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Original Article

Dupilumab efficacy and safety in Japanese patients with uncontrolled, moderate-to-severe asthma in the phase 3 LIBERTY ASTHMA QUEST study

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ACQ-5, 5-item Asthma Control Questionnaire; AQLQ(S), Standardized Asthma Quality of Life Questionnaire; GINA, Global Initiative for Asthma; ITT, intention-to-treat; LS, least squares; MedDRA, Medical Dictionary for Regulatory Activities; MMRM, mixed-effects model with repeated measures; ppb, parts per billion; q2w, every 2 weeks; TEAE, treatment-emergent adverse event

ABSTRACT

Background: In the LIBERTY ASTHMA QUEST (ClinicalTrials.gov: NCT02414854) study, dupilumab 200 mg and 300 mg every 2 weeks vs matched-volume placebo reduced severe asthma exacerbations and improved lung function (FEV₁), asthma control, and quality of life in patients with uncontrolled, moderate-to-severe asthma (N = 1902). Here, we examine the safety and efficacy of dupilumab in the subpopulation of Japanese patients who participated in QUEST (n = 114; 6%).

Methods: Endpoints assessed were annualized severe exacerbation rates and the effect of treatment over the 52-week treatment period on FEV₁, asthma control, asthma-related quality of life, and markers of type 2 inflammation.

Results: In Japanese patients, dupilumab 200 and 300 mg every 2 weeks vs matched placebo reduced severe asthma exacerbation rates by 44% (P = 0.33) and 75% (P = 0.03), respectively, and improved FEV₁ at Week 12 by 0.20 L (P = 0.05) and 0.17 L (P = 0.12). FEV₁ improvements were rapid (by Week 2) and sustained throughout treatment. Significant and/or numerical improvements vs placebo in asthma control and quality of life were also observed throughout treatment. For each endpoint, greater efficacy was observed in patients with elevated baseline levels of type 2 inflammatory biomarkers (blood eosinophils or FeNO). Dupilumab treatment significantly reduced levels of FeNO and total IgE, but not blood eosinophils.

Conclusions: In this subanalysis of QUEST, the efficacy and safety of dupilumab in Japanese patients was comparable to that observed in the overall intention-to-treat population, suggesting no variability in efficacy on the basis of Japanese ethnicity.

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Introduction

It is estimated that approximately 8% of the Japanese population have asthma and the prevalence of asthma in Japan is rapidly increasing at a rate of approximately 1.5-fold per decade.¹

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Current standard of care for both adults and adolescents with asthma recommends a stepwise approach beginning with short-acting β_2 -agonists (SABAs) in combination with inhaled corticosteroids (ICS), or increasing doses of ICS and long-acting β_2 -agonists (LABAs).^{1–3} Despite optimized use of ICS and LABA, however, asthma symptoms remain uncontrolled in a significant proportion of patients,⁴ leaving them with a substantial disease burden and reduced quality of life.⁵ Patients with uncontrolled asthma are at increased risk of asthma exacerbations and have significant morbidity that increases over time, placing a significant burden on both patients and their national healthcare system.⁶ Therefore, there is a need for novel treatments to improve the long-term health of patients with inadequately controlled, moderate-to-severe asthma.

Type 2 inflammation is common in many patients with asthma, and also in patients with atopic dermatitis, allergic rhinitis, and food allergies—conditions that are often associated as comorbidities in patients with asthma.⁷ Several biomarkers of type 2 inflammation have been identified, including blood and sputum eosinophils and fractional exhaled nitric oxide (FeNO), that can be used to assess the potential response to treatment in patients with uncontrolled asthma.⁸

Dupilumab, a fully human VelocImmune[®]-derived^{9,10} monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4 and IL-13, key drivers of type 2 inflammation in multiple diseases.¹¹ It is approved in Japan for patients aged ≥ 12 years with severe or refractory asthma whose symptoms are inadequately controlled with existing therapies,¹² and by the US Food and Drug Administration¹³ 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.^{8,14–16} In the EU, dupilumab is indicated as an 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 that are inadequately controlled with high-dose ICS plus another medicinal product for maintenance treatment.¹⁷ Dupilumab is also approved in the USA as an add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyps,^{13,18} and for the treatment of patients with inadequately controlled, moderate-to-severe atopic dermatitis, aged ≥ 12 years in the USA,¹³ and adults in the EU¹⁷ and other countries.^{19–21}

In a phase 3 randomized, double-blind, placebo-controlled study, LIBERTY ASTHMA QUEST (ClinicalTrials.gov: NCT02414854), treatment with dupilumab at either a dose of 200 mg or 300 mg every 2 weeks (q2w) reduced annualized severe exacerbation rates and improved lung function in the overall population.⁸ Furthermore, treatment effects were greater in patients with elevated type 2 biomarkers at baseline (blood eosinophils ≥ 150 cells/ μ L or FeNO ≥ 25 parts per billion [ppb]). Dupilumab was generally well tolerated in the safety population of the QUEST study.

This paper presents the outcomes in the subpopulation of Japanese patients with moderate-to-severe asthma who participated in the LIBERTY ASTHMA QUEST study. It assessed the effect of dupilumab treatment on the annual rate of severe exacerbations and change in forced expiratory volume in 1 second (FEV₁), as well as the impact of dupilumab on overall asthma control and health-related quality of life in Japanese patients.

Methods

Study design and patients

LIBERTY ASTHMA QUEST was a phase 3 multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-

group trial (ClinicalTrials.gov: NCT02414854). Here, we present the results of prespecified and post hoc analyses from the subpopulation of Japanese patients (i.e. patients of Asian ethnicity enrolled in centers in Japan) who participated in QUEST.

Full details of the LIBERTY ASTHMA QUEST study design and methodology have previously been published.^{8,22} In brief, after a 4-week screening period (± 1 week), a total of 1902 eligible patients ≥ 12 years of age with uncontrolled asthma were randomized in a 2:2:1:1 ratio to receive 52 weeks of add-on treatment with subcutaneous injections of dupilumab 200 mg (400 mg loading dose) or 300 mg (600 mg loading dose) q2w or a matched-volume placebo. Full inclusion criteria have been published previously^{8,22} and are detailed further in Supplementary Text 1. Briefly, eligible patients were those with physician-diagnosed asthma for ≥ 12 months whose asthma was persistent despite having received medium-to-high-dose ICS in combination with at least one other asthma controller medicine for at least 3 months. Patients were allowed to administer albuterol/salbutamol or levalbuterol/levo-salbutamol (metered-dose inhaler) as reliever medication; all use of reliever medications was documented by the patient in an electronic diary. Patients who use OCS were excluded at randomization.

LIBERTY ASTHMA QUEST was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization of Good Clinical Practice guidelines. Hence, the appropriate local institutional review boards and ethics committees approved the trial procedures and documentation for each participating country, and written informed consent was obtained from all patients (or their legal guardians) before participation. The study was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.; clinical trial data were collected by the study investigators and analyzed by the sponsors.

Study endpoints

Prespecified efficacy endpoints analyzed were the annualized rate of severe asthma exacerbations during the 52-week treatment period and change from baseline in pre-bronchodilator FEV₁ at Week 12. Severe exacerbations were defined as requiring the use of systemic corticosteroids for ≥ 3 days, or hospitalization or an emergency room visit because of asthma, requiring systemic corticosteroids. Change from baseline in pre-bronchodilator FEV₁ over the 52-week treatment period for the Japanese subpopulation was assessed post hoc.

Patient-reported outcomes over the 52-week treatment period (post hoc analyses) were assessed using the 5-item Asthma Control Questionnaire (ACQ-5) and the Standardized Asthma Quality of Life Questionnaire (AQLQ[S]). The ACQ-5 is a patient-reported measure of the adequacy of and change in asthma control that occur either spontaneously or as a result of treatment. Global scores range from 0 to 6, with higher scores indicating less asthma control.²³ The AQLQ(S) is a self-administered patient-reported outcome that measures functional impairments that are most troublesome to the patient as a result of their asthma. Global scores range from 1 to 7, with higher scores indicating better quality of life.²⁴ The minimal clinically importance difference for both questionnaires^{23,24} is 0.5. The effect of treatment over time on circulating levels of type 2 inflammation biomarkers (FeNO, serum total immunoglobulin E [IgE], and blood eosinophil counts) was also assessed post hoc, as superior efficacy had been observed in patients with elevated type 2 biomarkers in the overall population of QUEST.⁸ The annualized rate of severe exacerbations, pre-bronchodilator FEV₁, ACQ-5, and AQLQ(S) were also assessed post hoc in subgroups of Japanese patients with baseline eosinophil counts of ≥ 300 cells/ μ L or baseline FeNO levels of ≥ 25 ppb. Safety was evaluated based on the

incidence of treatment-emergent adverse events (TEAEs) and serious TEAEs, which were reported as a high-level term in the Medical Dictionary for Regulatory Activities (MedDRA), version 20.0.

Statistical analysis

Efficacy analyses were performed in the subgroup of Japanese patients in the overall intention-to-treat (ITT) population of QUEST, defined as all patients who underwent randomization. Data were analyzed according to the assigned intervention, whether an intervention was received or not. A negative binomial regression model was used to analyze the annualized rate of severe asthma exacerbations. All severe exacerbation events that occurred during the 52-week treatment period were included, regardless of whether the patient was on treatment or not. The total number of events onset from randomization up to Visit 18 or last contact date (whichever came earlier) were defined as the response variable, with the treatment groups, age, baseline eosinophil strata, baseline ICS dose level, and number of severe exacerbation events within 1 year prior to the study as covariates, and log-transformed standardized observation duration as an offset variable.

For the pre-specified analysis of change from baseline in FEV₁ at Week 12, least squares (LS) mean values were derived from a mixed-effects model with repeated measures (MMRM). Change from baseline in pre-bronchodilator FEV₁ values up to Week 12 was the response variable, and treatment, age, sex, baseline height, baseline eosinophil strata, baseline ICS dose level, visit, treatment by-visit interaction, baseline pre-bronchodilator FEV₁ value, and baseline-by-visit interaction were included as covariates. Post hoc analyses of change from baseline in continuous variables, including FEV₁ up to Week 52 and patient-reported outcomes, were reported as LS mean values derived from an MMRM. Change from baseline in pre-bronchodilator FEV₁ values up to Week 52 was the response variable, and treatment, age, sex, baseline height, baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline pre-bronchodilator FEV₁ value, and baseline-by-visit interaction were included as covariates. Change in asthma control (ACQ-5 score) and asthma-related quality of life (AQLQ[S] score) were also analyzed using MMRM, with change from baseline in ACQ-5 or AQLQ(S), respectively, up to Week 52 as the response variable, and treatment, age, baseline eosinophil strata, baseline ICS dose level, visit, treatment-by-visit interaction, baseline ACQ-5 or AQLQ(S) scores, respectively, and baseline-by-visit interaction included as covariates.

Median values (with 95% confidence intervals) were reported up to Week 52 for biomarker levels in the exposed population (defined as all patients exposed to study medication) of the Japanese population. The difference between dupilumab and matched placebo in change from baseline for each biomarker was analyzed based on a rank ANCOVA model adjusted for baseline biomarker, age, sex, baseline eosinophil strata, and baseline ICS dose level. A *P*-value of <0.05 for the comparison between each dupilumab dose and placebo (within each subgroup) was considered nominally statistically significant.

The safety population included all patients who received ≥1 dose or part of a dose of investigational treatment, analyzed according to the treatment received.

Results

Patient characteristics

Of the 1902 patients enrolled in the LIBERTY ASTHMA QUEST study, 114 (6%) were Japanese. Baseline demographics and clinical

characteristics for Japanese patients are shown in [Table 1](#) and [Supplementary Table 1](#). Patient characteristics were generally similar between the treatment arms. The mean (SD) age of the Japanese patients was 48.4 (16.4) years; 45 (39.5%) were male and 5 (4.4%) were adolescents; and the mean body mass index (BMI) (SD) was 25.11 (5.67) kg/m². The mean (SD) number of severe asthma exacerbations in the previous year in Japanese patients was 2.62 (2.97). Japanese patients had a median (Q1–Q3) baseline FeNO level of 29.5 (18.0–54.0) ppb, and median (Q1–Q3) baseline eosinophils of 250 (110–690) cells/μL.

Severe asthma exacerbations

In Japanese patients, dupilumab 200 mg and 300 mg q2w reduced annualized severe exacerbation rates vs matched-volume placebo during the 52-week treatment period (adjusted annualized rate of severe exacerbations: 0.46 vs 0.82, and 0.31 vs 1.23, respectively; [Fig. 1A](#)). The relative risk reductions vs matched-volume placebo for the 200 mg and 300 mg q2w dupilumab doses in Japanese patients were 44% (*P* = 0.33) and 75% (*P* = 0.03), respectively. Due to the low numbers of patients in each treatment group, a post hoc analysis was performed comparing combined dupilumab doses with combined placebo doses to increase statistical power, providing a relative risk reduction of 62% (*P* = 0.03) for combined dupilumab vs combined placebo ([Supplementary Fig. 1A](#)).

In Japanese patients with baseline blood eosinophil levels ≥300 cells/μL, dupilumab 200 mg and 300 mg q2w reduced adjusted annualized severe exacerbation rates vs matched-volume placebo during the 52-week treatment period (0.31 vs 1.43, and 0.03 vs 1.85, respectively; [Fig. 1B](#)). The magnitudes of these risk reductions were greater than those in the overall Japanese population, with relative risk reductions vs matched-volume placebo of 79% (*P* = 0.07) and 99% (*P* < 0.01) for dupilumab 200 mg and 300 mg q2w groups, respectively, as well as 91% (*P* < 0.001) for the analysis of combined dupilumab vs combined placebo groups ([Supplementary Fig. 1B](#)).

In the subgroup of Japanese patients with baseline FeNO levels ≥25 ppb, dupilumab 200 mg and 300 mg q2w reduced adjusted annualized severe exacerbation rates vs matched-volume placebo during the 52-week treatment period by 0.28 vs 1.07, and 0.15 vs 1.12, respectively ([Fig. 1C](#)). These equate to relative risk reductions vs matched-volume placebo of 74% (*P* = 0.07) and 87% (*P* < 0.01), respectively, as well as 81% (*P* < 0.01) for the analysis of the combined dose groups ([Supplementary Fig. 1C](#)). As with the subgroup of patients with elevated baseline blood eosinophils, these reductions were of greater magnitude than those observed in the overall Japanese subgroup. No significant differences in annualized event rates of severe exacerbation were seen for dupilumab 200 mg and 300 mg q2w vs placebo in patients with baseline blood eosinophil levels <300 cells/μL or FeNO <25 ppb ([Supplementary Table 2](#)).

Pre-bronchodilator FEV₁

Improvements in pre-bronchodilator FEV₁ were observed at Week 12 in dupilumab-vs placebo-treated Japanese patients ([Fig. 2A](#)). LS mean difference vs placebo was 0.20 L for the dupilumab 200 mg q2w dose group and 0.17 L for the 300 mg q2w dose group (*P* = 0.05 and *P* = 0.12, respectively), and 0.18 L (*P* = 0.02) for the analysis of the combined dupilumab doses ([Supplementary Fig. 2A](#)).

