefined criteria, the two placebo groups will be pooled together and all efficacy analyses will be performed with the pooled placebo group. The criteria to determine if the two placebo groups are similar will be specified in the SAP prior to database lock.~~
4	21-Sep-2015	To further meet the recommendation from EMA on stratification for patients on medium and high dose ICS to ensure that the benefit/risk is positive for both asthma populations, in addition to the added stratification factor of ICS dose level (medium, high).	The following text was added: The recruitment for patients on treatment of medium dose of ICS will stop when approximately 819 patients in this category have been randomized.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to control overall type I error rate at a 2-sided alpha of 0.05.	The following text was deleted: ~~The secondary endpoints will be tested follow the predefined hierarchical order for the dose that meets the statistical significance for both primary endpoints: annualized event rate of severe exacerbation and absolute change from baseline in FEV1 at Week 12.~~ ~~The primary family error rate will be controlled at 2-sided 5% level for 2 primary endpoints and 2 doses. The family error rate will be controlled at 2-sided 5% level for primary and secondary endpoints within the dose group. The overall family error rate will be controlled at 1-sided 5% level for all endpoints across dose groups.~~ The following text was added: If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a

(electronic 3.0)

Amendment Number	Date Approved	Rationale	Description of statistical changes
			hierarchical testing procedure at a 2-sided 5% significant level. The first four tests will be 1) % change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo 2) absolute change from baseline in AQLQ global score at Week 12 for 300 mg q2w versus placebo 3) % change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo, 4) absolute change from baseline in AQLQ global score at Week 12 for 200 mg q2w versus placebo. The remaining list of secondary endpoints to be tested in the hierarchical order will be specified in SAP. The overall familywise error rate will be strongly controlled at a 2-sided 5% level for all tested endpoints across dose groups.
4	21-Sep-2015	To meet the request from Food and Drug Administration (FDA) to include treated but not randomized patients in the safety population	The following text: The analysis population for the safety endpoints will be the safety population, defined as all randomized patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received. Was replaced with: The analysis population for the safety endpoints will be the safety population, defined as all ~~randomized~~ patients exposed to study medication, regardless of the amount of treatment administered. The safety analyses will be conducted according to the treatment that patients actually received.
7	9-Aug-2016	To meet the request from FDA to provide data on patients treated with dupilumab manufactured with the intended commercial process	In order to have additional patients treated with dupilumab manufactured using the intended commercial process, more patients may be randomized than the originally planned sample size (1638) .
7	9-Aug-2016	Examine if inclusion of the loading dose impacts duration of sustained efficacy with regard to exacerbations	Additional analysis to assess the sustained treatment effect was added.

1.6 STATISTICAL MODIFICATIONS MADE IN THE STATISTICAL ANALYSIS PLAN

This section summarizes major changes in statistical analysis features made in approved SAP versions from statistical considerations in protocol or previous SAP versions, with emphasis on changes after study start (after the first patient was enrolled). These changes are made before database lock.

The statistical analysis plan history table below gives the timing, rationale, and key details for major changes to the statistical analysis features in the statistical analysis plan.

Table 2 - Statistical analysis plan statistical changes

SAP version number	Date approved	Rationale	Description of statistical changes
1	24-Jun-2016	Expand the multiplicity control procedure for additional secondary endpoints, sub-populations.	The testing order of secondary endpoints was expanded from protocol, and the complete list of endpoints to be tested in the hierarchical order was specified in Table 6
1	24-Jun-2016	To be aligned with protocol amendment 07	Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided.
1	24-Jun-2016	To meet the request from FDA to assess any potential confounding effects of the loading dose on efficacy.	Sensitivity analyses were added to examine if the treatment effect of dupilumab is sustained throughout the 52-week treatment period or if there is any confounding effect of the use of the loading dose resulting in a larger treatment effect in the early part of the study. Annualized rates of severe exacerbation will also be analyzed versus placebo excluding efficacy data obtained during the first 4 weeks and 12 weeks of treatment of dupilumab/placebo respectively.
1	24-Jun-2016	To meet the request from FDA to provide data on patients treated with dupilumab manufactured with the intended commercial process	In order to have additional patients treated with dupilumab manufactured using the intended commercial process, more patients may be randomized than the originally planned sample size (1638). The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.
2	This version	The analyses for the intended commercial manufacture process will be specified in a separate SAP	Analyses of PK and FEV1 for the intended commercial manufacture process are removed from Section 2.4.4.1.2 and Section 2.4.6.1.1 in this

(electronic 3.0)

SAP version number	Date approved	Rationale	Description of statistical changes
			SAP
2	This version	Expand the multiplicity control procedure for additional secondary endpoints	Exacerbation requiring hospitalization or ER visit is added in the hierarchy of the multiplicity control procedure in Section 2.4.4.3
2	This version	Add analysis for severe exacerbation events resulting in hospitalization or ER visit.	The endpoint, Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit, is added in Section 2.1.3.2.2.2
2	This version	To solve the potential for non-convergence in the analysis of exacerbation event	Procedures of model handling are added when GLIMMIX procedure fails to achieve convergence in Section 2.4.4.1.1.
2	This version	Include multiple imputation in the sensitivity analysis of severe exacerbation per FDA feedback	PMM, control based PMM and tipping point analysis for severe exacerbation events are updated in Section 2.4.4.1.1.
2	This version	To solve the potential for non-convergence in MMRM models	Alternative model specification is added when MMRM model fails to achieve convergence in Section 2.4.4.1.2
2	This version	To add additional subgroup analysis and update subgroup definition based on characteristics of patient population.	Additional subgroup analysis based on Ethnicity (Hispanic, non-Hispanic) and baseline weight (<60kg, >=60kg) are added, definition of subgroups based on background controller medications are updated, subgroup with Baseline BMI<30 is split into two subgroups (<25, 25-<30) in Section 2.4.4.1.1.
2	This version	To obtained group-level estimate of post-bronchodilator FEV1 slope in treatment arm	Baseline by time interaction is removed from the mixed-effects model for post-bronchodilator FEV1 in Section 2.4.4.2.1
2	This version	To include additional handling of missing data in ACQ07	Spirometry data from the same day will be used to impute the 7th question if the value is missing in Section 2.5.3
2	This version	To be consistent with ISS SAP	The definition of AESI and selected AE groupings are updated in Section 2.1.4.1.
2	This version	To include combined PCSA criteria for adult and adolescence.	PCSA criteria in *Appendix A* are updated
2	This version	To be aligned with protocol amendment 07	Change from baseline in Health care resource utilization at Week 4 and 8 are removed in Section 2.1.3.2.2.

2 STATISTICAL AND ANALYTICAL PROCEDURES

2.1 ANALYSIS ENDPOINTS

2.1.1 Demographic and baseline characteristics

The baseline value of efficacy parameters is defined as the last available value up to randomization but prior to the first dose of study medication unless otherwise specified. The baseline value of safety parameters is defined as the last available value prior to the first dose of investigational medicinal product (IMP). The baseline value of the other parameters is defined as the last available value prior to the first dose of IMP if the patient is treated, or the last available value up to randomization if the patient is not exposed to IMP.

All baseline safety and efficacy parameters (apart from those listed below) are presented along with the post-baseline summary statistics in the safety and efficacy sections (Section 2.4.5 and Section 2.4.4).

Demographic characteristics

Demographic variables are

- Gender (Male, Female),
- Race (Caucasian/white, Black/of African descent, Asian/Oriental, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other)
- Age in years (quantitative and qualitative variable : <18, 18-64, 65–74, 75-84, and ≥85 years)
- Ethnicity (Hispanic, non-Hispanic)
- Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia, Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)
- Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)
- Weight in kg (quantitative and qualitative variable : <50, 50-<100 and ≥100 kg)
- BMI in kg/m2 (quantitative and qualitative variable: <30, ≥30 kg/m2)
- Alcohol drinking frequency (Never, At least monthly, At least weekly and At least daily) and number of standard alcohol drinks on a typical day when drinking (1 OR 2, >2)

Medical or surgical history

Medical (or surgical) history includes all the relevant medical (or surgical) history during the lifetime of the patient.

This information will be coded using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Comorbidity history will be summarized separately. The following comorbid diseases will be summarized.

- Atopic dermatitis history (Yes, Ongoing condition)
- Allergic conjunctivitis history (Yes, Ongoing condition)
- Allergic rhinitis history (Yes, Ongoing condition)
- Allergic conjunctivitis and/or rhinitis history (Yes, Ongoing condition)
- Chronic rhinosinusitis history (Yes, Ongoing condition)
- Nasal polyposis history (Yes, Ongoing condition)
- Eosinophillic esophagitis history (Yes, Ongoing condition)
- Food allergy history (Yes, Ongoing condition)
- Hives history (Yes, Ongoing condition)

A patient is considered to have atopic medical condition if he/she has any of the following: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE ≥100 IU/mL and at least one aeroantigen specific IgE is positive (≥0.35 IU/mL) at baseline.

Disease characteristics at baseline

The following baseline disease characteristics will be summarized by treatment group separately:

- ICS dose level (medium, high as defined in Appendix C)
- Age of asthma onset
- Time since first diagnosis of asthma (years)
- Smoking history (Never, Former*), time since cessation of smoking (months) and smoking quantity in pack-years for former smokers

  * *Current smokers are excluded from this study.*
- Time since last severe asthma exacerbation (months)
- Number of severe asthma exacerbation experienced within1 year before Visit 1 (quantitative variable and qualitative variable: 0, 1, 2, 3, ≥4)
- Eosinophil stratum at randomization (<0.3, ≥0.3 Giga/L)

- Baseline spirometry data including pre-bronchodilator FEV1 (L), percent predicted FEV1, post-bronchodilator FEV1 (L) and FEV1 reversibility (%).
- AM and PM PEF (L/min)
- AM and PM symptom scores
- Number of nocturnal awakenings/night
- ACQ-5 score
- ACQ-7 score
- AQLQ global score
- Number of inhalations of salbutamol/albuterol and levosalbutamol/levabuterol per day
- Hypersensitivity to aspirin/NSAID (Yes, Ongoing condition)

Severe asthma exacerbation prior to the study is defined as any treatment with 1 systemic (oral or parenteral) steroid bursts or more for worsening asthma or hospitalization or an emergency/urgent medical care visit for worsening asthma. Any technical details related to computation, dates, and imputations for missing dates are described in Section 2.5.

2.1.2 Prior or concomitant medications

All medications taken within 30 days before screening and until the end of the study, including asthma controller medications, systemic corticosteroids are to be reported in the case report form pages.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) version currently in effect at Sanofi at the time of database lock.

- Prior medications are those the patient used prior to first IMP injection. Prior medications can be discontinued before first administration or can be ongoing during treatment phase.
- Concomitant medications are any treatments received by the patient concomitantly to the IMP, from the first administration of IMP to the last administration of IMP + 98 days or until rollover to the LTS12551 study. A given medication can be classified as a prior medication, concomitant medication and posttreatment medication at the same time.
- Posttreatment medications are those the patient took in the period from the last administration of IMP + 99 days to the end of the study

2.1.2.1 Inhaled corticosteroid in combination with one or two other controllers

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination or concurrently with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor, but the sponsor will reimburse investigators for patients' use of controller drugs in the study to ensure all patients have access to their controllers.

Prior to screening, patients must be on a stable background therapy of a medium to high dose of ICS (≥250 mcg of fluticasone propionate twice daily or equipotent ICS daily dosage to a

maximum of 2000 mcg/day of fluticasone propionate or equivalent) [Note for Japan: subjects aged 18 years and older, ICS must be ≥200 mcg of fluticasone propionate twice daily or equivalent; subjects aged 12 to 17 years, ICS must be ≥100 mcg of fluticasone propionate twice daily or equivalent] in combination with a second controller medication (eg, long-acting beta agonist [LABA], leukotriene receptor antagonist [LTRA], theophylline, etc) for at least 3 months at a stable dose ≥1 month prior to Visit 1. Patients requiring a third controller are allowed to participate in this study. The third controller should also be used for at least 3 months at a stable dose ≥1 month prior to Visit 1(patients requiring systemic steroids as controller medication or biologics are excluded). If patients take two different ICS, the total daily dose of ICS should be calculated to evaluate the eligibility criteria on daily dose of ICS which will be still considered as one controller. Please refer to medium and high dose of ICS in Appendix C. The minimum daily dose of fluticasone propionate is 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equal to the upper limit of medium daily dose for fluticasone propionate as instructed in Appendix C. For ICS other than fluticasone propionate, please refer to the table in Appendix C which indicates the upper limit of the medium daily dose for each ICS which is equivalent to 500 mcg/day of fluticasone propionate. A list of recognized controller medications is provided in Appendix B. Number of controllers taken by each patient will be counted by therapeutic drug class. All drugs in a therapeutic class will be only counted once.

During the randomized treatment period, patient will continue to take their controller medication(s) used during the screening period. The dose and regimen should not be changed. Only a transient increase in dose of ICS in addition to other rescue medication will be allowed to treat acute symptoms of asthma as per investigator's guidance.

Upon completing the 52-week randomized treatment period, controller medication regimen for patients not continuing with the open label extension could be adjusted based on the investigator’s medical judgment. .

2.1.2.2 Reliever medication

Patients may administer albuterol/salbutamol or levalbuterol/levosalbutamol MDI as reliever medication as needed during the study. Nebulizer solutions may be used as an alternative delivery method.

Salbutamol/albuterol nebulizer and levosalbutamol/levalbuterol nebulizer use recorded in the electronic diary will be converted to number of puffs as shown on the following table:

Salbutamol/Albuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
2.5	4
5.0	8
7.5	12
10	16

*Conversion factor: salbutamol/albuterol nebulizer solution (2.5 mg) corresponds to 4 puffs

Example of salbutamol/albuterol Nebulizer-to-Puff Conversion: Patient received 3 salbutamol/albuterol nebulizer treatments (2.5 mg/treatment) between 7 and 11 AM. Total daily = 7.5 mg ->12 puffs.

Levosalbutamol/Levalbuterol Nebulizer Solution -Total Daily Dose (mg)	Number of Puffs*
1.25	4
2.5	8
3.75	12
5	16

*Conversion factor: levosalbutamol/levalbuterol nebulizer solution (1.25 mg) corresponds to 4 puffs

Example of levosalbutamol/levalbuterol Nebulizer-to-Puff Conversion: Patient received 3 levosalbutamol/levalbuterol nebulizer treatments (1.25 mg/treatment) between 7 and 11 AM. Total daily = 3.75 mg ->12 puffs.

Any technical details related to computation, dates, imputation for missing dates are described in Section 2.5.

2.1.3 Efficacy endpoints

Baseline for efficacy endpoints is defined as the last non-missing value up to randomization but prior to the administration of the first IMP unless otherwise specified.

2.1.3.1 Primary efficacy endpoint(s)

There are two primary endpoints for this study, the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period and the absolute change from baseline in pre-bronchodilator FEV1 at week 12.

A severe exacerbation event during the study is defined as a deterioration of asthma requiring:

- Use of systemic corticosteroids for ≥3 days; or
- Hospitalization or emergency room visit because of asthma, requiring systemic corticosteroids

Two events are considered as different if the start dates are separated by at least 4 weeks.

The annualized rate of severe exacerbation events during the 52-week treatment period is defined as the number of severe exacerbation events with onset during the 52-week treatment period per patient-year. Patients who permanently discontinue the study medication will be asked and encouraged to return to the clinic for all remaining study visits and their additional off-treatment severe exacerbation events up to Visit 18(Week 52) will be included.

2.1.3.2 Secondary efficacy endpoint(s)

2.1.3.2.1 Key secondary endpoint

The key secondary endpoint of this study is percent change from baseline in pre-bronchodilator FEV1 at Week 12.

2.1.3.2.2 Other secondary efficacy endpoints

The other secondary efficacy endpoints include:

- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.3 Giga/L
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients on high dose of ICS
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients on high dose of ICS
- Annualized rate of severe exacerbations events during the 52-week placebo-controlled treatment period for patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Percent change from baseline in pre-bronchodilator FEV1 at Week 12 in patients with a baseline blood eosinophil count ≥0.15 Giga/L
- Absolute change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Percent change from baseline in pre-bronchodilator FEV1 at Weeks 2, 4, 8, 24, 36, and 52
- Change from baseline in other lung function measurements (% predicted FEV1, morning [AM]/evening [PM] peak expiratory flow [PEF], forced vital capacity [FVC], forced expiratory flow [FEF] 25-75%, post-bronchodilator FEV1 at Weeks 2, 4, 8, 12, 24, 36, and 52
- Annualized rate of loss of asthma control (LOAC) event during the 52-week placebo-controlled treatment period
- Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period

- Time to first severe exacerbation event
- Time to first loss of asthma control event (LOAC)
- Change from baseline in Asthma Control Questionnaire (ACQ)-5 score and ACQ-7 score at Weeks 2, 4, 8, 12, 24, 36, and 52
- Change from baseline at Weeks 2, 4, 8 12, 24, 36, and 52 in:
  - Morning/evening asthma symptom score and nocturnal awakenings (e-diary)
  - Use of daily puffs of rescue medication
- Change from baseline in Health care resource utilization at Weeks 12, 24, 36, and 52
- Change from baseline in PROs at Week 12, 24, 36, and 52:
  - Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)
  - European Quality of Life Working Group Health Status Measure 5 Dimensions, 5 Levels (EQ-5D-5L)
  - Hospital Anxiety and Depression Scale (HADS)
  - 22-item Sino Nasal Outcome Test (SNOT-22) in those patients with comorbid bilateral nasal polyposis and/or chronic rhinosinusitis
  - Standardized Rhinoconjunctivitis Quality Of Life Questionnaire, ages 12+ (RQLQ(S)+12) in those patients with comorbid allergic rhinitis

Endpoints to be formally tested with multiplicity adjustments are listed in the testing order in Section 2.4.4.3 and Table 6.

2.1.3.2.2.1 Annualized rate of loss of asthma control (LOAC) event

LOAC event during the study is defined as any of the following:

- ≥6 additional reliever puffs of salbutamol/albuterol or levosalbutamol/levalbuterol in a 24 hour period (compared to baseline) on 2 consecutive days or
- ≥20% decrease in pre-bronchodilator FEV_1 compared to baseline or
- Increase in ICS dose ≥4 times than the dose at Visit 2 or
- A decrease in AM or PM peak flow of 30% or more on 2 consecutive days of treatment, based on the defined stability limit. The Treatment Period stability limit is defined as the respective mean AM or PM PEF obtained over the last 7 days prior to randomization (Day1); or
- Severe exacerbation event

The annualized rate of LOAC events during the 52-week treatment period is defined as the number of LOAC events with onset during the 52-week treatment period per patient-year.

2.1.3.2.2.2 Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit

Annualized rate of severe exacerbation event requiring hospitalization or emergency room visit (requiring systemic corticosteroids) during the 52-week treatment period and annualized rate of severe exacerbation event requiring hospitalization during the 52-week treatment period will also be analyzed.

2.1.3.2.2.3 Time to first severe exacerbation event/first LOAC event

If a patient has an event during the 52-week treatment period, regardless the patient is on the study treatment or discontinues the study treatment but remains in the study, the time to first severe exacerbation event/first LOAC event is defined as (onset date of the first severe exacerbation/LOAC event – randomization date +1).

If a patient has no severe exacerbation event/LOAC event during the study up to Visit 18/Week 52, then the patient will be considered as free of event until the date of visit at Visit 18 or the last contact date, whichever happens earlier.

2.1.3.2.2.4 Disease-specific efficacy measures

2.1.3.2.2.4.1 Spirometry

A spirometer that meets the 2005 American Thoracic Society (ATS) / European Respiratory Society (ERS) recommendations will be used. Spirometry should be performed in accordance with the ATS/ ERS guidelines (1). For pre-bronchodilator measured parameters, including FEV1, PEF, FVC and FEF 25-75%, spirometry will be performed after a wash out period of bronchodilators according to their duration of action, for example, withholding the last dose of salbutamol/albuterol or levosalbutamol/levalbuterol for at least 6 hours and withholding the last dose of LABA for at least 12 hours (ultra-long acting LABA like vilanterol should be withheld for at least 24 hours) and withholding the last dose of LAMA for at least 24 hours. This will be verified before performing the measurements.

At least three measurements fulfilling the ATS acceptability and repeatability criteria should be obtained at every visit, if possible. The acceptability criteria must be applied before the repeatability criteria. Unacceptable maneuvers must be discarded before applying the repeatability criteria. If a subject fails to provide repeatable and/or acceptable maneuvers, an explanation should be recorded. The largest FEV1 and largest FVC will be recorded after the data are examined from all of the acceptable curves, even if they do not come from the same curve. The FEF 25-75% should be obtained from the single curve that meets the acceptability criteria and gives the largest sum of FVC plus FEV1 (best test).

Japanese Respiratory Society predicted set are used for Japanese patients to calculated percent predicted FEV1 and NHANES III predicted set for all other patients.

2.1.3.2.2.4.2 Reversibility

A reversibility test will be administered following pulmonary function testing after asthma medications have been withheld for the appropriate intervals. Subjects will receive two to up to four puffs of albuterol/salbutamol or levalbuterol/levosalbutamol from a primed MDI. Alternatively and only if it is consistent with usual office practice (to be documented), reversibility may be performed using inhalation of nebulized albuterol/salbutamol or levalbuterol/levosalbutamol. Spirometry may be repeated several times within 30 minutes after administration of bronchodilator. FEV1 reversibility is calculated as Post-bronchodilator FEV1 - Pre-bronchodilator FEV1 and percent FEV1 reversibility is calculated as (Post-bronchodilator FEV1 - Pre-bronchodilator FEV1) / Pre-bronchodilator FEV1 * 100.

2.1.3.2.2.4.3 Post-bronchodilator (Post-BD) FEV1

Post-BD FEV1 is obtained from the spirometry performed after administration of reliever medications for reversibility test. The largest FEV1 will be recorded after the data are examined from all of the acceptable curves.

2.1.3.2.2.4.4 ACQ (Asthma Control Questionnaire)

The ACQ was designed to measure both the adequacy of asthma control and change in asthma control which occurs either spontaneously or as a result of treatment.

2.1.3.2.2.4.4.1 ACQ-7 (Asthma Control Questionnaire, 7-question version)

The ACQ-7 has 7 questions- the first 5 items assess the most common asthma symptoms: 1. frequency in past week awoken by asthma during the night, 2. severity of asthma symptoms in the morning, 3. limitation of daily activities due to asthma, 4. shortness of breath due to asthma and 5. wheeze, plus 6. short-acting bronchodilator use and 7. FEV1 (pre-bronchodilator % predicted). Patients are asked to recall how their asthma has been during the previous week and to respond to the symptom questions on a 7-point scale (0=no impairment, 6=maximum impairment) (see Appendix E).

Clinic staff scores the FEV1% predicted on a 7-point scale. The questions are equally weighted and the ACQ score is the mean of the 7 questions and therefore between 0 (totally controlled) and 6 (severely uncontrolled).

Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflecting inadequately controlled asthma. On the 7-point scale of the ACQ-7, a change or difference in score of 0.5 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Based on the manual of ACQ (2), any more than one missing value is not acceptable. If more than one of the questions have missing value, the global score is invalid and will be considered as missing. If only one question has missing score, it will be imputed (pro-rated) using the completed

questionnaires from the previous visit. For instance, answer to question 5 is missing at Visit 2, and all questions are completed at Visit 1. Then the question 5 score at Visit 2 is imputed as: (sum of score at Visit 2/sum of scores excluding question 5 at Visit 1) × score of question 5 at Visit 1. If the questionnaire from the previous visit is not complete either, the missing value will be imputed as the average of the completed questions within the current visit.

2.1.3.2.2.4.4.2 ACQ-5 (Asthma Control Questionnaire, 5-question version)

The ACQ-5 is short version of ACQ-7, and ACQ-5 score is the mean of the first 5 questions of ACQ-7 and, therefore, between 0 (totally controlled) and 6 (severely uncontrolled). The last two questions on the ACQ-7, assessing lung functions, are not included in ACQ-5. Higher score indicates lower asthma control. Patients with a score below 1.0 reflect adequately controlled asthma and patients with scores above 1.0 reflect inadequately controlled asthma. On the 7-point scale of the ACQ-5, a change or difference in score of 0.5 at patient level is the smallest change that can be considered clinically important, corresponding to the Minimal Clinically Important Difference (MCID) defined by the developer.

Missing scores will be handled in the same way as for ACQ-7 score.

2.1.3.2.2.5 Disease-specific, daily efficacy assessment

On a daily basis throughout the study, the patient uses an electronic diary / PEF meter to:

- Measure morning and evening PEF
- Respond to the morning and evening asthma symptom scale questions
- Indicate the number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
- Record the number of nocturnal awakenings due to asthma symptoms

2.1.3.2.2.5.1 Morning (AM) and Evening (PM) Peak expiratory flow (PEF)

At screening (Visit 1), patients will be issued an electronic diary/PEF. Patients will be instructed on the use of the device, and written instructions on the use of the electronic PEF meter will be provided to the patients. In addition, the investigator will instruct the patients on how to record the following variables in the electronic PEF meter:

- AM PEF performed within 15 minutes after arising (between 5:30 AM and 10 AM) prior to taking any albuterol or levalbuterol
- PM PEF performed in the evening (between 5:30 PM and 10 PM) prior to taking any albuterol or levalbuterol
- Patients should try to withhold albuterol or levalbuterol for at least 6 hours prior to measuring their PEF
- Three PEF efforts will be performed by the patient; all 3 values will be recorded by the electronic PEF meter, and the highest value will be used for evaluation

Baseline AM PEF will be the mean AM measurement recorded in the 7 days prior to randomization including the morning diary completed on the randomization day prior to the first administration of IMP, and baseline PM PEF will be the mean PM measurement recorded for the 7 days prior to the randomization. There should be at least 4 days' measurement out of the 7 days for setting up the period stability limit/baseline, and the first dosing visit should be rescheduled until data for 4 days are available. In case less than 4 days' measurement is available during the 7 days prior to randomization, the baseline AM/PM PEF is the mean of the 4 AM/PM PEF prior to and closest to randomization during the whole screening period. Calculation of periodical average of post-baseline AM/PM PEF is specified in Section 2.5.2.

