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Article type : Original Article: Asthma and Lower Airway Disease

Dupilumab is effective in type 2-high asthma patients receiving high-dose inhaled corticosteroids at baseline

Short title: Dupilumab in type 2-high asthma with high-dose steroids

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.14611](https://doi.org/10.1111/ALL.14611)

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Abstract: 249/250

Main text: 3569/3500

Figures and/or tables: 3 Figures, 1 Table/6

References: 42

Supplementary materials: 6 Figures, 9 Tables

Funding information

Research sponsored by Sanofi and Regeneron Pharmaceuticals, Inc. ClinicalTrials.gov numbers: NCT01854047 (phase 2b) and NCT02414854 (phase 3 LIBERTY ASTHMA QUEST). Medical writing/editorial assistance provided by Martina Fuchsberger, PhD, of Excerpta Medica, funded by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.

CONFLICTS OF INTEREST

Arnaud Bourdin reports non-financial support from GSK, during the conduct of the study; personal fees from AstraZeneca, grants and personal fees from Boehringer Ingelheim, Chiesi, GSK, Novartis, and Sanofi-Regeneron; other from Acceleron, Actelion, Galapagos, MSD, Nuvaira, Pulmonx, United Therapeutic, and Vertex, outside the submitted work; .. Alberto A. Papi reports grants, personal fees, non-financial support and other from GlaxoSmithKline, Boehringer Ingelheim, Chiesi Farmaceutici, and TEVA; grants, personal fees and non-financial support from AstraZeneca and Menarini; personal fees, non-financial support and other from Mundipharma, Zambon, Novartis, and Sanofi/Regeneron; personal fees from Roche and Edmondpharma; and grants from Fondazione Maugeri and Fondazione Chiesi; outside the submitted work; Jonathan Corren reports research support from Sanofi outside the submitted work. J. Christian Virchow reports personal fees from AstraZeneca, Avontec, Bayer, Bencard, Bionorica, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, Leti, MEDA, Merck, MSD, Mundipharma, Novartis, Nycomed/Altana, Pfizer, Revotar, Sandoz-Hexal, Stallergens, Teva, UCB/Schwarz-Pharma, Zydus/Cadila, and possibly others; other for Avontec, Boehringer Ingelheim, Chiesi, Essex/Schering-Plough, GSK, Janssen-Cilag, MEDA, MSD, Mundipharma, Novartis, Regeneron, Revotar, Roche, Sanofi-Aventis, Sandoz-Hexal, Teva, UCB/Schwarz-Pharma, and possibly others; and research grants from Deutsche Forschungsgesellschaft, Land Mecklenburg-Vorpommern, GSK, and MSD. Megan S. Rice reports personal fees and other from Sanofi, outside the submitted work. Yamo Deniz Rice reports personal fees and other from Regeneron Pharmaceuticals, Inc., outside the submitted work. Michel Djandji reports personal fees and other from Sanofi, outside the submitted work; Paul Rowe reports personal fees and other from Sanofi, outside the submitted work. Ian D. Pavord reports personal fees from AstraZeneca, Boehringer Ingelheim, Aerocrine, Almirall, Novartis, GlaxoSmithKline, Genentech, and Regeneron; other from Teva, Chiesi, Sanofi, Circassia, and Knopp; grants from NIHR, outside the submitted work.

AUTHOR'S CONTRIBUTIONS

MSR, YD, and MD contributed to project concept, study design, and study implementation; AB, AP, and JC contributed to data collection; MSR contributed to data and statistical analysis; all author contributed to manuscript editing; all author critically reviewed and approved the final version of the manuscript.

Abstract

Background: Dupilumab blocks the shared receptor component for interleukin (IL)-4/IL-13, key drivers of type 2 inflammation. In phase 2b (NCT01854047) and phase 3 LIBERTY ASTHMA QUEST (NCT02414854), add-on dupilumab 200/300 mg every 2 weeks (q2w) reduced severe exacerbations, improved prebronchodilator (pre-BD) forced expiratory volume in 1 second (FEV₁) and quality-of-life measures and was generally well tolerated in patients with uncontrolled, persistent (phase 2b) or moderate-to-severe (phase 3) asthma.

Methods: In patients on high-dose inhaled corticosteroids (ICS) with type 2-high asthma (subgroups including baseline blood eosinophils $\geq 150/300$ cells/ μ L and/or fractional exhaled nitric oxide [FeNO] ≥ 25 ppb), annualized severe exacerbation rates over the treatment period, changes from baseline in pre-BD FEV₁ and asthma control (5-item Asthma Control Questionnaire [ACQ-5]) were analyzed.

Results: In high-dose ICS type 2-high subgroups, dupilumab 200/300 mg q2w versus placebo in the phase 2b (24 weeks) and phase 3 (52 weeks) studies significantly reduced severe exacerbations by 55%-69%/57%-60% (all $P < .05$) and 53%-69%/48%-66% (all $P < .001$), respectively, except in patients with ≥ 300 eosinophils/ μ L in phase 2b study (24%/50% ($P = .52/.15$)). Across subgroups, pre-BD FEV₁ improved by 0.18-0.22 L/0.19-0.24 L (all $P < .05$) and 0.23-0.36 L/0.15-0.25 L (all $P < .01$) and ACQ-5 scores were reduced by 0.46-0.55/0.47-0.85 (all $P < .05$) and 0.38-0.50/0.24-0.30 (all $P < .05$), respectively, except dupilumab 200 mg q2w in phase 2b in patients with FeNO ≥ 25 ppb (0.41; $P = .09$). Dupilumab was also effective in patients taking medium-dose ICS.

Conclusion: Dupilumab significantly reduced severe exacerbations and improved lung function and asthma control in patients with type 2-high asthma on high-dose ICS at baseline.

(Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov numbers: NCT01854047 [phase 2b] and NCT02414854 [phase 3 LIBERTY ASTHMA QUEST])

Keywords: asthma control, exacerbations, inhaled corticosteroids, moderate-to-severe asthma, prebronchodilator FEV₁

1 | INTRODUCTION

Inhaled corticosteroids (ICS) have been the mainstay treatment of persistent asthma for more than 40 years. By targeting the glucocorticoid receptor, ICS inhibit the release of cytokines and other proinflammatory mediators, decrease eosinophil and mast cell recruitment, and inhibit nuclear transcription factors, thus suppressing adhesion molecule function and inducible nitric oxide synthase.¹⁻⁴ However, the largest clinical benefits are seen at low-dose ICS, with diminishing returns due to increased systemic adverse events at higher doses.⁵

Uncontrolled, moderate-to-severe asthma accounts for approximately 20% of all asthma cases^{6,7} and includes patients who have persistent symptoms and/or exacerbations despite the use of high-dose ICS and controller medicines. This population is at an increased risk of exacerbations, with many patients having substantially reduced lung function and impaired quality of life, all of which culminate in considerable healthcare resource use and associated costs.⁸ Type 2-high asthma, characterized by type 2 inflammation, occurs in approximately 50% of patients with asthma.⁹ It includes the allergic phenotype, characterized by increased expression of specific immunoglobulin E (IgE) to aeroallergens; eosinophilic phenotype, characterized by eosinophilia evident in the blood, airways, and/or tissue⁹⁻¹¹; and nonallergic, adult-onset, intrinsic phenotype. In recent years, add-on biologic treatments for use in patients with uncontrolled moderate-to-severe or persistent asthma have been developed that specifically target elements of type 2 inflammation such as interleukin (IL)-4, IL-5, and IL-13 which play crucial roles in the pathogenesis of asthma.^{12,13} One such agent, dupilumab, is a fully human VelocImmune®-derived monoclonal antibody that blocks the shared receptor component for IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.¹⁴⁻¹⁷

In the phase 2 studies (NCT01312961 and NCT01854047), dupilumab- vs placebo-treated patients with uncontrolled persistent asthma had a significantly reduced severe exacerbation rate and improved prebronchodilator (pre-BD) forced expiratory volume in 1 second (FEV₁).^{18,19} Of importance, these findings were consistent irrespective of baseline blood eosinophil count, a biomarker for type 2 inflammation.¹⁹ In the subsequent phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab significantly reduced severe asthma exacerbations and improved pre-BD FEV₁ in the overall intention-to-treat (ITT) population of patients with uncontrolled, moderate-to-severe asthma.²⁰ Treatment effects were of greater magnitude in subgroups of patients with elevated baseline levels of the type 2 biomarkers (blood eosinophils ≥ 150 cells/ μ L

or fractional exhaled nitric oxide [FeNO] ≥ 25 ppb). Dupilumab was generally well tolerated by patients in each of the studies.

This analysis across the dupilumab phase 2b and phase 3 QUEST studies further assessed the effect of dupilumab on severe exacerbations, pre-BD FEV₁, and asthma control in subgroups of patients with different characteristics of type 2-high disease who were taking high-dose ICS at baseline. Given the evidence from previous studies and in other biologics, we expected dupilumab to also be effective in this patient population. For completeness and transparency, we also repeated the analysis in patients with elevated type 2 biomarkers taking medium-dose ICS at baseline and have included the findings in the supplementary appendix.

2 | METHODS

2.1 | Study design and patients

The phase 2b study (NCT01854047) was a randomized, double-blind, placebo-controlled, parallel-group study conducted in adults (aged ≥ 18 years) with an asthma diagnosis for at least 12 months based on the Global Initiative for Asthma 2009 guidelines²¹ and receiving treatment with high- (>1000 $\mu\text{g}/\text{day}$) or medium- (500-1000 $\mu\text{g}/\text{day}$) dose ICS plus long-acting β_2 -agonists. Patients were randomly assigned (1:1:1:1:1) to receive subcutaneous dupilumab 200 or 300 mg every 2 weeks (q2w) or every 4 weeks or placebo, over a 24-week period. Full details of the study design and conduct, including inclusion and exclusion criteria, have been published previously.¹⁹ For this post hoc analysis, only the data from patients randomized to dupilumab q2w regimens (the approved dosing regimen) and placebo were included.

LIBERTY ASTHMA QUEST was a phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study that assessed the efficacy and safety of dupilumab in patients with uncontrolled asthma treated with high- (>1000 $\mu\text{g}/\text{day}$) or medium- (500-1000 $\mu\text{g}/\text{day}$) dose ICS (**Supplementary Table 1**). Patients ≥ 12 years were randomized in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab 200 or 300 mg q2w or volume-matched placebo for 52 weeks. The study was open to all patients irrespective of eosinophilic status or any other biomarker requirement. Full details of study design, methodology, and eligibility criteria have been reported previously.^{20,22}

In both the phase 2b study and LIBERTY ASTHMA QUEST, atopy was self-reported by patients; no further clinical assessments were conducted to verify.

Both studies were conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines of the International Conference on Harmonization and with applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Study conduct and documentation were monitored by local institutional review boards or ethics committees, and all the patients provided written informed consent before participating in the trial. Adolescent patients provided assent according to the ethics committee and approved standard practice for pediatric patients at each participating center.

2.2 | Study endpoints

Annualized severe exacerbation rates (defined as number of severe exacerbations per patient-year), change from baseline in pre-BD FEV₁ (L) and asthma control (using the patient-reported 5-item Asthma Control Questionnaire [ACQ-5]²³) were assessed over the 24-week (phase 2b study) and 52-week (QUEST) treatment periods. A responder analysis of ACQ-5 scores was conducted in which the proportion of patients with a response to treatment (responders) was defined as those with an improvement from baseline in ACQ-5 score that reached or exceeded the threshold of the minimum clinically important difference (MCID) of 0.5.²⁴ In line with the primary analyses for these studies, patients with improvement from baseline of <0.5 or with a missing value were considered as nonresponders for that timepoint.

2.3 | Statistical analysis

Prespecified efficacy analyses were performed on subgroups of patients in the overall ITT population categorized by ICS controller requirement at baseline (adapted from GINA 2014²⁵; **Supplementary Table 1**), and post hoc analyses, which further stratified the groups by baseline levels of blood eosinophils or FeNO. The subgroups examined were high-dose ICS and eosinophils ≥ 150 cells/ μ L, high-dose ICS and eosinophils ≥ 300 cells/ μ L, high-dose ICS and FeNO ≥ 25 ppb, high-dose ICS and eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb, and high-dose ICS ITT subgroups. The same analyses were also performed on equivalent subgroups for completeness and transparency in patients taking medium-dose ICS. The ITT population was defined as all patients who were randomized, and data were analyzed according to the assigned intervention and whether an intervention was received. Results are presented separately for each study.

In both studies, the annualized rate of severe asthma exacerbations was analyzed using a negative binomial regression model.^{19,20,22} Change from baseline in FEV₁ (L) and ACQ-5 were analyzed using mixed-

effects models with repeated measures. Additional model details are provided in the supplementary materials.

Descriptive statistics have been employed to present the data; a P value of $< .05$ for the comparison between each dupilumab dose and placebo (within each subgroup) was considered statistically significant.

3 | RESULTS

3.1 | Baseline characteristics

In the phase 2b study, 307 patients were randomized to dupilumab q2w regimens, and 158 patients were randomized to placebo (**Supplementary Figure 1A**). Of these 465 patients, 231 (49.6%) received high-dose ICS, and 221 (47.5%) received medium-dose ICS at baseline. In QUEST, a total of 1902 patients were randomized (placebo: $n = 638$, dupilumab: $n = 1264$; **Supplementary Figure 1B**). Fifteen (0.8%) patients were on low-dose ICS at study entry (in violation of the protocol) and are not included in this analysis, resulting in an analysis population of 1887. Of these, 979 (51.9%) were on high-dose ICS at baseline, and 908 (48.1%) patients received medium-dose ICS (**Table 1**). In each study, the subgroups of patients receiving high-dose ICS had relatively worse lung function, asthma control, and prior exacerbations, indicative of their greater disease severity and needed a higher dose of controller medication (**Table 1**). Furthermore, baseline demographics for each subgroup are shown in **Supplementary Tables 2-5**.

3.2 | Annualized rate of severe asthma exacerbations

In the overall ITT population of the phase 2b study, dupilumab 200 and 300 mg q2w compared with placebo significantly reduced adjusted annualized severe exacerbation rates in the subgroup receiving high-dose ICS at baseline by 56% ($P = .004$) and 57% ($P = .002$), respectively (**Figure 1**). Numerical reductions vs placebo were observed in the subgroup on high-dose ICS with blood eosinophil counts ≥ 300 cells/ μL at baseline ($P = .524$ and $P = .149$, respectively), and significant reductions vs placebo were observed in subgroups on high-dose ICS with blood eosinophil count ≥ 150 cells/ μL ($P < .05$ and $P < .01$), FeNO ≥ 25 ppb ($P < .01$ and $P < .05$), and blood eosinophil count ≥ 150 cells/ μL or FeNO ≥ 25 ppb ($P < .01$ for both) (**Figure 1**). In the phase 2b study, adjusted severe exacerbation rates could not be calculated for the subgroups of patients receiving medium-dose ICS as the number of events was deemed too small to provide valid estimates from an adjusted model, therefore unadjusted data are presented. In the subgroup receiving medium-dose ICS at baseline, the

reductions in the unadjusted annualized severe exacerbation rate for patients receiving dupilumab 200 and 300 mg q2w vs placebo were 67.5%/62.4% vs 46.3% (**Supplementary Figure 2**). Consistent numerical improvements vs placebo were also observed for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (**Supplementary Figure 2**).

In the overall ITT population of QUEST, dupilumab 200 and 300 mg q2w compared with placebo significantly reduced adjusted annualized severe exacerbation rates in patients receiving high-dose ICS at baseline by 46% ($P < .001$) and 39% ($P = .002$), respectively (**Figure 1**); when further stratified by baseline type 2 biomarker status (blood eosinophil count and/or FeNO levels), a greater magnitude of treatment effect was observed in patients with type 2-high phenotype with reductions vs placebo ranging from 48% to 69% (all $P < .001$) (**Figure 1**). In patients on medium-dose ICS at baseline, significant reductions in adjusted annualized severe exacerbation rates by 51% ($P = .0004$) and 53% ($P < .0001$), respectively, were observed; this was also seen for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (**Supplementary Figure 2**).

3.3 | Prebronchodilator FEV₁

In the overall ITT population of the phase 2b study, treatment with dupilumab 200 and 300 mg q2w vs placebo improved pre-BD FEV₁ in patients receiving high-dose ICS at baseline by least squares (LS) mean difference (95% confidence interval [CI]) of 0.14 L (0.03-0.24; $P = .011$) and 0.19 L (0.09-0.30; $P = .0002$), respectively by Week 2. This improvement was sustained up to 24 weeks (0.21 L [0.09-0.32; $P = .0005$] and 0.22 L [0.11-0.34; $P = .0001$]; **Supplementary Figure 3**). When further stratified by baseline eosinophils or FeNO levels, statistically significant improvements vs placebo were consistently observed as early as Week 2 (LS mean difference range: 0.14-0.21 L and 0.18-0.23 L, all $P < .05$, respectively), with one exception (dupilumab 200 mg q2w patients with a baseline blood eosinophil count of ≥ 300 cells/ μ L [0.09 L; $P = .263$]), where a statistically significant improvement was reached first by Week 4. In all subgroups, these improvements were maintained throughout the 24-week treatment duration (LS mean difference range: 0.18-0.22 L and 0.19-0.24 L, respectively; all $P < .05$) (**Figure 2, Supplementary Table 6**). Improvements in pre-BD FEV₁ were also observed for the medium-dose ICS group; at Week 2, the LS mean difference (95% CI) vs placebo was 0.14 L (0.03-0.26; $P = .01$) and 0.11 L (-0.01 to 0.22; $P = .06$). This numerical improvement was sustained up to 24 weeks (0.13 L [-0.01 to 0.26; $P = .06$] and 0.09 L [-0.04 to 0.22; $P = .18$]; **Supplementary**

Figure 3). Similar results were observed for each subgroup when further stratified by blood eosinophil and FeNO levels at baseline (**Supplementary Figure 4, Supplementary Table 7**).