Greater improvements in pre-bronchodilator FEV₁ were observed at Week 12 in Japanese patients with baseline blood eosinophil levels ≥300 cells/μL and baseline FeNO levels ≥25 ppb ([Fig. 2B,C](#)). Despite the low patient numbers in the subgroup of

Table 1
Selected baseline demographic and clinical characteristics of the Japanese ITT population.

Characteristic	Japanese ITT population						Overall (N = 114)
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		
	Placebo (n = 19)	Dupilumab (n = 37)	Placebo (n = 17)	Dupilumab (n = 41)	Placebo (n = 36)	Dupilumab (n = 78)	
Age (years)	47.1 (16.9)	49.0 (16.0)	51.4 (12.9)	47.2 (18.2)	49.1 (15.1)	48.1 (17.1)	48.4 (16.4)
Male, n (%)	8 (42.1)	19 (51.4)	5 (29.4)	13 (31.7)	13 (36.1)	32 (41.0)	45 (39.5)
Pre-bronchodilator FEV ₁ (L)	1.58 (0.44)	1.77 (0.70)	1.76 (0.43)	1.75 (0.64)	1.66 (0.44)	1.76 (0.66)	1.73 (0.60)
Pre-bronchodilator FEV ₁ percent predicted (%)	60.32 (13.02)	59.11 (14.24)	66.59 (8.31)	65.17 (13.17)	63.28 (11.35)	62.29 (13.93)	62.61 (13.13)
FEV ₁ reversibility (%)	21.00 (11.44)	20.63 (19.64)	21.55 (17.95)	20.11 (17.54)	21.26 (14.65)	20.35 (18.44)	20.64 (17.28)
No. of exacerbations in past year	2.68 (2.38)	2.35 (1.98)	3.00 (3.26)	2.68 (3.80)	2.83 (2.79)	2.53 (3.06)	2.62 (2.97)
High-dose ICS use, n (%)	9 (47.4)	16 (43.2)	6 (35.3)	15 (36.6)	15 (41.7)	31 (39.7)	46 (40.4)
ACQ-5 [†] total score	2.28 (0.59)	2.20 (0.45)	2.56 (0.69)	2.22 (0.57)	2.42 (0.65)	2.21 (0.51)	2.28 (0.56)
AQLQ(S) [‡] global score	4.62 (0.78)	5.17 (0.91)	4.64 (0.93)	5.03 (0.91)	4.63 (0.84)	5.10 (0.91)	4.95 (0.91)
Ongoing atopic or allergic condition [§] , n (%)	18 (94.7)	33 (89.2)	13 (76.5)	36 (87.8)	31 (86.1)	69 (88.5)	100 (87.7)
Nasal polyposis or CRS, n (%)	2 (10.5)	12 (32.4)	7 (41.2)	8 (19.5)	9 (25.0)	20 (25.6)	29 (25.4)
Former smoker, n (%)	6 (31.6)	10 (27.0)	6 (35.3)	4 (9.8)	12 (33.3)	14 (17.9)	26 (22.8)
Number of pack-years	5.74 (3.65)	3.30 (2.38)	1.43 (1.04)	5.19 (3.44)	3.59 (3.41)	3.84 (2.72)	3.72 (3.00)
BMI (kg/m ²)	25.32 (5.08)	24.81 (4.26)	26.08 (7.55)	24.88 (6.30)	25.68 (6.29)	24.85 (5.39)	25.11 (5.67)
Biomarker levels							
FeNO (ppb), median (Q1–Q3)	25.0 (15.0–51.0)	28.0 (19.0–49.0)	41.0 (25.0–84.0)	37.0 (17.0–53.0)	35.0 (19.0–67.5)	29.0 (18.0–53.0)	29.5 (18.0–54.0)
Total IgE (IU/mL), median (Q1–Q3)	456 (189–924)	331 (124–1043)	200 (78–248)	323 (139–504)	240 (136–595)	326 (124–606)	303 (124–606)
Blood eosinophil count (cells/ μL), median (Q1–Q3)	280 (150–1040)	250 (100–670)	280 (120–800)	250 (110–490)	280 (135–840)	250 (100–600)	250 (110–690)

Values are shown as mean (SD), unless stated otherwise.

ACQ-5, 5-item Asthma Control Questionnaire; AQLQ(S), Standardized Asthma Quality of Life Questionnaire; BMI, body mass index; ICS, inhaled corticosteroids; CRS, chronic rhinosinusitis; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.

[†] ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or because of treatment. Higher scores indicate less control; a total score is calculated ranging from 0 to 6; the minimal clinically important difference is 0.5.

[‡] AQLQ(S) is a patient-reported measure of the impact of asthma on quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7; the minimal clinically important difference is 0.5.

[§] A patient is considered to have ongoing atopic medical condition if he/she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic esophagitis, food allergy, hives; or has baseline total IgE (≥ 100 IU/mL) and at least one aeroantigen-specific IgE is positive (≥ 0.35 IU/mL) at baseline.

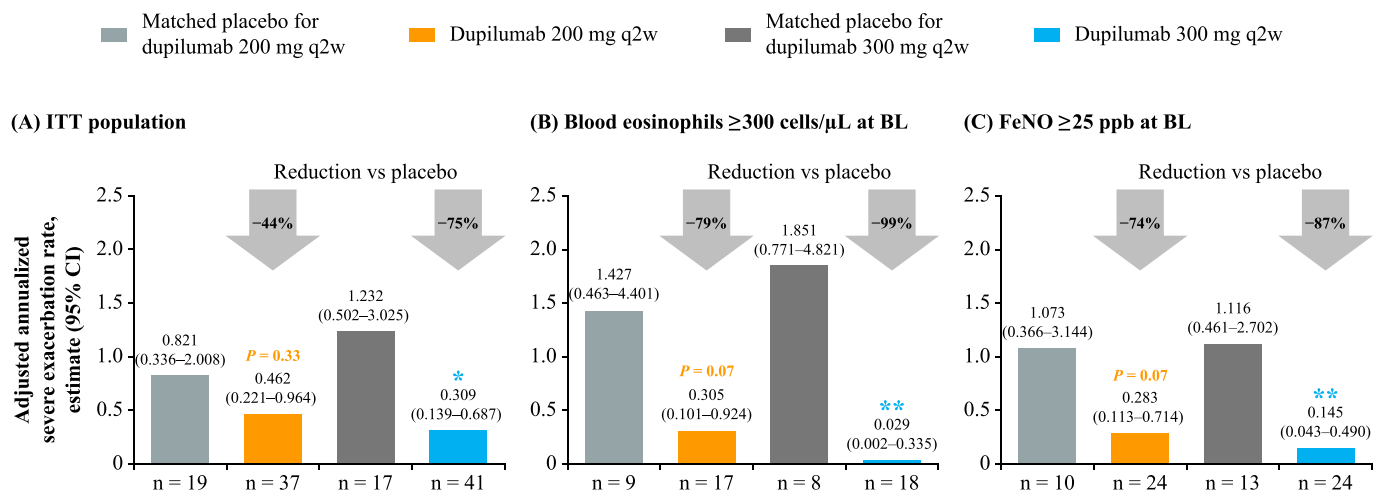


Fig. 1. Reduction of annualized rate of severe exacerbations during the 52-week intervention period in (A) the Japanese ITT population, (B) Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and (C) Japanese patients with FeNO levels ≥ 25 ppb. * $P < 0.05$; ** $P < 0.01$ vs matched placebo. BL, baseline; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion; q2w, every 2 weeks.

patients with baseline blood eosinophils ≥ 300 cells/ μ L, the improvements in pre-bronchodilator FEV₁ at Week 12 observed in these patients were statistically significant vs matched placebo for both the 200 mg and 300 mg q2w dupilumab doses ($P < 0.01$ and $P = 0.02$, respectively). In patients with baseline FeNO levels ≥ 25 ppb, the improvement in pre-bronchodilator FEV₁ at Week 12

was statistically significant vs matched placebo for the dupilumab 300 mg q2w dose group ($P = 0.03$). A significant improvement vs placebo was also observed in the analysis of the combined dupilumab dose group for Japanese patients with either elevated eosinophils or FeNO at baseline ($P < 0.001$ and $P < 0.01$, respectively; [Supplementary Fig. 2B,C](#)). No significant differences were seen for

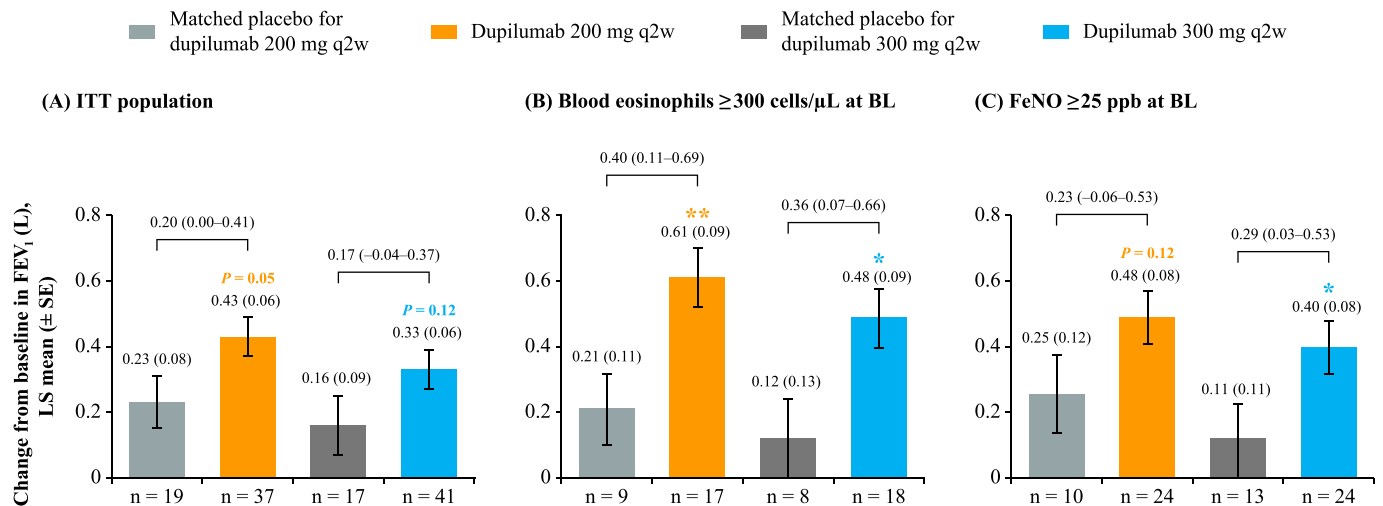


Fig. 2. Magnitude of change from baseline in pre-bronchodilator FEV₁ at Week 12 in (A) the Japanese ITT population, (B) Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and (C) Japanese patients with FeNO levels ≥ 25 ppb. * $P < 0.05$; ** $P < 0.01$ vs matched placebo. BL, baseline; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; q2w, every 2 weeks; SE, standard error.

dupilumab 200 mg and 300 mg q2w vs placebo in patients with baseline blood eosinophil levels < 300 cells/ μ L or FeNO < 25 ppb (Supplementary Table 2).

Improvements in pre-bronchodilator FEV₁ occurred rapidly; these were observed by the first assessment at Week 2 and sustained throughout the 52-week treatment period (Fig. 3). This was also the case in the analysis of combined doses (Supplementary Fig. 3).

Asthma control (ACQ-5 scores)

In Japanese patients, both doses of dupilumab significantly reduced ACQ-5 scores (indicating an improvement in asthma control) by Week 12 vs matched placebo, with an LS mean of -1.40 vs -0.72 and -1.21 vs -0.52 for the 200 mg q2w and 300 mg q2w doses, respectively (both $P < 0.01$) (Supplementary Fig. 4A). At Week 52, non-significant, numerical improvements were observed in both dose groups (-1.57 vs -1.06 and -1.29 vs -1.10 , respectively). Similar findings were observed in the analysis of combined dupilumab groups (Supplementary Fig. 5A).

A similar pattern of early and sustained improvement in ACQ-5 scores was seen in the subgroups of Japanese patients with eosinophils ≥ 300 cells/ μ L and FeNO ≥ 25 ppb at baseline (Supplementary Fig. 4B,C), with the magnitude of improvement greater in these subgroups than observed in the overall Japanese subgroup. In Japanese patients with baseline blood eosinophils ≥ 300 cells/ μ L, the LS mean difference in ACQ-5 score vs matched placebo was statistically significant at Week 12 for both dupilumab 200 mg q2w ($P < 0.05$) and dupilumab 300 mg q2w ($P < 0.001$). In Japanese patients with elevated FeNO at baseline, the LS mean difference in ACQ-5 score vs matched placebo at Week 12 was also statistically significant for both dupilumab doses (both $P < 0.01$). Statistically significant improvements vs placebo were also observed at Week 12 in the combined dupilumab group for patients with elevated baseline levels of eosinophils or FeNO (both $P < 0.001$) (Supplementary Fig. 5B,C). At Week 12, the LS mean difference to placebo was statistically significant for dupilumab 200 mg q2w in patients with baseline blood eosinophil levels < 300 cells/ μ L ($P = 0.02$; Supplementary Table 2). No significant differences in changes from baseline rates were seen for dupilumab 200 mg and 300 mg q2w vs placebo in patients with baseline FeNO < 25 ppb (Supplementary Table 2).

Asthma-related quality of life (AQLQ[S] score)

In Japanese patients, both doses of dupilumab improved AQLQ(S) scores by Week 12 relative to placebo (0.20 [$P = 0.36$] and 0.48 [$P = 0.03$] points vs matched placebo for dupilumab 200 mg q2w and 300 mg q2w, respectively), with this effect sustained to Week 52 (0.27 [$P = 0.25$] and 0.33 [$P = 0.16$], respectively) (Supplementary Fig. 6A). Early and sustained improvements in total AQLQ(S) scores vs matched placebo were also observed in the subgroups of Japanese patients with baseline eosinophil levels ≥ 300 cells/ μ L or baseline FeNO ≥ 25 ppb (Supplementary Fig. 6B,C). As with the ACQ-5 data, greater improvements in AQLQ(S) scores were observed in these subgroups of patients compared with the overall Japanese subgroup. In patients treated with dupilumab 300 mg q2w, the improvements in AQLQ(S) were statistically significant vs placebo at Week 12 in patients with elevated eosinophils or elevated FeNO at baseline ($P < 0.001$ and $P < 0.01$, respectively). Numerical but non-significant improvements were observed for patients treated with dupilumab 200 mg q2w in either subgroup of patients with elevated baseline biomarkers. In the analysis of the combined dupilumab dose groups, statistically significant improvements in AQLQ(S) score vs placebo were observed at Week 12 in the overall subgroup of Japanese patients ($P < 0.05$) as well as in either subgroup of patients with elevated baseline biomarkers (both $P < 0.01$) (Supplementary Fig. 7). No significant differences were seen for dupilumab 200 mg and 300 mg q2w vs placebo in patients with baseline blood eosinophil levels < 300 cells/ μ L or FeNO < 25 ppb (Supplementary Table 2).