2.1.3.2.2.5.2 Asthma Symptom Score Numerical Rating Scale (NRS)

Patients will record overall symptom scores in an electronic diary twice a day prior to measuring PEF. The patient's overall asthma symptoms experienced during the waking hours will be recorded in the evening (PM symptom score). Symptoms experienced during the night will be recorded upon arising (AM symptom score). The baseline AM/PM symptom score will be computed following the same algorithm used for baseline AM/PM PEF. Scores range between 0-4 with 0 indicating more mild symptoms and 4 indicating more severe symptoms. Calculation of periodical average of post-baseline AM/PM symptom score is specified in Section 2.5.2.

2.1.3.2.2.5.3 Use of rescue/reliever medicine

The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations will be recorded daily by the patients in an electronic diary/PEF meter. In the case that Nebulizer solutions are used as an alternative delivery method, the nebulizer dose will be converted to number of puffs according to Section 2.1.2.2. Each patient should be reminded that salbutamol/albuterol or levosalbutamol/levalbuterol should be used only as needed for symptoms, not on a regular basis or prophylactically. The baseline number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day will be based on the mean of the 7 days prior to randomization.

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The baseline reliever med use will be calculated as follows: The mean of reliever puffs taken in each of the 7 diary days (minimum 4 diary days) prior to randomization, including the diary day that ends with the morning diary completed on the randomization day. A diary day cannot be included in the calculation if it is not complete, meaning if an evening or morning diary is missing for that diary day. Out of the 7 diary days, if less than 4 are incomplete, the baseline reliever use is the mean of reliever puffs in each of the complete dairy days. If 4 or more diary days are incomplete, the baseline reliever use is the mean of reliever puffs taken in the closest 4 diary days with complete reliever use information prior to randomization. Calculation of periodical average of post-baseline use of reliever puffs is specified in Section 2.5.2.

2.1.3.2.2.6 Patient-reported outcomes

2.1.3.2.2.6.1 Asthma Quality of Life Questionnaire) Asthma Quality Of Life Questionnaire with Standardized Activities (AQLQ (S)) Self-Administered (≥12 years)

The AQLQ(S) was designed as a self-administered patient reported outcome to measure the functional impairments that are most troublesome to adolescents and adults ≥12 years of age as a result of their asthma (see Appendix G). The instrument is comprised of 32 items, each rated on a 7-point Likert scales from 1 to 7. The AQLQ(S) has 4 domains. The domains and the number of items in each domain are as follows:

- Symptoms (12 items)
- Activity limitation (11 items)
- Emotional function (5 items)
- Environmental Stimuli (4 items)

Individual items are equally weighted. The overall score is the mean of response to each of the 32 questions. The score of each domain is the mean of response to each of the questions in that domain. The overall score and domain scores ranges from 1 to 7. Higher scores indicate better quality of life.

To have a valid overall score, it is not acceptable to have more than three missing responses or more than one missing response per domain. For the symptoms and activity limitation domain score, only one missing value per domain is acceptable. For the emotional function and environmental stimuli domain scores, no missing value is acceptable. For responses with more than acceptable amount of missing value(s), the overall or the domain score will be considered as missing. For responses with amount of missing value(s) within accept range, the missing score will be interpolated using the previous completions of the questionnaire following the similar algorithm used for ACQ.

The instrument has been used in many clinical trials, and it has been shown to be reliable, valid (patient interviews), and sensitive to change. The patient level MCID for AQLQ(S) is 0.5 (3).

2.1.3.2.2.6.2 22-item Sinonasal Outcome Test in those patients comorbid with bilateral nasal polyposis and/or chronic rhinosinusitis

SNOT-22 is a validated questionnaire to assess the impact of chronic rhinosinusitis with or without nasal polyposis on health-related quality of life (see Appendix H). The SNOT-22 has 22 items, 5 domains and a global score. The 5 domains include Nasal (range 0-30), Ear (range 0-15), Sleep (0-20), General and Practical (0-30), and Emotional (0-15). The range of the global score is 0-110. Lower scores indicate less impact and the recall period is past 2 weeks. The domains and the items in each domain are as follows:

- Nasal: item 2, 3, 4, 6, 7, 12
- Ear: item 8, 9, 10

- Sleep: item 13, 14, 15, 16
- General and Practical: item 1, 5, 11, 17, 18, 19
- Emotional: item 20, 21, 22

The global score is the sum of response to each of the 22 questions. For responses with some item scores are missing, the global score will be imputed as mean of the completed scores × 22, providing at least 50% of items have been completed. If more than 50% of items are missing, the global score is set to missing. The score for each domain is the sum of response to each question in that domain. Missing score will be imputed as mean of the completed items in that domain × total number of items in that domain, providing at least 50% of items in that domain have been completed. If more than 50% of items in a domain are missing, the score for that domain is set to missing.

2.1.3.2.2.6.3 Hospital Anxiety and Depression Scale

The HADS is a general scale to detect states of anxiety and depression already used and validated in asthma, which includes HADS-A and HADS-D subscales (see Appendix I). The instrument is comprised of 14 items: 7 related to anxiety and 7 to depression. Each item on the questionnaire is scored from 0-3. The anxiety/depression score is the sum of the scores of the 7 related items; one can score between 0 and 21 for either anxiety or depression. And the total score is the sum of the scores of the 14 items ranging from 0-42.

The HADS was found to perform well in assessing anxiety disorders and depression in both somatic and psychiatric cases and (not only in hospital practice for which it was first designed) in primary care patients and the general population (4).

2.1.3.2.2.6.4 EQ-5D-5L

EQ-5D-5L is a standardized health-related quality of life questionnaire developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (5). EQ-5D is designed for self-completion by patients.

The EQ-5D essentially consists of 2 pages - the EQ-5D descriptive system and the EQ VAS (see Appendix J). The EQ-5D descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. EQ-5D-5L health status will be converted into a single index value by using EQ-5D-5L value sets based on UK population. The EQ Visual Analogue Scale (VAS) records the respondent's self-rated health on a vertical visual analogue scale. The EQ VAS 'thermometer' has endpoints of 100 (Best imaginable health state) at the top and 0 (Worst imaginable health state) at the bottom.

2.1.3.2.2.6.5 Standardized Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ(S))+12 in those patients with comorbid allergic rhinitis.

RQLQ(S)+12 (see Appendix K) is a self-administered questionnaire with standardized activities developed to measure health-related quality of life signs and symptoms that are most problematic in those 12 to 75 years of age, as a result of perennial or seasonal allergic rhinitis. There are 28 items on the RQLQ(S) in 7 domains: 1. Activities (3 items), 2. Sleep (3 items), 3. Non-nose/eye Symptoms (7 items), 4. Practical Problems (3 items), 5. Nasal Symptoms (4 items), 6. Eye Symptoms (4 items) and 7. Emotional (4 items). The RQLQ(S)+12 responses are based on 7-point Likert scale with responses ranging from 0 (not troubled) to 6 (extremely troubled). Individual items within the RQLQ(S)+12 are equally weighted. The overall score is calculated as the mean score of all items. And the score for each domain is calculated as the mean score of the items in each of the domains. No interpolation will be performed for missing scores. Higher scores indicated more health-related quality of life impairment (lower scores better). The instrument takes approximately 7 minutes to complete. An MID of 0.5 has been established as the minimal important difference indicative of a clinically meaningful change (6).

2.1.4 Safety endpoints

The safety analysis will be based on the reported adverse events and other safety information, such as clinical laboratory data, vital signs, ECG and physical examination.

Observation period

The observation period will be divided into 4 epochs:

- The **screening** epoch is defined as the time from the signed informed consent date up to the time prior to first administration of the IMP.
- The **treatment** epoch is defined as the time from the first administration of the IMP to the last administration of the IMP + 14 days or until rollover to the LTS12551 study.
- The **residual treatment** epoch is defined as the time from the last administration of the IMP +15 days to the last administration of the IMP + 98 days or until rollover to the LTS12551 study.
- The treatment-emergent adverse event period will include both **treatment** and **residual treatment** epochs.
- The **posttreatment** epoch is defined as the period of time starting the day after the end of the treatment-emergent adverse event period up to the end of the study (defined as last protocol planned visit or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

The on-study observation period is defined as the time from start of treatment until the end of the study (defined as last protocol planned visit or lost to follow-up or the resolution/stabilization of all serious adverse events and adverse events with pre-specified monitoring).

2.1.4.1 Adverse events variables

Adverse event observation period

- Pretreatment adverse events are adverse events that developed or worsened or became serious from the signed informed consent date up to first administration of IMP
- Treatment-emergent adverse events are adverse events that developed or worsened or became serious during the treatment-emergent adverse event period
- Posttreatment adverse events are adverse events that developed or worsened or became serious during the posttreatment period

All adverse events (including serious adverse events and adverse events with pre-specified monitoring/of special interests) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the version of Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock.

Adverse events of special interest (AESI) and other selected AE groupings will be searched based on the criteria in Table 3:

Table 3 - Criteria for adverse events of special interest and other selected AE groupings

AE Grouping	Criteria
AESI	
Anaphylactic reaction	Anaphylactic reaction algorithmic approach (*Introductory Guide for Standardised MedDRA Queries (SMQs) Version 18.1*): includes anaphylactic reaction narrow SMQ (20000021) terms; for selection based on occurrence of multiple events, the events must have occurred within 24 hours of each other
Hypersensitivity (medically reviewed)	SMQ hypersensitivity (20000214) narrow search and [AE corrective treatment/therapy='Y' or Action taken with IMP='Drug withdrawn' or Action taken with IMP='Drug interrupted'] followed by blinded medical review (documented process) for selection of relevant events
Serious injection site reactions or severe injection site reactions that last longer than 24 hours	HLT = 'Injection site reaction' and either with serious status, or with severe status and (AE end date/time - AE start date/time) ≥ 24 hours or ongoing
Severe or serious infection	Primary SOC = 'Infections and infestations' and with severe or serious status
Parasitic infection	Infection Type 'Parasitic' checked on eCRF Infection Defined as AESI Complementary Form
Opportunistic infection	Infection Type 'Opportunistic' checked on eCRF Infection Defined as AESI Complementary Form
Drug-related hepatic disorder	Drug-related hepatic disorders-Comprehensive search narrow SMQ (20000006)

(electronic 3.0)

AE Grouping	Criteria
Pregnancy	Primary SOC = 'Pregnancy, puerperium and perinatal conditions' or PT in (Aborted pregnancy, False negative pregnancy test, Pregnancy test positive, Pregnancy test urine positive, Ectopic pregnancy termination)
Symptomatic overdose with IMP	Is the event a Symptomatic Overdose with IMP? is answered Yes on AE eCRF.
Symptomatic overdose with non-IMP	Is the event a Symptomatic Overdose with non-IMP? is answered Yes on AE eCRF
Other selected AE grouping	
Injection site reaction	HLT = 'Injection site reaction'
Malignancy	Sub-SMQ (20000091)– Malignant or unspecified tumors
Suicidal behavior	PT in (Completed suicide, Suicidal ideation, Depression suicidal, Suicidal behavior, Suicide attempt)
Partner pregnancy	PT in (Pregnancy of partner, Miscarriage of partner)
Conjunctivitis (narrow)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis)
Conjunctivitis (broad)	PT in (Conjunctivitis, Conjunctivitis allergic, Conjunctivitis bacterial, Conjunctivitis viral, Atopic keratoconjunctivitis, Blepharitis, Dry eye, Eye irritation, Eye pruritus, Lacrimation increased, Eye discharge, Foreign body sensation in eyes, Photophobia, Xerophthalmia, Ocular hyperaemia, Conjunctival hyperaemia)
Hypereosinophilia	HLT = 'Eosinophilic disorders' or PT = 'Eosinophil count increased'

In addition, AESIs reported by the investigator in CRF will be summarized separately.

2.1.4.2 Deaths

The deaths observation period are per the observation periods defined above.

- Death on-study: deaths occurring during the on-study observation period
- Death on-treatment: deaths occurring during the treatment-emergent adverse event period
- Death poststudy: deaths occurring after the end of the study

2.1.4.3 Laboratory safety variables

Clinical laboratory data consists of blood analysis, including hematology, clinical chemistry, and urinalysis. Clinical laboratory values after conversion will be analyzed in standard international units and international units will be used in listings and tables. The same set of analysis will also be prepared in US units.

Blood samples for clinical laboratories will be taken at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64) and early termination unless otherwise specified. The laboratory parameters will be classified as follows:

- Hematology
  - **Red blood cells and platelets and coagulation**: hemoglobin, hematocrit, red blood cell count, platelet count
  - **White blood cells**: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils
- Clinical chemistry
  - **Metabolism**: glucose, total cholesterol, total protein, creatine phosphokinase
  - **Electrolytes**: sodium, potassium, chloride, bicarbonate
  - **Renal function**: creatinine, blood urea nitrogen, uric acid
  - **Liver function**: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactate dehydrogenase, total bilirubin (in case of values above the normal range, differentiation in conjugated and non-conjugated bilirubin), albumin
  - **Pregnancy test**: serum β-human chorionic gonadotropin (all female patients) will be performed at screening (Visit 1) in women of childbearing potential
  - **Hepatitis screen**: clinical laboratory testing at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study) add hepatitis screen including hepatitis B surface antigen (HBs Ag), hepatitis B Surface antibody (HBs Ab), hepatitis B core antibody (HBc Ab), hepatitis C virus antibodies (HCV Ab), In case of results showing HBs Ag (negative), HBs Ab (negative) and HBc Ab (positive), an HBV DNA testing may be performed prior to randomization to rule out a false positivity if the investigator believes the patient is a false positive, or to clarify the serological status if the investigator finds it unclear to interpret in absence of known HBV infection. In case of results showing HCV Ab (positive), an HCV RNA testing may be performed to rule out a false positivity, if the investigator believes the patient is a false positive.
  - **Hepatitis B viral load** will be tested at Visit 2, then every 12 weeks until Visit 14 and end of treatment period for patients in Japan or other countries/regions if there is local regulatory requirement who are HBs Ag negative and HBs Ab positive at screening.
  - **HIV screen**: anti-HIV-1 and HIV-2 antibodies will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)
  - **Anti-nuclear antibody (ANA)** will be tested at Visit 1 and Visit 17 (only applicable for patients planned to participate in the OLE study)

    Note: Anti-ds DNA antibody will be tested if ANA is positive (≥1:160 titer).

- Serum immunoglobulins (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): quantitative immunoassays for total IgG, IgG subclasses 1-4, IgM, and IgA.

Urine samples will be collected as follows:

- **Urinalysis** (limited to Visit 1(Week -4±1), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64)): Urine dipstick analysis specific gravity, pH, glucose, ketones, blood, protein, nitrate, leukocyte esterase, urobilinogen and bilirubin (by dipstick). If any parameter on the dipstick is abnormal, a urine sample should be sent to the central laboratory for testing. If positive for proteins, microscopic analysis is performed by central laboratory.
- A **urine dipstick pregnancy test** will be performed at Visit 2 prior to randomization and Visit 4 (Week 4), Visit 6 (Week 8), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 12 (Week 28), Visit 13 (Week 32), Visit 14 (Week 36), Visit 15 (Week 40), Visit 16(Week 44), Visit 17(Week 48), Visit 18(Week 52),Visit 21(Week 64)

Technical formulas are described in Section 2.5.1.

2.1.4.4 Vital signs variables

Vital signs include: including blood pressure (mmHg), heart rate (beats per minute), respiratory rate (breaths per minute), body temperature (degrees Celsius) and body weight (kg) will be measured at the screening and randomization visits (Visits 1 and 2) and every subsequent visit. Height (cm) will be measured at screening (Visit 1) for all patients and will be measured throughout the study for adolescent patients. Vital signs will be measured in the sitting position using the same arm at each visit, and will be measured prior to receiving investigational product at the clinic visits.

2.1.4.5 Electrocardiogram variables

One recording of a standard 12-lead ECG will be performed centrally at Visit 1(Week -4±1), Visit 3 (Week 2), Visit 4 (Week 4), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36), Visit 18(Week 52), and Visit 21 (Week 64). At the post-randomization visits, ECGs will be performed prior to investigational product administration. A minimum of 3 complexes in an appropriate lead (lead II) will be averaged to determine the PR-interval, QT/QTc-interval, QRS-complex and heart rate will be measured for each ECG. All ECG recordings will be centrally read by independent experts.

2.1.4.6 Physical Examination

Physical examinations will be performed at Visit 1(Week -4±1), Visit 11 (Week 24), Visit 18(Week 52), and Visit 21 (Week 64) including an assessment of general appearance, skin, eyes, ear/nose/throat, heart, chest, abdomen, reflexes, lymph nodes, spine, and extremities. All deviations from normal will be recorded, including those attributable to the patient's disease.

Refer to Section 1.2 Study Flow Chart for the schedule of physical examination performed throughout this study.

2.1.5 Pharmacokinetic variables

Predose serum dupilumab concentrations at Visit 2 (Day 1), dupilumab trough levels at Week 2, Week 4, Week 8, Week 12, Week 16, Week 24, Week 36, Week 52 and follow-up serum dupilumab at Week 56, Week 60, Week 64 will be provided.

2.1.6 Anti-drug antibody (ADA) variables

Anti-dupilumab antibody (ADA) status (negative or titer value, if positive in the ADA assay) at Visit 2 (Day 1), Week 12, Week 24, Week 52 and follow up at Week 64 will be provided. Patients who discontinue early from treatment or patients who choose not to participate in the OLE study visit may be asked to return to the clinic to have additional ADA samples collected for analysis based on the overall clinical presentation at that time.

Status in the ADA assay will be classified as the following:

1. Pre-existing immunoreactivity is defined as:

   An ADA positive response in the assay at baseline with all post treatment ADA results negative, OR an ADA positive response at baseline with all post treatment ADA responses less than 4-fold over baseline titer levels.

2. Treatment-emergent response is defined as:

   An ADA positive response in the assay post first dose, when baseline results are negative or missing.

3. Treatment-emergent ADA responses are further classified as Persistent, Indeterminate or Transient
   a) Persistent Response - defined as a treatment-emergent ADA response with two or more consecutive ADA positive sampling time points, separated by greater than (>) 12-week period (84 days), with no ADA negative samples in between.
   b) Indeterminate Response - defined as a treatment-emergent response with only the last collected sample positive in the ADA assay
   c) Transient Response - defined as a treatment-emergent response that is not considered persistent OR indeterminate

4. Treatment-boosted response is defined as:

   An ADA positive response in the assay post first dose that is greater-than or equal to 4-fold over baseline titer levels, when baseline results are positive.

Titer values (Titer value category)

- Low (Titer < 1000)
- Moderate (1,000 ≤ Titer ≤ 10,000)

- High (Titer > 10,000)

ADA positive samples will be further characterized for presence of neutralizing antibody response in the NAb assay.

2.1.7 Pharmacodynamics/genomics endpoints

Eotaxin-3, eosinophil cationic protein (ECP), total IgE and Thymus and Activation-Regulated Chemokine (TARC) will all be assayed at Visit 2(Week 0), Visit 8 (Week 12), Visit 11 (Week 24), Visit 14 (Week 36) and Visit 18(Week 52).

Periostin will be assayed at Visit 2(Week 0), Visit 4 (Week 4), Visit 8 (Week 12) and Visit 18(Week 52). And antigen-specific IgE panels will be collected at Visit 2(Week 0), Visit 8 (Week 12) and Visit 18(Week 52).

Blood eosinophil count will be measured as part of the standard 5-part WBC differential cell count on a hematology autoanalyzer.

Exhaled nitric oxide will be analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). This assessment should be conducted prior to spirometry and following a fast of at least 1 hour at Visit 1(Week -4±1), Visit 2 (Week 0), Visit 3 (Week 2),Visit 4 (Week 4), Visit 8 (Week 12), Visit 9 (Week 16), Visit 10 (Week 20), Visit 11 (Week 24), Visit 14 (Week 36), Visit 17(Week 48), Visit 18(Week 52), Visit 19(Week 56), Visit 20(Week 60), Visit 21(Week 64)

Pharmacogenetic testing is optional and voluntary. A separate written informed consent form must be signed before sampling. For those patients who signed the optional pharmacogenetic informed consent form, blood samples for exploratory genetic analysis of DNA or RNA will be collected at the study visit as specified in the study flow chart, and these samples will be stored for future analysis.

2.1.8 Vaccine response

Subjects planning to receive vaccinations for tetanus (alone or combined), influenza, pneumococcus or meningococcus during the study may optionally sign a separate informed consent for collection of 2 blood samples for assay of vaccine IgG in serum for each vaccine: the first should be drawn within 6 weeks prior to vaccination and then the second should be drawn 3 to 4 weeks after vaccination (up to 6 weeks afterward allowed). Vaccinations should preferably occur after completion of at least 12 weeks of treatment, while remaining in compliance with the patient's recommended immunization schedule. Blood collections should be conducted at regularly scheduled study visits but, if this is not feasible, could also be done at unscheduled visits. The details on the date(s) of vaccination and the specific vaccines that are administered, such as brand and antigenic strains, should be collected (see Appendix L).

2.1.9 Health economic endpoints

A questionnaire of health care resource utilization (reliever medication, specialist visit, hospitalization, emergency or urgent medical care facility visit, outcome, sick leaves, school days loss, etc) will be administered at Visit 2 and every 4 weeks thereafter.

2.2 DISPOSITION OF PATIENTS

This section describes patient disposition for both patient study status and the patient analysis populations.

Screened patients are defined as any patients signed the informed consent.

Randomized patients consist of all patients with a signed informed consent form who have had a treatment kit number allocated and recorded in the IRT database, regardless of whether the treatment kit was used.

For patient study status, the total number of patients in each of the following categories will be presented in the clinical study report summary table:

- Screened patients
- Screen failure patients and reasons for screen failure
- Nonrandomized but treated patients
- Randomized patients
- Randomized but not treated patients
- Randomized and treated patients
- Patients who did not complete the 52-week treatment as per protocol
- Patients who discontinued study treatment by main reason for permanent treatment discontinuation
- Patients who withdraw from study prior to Week 52
- Patients who withdraw from study prior to Week 52 by main reason for study discontinuation.
- Patients who withdraw from study
- Patients who withdraw from study by main reason for study discontinuation
- Status at last study contact

For all categories of patients (except for the screened and nonrandomized categories) percentages will be calculated using the number of randomized patients as the denominator. Reasons for treatment discontinuation will be supplied in tables giving numbers and percentages by treatment group. This summary will be provided by treatment group and may also be further subgrouped by region/stratum as applicable.

All critical or major deviations potentially impacting efficacy analyses, randomization, and drug-dispensing irregularities, and other major or critical deviations will be summarized in tables giving numbers and percentages of deviations by treatment group.

Additionally, efficacy populations will be summarized by number of patients on the randomized population.

- Efficacy population: intent-to-treat (ITT) population

The analysis populations for safety, pharmacokinetics/pharmacodynamics will be summarized by number of patents on the safety population.

- Safety population
- PK population
- ADA population

2.2.1 Randomization and drug dispensing irregularities

Randomization and drug-dispensing irregularities occur whenever:

5. A randomization is not in accordance with the protocol-defined randomization method, such as a) an ineligible patient is randomized, b) a patient is randomized based on an incorrect stratum, c) a patient is randomized twice, or d) in a dynamic randomization scheme the treatment assignment is, in fact, not random, due to a computer program error.

   OR

6. A patient is dispensed an IMP kit not allocated by the protocol-defined randomization, such as a) a patient at any time in the study is dispensed a different treatment kit than as randomized (which may or may not contain the correct-as-randomized IMP), or b) a nonrandomized patient is treated with IMP reserved for randomized patients.

Randomization and drug-dispensing irregularities will be monitored throughout the study and reviewed on an ongoing basis.

All randomization and drug-dispensing irregularities will be documented in the clinical study report. If the number of irregularities is large enough to make a tabular summary useful, the irregularities will be categorized and summarized among randomized patients (number and percentages). Nonrandomized, treated patients will be described separately.

Randomization and drug-dispensing irregularities to be prospectively identified include but are not limited to:

Randomization and drug allocation irregularities
Kit dispensation without IRT transaction
Erroneous kit dispensation
Kit not available

Randomization by error
Patient randomized twice
Stratification error
Patient switched to another site

2.3 ANALYSIS POPULATIONS

Patients treated without being randomized will not be considered randomized and will not be included in any efficacy population, but will be included in the safety population.

The randomized population includes any patient who has been allocated to a randomized treatment regardless of whether the treatment kit was used.

For any patient randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be assessed separately.

2.3.1 Efficacy populations

The primary efficacy analysis population will be the ITT population as defined in Section 2.3.1.1.

2.3.1.1 Intent–to-treat population

The intent-to-treat population is the randomized population analyzed according to the treatment group allocated by randomization.

Patients will be analyzed in the treatment group to which they are randomized.

2.3.2 Safety population

The safety population is defined as:

- All patients who actually received at least 1 dose or part of a dose of the IMP, analyzed according to the treatment patients actually received.

In addition:

- Randomized patients for whom it is unclear whether they took the IMP will be included in the safety population as randomized
- For patients on placebo but accidentally exposed to dupilumab, the treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.
- For patients on placebo but accidentally exposed to the other placebo dose, the treatment group allocation for as-treated analysis will be the treatment as randomized.

- For patients on dupilumab but accidentally receive different treatment from the planned, the actual treatment group allocation for as-treated analysis will be the lowest exposed dupilumab dose group.