In the overall ITT population of the QUEST study, dupilumab 200 and 300 mg q2w vs placebo rapidly improved pre-BD FEV₁ in the high-dose ICS subgroup by LS mean difference (95% CI) of 0.12 L (0.05-0.18; $P = .0004$) and 0.16 L (0.09-0.22; $P < .0001$), respectively at Week 2. This improvement was sustained over the 52-week treatment period (0.20 L [0.12-0.28; $P < .0001$] and 0.13 L [0.05-0.21; $P = .002$]; **Supplementary Figure 3**). When further stratified by baseline eosinophils or FeNO levels, statistically significant improvements vs placebo were consistently observed as early as Week 2 (LS mean difference range: 0.13-0.23 L and 0.19-0.30 L, respectively; all $P < .001$) and were maintained throughout the 52-week treatment period (LS mean difference range: 0.23-0.36 L and 0.15-0.25 L, respectively; all $P < .05$) (**Figure 2, Supplementary Table 6**). At Week 2, treatment with dupilumab 200 and 300 mg q2w vs placebo also significantly improved pre-BD FEV₁ in the medium-dose ICS subgroup by LS mean difference (95% CI) 0.18 L [0.11-0.25] and 0.14 L [0.07-0.21], respectively; both $P < .0001$; with sustained improvements by Week 52 of 0.20 L (0.11-0.29; $P < .0001$), and 0.14 L (0.06-0.23; $P = .0009$), respectively (**Supplementary Figure 3**). Similar results were observed in subgroups further stratified by baseline eosinophils or FeNO levels (**Supplementary Figure 4, Supplementary Table 7**)

3.4 | Asthma control (ACQ-5 scores)

In the overall ITT population of the phase 2b study, treatment with dupilumab 200 and 300 mg q2w vs placebo improved asthma control in patients requiring high-dose ICS at baseline (LS mean difference from baseline [95% CI] at Week 24: -0.49 [-0.82 to -0.16; $P = .004$] and -0.42 [-0.74 to -0.10; $P = .01$, respectively]; **Supplementary Figure 5**). These improvements were also observed in the subgroups stratified by baseline eosinophils or FeNO (**Figure 3**). Improvements in ACQ-5 scores were also seen in patients requiring medium-dose ICS at baseline (LS mean difference from baseline [95% CI] at Week 24: -0.35 [-0.65 to -0.05; $P = .02$] and -0.28 [-0.57 to 0.01; $P = .06$], respectively; **Supplementary Figure 5**) and in the subgroups stratified by baseline eosinophils or FeNO (**Supplementary Figure 6**)

Similarly, in the overall ITT population of QUEST, consistent improvements in asthma control were observed for patients with high-dose ICS at baseline (LS mean difference from baseline [95% CI] vs placebo at Week 24: -0.31 [-0.51 to -0.11; $P = .002$] and -0.13 [-0.33 to 0.07; $P = .21$], respectively; Week 52: -0.34 [-0.54 to -0.14; $P = .0009$] and -0.15 [-0.35 to 0.05; $P = .14$], respectively; **Supplementary Figure 5**) and in

subgroups stratified by baseline eosinophils or FeNO (**Figure 3**). This was also the case in patients requiring medium-dose ICS at baseline (LS mean difference from baseline [95% CI] vs placebo at Week 24: -0.40 [-0.59 to -0.22 ; $P = .0001$] and -0.27 [-0.45 to -0.09 ; $P = .003$], respectively; Week 52: -0.44 [-0.63 to -0.24 ; $P < .0001$] and -0.29 [-0.48 to -0.10 ; $P = .002$], respectively; **Supplementary Figure 5**) and in the subgroups stratified by baseline eosinophils or FeNO (**Supplementary Figure 6**).

3.5 | ACQ-5 responder analysis

Many of the improvements in asthma control were clinically significant as evidenced by the differences vs placebo in ACQ-5 scores reaching or exceeding the MCID of 0.5.²⁴ In the high-dose ICS subgroup of the phase 2b study, after 24 weeks, the proportion of responders in dupilumab-treated patients was 75% (56/75 patients; odds ratio [OR] 2.59 [1.29, 5.20]; $P = .007$) and 76% (60/79 patients; OR 2.85 [1.43, 5.68]; $P = .003$) vs 53% (41/77) of placebo-treated patients.

In the overall ITT population of QUEST, at 24 weeks, a numerical increase in responders was observed in the high-dose ICS at baseline subgroup treated with dupilumab 200 and 300 mg q2w vs matched placebos, respectively: 75% (238/317 patients) vs 69% (118/172 patients) (OR vs placebo [95%CI] 1.36 [0.90, 2.08]; $P = .15$) and 72% (231/323) vs 62% (104/167) (OR 1.51 [1.00, 2.26]; $P = .05$)). (**Supplementary Table 8**).

Numerical improvements in responder rates were also observed in the medium-dose ICS subgroups for both studies (**Supplementary Table 9**).

4 | DISCUSSION

In this analysis of data from the pivotal phase 2b and phase 3 LIBERTY ASTHMA QUEST studies, dupilumab 200 and 300 mg q2w vs placebo reduced severe exacerbation rates and improved FEV₁ (L), asthma control (ACQ-5), and rate of responders (ACQ improvement of MCID ≥ 0.5) in patients with uncontrolled, type 2-high persistent or moderate-to-severe asthma taking high-dose ICS at baseline. Improvements were observed across each of the subgroups as early as the first timepoint assessed and were sustained until treatment end in both studies.

There are currently 5 biologic add-on treatments for patients with uncontrolled severe asthma, which target underlying type 2 inflammatory processes: dupilumab, benralizumab, reslizumab, mepolizumab, and omalizumab. As previously outlined, dupilumab blocks the shared receptor component for IL-4/IL-13, key and

central drivers of type 2 inflammation.¹⁴⁻¹⁷ It is approved in the EU²⁶ as add-on maintenance treatment in patients aged ≥ 12 years with severe asthma with type 2 inflammation characterized by raised blood eosinophils and/or raised FeNO who are inadequately controlled with a high-dose ICS plus another medicinal product for maintenance treatment. It is also approved in the USA²⁷ and other countries²⁸ as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ≥ 12 years with an eosinophilic phenotype or with oral corticosteroid-dependent asthma.^{19,20,29} Benralizumab, reslizumab, and mepolizumab are monoclonal antibodies targeting IL-5, a key component in eosinophil activation, proliferation, and degranulation. Benralizumab binds the alpha chain of the IL-5 (IL-5 α) eosinophil cell surface receptor, blocking IL-5 binding, and has been evaluated in phase 3 studies in patients ≥ 12 years.³⁰ Mepolizumab and reslizumab bind directly to IL-5, which in turn blocks binding with IL-5 α .^{31,32} Mepolizumab has been evaluated in patients aged ≥ 6 years and reslizumab in patients ≥ 18 years. Omalizumab, an anti-IgE monoclonal antibody which has been evaluated in patients ≥ 6 years, binds IgE and inhibits basophil and mast cell release of proinflammatory mediators.³³

Consistent with findings from the parent studies and other dupilumab studies,^{19,20,29} a generally greater magnitude of dupilumab efficacy was observed in patients with a type 2-high endotype. In the QUEST study, the highest magnitude of reduction in annualized severe exacerbation rate was observed in patients with type 2-high endotypes, with differences vs placebo of 48%-69%, compared with 39%-46% in all patients in the high-dose ICS subgroup and of 58%-74%, compared with 51%-53% in all patients in medium-dose ICS subgroup. Of note, in the QUEST study, in patients taking high-dose ICS a significant reduction in the adjusted annualized severe exacerbation rate with dupilumab vs matched placebo was observed in the subgroup of patients with baseline eosinophils ≥ 300 μ /L; a similar trend was observed in the Phase 2b study although the effect did not reach statistical significance, likely due to low patient numbers in the subgroups of the Phase 2b study. These observations were also seen in patients taking medium-dose ICS in the QUEST study; in the phase 2b study, adjusted severe exacerbation rates could not be calculated for the subgroups of patients receiving medium-dose ICS as the number of events was deemed too small to provide valid estimates from an adjusted model, but non-significant reductions in the unadjusted annualized severe exacerbation rate were observed with dupilumab vs matched placebo. In both the phase 2b and QUEST studies, higher magnitudes of responses were seen in change from baseline in FEV₁ compared with matched placebo in patients with type 2-high asthma taking high-dose ICS. This result was echoed in patients taking medium-dose ICS in the phase 3 QUEST study.

Similar findings have also been observed with the other biologic add-on therapies in patients with type 2-high asthma on medium-to-high-dose ICS. In the benralizumab phase 3 SIROCCO and CALIMA studies, significant reductions in annual asthma exacerbation rates and improvements in FEV₁ and asthma symptom scores compared with placebo were observed in patients with high-dose ICS and baseline blood eosinophils ≥ 300 cells/ μ L.^{34,35} The phase 3 BREATH reslizumab studies also demonstrated reductions of clinical asthma exacerbations of 50%-59% and improvements in FEV₁, asthma control, forced vital capacity, and rescue short-acting beta agonist use compared with placebo in patients with eosinophils ≥ 400 cells/ μ L (ITT population), and with lower efficacy in patients with < 400 cells/ μ L (ITT population).^{36,37} Higher efficacy in reduction of severe exacerbations, and improvement of FEV₁ and ACQ-5 in patients with higher baseline blood eosinophils compared with patients with lower levels were also demonstrated in the DREAM, MENSA, and MUSCA phase 3 mepolizumab studies.³⁸⁻⁴⁰ Finally, significantly greater reductions in asthma exacerbations were seen in patients with raised FeNO (≥ 19.5 ppb), eosinophils (≥ 260 cells/ μ L), and periostin (≥ 50 ng/mL) who were treated with omalizumab in the EXTRA phase 3 study, compared with placebo recipients.⁴¹ Although elevated eosinophils in peripheral blood have been associated with type 2 asthma, their levels can be significantly influenced by the use of ICS.⁴² Thus, peripheral blood eosinophilia as a type 2 inflammation marker should always be interpreted in view of the current dose of ICS. This could also account for the efficacy of dupilumab being demonstrated irrespective of the baseline ICS dose used by the patients.

The strength of this analysis is its randomized, double-blind design, its large population sizes, and the inclusion of patients regardless of ICS dose at baseline. One of the limitations was that the findings are constrained by the low sample sizes in some of the subgroups, as these were not defined a priori. The studies were not powered specifically to investigate differences between patients with asthma with high/medium-dose ICS and eosinophils ≥ 150 cells/ μ L or ≥ 300 cells/ μ L, FeNO ≥ 25 ppb, or eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb. Also, a large placebo effect on asthma control was observed in the QUEST study, possibly due to increased adherence in patients in the placebo group, which may have contributed to the differences in ACQ-5 improvement from baseline for dupilumab vs placebo not being statistically significant. Finally, due to the timings of the trial, old versions of the GINA guidelines were used when designing the studies and this analysis.

5 | CONCLUSIONS

Accepted Article

In conclusion, the outcomes of these 2 pivotal dupilumab studies confirm that dupilumab is effective across a spectrum of patients on high-dose ICS at baseline with raised type 2 biomarkers and 1 or 2 additional controllers. Efficacy was also demonstrated in patients with type 2-high asthma on medium-dose ICS at baseline with 1–2 additional controllers. Improvements in lung function were seen within 2 weeks, sustained throughout treatment, and generally of greater magnitude in subgroups of patients with elevated baseline levels of type 2 biomarkers (blood eosinophils ≥ 150 cells/ μ L or ≥ 300 cells/ μ L or FeNO ≥ 25 ppb).

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TABLES

TABLE 1 Baseline demographic and disease characteristics in phase 2b and phase 3 QUEST studies by baseline ICS dose

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	77	75	79	172	317	167	323
Age, mean (SD), years	50.3 (10.9)	54.0 (11.6)	48.3 (12.4)	48.9 (14.1)	49.5 (13.8)	49.5 (13.9)	49.1 (14.9)
Age < 18 years, n (%)	0	0	0	6 (3.5)	6 (1.9)	3 (1.8)	11 (3.4)
Female sex, n (%)	54.0 (70.1)	43 (57.3)	52 (65.8)	110 (64.0)	199 (62.8)	119 (71.3)	203 (62.8)
Ongoing atopic medical condition, n (%)	57 (75.0)	52 (69.3)	59 (74.7)	147 (85.5)	257 (81.1)	136 (81.4)	262 (81.1)
Prebronchodilator FEV ₁ , mean (SD), L	1.70 (0.50)	1.73 (0.54)	1.80 (0.53)	1.74 (0.55)	1.69 (0.56)	1.65 (0.50)	1.70 (0.60)
Percent predicted, mean (SD)	58.97 (10.79)	59.45 (11.45)	60.14 (10.79)	58.10 (12.77)	56.38 (13.48)	56.43 (13.33)	56.37 (14.40)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.11 (0.62)	2.06 (0.69)	2.03 (0.61)	2.11 (0.71)
FEV ₁ reversibility [‡] , mean (SD), %	25.79 (12.12)	25.61 (19.02)	27.59 (17.25)	23.57 (15.65)	28.23 (23.58)	27.04 (16.43)	28.20 (26.72)

Severe asthma exacerbations in past year, mean (SD), n	2.57 (2.72)	2.19 (1.75)	2.77 (2.77)	2.26 (1.77)	2.24 (2.11)	2.57 (2.33)	2.22 (1.67)
ACQ-5 score [§] , mean (SD)	2.82 (0.82)	2.88 (0.74)	2.98 (0.86)	2.82 (0.76)	2.90 (0.87)	2.89 (0.82)	2.91 (0.79)
AQLQ(S) global score, mean (SD)	3.84 (1.06)	3.91 (1.16)	3.70 (1.15)	4.15 (1.05)	4.18 (1.10)	4.13 (1.04)	4.04 (1.02)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	280.0 (190.0-450.0)	280.0 (150.0-550.0)	260.0 (160.0-420.0)	280.0 (130.0-485.0)	250.0 (130.0-470.0)	280.0 (150.0-510.0)	250.0 (130.0-470.0)
Total IgE, median (IQR), IU/mL	216.0 (94.0-463.0)	151.0 (47.0-428.0)	163.0 (78.0-405.0)	176.0 (52.0-406.0)	151.0 (51.0-459.0)	160.5 (62.0-363.0)	175.5 (59.5-450.0)
FeNO, median (IQR), ppb	30.0 (18.0-41.0)	27.0 (15.0-41.0)	29.0 (13.0-62.0)	23.0 (14.0-38.0)	23.0 (14.0-39.0)	27.0 (15.5-43.5)	24.0 (15.0-42.0)
Medium-dose ICS at baseline, n	78	69	74	144	310	151	303
Age, mean (SD), years	47.4 (14.1)	47.9 (14.6)	46.7 (12.6)	47.5 (17.3)	46.2 (16.6)	46.7 (15.5)	46.4 (16.1)
Age < 18 years, n (%)	0	0	0	15 (10.4)	28 (9.0)	15 (9.9)	23 (7.6)
Female sex, n (%)	48 (61.5)	47 (68.1)	48 (64.9)	87 (60.4)	186 (60.0)	96 (63.6)	191 (61.6)
Ongoing atopic medical condition, n (%)	55 (73.3)	55 (80.9)	49 (69.0)	118 (81.9)	249 (80.3)	127 (84.1)	255 (84.2)
Prebronchodilator FEV ₁ , mean (SD), L	1.95 (0.58)	1.87 (0.52)	1.91 (0.54)	1.80 (0.67)	1.88 (0.66)	1.86 (0.62)	1.87 (0.59)

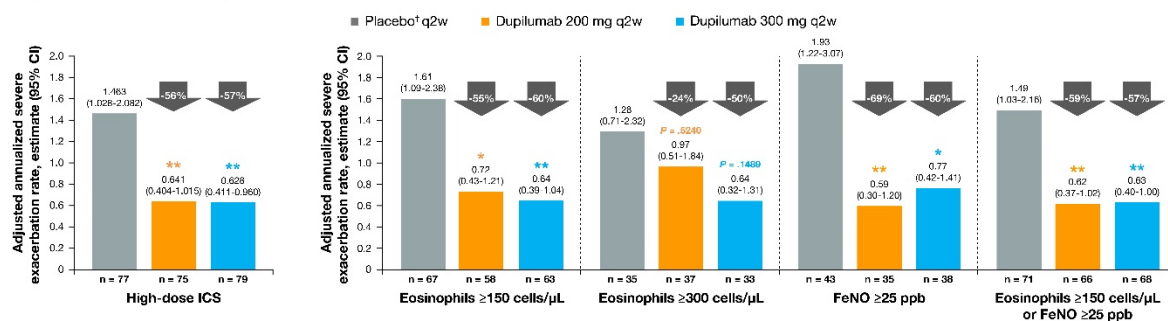
Percent predicted, mean (SD)	62.9 (10.5)	62.9 (10.3)	61.3 (10.2)	58.9 (13.7)	60.4 (13.2)	60.4 (14.3)	60.6 (12.2)
Post-bronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.23 (0.79)	2.27 (0.79)	2.25 (0.77)	2.24 (0.73)
FEV ₁ reversibility [‡] , mean (SD), %	29.84 (16.08)	27.89 (16.40)	26.89 (15.92)	27.17 (21.48)	26.39 (21.95)	25.99 (19.05)	23.31 (20.14)
Severe asthma exacerbations in past year, mean (SD), n	1.95 (1.67)	1.45 (0.83)	1.96 (1.59)	1.85 (1.30)	1.91 (3.14)	2.03 (1.71)	1.82 (2.03)
ACQ-5 score [§] , mean (SD)	2.57 (0.76)	2.55 (0.86)	2.64 (0.68)	2.59 (0.68)	2.62 (0.70)	2.61 (0.69)	2.62 (0.70)
AQLQ(S) global score [¶] , mean (SD)	4.35 (1.10)	4.19 (1.15)	4.14 (1.07)	4.39 (0.97)	4.43 (1.05)	4.52 (0.98)	4.53 (1.03)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	245.0 (150.0-420.0)	240.0 (180.0-400.0)	270.0 (160.0-380.0)	260.0 (140.0-490.0)	250.0 (120.0-450.0)	245.0 (130.0-420.0)	250.0 (130.0-450.0)
Total IgE, median (IQR), IU/mL	182.0 (84.0-430.0)	237.0 (51.0-647.0)	168.5 (73.0-409.0)	173.5 (75.0-493.0)	158.0 (65.0-441.0)	188.0 (52.5-482.0)	172.5 (66.0-454.0)
FeNO, median (IQR), ppb	28.0 (16.0-53.0)	32.0 (18.0-52.0)	28.0 (16.0-48.0)	27.0 (16.0-51.5)	24.0 (16.0-47.0)	27.0 (16.0-51.0)	24.0 (13.0-43.0)

[‡]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). [‡]FEV₁ (L) reversibility indicates the change in FEV₁ between prebronchodilator and postbronchodilator measurements. [§]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 between 0 (totally controlled) and 6 (severely uncontrolled). [¶]AQLQ(S) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = “not impaired at all” to 1 = “severely impaired”). ACQ-5, 5-item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

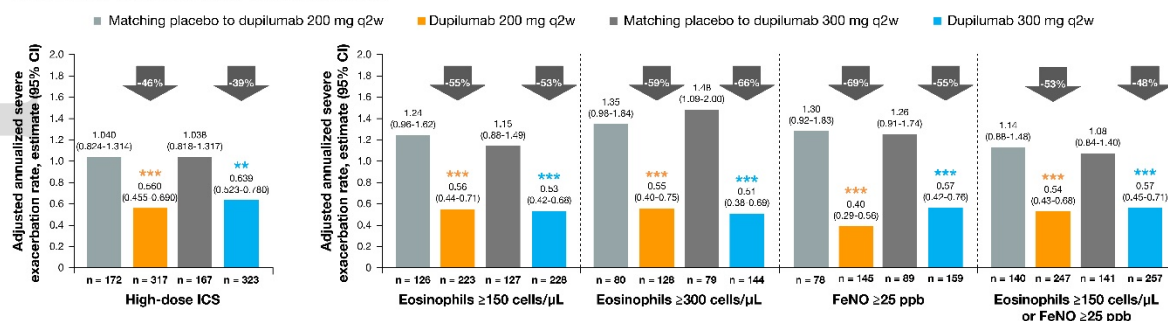
FIGURES

FIGURE 1 Annualized rate of severe exacerbations in dupilumab-treated patients (q2w) vs placebo during the 24-week treatment period in the phase 2b study and 52-week treatment period in the phase 3 QUEST study on high-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels. *In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P < .01$, * $P < .05$ vs placebo. CI, confidence interval; FeNO, fractional exhaled nitric oxide; q2w, every 2 weeks.