Biomarkers of type 2 inflammation

Relative to baseline levels (shown in Supplementary Table 3), treatment with dupilumab (200 mg q2w or 300 mg q2w) significantly reduced the levels of type 2 inflammation biomarkers, such as FeNO and total serum IgE at Week 12, compared with matched placebo. Japanese patients treated with dupilumab (q2w 200 mg, 300 mg, or combined groups) showed a greater reduction in FeNO from baseline to Week 12 compared with those receiving matched placebo, with the improvements sustained through to Week 52. These improvements were statistically significant for the dupilumab 300 mg q2w dose and combined groups at both Week 12 and

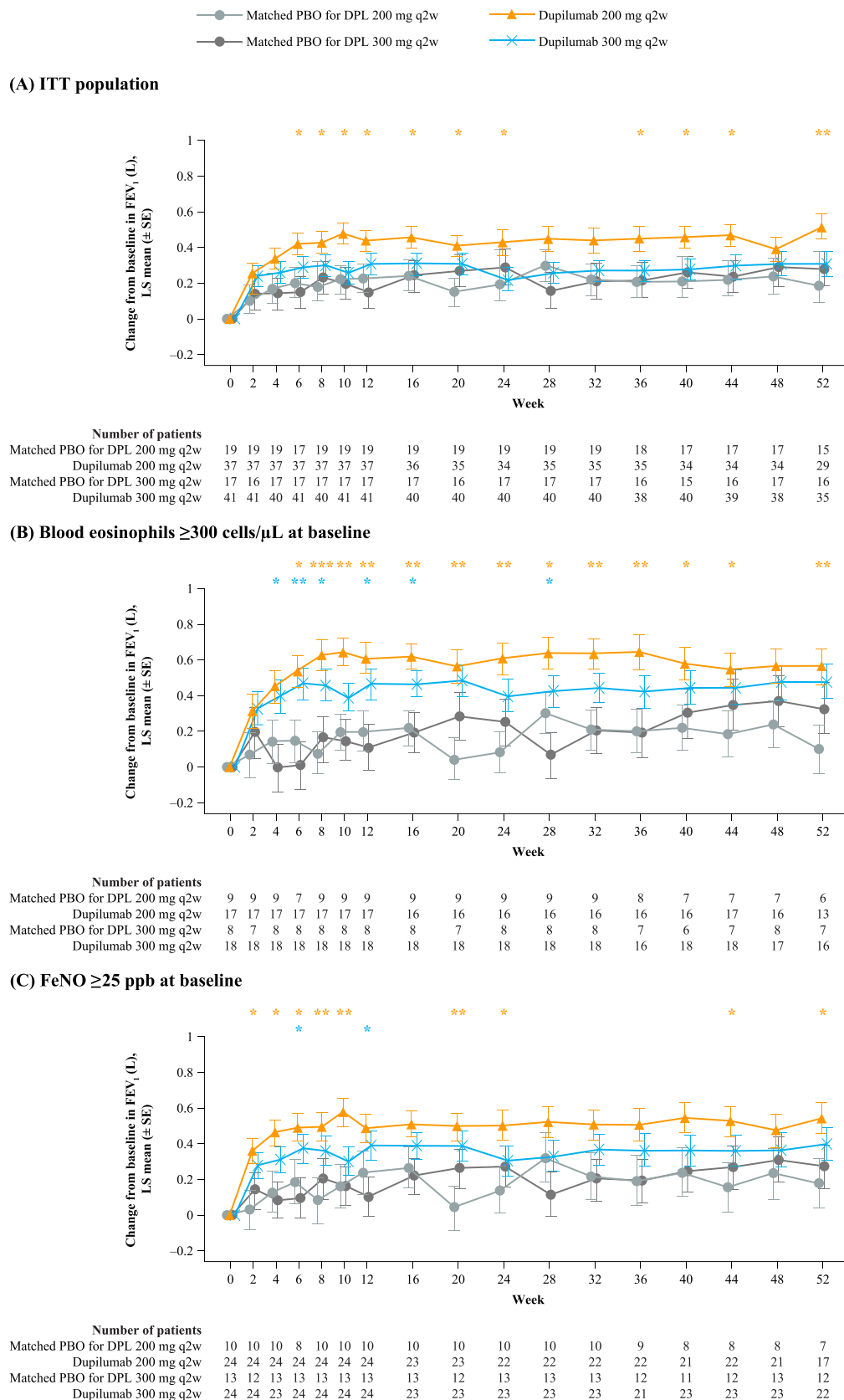


Fig. 3. Change from baseline in pre-bronchodilator FEV₁ during the 52-week intervention period in (A) the Japanese ITT population, (B) Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and (C) Japanese patients with FeNO levels ≥ 25 ppb. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo. DPL, dupilumab; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.

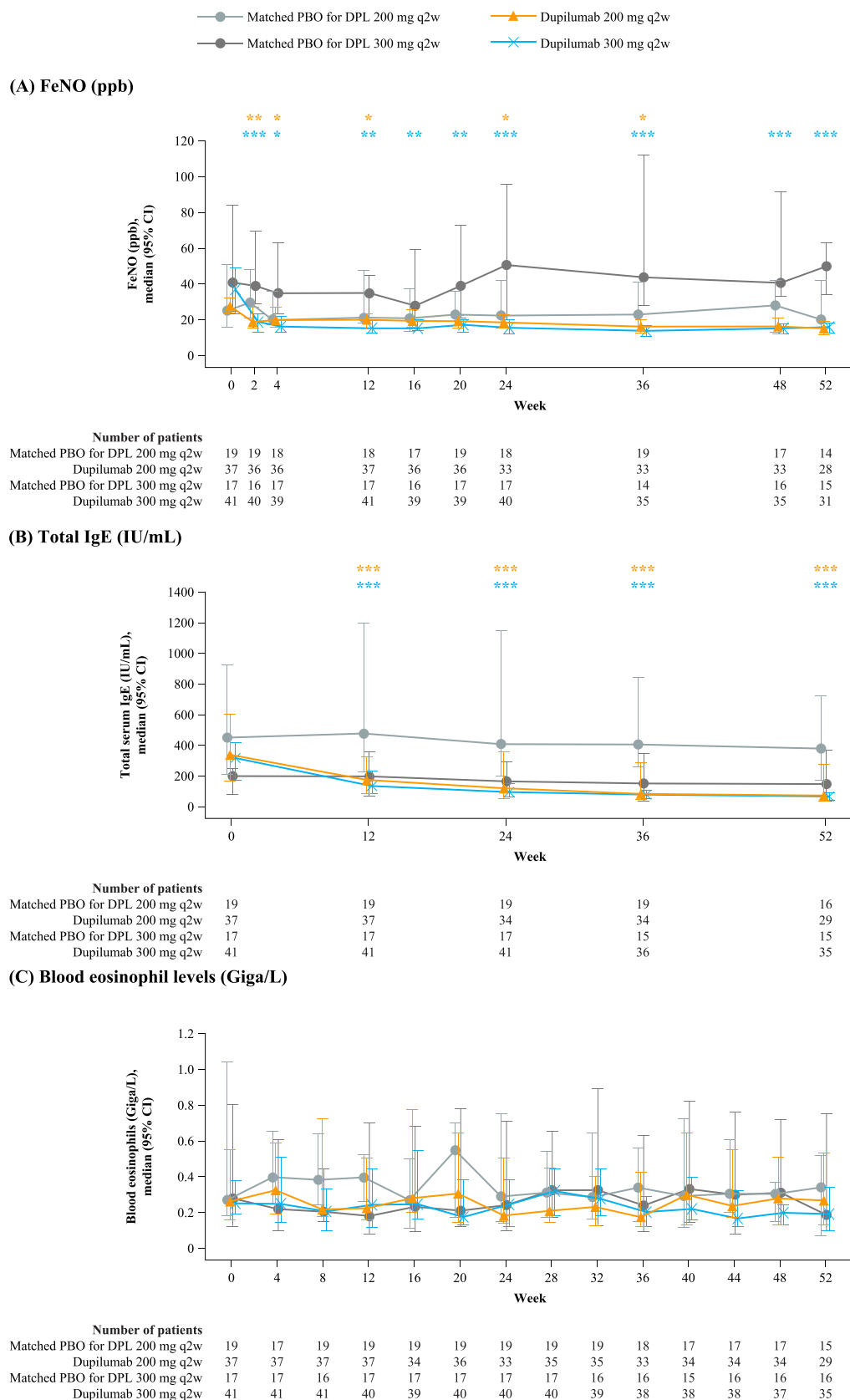


Fig. 4. Change from baseline in biomarkers of type 2 inflammation: (A) FeNO, (B) serum total IgE, and (C) blood eosinophils, during the 52-week intervention period in the Japanese population (exposed population) for dupilumab 200 mg q2w and 300 mg q2w doses vs matched placebo. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo. P-values were adjusted by (A) baseline FeNO, (B) baseline serum total IgE, or (C) baseline blood eosinophils, respectively, and age, sex, baseline eosinophil strata, and baseline ICS dose level comparing dupilumab vs matched placebo. CI, confidence interval; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks.

52 compared with matched placebo (Week 12: $P < 0.01$ and $P < 0.001$, respectively; Week 52: $P < 0.001$ and $P < 0.0001$, respectively) (Fig. 4A, Supplementary Fig. 8A). In patients with baseline eosinophil counts <300 cells/ μ L, numerical reductions in FeNO levels were observed at Week 52 (Supplementary Table 2).

Levels of total serum IgE were significantly reduced in Japanese patients treated with dupilumab when compared with matched placebo ($P < 0.001$) over the 52-week treatment period in all treatment groups (Fig. 4B, Supplementary Fig. 8B). A significant reduction in total serum IgE level at Week 52 was also observed in patients with eosinophil levels of <300 cells/mL at baseline, and in patients with baseline FeNO levels <25 ppb and receiving 200 mg dupilumab q2w, but not 300 mg dupilumab q2w (Supplementary Table 2). Levels of blood eosinophils remained close to baseline levels in all treatment arms throughout the 52-week intervention period (Fig. 4C, Supplementary Fig. 8C). Similar results were observed in patients with eosinophil levels of <300 cells/ μ L or FeNO levels <25 ppb at baseline (Supplementary Table 2).

Safety in the overall Japanese population

The incidence of adverse events in the Japanese ITT population was similar across intervention groups (89.7% in the combined dupilumab groups and 94.4% in the combined placebo groups) (Table 2). Adverse events leading to permanent treatment discontinuation were observed in 9.0% (7/78) of patients in the dupilumab group vs 2.8% (1/36) of patients in the placebo group. Reasons for permanent discontinuation were herpes zoster infection ($n = 1$), adenocarcinoma of the colon ($n = 1$), rectal tubular

adenocarcinoma ($n = 1$), small intestine carcinoma ($n = 1$), anaphylactic reaction ($n = 1$), episcleritis ($n = 1$), pregnancy ($n = 1$), and injection-site erythema and pruritus ($n = 1$). Narratives for the 8 patients are provided in Supplementary Text 2. No patients experienced adverse events leading to death. The most frequent adverse event irrespective of treatment received was viral upper respiratory tract infection (56.4% in dupilumab-treated patients vs 55.6% in the placebo groups). The most frequent adverse event that also occurred at higher rates among dupilumab-treated patients was injection-site reaction (observed in 21.6% of patients receiving dupilumab 200 mg q2w vs none of those receiving matched placebo, and by 12.2% of patients receiving dupilumab 300 mg q2w vs 5.9% of those receiving matched placebo). Eosinophilia was reported as a TEAE by 2.6% of patients (2/78) who received dupilumab vs no patients who received placebo; 2 events occurred in one of the patients. None of the events were considered serious or resulted in permanent discontinuation of dupilumab; all 3 events were of mild intensity and each resolved. Patient narratives for the 2 patients are provided in Supplementary Text 3.

Discussion

This analysis of the LIBERTY ASTHMA QUEST phase 3, randomized, placebo-controlled trial was carried out to assess the efficacy and safety of add-on treatment with dupilumab in Japanese patients with uncontrolled, moderate-to-severe asthma despite medium- or high-dose ICS and up to 2 additional controller medications.

Table 2
Treatment-emergent adverse events (safety population).

	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo (n = 19)	Dupilumab (n = 37)	Placebo (n = 17)	Dupilumab (n = 41)	Placebo (n = 36)	Dupilumab (n = 78)
Any TEAE, n (%)	17 (89.5)	32 (86.5)	17 (100)	38 (92.7)	34 (94.4)	70 (89.7)
Any serious TEAE, n (%)	1 (5.3)	4 (10.8)	2 (11.8)	6 (14.6)	3 (8.3)	10 (12.8)
Any TEAE leading to death, n (%)	0	0	0	0	0	0
Any TEAE leading to permanent treatment discontinuation, n (%)	0	2 (5.4)	1 (5.9)	5 (12.2)	1 (2.8)	7 (9.0)
TEAEs occurring in $\geq 5\%$ of patients (MedDRA PT)[†]						
Viral upper respiratory tract infection	13 (68.4)	24 (64.9)	7 (41.2)	20 (48.8)	20 (55.6)	44 (56.4)
Bronchitis	5 (26.3)	4 (10.8)	4 (23.5)	2 (4.9)	9 (25.0)	6 (7.7)
Pharyngitis	2 (10.5)	3 (8.1)	3 (17.6)	2 (4.9)	5 (13.9)	5 (6.4)
Influenza	4 (21.1)	2 (5.4)	0	5 (12.2)	4 (11.1)	7 (9.0)
Otitis media	1 (5.3)	0	3 (17.6)	0	4 (11.1)	0
Accidental overdose [‡]	2 (10.5)	1 (2.7)	1 (5.9)	1 (2.4)	3 (8.3)	2 (2.6)
Sinusitis	2 (10.5)	0	1 (5.9)	0	3 (8.3)	0
Headache	1 (5.3)	4 (10.8)	1 (5.9)	3 (7.3)	2 (5.6)	7 (9.0)
Gastroenteritis	0	1 (2.7)	2 (11.8)	4 (9.8)	2 (5.6)	5 (6.4)
Nausea	1 (5.3)	0	1 (5.9)	2 (4.9)	2 (5.6)	2 (2.6)
Contusion	2 (10.5)	1 (2.7)	0	1 (2.4)	2 (5.6)	2 (2.6)
Urticaria	0	0	2 (11.8)	1 (2.4)	2 (5.6)	1 (1.3)
Rhinitis allergic	2 (10.5)	0	0	1 (2.4)	2 (5.6)	1 (1.3)
Dermatitis contact	2 (10.5)	1 (2.7)	0	0	2 (5.6)	1 (1.3)
Migraine	2 (10.5)	0	0	0	2 (5.6)	0
Pyrexia	1 (5.3)	1 (2.7)	0	4 (9.8)	1 (2.8)	5 (6.4)
Upper respiratory tract infection	0	2 (5.4)	1 (5.9)	2 (4.9)	1 (2.8)	4 (5.1)
Back pain	0	0	1 (5.9)	1 (2.4)	1 (2.8)	1 (1.3)
Injection-site reaction [§]	0	8 (21.6)	1 (5.9)	5 (12.2)	1 (2.8)	13 (16.7)
Injection-site erythema	0	7 (18.9)	1 (5.9)	4 (9.8)	1 (2.8)	11 (14.1)
Injection-site pruritus	0	3 (8.1)	0	3 (7.3)	0	6 (7.7)
Injection-site pain	0	2 (5.4)	0	2 (4.9)	0	4 (5.1)

n (%) = number and percentage of patients with at least one TEAE; percentages are calculated using number of patients under the treatment group as denominator.

MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; q2w, every 2 weeks; TEAE, treatment-emergent adverse event.

[†] Adverse events in this category were reported according to the preferred terms in the MedDRA, version 20.0, unless otherwise indicated.

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

[§] Injection-site reaction is a high-level term in MedDRA.

In the Japanese patients who participated in the QUEST study, add-on treatment with dupilumab 200 or 300 mg q2w reduced the annual rate of severe exacerbations and improved lung function as assessed by pre-bronchodilator FEV₁ compared with matched placebo. Baseline characteristics in the Japanese patients were similar to those in the overall QUEST population,⁸ with the exception of BMI, which was lower in the Japanese patients compared with the overall study population (mean [SD]: 25.11 [5.67] vs 29.20 [6.77] kg/m², respectively), and their number of severe asthma exacerbations in the previous year (mean [SD]: 2.62 [2.97] vs 2.09 [2.15], respectively). Improvements in pre-bronchodilator FEV₁ were observed with dupilumab vs placebo as early as Week 2 and were sustained throughout the 52-week treatment period. Both the incidence of severe exacerbations and FEV₁ and severe exacerbation rate showed similar improvements to those observed in the overall QUEST population of the LIBERTY ASTHMA QUEST trial,⁸ with relative risk reductions vs matched placebo for the 200 mg and 300 mg q2w groups for the overall population of 48% and 46%, respectively (both $P < 0.001$), vs 44% ($P = 0.33$) and 75% ($P = 0.03$) observed here for Japanese patients. Likewise, in the overall QUEST population, the LS mean differences at Week 12 in pre-bronchodilator FEV₁ vs matching placebo were 0.14 L and 0.13 L for the 200 mg q2w and 300 mg q2w doses, respectively (both $P < 0.001$),⁸ vs 0.20 L ($P = 0.05$) and 0.17 L ($P = 0.12$) observed in Japanese patients.

In Japanese patients with baseline blood eosinophils <300 cells/ μ L and FeNO levels <25 ppb, some numerical, but mostly non-significant, improvements were observed. This is likely driven by the low numbers in the subgroups of patients and the divergence from the larger overall dataset examining the patient subgroup with a baseline blood eosinophils levels of <150 cells/ μ L.

Compared with the overall Japanese subgroup, the reductions in the risk of severe exacerbations and the improvements in pre-bronchodilator FEV₁ were greater in those with elevated baseline blood eosinophils ≥ 300 cells/ μ L and FeNO levels ≥ 25 ppb. This finding is in line with previous studies of dupilumab in patients with uncontrolled moderate-to-severe asthma,^{8,15,16} where the greatest clinical improvements have been observed in patients with elevated levels of these biomarkers of type 2 inflammation.

Dupilumab treatment also resulted in improved asthma control and benefits in health-related quality of life compared with matched placebo in Japanese patients, supporting the findings for these patient-reported outcomes observed in the overall QUEST population.⁸ This analysis also shows that the benefits of dupilumab were of greater magnitude in the subgroups of Japanese patients with elevated baseline levels of blood eosinophils or FeNO.

In Japanese patients, as also observed in the overall QUEST population,⁸ dupilumab treatment significantly reduced circulating levels of total IgE and FeNO levels over time, although in Japanese patients, no effect was observed on median eosinophil levels.

Other biologic anti-asthma drugs have also been shown to be effective and well tolerated in Japanese patients with severe uncontrolled asthma. A post hoc analysis of the phase 3 CALIMA trial reported that benralizumab reduced asthma exacerbations and improved symptoms and lung function in Japanese patients with severe, uncontrolled eosinophilic asthma.²⁵ The improvements observed in the Japanese cohort were more pronounced than in the overall CALIMA population.^{25,26} Similarly, in the phase 3 MENSA study, mepolizumab significantly reduced asthma exacerbation rates and improved lung function and asthma control in the overall population compared with placebo, and the effect of mepolizumab on the exacerbation rate was notably more robust in the Japanese subgroup of patients than in the overall population in the MENSA trial,²⁷ an observation that the authors attributed to a more severe baseline disease burden in the Japanese patients in MENSA.²⁸

Dupilumab had an acceptable safety profile in Japanese patients, with no new safety signals identified in this population; TEAEs that occurred were similar to those in the overall QUEST trial population.

Although the data in this analysis are derived from a randomized, double-blind, placebo-controlled clinical trial, the findings are limited by the post hoc nature of some of the analyses and the low sample sizes in the subgroups of patients with eosinophils <300 cells/ μ L, ≥ 300 cells/ μ L, FeNO <25 ppb, and FeNO ≥ 25 ppb at baseline.

In conclusion, dupilumab reduced the risk of severe asthma exacerbations, and improved lung function, asthma control, and asthma-related quality of life in Japanese patients with uncontrolled, moderate-to-severe asthma. These findings are consistent with the results of the overall LIBERTY ASTHMA QUEST study population and provide no evidence of any variation in dupilumab efficacy on the basis of Japanese ethnicity compared with the overall ITT population. As in the overall QUEST population, robust clinical improvements associated with add-on dupilumab therapy were observed in patients with elevated markers of type 2 inflammation, namely, increased blood eosinophil levels and high FeNO concentrations at baseline. Dupilumab was generally well tolerated in Japanese patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.04.002>.

Conflict of interest

YTO has been a consultant for AstraZeneca, Kyorin Pharmaceutical, and Sanofi and received research grants from Kyorin Pharmaceutical and Meiji Seika Pharma. TF received research grants from Maruho Co., Ltd and lecture fees from Maruho Co., Ltd, MSD Co. Ltd., Pfizer and Novartis Pharma. KA, MM, YTa, MSR, PR, and NP are employees of Sanofi. AT is a former employee of Sanofi. YD is an employee and shareholder of Regeneron Pharmaceuticals, Inc. NMHG is a former employee and is a shareholder of Regeneron Pharmaceuticals, Inc. The rest of the authors have no conflict of interest.

Authors' contributions

YTO, NMHG, and AT were involved with the study concept and design. YTO, YN, TF, and ME contributed to data acquisition. All authors contributed to data analysis and interpretation, provided critical feedback during manuscript development, and approved the final manuscript.

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ONLINE-ONLY SUPPLEMENTARY DATA

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

Supplementary data for the article:

Dupilumab efficacy and safety in Japanese patients with uncontrolled, moderate-to-severe asthma in the phase 3 LIBERTY ASTHMA QUEST study

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Supplementary Text 1: Detailed inclusion/exclusion criteria

Inclusion criteria: Eligible patients were adults and adolescent patients (age ≥ 12 years) with a physician diagnosis of persistent asthma for ≥ 12 months, based on the Global Initiative for Asthma (GINA) 2017 Guidelines,¹ who were receiving treatment with medium-to-high-dose inhaled corticosteroids (ICS) (fluticasone propionate ≥ 250 μg twice daily or equipotent ICS daily dosage) plus ≥ 2 additional controller medications. Additionally, eligible patients had a pre-bronchodilator forced expiratory volume in 1 second (FEV_1) that was $\leq 80\%$ of the predicted normal for adults ($\leq 90\%$ for adolescents) prior to randomization, FEV_1 reversibility of $\geq 12\%$ and 200 mL after 200–400 μg of albuterol/salbutamol or levalbuterol/levosalbutamol before randomization; a score on the 5-item Asthma Control Questionnaire (ACQ-5) of ≥ 1.5 (screening and baseline); and at least one hospital admission for worsening of asthma in the previous year or treatment with systemic corticosteroid for at least 3 days.

Exclusion criteria: The main exclusion criteria were age < 12 years (or the legal minimum age for adolescents in clinical trials); body weight < 30 kg; a diagnosis of chronic obstructive pulmonary disease or any other disease that could have a negative effect on lung function; a severe exacerbation during the month preceding the screening period; current/recent cigarette smokers; no anti-IgE therapy within 130 days of screening, no other biologic therapy within 2 months of screening, and no other biologic/immunosuppressant therapy within 6 months of screening.

Reference

1. Global Initiative for Asthma (GINA). 2017 GINA Report, Global Strategy for Asthma Management and Prevention. <http://www.ginasthma.org>. Accessed 24th Sep 2019.

Supplementary Text 2: Narratives of events leading to permanent treatment discontinuation

Overview: Eight Japanese patients had adverse events that resulted in permanent treatment discontinuation in the trial: 2 patients (5.4%) in the dupilumab 200 mg q2w (every 2 weeks) group, 5 patients (12.2%) in the dupilumab 300 mg q2w group, and 1 patient (5.9%) in the placebo 2 mL q2w group.

Patient 1: Female patient, aged 69 years

A 69-year old female patient in the dupilumab 200 mg q2w group experienced an adverse event of alanine aminotransferase (ALT) increase of mild intensity on Day 222 of the study, which became moderate in intensity 11 days later. Also, on Day 222, the patient had a serious adverse event of duodenum papilla cancer (small intestine carcinoma), which was considered to be severe in intensity as it required or prolonged hospitalization. This event was considered to be the cause of the ALT increase and investigational treatment was discontinued on the same day. Pertinent medical history included hypertension, which was controlled. On the day of the event, the patient had felt queasy and had pyrexia. Two days later, she had a temperature of 37°C but no vomiting or diarrhea. On an unspecified date before the event, the patient had experienced abdominal pain. On Day 225, symptoms had improved but the patient had acute gastritis and received corrective treatment with oral *Bacillus subtilis*, *Lactobacillus acidophilus*, and *Streptococcus faecalis* 3 g/day. On Day 233, the patient had a non-protocol visit as she experienced malaise, impaired appetite, dark-colored urine, and jaundice-like symptoms. Within the 12 months preceding the event, the patient had not received a blood transfusion, had no exposure to potential hepatotoxic agents, and had not used addictive drugs. The patient had not traveled in countries at risk of viral hepatitis within the last 6 months preceding the event and had not consumed alcohol within the 7 days preceding the event. Laboratory tests revealed: ALT 5.68× the upper limit of normal (ULN), aspartate aminotransferase (AST) 4.06×ULN, alkaline phosphatase 2.90×ULN, and bilirubin 4.85×ULN. Corrective treatment for ALT increase included intravenous (IV) amino acids 500 mL daily (on Day 233, and from Day 246 to 248), IV ammonium glycyrrhizate/cysteine/glycine 80 mL daily (on Day 233, and from Day 246 to 248), and IV ursodeoxycholic acid 600 mg daily (dates not reported). Corrective treatment also included IV metoclopramide hydrochloride 2 mL daily (Days 246 to 248), IV amino acids NOS with electrolytes NOS/glucose/TH 1000 mL daily (Days 249 to 251), IV Veen-D 500 mL daily (Days 252 to 254), IV flurbiprofen axetil 5 mL daily (Days 256 to 258), IV human albumin 500 mL daily (Days 260 to 265), IV paracetamol 1000 mg daily (Day 265), oral ursodeoxycholic acid 300 mg daily (from Day 265 until Day 423), oral paracetamol 400 mg daily (Day 409), oral garenoxacin mesilate 400 mg daily (Days 409 to 418), and intramuscular triamcinolone 20 mg daily (Day 410). The event of duodenum papilla cancer was considered resolved on Day 424. Since Day 424, the patient has received IV cisplatin 40 mg daily, IV dexamethasone sodium phosphate 9.9 mg daily, IV gemcitabine hydrochloride 1600 mg daily, IV granisetron hydrochloride 3 mg daily, IV magnesium sulfate 20 mL daily, and IV sodium chloride 150 mL and 1000 mL daily, and since Day 459 she has received amphotericin B 4 mL daily. On Day 233, after treatment with amino acids and glycyrrhizate/cysteine/glycine, laboratory values showed ALT of 6.45×ULN and total bilirubin of 4.85×ULN, which met the criteria for termination of study treatment as per protocol. ALT, AST, and bilirubin remained elevated throughout the rest of the study. On Day 239, an abdominal ultrasound revealed cholestasis, gall bladder enlargement and sludge, intrahepatic duct/common bile duct dilatation, pancreatic duct dilatation, renal cyst

on both sides, and suspected uterine myoma. On Day 249, the patient saw a gastroenterologist for reduced dietary intake and vomiting and was hospitalized for endoscopic retrograde biliary drainage. Laboratory tests showed high level of cancer antigen (CA19-9) at 69.15 U/mL (normal range: 0–37 U/mL). On the same day, an abdominal computed tomography (CT) scan revealed ectasia of bile duct and gall sand accumulation. On Day 252, magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography showed suspicion of pancreas head cancer with no apparent metastasis. On Day 254, endoscopic ultrasound fine needle aspiration was performed for suspected pancreas cancer and indicated adenocarcinoma. On Day 255, abdominal CT (contrast enhanced) revealed suspicion of distal bile duct cancer or cancer of head of pancreas. On Day 259, a pathological examination of a mass of unclear margin over the duodenal papilla revealed duodenum papilla cancer (adenocarcinoma), stage III (T3N0M0). Mild vascular and neural invasion were observed. The pancreatic margin, hepatic side margin of the bile duct, and detached margin were negative. No malignant findings were noted in the gall bladder. On Day 260, the patient underwent subtotal stomach-preserving pancreaticoduodenectomy for the pancreas cancer with obstructive jaundice (total bilirubin was 24 mg/dL). Pancreatic head tumor excision and cholecystectomy were performed. A pancreatic tube, gallbladder tube, inferior liver surface drain, pancreaticojejunostomy drain, and anteroposterior drain were placed. On Day 272, the patient had a non-serious adverse event of moderate intensity, reported as “*Staphylococcus epidermidis* bacteremia.” On that day, the patient developed pyrexia, which was considered to be caused by bile duct tube obstruction. As no drainage from the bile duct tube was noted, the bile duct tube was irrigated. Drainage was observed, and body temperature decreased after the tube irrigation. On the same day, a bile culture was positive for *Klebsiella pneumonia* and *Enterococcus faecalis* and a blood culture was positive for *S. epidermidis*. Corrective treatment was given and included IV meropenem 3 g daily (from Day 272 to 276) and IV levofloxacin 500 mg daily (from Day 277 to 282). The event of *S. epidermidis* bacteremia resolved on Day 277. On Day 284, the patient was discharged from the hospital in stable condition. Laboratory tests on Day 353 showed an increase in CA19-9. On Day 373, an abdominal CT revealed a soft-tissue shadow in the dorsal side of the superior mesenteric vein. Differentiation between a postoperative change or fluid accumulation and recurrent tumor was difficult. On Day 379 of the study, the patient had an adverse event of moderate intensity, reported as metastases to liver. The event became serious on Day 395 as it was considered another medically important event. On Day 379, a positron emission tomography-CT led to the diagnosis of Vater's papilla cancer and postoperative suspicion of liver metastasis. On Day 392, a lower gastrointestinal endoscopy showed a minute Isp polyp in the hepatic flexure. Diverticula were observed sporadically in the cecum and ascending colon. On the same day, endoscopic mucosal resection and polypectomy were performed, which showed abnormal results. Corrective treatment included chemotherapy since Day 431. On Day 459, it was decided that the event of liver metastasis of duodenum papilla cancer was to be followed up within routine medical care thereafter, because it was unrelated to the study drug, and it had a low chance of recovery and was stable without aggravation. Therefore, the study investigation on this case was discontinued. The patient recovered from the events of ALT increase and duodenal papilla cancer on Day 424. At the time of this report, the patient had not recovered from the event of liver metastasis of duodenum papilla cancer. The investigator's assessment of causality for the duodenum papilla cancer, which resulted in withdrawal of investigational treatment, was that it was not related to dupilumab.