2.3.3 Population for pharmacokinetics/pharmacodynamics analyses

The **PK population** will consist of all patients in the safety population with at least one evaluable serum concentration data. Patients will be analyzed according to the treatment actually received.

ADA population will consist of all patients in the safety population who had at least one reportable ADA results (either 'ADA negative' or 'ADA positive') after first dose of the study treatment.

Biomarkers will be analyzed in the **exposed population**, consisting of patients in the safety population.

2.4 STATISTICAL METHODS

2.4.1 Demographics and baseline characteristics

Continuous data will be summarized using the number of available data, mean, standard deviation (SD), median, minimum and maximum for each treatment group. Categorical and ordinal data will be summarized using the number and percentage of patients in each treatment group.

Parameters will be summarized on the randomized population analyzed in the treatment group to which they were randomized. Analyses for the safety population will be included in the appendices if the size of the safety population is different (>10%) from the size of that in the primary analysis population for any treatment group.

Parameters described in Section 2.1.1 will be summarized by treatment group and overall treatment groups using descriptive statistics.

Medical and surgical history will be summarized by treatment group and by system organ class (SOC) and preferred term (PT) sorted by internationally agreed order of SOC and by the decreasing frequency of PT within SOC based on the overall incidence across treatment groups. Atopic medical history will be summarized separately.

No statistical testing on demographic and baseline characteristic data will be performed.

No specific description of the safety parameters will be provided at baseline. If relevant, the baseline values will be described along with each safety analysis.

2.4.2 Prior or concomitant medications

The prior and concomitant medications will be presented for the randomized population.

Medications will be summarized by treatment group according to the WHO-DD dictionary, considering the first digit of the anatomic category (ATC) class (anatomic category) and the first 3 digits of the ATC class (therapeutic category). All ATC codes corresponding to a medication will be summarized, and patients will be counted once in each ATC category (anatomic or therapeutic) linked to the medication. Therefore patients may be counted several times for the same medication.

The table for prior medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the overall incidence across treatment groups. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

Concomitant medication received during first IMP to last IMP +14 days and concomitant medication received during first IMP to last IMP +98 days will be summarized separately. The tables for concomitant medications will be sorted by decreasing frequency of ATC followed by all other therapeutic classes based on the incidence in the dupilumab 300 q2w group. In case of equal frequency regarding ATCs (anatomic or therapeutic categories), alphabetical order will be used.

In addition, inhaled corticosteroid in combination with other controllers and reliever medications will be summarized separately.

On a daily basis throughout the study, the patient uses an electronic diary to record daily use of ICS in combination with other controllers as used just prior to screening. The controller drugs will not be dispensed or supplied by the sponsor.

2.4.2.1 ICS in combination with other controllers

ICS and other asthma controller medications will be identified as the medications reported on the 'Prescribed Asthma Controller Medications' eCRF page.

Prior asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the overall treatment group.

Concomitant asthma controller medications will be summarized by treatment group sorted by decreasing frequency of standard medication name on the incidence in the dupilumab 300 q2w group.

The total daily dose of ICS in asthma controller medication at randomization will be classified as medium-dose or high-dose according to Appendix C. If a patient takes more than one medication containing ICS, the ICS dose of different products will be standardized according to equivalent dose specified in Table 4 and Table 5. The equivalent dose is determined based on the thresholds in Appendix C. After conversion, the total daily dose for inhaled corticosteroid will be calculated and classified as medium or high dose.

Table 4 – Equivalent dose for inhaled corticosteroids for adults and adolescents (≥ 12 years)

Inhaled corticosteroid	Equivalent dose (mcg) to 500 mcg Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	200-*
BECLOMETASONE DIPROPIONATE (CFC)	1000
BECLOMETASONE DIPROPIONATE (HFA)	400
BUDESONIDE (DPI)	800
CICLESONIDE (HFA)	320
MOMETASONE FUROATE	440
TRIAMCINOLONE ACETONIDE	2000

ADAPTED FROM GINA 2016 GUIDELINES
HFA=hydrofluoroalkane, DPI= Dry Powder Inhaler
* Fluticason furoate (FF) dose >=200 mcg is converted to equivalent fluticasone propionate(DPI or HFA) dose of (FF dose +1)×2.5; FF dose <200 mcg is converted to equivalent fluticasone propionate (DPI or HFA) dose of FF dose ×2.5.
Example: A patient received 400 mcg budesonide (DPI) and 440 mcg mometasone furoate. They are equivalent to 250 mcg and 500 mcg fluticasone propionate correspondingly. The combined total daily dose is equivalent to 750 mcg fluticasone propionate and classified as high dose.

Table 5 – Equivalent dose of inhaled corticosteroid for adults and children (Japan)

Inhaled corticosteroid	Equivalent dose (mcg) to 400 Fluticasone propionate (DPI or HFA)
FLUTICASONE FUROATE	100
BECLOMETHASONE DIPROPIONATE -HFA	400
CICLESONIDE -HFA	400
BUDESONIDE-DPI	800
BUDESONIDE INHALATION SUSPENSION	1.0 mg
BUDESONIDE INHALATION SOLUTION	1000
MOMETASONE FUROATE-DPI	400

Adapted from Japanese Guideline for Adult Asthma 2014 and Japanese Guideline for Childhood Asthma 2014
Example: A patient received 400 mcg Beclomethasone dipropionate -HFA and 400 mcg Ciclesonide-HFA. They are both equivalent to 400 fluticasone propionate. The combined total daily dose is equivalent to 800 fluticasone propionate.

Number and percentage of patients on high-dose ICS, medium-dose ICS, any non-ICS controller medication, LABA, LAMA and LTRA at baseline will also be summarized.

2.4.2.1.1 Compliance

During the study, the daily intake of each prescribed asthma controller medication will be recorded on the electronic diary every evening. Compliance for the controller medications with ICS component and overall compliance to all prescribed controller medications will be calculated for each patient. For each day, a patient is considered as compliant with the prescribed controller medication with ICS component if the actual dose of each controller medication with ICS component is same as or greater than the prescribed dose. Similarly, a patient is considered as compliant with all controller medication if the actual dose of each controller medication is same as or greater than the prescribed dose.

Compliance for controller medication(s) with ICS component is defined as the number of days when the patient is compliant with the prescribed controller medication(s) with ICS component divided by the number of days the patient stays in the treatment period (from first dose to last dose + 14 days). **Overall controller medication(s) compliance** is defined as the number of days when the patient is compliant with all prescribed controller medication divided by the number of days the patient stays in the treatment period.

2.4.3 Extent of investigational medicinal product exposure and compliance

The extent of IMP exposure and compliance will be assessed and summarized by actual treatment within the safety population (Section 2.3.2).

2.4.3.1 Extent of investigational medicinal product exposure

The extent of IMP exposure will be assessed by the duration of IMP exposure.

Duration of IMP exposure is defined as last dose date – first dose date + 14 days, regardless of unplanned intermittent discontinuations (see Section 2.5.3 for calculation in case of missing or incomplete data).

Duration of IMP exposure will be summarized descriptively as a quantitative variable (number, mean, SD, median, minimum, and maximum). In addition, duration of treatment exposure will also be summarized categorically by numbers and percentages for each of the following categories and cumulatively according to these categories:

>0 and ≤2 weeks

>2 and ≤4 weeks

>4 and ≤8 weeks

>8 and ≤12 weeks

>12 and ≤16 weeks

…

….

>48 and ≤52 weeks

>52 weeks

Additionally, the cumulative duration of treatment exposure will be provided, defined as the sum of the duration of treatment exposure for all patients, and will be expressed in patient years.

2.4.3.2 Compliance

A given administration will be considered noncompliant if the patient did not take the planned dose of treatment as required by the protocol. No imputation will be made for patients with missing or incomplete data.

Percentage of compliance for a patient will be defined as the number of administrations that the patient was compliant divided by the total number of administrations that the patient was planned to take during the treatment epoch defined in Section 2.1.4.

Above-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a higher dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Under-planned dosing percentage for a patient will be defined as the number of administrations that the patient took a lower dose than planned divided by the total number of administrations that the patient was planned to take during the treatment epoch.

Treatment compliance, above-planned, and under-planned dosing percentages will be summarized descriptively as quantitative variables (number, mean, SD, median, minimum, and maximum). The percentage of patients whose compliance is <80% will be summarized. In addition, numbers and percentages of patients with at least 1 above-planned dose administration will also be provided, as well as numbers and percentages of patients with 0, (0, 20%], and >20% under-planned dose administrations.

Cases of overdose (defined as at least twice the intended dose during an interval of less than 11 days) will constitute serious adverse events and will be listed as such. More generally, dosing irregularities will be listed in Section 2.2.1.

2.4.4 Analyses of efficacy endpoints

2.4.4.1 Analysis of primary efficacy endpoint(s)

2.4.4.1.1 Annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of the annualized rate of severe exacerbation events during the 52-week placebo-controlled treatment period is to assess the efficacy of dupilumab in an intention-to-treat setting. In this primary approach, off-treatment measurements of patients who prematurely discontinue treatment will be included for the analysis. Patients who permanently discontinue the study medication will be encouraged to return to the clinic for all remaining study visits. If a patient stays in study until the end of 52-week treatment period, all severe exacerbation events that happen up to Visit 18 will be included in the primary analysis, regardless if the patient is on treatment or not. And the observation duration is defined as from randomization to Visit 18. If a patient withdraws from study prior to the end of 52-week treatment period, all observed severe exacerbation events up to the last contact date will be included in the analysis, and the observation duration is defined as from randomization to the last contact date. No imputation will be performed for the unobserved events that may happen after study discontinuation and up to Week 52. This estimand compares the rate of severe exacerbation for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

The annualized rate of severe exacerbation events will be analyzed using a negative binomial regression model. The model will include the total number of events occurring during the observation period defined above as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Treatment groups, region, baseline eosinophil strata and baseline ICS dose level will be treated as categorical variable. Age and number of severe exacerbation events within 1 year prior to the study will be treated as continuous variable. Severe asthma exacerbation event prior to the study is defined as treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once or hospitalization or emergency medical care visit for worsening asthma (as defined in section Section 2.1.1). Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated annualized event rate for each treatment group and its two-sided 95% confidence intervals will be derived from the negative binominal model. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence interval of the rate ratio based on the negative binomial model and its p-value will be provided.

Based on EMEA feedback, the rate difference between each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate difference and its p-value derived using delta method will also be provided as supportive information.

Sample SAS code can be found below:

```
proc glimmix data=event;
  class eosblgpn ics trt01pn cntygr1n;
  model numevents=trt01pn age eosblgpn ics cntygr1n asmanum
                  /offset=logdur dist=negbin link=log solution;
run;
```

If the model fails to achieve convergence, different estimation algorithms will be applied following the order: default→LAPLACE→QUAD(8). If the issue still exists, other handling may be considered. The adjustment will be added to the footnote of the corresponding outputs.

The gross estimated of annualized events rate will also be presented by each treatment group. Mean cumulative function plot will be provided for descriptive purpose.

Estimand of clinical efficacy of dupilumab versus placebo

An analysis to assess the efficacy of dupilumab if patients adhere to the treatment as directed is also specified. In this approach, off-treatment measurements of patients who prematurely discontinue treatment will be excluded from the analysis. A negative binomial model with the same set of covariates as specified in the primary analysis will be used. This model will include severe exacerbation events occurring during the treatment epoch as the response variable and the log transformed duration of the treatment epoch will be the offset variable. This approach defines the estimand to be the efficacy of dupilumab with treatment adherence (7).

Handling of missing data

If patients withdraw from the study before Visit 18 (Week 52), severe exacerbation events that may occur after study discontinuation will not be observed. These patients are considered as patients with missing data on severe exacerbation. Number of patients with missing data, reasons and timing for patient withdrawals will be summarized by treatment groups. Summary statistics of selected demographic and baseline disease characteristics will be provided for patients with missing data and patients with complete data separately. Graphical summaries of the dropout patterns such as Kaplan-Meier plots of time to study discontinuation with different reasons of discontinuation may be provided to examine if there is any different missing pattern between treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model

- *Pattern mixture model* ***- multiple imputation (PMM-MI)***

  For each patient with missing data of severe exacerbation events, individual monthly event probability will be estimated using observed data with adjustment of the planned treatment

group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. And binary event will be imputed on monthly basis using multiple imputation.

- *Control-based PMM-MI*

For each patient with missing data of severe exacerbation events, individual monthly event probability will be estimated using observation in the matching placebo arms only, with adjustment of age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study. And binary event will be imputed on monthly basis using multiple imputation.

- *Tipping point analysis*

For each patient with missing data of severe exacerbation events, the monthly event will be imputed in a similar fashion as PMM-MI based on various odds values. If the patient is on dupilumab, the predicted odds will be increased; if the patient is on Placebo, the predicted odds value will be decreased. The adjusted rate will then be used to impute the number of events that would occur during the missing observation period. A sequence of increasing/decreasing ratio will be used to generate different imputed datasets.

For each of the above methods, a negative binomial model will be fitted using each of the complete datasets composed of observed and imputed data, including the total number of observed and imputed events during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable for patients who complete the 52-Week treatment/study period, and log transformed 52 weeks will be the offset variable for patients who discontinue the study before Visit 18 (Week 52). SAS MIANALYZE procedure will be used to generate statistical inferences by combining results from the analysis with each dataset using Rubin's formula.

More details of the imputation and analyses methods are provided in Appendix D.

Subgroup analyses

To assess consistency of treatment effects across the subgroup levels, subgroup analyses will be performed for the annualized rate of severe exacerbation event during the 52-week treatment period by:

- Age group: < 18, 18-64, ≥ 65 years; < 18 , ≥ 18 years
- Gender (Male, Female)
- Region (Asia: Japan, South Korea and Taiwan; Latin America: Argentina, Brazil, Colombia, Chile and Mexico; East Europe: Hungary, Poland, Russia, Turkey and Ukraine; Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA)

- Territory (North America: Canada and USA; European Union: France, Germany, Hungary, Italy, Poland, Spain and United Kingdom; Rest of World: Argentina, Australia, Brazil, Colombia, Chile, Japan, Mexico, Russia, South Africa, South Korea, Taiwan, Turkey and Ukraine)
- Race (Caucasian/White, Black/of African descent, Asian/Oriental, all the other)
- Ethnicity (Hispanic, non-Hispanic)
- Baseline blood eosinophil level (≥ 0.3 Giga/L, <0.3 Giga/L; ≥ 0.15 Giga/L, < 0.15 Giga/L)
- Background ICS dose levels at randomization (medium, high)
- Background controller type at randomization (ICS and LABA only, ICS and LABA and Anti-leukotrienes only, Other; ICS, LABA and any third controller, Other)
- Baseline FEV1 (≤ 1.75, > 1.75 L)
- ACQ-5 (≤ 2, >2)
- Number of severe asthma exacerbation prior to the study as defined in Section 2.1.1 (1,>1)
- Baseline weight (< 70, ≥ 70 - < 90, ≥ 90 kg; <60, ≥ 60 kg)
- Baseline BMI (< 25, 25- <30, ≥ 30 kg/m^2)
- Smoking history (Former, Never)
- Atopic medical condition (Yes, No)
- Age of onset of asthma (<18, 18-40, >40 years)
- Baseline predicted FEV1% (<60%, 60%-90%)
- Baseline periostin(NG/ML) (< median, ≥ median)
- Baseline fractional exhaled nitric oxide (FeNO) (< 25, ≥25- < 50, ≥50 ppb)

Treatment by subgroup interaction and its p-value will be derived from a negative binomial model. This model will include the total number of events occurring during the observation period as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, number of severe exacerbation events within 1 year prior to the study, subgroup (if different than the aforementioned covariates) and treatment by subgroup interaction as covariates. Log transformed observation duration will be the offset variable. If quantitative treatment by subgroup interaction is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be performed to evaluate possible qualitative interaction. Summary statistics of severe exacerbations will be provided within each subgroup. Forest plot of relative risks and corresponding CIs and forest plot of risk differences and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

For local submission, efficacy analyses may be performed in specific countries/regions, eg, Japan.

Loading dose evaluation (Sustained treatment effect evaluation)

To examine if the loading dose has any confounding effect on annualized rate of severe exacerbation during the 52-week randomized treatment period, a sensitivity analysis for the annualized rate of severe asthma exacerbation will be performed. It will include severe exacerbation events occurring after the first four weeks and 12 weeks, respectively, and only on-treatment events will be included to avoid possible confounding effect due to off-treatment data. Due to potential insufficient number of events after excluding data from the first 12 week, two dupilumab groups will be combined and two placebo groups will be combined. Results of the sensitivity analysis will be compared to the result of on-treatment analysis including all on-treatment severe exacerbation events during the study.

2.4.4.1.2 Absolute change from baseline in pre-bronchodilator (pre-BD) FEV_1 at Week 12

Primary statistical model (ITT analysis) and adjustment for covariates

The primary analysis of change from baseline in pre-BD FEV1 at Week 12 is to assess the efficacy of dupilumab in a real-world setting. The absolute change from baseline in FEV1 at Week 12 will be analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction as covariates. Treatment groups, sex, region, baseline eosinophil strata, baseline ICS dose level, and visit will be treated as categorical variables. Age and height will be treated as continuous variable. For patients who discontinue the treatment before Week 12, they will be asked and encouraged to return to the clinic for all remaining study visit and the additional off study-treatment pre-BD FEV1 values measured up to Week 12 will be included in the primary analysis. For patients who withdraw from the study before Week 12, pre-BD FEV1 values will be missing after study discontinuation. No imputation will be performed for missing values in the primary analysis. This estimand compares the change from baseline in pre-BD FEV1 for the patients randomized to the dupilumab and placebo arms, regardless of what treatment patients actually received. It assesses the benefits of the treatment policy or strategy relative to placebo (7).

An unstructured correlation matrix will be used to model the within-patient errors. Parameters will be estimated using restricted maximum likelihood method with the Newton-Raphson algorithm. Statistical inferences on treatment comparisons for the change from baseline in pre-BD FEV1 at Week 12 will be derived from the mixed-effect model. Difference in LS mean change from baseline, the corresponding 95% CI and the p-value with Kenward-Roger adjustment will be provided for comparison for each dupilumab group against its matching placebo. In addition, descriptive statistics including number of patients, mean, standard error and LS mean of change from baseline will be provided.

A sample SAS code can be found below:

```
proc mixed data=adsd.adre method=reml;
      where paramcd='FEV1' and avisitn ge 3 and avisitn le 8 and ittfl='Y';
      class subjid sex eosblgpn ics trt01pn avisitn cntygr1n;
      model chg = trt01pn sex age height ics eosblgpn cntygr1n avisitn
trt01p*avisitn base base*avisitn/ddfm=kr residual;
      repeated avisitn/type=un subject=subjid;
      lsmeans trt01pn*avisitn /pdiff cl ;
     estimate '300 mg q2w vs Placebo 2ml q2w at Week 12 Visit 8'
     trt01pn 0 -1 0 1  trt01pn*avisitn   0 0 0  0
                                         0 0 0 -1
                                         0 0 0  0
                                         0 0 0  1/ cl;
run;
```

If MMRM model fails to achieve convergence due to complexity of model specification, we may add some procedures to handle this issue including: 1) using maximum likelihood estimation instead of restricted maximum likelihood method; 2) covariance structure selection to reduce the number of unknown parameters to be estimated, the path is UN→TOEPH→TOEP→AR(1)→CS. The adjustment will be added to the footnote of the corresponding outputs.

Estimand of clinical efficacy of dupilumab versus placebo

To assess the treatment effect when the patients adhere to the study treatment as directed, on-treatment pre-BD FEV1 measurements will be analyzed using the similar MMRM model as for the primary analyses, including same set of covariates and estimation algorithm. The model will include on-treatment change from baseline in pre-BD FEV1 values up to Visit 8 (Week 12) as response variables. A pre-BD FEV1 value is considered as on-treatment if it's measured before or on the last dose date + 14 days.

Sensitivity analyses with different censoring methods for pre-BD FEV1 potentially confounded by systemic corticosteroid use

In addition, two sets of sensitivity analyses with different methods of handling pre-BD FEV1 measurements confounded by the systemic corticosteroid use will be performed:

- Censoring method 1: pre-BD FEV_1 measurements collected from systemic corticosteroid start date to systemic corticosteroid end date + 14 days will be excluded in order to reduce the confounding effect of systemic corticosteroids
- Censoring method 2: All pre-BD FEV_1 measurements collected on and after first day of systemic corticosteroid use will be excluded.

The above two censoring methods will be applied to both primary analyses and on-treatment analysis. On-treatment analysis with data censoring method 1 will be used to provide treatment effect size estimates without confounding effect of systemic corticosteroid use.

Handling of missing data

If a patient misses scheduled pre-BD FEV1 measurement during the first 12-week treatment, or withdraws from the study before Visit 8 (Week 12), he/she will have missing pre-BD FEV1 data at some time points up to Week 12. Descriptive statistics of pre-BD FEV1 by visit up to Week 12 will be summarized for patients with some missing data and patients with complete data up to Week 12 separately. Number of patients with missing pre-BD FEV1, reasons and timing for missing pre-BD FEV1 will be summarized by treatment groups. In addition, following sensitivity analyses will be conducted to assess the robustness of the conclusion of the main model:

- *Pattern mixture model-multiple imputation (PMM-MI)*

  Missing pre-BD FEV1 values will be imputed multiple times with adjustment for covariates including treatment groups, baseline eosinophil groups, age, sex, height, region, baseline ICS dose level and reason of treatment discontinuation. Each of the complete datasets will be analyzed using the ANCOVA model with change from baseline in pre-BD FEV1 at Week 12 as the response variable, treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline pre-BD FEV1 value as covariates. Then the SAS MIANALYZE procedure will be used to generate statistical inference by combining results using Rubin's formula.

- *Control based PMM-MI*

  The analysis is similar as the standard PMM-MI described above, except that it assumes that after withdrawal from the study, patients from the dupilumab groups would exhibit the same future evolution of pre-BD FEV1 as patients on the placebo who were not exposed to dupilumab.

- *Tipping point analysis*

  First, missing values will be imputed by PMM-MI as illustrated above. The imputed values in placebo group will then be shifted by adding a sequence of positive values and the imputed values in dupilumab group will be shifted by subtracting a sequence of positive values. For each combination of the shift parameters, each of the imputed and shifted datasets will be analyzed with the ANCOVA model and their results will be combined using Rubin's formula to generate statistical inference. LS mean difference between dupilumab and placebo in change from baseline in pre-BD FEV1 at week 12 and the corresponding p-values will be provided for each combination of shift parameters.

  More details of the imputation and analyses methods are included in Appendix D.

Subgroup analysis

To assess the consistency treatment effects across the subgroup levels, subgroup analyses will be conducted for the change from baseline in pre-BD FEV1 at Week 12 with the same set of subgroups as defined for the annualized rate of severe exacerbation events. Treatment-by-subgroup interaction at Week 12 and its p-value will be derived from a MMRM model. The model will include change from baseline in pre-BD FEV1 values up to Week 12 as response variables,

and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value, baseline-by-visit interaction, subgroup (if different than the aforementioned covariates), subgroup-by-treatment interaction and subgroup-by-treatment-by-visit interaction as covariates. If quantitative treatment by subgroup interaction at Week 12 is detected with nominal p-value < 0.05 for any subgroup factor, the Gail-Simon test will be used to test the qualitative interaction. Summary statistics of change from baseline in pre-bronchodilator FEV1 will be provided within each subgroup. Forest plot of LS mean difference and corresponding CIs comparing each dupilumab dose group vs. its matching placebo for the subgroups will be provided.

Distribution of change from baseline in pre-BD FEV1

Cumulative distribution function of change from baseline in pre-BD FEV1 at Week 12 and Week 52 will be presented.

For each subgroup, a MMRM model will be used to analyze change from baseline in pre-BD FEV1 at Week 12. Change from baseline in pre-BD FEV1 up to Week 12 will be included as response variable. Treatment groups, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-BD FEV1 value and baseline-by-visit interaction will be included as covariates. LS mean change from baseline in pre-BD FEV1 at Week 12 for each treatment group and LS mean difference in change from baseline in pre-BD FEV1 at Week 12 for each dupilumab treatment group compared to placebo will be derived from the MMRM model for each subgroup.

2.4.4.2 Analyses of secondary efficacy endpoints

2.4.4.2.1 Absolute/percent change from baseline for continuous endpoints

The key secondary endpoint, percent change from baseline in pre-bronchodilator FEV1 at Week 12, will be analyzed in the same way as for change from baseline in FEV1 at Week 12, with the only difference that percent changes, instead of absolute changes, from baseline in FEV1 up to Week 12 will be included as the response variables. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in ACQ-5 and AQLQ at Week 24 will be analyzed using MMRM including change from baseline up to Week 24 as response variables, regardless if the patient is on treatment or not when the endpoint is measured. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value, and baseline-by-visit interaction as covariates. MMRM model including measurements up to Week 52 will also be used to derive LS mean change at all time-points. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

Change from baseline in other continuous endpoint at all time-points will be analyzed using MMRM model including measurements up to Week 52. The model will include change from baseline in the endpoint values from Week 2 to Week 52 as response variables, regardless if the patient is on treatment or not when the endpoint is measured, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline endpoint value and baseline-by-visit interaction as covariates. Sex and baseline height will be included as covariates only in the models for spirometry parameters. Differences in LS means, the corresponding 95% CI and the p-value will be provided for comparisons of each dupilumab dose against its matching placebo along with descriptive statistics.

For post-bronchodilator FEV1, the rate of change in FEV1 (termed as FEV1 slope) will be compared between each dupilumab dose against its matching placebo. Change from baseline in post-bronchodilator FEV1 after Week 4 and after Week 8 will be analyzed correspondingly using linear mixed-effects model with treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization, and treatment-by-time interaction and baseline post-bronchodilator FEV1 as covariates.