Dupilumab Phase 2b Study



Dupilumab Phase 3 LIBERTY ASTHMA QUEST

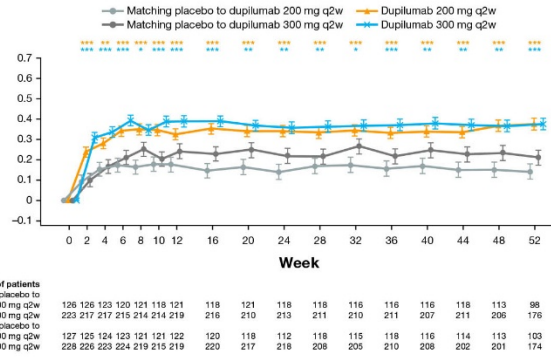
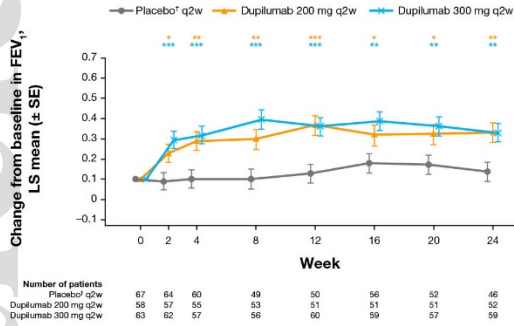


16 **FIGURE 2** LS mean change from baseline in FEV₁ (L) during the 24-week treatment period in the phase 2b
17 study in patients with uncontrolled, persistent asthma and 52-week treatment period in the phase 3 QUEST
18 study in patients with uncontrolled, moderate-to-severe asthma on high-dose ICS at baseline and further
19 stratified by baseline eosinophil and FeNO levels. †In the phase 2b study, the same amount of placebo was
20 given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P <$
21 $.01$, * $P < .05$ vs placebo. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS,
22 inhaled corticosteroids; LS, least squares; q2w, every 2 weeks; SE, standard error.

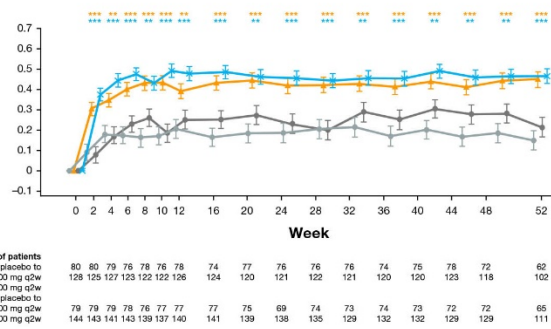
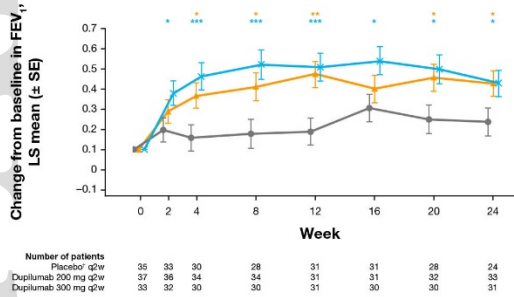
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

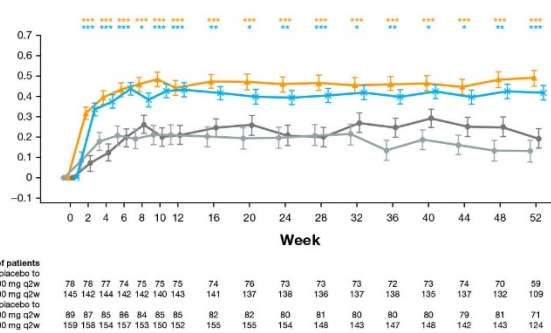
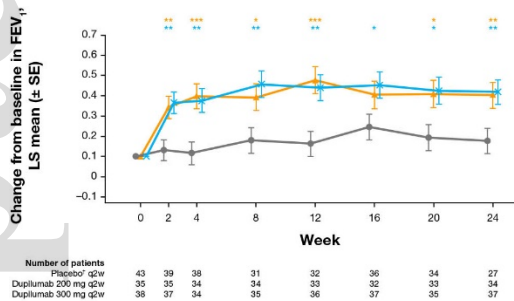
Baseline blood eosinophils ≥ 150 cells/ μ L



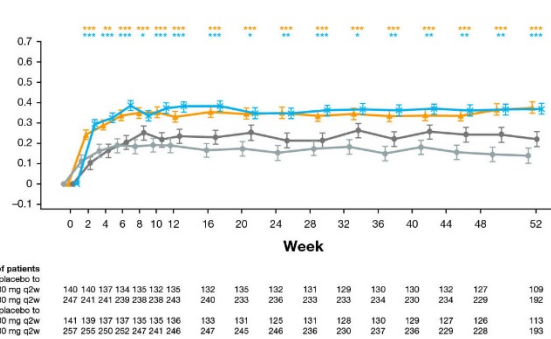
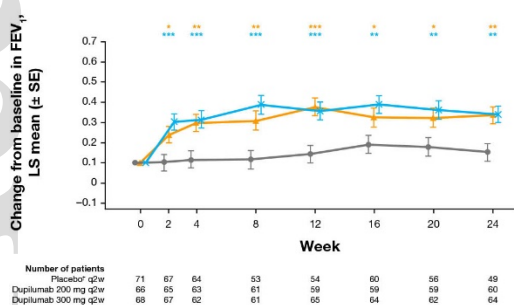
Baseline blood eosinophils ≥ 300 cells/ μ L



Baseline FeNO ≥ 25 ppb



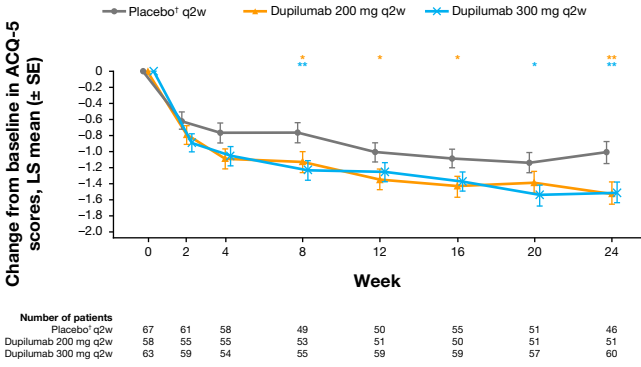
Baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb



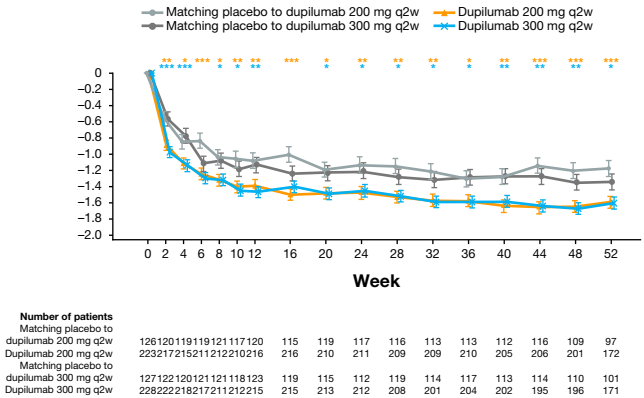
26 **FIGURE 3** LS mean change from baseline in ACQ-5 scores during the 24-week treatment period in the phase
27 2b study in patients with uncontrolled, persistent asthma and 52-week treatment period in the phase 3
28 QUEST study in patients with uncontrolled, moderate-to-severe asthma on high-dose ICS at baseline and
29 further stratified by baseline eosinophil and FeNO levels. [†]In the phase 2b study, the same amount of placebo
30 was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$,
31 ** $P < .01$, * $P < .05$ vs placebo. ACQ-5, 5-item Asthma Control Questionnaire; FeNO, fractional exhaled nitric
32 oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; LS, least squares; q2w, every 2
33 weeks; SE, standard error.

Dupilumab phase 2b study

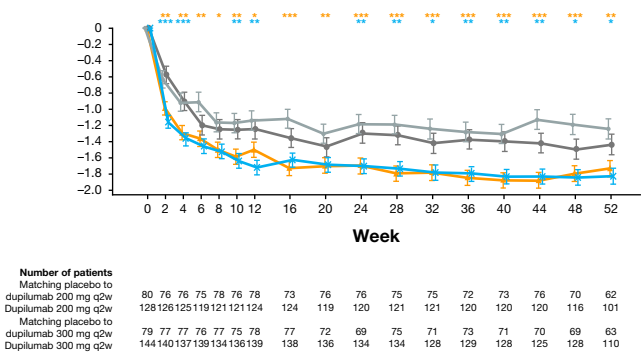
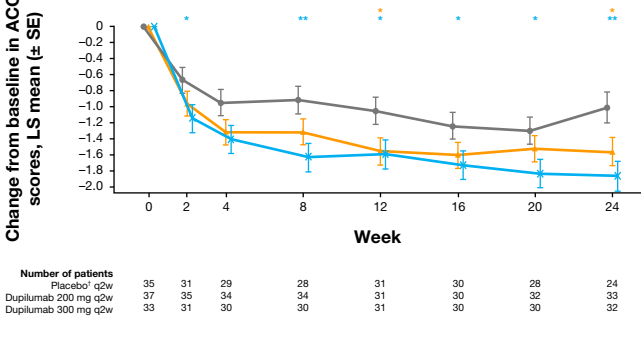
Baseline blood eosinophils ≥ 150 cells/ μ L



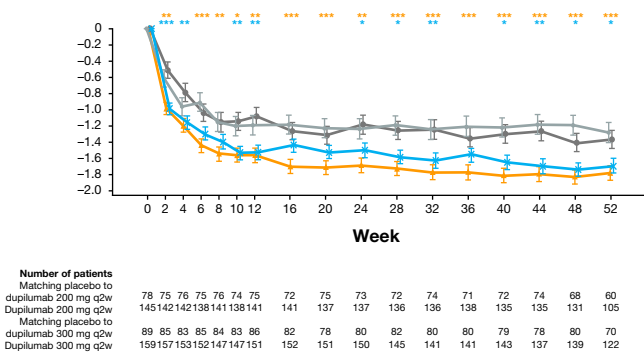
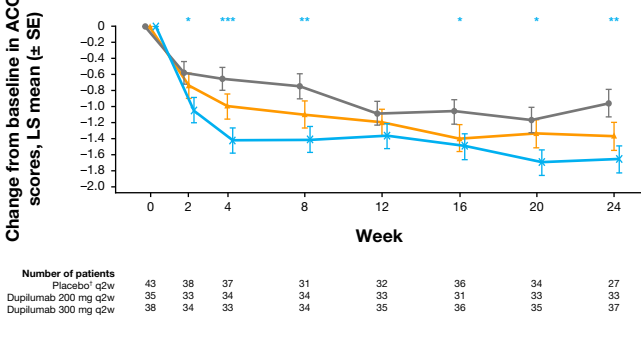
Dupilumab phase 3 LIBERTY ASTHMA QUEST



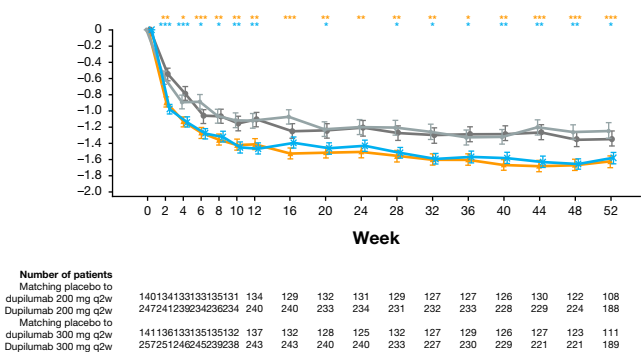
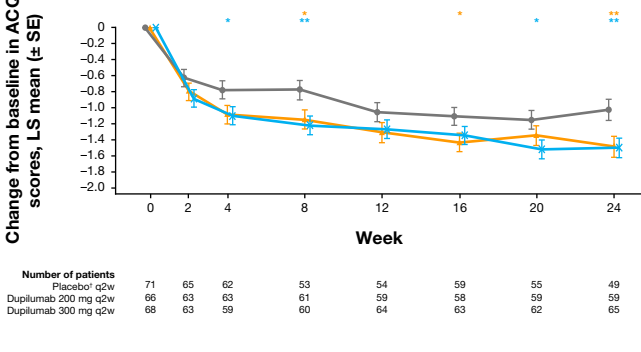
Baseline blood eosinophils ≥ 300 cells/ μ L

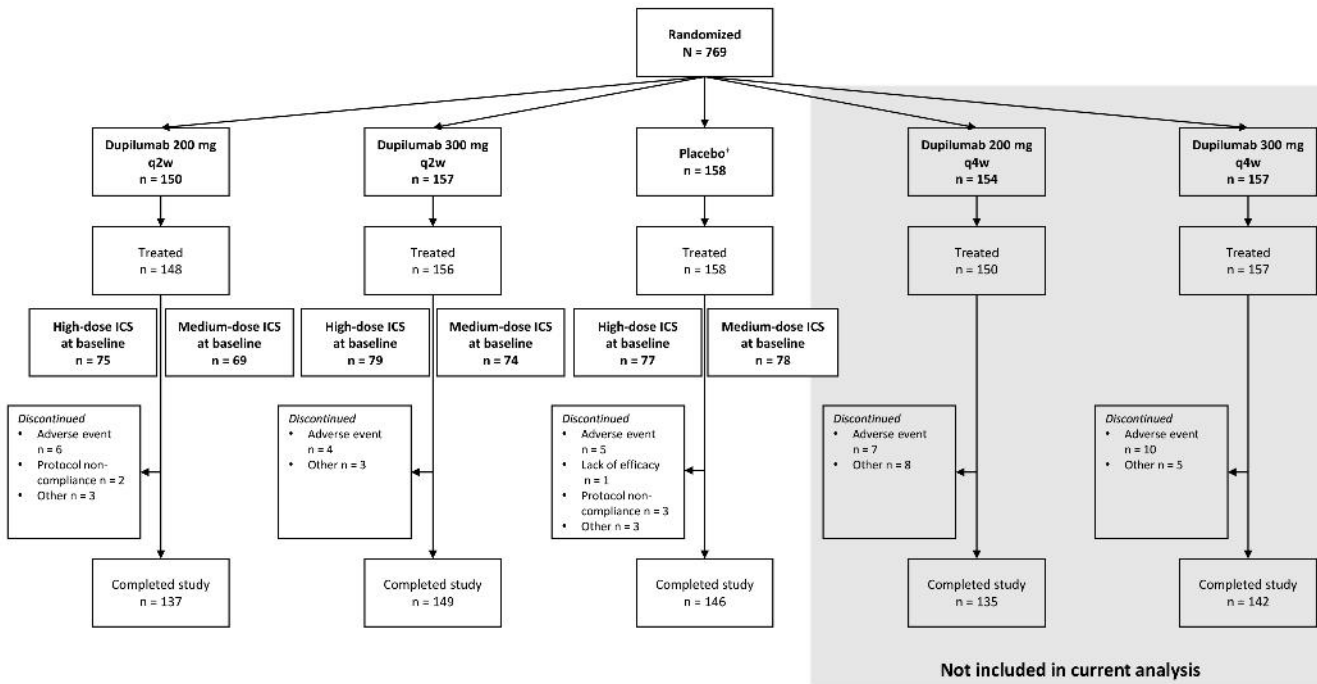


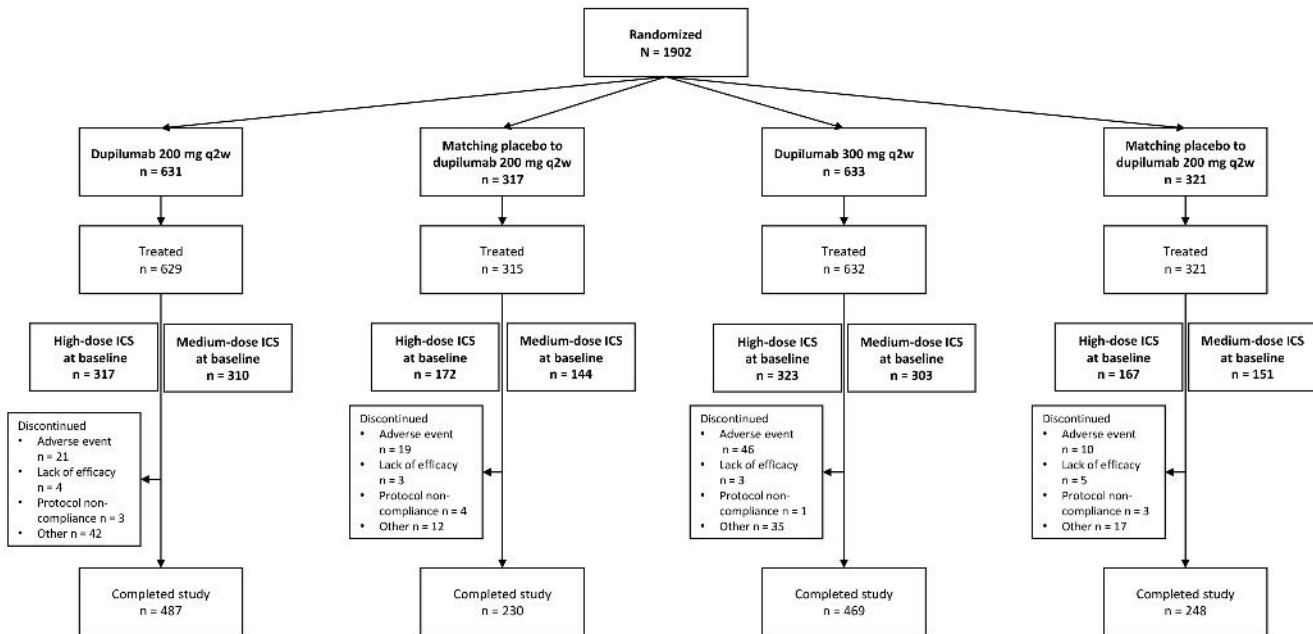
Baseline FeNO ≥ 25 ppb



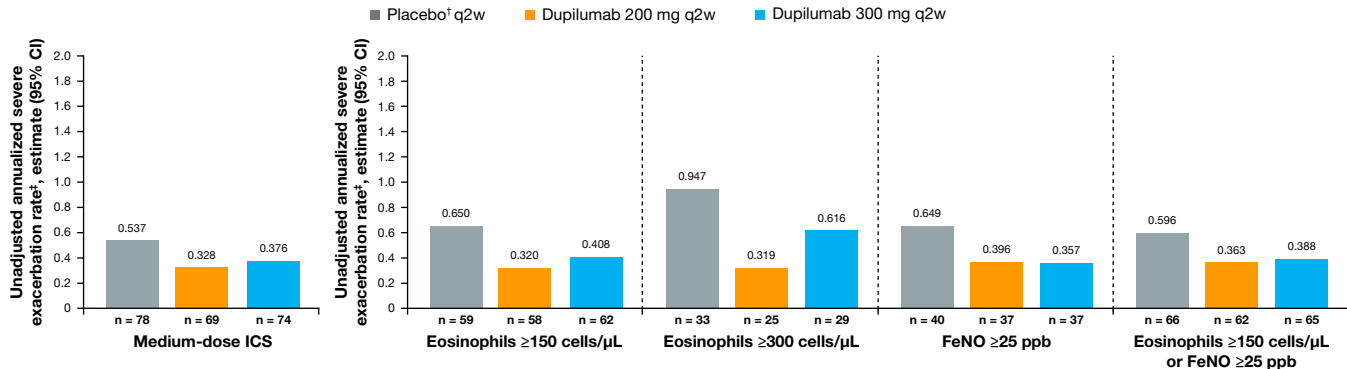
Baseline blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb



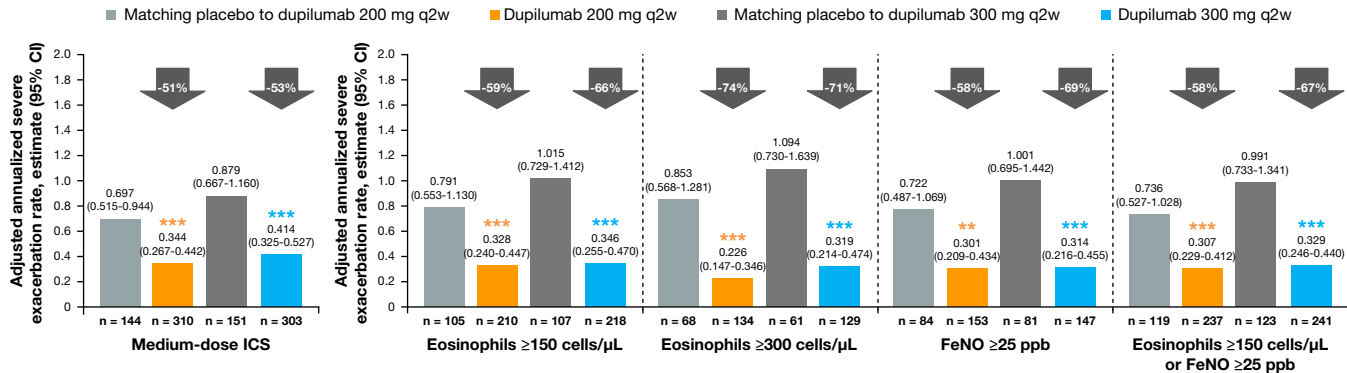




Dupilumab Phase 2b Study



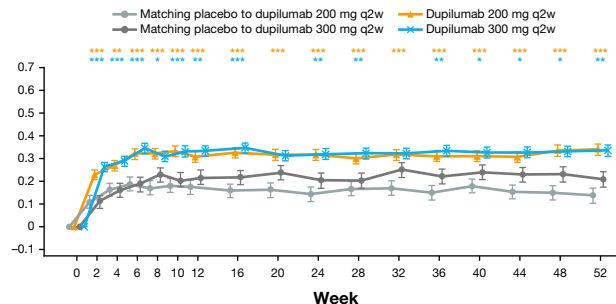
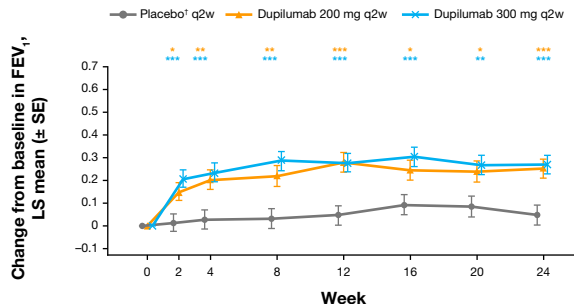
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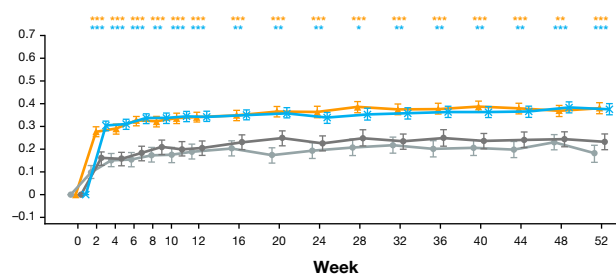
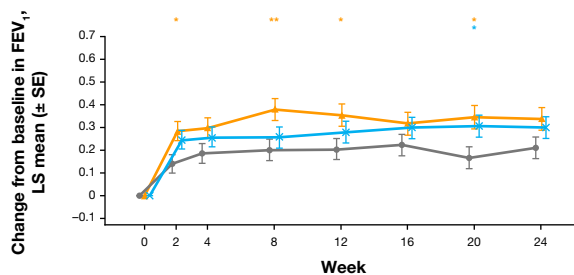
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

High-dose ICS at baseline (ITT population)



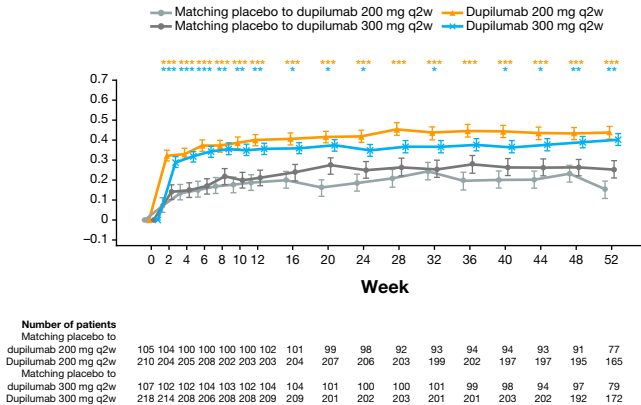
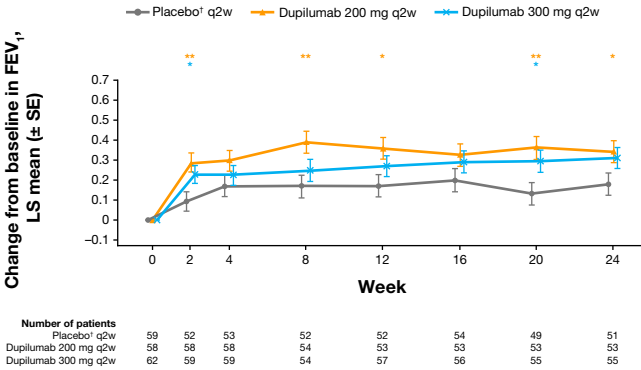
Medium-dose ICS at baseline (ITT population)



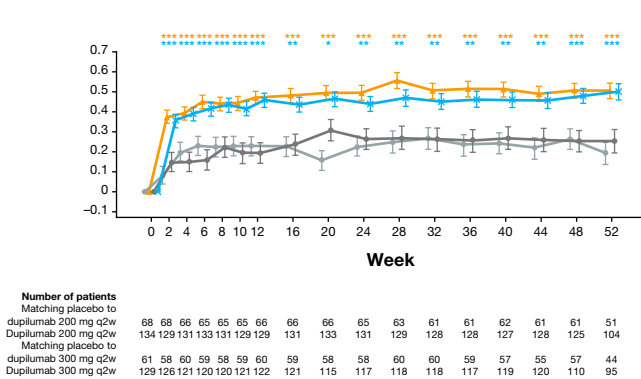
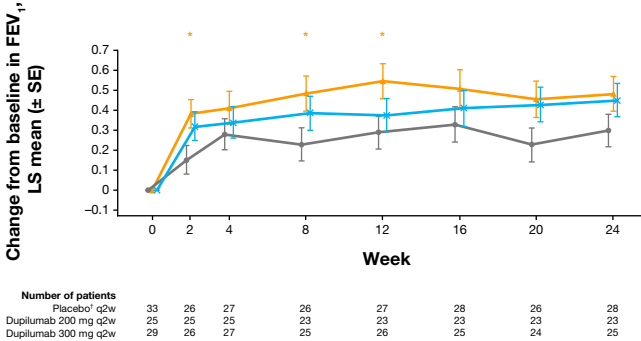
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

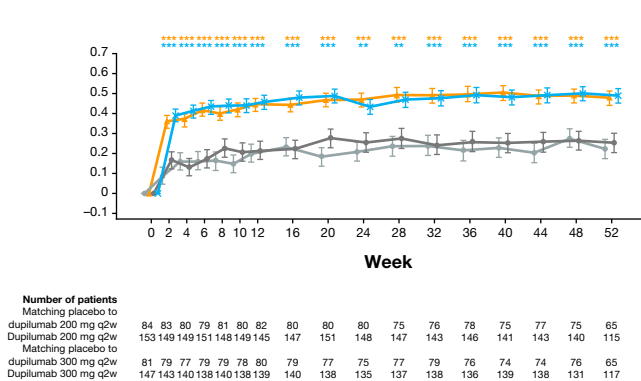
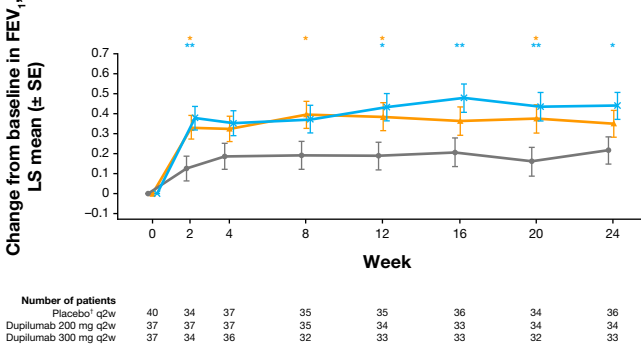
Baseline blood eosinophils ≥150 cells/μL



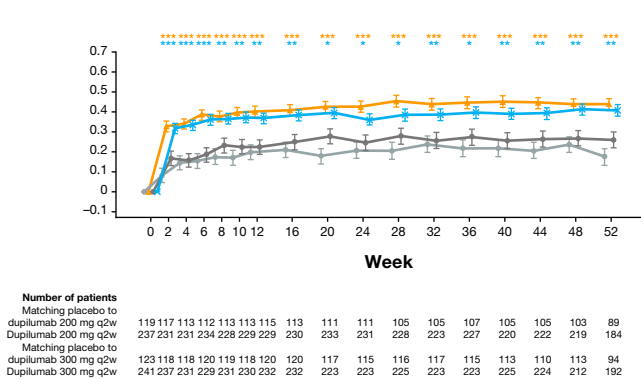
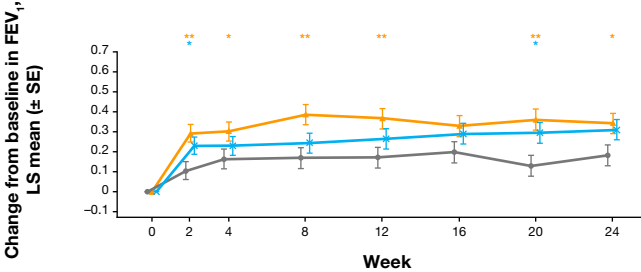
Baseline blood eosinophils ≥300 cells/μL



Baseline FeNO ≥25 ppb

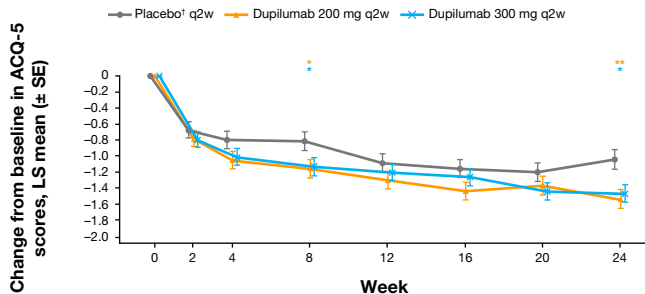


Baseline blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb

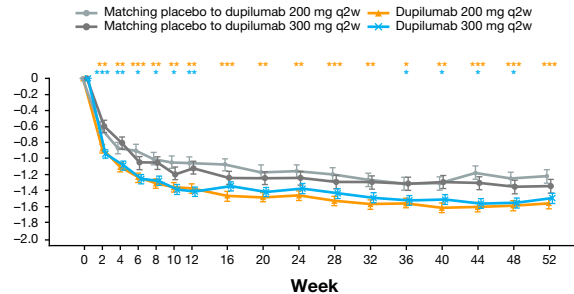


Dupilumab phase 3 LIBERTY ASTHMA QUEST

High-dose ICS at baseline (ITT population)

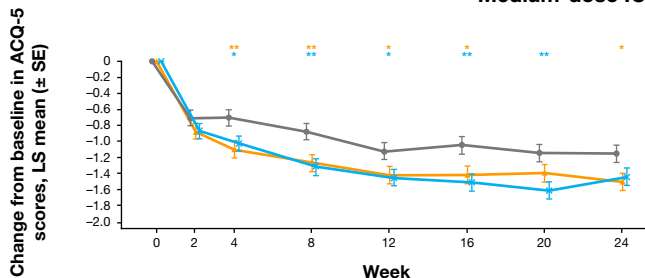


Number of patients									
Placebo ^a q2w	77	70	68	57	58	64	60	53	
Dupilumab 200 mg q2w	75	71	71	67	67	65	66	66	
Dupilumab 300 mg q2w	79	74	70	70	74	74	71	75	

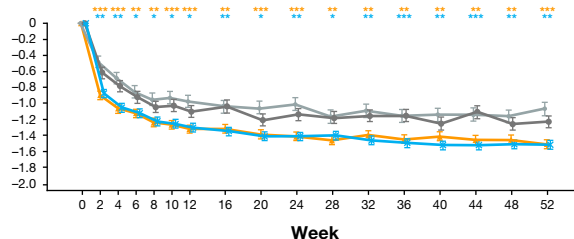


Number of patients																	
Matching placebo to																	
dupilumab 300 mg q2w	172	166	165	163	167	163	164	160	164	162	160	158	158	157	160	153	133
Dupilumab 200 mg q2w	317	306	307	299	302	300	305	306	300	300	295	295	294	291	289	283	239
Matching placebo to																	
dupilumab 300 mg q2w	167	160	159	161	160	158	163	158	153	151	158	155	152	151	148	132	
Dupilumab 300 mg q2w	323	316	309	308	298	299	304	305	298	298	291	285	288	277	276	238	

Medium-dose ICS at baseline (ITT population)



Number of patients									
Placebo† q2w	78	69	72	68	70	71	66	71	
Dupilumab 200 mg q2w	69	68	69	61	61	62	62	62	
Dupilumab 300 mg q2w	74	68	71	64	68	68	67	67	

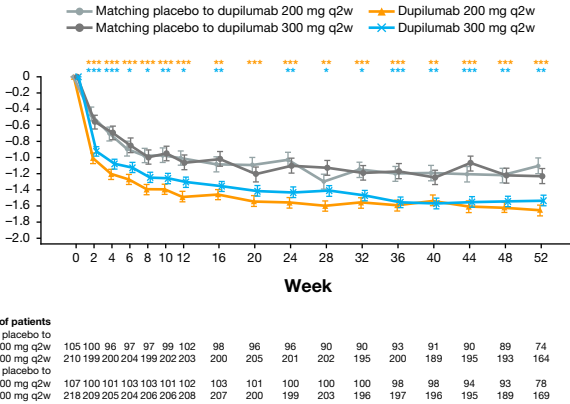
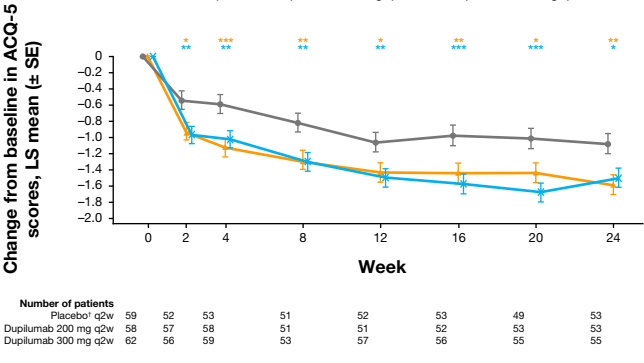


Number of patients																	
Matching placebo to																	
dupilumab 200 mg q2w	144	137	132	133	134	135	139	134	132	133	126	122	127	124	122	120	103
Dupilumab 300 mg q2w	310	291	289	297	290	294	297	288	296	290	289	281	289	275	280	275	231
Matching placebo to																	
dupilumab 300 mg q2w	151	143	144	146	147	144	146	147	145	143	144	144	142	140	137	133	111
Dupilumab 300 mg q2w	305	292	289	287	288	288	292	291	281	280	283	277	279	271	268	238	238

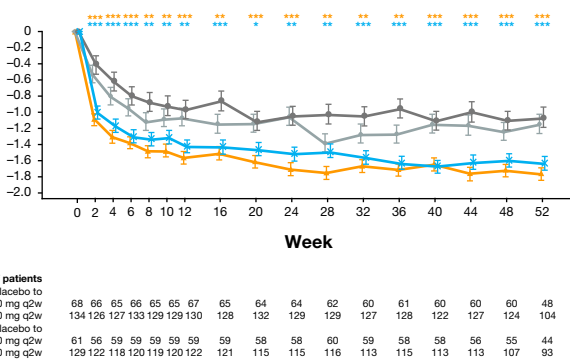
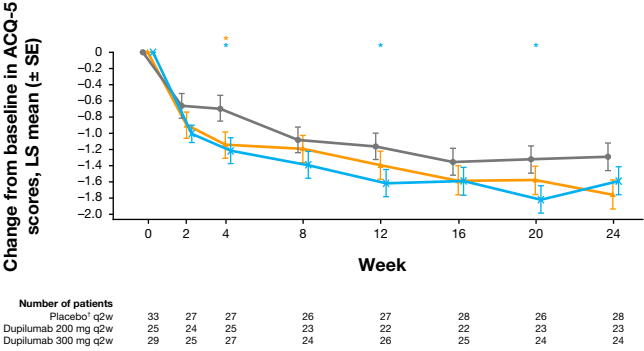
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

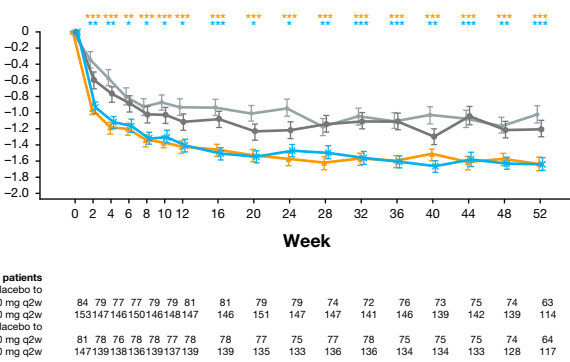
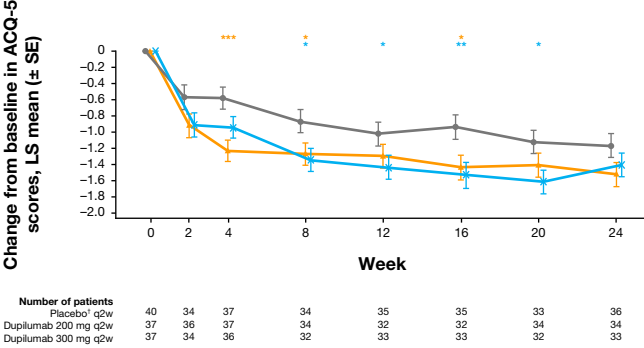
Baseline blood eosinophils ≥150 cells/μL



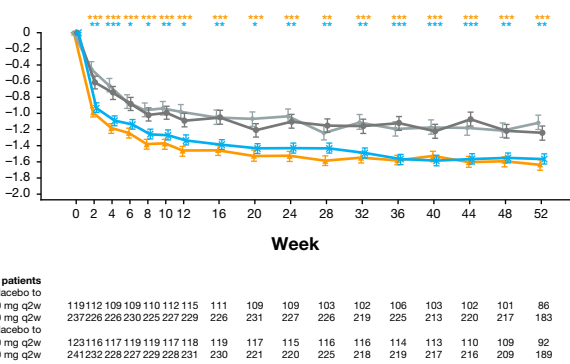
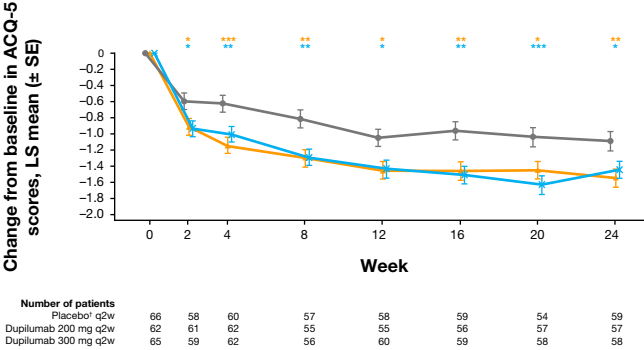
Baseline blood eosinophils ≥300 cells/μL



Baseline FeNO ≥25 ppb



Baseline blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb



ONLINE-ONLY SUPPLEMENTARY APPENDIX

These supplementary data have been provided by the authors to give the readers additional information about the study.