Patient 2: Male patient, aged 64 years

A 64-year old male patient in the dupilumab 200 mg q2w group experienced an adverse event of mild intensity on Day 9 of the study. The event was reported as rectal tubular adenocarcinoma (rectal adenocarcinoma) and was reported as serious on Day 63 as it required or prolonged hospitalization. Pertinent medical history included hypertension, nephrotic syndrome, focal segmental glomerulosclerosis, dyslipidemia, and *Helicobacter* gastritis. On Day 9, as a regular health check, endoscopy of the large intestine was performed, which revealed 4 polyps of the large intestine. Following a biopsy, pathology results showed mild-to-moderate atypical adenoma and the patient was diagnosed with a malignant rectal tumor. On Day 30, a CT of the chest and abdomen showed no apparent metastases to lymph nodes or distant metastasis. On Day 63, the patient was hospitalized, and on Day 64, corrective treatment of 2 polypectomies was performed. Endoscopic submucosal dissection was performed on a large intestine polyp of approximately 21–25 mm in the upper rectum, and endoscopic mucosal resection for a large intestine polyp of approximately 10 mm in the lower rectum. A small hemorrhage was observed after surgery, which stopped spontaneously, and the patient's condition showed no remarkable changes thereafter. On Day 69, the patient was discharged from hospital. Investigational product was permanently discontinued on Day 72 as a result of the event. On Day 100, the patient recovered from the event, and on Day 105, histopathological examination of both polyps confirmed moderately differentiated tubular adenocarcinoma. The investigator's assessment of causality for rectal tubular adenocarcinoma was that it was not related to dupilumab, but a non-investigational medical product.

Patient 3: Female patient, aged 55 years

A 55-year old female patient in the dupilumab 300 mg q2w group with a pertinent medical history of hypertension, seasonal allergy, and angina pectoris experienced an injection-site reaction on Day 18 of the study, following administration of the second dose of investigational product to the right lower abdomen. The adverse event was reported to be of moderate intensity, and on the same day (Day 18), the patient developed severe erythema and pruritus at the injection sites (with a largest diameter of 54 mm). No corrective treatment was given, and the investigational product was permanently discontinued on the same day. On Day 32, the patient's eosinophil count was within the normal range (0.26 Giga/L). She was deemed to have recovered from the injection-site reaction with associated symptoms of injection-site erythema and injection-site pruritus on Day 72. On Day 365, her eosinophil count (0.13 Giga/L) and white blood cell (WBC) count (4.6 Giga/L) were within the normal range. No antidrug antibodies (ADA) to dupilumab were detected. The investigator's assessment of causality for the erythema and pruritus at the injection-site reaction was that they were related to dupilumab.

Patient 4: Male patient, aged 51 years

A 51-year old male patient in the dupilumab 300 mg q2w group underwent endoscopy of the large bowel on Day 228 of the study, which revealed ascending colon adenocarcinoma (adenocarcinoma of the colon). This adenocarcinoma was recorded as a serious adverse event of severe intensity, for which he was hospitalized 4 days later. Investigational treatment was discontinued on Day 236. Pertinent medical history included hyperuricemia, hypertension, seasonal allergy, Type 2 diabetes, iron deficiency anemia, and chronic kidney disease. On Day 194, the patient had reported increased shortness of breath and was referred to cardiology, where blood tests revealed hemoglobin of 104 g/dL, hematocrit of 0.35, a red blood cell (RBC) count of 4.4 Tera/L, a platelet count of 463 Giga/L, and a WBC count of 9.6 Giga/L. A subsequent

consultation with a cardiologist revealed a normal X-ray and ECG, and no cardiac abnormalities were found. The patient's shortness of breath was suspected to be due to anemia, and he was referred for upper and lower endoscopy. In addition to the colon carcinoma detected in the large bowel on Day 228, on the same day, upper gastrointestinal endoscopy revealed the presence of gastric polyps, which were biopsied. Following a CT scan, liver metastasis was confirmed, and the patient was referred to inpatient treatment. On Day 232, he was hospitalized, and on Day 235, underwent lower gastrointestinal endoscopy, which showed a tumor (size: 14.2 cm) with circumferential stenosis in the ascending colon, and well-differentiated tubular adenocarcinoma. Based on these findings, the patient was diagnosed with adenocarcinoma of the ascending colon. The patient had no history of polyps and no family history of polyps or colon cancer. The investigational product was discontinued after administration on Day 236. The patient was started on a liquid diet (900 kcal) following admission for nutritional management, and his fasting blood sugar levels remained around 120–130 mg/dL, which resulted in weight loss (128 kg at the time of the surgery from 134 kg on admission). The patient had pain in the right shoulder and left leg after arousal, which showed tendency to improve with on-demand pentazocine. Meals were gradually solidified, with the patient able to consume porridge. The patient also received paracetamol/tramadol hydrochloride. Corrective treatment included oral magnesium citrate at 50 mL/day and oral magnesium carbonate and magnesium oxide at 0.33 g TID, oral diazepam 5 mg and oral prednisolone 60 mg, oral isosorbide dinitrate 5 mg, oral amoxicillin trihydrate 750 mg daily, and hydrocortisone 200 mg. The patient underwent a laparoscopically assisted right hemicolectomy as corrective treatment for the event, and received IV fentanyl for 3 days for postoperative pain management. He was discharged from hospital and began chemotherapy with 200 mg oxaliplatin via hemodialysis and was started on oral capecitabine at 4200 mg/day, and 3600 mg/day ongoing since. On Day 335, the patient visited the coloproctology department for follow-up and complained of numbness in hands and feet. The chemotherapy was discontinued. The patient also received subcutaneous 100 mg mepolizumab. On Day 365, the patient's condition remained unchanged with persisting numbness in hands and feet. On Day 449, at the end of study visit, the numbness in the hands and feet was reported to be resolving, and the patient had no problems in daily life. He stated that he was to be continued on follow-up care at the coloproctology department as an outpatient. At the time of this report, the patient had not recovered from the event. The investigator's assessment of causality for the ascending colon adenocarcinoma was that it was not related to dupilumab.

Patient 5: Female patient, aged 41 years

A 41-year old female patient in the dupilumab 300 mg q2w group experienced a serious adverse event of mild intensity, reported as pregnancy, on Day 53 of the study. The event was serious, as it required or prolonged hospitalization. Pertinent medical history included iron deficiency anemia, cholecystectomy, genital herpes, depression, and *Mycoplasma* infection. The date of the last menstrual period and pregnancy onset was Day 53. The patient exposure at the time of pregnancy was 53 days. The patient had 3 previous live births without congenital anomalies or malformations and did not use any contraception method. On Day 86, a urine pregnancy test revealed the patient's pregnancy, and on Day 93, the patient was hospitalized. On Day 94, the patient underwent an induced abortion intentionally. No abnormality was seen in the fetus. Corrective treatment included oral methylergometrine maleate 0.75 mg daily (from Day 94 to 96) and IV methylergometrine maleate 0.2 mg daily (on Day 95), IV cefazolin sodium 1 g daily, IV fentanyl injection 0.1 mg daily, oral paracetamol 400 mg daily, IV propofol 500 mg daily (all on Day 95), and oral cefcapene pivoxil hydrochloride 100 mg daily (from Day 95 to 96). The investigational product was permanently discontinued due to the event, with last administration

on Day 73. The patient recovered from the event on Day 95 and was discharged from the hospital on Day 96. On Day 100 of the study, the patient had a serious adverse event of moderate intensity, reported as depression aggravated (depression), and she was hospitalized on the same day. The patient underwent a postpartum depression test that did not show any abnormal finding. Corrective treatment included oral lorazepam 0.5 mg daily (from Day 99 to 104); oral risperidone 2 mg daily (from Day 99 to 104), 1 mg (on Day 107); oral levomepromazine maleate 25 mg (on Day 107); oral lithium carbonate 800 mg daily (from Day 107 to 108), 1000 mg daily (from Day 107 to 178); oral zotepine 75 mg (from Day 107 to 108 and from Day 135 to 136), 25 mg daily (from Day 109 to 123); oral clonazepam 1.5 mg daily (from Day 112 to Day 185); oral zolpidem tartrate 5 mg daily (on Day 119); oral valproate sodium 400 mg daily (from Day 119 to 121); oral quazepam 15 mg daily (from Day 135 to 136); oral carbamazepine 400 mg daily (from Day 176 to 178); and oral nitrazepam 5 mg daily (from Day 176 to 178). The patient recovered from the event of depression on Day 176 and was discharged from the hospital on the same day. The investigator's assessment of causality for the pregnancy was that it was not related to dupilumab.

Patient 6: Female patient, aged 66 years

A 66-year old female patient in the dupilumab 300 mg q2w group experienced an adverse event of moderate intensity on Day 168 of the study, which was reported as episcleritis “unknown” (episcleritis). Pertinent medical history included endometriosis, laparoscopic surgery, dermatitis contact, sudden hearing loss, pain in extremity, and dyslipidemia. Corrective treatment for the episcleritis included ophthalmic fluorometholone 4 gtt daily (from Day 168 to 183) and 8 gtt daily (from Day 246 to 257); ophthalmic moxifloxacin hydrochloride 4 gtt daily (from Day 168 to 183, from Day 211 to 228, and from Day 258 to 282) and 8 gtt daily (from Day 246 to 257); artificial tears (90046201) 4 gtt daily (from Day 224 to 241), and oral PA (NOS) 3 g daily (on Day 251), dose not specified (from Day 263 to 266 and from Day 281 to 290) and 9 g daily (on Day 310). The investigational product was permanently discontinued due to this event, with last administration on Day 295. No laboratory values were available for that day. The patient recovered from the event on Day 319. On Day 320, the patient had an accidental fall at home due to carelessness leading to femur and wrist fractures, which were described as closed fractures. The events were reported as accidental fall (fall), fractures of left lower end of femur (femur fracture), and right scaphoid bone fracture (wrist fracture); they were of severe intensity and considered serious as they required or prolonged hospitalization. On Day 343, the patient was moved to a different hospital for rehabilitation treatment. No corrective treatment was given for the event of the fall and the patient recovered from the event the same day. Corrective treatment was given for femur and wrist fractures and included left femur/right scaphoid bone osteosynthesis (on Day 324), ultrasonic fracture treatment (on Day 331), IV atropine sulfate 1 mL daily (on Day 324), IV dexamethasone sodium phosphate 1 mL (on Day 324), IV droperidol (dose not reported, on Day 324), IV famotidine 20 mL daily (on Day 324), IV fentanyl 6 mL daily (on Day 324), IV flurbiprofen axetil 5 mL (on Day 324), IV lidocaine 5 mL daily (on Day 324), inhaled oxygen 600 L daily (on Day 324), IV propofol 50 mL daily (on Day 324), IV ropivacaine hydrochloride 20 mL (on Day 324), inhalational sevoflurane 20.91 mL daily (on Day 324), IV xylocaine-epinephrine 10 mL daily (on Day 324), IV cefazolin sodium 2 g daily (from Day 324 to 325), oral loxoprofen sodium 120 mg daily (from Day 325 to 329), oral rebamipide 200 mg daily (from Day 325 to 329), and oral epinastine hydrochloride 20 mg (since Day 344). The patient recovered from the events of femur fracture and wrist fracture on Day 392 and was discharged from the hospital on the same day. Action taken with the investigational product was not applicable. On Day 374 of the study, the patient had an adverse event of mild intensity, reported as generalized urticaria “unknown cause” (urticaria). Corrective treatment for the

urticaria included transdermal Valisone-G (dose not reported, from Day 374 to 391). The patient recovered from urticaria on 391. The patient had no antidrug antibodies (ADA) to dupilumab. The investigator's assessment of causality for the episcleritis event that resulted in treatment discontinuation was that it was related to dupilumab.

Patient 7: Female patient, aged 32 years

A 32-year old female patient in the dupilumab 300 mg q2w group with no other pertinent medical history experienced a serious adverse event of moderate intensity on Day 16 of the study, which was reported as an asthma exacerbation (asthma) that required or prolonged hospitalization. On the same day, 15 days after the first administration of investigational product, and 4 days after the most recent dose, the patient made an unscheduled visit to the study site complaining of physical deterioration. Her peak expiratory flow was 250 and forced expiratory volume in 1 second (FEV₁) was 0.88 L. Blood tests and pulmonary function tests were performed, which led to a diagnosis of asthma exacerbation. There were no trigger factors reported such as infection (e.g. cold, flu), exercise, changes in air temperature, allergens (e.g. animals, house/dust mites, pollen, or food), cigarette smoke, laughing, strong smells, or chemicals. The patient was hospitalized immediately. Corrective treatment included IV methylprednisolone sodium succinate 80 mg daily (on Days 16 and 19), 160 mg daily (from Day 17 to 18); oral prednisolone 30 mg daily (from Day 20 to 23); and inhalational salbutamol sulfate (dose and dates not reported). No action was taken with regards to the investigational product. On Day 22, pulmonary function tests showed an improved FEV₁ at 1.55 L. The possibility of chronic obstructive pulmonary disease was low, but lung disease was suspected. Compared with the mean value of others of the same gender and same age, the patient's values were much worse, so a retest by a specialist was required. Regular administration of salbutamol sulfate was changed to "as-needed" inhalation at the time of an asthma attack. On Day 24, the patient recovered from the event and was discharged from the hospital. On Day 34, peak expiratory flow was 320–360 and FEV₁ was 1.53 L. On Day 144 of the study, the patient had a serious adverse event of severe intensity, reported as anaphylaxis (anaphylactic reaction); her blood pressure was 101/67 mmHg and heart rate was 91 beats/min. The event was serious because it required or prolonged hospitalization. The patient had received a dose of investigational product in the left upper arm around 11:30. Before receiving the injection, the patient reported having slight right hypochondrial pain due to suspected gallstone but the physician judged that investigational product injection was possible. During the injection, the patient complained of severe pain at the injection site. Immediately after administration, the patient started trembling and hyperventilating and within 10 seconds, the patient had collapsed and lost consciousness. SpO₂ was 98–100% on room air. At this time, the patient was diagnosed with vagal reaction (considered as a non-serious adverse event). However, considering the patient's history of a previous reaction to lebrikizumab, she was taken to the emergency room, where she recovered consciousness and her hyperventilation resolved gradually, but the patient was still unable to communicate. Within 10 minutes of the investigational product injection, the patient experienced wheezing, flushing and erythema of the upper body, face and neck edema, nausea (without vomiting), and sweating. As wheezing and flushing were symptoms suggestive of anaphylaxis, the patient was diagnosed with anaphylaxis. Corrective treatment included intramuscular epinephrine 0.3 mg daily (on Day 144), oral famotidine 20 mg daily (on Day 144), IV methylprednisolone sodium succinate 80 mg daily and 125 mg daily (on Day 144), topical hydrocortisone acetate as needed (from Day 144 to 145), and oral loratadine 10 mg daily (from Day 144 to 145). At 11:45, blood pressure was 155/90 mmHg, heart rate was 91 beats/min, and SpO₂ was 100% (on room air). Within 5 minutes of epinephrine injection, the patient became alert and was able to speak. Other symptoms (wheezing, flushing,

facial erythema and cervical edema, and nausea) recovered gradually. At 11:50, blood pressure was 140/64 mmHg, heart rate was 104 beats/min, and SpO₂ was 100%, and at 11:57, blood pressure was 129/68 mmHg, heart rate was 78 beats/min, and SpO₂ was 100%. At 13:00, the patient was admitted to the intensive care unit. At the time of admission, only erythema on both arms continued and other symptoms disappeared. Blood pressure was 116/59 mmHg, and SpO₂ was 97%. In the morning of Day 145, blood pressure was 113/58 mmHg and heart rate was 71 beats/min. Erythema and itching were no longer present, and the patient was discharged from the hospital with no symptoms. The IMP was permanently discontinued due to the event of anaphylactic reaction; the last IMP administration was on Day 144. The patient recovered from the event on Day 144. The patient had no antidrug antibodies (ADA) to dupilumab. The investigator's assessment of causality for the anaphylaxis was that it was related to dupilumab.