In addition to the MMRM analyses for change from baseline in ACQ-5, ACQ-7 and AQLQ total score a responder analysis will also be performed for these endpoints at Week 12, 24, 36 and 52. For ACQ-5 score, a logistic regression model will be used to compare percentage of patients who reached MCID (responders) in each dupilumab dose group against its matching placebo at the time points aforementioned correspondingly. Patients with change from baseline in ACQ-5 $\leq$ -0.5 will be considered as responders. Patients with change from baseline in ACQ-5 >-0.5 or with missing value will be considered as non-responders. The model will include treatment, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level, and baseline ACQ-5 score as covariates. Odds ratio of being a responder comparing each dupilumab dose group to its matching placebo group will be provided along with the corresponding 95% CI and p-value. Descriptive statistics including number and percentage of responders will also be provided. Responder analysis for ACQ-7 and AQLQ global score will be performed in the same way. For ACQ-7, a patient is considered as a responder if change from baseline in ACQ-7 score $\leq$ -0.5, or as a non-responder if change from baseline in ACQ-7 score > -0.5 or missing. For AQLQ global score, a patient is considered as a responder if change from baseline in AQLQ global score $\geq$0.5, or as a non-responder if change from baseline < 0.5 or missing. ACQ-7 score will also be analyzed in adolescent patient population separately.

2.4.4.2.2 Annualized event rate

Annualized rate of loss of asthma control (LOAC) event and annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week placebo-controlled treatment period will be analyzed in the similar method as for the annualized rate of severe exacerbation events using a negative binomial regression model. The model will include the total number of events occurring during the 52 weeks as the response variable, with the treatment group, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Log transformed observation duration will be the offset variable.

Pairwise comparisons of the annualized event rates between each dose of dupilumab and its matching placebo will be derived by testing each dupilumab group versus its matching placebo separately. The estimated event rate for each treatment group and its two-sided 95% confidence intervals will be provided. The event rate ratio of each dupilumab group and its matching placebo, two-sided 95% confidence intervals of the rate ratio and its p-value will also be provided.

2.4.4.2.3 Time to event variables

A Cox regression model will be used to assess treatment differences in time to events defined in Section 2.1.3.2.2.3.

The model will include the time to the first event as the dependent variable, and four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline ICS dose level and number of severe exacerbation events within 1 year prior to the study as covariates. Hazard ratio will be estimated for pairwise comparison between each dose of dupilumab and its matching placebo. The Kaplan-Meier method will be used to derive the probabilities that a patient would experience events up to Week 12, 24, 36 and 52 per each treatment group. Kaplan-Meier curves will be generated; quartiles and point probabilities will be calculated. Interval estimates will be calculated using 95% point wise confidence intervals.

Sample SAS codes can be found as below:

```
proc phreg data=timeto;
      class subjid eosblgpn ics trt01pn cntygr1n /param=GLM;
      model aval*CNSR(1) =trt01pn age eosblgpn ics cntygr1n asmanum;
      contrast '200 mg q2w vs Placebo rate ratio' trt01pn -1 0 1 0
      0/estimate=exp;
      contrast '300 mg q2w vs Placebo rate ratio' trt01pn 0 -1 0 1
      1/estimate=exp;
run;
```

2.4.4.3 Multiplicity issues

To strongly control the type-I error rate for the primary family (two primary endpoints and two doses), a hierarchical testing procedure will be applied at a 2-sided 5% significant level, ie, each hypothesis will be formally tested only if the preceding one is significant at the 5% level. The hierarchy of the tests will be: 1) annualized severe exacerbation rate for 300 mg q2w versus placebo, 2) absolute change from baseline in FEV1 at Week 12 for 300 mg q2w versus placebo, 3) annualized severe exacerbation rate for 200 mg q2w versus placebo, 4) absolute change from baseline in FEV1 at Week 12 for 200 mg q2w versus placebo.

If both doses are significant for both primary endpoints, a selective set of secondary endpoints will be tested following a hierarchical testing procedure at a 2-sided 5% significant level. The complete list of the endpoints with their testing order is specified in Table 6.

Table 6 – Hierarchical testing order

	Endpoints	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w
Primary endpoints	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population	3	1
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population	4	2
Secondary endpoints	Percent change from baseline in pre-bronchodilator FEV1 at Week 12 - ITT population	11	5
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >=0.15 Giga/L	12	6
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >=0.15 Giga/L	13	7
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil >= 0.3 Giga/L	14	8
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline eosinophil >= 0.3 Giga/L	15	9
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with baseline eosinophil <0.3Giga/L	16	10
	Annualized rate of severe exacerbation events during the 52-week treatment period - ITT population with high dose ICS at baseline	22	17
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with high dose ICS/LABA at baseline	23	18
	Change from baseline in AQLQ global score at Week 24 - ITT population	24	19
	Change from baseline in AQLQ global score at Week 24 - ITT population with baseline eosinophil >= 0.3 Giga/L	25	20
	Change from baseline in ACQ-5 score at Week 24 - ITT population	26	21
	Annualized rate of severe exacerbation events resulting in hospitalization or emergency room visit during the 52-week treatment period - ITT population	28	27
	Change from baseline in pre-bronchodilator FEV_1 at Week 12 - ITT population with baseline blood eosinophil <0.3 Giga/L	30	29

2.4.5 Analyses of safety data

The summary of safety results will be presented by treatment group.

General common rules

All safety analyses will be performed on the safety population as defined in Section 2.3.2, unless otherwise specified, using the following common rules:

- The baseline value is defined as the last available value before the first dose of IMP.
- The potentially clinically significant abnormality (PCSA) values are defined as abnormal values considered medically important by the Sponsor according to predefined criteria/thresholds based on literature review and defined by the Sponsor for clinical laboratory tests, vital signs, and ECG (Appendix A)
- PCSA criteria will determine which patients had at least 1 PCSA during the treatment-emergent adverse event period, taking into account all evaluations performed during the treatment-emergent adverse event period, including nonscheduled or repeated evaluations. The number of all such patients will be the numerator for the on-treatment PCSA percentage.
- The treatment-emergent PCSA denominator by group for a given parameter will be based on the number of patients assessed for that given parameter in the treatment-emergent adverse event period by treatment group on the safety population. Number (%) of patients with at least 1 PCSA will be summarized regardless of baseline PCSA status and also by baseline PCSA status.
- For quantitative safety parameters based on central laboratory/reading measurements, descriptive statistics will be used to summarize results and change from baseline values by visit and treatment group. Summaries will include the endpoint value and/or the worst on-treatment value. The endpoint value is commonly defined as the value collected at the end of treatment. If this value is missing, this endpoint value will be the closest value prior to the end of treatment epoch. The worst value is defined as the nadir and /or the peak post-baseline (up to the end of treatment epoch or EOT) according to the direction (minimum or maximum) of the abnormality as defined in the PCSA list
- The analysis of the safety variables will be essentially descriptive and no systematic testing is planned.
- All safety values including unscheduled measurements will be assigned to the appropriate safety analysis visit window defined in Section 2.5.3.

2.4.5.1 Analyses of adverse events

General information

The primary focus of adverse event reporting will be on treatment-emergent adverse events. Pretreatment adverse events will be described separately.

If an adverse event date/time of onset (occurrence, worsening, or becoming serious) is incomplete, an imputation algorithm will be used to classify the adverse event as pretreatment or treatment-emergent. The algorithm for imputing date/time of onset will be conservative and will classify an adverse event as treatment emergent unless there is definitive information to determine it is pretreatment. Details on classification of adverse events with missing or partial onset dates are provided in Section 2.5.3.

Adverse event incidence tables will present by SOC, HLGT, HLT, and PT, sorted in alphabetical order for each treatment group, the number (n) and percentage (%) of patients experiencing an adverse event. Multiple occurrences of the same event in the same patient will be counted only once in the tables within a treatment phase. The denominator for computation of percentages is the safety population within each treatment group. Sorting will be based on results for the dupilumab 300 mg q2w group.

Analysis of all treatment-emergent adverse events

The following treatment-emergent adverse event summaries will be generated for the safety population.

- Overview of treatment-emergent adverse events, summarizing number (%) of patients with any
  - Treatment-emergent adverse event
  - Serious treatment-emergent adverse event
  - Treatment-emergent adverse event leading to death
  - Treatment-emergent adverse event leading to permanent treatment discontinuation
- All treatment-emergent adverse events by primary system organ class, showing number (%) of patients with at least 1 treatment-emergent adverse event, sorted by internationally agreed order of primary system organ class
- All treatment-emergent adverse event by primary SOC, HLGT, HLT, and PT, showing number (%) of patients with at least 1 treatment-emergent adverse event sorted by the SOC internationally agreed order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- Number (%) of patients experiencing TEAE(s) presented by PT, sorted by decreasing incidence of PT
- All treatment-emergent adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- All treatment-emergent adverse events regardless of relationship and related by primary SOC, HLGT, HLT and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events by maximal severity, presented by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent adverse event by severity (ie, mild, moderate, or severe), sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC
- Number (%) of patients experiencing treatment-emergent adverse event(s) presented by primary and secondary SOC, HLGT, HLT, and PT sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order

- A listing of all treatment-emergent adverse events will be presented

Analysis of all treatment-emergent serious adverse event(s)

- All treatment-emergent serious adverse events by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 serious treatment-emergent adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events regardless of relationship and related to IMP, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent serious adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 treatment-emergent serious adverse event, sorted by the internationally agreed SOC order and by decreasing incidence of PTs within each SOC.
- A listing of all treatment-emergent serious adverse events will be presented

Analysis of all treatment-emergent adverse event(s) leading to permanent treatment discontinuation or drug interruption

- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC, HLGT, HLT, and PT, showing the number (%) of patients sorted by the internationally agreed SOC order. The other levels (HLGT, HLT, PT) will be presented in alphabetical order
- All treatment-emergent adverse events leading to permanent treatment discontinuation or drug interruption, by primary SOC and PT, showing number (%) of patients with at least one TEAE, will be presented by SOC internationally agreed order and by decreasing incidence of PTs within each SOC.

Analysis of adverse events of special interest (AESI) and other selected AE groupings

- All treatment-emergent adverse events, by selected standardized MedDRA query (SMQ) and PT or by laboratory values (as in ALT elevation), showing the number (%) of patients with at least 1 PT, sorted by decreasing incidence of PTs within each SMQ
- For each prespecified AESI and selected AE grouping,
  - Number (%) of patients with any specific TEAE
  - Number (%) of patients with any specific serious AE (regardless of treatment emergent status)
  - Number (%) of patients with any specific treatment emergent serious AE
  - Number (%) of patients with any specific AE leading to death
  - Number (%) of patients with any specific TEAE leading to permanent study drug discontinuation

- Number (%) of patients with any specific TEAE by maximum intensity, corrective treatment, and final outcome
- Number of any specific TEAE adjusted by the exposure duration
- All of the specific TEAE, by PT, showing the number (%) of patients, sorted by decreasing incidence of PT
- Number of patients with any specific TEAE adjusted by the exposure duration at risk. For each specific TEAE, Kaplan-Meier estimates of cumulative incidence at Week 12, 24, 36 and 52 and K-M plot may be provided to depict the course of onset over time if the number of events is large enough

- Number (%) of patients with injection site reactions by the related injection.
- Number (%) of patients with different number of injection site reactions.

Analysis of pretreatment adverse events

- All pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All serious pretreatment adverse events by primary SOC and PT, showing the number (%) of patients with at least 1 pretreatment adverse event, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to permanent treatment discontinuation by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

If only a few patients have pretreatment adverse events leading to permanent treatment discontinuation, a listing will be presented instead of the summary table above.

2.4.5.2 Deaths

The following summaries of deaths will be generated for the safety population.

- Number (%) of patients who died by study period (on-study, on-treatment, poststudy)
- Deaths in nonrandomized patients or randomized but not treated patients

- Treatment-emergent adverse events leading to death (death as an outcome on the adverse event case report form page as reported by the Investigator) by primary SOC , HLGT, HLT, and PT showing number (%) of patients sorted by internationally agreed SOC order, with HLGT, HLT, and PT presented in alphabetical order within each SOC .
- All pretreatment adverse events leading to death by primary SOC and PT, showing the number (%) of patients, sorted by the internationally agreed SOC order and decreasing incidence of PTs within each SOC

A listing of deaths will be provided.

2.4.5.3 Analyses of laboratory variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all laboratory variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For each continuous parameters listed in Section 2.1.4.3, mean changes from baseline with the corresponding standard error will be plotted over time in each treatment group. This section will be organized by biological function as specified in Section 2.1.4.3.

The incidence of PCSAs (list provided in Appendix A) at any time during the treatment-emergent adverse event period will be summarized by biological function and treatment group whatever the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

For parameters for which no PCSA criteria are defined, similar table(s) using the normal range will be provided.

For PCSA analyses, the laboratory measurements obtained at either scheduled or unscheduled visits should be used; and, both the centralized and local test results should be used, as long as their available dates/time is different from each other's. Centralized data will be used preferentially to the local measures in the PCSA analyses when measurements are performed on the same date and at the same time for a given laboratory test.

A listing of PCSAs will be provided.

Drug-induced liver injury

If there is any imbalance in the incidence of liver-related adverse events across the treatment groups, analysis of liver-related adverse events will be performed.

The liver function tests, namely AST, ALT, alkaline phosphatase, and total bilirubin, are used to assess possible drug-induced liver toxicity. The proportion of patients with PCSA values at any postbaseline visit by baseline status will be displayed by treatment group for each parameter. The

proportion of patients with PCSA values at any postbaseline visit will also be displayed by duration of exposure for each treatment group.

Time to onset of the initial ALT and AST elevation (>3 x ULN) and total bilirubin elevation (>2 x ULN) (time to first observation of ALT > 3 x ULN or total bilirubin > 2 x ULN, whichever comes first) will be analyzed using Kaplan-Meier estimates, presented by treatment group. Consideration should be given to the impact of the spacing of scheduled tests. A graph of distribution of peak values of ALT versus peak values of total bilirubin will also be presented. Note that the ALT and total bilirubin values are presented on a logarithmic scale. The graph will be divided into 4 quadrants with a vertical line corresponding to 3 x ULN for ALT and a horizontal line corresponding to 2 x ULN for total bilirubin.

Listing of possible Hy's law cases identified by treatment group (eg, patients with any elevated ALT>3 x ULN, and associated with an increase in bilirubin ≥2 x ULN) with ALT, AST, alkaline phosphatase, total bilirubin, and the following complementary parameters: conjugated bilirubin and creatine phosphokinase, serum creatinine, complete blood count, HCV RNA.

Summarize the normalization by parameter (to ≤1 x ULN or return to baseline) of elevated liver function tests by categories of elevation (3 x, 5 x, 10 x, 20 x ULN for ALT and AST, 1.5 x ULN for alkaline phosphatase, and 1.5 x and 2 x ULN for total bilirubin), with the following categories of normalization: never normalized, normalized despite treatment continuation of IMP, or normalized after IMP discontinuation. Note that a patient will be counted only under the maximum elevation category.

Change in Blood Eosinophil

Mean changes from baseline in eosinophil with the corresponding standard error will be plotted over time in each treatment group for patients with baseline blood eosinophil < 0.5 Giga/L and patients with baseline blood eosinophil >=0.5 Giga/L. Number (%) of patients with post-baseline peak blood eosinophil >= 1 Giga/L, >=3 Giga/L and >=5 Giga/L will also be summarized in each treatment group and by baseline blood eosinophil status (All, <0.5 Giga/L,>=0.5 Giga/L).

2.4.5.4 Analyses of vital sign variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all vital signs variables (values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at same time points) in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing

- Abnormal according to PCSA criterion or criteria

2.4.5.5 Analyses of electrocardiogram variables

The summary statistics (including number, mean, median, Q1, Q3, standard deviation, minimum and maximum) of all ECG variables (central laboratory values and changes from baseline) will be calculated for each visit or study assessment (baseline, each postbaseline time point, last on-treatment and/or worst on-treatment value) by treatment group. For all parameters, mean changes from baseline with the corresponding standard error will be plotted over time (at the same time points) in each treatment group.

The incidence of PCSAs at any time during the treatment-emergent adverse event period will be summarized by treatment group irrespective of the baseline level and/or according to the following baseline status categories:

- Normal/missing
- Abnormal according to PCSA criterion or criteria

2.4.6 Analyses of pharmacokinetic and pharmacodynamics variables

2.4.6.1 Pharmacokinetic analyses

2.4.6.1.1 Analyses of serum concentrations of SAR231893 (REGN668)

Serum concentrations of SAR231893 (REGN668) will be summarized in the PK population using arithmetic and geometric means, SD, standard error of the mean (SEM), coefficient of variation (CV), minimum, median and maximum per sampling time. If date and/or time of the drug injection and/or sampling is missing then the concentration will not be taken into account. For drug-treated patients, where concentration values are below the lower limit of quantification (LLOQ), one-half of the LLOQ will be used. Values will be expressed in the tables with no more than three significant figures. For patients in the placebo group, concentration values are below the LLOQ will be taken into account with a plasma concentration considered equal to 0.

2.4.6.1.2 Analyses of ADA variables

The following summary will be provided based on ADA population:

- Number (%) of patients with pre-existing immunoreactivity
- Number (%) of patients with treatment-emergent ADA
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-emergent ADA, and patients with persistent, indeterminate and transient ADA response
- Number (%) of patient with transient treatment-emergent ADA
- Number (%) of patients with persistent treatment-emergent ADA

- Number (%) of patients with indeterminate treatment-emergent ADA
- Number (%) of patients with treatment-boosted ADA.
- The summary statistics (including number, median, Q1, Q3, minimum and maximum) of the peak post-baseline titer for patients with treatment-boosted ADA
- The summary statistics (including number, mean, SD, median, Q1, Q3, minimum and maximum) of the ratio of peak post-baseline titer to baseline titer for patients with treatment-boosted ADA
- Listing of ADA peak titer levels and neutralizing antibody status
- Number(%) of patients with neutralizing antibody status

Kinetics of treatment-emergent ADA response

Number (%) of patients with ADA treatment-emergent ADA positive response at each visit will be summarized by each dose regimen group.

Plot of percentage of patients with ADA treatment-emergent ADA positive response at each visit will be provided by each dose regimen group.

Impact of ADA on PK

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and serum concentration of dupilumab may be explored for each dupilumab dose group. Plot of serum concentration of functional SAR231893 (REGN668) versus visit will be provided by ADA classifications for each dupilumab dose group. Individual patient plots of PK according to ADA status will be provided to determine which individuals may have had PK impacted by ADAs.

Association of ADA with clinical efficacy endpoints

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent, persistent, indeterminate and transient response, treatment-boosted) and following efficacy endpoints may be explored for each dupilumab dose group:

- Annualized rate of severe exacerbation events
- Change from baseline in Pre-BD FEV1

Association of ADA with clinical safety endpoints

Association of safety versus ADA status may be analyzed in the ADA population. The safety assessment may focus on the following events:

- Severe injection site reactions last longer than 24 hours or serious injection site reactions
- Hypersensitivity reactions (SMQ hypersensitivity narrow search and confirmed by medical review)

- Anaphylactic reactions (SMQ anaphylactic reaction narrow search)

In response to AESI like anaphylaxis or hypersensitivity additional ADA samples closer to the event may be analyzed, based on the judgment of the medical investigator and/or medical monitor.

Associations between ADA variables (eg, ADA peak titers, neutralizing antibody status, treatment-emergent and treatment-boosted) and safety may be explored.

2.4.6.2 Pharmacodynamics/genomics analyses

All biomarkers listed in Section 2.1.6 will be summarized in the Exposed population defined as patients who actually received at least 1 dose or part of a dose of the IMP. Baseline values will be the last value collected prior to the first IMP. For randomized but not treated patients, baseline value will be the last value collected prior to the randomization. Descriptive statistics (including number, mean, SD, median, Q1, Q3, min, max) of biomarkers at baseline will be summarized.

For all parameters including antigen-specific IgEs with a positive (≥0.35 IU/mL) incidence of greater than 25% at baseline, values at each visit, absolute change from baseline and percent changes from baseline will be summarized in descriptive statistics by treatment group and time point. Values reported as below the LLQ (lower limit of quantitation) will be imputed as a value one half of the LLQ.

Number and percentage of patients with no positive (≥0.35 IU/mL) antigen-specific IgE result, with positive (≥0.35 IU/mL) result for only one antigen, and with positive (≥0.35 IU/mL) results for at least two antigens will be summarized by treatment group and time point. Same analysis will also be performed using LLQ as the threshold.

Summary plots (mean +/- standard error of the mean) on values at each visit, absolute changes from baseline and percent changes from baseline will be provided for each biomarker by treatment group.

Exploratory analysis of DNA/RNA will be addressed in a separate document.

2.4.7 Analyses of vaccine response

For patients who receive vaccination, vaccine IgG in serum prior and after vaccination will be summarized by treatment groups with descriptive statistics.

2.4.8 Analyses of health economics variables

Analyses of health care resource utilization will be performed under the responsibility of the Health Economics and Reimbursement Argumentation department of Sanofi. Methods and results will be made available in a separate report.

2.5 DATA HANDLING CONVENTIONS

2.5.1 General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

Age is calculated as:

Integer part of (informed consent date -birth date)/365.25

Age of onset of asthma is calculated as:

Integer part of (asthma onset date - birth date)/365.25

Time since first diagnosis of asthma (years) is calculated as:

(Year of randomization -Year of first diagnosis of asthma) + (month of randomization - month of first diagnosis of asthma)/12

Time since cessation of smoking is calculated as:

(Year of randomization - Year of cessation)×12 + (month of randomization -month of cessation)

Time since last asthma exacerbation (months) is calculated as:

(Year of randomization – Year of last asthma exacerbation)×12 + (month of randomization – month of last asthma exacerbation)

BMI is calculated as:

Weight in kg / (height^2 in meters)

Smoking quantity (pack-year) is calculated as following:

Number of pack-year= (packs smoked per day) × (years as a smoker)

Renal function formulas

For patients ≥ 18 years old, creatinine clearance (CLcr) value will be derived using the equation of Cockroft and Gault:

CLcr (ml/min) = (140 - age) × weight (kg) × (1 - 0.15 × sex (0-M, 1-F))/ (0.814 × creatinine (μmol/l))

CLcr will be calculated using the last weight measurement on or before the visit of the creatinine measurement and age at the lab sampling date. Here age is calculated as following:

Age = integer part of (lab sampling date - birth date)/365.25

For patients < 18 years old, CLcr value will be derived using the equation of GFR Bedside Schwartz

$$GFR\ (mL/min/1.73\ m2) = k \times height\ (cm) / sCr\ (mg/dL)] ,$$

Where the coefficient k=0.65 for adolescent male patients, or k=0.55 for adolescent female patients.

2.5.2 Data handling conventions for secondary efficacy variables

Calculation of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations/day

A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. The number of salbutamol/albuterol or levosalbutamol/levalbuterol inhalations per day is the sum of number of inhalations recorded in one diary day including the evening diary and the following day's morning diary.

Periodical average of daily efficacy endpoints at designated study days

For the daily efficacy endpoints, the time period used to calculate the periodical average at each designated study day is summarized in Table 7. Randomization day is used as the reference day (Day 1).

Table 7 - Periodical average of daily efficacy assessment

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 15	2-15	1-14	Diary day 1-14
Day 29	16-29	15-28	Diary day 15-28
Day 43	30-43	29-42	Diary day 29-42
Day 57	44-57	43-56	Diary day 43-56
Day 71	58-71	57-70	Diary day 57-70
Day 85	72-85	71-84	Diary day 71-84
Day 113	86-113	85-112	Diary day 85-112
Day 141	114-141	113-140	Diary day 113-140
Day 169	142-169	141-168	Diary day 141-168

Time point	Morning PEF, asthma symptom score, number of awakenings	Evening PEF, asthma symptom score	Number of inhalations/day of salbutamol/albuterol or levosalbutamol/levalbuterol for symptom relief
Day 197	170-197	169-196	Diary day 169-196
Day 225	198-225	197-224	Diary day 197-224
Day 253	226-253	225-252	Diary day 225-252
Day 281	254-281	253-280	Diary day 253-280
Day 309	282-309	281-308	Diary day 281-308
Day 337	310-337	309-336	Diary day 309-336
Day 365	338-365	337-364	Diary day 337-364
Day 393	366-393	365-392	Diary day 365-392
Day 421	394-421	393-420	Diary day 393-420
Day 449	422-449	421-448	Diary day 421-448

Note: A diary day is defined as the period beginning with an Evening diary, and ending with the following day's Morning Diary. For example, diary day 14 includes the evening dairy on day 14 and the morning dairy on day 15.

2.5.3 Missing data

For categorical variables, patients with missing data are not included in calculations of percentages unless otherwise specified. When relevant, the number of patients with missing data is presented.

Handling of missing answer to the 7th question in ACQ-7

If the score is missing from the site report, the FEV1 % predicted value from spirometry test will be used to derive the 7th score. Only the spirometry performed on the same day when ACQ-7 is evaluated will be used. And if there are multiple FEV1% predicted values available on the same day, the lowest one will be used to score the 7th item. If the score of the 7th question is still missing but the questionnaire is complete at the prior visit, the missing score for the 7th question will be imputed as: (score of the 7th question at the prior visit) □ (sum of scores of the first six questions at the current visit) / (sum of scores of the first six questions at the prior visit). If the questionnaire from the prior visit is not complete either or if the ACQ-7 score at the prior visit is 0, which makes it infeasible to implement the algorithm, the missing score will be imputed as the average of the other six questions at the current visit. If scores of the first six questions are missing, then the ACQ-7 score for the current visit will be missing.