Supplementary data for the article:

Dupilumab is Effective in Type-2 high Asthma Patients Receiving High-dose Inhaled Corticosteroids at Baseline

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Inc., Tarrytown, NY, USA; ⁷Sanofi, Bridgewater, NJ, USA; ⁸University of Oxford, Oxford, United Kingdom

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Additional details on statistical models*Severe exacerbations – negative binomial regression models*

In the phase 2b study, the total number of events occurring between randomization and study end (Week 24) was the response variable, with treatment, baseline eosinophil strata, pooled countries/regions and number of asthma events prior to the study as covariates. Log-transformed standardized study duration was the offset variable.

For QUEST, the total number of events from randomization up to Week 52 or last contact date (whichever was earlier) was included as the response variable, with the four treatment groups, age, region (pooled country), baseline eosinophil strata and number of severe exacerbations in the previous year as covariates. Log-transformed standardized observation duration was the offset variable.

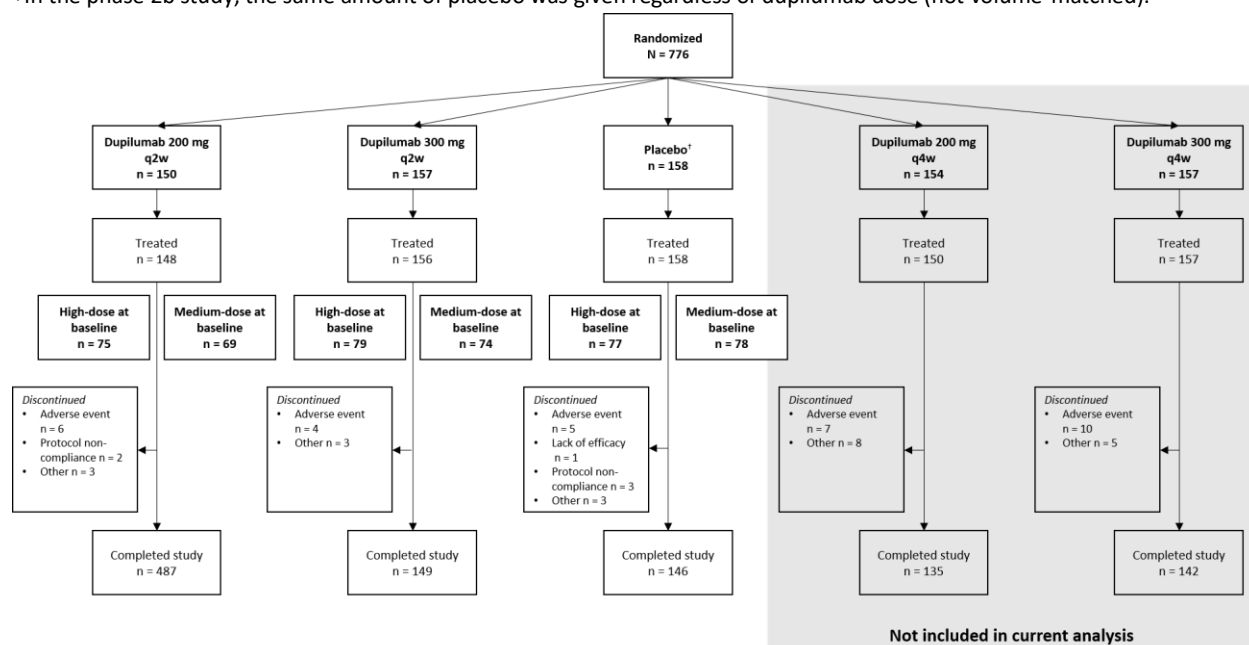
FEV₁ and ACQ-5 – mixed effects models with repeated measures

In both studies, the model included change in FEV₁, change ACQ-5 from baseline, and ACQ-5 responder analysis up to Week 24 (phase 2b) or Week 52 (QUEST) as the dependent variable, and for treatment, baseline eosinophil strata (phase 2b study: <0.2 Giga/L, 0.2–2.99 Giga/L, and ≥0.3 Giga/L; phase 3 QUEST study: <0.3 Giga/L and ≥0.3 Giga/L), pooled countries/regions, visit, treatment-by-visit interaction, FEV₁ or ACQ-5 baseline value and baseline-by-visit interaction as covariates. The QUEST model additionally included age as a covariate. In the QUEST model for FEV₁, sex and baseline height were also included as covariates.

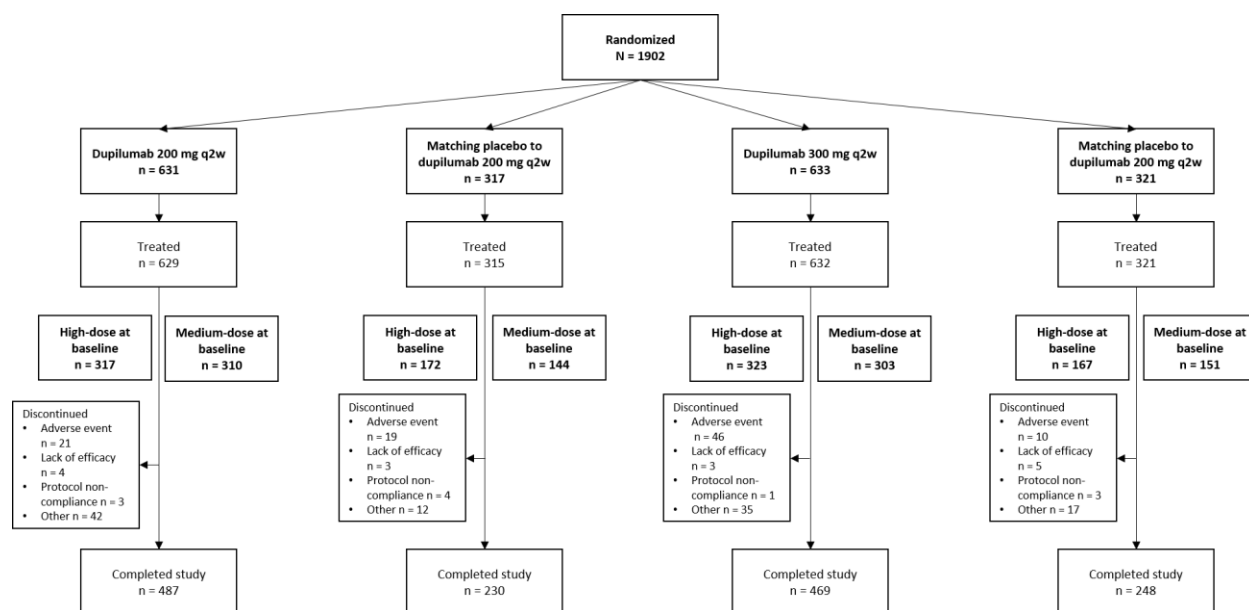
Supplementary Figure 1 Study flowcharts for the phase 2b study (A) and phase 3 Liberty Asthma QUEST study (B)

A) Dupilumab phase 2b study (NCT01854047; Wenzel S, *et al.* Lancet 2016;388:31-44.)

†In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched).



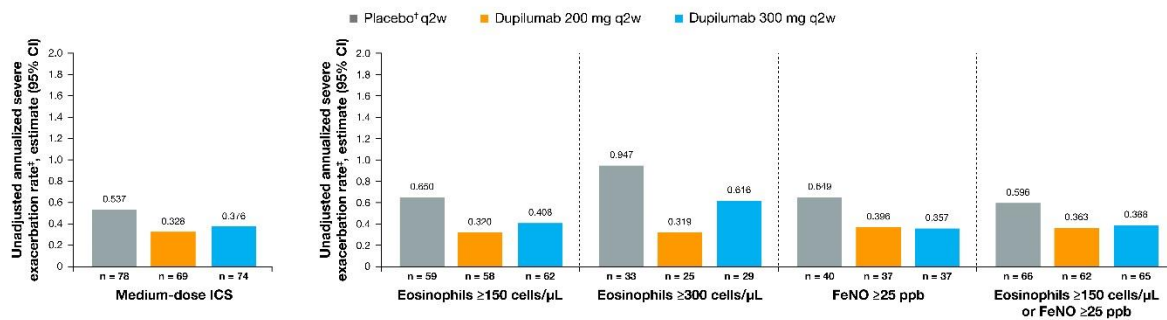
B) Phase 3 Liberty Asthma QUEST study (NCT02414854, Castro M, *et al.* N Engl J Med 2018;378:2486-96).



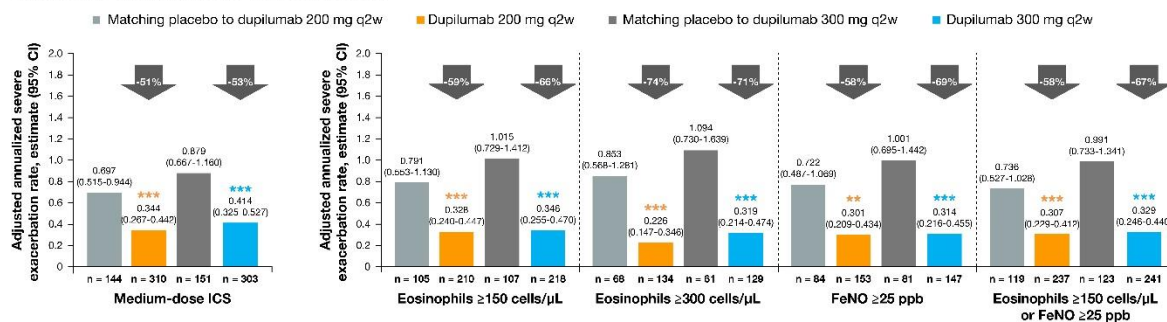
Supplementary Figure 2 Annualized rate of severe exacerbations in dupilumab treated patients (q2w) versus placebo during the 24-week treatment period in the phase 2b study (A) and 52-week treatment period in the phase 3 QUEST study (B) on medium-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels

† In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). †In the phase 2b study, adjusted severe exacerbation rates could not be calculated for the subgroups of patients receiving medium-dose ICS as the number of events was deemed too small to provide valid estimates from an adjusted model. *** $P < .001$ vs placebo., ** $P < .01$ vs placebo., * $P < .05$ vs placebo. CI, confidence interval; EOS, blood eosinophils; FeNO, fractional exhaled nitric oxide; q2w, every 2 weeks.

Dupilumab Phase 2b Study

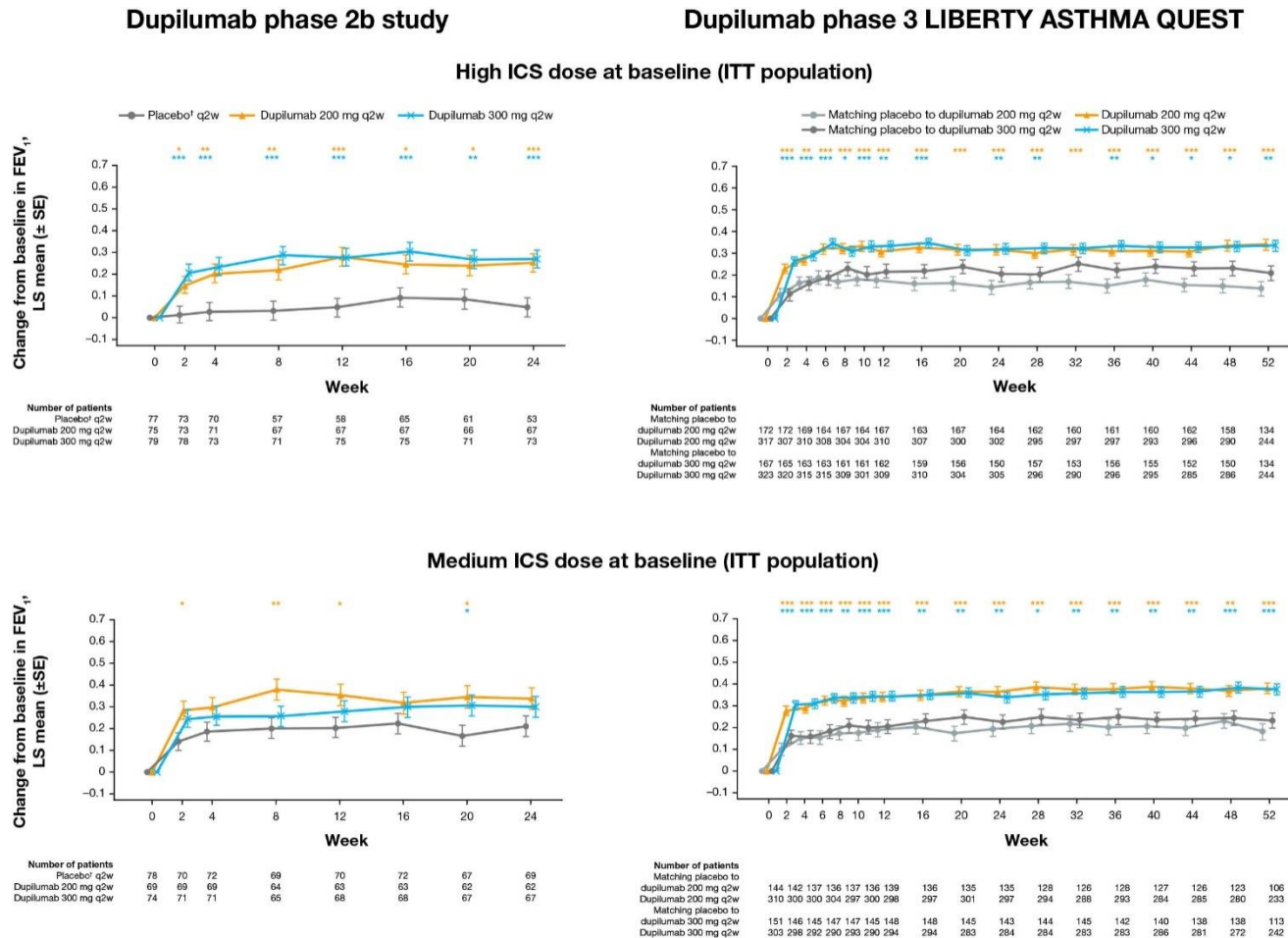


Dupilumab Phase 3 LIBERTY ASTHMA QUEST



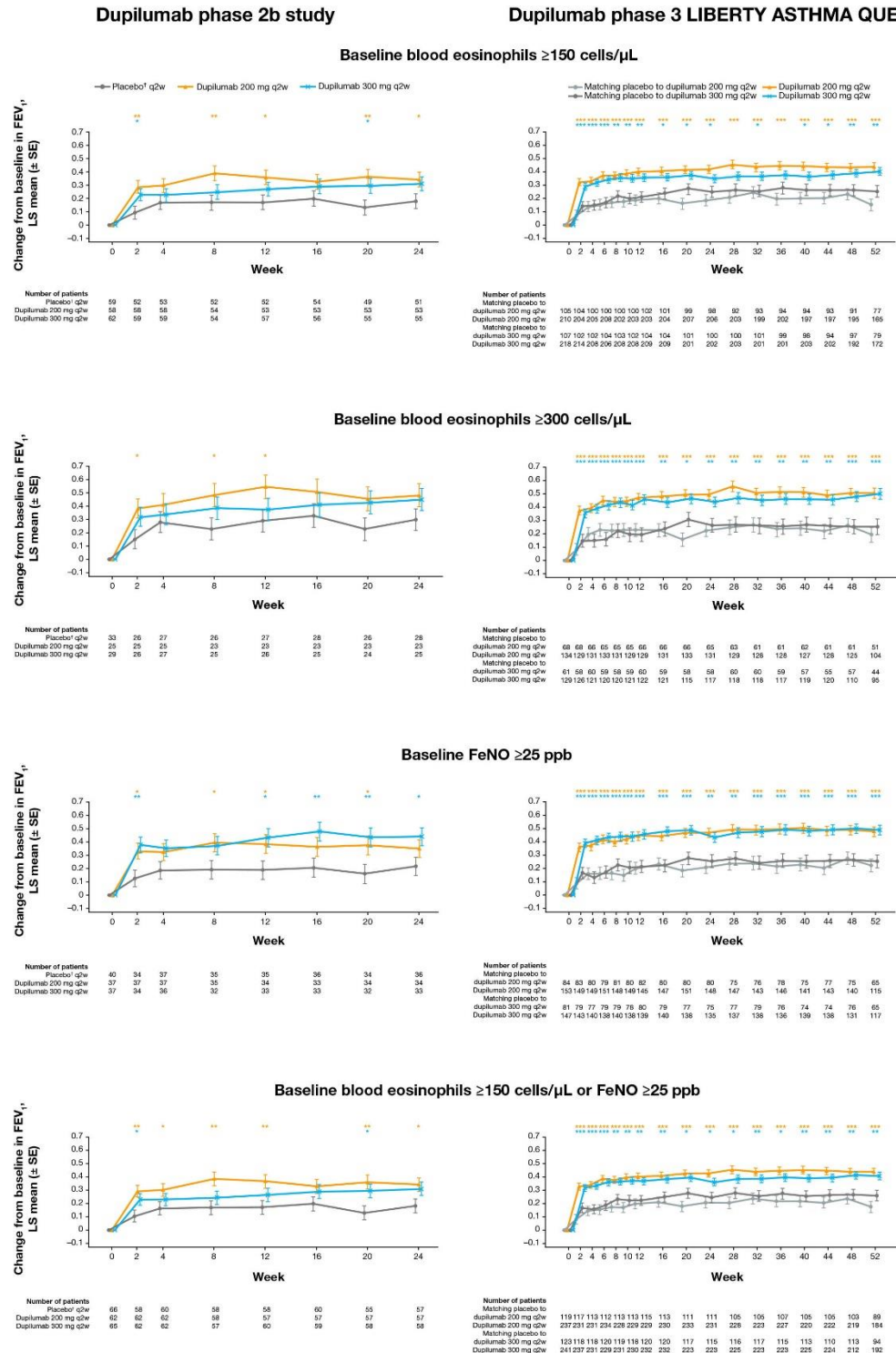
Supplementary Figure 3 LS mean change from baseline in prebronchodilator FEV₁ (L) during the 24-week treatment period in the phase 2b study and 52-week treatment period in the phase 3 QUEST study in patients with asthma on high-dose or medium-dose ICS at baseline (ITT population)

† In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P < .01$, * $P < .05$ vs placebo. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; LS, least squares; q2w, every 2 weeks; SE, standard error



Supplementary Figure 4 LS mean change from baseline in FEV₁ (L) during the 24-week treatment period in the phase 2b study and 52-week treatment period in the phase 3 QUEST study in patients with asthma requiring medium-dose ICS at baseline and further stratified by baseline eosinophil counts and FeNO levels

† In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P < .01$, * $P < .05$ vs placebo. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; LS, least squares; q2w, every 2 weeks; SE, standard error.