Patient 8: Female patient, aged 66 years

A 66-year old female patient in the placebo 2 mL q2w group, with a pertinent medical history of controlled hypertension, experienced an adverse event of moderate intensity on Day 200 of the study. The event was reported as herpes zoster and occurred on the same day the patient had experienced a rash and pain in the right shoulder. The patient visited the clinic on Day 204, and on Day 206 was diagnosed with herpes zoster. The type of infection was reported as viral and the sites of infection were palm, elbow, and shoulder. The diagnosis was based on clinical features and symptoms. No WBC or neutrophil count values were available on the day of the infection. On Day 208, the patient's WBC count was 5.2 Giga/L and her neutrophil count 3.43 Giga/L. The infection was considered opportunistic, the causative agent was varicella-zoster virus, and the site of infection was skin. No diagnostic imaging or culture was reported. Corrective treatment included oral pregabalin 50 mg (from Day 203 to 204), 200 mg (from Day 213 to 215), 250 mg (from Day 216 to 224), 300 mg (from Day 225 to 253), 225 mg (from 254 to 265 and from Day 278 to 286); oral celecoxib 200 mg (from Day 205 to 206 and from Day 225 to 237); oral tizanidine hydrochloride 3 mg (from Day 204 to 205); valaciclovir hydrochloride (dose and dates not provided); and organ lysate, standardized (neurotropin) (dose and dates not provided). The investigational product was permanently discontinued due to the event, with last administration on Day 194. The patient recovered from the event on Day 309, and her last known WBC and neutrophil values were 4.5 Giga/L and 3.1 Giga/L, respectively. The investigator's assessment of causality for the herpes zoster was that it was related to the investigational medicinal product (placebo).

Supplementary Text 3: Narratives of eosinophilia cases associated with symptoms

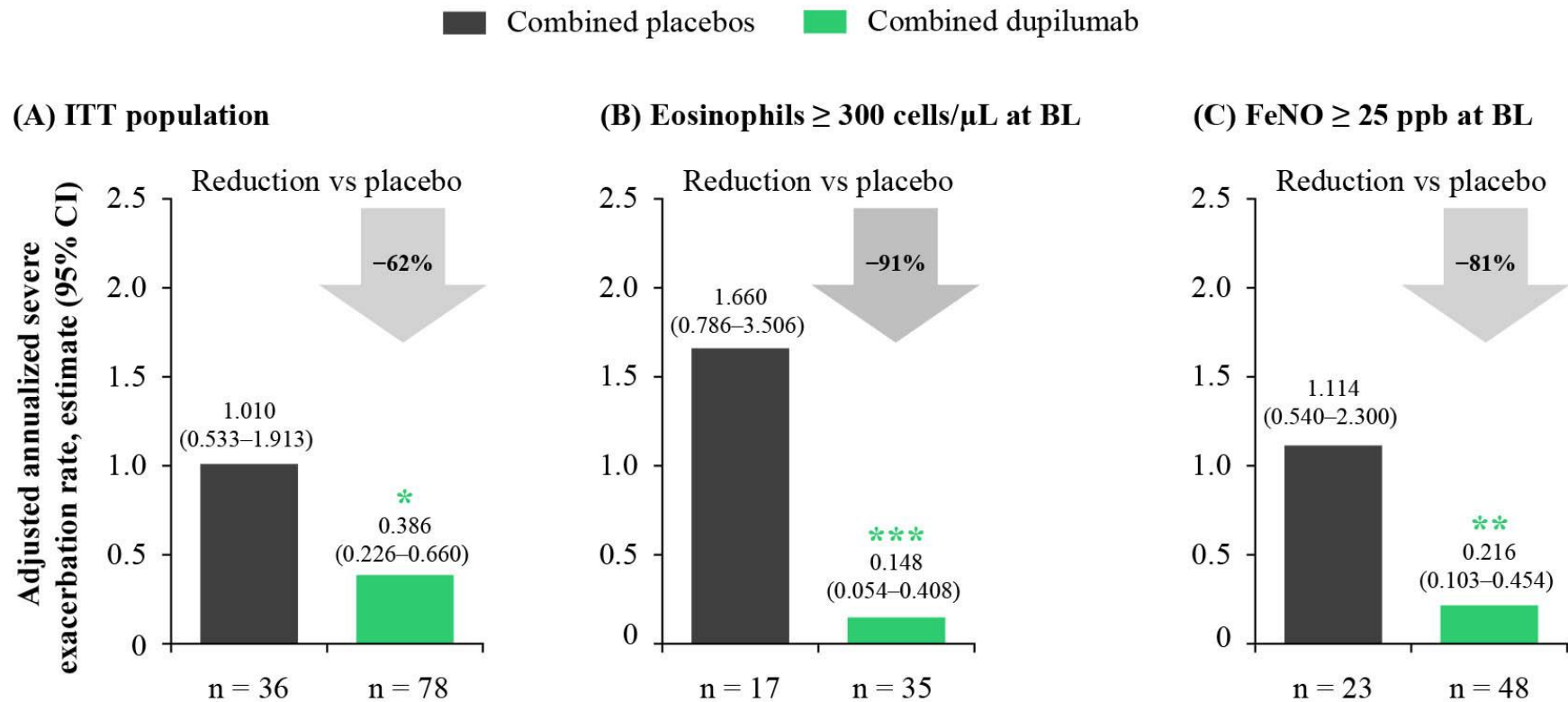
All cases of patients with eosinophilia treatment-emergent adverse events (TEAEs) meeting any of the following criteria were medically reviewed after database lock: serious AE; moderate or severe intensity; leading to permanent treatment discontinuation; and peak eosinophil count ≥ 5000 cells/ μ L. Two patients in the 300 mg q2w (every 2 weeks) dupilumab/matching placebo group had eosinophilia TEAEs that met these criteria and are described below.

Patient	Event	Narrative
Patient 1	Event 1	65-year-old female – Onset: Day 29 relative to first dose of IP – Duration: 29 days – Related to IP: No – Intensity: Mild – Permanent treatment discontinuation: No – Serious: No – Outcome: Recovered
Patient 2	Event 1	62-year-old female – Onset: Day 29 relative to first dose of IP – Duration: 112 days – Related to IP: No – Intensity: Mild – Permanent treatment discontinuation: No – Serious: No – Outcome: Recovered
	Event 2	– Onset: Day 169 relative to first dose of IP – Duration: 170 days – Related to IP: No – Intensity: Mild – Permanent treatment discontinuation: No – Serious: No – Outcome: Recovered
IP, investigational product.		

Supplementary Fig. 1. Reduction of annualized rate of severe exacerbations during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb, for both dupilumab doses vs both placebos combined.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

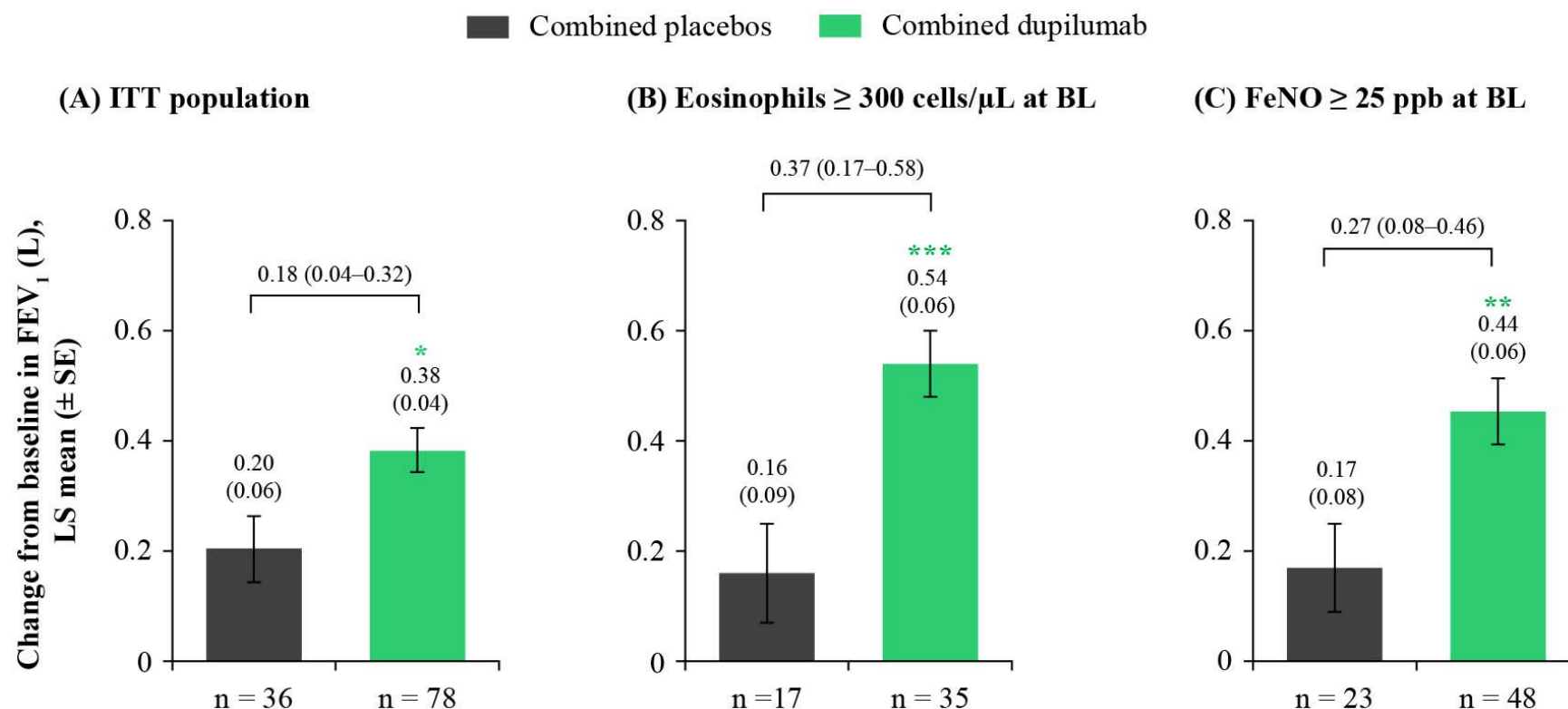
BL, baseline; CI, confidence interval; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion.



Supplementary Fig. 2. Magnitude of change from baseline in pre-bronchodilator FEV₁ at Week 12 in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb, for both dupilumab doses vs both placebos combined.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

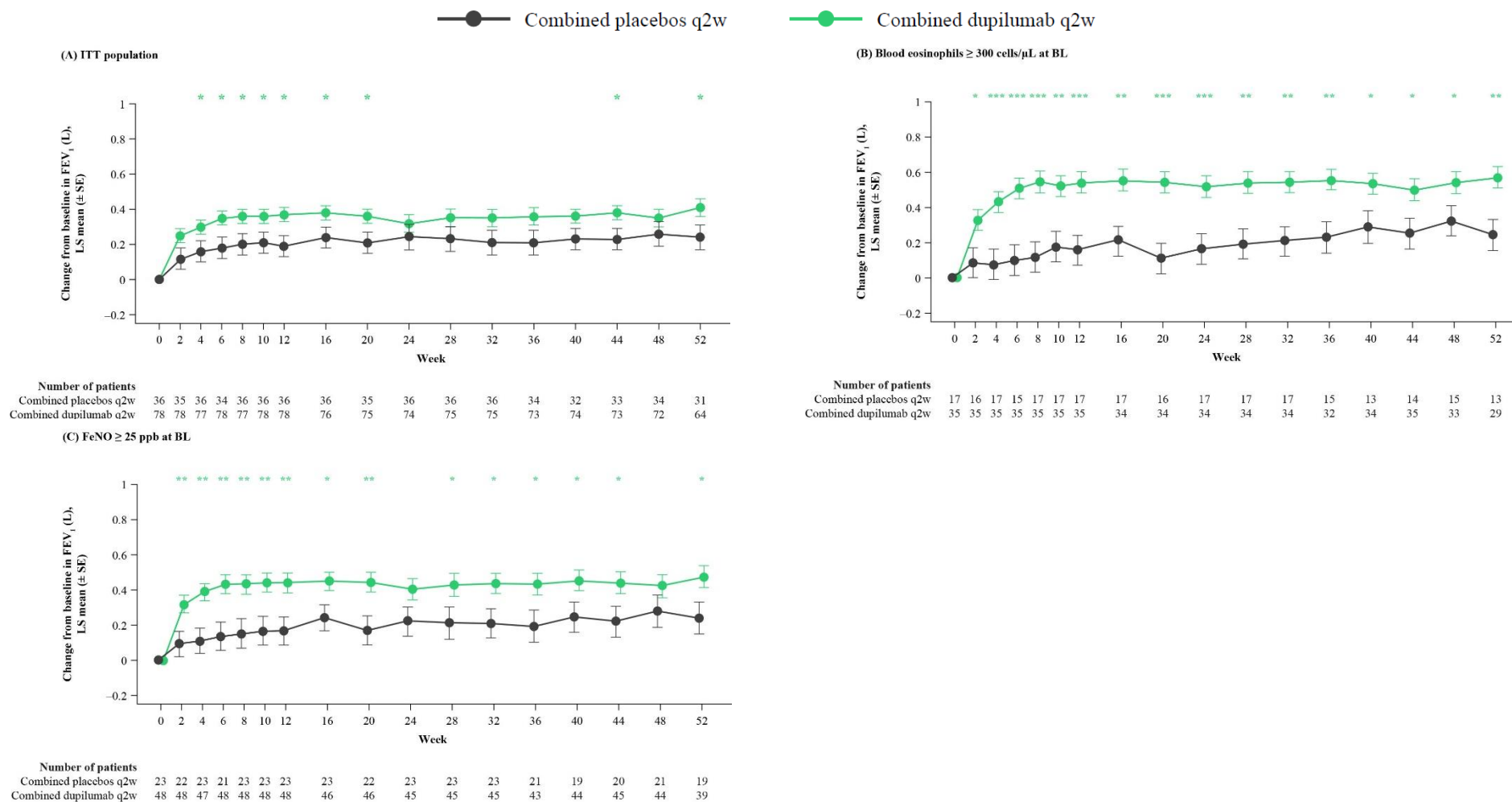
BL, baseline; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; SE, standard error.