Handling of computation of treatment duration if investigational medicinal product end of treatment date is missing

For the calculation of the treatment duration, the date of the last dose of IMP is equal to the date of last administration reported on the Investigational Product Administration report form page. If this date is missing, the exposure duration should be left as missing.

The last dose injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of medication missing/partial dates

No imputation of medication start/end dates or times will be performed. If a medication date or time is missing or partially missing and it cannot be determined whether it was taken prior or concomitantly, it will be considered a prior and concomitant medication.

Handling of adverse events with missing or partial date/time of onset

Missing or partial adverse event onset dates and times will be imputed so that if the partial adverse event onset date/time information does not indicate that the adverse event started prior to treatment or after the treatment-emergent adverse event period, the adverse event will be classified as treatment-emergent. No imputation of adverse event end dates/times will be performed. These data imputations are for categorization purpose only and will not be used in listings. No imputation is planned for date/time of adverse event resolution.

Handling of adverse events when date and time of first investigational medicinal product administration is missing

When the date and time of the first IMP administration is missing, all adverse events that occurred on or after the day of randomization should be considered as treatment-emergent adverse events. The exposure duration should be kept as missing.

The last dose injection should be clearly identified in the case report form and should not be approximated by the last returned package date.

Handling of missing assessment of relationship of adverse events to investigational medicinal product

If the assessment of the relationship to IMP is missing, then the relationship to IMP has to be assumed and the adverse event considered as such in the frequency tables of possibly related adverse events, but no imputation should be done at the data level.

Handling of missing severity of adverse events

If the severity is missing for 1 of the treatment-emergent occurrences of an adverse event, the maximal severity on the remaining occurrences will be considered. If the severity is missing for all the occurrences, a “missing” category will be added in the summary table.

Handling of potentially clinically significant abnormalities

If a patient has a missing baseline he will be grouped in the category "normal/missing at baseline."

For PCSAs with 2 conditions, one based on a change from baseline value or a normal range and the other on a threshold value, with the first condition being missing, the PCSA will be based only on the second condition.

For a PCSA defined on a threshold and/or a normal range, this PCSA will be derived using this threshold if the normal range is missing; eg, for eosinophils the PCSA is >0.5 GIGA/L or >ULN if ULN ≥0.5 GIGA/L. When ULN is missing, the value 0.5 should be used.

Measurements flagged as invalid by the laboratory will not be summarized or taken into account in the computation of PCSA values.

2.5.4 Windows for time points

For the safety assessment, the reference date for the derivation of relative days of events or findings will be the date of first IMP administration. Selected safety variables will be summarized by the analysis window define in Table 8 for the by visit descriptive analysis. All available values from central lab will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 8 – Time window for safety endpoints

		Time windows for							
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Urinalysis, Serum immunoglobulins**	**Hepatitis B viral load**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 1 (Week -4±1)	-28±7	<-14	1-	<-14	1-		1-		1-
Visit 2 (Week 0)	1	-14-1-		-14-1-		1-		1-	
Visit 3 (Week 2)	15	1+-21	1+-21						
Visit 4 (Week 4)	29	22-35	22-56	1+-42		1+-42			
Visit 5 (Week 6)	43	36-49							
Visit 6 (Week 8)	57	50-63		43-70		43-70			
Visit 7 (Week 10)	71	64-77							
Visit 8 (Week 12)	85	78-98	57-126	71-98		71-98	1-126	1-126	
Visit 9 (Week 16)	113	99-126		99-126		99-126			

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		Time windows for							
Visit	Target Day	Vital signs	ECG endpoints	Clinical lab testing	Serum Pregnancy test	Urine Pregnancy test	Urinalysis, Serum immunoglobulins	Hepatitis B viral load	Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy
Visit 10 (Week 20)	141	127-154		127-154		127-154			
Visit 11 (Week 24)	169	155-182	127-210	155-182		155-182	127-210	127-210	
Visit 12 (Week 28)	197	183-210		183-210		183-210			
Visit 13 (Week 32)	225	211-238		211-238		211-238			
Visit 14 (Week 36)	253	239-266	211-308	239-266		239-266	211-308	211-308	
Visit 15 (Week 40)	281	267-294		267-294		267-294			
Visit 16 (Week 44)	309	295-322		295-322		295-322			
Visit 17 (Week 48)	337	323-350		323-350		323-350			1+

		Time windows for							
Visit	**Target Day**	**Vital signs**	**ECG endpoints**	**Clinical lab testing**	**Serum Pregnancy test**	**Urine Pregnancy test**	**Urinalysis, Serum immunoglobulins**	**Hepatitis B viral load**	**Hepatitis screen, HIV screen, ANA and Anti-ds DNA antibogy**
Visit 18 (Week 52)	365	351-378	309-406	351-378		351-406	309-406	>308	
Visit 19 (Week 56)	393	379-406		379-406					
Visit 20 (Week 60)	421	407-434		407-434					
Visit 21 (Week 64)	449	>434	>406	>434		>406	>406		

1^{-}: up to 1st dose date/time; 1^{+}: after 1st dose date/time;

For the efficacy assessment, the reference date for the derivation of relative days of events or findings will be the randomization day. If a patient receives IMP prior to the randomization by mistake, the reference date of efficacy assessment will be the date of the first IMP administration for that patient. For the primary analyses, all available values of scheduled measurements will be assigned to the appropriate visit window according to Table 9. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For the on-treatment sensitivity analyses, only scheduled measurements collected during the treatment epoch will be assigned to a time window.

Table 9 – Time window for efficacy variables

		Time windows for		
Visit	**Target Day**	**Pre-bronchodilator Spirometry, ACQ-5, ACQ-7**	**Post-bronchodilator spirometry, reversibility**	**AQLQ(S), EQ-5D-5L, HADS, SNOT-22, RQLQ(S)+12**
Visit 1 (Week -4±1)	-28±7	<-14		
Visit 2 (Week 0)	1	-14-1^{-}	1^{-}	1^{-}
Visit 3 (Week 2)	15	1^{+}-21	1^{+}-21	
Visit 4 (Week 4)	29	22-35	22-42	
Visit 5 (Week 6)	43	36-49		
Visit 6 (Week 8)	57	50-63	43-70	
Visit 7 (Week 10)	71	64-77		
Visit 8 (Week 12)	85	78-98	71-126	1-126
Visit 9 (Week 16)	113	99-126		
Visit 10 (Week 20)	141	127-154		
Visit 11 (Week 24)	169	155-182	127-210	127-210
Visit 12 (Week 28)	197	183-210		
Visit 13 (Week 32)	225	211-238		
Visit 14 (Week 36)	253	239-266	211-308	211-308
Visit 15 (Week 40)	281	267-294		
Visit 16 (Week 44)	309	295-322		
Visit 17 (Week 48)	337	323-350		
Visit 18 (Week 52)	365	351-378	309-406	309-406
Visit 19 (Week 56)	393	379-406		
Visit 20 (Week 60)	421	407-434		
Visit 21 (Week 64)	449	>434	>406	>406

1^{-}: up to randomization and before 1st dose date/time; 1^{+}: after randomization or 1st dose date/time

(electronic 3.0)

For the pharmacokinetics/pharmacodynamics variables summary, the reference date for the derivation of relative days of measurements will be the date of first IMP administration if the patient is treated with study treatment, or the randomization date if the patient is not treated. Pharmacokinetics /pharmacodynamics variables will be summarized by the analysis window defined in Table 10 for the by visit descriptive analyses. All available values of measurements will be assigned to the appropriate visit window. In the event of multiple measurements of the same test in the same window, the one closest to the targeted visit date will be used for the by-visit summary. If they are at the same distance to the target day, the latest one will be used. For procedures planned on Visit 2, if it is done on the same date as the first IMP injection but the performance time is missing, it will belong to Visit 2 time window.

Table 10 – Time window for pharmacokinetics/pharmacodynamics variables

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin
Visit 1 (Week -4±1)	-28±7		<-14				
Visit 2 (Week 0)	1	1-	-14-1-	1-	1-	1-	1-
Visit 3 (Week 2)	15		1+-21	1+-21			
Visit 4 (Week 4)	29		22-56	22-42			1+-56
Visit 5 (Week 6)	43						
Visit 6 (Week 8)	57			43-70			
Visit 7 (Week 10)	71						
Visit 8 (Week 12)	85	1+-126	57-98	71-98	1-126	1-126	57-224
Visit 9 (Week 16)	113		99-126	99-140			
Visit 10 (Week 20)	141		127-154				
Visit 11 (Week 24)	169	127-210	155-210	141-210	127-266	127-266	
Visit 12 (Week 28)	197						
Visit 13 (Week 32)	225						
Visit 14 (Week 36)	253	211-308	211-294	211-308			
Visit 15 (Week 40)	281						
Visit 16 (Week 44)	309						
Visit 17 (Week 48)	337		295-350				
Visit 18 (Week 52)	365	>308	351-378	309-378	267-406	>267	>224
Visit 19 (Week 56)	393		379-406	379-406			
Visit 20 (Week 60)	421		407-434	407-434			
Visit 21 (Week 64)	449		>434	>434	>406		

Visit	Target day	Time windows for					
		Eotaxin-3, ECP, total IgE, TARC	Exhaled NO	Systemic drug concentration	Anti-drug antibodies	Antigen-specific IgE	Periostin

1-: up to 1st dose date/time or randomization if patient is not treated; 1+: after 1st dose date/time or randomization date if patient is not treated;

2.5.5 Unscheduled visits

Unscheduled visit measurements of laboratory data, vital signs, and ECG will be included in the by-visit summaries, computation of baseline, worst values, and PCSAs.

2.5.6 Pooling of centers for statistical analyses

Due to the large number of centers, the randomization is stratified by country. Due to small sample size in some countries, the countries will be pooled into regions as defined below for the analyses:

- East Europe: Hungary, Poland, Russia, Turkey and Ukraine
- Western Countries: Australia , Canada, France, Germany, Italy, South Africa, Spain, United Kingdom and USA
- Asia: Japan, South Korea and Taiwan;
- Latin America: Argentina, Brazil, Colombia, Chile and Mexico

2.5.7 Statistical technical issues

None.

3 INTERIM ANALYSIS

No interim analysis is planned.

4 DATABASE LOCK

The database lock is planned based on the time when approximately 1638 patients (originally planned sample size) complete Week 52 visit or discontinue from the study before Week 52. Analyses will be based on all data collected up to this database lock and will be considered as the final analyses in the CSR. Additional data between database lock and last patient completing last visit will be summarized in CSR addendum.

5 SOFTWARE DOCUMENTATION

All summaries and statistical analyses will be generated using SAS version 9.4 or higher.

6 REFERENCES

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Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. N Engl J Med. DOI: 10.1056/NEJMoa1804092

Supplementary Appendix

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma Patients from the Phase 3 LIBERTY ASTHMA QUEST Study

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2. Supplementary Methods

2.1. Patient eligibility criteria

Key inclusion criteria

Adults and adolescent patients (aged ≥12 years) with a physician diagnosis of asthma for ≥12 months, based on the Global Initiative for Asthma (GINA) 2014 Guidelines[1] and the following criteria:

- Existing treatment with medium-to-high-dose inhaled glucocorticoid (≥250 µg of fluticasone propionate twice daily or equipotent inhaled glucocorticoid daily dosage to a maximum of 2000 µg/day of fluticasone propionate or equivalent) in combination with a second controller (i.e. long-acting β adrenoceptor agonists or leukotriene receptor antagonists) for ≥3 months with a stable dose of inhaled glucocorticoids ≥1 month prior to Visit 1.
  - Note for Japan: for patients aged ≥18 years, inhaled glucocorticoids must be ≥200 µg of fluticasone propionate twice daily or equivalent; for patients aged 12 to 17 years, inhaled glucocorticoids must be ≥100 µg of fluticasone propionate twice daily or equivalent.
  - Patients requiring a third controller for their asthma will be considered eligible for this study, and it should also be used for ≥3 months with a stable dose ≥1 month prior to Visit 1.

- Pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≤ 80% of predicted normal for adults and ≤ 90% of predicted normal for adolescents at Visits 1 and 2, prior to randomization.
- 5-Item Asthma Control Questionnaire (ACQ-5) score ≥1.5[2,3] at Visits 1 and 2, prior to randomization.
- Reversibility of at least 12% and 200 mL in FEV_1 after the administration of 200 to 400 µg albuterol/salbutamol or levalbuterol/levosalbutamol (2 to 4 inhalations of albuterol/salbutamol or levalbuterol/levosalbutamol, or of a nebulized solution of albuterol/salbutamol or levalbuterol/levosalbutamol, if considered as a standard office practice) before randomization.
- Must have experienced, within 1 year prior to Visit 1, any of the following events:
  - Treatment with a systemic steroid (oral or parenteral) for worsening asthma at least once.
  - Hospitalization or emergency medical care visit for worsening asthma.

Key exclusion criteria

- Patients aged <12 years or the minimum legal age for adolescents in the country of the investigative site, whichever is higher (for those countries where local regulations permit enrollment of adults only, patient recruitment will be restricted to those who are aged ≥18 years)
- Patients who weigh <30 kg
- Patients with chronic obstructive pulmonary disease or other lung diseases (i.e. idiopathic pulmonary fibrosis, Churg-Strauss syndrome, etc.) that may impair lung function
- Patients who experience a severe asthma exacerbation (defined as a deterioration of asthma resulting in emergency treatment, hospitalization due to asthma, or treatment with systemic steroids at any time from 1 month prior to the screening visit up to and including the baseline visit)
- Patients with evidence of lung disease(s) other than asthma, either clinical evidence or imaging (i.e. chest X-ray, computed tomography [CT], magnetic resonance imaging [MRI]) within 12 months of Visit 1 as per local standard of care
  - Note for Japan: According a request from the health authority, chest X-ray should be performed at screening visit if there is no chest imaging (chest X-ray, CT, MRI) available within 3 months prior to screening to exclude patients with suspected active or untreated latent tuberculosis
- Current smoker or cessation of smoking within 6 months prior to Visit 1

- Previous smoker with a smoking history >10 pack-years
- Comorbid disease that might interfere with the evaluation of the investigational medicinal product (IMP)

2.2 Data and safety monitoring committee

The data and safety monitoring committee consisted of top leading experts in areas of expertise, including but not limited to: Pediatric Allergy and Immunology, Dermatology and Epidemiology, Internal Medicine, Allergy, Asthma and Immunology, Dermatology, Epidemiology and Large-Scale Data Review.

2.3. Statistical analysis

Efficacy analyses were performed on the intent-to-treat (ITT) population, defined as all randomized patients by allocated treatment regardless of whether or not treatment was received. The annualized rate of severe exacerbations was analyzed using a negative binomial regression model, with the total number of events occurring during the 52-week treatment period as the response variable. The four treatment groups: age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, and number of severe exacerbations within 1 year prior to the study were included as covariates, and log-transformed observation duration was the offset variable. Patients who discontinued study medication were encouraged to return to the clinic for all remaining study visits, and all severe exacerbations up to Week 52 were included in the primary analysis, regardless of whether or not the patient was receiving treatment. Changes from baseline in continuous endpoints such as FEV_1 and patient-reported outcomes were analyzed using a mixed-effects model with repeated measures (MMRM). The model included changes from baseline values as response variables. Treatment, age, baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment-by-visit interaction, baseline value, and baseline-by-visit interaction were included as covariates. Sex and baseline height were included as covariates only in the models for spirometry parameters. For patients who discontinued study treatment and stayed in the study, off-treatment measurements were included in the primary model. An unstructured correlation matrix was used to model within-patient errors. Parameters were estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm. Time-to-event endpoints were analyzed using a Cox regression model, with time to event as the dependent variable; treatment, age, number of asthma exacerbation events within 1 year prior to the study, region (pooled country), baseline eosinophil strata, and baseline inhaled glucocorticoid dose level were included as covariates. The Kaplan-Meier method was used to estimate the probability of a

patient experiencing a severe exacerbation. Descriptive statistics were used for demographic and clinical characteristics, pharmacodynamic variables, safety variables (including adverse events [AEs]), vital signs, and findings on physical examination, clinical laboratory testing, and electrocardiogram (ECG).

For patients who withdrew from the study prior to Visit 18 (Week 52), severe exacerbation events were observed after study discontinuation. These patients were considered as patients with missing data on severe exacerbation outcomes. Similarly, if a patient missed scheduled pre-bronchodilator FEV_1 measurement during the first 12-week treatment, or withdrew from the study before Visit 8 (Week 12), he/she will have missing pre-bronchodilator FEV_1 data at some time points up to Week 12. Sensitivity analyses including pattern mixture model-multiple imputation (PMM-MI), control-based PMM-MI and tipping point analysis were conducted to confirm the robustness of primary analysis results for the two primary endpoints.

2.4. Pharmacodynamics

Blood eosinophil counts were measured as part of the standard 5-part white blood cell (WBC) differential cell count on a hematology autoanalyzer. Eotaxin-3 was measured in heparinized plasma using the Human Eotaxin-3 Quantikine ELISA kit (R&D Systems, Minneapolis, MN, USA). IgE and eosinophil cationic protein levels were measured with a quantitative ImmunoCAP assay (Phadia, Uppsala, Sweden), thymus and activation-regulated chemokine (TARC) levels were measured with the Quantikine® ELISA Kit (Cat# DDN00; R&D Systems), and periostin levels were assayed with the Shino-Test Corporation Periostin ELISA Kit (Human; Shino-Test Corporation, Tokyo, Japan). Fractional exhaled nitric oxide (FE_{NO}) was measured and analyzed using a NIOX instrument (Aerocrine AB, Solna, Sweden), or similar analyzer using a flow rate of 50 mL/s, and reported in parts per billion (ppb). All pharmacodynamic assessments were performed at a central laboratory (either Pharmaceutical Product Development or Viracor), with the exceptions of FE_{NO}, which was assayed at the clinical site, and periostin, which was assayed at the Sanofi facility in Framingham, MA, USA.

2.5. Narratives of patient deaths

Overview: There were 8 patient deaths in this trial: 1 patient (0.2%) in the dupilumab 200 mg q2w (every 2 weeks) group, 4 patients (0.6%) in the dupilumab 300 mg q2w group, and 3 patients (1.0%) in one of the placebo groups. One additional patient in the dupilumab 300 mg q2w group died

approximately 6 months after discontinuing dupilumab. All deaths were considered by the investigator to be unrelated to the study. A description of the death cases by treatment group is presented below.

Patient 1: Female patient, aged 76 years

A 76-year-old female patient from Chile in the dupilumab 200 mg q2w group experienced a pulmonary embolism on Day 311 that resulted in death on Day 354. Pertinent medical history included hypertension, osteoarthritis, and menopause. On Day 223 the patient developed a serious adverse event (SAE) of a urinary tract infection; the patient was hospitalized and treated with antibiotics (ceftriaxone, ciprofloxacin). On Day 236, eosinophil count was within normal range (20 cells/µL). As a result of this event, the IMP was permanently discontinued (last administration on Day 288). On Day 277, eosinophil count was within normal range (580 cells/µL). On Day 311, the patient was hospitalized due to asthmatic crisis and sinus tachycardia. Continuous nebulization with fenoterol hydrobromide/ipratropium bromide, oxygen, furosemide, hydrocortisone, and enoxaparin sodium were given as corrective treatment. A CT scan showed (per information provided after the cut-off date) pulmonary thromboembolism, cardiomegaly, moderate left pleural effusion, and left posterior basal atelectasis. Pleurocentesis as corrective treatment and 4 mL of turbid fluid was removed (pleural fluid chemistry and culture/sensitivity reports not provided). D-Dimer was >20 µg/mL. Final diagnosis was pulmonary embolism, and the patient was started on subcutaneous (SC) enoxaparin sodium and oral acenocumarol. On Day 320, the patient was hospitalized again due to an SAE of urinary tract infection; urine culture grew 100,000 colony-forming units (CFU)/mL of extended spectrum lactamase producing *Klebsiella pneumoniae*. The patient was treated with intravenous (IV) vancomycin hydrochloride and imipenum. On Day 354, while in the hospital, the patient developed acute respiratory failure and died due to acute respiratory insufficiency; massive pleural effusion (CT scan performed did not show any pulmonary metastasis). Per information received from the investigator after the cut-off date, an ovarian malignancy with pulmonary metastasis was suspected due to ascites and pleural effusion; however, given the patient´s poor general condition, no further investigations were performed. Autopsy was not performed. The investigator's assessment of causality for the pulmonary embolism was not related to dupilumab.

Patient 2: Female patient, aged 61 years

A 61-year-old female patient from Argentina in the dupilumab 300 mg q2w group experienced a cardiorespiratory arrest on Day 124, which resulted in death on the same day. Pertinent medical history for this postmenopausal patient included hypertension, osteoporosis, rheumatoid arthritis, and

kyphosis. At baseline, pre-bronchodilator FEV_1 was 0.55 L (24% predicted), forced vital capacity (FVC) was 1.1 L (38% predicted), post-bronchodilator FEV_1 was 0.58 L (26% predicted) and FVC was 1.15 L (39% predicted). On Day 107, the patient was hospitalized due to paraplegia resulting from spinal cord injury at T4 to T7 level and spinal stenosis, sequelae from multiple osteoporotic fractures with sequestrated T5 to T6 vertebrae. A neurosurgeon and traumatologist were consulted, and they did not recommend surgery as it was a high-risk procedure with very few chances of recovery. Last recorded spirometry prior to hospitalization on Day 83 showed FEV_1 of 0.75 L (compared to baseline value of 0.55 L). Pulmonary function tests were not available during this hospitalization. Dupilumab was temporarily discontinued due to pathological fracture and subsequently permanently discontinued due to osteoporosis; with the last dose administered on Day 99. On Day 124, while in the hospital, the patient experienced cardiorespiratory arrest of unknown etiology. No acute asthma exacerbation was noted in the days preceding death. No autopsy was performed. The investigator's assessment of causality for the cardiorespiratory arrest was not related to dupilumab.

Patient 3: Male patient, aged 70 years

A 70-year-old male patient from Chile in the dupilumab 300 mg q2w group with a baseline pre-bronchodilator FEV_1 of 0.73 L (29% predicted) experienced respiratory depression and cardiorespiratory arrest on Day 125, which required hospitalization and resulted in death on Day 145. Pertinent medical history included allergic rhinitis, arterial hypertension, testicular seminoma, and depression. The spirometry assessment on Day 113 showed an FEV_1 of 0.83 L. On Day 122, the patient was noted to be in a confusional state followed by psychotic delusions. Dupilumab was interrupted with the last administration on Day 113. On Day 125, while waiting to be treated in the ambulatory emergency room (ER), the patient developed respiratory depression, was taken to the hospital, where he was found to be dyspneic with distal cyanosis, oxygen saturation 90 to 91%, in respiratory depression and confusional state. Electroencephalography (EEG) was consistent with severe diffuse continuous slowness and symmetric of low amplitude; epileptiform changes were not registered. The patient was hospitalized and subsequently intubated and placed on mechanical ventilation. Laboratory tests showed respiratory acidosis. The patient began to have myoclonic seizures, received IV diazepam and phenytoin, became hypotensive, not responding to fluid therapy, and was started on noradrenaline drip. Diagnosis was a hypoxic cardiorespiratory arrest and ischemic encephalopathy. The cardiorespiratory arrest was considered to be a consequence of a severe hypoxemic condition secondary to the respiratory depression. On Day 128, a digital EEG showed severe diffuse continuous slowness of generalized low amplitude. On Day 140, an ECG showed left ventricular hypertrophy, severe pulmonary hypertension,

and mitral valve insufficiency. CT angiography of the chest and lower extremities revealed moderate-to-severe bilateral pleural effusion without signs of pulmonary thromboembolism and deep venous thrombosis in both lower extremities. On Day 145, despite treatment in the intensive care unit (ICU), the patient developed shock and died. No autopsy was performed. The investigator's assessment of causality for both events was not related to dupilumab.

Patient 4: Female patient, aged 65 years

A 65-year-old female patient from Mexico in the dupilumab 300 mg q2w group died suddenly without any witnesses on Day 159 while the patient was traveling. It was reported that the patient had no previous symptoms and did not receive any medical attention during the event. Pertinent medical history included systemic arterial hypertension and a body mass index (BMI) of 42.4 kg/m^2. At the screening visit, electrocardiogram (ECG) showed sinus rhythm with nonspecific T wave abnormality and was considered clinically not significant. All subsequent ECGs on Days 14, 28, and 84 showed sinus rhythm with nonspecific T wave abnormality. Her baseline FEV_1 was 0.90 L (52% of predicted) and fluctuated between 0.89 L to 1.3 L with the last FEV_1 on Day 141 of 0.8 L. Prior to death, the patient had no worsening of asthma symptoms reported in the e-diary (no nighttime awakenings, stable dose of reliever medication, no use of nebulizer or oral steroids). Cause of death was reported as acute myocardial infarction. No autopsy was performed. The investigator's assessment of causality of this event was not related to dupilumab.