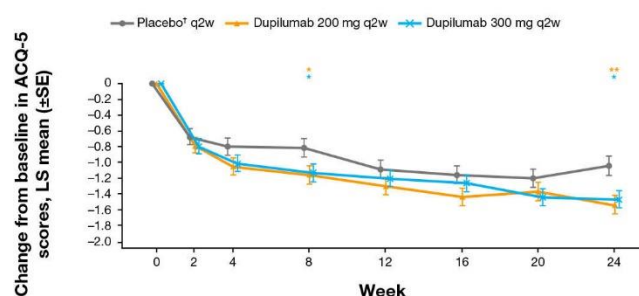
Supplementary Figure 5 LS mean change from baseline in ACQ-5 scores during the 24-week treatment period in the phase 2b study and 52-week treatment period in the phase 3 QUEST study in patients with asthma on high-dose or medium-dose ICS at baseline (ITT population)

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 between 0 (totally controlled) and 6 (severely uncontrolled). † In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P < .01$, * $P < .05$ vs placebo. LS, least squares; q2w, every 2 weeks; SE, standard error

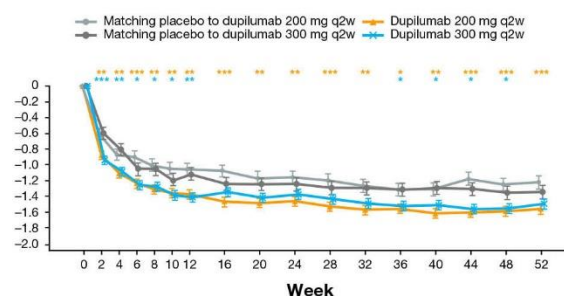
Dupilumab phase 2b study

Dupilumab phase 3 LIBERTY ASTHMA QUEST

High-dose ICS at baseline (ITT population)

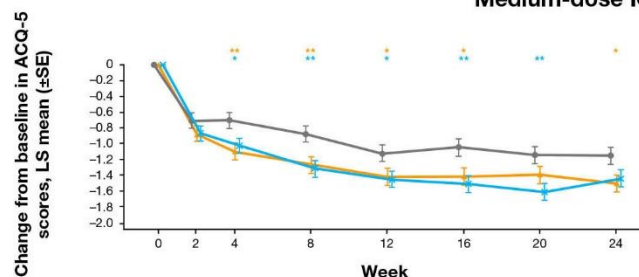


Number of patients	77	70	68	57	58	64	60	53
Placebo† q2w	77	70	68	57	58	64	60	53
Dupilumab 200 mg q2w	75	71	71	67	67	65	66	66
Dupilumab 300 mg q2w	79	74	70	70	74	74	71	75

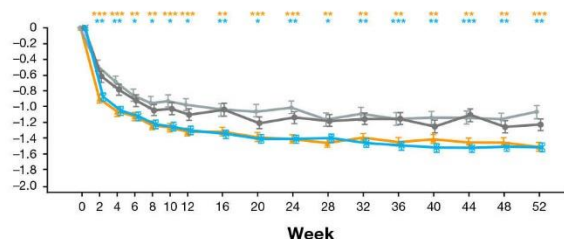


Number of patients	172	166	166	163	167	163	164	160	164	162	160	158	158	157	160	153	133
Matching placebo to dupilumab 200 mg q2w	172	166	166	163	167	163	164	160	164	162	160	158	158	157	160	153	133
Dupilumab 200 mg q2w	317	308	307	299	302	300	305	306	300	300	295	295	294	291	289	283	239
Matching placebo to dupilumab 300 mg q2w	167	160	159	161	160	158	163	158	153	151	158	151	155	152	151	148	132
Dupilumab 300 mg q2w	323	316	309	308	298	299	304	305	298	298	291	285	288	287	277	276	238

Medium-dose ICS at baseline (ITT population)



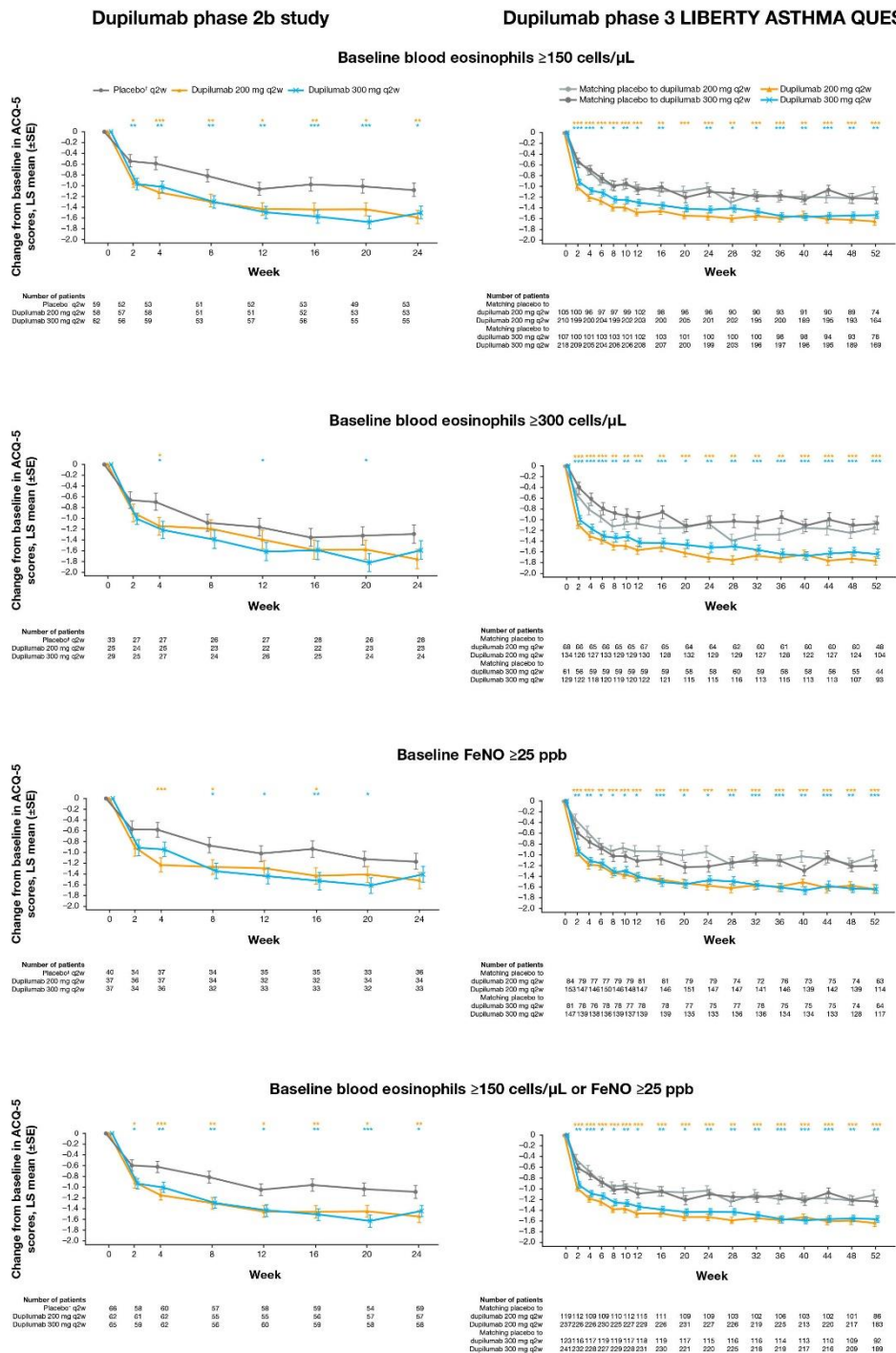
Number of patients	78	69	72	68	70	71	66	71
Placebo† q2w	78	69	72	68	70	71	66	71
Dupilumab 200 mg q2w	69	68	69	61	61	62	62	62
Dupilumab 300 mg q2w	74	68	71	64	68	68	67	67



Number of patients	144	137	132	133	134	135	139	134	132	133	126	122	127	124	122	120	103
Matching placebo to dupilumab 200 mg q2w	144	137	132	133	134	135	139	134	132	133	126	122	127	124	122	120	103
Dupilumab 200 mg q2w	310	291	289	297	290	294	297	288	296	290	289	281	289	275	280	275	231
Matching placebo to dupilumab 300 mg q2w	151	143	144	146	147	144	146	147	145	143	144	144	142	140	137	133	111
Dupilumab 300 mg q2w	303	292	289	287	288	288	292	291	281	280	283	277	279	278	271	268	238

Supplementary Figure 6 LS mean change from baseline in ACQ-5 scores during the 24-week treatment period in the phase 2b study (A) and 52-week treatment period in the phase 3 QUEST study (B) in patients with asthma requiring medium-dose ICS at baseline and further stratified by baseline eosinophil counts and FeNO levels

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 between 0 (totally controlled) and 6 (severely uncontrolled). † In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). *** $P < .001$, ** $P < .01$, * $P < .05$ vs placebo. FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; LS, least squares; q2w, every 2 weeks; SE, standard error.



Supplementary Table 1 Definition of low, medium and high doses of ICS – adults and adolescents ≥ 12 years*

Inhaled corticosteroid	Total daily dose (µg)		
	Low	Medium	High
Beclometasone dipropionate (CFC)	200–500	> 500–1000	> 1000
Beclometasone dipropionate (HFA)	100–200	> 200–400	> 400
Budesonide (DPI)	200–400	> 400–800	> 800
Ciclesonide (HFA)	80–160	> 160–320	> 320
Fluticasone propionate (DPI or HFA) [#]	100–250	> 250–500	> 500
Mometasone furoate	110–220	> 220–440	> 440
Triamcinolone acetonide	400–1000	> 1000–2000	> 2000

*Adapted from GINA 2014.

[#] The minimum daily medium dose of fluticasone propionate was 500 mcg (≥250 mcg of fluticasone propionate twice daily), which is equivalent to the upper limit of the medium daily dose for fluticasone propionate.

CFC, chlorofluorocarbon propellant; DPI, dry powder inhaler; HFA, chlorofluorocarbon propellant.

Supplementary Table 2 Baseline demographic and disease characteristics of patients in phase 2b and phase 3 QUEST studies on high- or medium-dose ICS and with eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 ppb at baseline

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	71	66	68	140	247	141	257
Age, mean (SD), years	50.4 (11.3)	53.3 (11.2)	48.9 (12.0)	48.8 (14.4)	49.3 (13.7)	49.0 (13.4)	48.9 (14.6)
Age < 18 years, n (%)	0	0	0	5 (3.6)	4 (1.6)	2 (1.4)	7 (2.7)
Female sex, n (%)	49 (69.0)	37 (56.1)	43 (63.2)	85 (60.7)	150 (60.7)	99 (70.2)	168 (65.4)
Any comorbidity medical history, [‡] n (%)	56 (80.0)	50 (75.8)	54 (79.4)	113 (80.7)	200 (81.0)	112 (79.4)	203 (79.0)
Ongoing atopic medical condition, n (%)	52 (74.3)	48 (72.7)	53 (77.9)	121 (86.4)	201 (81.4)	117 (83.0)	212 (82.5)
Prebronchodilator FEV ₁ , mean (SD), L	1.69 (0.50)	1.74 (0.54)	1.78 (0.48)	1.75 (0.58)	1.68 (0.55)	1.65 (0.47)	1.69 (0.58)
Percent predicted, mean (SD)	58.3 (10.8)	59.0 (11.3)	60.1 (11.1)	58.0 (12.7)	56.1 (13.6)	56.2 (12.6)	56.7 (13.7)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.1 (0.6)	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	26.1 (12.3)	26.0 (19.8)	27.9 (18.0)	24.3 (16.4)	27.0 (21.5)	27.8 (16.0)	28.8 (23.8)
Severe asthma exacerbations in past year, mean (SD), n	2.63 (2.8)	2.20 (1.8)	2.97 (2.9)	2.2 (1.7)	2.2 (1.7)	2.6 (2.4)	2.2 (1.8)
ACQ-5 score, mean (SD)	2.8 (0.8)	2.8 (0.7)	3.0 (0.9)	2.8 (0.7)	2.9 (0.9)	2.9 (0.8)	2.9 (0.8)
AQLQ(S) global score, ^{††} mean (SD)	3.9 (1.1)	4.0 (1.2)	3.8 (1.1)	4.2 (1.0)	4.2 (1.1)	4.1 (1.0)	4.1 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	290.0 (220.0-480.0)	335.0 (170.0-560.0)	285.0 (210.0-460.0)	335.0 (220.0-550.0)	300.0 (190.0-560.0)	370.0 (210.0-585.0)	320.0 (200.0-520.0)
Total IgE, median (IQR), IU/mL	236.0 (94.0-484.0)	173.0 (63.0-466.0)	204.5 (86.0-407.5)	245.0 (70.0-464.0)	181.5 (64.0-562.0)	202.5 (77.5-442.0)	200.0 (71.0-520.0)
FeNO, median (IQR), ppb	31.0 (24.0-42.0)	29.0 (17.0-44.0)	37.0 (14.0-63.0)	27.0 (16.0-44.0)	28.0 (16.0-44.0)	33.0 (18.0-50.0)	28.5 (18.5-49.5)
Medium-dose ICS at baseline, n	66	62	65	119	237	123	241
Age, mean (SD), years	47.1 (14.0)	46.8 (14.6)	46.5 (12.7)	47.3 (17.5)	45.1 (16.6)	46.6 (15.1)	46.1 (16.2)
Age < 18 years, n (%)	0	0	0	13 (10.9)	23 (9.7)	12 (9.8)	18 (7.5)
Female sex, n (%)	41 (62.1)	42 (67.7)	43 (66.2)	68 (57.1)	131 (55.3)	77 (62.6)	140 (58.1)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Any comorbidity medical history, [‡] n (%)	48 (76.2)	52 (85.2)	44 (71.0)	98 (82.4)	188 (79.3)	99 (80.5)	199 (82.6)
Ongoing atopic medical condition, n (%)	47 (74.6)	49 (80.3)	42 (67.7)	98 (82.4)	197 (83.1)	104 (84.6)	207 (85.9)
Prebronchodilator FEV ₁ , mean (SD), L	1.94 (0.60)	1.88 (0.50)	1.90 (0.51)	1.80 (0.69)	1.94 (0.69)	1.86 (0.63)	1.88 (0.60)
Percent predicted, mean (SD)	62.2 (10.6)	63.1 (9.9)	61.3 (10.5)	58.5 (14.3)	60.5 (13.4)	60.3 (14.5)	60.4 (12.5)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.2 (0.8)	2.3 (0.8)	2.3 (0.8)	2.2 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	30.0 (16.0)	27.4 (15.8)	26.2 (16.2)	27.7 (21.6)	27.1 (22.1)	26.3 (19.2)	23.0 (18.9)
Severe asthma exacerbations in past year, mean (SD), n	2.0 (1.8)	1.4 (0.8)	2.0 (1.7)	1.9 (1.4)	2.0 (3.5)	2.1 (1.8)	1.9 (2.2)
ACQ-5 score, [¶] mean (SD)	2.5 (0.8)	2.5 (0.8)	2.7 (0.7)	2.6 (0.7)	2.6 (0.7)	2.7 (0.7)	2.7 (0.7)
AQLQ(S) global score, ^{††} mean (SD)	4.4 (1.1)	4.2 (1.2)	4.0 (1.0)	4.4 (1.0)	4.5 (1.1)	4.4 (1.0)	4.5 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	290.0 (180.0-440.0)	250.0 (200.0-430.0)	280.0 (190.0-390.0)	360.0 (190.0-560.0)	330.0 (190.0-550.0)	290.0 (190.0-470.0)	320.0 (190.0-520.0)
Total IgE, median (IQR), IU/mL	207.0 (98.0-448.0)	255.0 (85.0-772.0)	183.0 (72.0-426.0)	207.5 (88.0-554.0)	173.0 (77.0-469.0)	222.0 (63.0-633.0)	196.0 (75.0-482.0)
FeNO, median (IQR), ppb	37.0 (20.0-59.0)	35.0 (19.0-53.0)	30.0 (21.0-49.0)	33.0 (22.0-57.0)	30.5 (20.0-58.5)	31.5 (20.0-56.0)	29.0 (18.0-49.0)

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). [‡]Includes any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives. [§]FEV₁ (L) reversibility indicates the change in FEV₁ between prebronchodilator and postbronchodilator measurements. [¶]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 between 0 (totally controlled) and 6 (severely uncontrolled). ^{††}AQLQ(S) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = “not impaired at all” to 1 = “severely impaired”). ACQ-5, 5-item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

Supplementary Table 3 Baseline demographic and disease characteristics of patients in phase 2b and phase 3 QUEST studies on high- or medium-dose ICS and with eosinophils ≥ 150 cells/ μ L at baseline