Supplementary Fig. 3. Change from baseline in pre-bronchodilator FEV₁ during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb, for both dupilumab doses vs both placebos combined.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

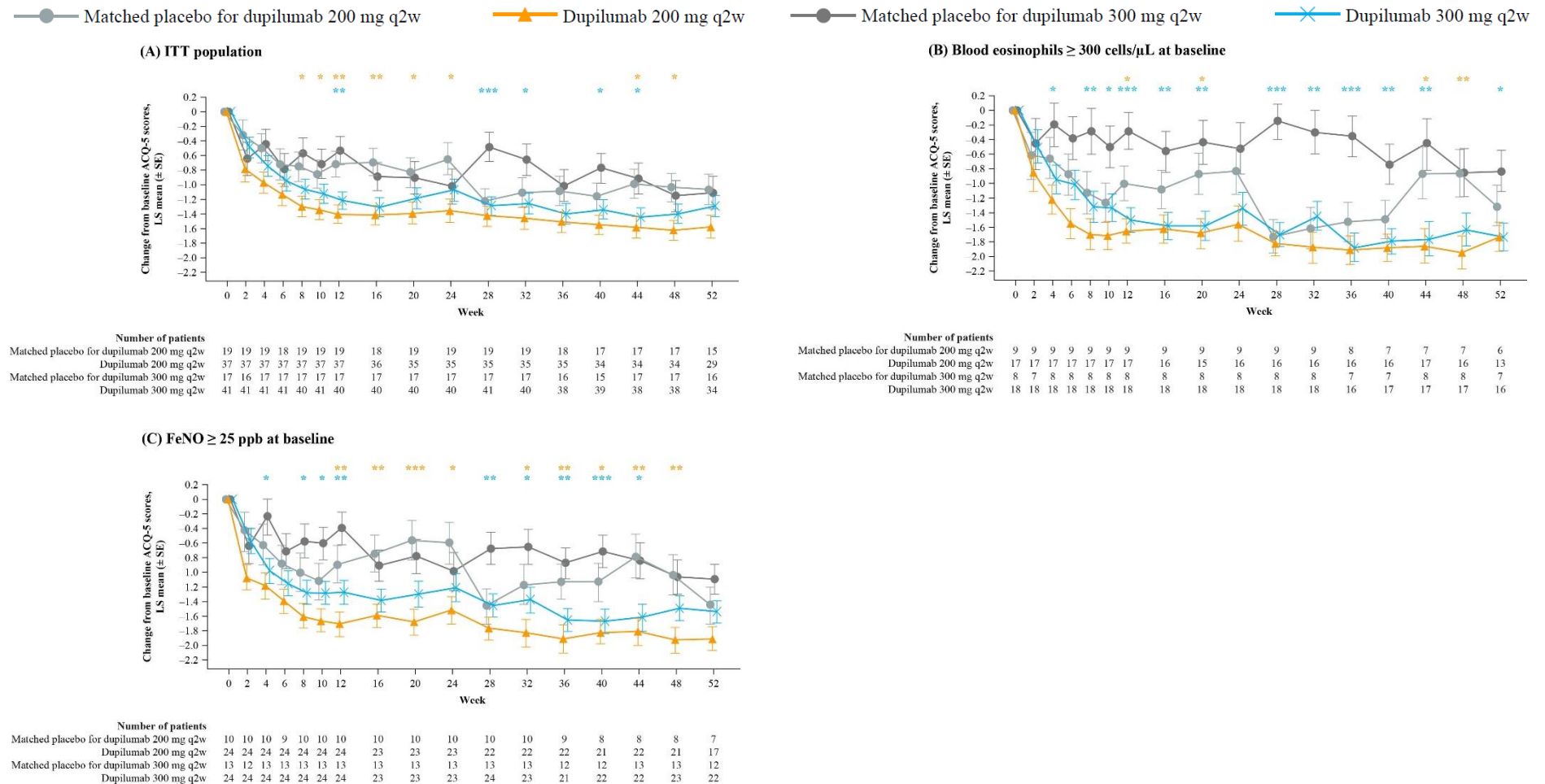
DPL, dupilumab; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.



Supplementary Fig. 4. Change from baseline in total asthma control (ACQ-5) scores during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb at baseline.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

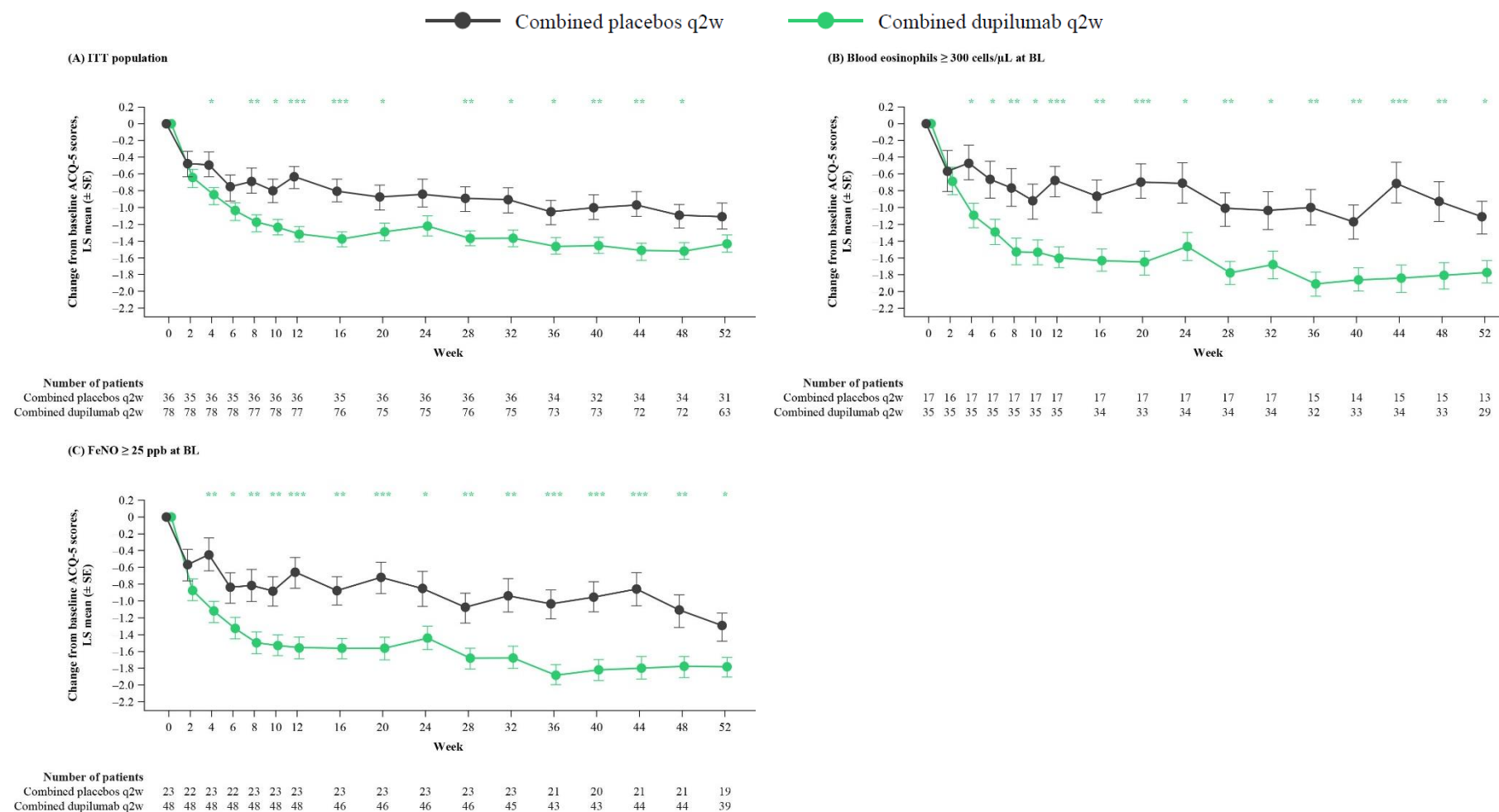
ACQ-5, 5-item Asthma Control Questionnaire; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.



Supplementary Fig. 5. Change from baseline in total asthma control (ACQ-5) scores during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb at baseline, for both dupilumab doses vs both placebos combined.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

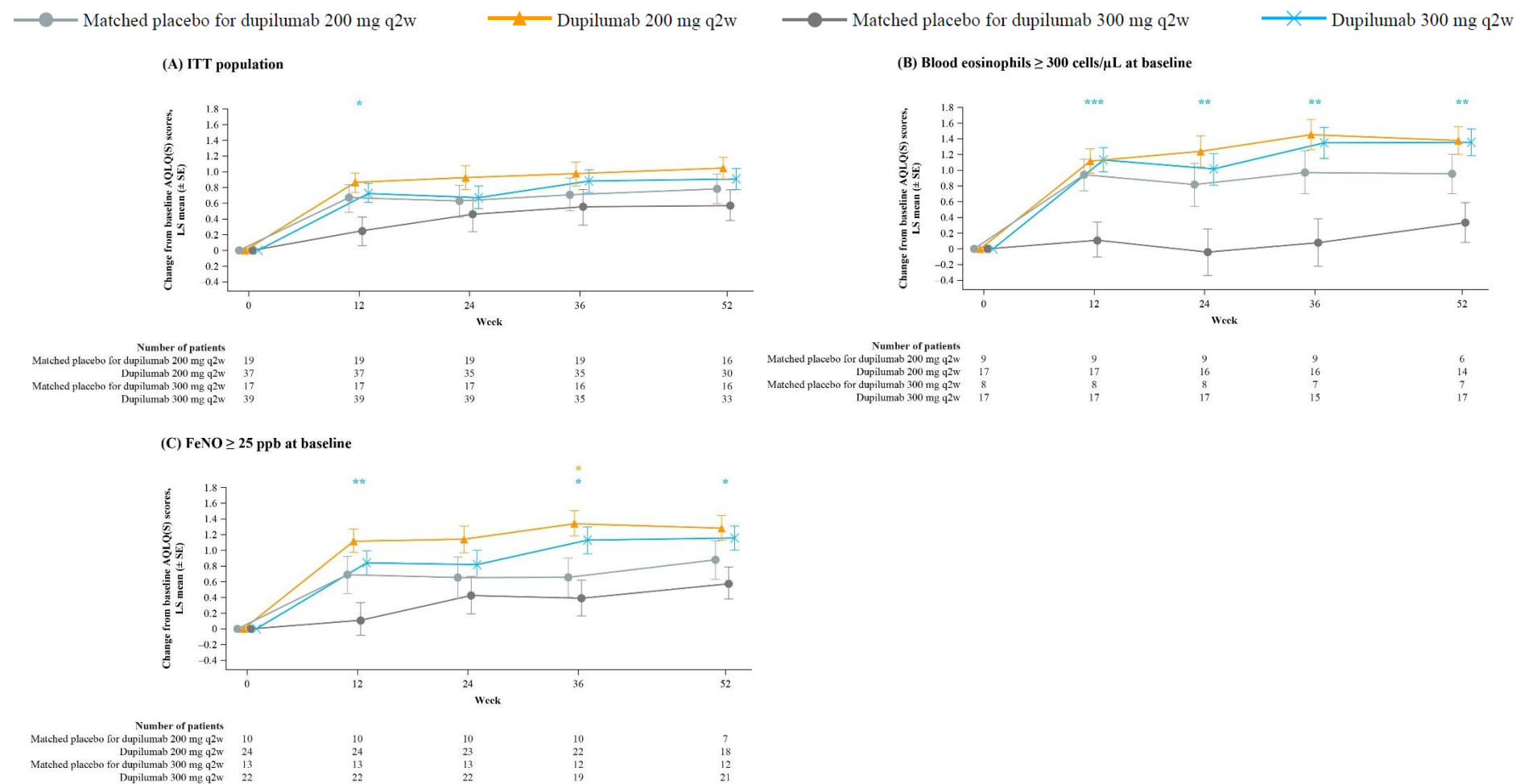
ACQ-5, 5-item Asthma Control Questionnaire; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.



Supplementary Fig. 6. Change from baseline in asthma-related quality of life (AQLQ[S]) scores during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb at baseline.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

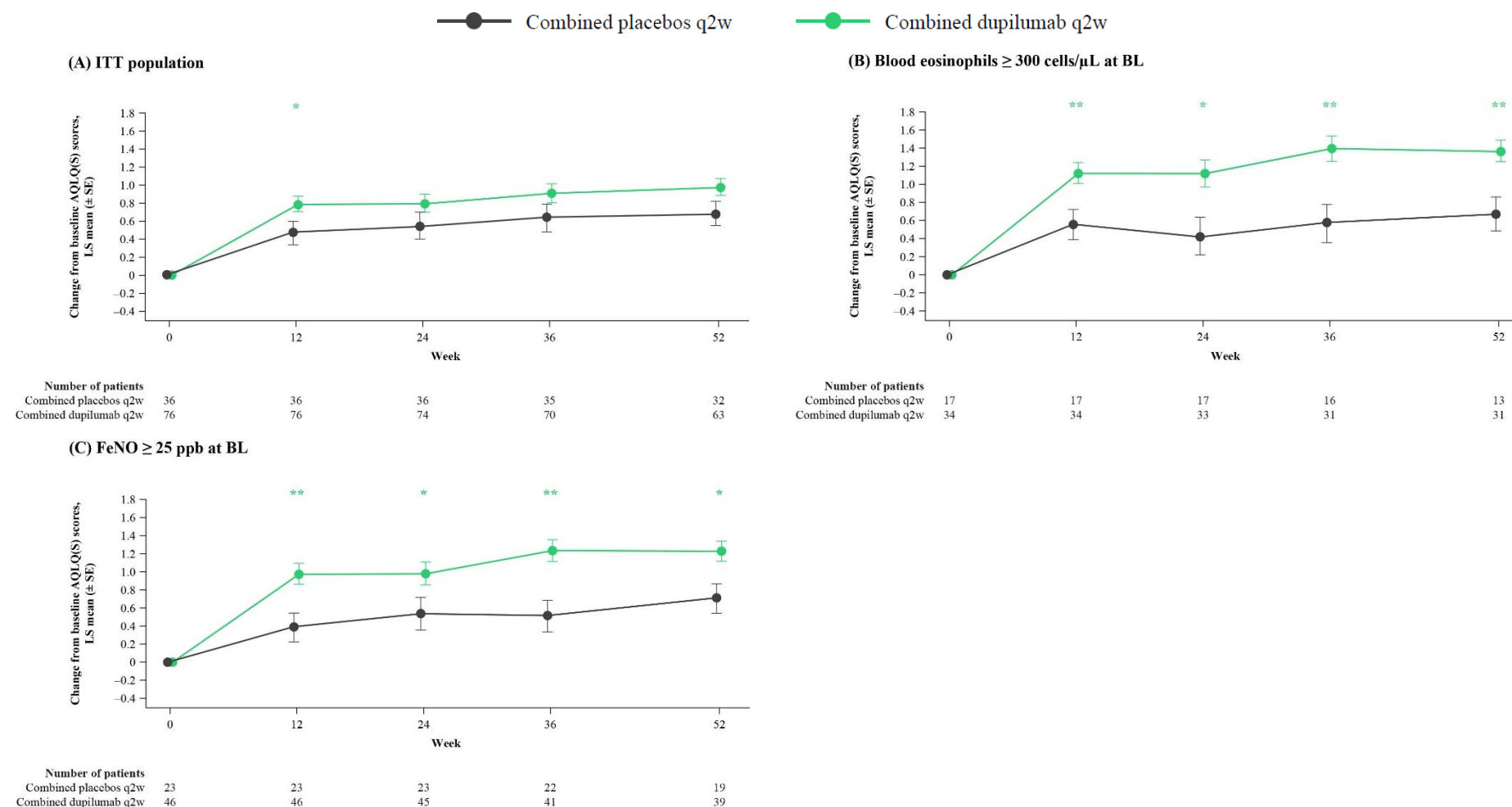
AQLQ(S), Standardized Asthma Quality of Life Questionnaire; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.