Patient 5: Male patient, aged 59 years

A 59-year-old male patient from the USA with a BMI of 41.81 kg/m^2 in the dupilumab 300 mg q2w group experienced cardiac failure congestive on Day 88, ventricular tachycardia on Day 159, and multiple organ dysfunction syndrome on Day 162 requiring hospitalization and resulting in death on Day 165. Pertinent medical history included obesity, sleep apnea syndrome, rheumatic fever, hypertension, peripheral edema, diverticulitis, and a history of chest pain for 6 months prior to enrollment. The patient had a family history of premature coronary disease. At the time of enrollment his ECG revealed 1st degree atrioventricular block and right axis deviation. ECG prior to enrollment showed non-severe "leaky valves" (not otherwise specified). On Day 88, the patient experienced extreme shortness of breath, chest tightness, and extreme fatigue and was admitted to the hospital. ECG showed sinus rhythm, right axis deviation, possible old anterior infarct (age undetermined). Troponin was mildly abnormal at 0.188 and brain natriuretic peptide (BNP) was elevated to 1600 (units not specified). ECG showed ejection fraction of 40%. Cardiac catheterization revealed non-obstructive disease of the

proximal left anterior descending artery and left circumflex and some non-obstructive disease in the right coronary artery. He was diagnosed with congestive heart failure, and furosemide, lisinopril carvedilol, heparin, glyceryl trinitrate and acetylsalicylic acid were given as corrective treatment. As a result, dupilumab was permanently discontinued. On Day 99, the patient presented to the ER with substernal/epigastric sharp chest pain and was hospitalized. Physical examination revealed regular rate and rhythm, no murmurs, gallops, or rubs, and 1 to 2+ pitting edema of bilateral lower extremities. Troponin was 0.149. A chest X-ray revealed cardiomegaly and partial atelectasis of the right lower lobe. He was discharged from the hospital on Day 101. On Day 118, the patient had an SAE of severe intensity reported as acute cholecystitis. An ultrasound showed gallstones and sludge; the patient was admitted and underwent laparoscopic cholecystectomy. The congestive heart failure event worsened to severe intensity on the same day. In the investigator's opinion, acute cholecystitis contributed to decompensated congestive heart failure. On Day 129, the patient experienced acute chest pain and was again hospitalized. Subsequently, the patient was transferred to the coronary care unit. A 12-lead ECG was abnormal and showed sinus rhythm, right axis deviation, right bundle branch block, lateral infarct of undetermined age, possible anterior infarct of undetermined age, inferior T wave changes non-specific, and low QRS voltages in precordial leads. On Day 159, the patient had atrial fibrillation and ventricular tachycardia. Corrective treatment included nitroglycerin, cephalexin, amiodarone, and dopamine. Three days later, the patient experienced multiple organ failure (associated with hypotension and tachycardia) requiring intubation and complications of acute kidney injury requiring dialysis. Temporary trans-venous pacemaker insertion and cardioversion were performed due to severe bradycardia, paroxysmal atrial fibrillation, and severe congestive heart failure, but the patient died on Day 165. The investigator's assessment of causality for these events was not related to dupilumab.

Patient 6: Male patient, aged 43 years

A 43-year-old male patient from Argentina in the placebo (1.14 mL) group completed suicide on Day 92. The patient had no previous history of suicide attempt or of suicidal ideation. The patient previously had anxiety and received alprazolam or clonazepam, but the medication was stopped many months before the event. It was also reported that the patient had recently suffered from a violent assault. The patient was injured by thieves who took his car, and he was also worried about his father-in-law's health. The last dupilumab administration was on Day 83. According to the family, the cause of death was reported as mechanical asphyxia. The investigator's assessment of causality was not related to dupilumab.

Patient 7: Male patient, aged 69 years

A 69-year-old male patient from the USA in the placebo (1.14 mL) group experienced anaplastic thyroid cancer on Day 109 that resulted in death on Day 204. On Day 109, the patient (with a medical history of thyroid cancer >5 years before study entry and thyroidectomy) had throat pain, acute odynophagia on the right side, and coughing after drinking liquids, and had lost 12 pounds over the prior few weeks. The patient also had noted changes in voice quality, fatigue, hearing loss, difficulty in breathing and swallowing, and dental problems. Flexible laryngoscopy showed a right vocal cord paralysis. A CT scan of the chest revealed soft tissue mass and enlarged lymph nodes in the right upper paratracheal region, infiltrating the esophagus and extending to the posterior aspect of the trachea. Fine-needle aspiration showed poorly differentiated malignant carcinoma composed of poorly cohesive tumor cells with bizarre, pleomorphic nuclei with eccentric cytoplasm, and abundant mitotic activity. The dupilumab was permanently discontinued due to this event with the last administration on Day 90. On Day 204 (4 months after the last dupilumab administration), the patient died due to anaplastic thyroid cancer. The investigator's assessment of causality of anaplastic thyroid cancer was not related to dupilumab.

Patient 8: Female patient, aged 76 years

A 76-year-old female patient from the USA in the placebo (1.14 mL) group experienced a pulmonary embolism on Day 179 that resulted in death on the same day. The patient’s pertinent medical history included allergic rhinitis, hypertension, hyperlipidemia, osteoporosis, vertigo, osteoarthritis, total hysterectomy, oophorectomy, left knee replacement, right carpel tunnel repair, jaw surgery mandibular advancement, insomnia, and anxiety. On Day 177, the patient underwent a right total knee arthroplasty as corrective treatment for osteoarthritis and her immediate postoperative period was uneventful. The patient was started on apixaban 2.5 mg twice a day for deep vein thrombosis (DVT) prophylaxis. On Day 179, 2 days after the surgery, the patient was found not breathing and in asystole; underwent prolonged resuscitation and intubation and was placed on vasopressors in the ER; and was admitted to the ICU. The patient remained in profound shock and again arrested, but was quickly resuscitated with additional epinephrine. The ECG revealed left ventricular ejection fraction of 70% to 75%, a flattened septum in the systole, diastole consistent with right ventricle pressure and volume overload, and a suspected saddle thrombus in the main pulmonary artery. The patient had a cardiac arrest secondary to the pulmonary embolism. The patient continued to do poorly and was not able to maintain pressure support. The family elected to discontinue resuscitation, and life support measures were turned off. No autopsy was performed. The investigator's assessment of causality of pulmonary embolism was not related to dupilumab.

2.6. Narratives of eosinophilia cases associated with symptoms

All cases of patients with eosinophilia treatment emergent adverse events (TEAEs), meeting any of the following criteria, were medically reviewed after database lock: serious AE; moderate or severe intensity; leading to permanent treatment discontinuation; and peak eosinophil count ≥5000 cells/µL. A total of 34 out of the 56 patients had eosinophilia TEAEs that met these criteria. In 4 cases, increased blood eosinophil levels were temporarily associated with symptoms. Two were reported as SAEs. A description of these 4 cases is below:

Patient 1: Male patient, aged 50 years

A 50-year-old white male with asthma for approximately 3 years, was randomized to the dupilumab 300 mg q2w treatment group. The patient had an ongoing history of chronic rhinosinusitis and nasal polyps. The patient also had a history of hypereosinophilia, and presented with elevated eosinophil count at screening (1140 cells/µL) which resolved by the baseline visit (570 cells/µL), while other blood cell counts were within the normal ranges. The patient experienced three asthma exacerbations in the year prior to enrollment including one requiring hospitalization. The last exacerbation was approximately 5 months prior to randomization.

The patient received the loading dose of the IMP on Day 1 and the second dose on Day 16. A few hours after the second dose, the patient developed injection site erythema, severe chills with fever, myalgia, arthralgia, and slight worsening of asthma symptoms. No blood was drawn for laboratory tests at that visit. The patient's vital signs and ECG were normal. No lymphadenopathy and no sign of upper respiratory infection were reported to suggest an alternate cause of fever or myalgia. The patient did not have any prior history of myalgia or arthralgia that was not associated with viral infection. Hydrocortisone butyrate was administered SC with resolution of fever (Day 18), and injection site erythema (Day 22); however, myalgia and arthralgia persisted. During this time there were worsening respiratory symptoms and the patient was treated with oral paracetamol for pain and oral thiocolchicoside (a muscle relaxant).

The laboratory values on Day 30 showed an eosinophil count of 10280 cells/µL, with a WBC count of 20000 cells/µL and neutrophil count equal to 29.1%. Blood eosinophil count decreased to 670 cells/µL on Day 40. The patient's other symptoms also resolved in this time frame. The investigator reported "worsening of hypereosinophilia" as an SAE with seriousness criteria of "other medically important event", and considered at this time that the previously reported events of fever, myalgia, and arthralgia were also due to hypereosinophilia. The IMP was permanently discontinued due to hypereosinophilia.

Patient 2: Male patient, aged 56 years

A 56-year-old white male patient with a history of asthma for approximately 6 years, was randomized to the dupilumab 300 mg q2w treatment group. The patient experienced five asthma exacerbations in the year prior to enrollment, none requiring hospitalization or urgent medical care. The last exacerbation prior to the enrollment was approximately 4 months prior to randomization. The patient received the first dose of the IMP on Day 1. The patient's eosinophil count was 660 cells/µL at baseline, 1840 cells/µL on Day 30, and 2080 cells/µL on Day 113.

Approximately 4 months after randomization, on Day 118 (5 days after the most recent dose of the IMP) the patient experienced fever requiring hospitalization, an SAE that ultimately was determined by the investigator to be chronic eosinophilic pneumonia. No other information was provided. About 2 weeks later, on Day 132, the patient was hospitalized for the same AE. The patient had persistent fever and an increase of peripheral eosinophilia, but denied coughing, dyspnea, lack of energy, weight loss, or night sweats. Spirometry was within normal ranges. The patient had no symptoms or signs of neuropathies. A chest X-ray showed widespread parenchymal thickening bilaterally, more extended to the para hilar region on the right. No pleural effusion was seen. The cardiothoracic contour was within normal limits. Laboratory results (blood drawn on Day 133) revealed a WBC count of 10360 cells/µL, eosinophils 26.2%, and eosinophils count 2710 cells/µL. The last dose of the IMP was on Day 127, after which the IMP was discontinued. The patient was treated with oral levofloxacin and parenteral piperacillin/tazobactam and oral prednisone (initial dose of 25 mg for 1 month then downtitrated thereafter and ongoing as of the data cut-off date). On Day 140 the patient had bronchoscopy with bronchoalveolar lavage (BAL). BAL fluid showed no eosinophils but was characteristic of neutrophilic pneumonitis.

Further investigation for eosinophilia included negative FLIPI (follicular lymphoma international prognostic index)-1 mutations and negative anti-nuclear antibody (ANA) and extractable nuclear antigen (ENA) panels. On Day 170, histological examination of the lung (needle biopsy) showed inflammatory infiltrates rich in eosinophil granulocytes. The transbronchial biopsies did not reveal any necrotizing or granulomatous vasculitis, and the diagnosis of chronic eosinophilic pneumonia of severe intensity was made. The patient was treated with oral glucocorticoids with resolution of chest X-ray findings and eosinophilia (eosinophil count 70 cells/µL, Day 296).

Patient 3: Female patient, aged 28 years

A 28-year-old white female in the dupilumab 300 mg q2w group experienced an AE of mild intensity, reported as eosinophilia on Day 114. The patient was diagnosed with asthma approximately 6 years earlier, and experienced three asthma exacerbations in the year prior to enrollment, one of which required hospitalization or urgent medical care. The last exacerbation was experienced approximately 4 months prior to the enrollment. The patient had a medical history of thyroiditis, chronic gastritis, duodenitis, and mitral valve prolapse.

The patient had an eosinophil count of 690 cells/µL at screening and 45 cells/µL at baseline. The patient experienced a TEAE of lymphadenitis of moderate intensity and unknown etiology (Day 105) which resolved within 4 days. The eosinophil count started to increase after the first dupilumab dose and remained elevated. On Day 114 the eosinophil count was 3220 cells/µL, WBC count was 16100 cells/µL (normal range: 3700 to 11000 cells/µL, baseline value: 15600 cells/µL), neutrophils were 8710 cells/µL (normal range: 1700 to 7900 cells/µL, baseline value 12450 cells/µL) and platelets were 484000 cells/µL (normal range: 125000 to 375000 cells/µL, baseline value: 315000 cells/µL).

Myositis of unknown etiology and of moderate intensity was subsequently reported (Day 121) treated with a non-steroidal anti-inflammatory drug (NSAID) and patient recovered within 3 days. Throughout the study creatine phosphokinase (CPK) levels remained well within the normal limits (24-169 IU/L). On Day 142 eosinophil count reached a peak of 8650 cells/µL and started to decrease afterwards. WBC count was 20300 cells/µL, and platelet count was 476000 cells/µL.

On Day 170, the patient experienced radiculopathy of unknown etiology requiring treatment with NSAIDs that recovered in 2 weeks. The patient experienced four asthma exacerbations requiring systemic steroid treatment during the study. No reduction of the eosinophil count was observed at the time of steroids administration. The FEV_1 fluctuated over the course of the study, overall no improvement in FEV_1 was observed. The TEAE of hypereosinophilia was reported as recovered on Day 367, with an eosinophil count of 2310 cells/µL. The IMP treatment was continued with no interruption.

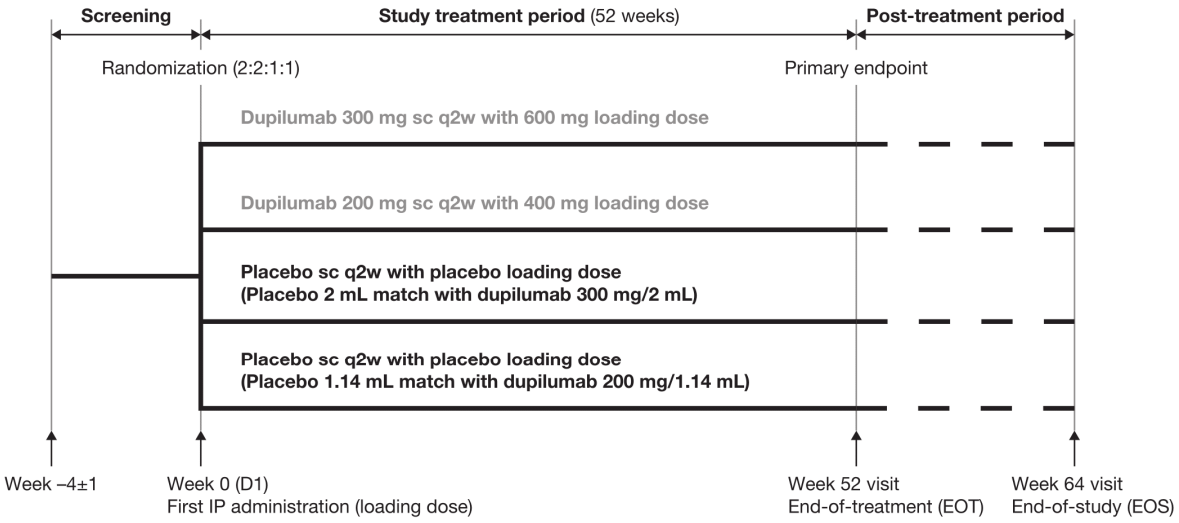
Patient 4: Female patient, aged 52 years

A 52-year-old white female in the dupilumab 300 mg q2w group (with ongoing medical history of hives and history of two asthma exacerbations within the year preceding inclusion in the study) had an eosinophil count of 1770 cells/µL at screening and 1210 cells/µL at baseline. She experienced a TEAE of moderate intensity, reported as eosinophil count increased to 3040 cells/µL on Day 105. Subsequently, on Day 127, the patient developed pneumonitis of moderate intensity attributed to the increased eosinophils. X-ray of the chest showed infiltrates in both lungs. On Day 131, eosinophil count reached a

peak of 4920 cells/µL. The IMP was permanently discontinued due to the AE with the last dose administered on Day 120. Prednisone was given as corrective treatment. The patient recovered from pneumonitis on Day 145 and from the eosinophilia on Day 215, with an eosinophil count of 940 cells/µL.

3. Figures and Tables

Figure S1. LIBERTY ASTHMA QUEST Study Design.*



*D1 denotes Day 1, IP investigational product, q2w every 2 weeks, SC subcutaneous.

Patients were allowed to continue on to the extension study (LTS12551) after completion of treatment; thus, they would have had no post-treatment follow-up period.

Figure S2. CONSORT Diagram of Patient Disposition.

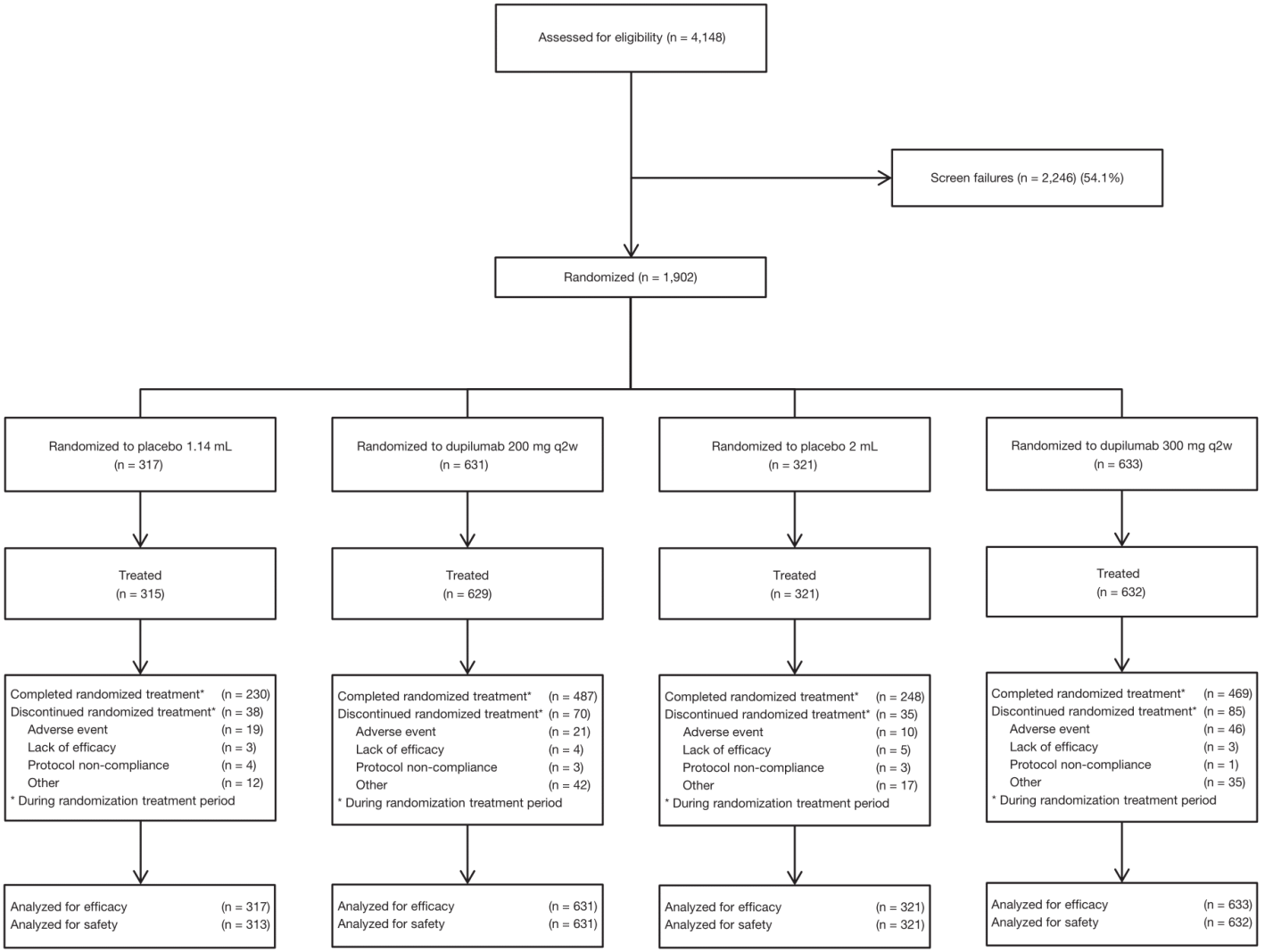
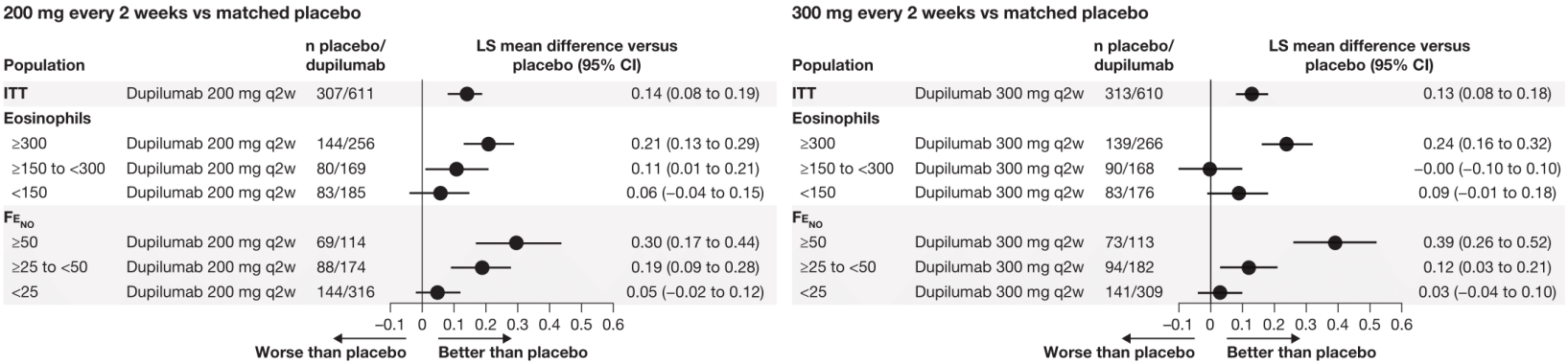


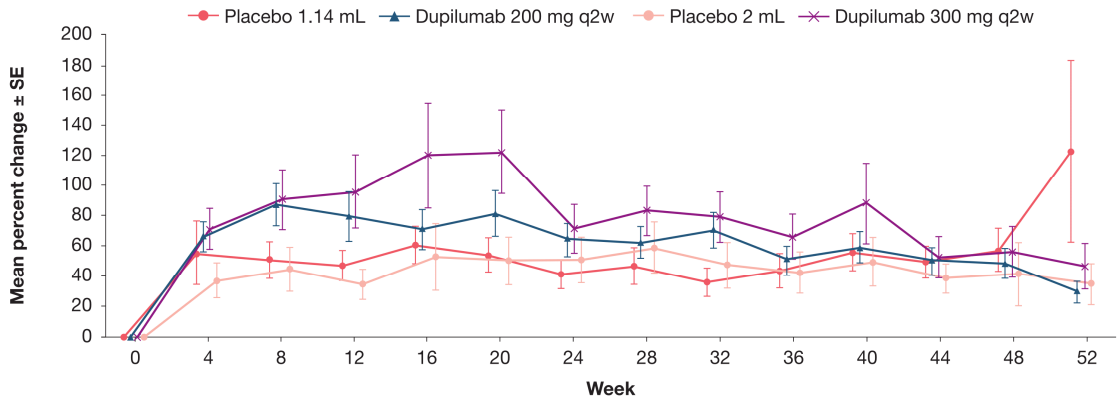
Figure S3. Forest Plots of Change from Baseline to Week 12 in FEV_1 in the ITT Population and in Subgroups Defined by Baseline Blood Eosinophils <150 cells/µl, ≥150 to <300 cells/µl, and ≥300 cells/µl and by Baseline FE_{NO} Levels <25 ppb, ≥25 to 50 ppb, and ≥50 ppb.*



*CI denotes confidence interval, FE_{NO} fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, ITT intent-to-treat, ppb parts per billion, q2w every 2 weeks.