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	67	58	63	126	223	127	228
Age, mean (SD), years	50.3 (11.5)	53.6 (10.7)	48.9 (11.5)	49.3 (14.3)	49.3 (13.9)	49.1 (13.1)	49.5 (14.1)
Age < 18 years, n (%)	0	0	0	5 (4.0)	4 (1.8)	1 (0.8)	5 (2.2)
Female sex, n (%)	48 (71.6)	31 (53.4)	39 (61.9)	77 (61.1)	137 (61.4)	91 (71.7)	148 (64.9)
Any comorbidity medical history, [‡] n (%)	53 (80.3)	44 (75.9)	51 (81.0)	101 (80.2)	180 (80.7)	101 (79.5)	183 (80.3)
Ongoing atopic medical condition, n (%)	49 (74.2)	42 (72.4)	50 (79.4)	108 (85.7)	178 (79.8)	105 (82.7)	191 (83.8)
Prebronchodilator FEV ₁ , mean (SD), L	1.67 (0.50)	1.72 (0.52)	1.79 (0.50)	1.73 (0.57)	1.67 (0.54)	1.65 (0.46)	1.69 (0.57)
Percent predicted, mean (SD)	57.8 (10.9)	57.8 (10.6)	59.3 (11.0)	57.9 (12.9)	55.8 (13.8)	56.1 (12.7)	56.5 (13.9)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.1 (0.6)	2.1 (0.7)	2.0 (0.6)	2.1 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	25.8 (11.8)	24.1 (14.6)	27.9 (18.7)	23.9 (14.8)	27.5 (21.8)	27.3 (15.8)	29.8 (24.4)
Severe asthma exacerbations in past year, mean (SD), n	2.7 (2.9)	2.3 (1.9)	3.0 (3.0)	2.3 (1.7)	2.2 (1.8)	2.6 (2.3)	2.2 (1.8)
ACQ-5 score, mean (SD)	2.8 (0.8)	2.8 (0.7)	3.0 (0.9)	2.9 (0.8)	2.9 (0.9)	2.9 (0.9)	2.9 (0.8)
AQLQ(S) global score, ^{††} mean (SD)	3.9 (1.1)	4.0 (1.2)	3.8 (1.1)	4.1 (1.0)	4.2 (1.1)	4.1 (1.0)	4.1 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	300.0 (240.0-500.0)	375.0 (220.0-560.0)	300.0 (220.0-480.0)	370.0 (240.0-570.0)	330.0 (230.0-600.0)	390.0 (250.0-640.0)	355.0 (230.0-560.0)
Total IgE, median (IQR), IU/mL	216.0 (94.0-484.0)	178.5 (90.0-466.0)	202.0 (78.0-415.0)	244.0 (58.5-478.0)	159.5 (60.0-508.5)	210.0 (75.0-477.0)	209.5 (79.0-547.0)
FeNO, median (IQR), ppb	31.0 (21.0-44.0)	25.0 (16.0-41.0)	33.0 (13.5-64.5)	27.0 (15.0-40.0)	26.0 (15.0-43.0)	31.0 (17.0-47.0)	26.0 (17.0-50.0)
Medium-dose ICS at baseline, n	59	58	62	105	210	107	218
Age, mean (SD), years	46.2 (14.2)	46.6 (14.4)	46.9 (12.6)	46.1 (17.7)	44.9 (16.8)	46.4 (14.9)	45.8 (16.2)
Age < 18 years, n (%)	0	0	0	12 (11.4)	23 (11.0)	11 (10.3)	16 (7.3)
Female sex, n (%)	35 (59.3)	40 (69.0)	41 (66.1)	59 (56.2)	117 (55.7)	66 (61.7)	126 (57.8)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Any comorbidity medical history, [‡] n (%)	42 (73.7)	49 (86.0)	41 (69.5)	87 (82.9)	169 (80.5)	86 (80.4)	179 (82.1)
Ongoing atopic medical condition, n (%)	41 (71.9)	47 (82.5)	39 (66.1)	86 (81.9)	171 (81.4)	91 (85.0)	185 (84.9)
Prebronchodilator FEV ₁ , mean (SD), L	2.0 (0.6)	1.9 (0.5)	1.9 (0.5)	1.8 (0.7)	2.0 (0.7)	1.9 (0.6)	1.9 (0.6)
Percent predicted, mean (SD)	61.5 (10.2)	63.0 (9.8)	61.0 (10.6)	58.3 (14.4)	61.2 (12.9)	60.6 (14.6)	60.4 (12.6)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.3 (0.8)	2.4 (0.8)	2.3 (0.8)	2.2 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	29.2 (15.5)	27.8 (16.1)	26.3 (16.5)	27.3 (22.2)	27.0 (22.3)	25.6 (17.7)	22.2 (19.2)
Severe asthma exacerbations in past year, mean (SD), n	2.1 (1.8)	1.5 (0.9)	2.0 (1.7)	1.9 (1.4)	2.1 (3.7)	2.1 (1.9)	1.9 (2.2)
ACQ-5 score, [¶] mean (SD)	2.5 (0.8)	2.5 (0.9)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)	2.7 (0.7)
AQLQ(S) global score, ^{††} mean (SD)	4.4 (1.2)	4.2 (1.1)	4.1 (1.0)	4.4 (1.00)	4.5 (1.1)	4.4 (1.0)	4.5 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	320.0 (210.0-440.0)	255.0 (210.0-430.0)	280.0 (210.0-390.0)	390.0 (210.0-690.0)	365.0 (240.0-610.0)	330.0 (220.0-570.0)	340.0 (210.0-570.0)
Total IgE, median (IQR), IU/mL	214.5 (94.0-448.0)	255.0 (99.0-698.0)	148.5 (69.0-409.0)	205.0 (90.0-567.0)	163.5 (76.0-470.0)	236.0 (67.0-672.0)	193.5 (75.0-486.0)
FeNO, median (IQR), ppb	38.0 (17.0-62.0)	33.0 (18.0-54.0)	29.5 (21.0-49.0)	32.0 (20.0-56.0)	29.0 (18.0-59.0)	30.5 (19.0-55.0)	28.0 (16.0-48.0)

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). [‡]Includes any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives. [§]FEV₁ (L) reversibility indicates the change in FEV₁ between prebronchodilator and postbronchodilator measurements. [¶]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 between 0 (totally controlled) and 6 (severely uncontrolled). ^{††}AQLQ(S) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = “not impaired at all” to 1 = “severely impaired”). ACQ-5, 5-item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

Supplementary Table 4 Baseline demographic and disease characteristics of patients in phase 2b and phase 3 QUEST studies on high- or medium-dose ICS and with eosinophils ≥ 300 cells/ μ L at baseline

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	35	37	33	80	128	79	144
Age, mean (SD), years	48.7 (12.1)	53.8 (10.7)	48.9 (10.7)	49.0 (15.5)	48.5 (13.1)	49.0 (13.5)	50.0 (14.0)
Age < 18 years, n (%)	0	0	0	4 (5.0)	1 (0.8)	1 (1.3)	5 (3.5)
Female sex, n (%)	25 (71.4)	19 (51.4)	21 (63.6)	44 (55.0)	80 (62.5)	54 (68.4)	93 (64.6)
Any comorbidity medical history, [‡] n (%)	29 (82.9)	28 (75.7)	29 (87.9)	65 (81.3)	105 (82.0)	66 (83.5)	117 (81.3)
Ongoing atopic medical condition, n (%)	28 (80.0)	28 (75.7)	28 (84.8)	73 (91.3)	102 (79.7)	67 (84.8)	122 (84.7)
Prebronchodilator FEV ₁ , mean (SD), L	1.69 (0.58)	1.72 (0.47)	1.71 (0.48)	1.76 (0.61)	1.69 (0.59)	1.60 (0.45)	1.66 (0.58)
Percent predicted, mean (SD)	57.4 (11.1)	58.0 (10.4)	57.5 (11.3)	57.8 (13.4)	55.6 (14.5)	54.1 (12.2)	55.8 (14.6)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.1 (0.6)	2.1 (0.7)	2.0 (0.6)	2.1 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	22.1 (7.6)	21.2 (9.5)	26.5 (13.3)	25.0 (16.4)	27.0 (22.2)	24.4 (14.4)	30.3 (24.7)
Severe asthma exacerbations in past year, mean (SD), n	1.1 (2.1)	0.7 (1.1)	1.1 (1.3)	2.4 (1.8)	2.3 (1.6)	2.7 (2.4)	2.4 (1.8)
ACQ-5 score, mean (SD)	2.6 (0.8)	2.7 (0.7)	3.2 (0.9)	2.9 (0.7)	3.1 (1.0)	3.0 (0.8)	2.9 (0.8)
AQLQ(S) global score, ^{††} mean (SD)	3.9 (1.2)	4.0 (1.2)	3.6 (1.2)	4.1 (0.9)	4.0 (1.1)	4.1 (1.0)	4.2 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	480.0 (380.0-690.0)	550.0 (380.0-590.0)	470.0 (370.0-610.0)	495.0 (370.0-680.0)	540.0 (390.0-720.0)	530.0 (410.0-800.0)	500.0 (370.0-690.0)
Total IgE, median (IQR), IU/mL	276.0 (133.0-640.0)	175.0 (115.0-348.0)	290.0 (154.0-466.0)	320.0 (81.0-593.0)	189.5 (67.0-696.0)	241.0 (100.0-505.0)	241.0 (100.0-550.0)
FeNO, median (IQR), ppb	32.0 (24.0-45.0)	30.0 (19.0-49.0)	42.0 (29.0-77.0)	32.5 (20.0-50.0)	30.0 (20.0-49.0)	38.5 (21.0-57.0)	31.0 (22.0-61.0)
Medium-dose ICS at baseline, n	33	25	29	68	134	61	129
Age, mean (SD), years	42.7 (14.5)	46.2 (16.5)	46.7 (12.0)	44.2 (17.3)	44.9 (16.2)	47.4 (14.7)	44.5 (16.8)
Age < 18 years, n (%)	0	0	0	8 (11.8)	13 (9.7)	6 (9.8)	13 (10.1)
Female sex, n (%)	18 (54.5)	14 (56.0)	20 (69.0)	39 (57.4)	79 (59.0)	37 (60.7)	75 (58.1)

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Any comorbidity medical history, [‡] n (%)	27 (81.8)	22 (88.0)	19 (67.9)	59 (86.8)	111 (82.8)	52 (85.2)	104 (80.6)
Ongoing atopic medical condition, n (%)	26 (78.8)	21 (84.0)	19 (67.9)	54 (79.4)	110 (82.1)	52 (85.2)	109 (84.5)
Prebronchodilator FEV ₁ , mean (SD), L	2.05 (0.74)	1.92 (0.59)	1.83 (0.53)	1.81 (0.72)	1.92 (0.68)	1.89 (0.62)	1.84 (0.59)
Percent predicted, mean (SD)	61.9 (11.4)	61.8 (11.0)	59.5 (11.4)	58.1 (15.6)	60.4 (12.8)	60.8 (13.5)	59.1 (13.1)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.3 (0.8)	2.3 (0.8)	2.3 (0.8)	2.2 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	30.8 (19.2)	25.4 (16.1)	27.4 (20.2)	29.9 (25.3)	26.5 (17.9)	24.4 (17.2)	24.0 (22.3)
Severe asthma exacerbations in past year, mean (SD), n	1.9 (1.7)	1.6 (1.1)	1.7 (1.3)	2.0 (1.6)	2.0 (1.9)	2.3 (2.1)	2.1 (2.7)
ACQ-5 score, [¶] mean (SD)	2.5 (0.9)	2.5 (0.8)	2.7 (0.8)	2.6 (0.7)	2.6 (0.7)	2.7 (0.7)	2.6 (0.7)
AQLQ(S) global score, ^{††} mean (SD)	4.5 (1.3)	4.2 (1.1)	4.1 (1.1)	4.5 (1.0)	4.5 (1.0)	4.4 (1.0)	4.6 (1.1)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	440.0 (370.0-570.0)	450.0 (400.0-650.0)	450.0 (350.0-580.0)	540.0 (400.0-775.0)	530.0 (370.0-750.0)	470.0 (390.0-820.0)	500.0 (370.0-730.0)
Total IgE, median (IQR), IU/mL	249.0 (116.0-448.0)	264.0 (137.0-647.0)	183.0 (86.0-318.0)	209.5 (90.0-568.0)	187.0 (77.0-606.0)	297.0 (89.0-661.0)	230.0 (94.0-568.0)
FeNO, median (IQR), ppb	43.5 (26.0-100.0)	41.0 (24.0-80.0)	30.0 (15.0-51.0)	35.0 (24.0-65.0)	35.5 (22.0-69.0)	37.5 (21.5-65.0)	33.0 (19.0-59.0)

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). [‡]Includes any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives. [§]FEV₁ (L) reversibility indicates the change in FEV₁ between prebronchodilator and postbronchodilator measurements. [¶]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 between 0 (totally controlled) and 6 (severely uncontrolled). ^{††}AQLQ(S) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = “not impaired at all” to 1 = “severely impaired”). ACQ-5, 5-item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

Supplementary Table 5 Baseline demographic and disease characteristics of patients in phase 2b and phase 3 QUEST studies on high- or medium-dose ICS and with FeNO ≥ 25 ppb at baseline

	Dupilumab phase 2b				Dupilumab phase 3 QUEST		
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
High-dose ICS at baseline, n	43	35	38	78	145	89	159
Age, mean (SD), years	50.6 (10.6)	51.5 (11.6)	48.7 (12.1)	46.5 (14.7)	48.8 (13.4)	49.0 (13.9)	48.7 (15.0)
Age < 18 years, n (%)	0	0	0	4 (5.1)	2 (1.4)	2 (2.2)	7 (4.4)
Female sex, n (%)	31 (72.1)	20 (57.1)	29 (76.3)	42 (53.8)	88 (60.7)	56 (62.9)	100 (62.9)
Any comorbidity medical history, [‡] n (%)	35 (81.4)	27 (77.1)	32 (84.2)	67 (85.9)	123 (84.8)	70 (78.7)	126 (79.2)
Ongoing atopic medical condition, n (%)	32 (74.4)	25 (71.4)	32 (84.2)	71 (91.0)	120 (82.8)	74 (83.1)	133 (83.6)
Prebronchodilator FEV ₁ , mean (SD), L	1.67 (0.49)	1.80 (0.59)	1.67 (0.44)	1.87 (0.57)	1.71 (0.56)	1.65 (0.50)	1.68 (0.59)
Percent predicted, mean (SD)	58.3 (11.1)	60.2 (12.1)	60.1 (11.6)	58.7 (11.7)	56.2 (13.9)	55.2 (13.4)	56.5 (14.1)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.2 (0.6)	2.1 (0.7)	2.1 (0.6)	2.1 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	26.6 (12.3)	27.3 (21.9)	28.8 (21.5)	24.4 (18.2)	26.8 (21.3)	26.0 (14.0)	29.1 (23.9)
Severe asthma exacerbations in past year, mean (SD), n	3.0 (3.4)	1.9 (1.1)	2.9 (2.4)	2.2 (1.7)	2.2 (1.7)	2.6 (2.4)	2.3 (1.8)
ACQ-5 score, mean (SD)	2.7 (0.8)	2.8 (0.8)	2.9 (0.9)	2.8 (0.7)	2.9 (0.9)	2.9 (0.9)	2.9 (0.8)
AQLQ(S) global score, ^{††} mean (SD)	3.9 (1.1)	4.0 (1.3)	3.9 (1.2)	4.2 (1.1)	4.2 (1.1)	4.1 (1.0)	4.1 (1.0)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/ μ L	280.0 (190.0-590.0)	370.0 (160.0-570.0)	330.0 (220.0-510.0)	365.0 (200.0-650.0)	350.0 (190.0-600.0)	410.0 (210.0-680.0)	380.0 (180.0-570.0)
Total IgE, median (IQR), IU/mL	201.0 (85.0-515.0)	151.0 (90.0-303.0)	229.0 (92.0-404.0)	286.0 (87.5-447.0)	214.5 (79.5-663.0)	223.0 (95.0-489.0)	201.0 (71.0-550.0)
FeNO, median (IQR), ppb	37.0 (30.0-50.0)	41.0 (30.0-63.0)	61.0 (39.0-77.0)	39.5 (32.0-57.0)	41.0 (30.0-57.0)	42.0 (34.0-63.0)	42.0 (30.0-65.0)
Medium-dose ICS at baseline, n	40	37	37	84	153	81	147
Age, mean (SD), years	48.2 (14.7)	47.7 (16.0)	44.1 (13.1)	46.6 (18.3)	45.5 (16.2)	46.7 (16.1)	46.2 (16.1)
Age < 18 years, n (%)	0	0	0	11 (13.1)	13 (8.5)	9 (11.1)	11 (7.5)
Female sex, n (%)	22 (55.0)	22 (59.5)	27 (73.0)	49 (58.3)	80 (52.3)	50 (61.7)	89 (60.5)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Any comorbidity medical history, [‡] n (%)	33 (86.8)	29 (80.6)	25 (67.6)	68 (81.0)	124 (81.0)	67 (82.7)	124 (84.4)
Ongoing atopic medical condition, n (%)	32 (84.2)	28 (77.8)	24 (64.9)	67 (79.8)	132 (86.3)	70 (86.4)	127 (86.4)
Prebronchodilator FEV ₁ , mean (SD), L	1.99 (0.64)	1.86 (0.48)	1.82 (0.52)	1.78 (0.72)	1.95 (0.71)	1.89 (0.61)	1.86 (0.60)
Percent predicted, mean (SD)	63.4 (11.0)	62.5 (9.8)	60.6 (11.0)	58.5 (14.5)	60.2 (13.6)	61.8 (12.7)	60.1 (11.8)
Postbronchodilator FEV ₁ , mean (SD), L	NA	NA	NA	2.2 (0.9)	2.4 (0.8)	2.3 (0.8)	2.2 (0.7)
FEV ₁ reversibility, [§] mean (SD), %	31.3 (18.7)	27.3 (15.7)	29.4 (19.4)	28.6 (22.7)	27.8 (21.0)	27.0 (20.2)	24.2 (17.5)
Severe asthma exacerbations in past year, mean (SD), n	1.8 (1.3)	1.5 (1.0)	2.1 (1.6)	2.0 (1.5)	1.9 (1.8)	2.2 (2.1)	2.1 (2.6)
ACQ-5 score, [¶] mean (SD)	2.6 (0.9)	2.5 (0.9)	2.8 (0.7)	2.6 (0.7)	2.6 (0.7)	2.5 (0.7)	2.6 (0.7)
AQLQ(S) global score, ^{††} mean (SD)	4.5 (1.2)	4.2 (1.3)	3.9 (1.1)	4.4 (1.0)	4.6 (1.0)	4.6 (0.9)	4.6 (1.1)
Biomarker levels							
Blood eosinophil count, median (IQR), cells/μL	325.0 (195.0-475.0)	280.0 (200.0-430.0)	280.0 (210.0-460.0)	370.0 (180.0-710.0)	370.0 (190.0-600.0)	320.0 (170.0-580.0)	330.0 (190.0-650.0)
Total IgE, median (IQR), IU/mL	236.0 (124.5-467.0)	264.0 (99.0-823.0)	249.0 (84.0-564.0)	224.0 (97.0-556.0)	223.0 (104.0-574.0)	279.5 (109.5-701.0)	223.5 (88.5-504.0)
FeNO, median (IQR), ppb	47.0 (37.0-87.0)	43.0 (35.0-71.0)	46.0 (31.0-58.0)	49.5 (31.5-67.5)	47.0 (32.0-71.0)	47.0 (32.0-73.0)	43.0 (31.0-65.0)

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). [‡]Includes any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives. [§]FEV₁ (L) reversibility indicates the change in FEV₁ between prebronchodilator and postbronchodilator measurements. [¶]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 between 0 (totally controlled) and 6 (severely uncontrolled). ^{††}AQLQ(S) is a patient-reported measure of asthma-specific HRQoL. Higher scores indicate better HRQoL; a global score is rated on a 7-point Likert-like scale (7 = “not impaired at all” to 1 = “severely impaired”). ACQ-5, 5-item Asthma Control Questionnaire; AQLQ[S], Asthma Quality of Life Questionnaire [Standardized]; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; HRQoL, health-related quality of life; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IQR, interquartile range; NA, not applicable; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

Supplementary Table 6 LS mean change from baseline in prebronchodilator FEV₁ (L) at Weeks 2 and 24 in the phase 2b study in patients with uncontrolled, persistent asthma, and at Weeks 2 and 52 in the phase 3 QUEST study in patients with uncontrolled, moderate-to-severe asthma on high-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels