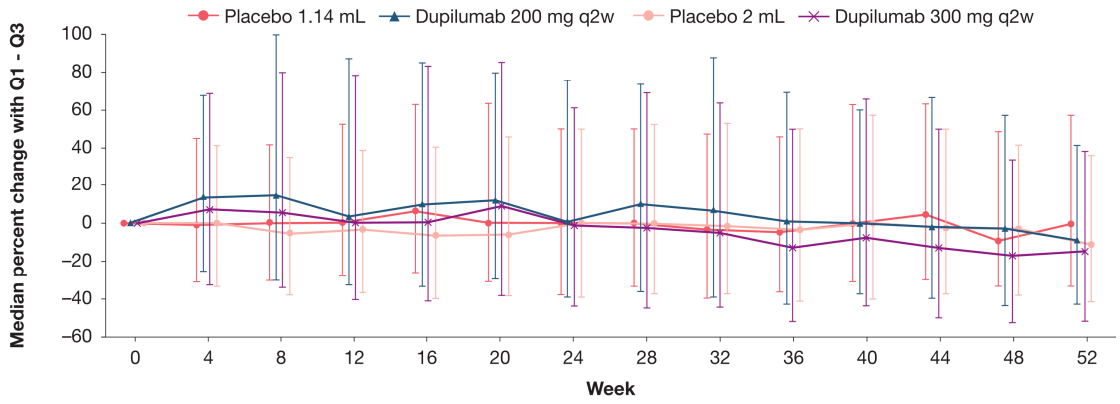
Figure S4. Mean Percent Change (±SE) From Baseline in Blood Eosinophils Over Time (A) and Median Percent Change (With Interquartile Range) From Baseline in Blood Eosinophils Over Time (B) in the Exposed Population.*

A



No. of patients														
Placebo 1.14 mL	313	298	297	294	286	279	282	273	271	271	265	265	258	222
Dupilumab 200 mg q2w	630	604	589	585	576	565	562	560	551	557	551	549	538	450
Placebo 2 mL	320	304	300	297	297	286	280	286	286	278	280	274	267	238
Dupilumab 300 mg q2w	632	609	573	574	575	558	548	550	534	535	532	525	515	443

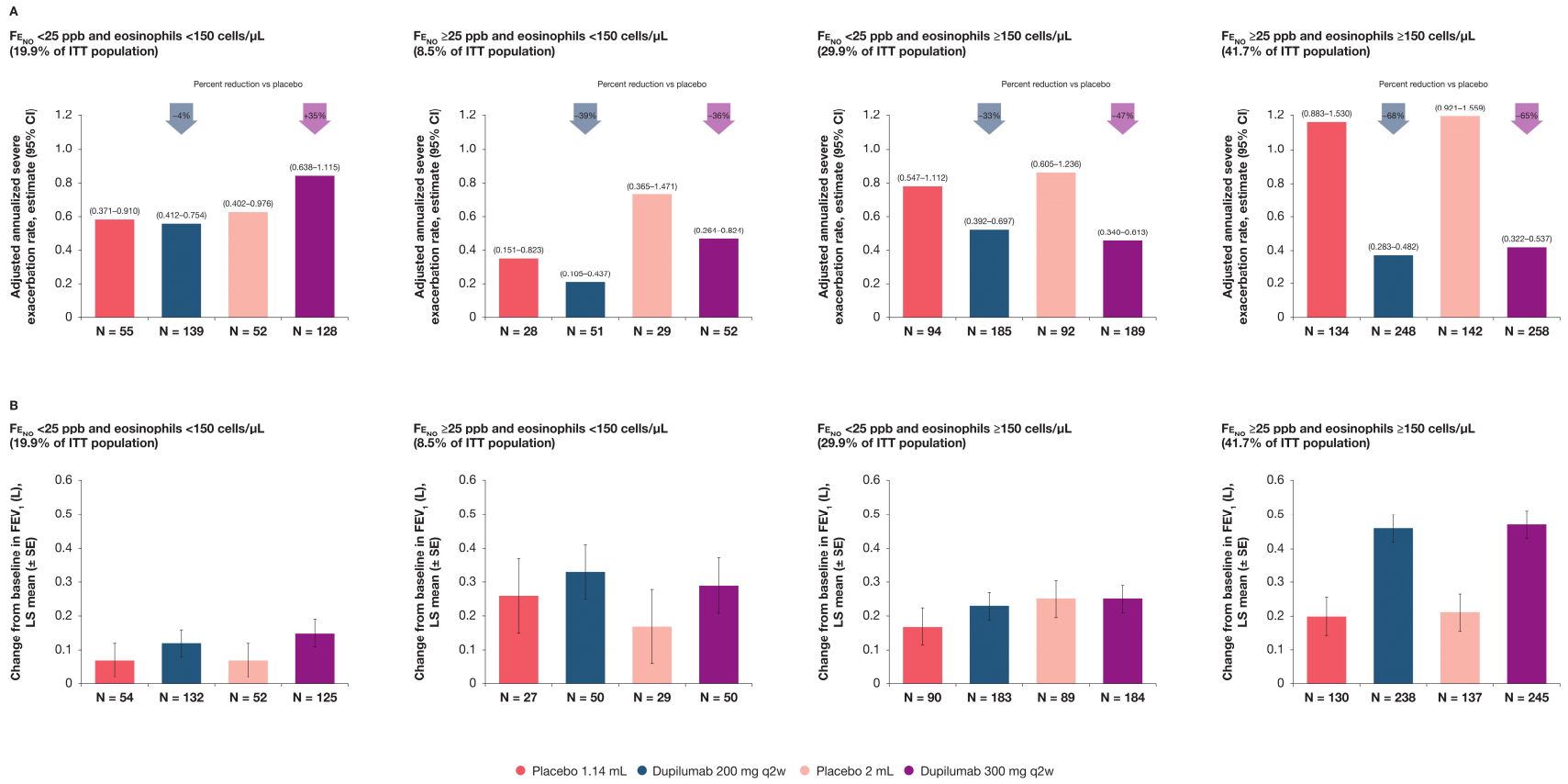
B



No. of patients														
Placebo 1.14 mL	313	298	297	294	286	279	282	273	271	271	265	265	258	222
Dupilumab 200 mg q2w	630	604	589	585	576	565	562	560	551	557	551	549	538	450
Placebo 2 mL	320	304	300	297	297	286	280	286	286	278	280	274	267	238
Dupilumab 300 mg q2w	632	609	573	574	575	558	548	550	534	535	532	525	515	443

*Q1 denotes quartile 1, q2w every 2 weeks, Q3 quartile 3, SE standard error.

Figure S5. Post Hoc Analysis of Severe Asthma Exacerbations (A) and Change From Baseline in FEV_1 (B) in Patients With High (≥25 ppb) or Low (<25 ppb) Baseline FE_{NO} Levels and High (≥150 cells/μL) or Low (<150 cells/μL) Baseline Blood Eosinophils.



*CI denotes confidence interval, FE_{NO} fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, ITT intent-to-treat, ppb parts per billion, q2w every 2 weeks, SE standard error.

Table S1. Summary of Study Outcome Measures per Hierarchical Testing Procedure.*

Outcome Measure	Time Frame	Dupilumab	
		200 mg q2w	300 mg q2w
Primary Efficacy Endpoints			
Annualized rate of severe asthma exacerbations	52 weeks	3	1
Absolute change from baseline in pre-bronchodilator FEV_1	Week 12	4	2
Secondary Efficacy Endpoints			
Percentage change from baseline in pre-bronchodilator FEV_1	Week 12	11	5
Annualized rate of severe asthma exacerbations in patients with ≥150 eosinophils/μL	52 weeks	12	6
Absolute change from baseline in pre-bronchodilator FEV_1 in pts with ≥150 eosinophils/μL	Week 12	13	7
Annualized rate of severe asthma exacerbations in patients with ≥300 eosinophils/μL	52 weeks	14	8
Absolute change from baseline in pre-bronchodilator FEV_1 in patients with ≥300 eosinophils/μL	Week 12	15	9
Annualized rate of severe asthma exacerbations in patients with <300 eosinophils/μL	52 weeks	16	10
Annualized rate of severe asthma exacerbations in patients on high-dose inhaled glucocorticoids	52 weeks	22	17
Absolute change from baseline in pre-bronchodilator FEV_1 in patients on high-dose inhaled glucocorticoids/long-acting β_2	Week 12	23	18
Change from baseline in AQLQ† [S] global score	Week 24	24	19
Change from baseline in AQLQ† [S] global score in patients with ≥300 eosinophils/μL	Week 24	25	20
Change from baseline in ACQ-5‡ score	Week 24	26	21
Annualized rate of severe asthma exacerbations resulting in hospitalization or emergency room visit	52 weeks	28	27
Absolute change from baseline in pre-bronchodilator FEV_1 in patients with <300 eosinophils/μL	Week 12	30	29

* Hierarchy testing order follows from 1 through to 30, indicated by arrows. Percentage change from baseline in pre-bronchodilator FEV_1 was the only key secondary endpoint. Hierarchy break occurred at 10. Reported significance values following the hierarchy break are therefore nominal.

ACQ-5 denotes 5-Item Asthma Control Questionnaire, AQLQ (S) Asthma Quality of Life Questionnaire (Standardized Version), ER emergency room, MCID minimal clinically important difference.

† AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales.[4]

‡ ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5.[2,3]

Table S2. Baseline Demographic and Clinical Characteristics (ITT Population).*

	Placebo	Dupilumab 200 mg q2w	Placebo	Dupilumab 300 mg q2w	Overall Population
	N = 317	N = 631	N = 321	N = 633	N = 1902
Mean (SD) age — yr	48.2 (15.6)	47.9 (15.3)	48.2 (14.7)	47.7 (15.6)	47.9 (15.3)
<18 yr — no. of patients (%)	21 (6.6)	34 (5.4)	18 (5.6)	34 (5.4)	107 (5.6)
Female sex — no. of patients (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Mean (SD) BMI — kg/m^2	29.76 (7.25)	29.05 (6.52)	29.21 (6.95)	29.07 (6.68)	29.20 (6.77)
Mean (SD) pre-bronchodilator FEV_1 — L	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)	1.78 (0.60)
Mean (SD) pre-bronchodilator FEV_1 — % predicted	58.43 (13.22)	58.38 (13.52)	58.35 (13.87)	58.51 (13.52)	58.43 (13.52)
Mean (SD) FEV_1 reversibility — %	25.06 (18.76)	27.39 (22.79)	26.45 (17.65)	25.73 (23.79)	26.29 (21.73)
Mean (SD) exacerbations in past year — no.	2.07 (1.58)	2.07 (2.66)	2.31 (2.07)	2.02 (1.86)	2.09 (2.15)
High-dose inhaled glucocorticoid use — no. of patients (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
Mean (SD) ACQ-5† score	2.71 (0.73)	2.76 (0.80)	2.77 (0.77)	2.77 (0.76)	2.76 (0.77)
Mean (SD) AQLQ‡ global score	4.26 (1.02)	4.31 (1.08)	4.30 (1.03)	4.28 (1.05)	4.29 (1.05)

	Placebo	Dupilumab 200 mg q2w	Placebo	Dupilumab 300 mg q2w	Overall Population
	N = 317	N = 631	N = 321	N = 633	N = 1902
Mean (SD) AM asthma symptom score§	1.16 (0.81)	1.14 (0.85)	1.12 (0.84)	1.12 (0.87)	1.14 (0.85)
Mean (SD) PM asthma symptom score§	1.27 (0.82)	1.26 (0.85)	1.23 (0.82)	1.27 (0.84)	1.26 (0.84)
Atopic/allergic ongoing condition — no. of patients (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Atopic dermatitis	35 (11.0)	61 (9.7)	38 (11.8)	62 (9.8)	196 (10.3)
Allergic rhinitis	221 (69.7)	421 (66.7)	225 (70.1)	438 (69.2)	1305 (68.6)
Nasal polyposis and/or chronic rhinosinusitis	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. of patients (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
Mean (SD) pack-years — no.	3.96 (2.81)	3.89 (2.69)	4.07 (3.12)	4.15 (3.04)	4.02 (2.89)
Biomarker levels					

	Placebo	Dupilumab 200 mg q2w	Placebo	Dupilumab 300 mg q2w	Overall Population
	N = 317	N = 631	N = 321	N = 633	N = 1902
Mean (SD) blood eosinophil count — cells/µL	370 (338)	349 (345)	391 (419)	351 (369)	360 (366)
Median (min to max) blood eosinophil count — cells/µL	270 (0 to 2200)	250 (0 to 3610)	265 (0 to 3580)	250 (0 to 4330)	255 (0 to 4330)
Mean (SD) FE_{NO} — ppb	34.47 (28.54)	34.45 (34.91)	38.39 (38.00)	34.01 (29.74)	34.97 (32.85)
Median (min to max) FE_{NO} — ppb	26.00 (3.0 to 197.0)	23.00 (3.0 to 387.0)	27.00 (5.0 to 351.0)	24.00 (4.0 to 202.0)	25.00 (3.0 to 387.0)
Mean (SD) total IgE — IU/mL	393.90 (624.70)	460.96 (817.75)	448.47 (796.66)	415.08 (701.40)	432.40 (746.66)
Median (min to max) total IgE — IU/mL	174.50 (1.0 to 5000.0)	154.00 (1.0 to 5000.0)	178.50 (3.0 to 5000.0)	174.00 (1.0 to 5000.0)	167.00 (1.0 to 5000.0)
Mean (SD) TARC — pg/mL	377.88 (288.22)	394.12 (457.89)	398.00 (344.16)	364.35 (295.58)	382.22 (364.25)
Median (min to max) TARC — pg/mL	296.00 (33.1 to 1970.0)	314.50 (15.6 to 8600.0)	300.00 (34.0 to 3210.0)	295.00 (15.6 to 3170.0)	302.00 (15.6 to 8600.0)
Mean (SD) periostin — ng/mL	79.62 (36.58)	79.88 (39.18)	80.94 (40.73)	78.49 (37.90)	79.55 (38.58)

	Placebo	Dupilumab 200 mg q2w	Placebo	Dupilumab 300 mg q2w	Overall Population
	N = 317	N = 631	N = 321	N = 633	N = 1902
Median (min to max) periostin — ng/mL	71.70 (27.8 to 244.9)	70.60 (20.5 to 368.2)	71.00 (25.1 to 312.8)	69.70 (19.2 to 298.5)	70.60 (19.2 to 368.2)
Mean (SD) eotaxin-3 — pg/mL	52.11 (86.35)	78.30 (340.04)	50.89 (57.85)	69.53 (481.53)	66.36 (342.53)
Median (min to max) eotaxin-3 — pg/mL	36.50 (2.0 to 1180.0)	39.15 (2.0 to 6430.0)	37.45 (2.0 to 723.0)	38.30 (2.0 to 12000.0)	38.20 (2.0 to 12000.0)

*ACQ-5 denotes 5-item Asthma Control Questionnaire, AQLQ (S) Asthma Quality of Life Questionnaire (Standardized Version), BMI body mass index, FE_{NO} fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, MCID minimal clinically important difference, min to max minimum to maximum, ppb parts per billion, q2w every 2 weeks, SD standard deviation, TARC thymus and activation-regulated chemokine.

†ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score ranging from 0 to 6 is calculated. The MCID is 0.5.[2,3]

‡AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales.[4]

§Asthma symptom scores are recorded in an electronic diary upon arising (AM symptom score) and in the evening (PM symptom score). Lower scores indicate more mild symptoms; AM and PM scores are calculated ranging from 0 to 4. There is no published reference for the MCID of 0.35.

Table S3. Summary of Primary and Secondary Efficacy Endpoints.*

	Randomized Treatment Group to Overall Population			
	Placebo (N = 317)	Dupilumab 200 mg q2w (N = 631)	Placebo (N = 321)	Dupilumab 300 mg q2w (N = 633)
Adjusted annualized rate of severe asthma exacerbations				
Estimate (95% CI)	0.871 (0.724 to 1.048)	0.456 (0.389 to 0.534)	0.970 (0.810 to 1.160)	0.524 (0.450 to 0.611)
Relative risk versus matching placebo† (95% CI)	—	0.523 (0.413 to 0.662)*	—	0.540 (0.430 to 0.680)*
Mean baseline (SD) pre-bronchodilator FEV_1 — L	1.76 (0.61)	1.78 (0.62)	1.75 (0.57)	1.78 (0.60)
Change from baseline in FEV_1 at Week 12				
LS mean (SE) change — L	0.18 (0.02)	0.32 (0.02)	0.21 (0.02)	0.34 (0.02)
LS mean difference versus matching placebo (95% CI)‡	—	0.14 (0.08 to 0.19)*	—	0.13 (0.08 to 0.18)*
Percent change from baseline in FEV_1 at Week 12				
LS mean (SE)	12.11 (1.56)	21.34 (1.13)	13.67 (1.56)	23.08 (1.13)
LS mean difference versus matching placebo (95% CI)‡	—	9.23 (5.54 to 12.92)	—	9.41 (5.74 to

				13.07)*
Adjusted annualized rate of severe asthma exacerbations in patients with ≥300 eosinophils/μL	N = 148	N = 264	N = 142	N = 277
Estimate (95% CI)	1.081 (0.846 to 1.382)	0.370 (0.289 to 0.475)	1.236 (0.972 to 1.571)	0.403 (0.317 to 0.512)
Relative risk versus matching placebo† (95% CI)	—	0.342 (0.244 to 0.480)	—	0.326 (0.234 to 0.454)*
Change from baseline in FEV_1 in patients with ≥300 eosinophils/μL at Week 12	N = 144	N = 256	N = 139	N = 266
LS mean (SE) change	0.21 (0.03)	0.43 (0.03)	0.22 (0.03)	0.47 (0.02)
LS mean difference versus matching placebo (95% CI)‡	—	0.21 (0.13 to 0.29)	—	0.24 (0.16 to 0.32)*

*Analyses were part of the hierarchical testing procedure prior to hierarchy break and as such are multiplicity controlled ($P < 0.001$). CI denotes confidence interval, FEV_1 forced expiratory volume in 1 second, LS least square, MMRM mixed-effects model with repeated measures, SD standard deviation, SE standard error.

†Derived using a negative binomial model, with the total number of events starting from randomization up to Visit 18 or last contact date as the response variable; the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, and number of severe exacerbation events in the year prior to the study as covariates; and log-transformed standardized observation duration as an offset variable.

‡Week 12 changes from baseline were derived using an MMRM approach, with absolute or percentage change from baseline in pre-bronchodilator FEV_1 values at Week 12 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates.

Table S4: Pre-specified Post-Bronchodilator FEV_1 Slope Analysis*

	Randomized Treatment Group			
	Placebo (N = 317)	Dupilumab 200 mg q2w (N = 631)	Placebo (N = 321)	Dupilumab 300 mg q2w (N = 633)
Post-bronchodilator FEV_1 slope during the 52-week treatment period after Week 4 (L/year)				
Number, n	311	622	319	626
Estimated post-BD FEV_1 slope†	−0.04 (0.02)	−0.00 (0.01)	−0.04 (0.02)	−0.00 (0.01)
LS mean difference versus matching placebo (95% CI)†		0.04 (0.00 to 0.08)		0.04 (0.00 to 0.08)
Post-bronchodilator FEV_1 slope during the 52-week treatment period after Week 8 (L/year)				
Number, n	310	618	316	623
Estimated post-BD FEV_1 slope†	−0.04 (0.02)	−0.00 (0.01)	−0.04 (0.02)	−0.00 (0.01)
LS mean difference versus matching placebo (95% CI)†		0.04 (−0.01 to 0.09)		0.03 (−0.01 to 0.08)

*Endpoints were pre-specified but were not part of the hierarchical testing order, and as such were not multiplicity controlled. CI denotes confidence interval, FEV_1 forced expiratory volume in 1 second and LS least square.

†Estimated from a mixed-effects model with repeated post-BD FEV_1 as outcome, and treatment, age, sex, height, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, time since randomization and treatment-by-time interaction and baseline post-BD FEV_1 as covariates. Intercept and time since randomization are random effects.

Table S5: Subgroup Analyses of Primary Endpoints by Baseline Blood Eosinophil Count and FE_{NO} Levels.*

Subgroup/Endpoint	Randomized Treatment Group - ITT Population			
	Placebo (N = 317)	Dupilumab 200 mg q2w (N = 631)	Placebo (N = 321)	Dupilumab 300 mg q2w (N = 633)
	Baseline EOS ≥300 cells/µL			
Annualized rate of severe exacerbations at Week 52	N = 148	N = 264	N = 142	N = 277
Estimate (95% CI)	1.081 (0.846 to 1.382)	0.370 (0.289 to 0.475)	1.236 (0.972 to 1.571)	0.403 (0.317 to 0.512)
Relative risk versus matching placebo†	—	0.342 (0.244 to 0.480)	—	0.326 (0.234 to 0.454)*
Change from baseline in FEV_1 (L) at Week 12	N = 144	N = 256	N = 139	N = 266
LS mean (SE) change	0.21 (0.03)	0.43 (0.03)	0.22 (0.03)	0.47 (0.02)
LS mean difference versus matching placebo (95% CI)§	—	0.21 (0.13 to 0.29)	—	0.24 (0.16 to 0.32)*
	Baseline EOS ≥150 to <300 cells/µL			
Annualized rate of severe exacerbations at Week 52	N = 84	N = 173	N = 95	N = 175
Estimate (95% CI)	0.867 (0.592 to 1.271)	0.559 (0.416 to 0.751)	0.844 (0.578 to 1.234)	0.471 (0.347 to 0.638)
Relative risk versus matching placebo†	—	0.644 (0.407 to 1.019)	—	0.557 (0.350 to 0.888)
Change from baseline in FEV_1 (L) at Week 12	N = 80	N = 169	N = 90	N = 168
LS mean (SE) change	0.17 (0.04)	0.28 (0.03)	0.25 (0.04)	0.25 (0.03)
LS mean difference versus matching		0.11 (0.01 to 0.21)		0.00 (−0.10, 0.10)

placebo (95% CI)‡				
Baseline EOS <150 cells/µL				
Annualized rate of severe exacerbations at Week 52†	N = 85	N = 193	N = 83	N = 181
Estimate (95% CI)	0.511 (0.346 to 0.755)	0.472 (0.358 to 0.623)	0.642 (0.445 to 0.927)	0.737 (0.575 to 0.946)
Relative risk versus matching placebo†	—	0.925 (0.580 to 1.474)	—	1.149 (0.747 to 1.767)
Change from baseline in FEV_1 (L) at Week 12‡	N = 83	N = 185	N = 83	N = 176
LS mean (SE) change	0.13 (0.04)	0.19 (0.03)	0.11 (0.04)	0.20 (0.03)
LS mean difference versus matching placebo (95% CI)‡	—	0.06 (−0.04 to 0.15)	—	0.09 (−0.01 to 0.18)
Baseline FE_{NO} ≥50 ppb				
Annualized rate of severe exacerbations at Week 52	N = 71	N = 119	N = 75	N = 124
Estimate (95% CI)	1.057 (0.722 to 1.547)	0.326 (0.221 to 0.480)	1.274 (0.901 to 1.801)	0.388 (0.270 to 0.558)
Relative risk versus matching placebo†	—	0.308 (0.183 to 0.519)	—	0.305 (0.188 to 0.494)
Change from baseline in FEV_1 (L) at Week 12	N = 69	N = 114	N = 73	N = 113
LS mean (SE) change	0.23 (0.05)	0.53 (0.04)	0.19 (0.05)	0.59 (0.04)
LS mean difference versus matching placebo (95% CI)‡	—	0.30 (0.17 to 0.44)	—	0.39 (0.26 to 0.52)
Baseline FE_{NO} ≥25 to 50 ppb				
Annualized rate of severe exacerbations at	N = 91	N = 180	N = 97	N = 186

Week 52				
Estimate (95% CI)	0.925 (0.648 to 1.322)	0.358 (0.258 to 0.495)	1.045 (0.739 to 1.478)	0.462 (0.343 to 0.622)
Relative risk versus matching placebo†	—	0.386 (0.243 to 0.616)	—	0.442 (0.282 to 0.693)
Change from baseline in FEV_1 (L) at Week 12	N = 88	N = 174	N = 94	N = 182
LS mean (SE) change	0.21 (0.04)	0.39 (0.03)	0.23 (0.04)	0.35 (0.03)
LS mean difference versus matching placebo (95% CI)‡	—	0.19 (0.09 to 0.28)	—	0.12 (0.03 to 0.21)
Baseline FE_{NO} <25 ppb				
Annualized rate of severe exacerbations at Week 52	N = 149	N = 325	N = 144	N = 317
Estimate (95% CI)	0.693 (0.525 to 0.916)	0.521 (0.418 to 0.650)	0.748 (0.565 to 0.992)	0.593 (0.478 to 0.735)
Relative risk versus matching placebo†	—	0.752 (0.541 to 1.046)	—	0.792 (0.572 to 1.098)
Change from baseline in FEV_1 (L) at Week 12	N = 144	N = 316	N = 141	N = 309
LS mean (SE) change	0.15 (0.03)	0.20 (0.02)	0.20 (0.03)	0.23 (0.02)
LS mean difference versus matching placebo (95% CI)‡	—	0.05 (−0.02 to 0.12)	—	0.03 (−0.04 to 0.10)

*P value (P < 0.001) indicates multiplicity controlled statistical significance. CI denotes confidence interval, EOS eosinophils, FE_{NO} fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, LS least square, MMRM mixed-effects model with repeated measures, NA not applicable, ppb parts per billion, q2w every 2 weeks, q4w every 4 weeks, and SE standard error.

†Derived using a negative binomial model with the total number of events starting from randomization up to Visit 18 or last contact date as the response variable; the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, and number of severe exacerbations in the year prior to the study as covariates; and log-transformed standardized observation duration as an offset variable.

‡Week 12 changes from baseline were derived using an MMRM approach, with change from baseline in pre-bronchodilator FEV_1 values at Week 12 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV_1 value, and baseline-by-visit interaction as covariates.