	Dupilumab Phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Patients with high-dose ICS at baseline (ITT population)							
Baseline, Mean (SD), L	n = 77 1.70 (0.50)	n = 75 1.73 (0.54)	n = 79 1.80 (0.53)	n = 172 1.74 (0.55)	n = 317 1.69 (0.56)	n = 167 1.65 (0.50)	n = 323 1.70 (0.60)
Change from baseline at Week 2, LS mean (SE), L	n = 73 0.01 (0.04)	n = 73 0.15 (0.04)	n = 78 0.21 (0.04)	n = 172 0.11 (0.03)	n = 307 0.23 (0.02)	n = 165 0.11 (0.03)	n = 320 0.26 (0.02)
LS mean difference vs matching placebo (95% CI)		0.14 (0.03–0.24)	0.19 (0.09–0.30)		0.12 (0.05–0.18)		0.16 (0.09–0.22)
P-value vs matching placebo		P = .0108	P = .0002		P = .0004		P < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 53 0.05 (0.04)	n = 67 0.25 (0.04)	n = 73 0.27 (0.04)	n = 134 0.14 (0.03)	n = 244 0.34 (0.02)	n = 134 0.21 (0.03)	n = 244 0.34 (0.02)
LS mean difference vs matching placebo (95% CI)		0.21 (0.09–0.32)	0.22 (0.11–0.34)		0.20 (0.12–0.28)		0.13 (0.05–0.21)
P-value vs matching placebo		P = .0005	P = .0001		P < .0001		P = .0017
Patients with ≥150 eosinophils/μL and high-dose ICS at baseline							
Baseline, Mean (SD), L	n = 67 1.67 (0.50)	n = 58 1.72 (0.52)	n = 63 1.79 (0.50)	n = 126 1.73 (0.57)	n = 223 1.67 (0.54)	n = 127 1.65 (0.46)	n = 228 1.69 (0.57)
Change from baseline at Week 2, LS mean (SE), L	n = 64 -0.01 (0.04)	n = 57 0.13 (0.04)	n = 62 0.19 (0.04)	n = 126 0.09 (0.03)	n = 217 0.24 (0.02)	n = 125 0.10 (0.03)	n = 226 0.31 (0.02)
LS mean difference vs matching placebo (95% CI)		0.14 (0.02–0.25)	0.21 (0.09–0.32)		0.14 (0.07–0.22)		0.21 (0.13–0.29)
P-value vs matching placebo		P = .0178	P = .0003		P = .0003		P < .0001
Change from baseline at end of	n = 46	n = 52	n = 59	n = 98	n = 176	n = 103	n = 174

	Dupilumab Phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
treatment, LS mean (SE), L	0.04 (0.05)	0.23 (0.05)	0.23 (0.04)	0.14 (0.04)	0.37 (0.03)	0.21 (0.04)	0.38 (0.03)
LS mean difference vs matching placebo (95% CI)		0.19 (0.07–0.32)	0.19 (0.07–0.32)		0.23 (0.14–0.33)		0.16 (0.07–0.26)
<i>P</i> -value vs matching placebo		<i>P</i> = .0028	<i>P</i> = .0022		<i>P</i> < .0001		<i>P</i> = .0005
Patients with ≥300 eosinophils/μL and high-dose ICS at baseline							
	n = 35	n = 37	n = 33	n = 80	n = 128	n = 79	n = 144
Baseline, Mean (SD), L	1.69 (0.58)	1.72 (0.47)	1.71 (0.48)	1.76 (0.61)	1.69 (0.59)	1.60 (0.45)	1.66 (0.58)
Change from baseline at Week 2, LS mean (SE), L	n = 33 0.10 (0.06)	n = 36 0.19 (0.06)	n = 32 0.28 (0.06)	n = 80 0.09 (0.04)	n = 125 0.30 (0.03)	n = 79 0.08 (0.04)	n = 143 0.37 (0.03)
LS mean difference vs matching placebo (95% CI)		0.09 (–0.07 to 0.26)	0.18 (0.01–0.35)		0.21 (0.11–0.31)		0.30 (0.20–0.39)
<i>P</i> -value vs matching placebo		<i>P</i> = .2634	<i>P</i> = .0342		<i>P</i> < .0001		<i>P</i> < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 24 0.13 (0.07)	n = 33 0.32 (0.06)	n = 31 0.33 (0.07)	n = 62 0.15 (0.05)	n = 102 0.45 (0.04)	n = 65 0.21 (0.05)	n = 111 0.46 (0.04)
LS mean difference vs matching placebo (95% CI)		0.19 (0.01–0.37)	0.19 (0.01–0.38)		0.30 (0.18–0.41)		0.25 (0.14–0.37)
<i>P</i> -value vs matching placebo		<i>P</i> = .0405	<i>P</i> = .0434		<i>P</i> < .0001		<i>P</i> < .0001
Patients with FeNO ≥25 ppb and high-dose ICS at baseline							
	n = 43	n = 35	n = 38	n = 78	n = 145	n = 89	n = 159
Baseline, Mean (SD), L	1.67 (0.49)	1.80 (0.59)	1.67 (0.44)	1.87 (0.57)	1.71 (0.56)	1.65 (0.50)	1.68 (0.59)
Change from baseline at Week 2, LS mean (SE), L	n = 39 0.03 (0.05)	n = 35 0.24 (0.06)	n = 37 0.26 (0.05)	n = 78 0.09 (0.04)	n = 142 0.32 (0.03)	n = 87 0.07 (0.04)	n = 158 0.33 (0.03)
LS mean difference vs matching placebo (95% CI)		0.21 (0.06–0.36)	0.23 (0.09–0.38)		0.23 (0.13–0.33)		0.27 (0.17–0.36)
<i>P</i> -value vs matching placebo		<i>P</i> = .0052	<i>P</i> = .0016		<i>P</i> < .0001		<i>P</i> < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 27 0.08 (0.06)	n = 34 0.30 (0.06)	n = 37 0.32 (0.06)	n = 59 0.13 (0.05)	n = 109 0.49 (0.04)	n = 71 0.19 (0.05)	n = 124 0.42 (0.04)

	Dupilumab Phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
LS mean difference vs matching placebo (95% CI)		0.22 (0.05–0.39)	0.24 (0.07–0.40)		0.36 (0.23–0.48)		0.22 (0.10–0.34)
<i>P</i> -value vs matching placebo		<i>P</i> = .0100	<i>P</i> = .0050		<i>P</i> < .0001		<i>P</i> = .0002
Patients with ≥150 eosinophils/μL or FeNO ≥25 ppb and high-dose ICS at baseline							
	n = 71	n = 66	n = 68	n = 140	n = 247	n = 141	n = 257
Baseline, Mean (SD), L	1.69 (0.50)	1.74 (0.54)	1.78 (0.48)	1.75 (0.58)	1.68 (0.55)	1.65 (0.47)	1.69 (0.58)
Change from baseline at Week 2, LS mean (SE), L	n = 67 0.00 (0.04)	n = 65 0.14 (0.04)	n = 67 0.20 (0.04)	n = 140 0.11 (0.03)	n = 241 0.24 (0.02)	n = 139 0.10 (0.03)	n = 255 0.29 (0.02)
LS mean difference vs matching placebo (95% CI)		0.14 (0.03–0.24)	0.20 (0.09–0.31)		0.13 (0.06–0.20)		0.19 (0.12–0.26)
<i>P</i> -value vs matching placebo		<i>P</i> = .0129	<i>P</i> = .0002		<i>P</i> = .0005		<i>P</i> < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 49 0.05 (0.04)	n = 60 0.24 (0.04)	n = 64 0.24 (0.04)	n = 109 0.14 (0.04)	n = 192 0.37 (0.03)	n = 113 0.22 (0.04)	n = 193 0.37 (0.03)
LS mean difference vs matching placebo (95% CI)		0.18 (0.06–0.30)	0.19 (0.07–0.30)		0.24 (0.15–0.32)		0.15 (0.06–0.24)
<i>P</i> -value vs matching placebo		<i>P</i> = .0025	<i>P</i> = .0017		<i>P</i> < .0001		<i>P</i> = .001

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ITT, intention-to-treat; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation; SE, standard error.

Supplementary Table 7 LS mean change from baseline in prebronchodilator FEV₁ (L) at Weeks 2 and 24 in the phase 2b study in patients with uncontrolled, persistent asthma, and at Weeks 2 and 52 in the phase 3 QUEST study in patients with uncontrolled, moderate-to-severe asthma on medium-dose ICS at baseline and further stratified by baseline eosinophil and FeNO levels

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Patients with medium-dose ICS at baseline (ITT population)							
Baseline, mean (SD), L	n = 78 1.95 (0.58)	n = 69 1.87 (0.52)	n = 74 1.91 (0.54)	n = 144 1.80 (0.67)	n = 310 1.88 (0.66)	n = 151 1.86 (0.62)	n = 303 1.87 (0.59)
Change from baseline at Week 2, LS mean (SE), L	n = 70 0.14 (0.04)	n = 69 0.28 (0.04)	n = 71 0.25 (0.04)	n = 142 0.10 (0.03)	n = 300 0.28 (0.02)	n = 146 0.16 (0.03)	n = 298 0.30 (0.02)
LS mean difference vs matching placebo (95% CI)		0.14 (0.03–0.26)	0.11 (–0.01 to 0.22)		0.18 (0.11–0.25)		0.14 (0.07–0.21)
P-value vs matching placebo		P = .0129	P = .0617		P < .0001		P < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 69 0.21 (0.05)	n = 62 0.34 (0.05)	n = 67 0.30 (0.05)	n = 106 0.18 (0.04)	n = 233 0.38 (0.03)	n = 113 0.23 (0.04)	n = 242 0.38 (0.03)
LS mean difference vs matching placebo (95% CI)		0.13 (–0.01 to 0.26)	0.09 (–0.04 to 0.22)		0.20 (0.11–0.29)		0.14 (0.06–0.23)
P-value vs matching placebo		P = .0639	P = .1821		P < .0001		P = .0009
Patients with ≥150 eosinophils/μL and medium-dose ICS at baseline							
Baseline, mean (SD), L	n = 59 1.95 (0.62)	n = 58 1.89 (0.50)	n = 62 1.89 (0.52)	n = 105 1.82 (0.69)	n = 210 1.97 (0.68)	n = 107 1.86 (0.62)	n = 218 1.88 (0.60)
Change from baseline at Week 2, LS mean (SE), L	n = 52 0.09 (0.05)	n = 58 0.29 (0.05)	n = 59 0.23 (0.05)	n = 104 0.07 (0.04)	n = 204 0.32 (0.03)	n = 102 0.14 (0.04)	n = 214 0.29 (0.03)
LS mean difference vs matching placebo (95% CI)		0.20 (0.07–0.32)	0.14 (0.01–0.26)		0.25 (0.16–0.34)		0.15 (0.06–0.24)
P-value vs matching placebo		P = .0027	P = .0345		P < .0001		P = .0006
Change from baseline at end of treatment, LS mean (SE), L	n = 51 0.18 (0.06)	n = 53 0.34 (0.05)	n = 55 0.31 (0.05)	n = 77 0.15 (0.04)	n = 165 0.44 (0.03)	n = 79 0.25 (0.04)	n = 172 0.40 (0.03)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
LS mean difference vs matching placebo (95% CI)		0.16 (0.01–0.31)	0.13 (–0.02 to 0.28)		0.29 (0.18–0.39)		0.15 (0.05–0.25)
P-value vs matching placebo		P = .0367	P = .0859		P < .0001		P = .0042
Patients with ≥300 eosinophils/μL and medium-dose ICS at baseline							
	n = 33	n = 25	n = 29	n = 68	n = 134	n = 61	n = 129
Baseline, mean (SD), L	2.05 (0.74)	1.92 (0.59)	1.83 (0.53)	1.81 (0.72)	1.92 (0.68)	1.89 (0.62)	1.84 (0.59)
Change from baseline at Week 2, LS mean (SE), L	n = 26 0.15 (0.07)	n = 25 0.38 (0.07)	n = 26 0.32 (0.07)	n = 68 0.08 (0.04)	n = 129 0.38 (0.03)	n = 58 0.15 (0.05)	n = 126 0.35 (0.03)
LS mean difference vs matching placebo (95% CI)		0.23 (0.03–0.43)	0.17 (–0.02 to 0.36)		0.29 (0.19–0.40)		0.20 (0.09–0.32)
P-value vs matching placebo		P = .0215	P = .0834		P < .0001		P = .0004
Change from baseline at end of treatment, LS mean (SE), L	n = 28 0.30 (0.08)	n = 23 0.48 (0.09)	n = 25 0.45 (0.08)	n = 51 0.19 (0.06)	n = 104 0.51 (0.04)	n = 44 0.25 (0.06)	n = 95 0.50 (0.04)
LS mean difference vs matching placebo (95% CI)		0.19 (–0.05 to 0.42)	0.15 (–0.08 to 0.38)		0.31 (0.18–0.45)		0.25 (0.11–0.39)
P-value vs matching placebo		P = .1194	P = .1888		P < .0001		P = .0005
Patients with FeNO ≥25 ppb and medium-dose ICS at baseline							
	n = 40	n = 37	n = 37	n = 84	n = 153	n = 81	n = 147
Baseline, mean (SD), L	1.99 (0.64)	1.86 (0.48)	1.82 (0.52)	1.78 (0.72)	1.95 (0.71)	1.89 (0.61)	1.86 (0.60)
Change from baseline at Week 2, LS mean (SE), L	n = 34 0.13 (0.06)	n = 37 0.33 (0.06)	n = 34 0.38 (0.06)	n = 83 0.09 (0.04)	n = 149 0.36 (0.03)	n = 79 0.17 (0.04)	n = 143 0.39 (0.03)
LS mean difference vs matching placebo (95% CI)		0.21 (0.05–0.36)	0.25 (0.09–0.42)		0.27 (0.17–0.37)		0.22 (0.12–0.33)
P-value vs matching placebo		P = .0111	P = .0026		P < .0001		P < .0001
Change from baseline at end of treatment, LS mean (SE), L	n = 36 0.22 (0.07)	n = 34 0.35 (0.07)	n = 33 0.44 (0.07)	n = 65 0.22 (0.05)	n = 115 0.48 (0.04)	n = 65 0.25 (0.05)	n = 117 0.49 (0.04)
LS mean difference vs matching placebo		0.13	0.22 (0.04–0.41)		0.26 (0.14–0.37)		0.24 (0.12–0.35)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
(95% CI)	(-0.05 to 0.31)						
<i>P</i> -value vs matching placebo		<i>P</i> = .1482	<i>P</i> = .0189		<i>P</i> < .0001		<i>P</i> < .0001
Patients with ≥150 eosinophils/μL or FeNO ≥25 ppb and medium-dose ICS at baseline							
	n = 66	n = 62	n = 65	n = 119	n = 237	n = 123	n = 241
Baseline, mean (SD), L	1.94 (0.60)	1.88 (0.50)	1.90 (0.51)	1.80 (0.69)	1.94 (0.69)	1.86 (0.63)	1.88 (0.60)
Change from baseline at Week 2, LS mean (SE), L	n = 58 0.11 (0.04)	n = 62 0.29 (0.04)	n = 62 0.23 (0.04)	n = 117 0.08 (0.04)	n = 231 0.33 (0.03)	n = 118 0.17 (0.03)	n = 237 0.31 (0.02)
LS mean difference vs matching placebo (95% CI)		0.19 (0.07–0.31)	0.13 (0.01–0.24)		0.24 (0.16–0.33)		0.15 (0.06–0.23)
<i>P</i> -value vs matching placebo		<i>P</i> = .0021	<i>P</i> = .0352		<i>P</i> < .0001		<i>P</i> = .0005
Change from baseline at end of treatment, LS mean (SE), L	n = 57 0.18 (0.05)	n = 57 0.34 (0.05)	n = 58 0.31 (0.05)	n = 89 0.17 (0.04)	n = 184 0.44 (0.03)	n = 94 0.26 (0.04)	n = 192 0.41 (0.03)
LS mean difference vs matching placebo (95% CI)		0.16 (0.02–0.30)	0.13 (-0.01 to 0.27)		0.26 (0.17–0.36)		0.15 (0.05–0.24)
<i>P</i> -value vs matching placebo		<i>P</i> = .0272	<i>P</i> = .0708		<i>P</i> < .0001		<i>P</i> = .0023

[†]In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched). CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ITT, intention-to-treat; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation; SE, standard error.

Supplementary Table 8 Proportion of patients with asthma requiring high-dose ICS at baseline reaching clinically significant improvements (MCID ≥ 0.5) in ACQ-5 scores (responder analyses)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST [§]			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Week 12, n	77	75	79	172	317	167	323
Responders [‡] , %	54.5	70.7	79.7	65.7	76.0	68.3	75.5
Odds ratio vs placebo (95% CI)		1.99 (1.01–3.94)	3.29 (1.60–6.74)		1.68 (1.10–2.56)		1.41 (0.91–2.17)
P-value		0.0482	0.0012		0.0168		0.1199
Week 24, n	77	75	79	172	317	167	323
Responders [‡] , %	53.2	74.7	75.9	68.6	75.1	62.3	71.5
Odds ratio vs placebo (95% CI)		2.59 (1.29–5.20)	2.85 (1.43–5.68)		1.36 (0.90–2.08)		1.51 (1.00–2.26)
P-value		0.0074	0.0030		0.1486		0.0483
Week 52, n	N/A	N/A	N/A	148	280	154	284
Responders [‡] , %	N/A	N/A	N/A	66.2	69.3	63.6	66.2
Odds ratio vs placebo (95% CI)		N/A	N/A		1.11 (0.72–1.71)		1.06 (0.70–1.62)
P-value		N/A	N/A		0.6380		0.7784

[†] In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). [‡] Responders were defined as patients with improvement from baseline in ACQ-5 ≥ 0.5 . [§] Patients who were ongoing in the 52-week randomized treatment period are excluded from the responder analysis at Week 52. Patients with improvement from baseline in ACQ-5 < 0.5 or with missing value at the time point were considered as non-responders.

CI, confidence interval; ICS, inhaled corticosteroids; MCID, minimum clinically important difference; N/A, not applicable; q2w, every 2 weeks.

Supplementary Table 9 Proportion of patients with asthma requiring medium-dose ICS at baseline reaching clinically significant improvements (MCID ≥ 0.5) in ACQ-5 scores (responder analyses)

	Dupilumab phase 2b			Dupilumab phase 3 QUEST			
	Placebo [†]	Dupilumab 200 mg q2w	Dupilumab 300 mg q2w	Matching placebo to dupilumab 200 mg q2w	Dupilumab 200 mg q2w	Matching placebo to dupilumab 300 mg q2w	Dupilumab 300 mg q2w
Week 12, n	78	69	74	144	310	151	303
Responders [‡] , %	67.9	69.6	71.6	65.3	77.4	70.9	75.2
Odds ratio vs placebo (95% CI)		1.09 (0.53–2.24)	1.14 (0.56–2.31)		1.85 (1.18–2.90)		1.27 (0.81–2.00)
P-value		0.8058	0.7164		0.0071		0.2907
Week 24, n	78	69	74	144	310	151	303
Responders [‡] , %	67.9	79.7	70.3	66.0	78.4	68.9	75.2
Odds ratio vs placebo (95% CI)		2.11 (0.96–4.64)	1.06 (0.52–2.15)		1.91 (1.22–3.00)		1.39 (0.89–2.17)
P-value		0.0620	0.8756		0.0049		0.1436
Week 52, n	N/A	N/A	N/A	126	281	133	274
Responders [‡] , %	N/A	N/A	N/A	57.1	69.8	63.2	74.1
Odds ratio vs placebo (95% CI)		N/A	N/A		1.74 (1.12–2.70)		1.68 (1.07–2.63)
P-value		N/A	N/A		0.0137		0.0230

[†] In the phase 2b study, the same amount of placebo was given regardless of dupilumab dose (not volume-matched as in the phase 3 QUEST study). [‡] Responders were defined as patients with improvement from baseline in ACQ-5 ≥ 0.5 . Patients with improvement from baseline in ACQ-5 < 0.5 or with missing value at the time point were considered as non-responders.

CI, confidence interval; ICS, inhaled corticosteroids; MCID, minimum clinically important difference; ; N/A, not applicable; q2w, every 2 weeks.