Table S6: Summary of Additional Secondary Endpoints.*

Endpoint	Randomized Treatment Group			
	Placebo (N = 317)	Dupilumab 200 mg q2w (N = 631)	Placebo (N = 321)	Dupilumab 300 mg q2w (N = 633)
	Change from baseline in AQLQ† (S) global score at Week 24			
LS mean (SE) change	0.94 (0.06)	1.14 (0.04)	1.00 (0.06)	1.15 (0.04)
LS mean difference versus matching placebo (95% CI) ‡	—	0.20 (0.06 to 0.34)	—	0.15 (0.01 to 0.28)
	Change from baseline in AQLQ† (S) global score at Week 52			
LS mean (SE) change	0.99 (0.06)	1.28 (0.04)	1.03 (0.06)	1.29 (0.04)
LS mean difference versus matching placebo (95% CI) ‡	—	0.29 (0.15 to 0.44)	—	0.26 (0.12 to 0.40)
	Change from baseline in AQLQ† (S) global score at Week 24 in patients with ≥300 eosinophils/µL			
LS mean (SE) change	0.96 (0.09)	1.37 (0.06)	0.98 (0.09)	1.32 (0.06)
LS mean difference versus matching placebo (95% CI) ‡	—	0.41 (0.20 to 0.62)	—	0.34 (0.13 to 0.54)
	Change from baseline in ACQ-5§ score at Week 2			
LS mean (SE) change	−0.56 (0.05)	−0.89 (0.04)	−0.61 (0.05)	−0.92 (0.04)
LS mean difference versus matching placebo (95% CI) ¶	—	−0.34 (−0.46 to −0.22)	—	−0.31 (−0.42 to −0.19)
	Change from baseline in ACQ-5§ score at Week 24			
LS mean (SE) change	−1.10 (0.06)	−1.44 (0.04)	−1.21 (0.06)	−1.40 (0.04)
LS mean difference versus matching placebo (95% CI) ¶	—	−0.35 (−0.48 to −0.21)	—	−0.19 (−0.32 to −0.05)

Change from baseline in ACQ-5§ score at Week 52				
LS mean (SE) change	−1.15 (0.06)	−1.54 (0.04)	−1.30 (0.06)	−1.52 (0.04)
LS mean difference versus matching placebo (95% CI) ¶	—	−0.39 (−0.53 to −0.25)	—	−0.22 (−0.36 to −0.08)
Change from baseline in AM symptom score# at Week 24				
LS mean (SE) change	−0.33 (0.03)	−0.52 (0.02)	−0.37 (0.03)	−0.49 (0.02)
LS mean difference versus matching placebo (95% CI) **	—	−0.19 (−0.27 to −0.11)	—	−0.12 (−0.20 to −0.04)
Change from baseline in AM symptom score# at Week 52				
LS mean (SE) change	−0.40 (0.04)	−0.55 (0.03)	−0.43 (0.04)	−0.58 (0.03)
LS mean difference versus matching placebo (95% CI) **	—	−0.15 (−0.24 to −0.06)	—	−0.16 (−0.24 to −0.07)
Change from baseline in PM symptom score# at Week 24				
LS mean (SE) change	−0.33 (0.04)	−0.53 (0.03)	−0.36 (0.04)	−0.51 (0.03)
LS mean difference versus matching placebo (95% CI) **	—	−0.20 (−0.28 to −0.11)	—	−0.15 (−0.24 to −0.06)
Change from baseline in PM symptom score# at Week 52				
LS mean (SE) change	−0.39 (0.04)	−0.57 (0.03)	−0.42 (0.04)	−0.57 (0.03)
LS mean difference versus matching placebo (95% CI) **	—	−0.18 (−0.28 to −0.09)	—	−0.14 (−0.24 to −0.05)
Change from baseline in AM PEF (L/min) at Week 24				
LS mean (SE) change	6.15 (3.49)	28.19 (2.51)	15.61 (3.47)	25.01 (2.50)
LS mean difference versus matching placebo (95% CI) ††	—	22.04 (13.70 to 30.38)	—	9.40 (1.11 to 17.68)

Change from baseline in AM PEF (L/min) at Week 52				
LS mean (SE) change	2.35 (3.94)	28.97 (2.82)	12.69 (3.91)	26.00 (2.82)
LS mean difference versus matching placebo (95% CI) ††	—	26.62 (17.20 to 36.04)	—	13.31 (3.94 to 22.67)
Change from baseline in PM PEF (L/min) at Week 24				
LS mean (SE) change	−2.86 (3.52)	19.62 (2.53)	8.14 (3.51)	16.53 (2.52)
LS mean difference versus matching placebo (95% CI) ††	—	22.48 (14.08 to 30.89)	—	8.39 (0.03 to 16.74)
Change from baseline in PM PEF (L/min) at Week 52				
LS mean (SE) change	−6.01 (3.96)	17.50 (2.84)	4.44 (3.95)	15.34 (2.84)
LS mean difference versus matching placebo (95% CI) ††	—	23.51 (14.04 to 32.99)	—	10.90 (1.47 to 20.32)

	Placebo 1.14 mL and 2 mL q2w combined (N = 638)	Dupilumab 200 mg and 300 mg q2w combined (N = 1264)
Annualized rate of severe exacerbation events requiring hospitalization or ER visit		
Estimate (95% CI)	0.065 (0.047 to 0.090)	0.035 (0.025 to 0.048)
Relative risk versus matching placebo‡‡	—	0.532 (0.347 to 0.816)

*All endpoints in this table were after the hierarchy break or were not part of the hierarchical testing order, and as such were not multiplicity controlled. ACQ-5 denotes the 5-item Asthma Control Questionnaire, AQLQ Asthma Quality of Life Questionnaire, CI confidence interval, ER emergency room, LS least square, MCID minimal clinically important difference, MMRM mixed-effects model with repeated measures, PEF peak expiratory flow, q2w every 2 weeks, q4w every 4 weeks, SE standard error.

†AQLQ is a patient-reported measure of asthma-specific health-related quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7. The MCID is 0.5 for all scales.[4]

‡Derived from MMRM model with change from baseline in AQLQ global score up to Week 24 or 52 as the response variable, and the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment by-visit interaction, baseline AQLQ global score and baseline-by-visit interaction as covariates.

§ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score is calculated ranging from 0 to 6. The MCID is 0.5.[2,3]

¶Derived from an MMRM model with change from baseline in ACQ-5 up to Week 24 or 52 as the response variable, and the four treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment by-visit interaction, baseline ACQ-5, and baseline-by-visit interaction as covariates.

#Asthma symptom scores are recorded in an electronic diary upon arising (AM symptom score) and in the evening (PM symptom score). Lower scores indicate more mild symptoms; AM and PM scores are calculated ranging from 0 to 4.

**Derived from MMRM model with change from baseline in AM/PM symptom score (periodical average) up to Week 52 as the response variable, and treatment, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment-by-visit interaction, baseline AM/PM symptom score, and baseline-by-visit interaction as covariates.

††Derived from MMRM model with change from baseline in AM/PM PEF values (periodical average) up to Week 52 as the response variable, and treatment, age, sex, baseline height, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, visit, treatment-by-visit interaction, baseline AM/PM PEF value, and baseline-by-visit interaction as covariates.

‡‡Derived using a negative binomial model with the total number of events starting from randomization up to Visit 18 or last contact date as the response variable; the two pooled treatment groups, age, region (pooled country), baseline eosinophil strata, baseline inhaled glucocorticoid dose level, and number of severe exacerbations in the year prior to the study as covariates; and log-transformed standardized observation duration as an offset variable.

Table S7: Summary of Change from Baseline in Type 2 Biomarker Levels.*

	Actual Treatment Group			
	Placebo (N = 313)	Dupilumab 200 mg q2w (N = 631)	Placebo (N = 321)	Dupilumab 300 mg q2w (N = 632)
Fractional exhaled nitric oxide (FE_{NO})				
Mean baseline (SD) — ppb	34.5 (28.7)	34.4 (34.9)	38.4 (38.0)	34.0 (29.8)
Median (min to max) baseline — ppb	26.0 (3.0 to 197.0)	23.0 (3.0 to 387.0)	27.0 (5.0 to 351.0)	24.0 (4 to 202.0)
Change from baseline to Week 12				
Mean change (SD) — ppb	−2.5 (21.0)	−14.9 (31.3)	−3.6 (29.6)	−15.6 (25.3)
Median (min to max) change — ppb	−1.0 (−81.0 to 78.0)	−6.0 (−371.0 to 69.0)	−1.0 (−309.0 to 69.0)	−7.0 (−177.0 to 62.0)
Mean change (SD) — %	8.301 (67.949)	−21.702 (49.439)	5.774 (62.937)	−26.743 (46.990)
Median (min to max) change — %	−7.020 (−83.93 to 500.00)	−28.571 (−95.87 to 360.00)	−5.806 (−91.96 to 450.00)	−33.333 (−93.16 to 266.67)
Change from baseline to Week 24				
Mean change (SD) — ppb	−2.8 (21.2)	−16.2 (32.6)	−4.6 (30.5)	−16.2 (26.0)
Median (min to max) change — ppb	−1.0 (−96.0 to 122.0)	−7.0 (−373.0 to 42.0)	−2.0 (−306.0 to 96.0)	−8.0 (−171.0 to 36.0)
Mean change (SD) — %	9.792 (70.545)	−24.117 (49.694)	4.519 (72.324)	−26.899 (51.855)
Median (min to max) change — %	−6.667 (−87.50 to 583.33)	−33.333 (−97.16 to 420.00)	−10.000 (−91.07 to 620.00)	−37.639 (−92.26 to 580.00)
Change from baseline to Week 52				

Mean change (SD) — ppb	−2.1 (20.2)	−16.0 (27.1)	−5.5 (36.2)	−16.2 (26.8)
Median (min to max) change — ppb	−1.0 (−76.0 to 103.0)	−8.0 (−188.0 to 46.0)	−2.0 (−307.0 to 218.0)	−8.0 (−177.0 to 54.0)
Mean change (SD) — %	5.345 (57.318)	−27.419 (47.765)	1.340 (62.117)	−25.616 (57.806)
Median (min to max) change — %	−5.882 (−82.35 to 381.48)	−36.842 (−96.41 to 383.33)	−10.128 (−91.37 to 380.00)	−35.857 (−93.44 to 600.00)
Total IgE (IU/mL)				
Mean baseline (SD) — IU/mL	394.2 (626.2)	460.6 (816.6)	448.5 (796.7)	415.0 (701.4)
Median (min to max) baseline — IU/mL	174.5 (1.0 to 5000.0)	154.0 (1.0 to 5000.0)	178.5 (3.0 to 5000.0)	174.0 (1.0 to 5000.0)
Change from baseline to Week 12				
Mean change (SD) — IU/mL	11.5 (306.6)	−161.4 (326.6)	−4.5 (174.1)	−143.4 (303.6)
Median (min to max) change — IU/mL	−1.0 (−1044.0 to 4545.0)	−53.0 (−2612.0 to 687.0)	−1.0 (−791.0 to 1337.0)	−56.5 (−4974.0 to 1384.0)
Mean change (SD) — %	23.888 (349.940)	−19.178 (207.088)	3.062 (33.718)	−10.414 (487.631)
Median (min to max) change — %	−1.908 (−55.18 to 6060.00)	−35.484 (−94.85 to 3816.67)	−0.327 (−53.95 to 266.67)	−36.314 (−99.48 to 11600.00)
Change from baseline to Week 24				
Mean change (SD) — IU/mL	10.5 (303.7)	−245.6 (461.1)	33.5 (372.2)	−210.4 (367.6)
Median (min to max) change — IU/mL	−1.5 (−1654.0 to 3851.0)	−84.0 (−4007.0to 571.0)	−1.0 (−931.0 to 3478.0)	−86.0 (−4241.0 to 871.0)
Mean change (SD) — %	27.038 (302.999)	−44.536 (98.156)	28.612 (380.242)	−46.743 (65.843)

Median (min to max) change — %	−2.367 (−70.83 to 5134.67)	−53.128 (−98.97 to 1841.94)	−0.745 (−65.31 to 6485.71)	−53.401 (−99.18 to 1060.00)
Change from baseline to Week 52				
Mean change (SD) — IU/mL	0.6 (427.5)	−313.4 (576.7)	−4.0 (322.1)	−294.8 (519.4)
Median (min to max) change — IU/mL	−2.0 (−1704.0 to 4925.0)	−109.0 (−4637.0 to 573.0)	−2.5 (−1000.0 to 3246.0)	−116.5 (−4994.0 to 862.0)
Mean change (SD) — %	32.375 (428.517)	−60.745 (67.116)	9.887 (68.110)	−58.427 (158.378)
Median (min to max) change — %	−2.941 (−68.51 to 6566.67)	−69.231 (−96.91 to 1202.70)	−4.420 (−80.12 to 652.94)	−69.969 (−99.88 to 3360.00)
Blood eosinophils (cells/µL)				
Mean baseline (SD) — cells/µL	369 (334)	351 (348)	391 (419)	351 (370)
Median (min to max) baseline — cells/µL	280 (0 to 2200)	250 (0 to 3610)	265 (0 to 3580)	250 (0 to 4330)
Change from baseline to Week 12				
Mean change (SD) — cells/µL	−12 (269)	117 (537)	−43 (350)	86 (528)
Median (min to max) change — cells/µL	5 (−1610 to 1630)	10 (−1790 to 5350)	−10 (−2220 to 1180)	0 (−2970 to 6660)
Mean change (SD) — %	46.375 (172.116)	78.610 (403.288)	34.649 (181.064)	93.299 (576.646)
Median (min to max) change — %	0.000 (−100.00 to 1400.00)	2.986 (−97.67 to 6900.00)	−3.704 (−100.00 to 1700.00)	0.000 (−100.00 to 10100.00)
Change from baseline to Week 24				

Mean change (SD) — cells/µL	−23 (333)	84 (617)	−32 (374)	54 (500)
Median (min to max) change — cells/µL	0 (−1290 to 2630)	0 (−2170 to 10200)	0 (−2970 to 1390)	0 (−3080 to 5350)
Mean change (SD) — %	39.519 (156.576)	62.538 (250.177)	49.673 (252.040)	68.958 (367.619)
Median (min to max) change — %	0.000 (−100.00 to 1200.00)	0.000 (−100.00 to 2850.00)	0.000 (−100.00 to 2300.00)	0.000 (−100.00 to 5800.00)
Change from baseline to Week 52				
Mean change (SD) — cells/µL	−3 (313)	20 (397)	−48 (347)	−7 (419)
Median (min to max) change — cells/µL	0 (−1670 to 1540)	−20 (−1690 to 3170)	−30 (−2330 to 1740)	−30 (−3670 to 3420)
Mean change (SD) — %	115.548 (876.073)	28.472 (150.256)	33.603 (206.264)	43.764 (301.609)
Median (min to max) change — %	0.000 (−99.26 to 12800.00)	−9.091 (−100.00 to 1900.00)	−11.438 (−100.00 to 2400.00)	−14.583 (−100.00 to 4300.00)
Thymus and activation-regulated chemokine (TARC; pg/mL)				
Mean baseline (SD) — pg/mL	377.8 (289.0)	393.8 (457.4)	398.0 (344.2)	364.7 (295.4)
Median baseline (min to max) — pg/mL	296.0 (33.0 to 1970.0)	314.5 (16.0 to 8600.0)	300.0 (34.0 to 3210.0)	295.0 (16.0 to 3170.0)
Change from baseline to Week 12				
Mean change (SD) — pg/mL	−12.6 (199.2)	−152.7 (391.7)	29.9 (472.7)	−137.1 (227.0)
Median change (min to max) — pg/mL	−1.0 (−1554 to 800)	−97.0 (−7560 to 835)	−7.1 (−617 to 7850)	−95.0 (−2011 to 1674)

Mean change (SD) — %	9.524 (57.895)	−26.218 (40.294)	14.583 (77.359)	−23.593 (86.178)
Median change (min to max) — %	−0.645 (−95.36 to 427.81)	−32.872 (−90.71 to 236.97)	−3.815 (−77.37 to 827.81)	−34.043 (−91.79 to 1747.6)
Change from baseline to Week 24				
Mean change (SD) — pg/mL	1.9 (277.0)	−158.0 (424.9)	117.0 (2202.8)	−133.7 (219.7)
Median change (min to max) — pg/mL	−7.5 (−1525.0 to 2820.0)	−102 (−7629.0 to 2327.0)	−0.5 (−910.0 to 37250.0)	−90.1 (−2005.0 to 590.0)
Mean change (SD) — %	13.058 (74.827)	−25.461 (49.707)	16.527 (115.457)	−25.518 (41.045)
Median change (min to max) — %	−2.439 (−83.53 to 580.58)	−34.914 (−94.24 to 348.72)	−0.136 (−79.92 to 1354.55)	−33.901 (−92.12 to 220.92)
Change from baseline to Week 52				
Mean change (SD) — pg/mL	−10.4 (194.9)	−157.4 (445.9)	137.7 (2156.4)	−122.8 (218.0)
Median change (min to max) — pg/mL	−5.0 (−1456.0 to 1090.0)	−100.0 (−8187.0 to 885.0)	8.5 (−669.0 to 33650.0)	−85.0 (−2196.0 to 590.0)
Mean change (SD) — %	11.148 (68.623)	−26.219 (42.843)	25.898 (147.862)	−22.740 (50.189)
Median change (min to max) — %	−1.932 (−86.99 to 519.34)	−33.185 (−97.86 to 233.64)	2.603 (−70.99 to 1725.64)	−33.514 (−91.24 to 586.71)
Periostin (ng/mL)				
Mean baseline (SD) — ng/mL	79.83 (36.60)	79.85 (39.12)	80.94 (40.73)	78.42 (37.94)
Median baseline (min to max) — ng/mL	72.1 (27.8 to 244.9)	70.6 (20.5 to 368.2)	71 (25.1 to 312.8)	69.7 (19.2 to 298.5)
Change from baseline to Week 12				

Mean change (SD) — ng/mL	−1.12 (23.46)	−16.33 (32.15)	−1.27 (26.71)	−15.23 (30.51)
Median change (min to max) — ng/mL	−0.6 (−119.7 to 106.6)	−8.3 (−266.4 to 66.4)	−0.6 (−103.5 to 127.6)	−10.6 (−234.5 to 154.3)
Mean change (SD) — %	2.223 (27.144)	−12.577 (29.754)	1.911 (28.007)	−13.007 (28.693)
Median change (min to max) — %	−1.211 (−48.88 to 121.94)	−12.793 (−75.76 to 296.59)	−1.068 (−92.47 to 141.78)	−15.209 (−78.56 to 237.75)
Change from baseline to Week 52				
Mean change (SD) — ng/mL	−4.58 (22.00)	−18.64 (34.67)	−5.05 (27.89)	−18.90 (30.84)
Median change (min to max) — ng/mL	−3.6 (−108.4 to 75.7)	−11.4 (−260 to 70.4)	−4.1 (−110.3 to 189.5)	−12.45 (−202.4 to 130.1)
Mean change (SD) — %	−1.781 (25.764)	−14.797 (31.255)	−2.371 (29.818)	−17.797 (24.443)
Median change (min to max) — %	−5.085 (−70.89 to 134.18)	−17.213 (−77.16 to 343.41)	−6.937 (−70.84 to 236.28)	−18.932 (−72.28 to 75.11)
		Eotaxin-3 (pg/mL)		
Mean baseline (SD) — pg/mL	52.172 (86.619)	78.202 (339.495)	50.892 (57.855)	69.516 (481.528)
Median baseline (min to max) — pg/mL	36.5 (1.95 to 1180.0)	39.2 (1.95 to 6430.0)	37.45 (1.95 to 723.0)	38.3 (1.95 to 12000.0)
Change from baseline to Week 12				
Mean change (SD) — pg/mL	−3.146 (27.402)	−35.518 (136.966)	−1.795 (30.136)	−39.130 (354.372)
Median change (min to max) — pg/mL	−0.2 (−164.0 to 114.8)	−14.6 (−2110.0 to 245.3)	0 (−233.0 to 119.6)	−13.8 (−8750.0 to 33.0)
Mean change (SD) — %	20.212 (145.490)	−14.217 (137.041)	30.046 (260.896)	−24.921 (107.368)

Median change (min to max) — %	−0.719 (−95.19 to 1571.73)	−39.496 (−98.78 to 1443.59)	0 (−96.89 to 3858.97)	−40.912 (−98.73 to 1264.1)
Change from baseline to Week 24				
Mean change (SD) — pg/mL	−1.547 (33.785)	−31.269 (152.042)	−6.366 (35.547)	−43.019 (443.011)
Median change (min to max) — pg/mL	−0.600 (−235.00 to 270.00)	−16.450 (−2872.00 to 1650.00)	−2.600 (−315.20 to 200.60)	−13.500 (−10690.00 to 115.00)
Mean change (SD) — %	32.257 (189.230)	−13.742 (159.982)	15.173 (139.798)	−23.079 (107.621)
Median change (min to max) — %	−2.245 (−96.88 to 1889.74)	−42.102 (−98.78 to 2061.21)	−8.120 (−96.88 to 1315.38)	−39.467 (−98.61 to 1587.18)
Change from baseline to Week 52				
Mean change (SD) — pg/mL	−1.426 (51.882)	60.847 (2197.545)	−1.086 (42.110)	−48.750 (526.878)
Median change (min to max) — pg/mL	0.000 (−528.00 to 337.30)	−12.700 (−3178.00 to 48070.00)	−0.800 (−312.10 to 205.90)	−13.800 (−11374.00 to 222.50)
Mean change (SD) — %	26.364 (130.148)	−1.059 (213.490)	51.897 (303.212)	−23.008 (112.570)
Median change (min to max) — %	0.000 (−94.07 to 1094.87)	−34.323 (−99.58 to 3294.87)	−2.658 (−95.14 to 3156.41)	−38.791 (−97.19 to 1780.00)
ECP (ng/mL)				
Mean baseline (SD) — ng/mL	25.5 (27.2)	26.6 (30.8)	27.1 (30.0)	24.2 (27.1)
Median baseline (min to max) — ng/mL	17.0 (1.0 to 200.0)	16.0 (1.0 to 200.0)	17.0 (1.0 to 198.0)	16.0 (1.0 to 200.0)
Change from baseline to Week 12				
Mean change (SD) — ng/mL	1.4 (24.8)	6.0 (34.5)	1.8 (27.7)	7.0 (34.5)

Median change (min to max) — ng/mL	0.0 (−126 to 133)	1.0 (−131 to 183)	1.0 (−121 to 143)	1.0 (−151 to 189)
Mean change (SD) — %	85.511 (649.056)	60.658 (175.463)	55.327 (241.598)	74.312 (229.776)
Median change (min to max) — %	0.000 (−86.67 to 9800.00)	7.692 (−95.24 to 1357.14)	3.393 (−86.36 to 3500.00)	10.000 (−88.89 to 2983.33)
Change from baseline to Week 24				
Mean change (SD) — ng/mL	−1.8 (23.5)	1.6 (31.1)	−1.6 (26.4)	2.2 (30.1)
Median change (min to max) — ng/mL	−1.0 (−101 to 118)	0.0 (−156 to 179)	−1.0 (−131 to 119)	0.0 (−174 to 167)
Mean change (SD) — %	42.280 (205.659)	41.932 (152.300)	49.919 (303.231)	50.156 (178.794)
Median change (min to max) — %	−8.013 (−93.33 to 2200.00)	0.000 (−97.14 to 1050.00)	−5.370 (−99.02 to 4500.00)	0.000 (−94.74 to 2200.00)
Change from baseline to Week 52				
Mean change (SD) — ng/mL	−4.1 (20.9)	−2.9 (29.0)	−4.5 (25.6)	−3.8 (26.8)
Median change (min to max) — ng/mL	−2.0 (−108 to 78)	−2.0 (−164 to 183)	−1.0 (−106 to 131)	−2.0 (−177 to 166)
Mean change (SD) — %	22.964 (173.486)	20.283 (125.902)	17.014 (106.500)	27.929 (312.504)
Median change (min to max) — %	−16.667 (−97.06 to 2000.00)	−12.500 (−92.31 to 1076.47)	−10.875 (−93.14 to 681.82)	−20.000 (−96.97 to 6400.00)

*Endpoints were not part of the hierarchical testing order, and as such were not multiplicity controlled. ECP denotes eosinophil cationic protein, min to max denotes minimum to maximum, ppb parts per billion, q2w every 2 weeks, SD standard deviation.

Table S8: Summary of Interaction Test For Efficacy.*

	Dupilumab 200 mg q2w vs Matching Placebo P Value	Dupilumab 300 mg q2w vs Matching Placebo P Value	Overall P Value
Annualized rate of severe exacerbation during 52-week treatment period†			
Blood eosinophil (cells/μL)	<0.001	<0.001	<0.001
FE_{NO} (ppb)	0.0076	<0.001	<0.001
Periostin (ng/mL)	0.1667	0.1347	0.1046
ECP (ng/mL)	0.0766	0.1302	0.079
Total IgE (IU/mL)	0.4161	0.2755	0.3036
TARC (pg/mL)	0.9688	0.5591	0.7689
Eotaxin-3 (pg/mL)	0.8099	0.1845	0.4494
Pre-bronchodilator FEV_1 at Week 12‡			
Blood eosinophil (cells/μL)	0.0361	<0.001	<0.001
FE_{NO} (ppb)	<0.001	<0.001	<0.001
Periostin (ng/mL)	0.0154	0.0195	<0.001
ECP (ng/mL)	0.3076	0.0049	0.0102
Total IgE (IU/mL)	0.0270	0.0483	0.0245
TARC (pg/mL)	0.6540	0.3062	0.3759

Eotaxin-3 (pg/mL)	0.0421	0.0134	0.0151

*Endpoints were not part of the hierarchical testing order, and as such P values were not multiplicity controlled. ECP denotes eosinophil cationic protein, FEV_1 forced expiratory volume in 1 second, ITT intent-to treat, q2w every 2 weeks.

†P values of testing treatment-by-biomarker interaction effects based on un-penalized negative binomial regression spline models in the ITT population.

‡P values of testing treatment-by-biomarker interaction effects based on un-penalized regression spline models in the ITT population.

Table S9: Summary of Adjudicated MACE.*

	Safety Population					
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (N = 313)	Dupilumab (N = 631)	Placebo (N = 321)	Dupilumab (N = 632)	Placebo (N = 634)	Dupilumab (N = 1263)
	No. of patients (%)					
MACE	2 (0.6)	1 (0.2)	0	4 (0.6)	2 (0.3)	5 (0.4)
MACE + hospitalization for unstable angina (with or without urgent revascularization)	2 (0.6)	1 (0.2)	0	5 (0.8)	2 (0.3)	6 (0.5)
CV death	1 (0.3)	0	0	3 (0.5)	1 (0.2)	3 (0.2)
Non-fatal CV event						
Arrhythmia not associated with ischemia	0	0	0	2 (0.3)	0	2 (0.2)
Other†	1 (0.3)	2 (0.3)	1 (0.3)	2 (0.3)	2 (0.3)	4 (0.3)
Non-fatal myocardial infarction	0	1 (0.2)	0	1 (0.2)	0	2 (0.2)
Unstable angina	0	0	0	1 (0.2)	0	1 (<0.1)
Venous thromboembolic event	0	0	0	1 (0.2)	0	1 (<0.1)
Stroke	1 (0.3)	0	0	0	1 (0.2)	0

*CV denotes cardiovascular, MACE major adverse cardiovascular events, q2w every 2 weeks.

†These cases were all adjudicated syncope except for 1 case of coronary artery bypass graft in the dupilumab 200 mg q2w group.

Table S10: Summary of Eosinophil Levels Among Patients with Adjudicated CV Event.*

	Safety Population With Adjudicated Cardiovascular Event					
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (N = 3)	Dupilumab (N = 3)	Placebo (N = 1)	Dupilumab (N = 10)	Placebo (N = 4)	Dupilumab (N = 13)
Mean baseline (SD) — cells/µL	233 (176)	243 (196)	0 (NC)	154 (132)	175 (185)	175 (145)
Mean level prior to adjudicated CV event (SD) — cells/µL	333 (194)	207 (156)	80 (NC)	251 (258)	270 (203)	241 (233)
Mean level at end of treatment (SD) — cells/µL	337 (217)	160 (69)	70 (NC)	279 (276)	270 (222)	252 (246)

*CV denotes cardiovascular, NC non-calculable, q2w every 2 weeks, SD standard deviation.

4. References

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