Supplementary Fig. 7. Change from baseline in asthma-related quality of life (AQLQ[S]) scores during the 52-week intervention period in **(A)** the Japanese ITT population, **(B)** Japanese patients with baseline blood eosinophil levels ≥ 300 cells/ μ L, and **(C)** Japanese patients with FeNO levels ≥ 25 ppb at baseline, for both dupilumab doses vs both placebos combined.

* $P < 0.05$; ** $P < 0.01$ vs matched placebo.

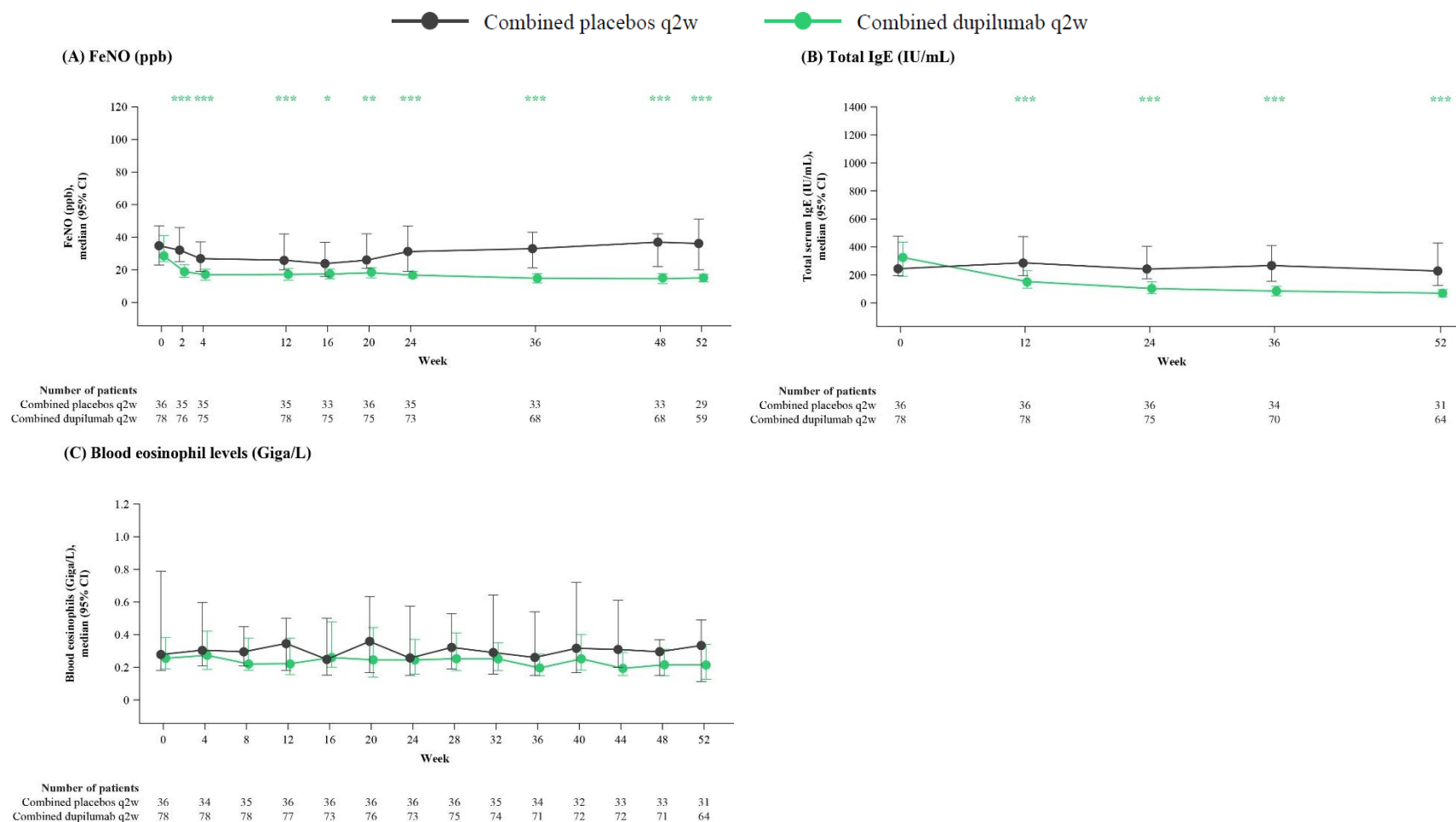
AQLQ(S), Standardized Asthma Quality of Life Questionnaire; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks; SE, standard error.



Supplementary Fig. 8. Change from baseline in biomarkers of type 2 inflammation: **(A)** FeNO, **(B)** serum total IgE, and **(C)** blood eosinophils, during the 52-week intervention period in the Japanese ITT population for dupilumab 200 mg q2w and 300 mg q2w combined vs combined placebos.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$ vs matched placebo.

P -values were adjusted by **(A)** baseline FeNO, **(B)** baseline serum total IgE, or **(C)** baseline blood eosinophils, respectively, and age, sex, baseline eosinophil strata, and baseline ICS dose level comparing dupilumab vs. matched placebo. CI, confidence interval; DPL, dupilumab; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; LS, least squares; PBO, placebo; q2w, every 2 weeks.



Supplementary Table 1. Selected baseline demographic and clinical characteristics of the Japanese ITT population.

	Japanese ITT population						
Characteristic	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		Overall (N = 114)
	Placebo (n = 19)	Dupilumab (n = 37)	Placebo (n = 17)	Dupilumab (n = 41)	Placebo (n = 36)	Dupilumab (n = 78)	
Age (years)	47.1 (16.9)	49.0 (16.0)	51.4 (12.9)	47.2 (18.2)	49.1 (15.1)	48.1 (17.1)	48.4 (16.4)
< 18 years, n (%)	2 (10.5)	0	0	3 (7.3)	2 (5.6)	3 (3.8)	5 (4.4)
≥ 18 years, n (%)	17 (89.5)	37 (100)	17 (100)	38 (92.7)	34 (94.4)	75 (96.2)	109 (95.6)
BMI (kg/m ²)	25.32 (5.08)	24.81 (4.26)	26.08 (7.55)	24.88 (6.30)	25.68 (6.29)	24.85 (5.39)	25.11 (5.67)
< 25 kg/m ² , n (%)	8 (42.1)	23 (62.2)	7 (41.2)	24 (58.5)	15 (41.7)	47 (60.3)	62 (54.4)
≥ 25 to < 30 kg/m ² , n (%)	8 (42.1)	8 (21.6)	6 (35.3)	12 (29.3)	14 (38.9)	20 (25.6)	34 (29.8)
≥ 30 kg/m ² , n (%)	3 (15.8)	6 (16.2)	4 (23.5)	5 (12.2)	7 (19.4)	11 (14.1)	18 (15.8)
Age at asthma onset (years)	31.8 (17.9)	30.1 (19.3)	35.9 (20.4)	29.2 (20.4)	33.8 (19.0)	29.7 (19.7)	30.9 (19.5)
< 18 years, n (%)	4 (21.1)	9 (24.3)	4 (23.5)	14 (34.1)	8 (22.2)	23 (29.5)	31 (27.2)
≥ 18 to ≤ 40 years, n (%)	6 (31.6)	16 (43.2)	5 (29.4)	13 (31.7)	11 (30.6)	29 (37.2)	40 (35.1)
> 40 years, n (%)	9 (47.4)	12 (32.4)	8 (47.1)	14 (34.1)	17 (47.2)	26 (33.3)	43 (37.7)
Values are shown as mean (SD), unless stated otherwise. BMI, body mass index; ITT, intention-to-treat; q2w, every 2 weeks; SD, standard deviation.							

Supplementary Table 2 Dupilumab efficacy in Japanese patients with asthma with baseline levels of blood eosinophils < 300 cells/ μ L and FeNO < 25 ppb.

	Japanese ITT population					
Assessment	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
Japanese patients with blood eosinophils < 300 cells/μL at baseline						
Annualized event rate of severe exacerbation, estimate (95% CI)	n = 10 0.589 (0.156–2.219)	n = 20 0.577 (0.227–1.468)	n = 9 0.515 (0.113–2.339)	n = 23 0.574 (0.210–1.567)	n = 19 0.556 (0.203–1.518)	n = 43 0.575 (0.295–1.123)
Relative risk reduction vs placebo (95% CI)	–	0.980 (0.197–4.884) <i>P</i> = 0.98	–	1.113 (0.166–7.487) <i>P</i> = 0.91	–	1.036 (0.296–3.620) <i>P</i> = 0.96
Change from baseline in pre-BD FEV ₁ (L) at Week 12, LS mean (SE)	n = 10 0.26 (0.12)	n = 20 0.33 (0.08)	n = 9 0.23 (0.12)	n = 23 0.19 (0.08)	n = 19 0.24 (0.08)	n = 43 0.26 (0.06)
LS mean difference vs matching placebo (95% CI)	–	0.08 (–0.21 to 0.36) <i>P</i> = 0.59	–	–0.04 (–0.33 to 0.26) <i>P</i> = 0.79	–	0.02 (–0.18 to 0.23) <i>P</i> = 0.83
Change from baseline in pre-BD FEV ₁ (L) at Week 52, LS mean (SE)	n = 9 0.22 (0.14)	n = 16 0.52 (0.10)	n = 9 0.28 (0.14)	n = 19 0.18 (0.10)	n = 18 0.24 (0.10)	n = 35 0.34 (0.07)
LS mean difference vs matching placebo (95% CI)	–	0.31 (–0.03 to 0.65) <i>P</i> = 0.08	–	–0.10 (–0.45 to 0.24) <i>P</i> = 0.56	–	0.10 (–0.15 to 0.36) <i>P</i> = 0.42
Change from baseline in ACQ-5 [†] total score at Week 12, LS mean (SE)	n = 10 –0.39 (0.26)	n = 20 –1.17 (0.18)	n = 9 –0.70 (0.28)	n = 22 –0.97 (0.18)	n = 19 –0.53 (0.19)	n = 42 –1.07 (0.13)
LS mean difference vs matching placebo (95% CI)	–	–0.78 (–1.42 to 0.14) <i>P</i> = 0.02	–	–0.26 (–0.94 to 0.42) <i>P</i> = 0.44	–	–0.54 (–1.00 to –0.08) <i>P</i> = 0.02
Change from baseline in ACQ-5 [†] total score at Week 52, LS mean (SE)	n = 9 –0.74 (0.32)	n = 16 –1.34 (0.23)	n = 9 –1.36 (0.34)	n = 18 –0.92 (0.22)	n = 18 –1.02 (0.23)	n = 34 –1.12 (0.16)
LS mean difference vs matching placebo (95% CI)	–	–0.60 (–1.39 to 0.18) <i>P</i> = 0.13	–	0.44 (–0.38 to 1.26) <i>P</i> = 0.28	–	–0.11 (–0.67 to 0.46) <i>P</i> = 0.71
Change from baseline in AQLQ(S) [‡] global score at Week 12, LS mean (SE)	n = 10 0.42 (0.28)	n = 20 0.61 (0.19)	n = 9 0.28 (0.29)	n = 22 0.41 (0.19)	n = 19 0.35 (0.20)	n = 42 0.51 (0.13)
LS mean difference vs matching placebo (95% CI)	–	0.19 (–0.50 to 0.88) <i>P</i> = 0.59	–	0.13 (–0.56 to 0.82) <i>P</i> = 0.71	–	0.15 (–0.33 to 0.64) <i>P</i> = 0.53
Change from baseline in AQLQ(S) [‡] global score at Week 52, LS mean (SE)	n = 10 0.61 (0.28)	n = 16 0.74 (0.20)	n = 9 0.70 (0.29)	n = 16 0.53 (0.20)	n = 19 0.65 (0.20)	n = 32 0.63 (0.14)
LS mean difference vs matching placebo (95% CI)	–	0.14 (–0.57 to 0.84) <i>P</i> = 0.70	–	–0.17 (–0.88 to 0.53) <i>P</i> = 0.62	–	–0.02 (–0.51 to 0.47) <i>P</i> = 0.93
FeNO (ppb) at Week 52, mean (SD)	n = 9 21.6 (11.9)	n = 15 16.5 (9.8)	n = 8 68.8 (97.5)	n = 16 14.0 (5.6)	n = 17 43.8 (69.4)	n = 31 15.2 (7.9)
FeNO (ppb) at Week 52, median (95% CI)	20.0 (11.0–41.0)	13.0 (10.0–19.0)	40.0 (19.0–307.0)	12.5 (12.0–16.0)	20.0 (15.0–42.0)	13.0 (12.0–15.0)

	Japanese ITT population					
Assessment	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
Median change from baseline (95% CI) <i>P</i> -value vs matching placebo	−3.0 (−31.0 to 4.0)	−5.0 (−17.0 to −1.0) <i>P</i> = 0.66	1.5 (−11.0 to 218.0)	−8.0 (−25.0 to 0.0) <i>P</i> = 0.17	−2.0 (−5.0 to 5.0)	−7.0 (−17.0 to −3.0) <i>P</i> = 0.012
Serum total IgE (IU/mL) at Week 52, mean (SD)	n = 10 417.8 (354.0)	n = 16 245.2 (356.2)	n = 8 192.0 (274.2)	n = 18 86.7 (65.1)	n = 18 317.4 (332.6)	n = 34 161.3 (257.5)
Serum total IgE (IU/mL) at Week 52, median (95% CI)	262.0 (107.0–807.0)	61.0 (37.0–414.0)	55.0 (17.0–776.0)	69.5 (42.0–113.0)	170.0 (72.0–507.0)	69.5 (42.0–113.0)
Median change from baseline (95% CI) <i>P</i> -value vs matching placebo	11.0 (−25.0 to 79.0)	−137.0 (−217.0 to −95.0) <i>P</i> = 0.002	−9.0 (−43.0 to 13.0)	−244.5 (−369.0 to −100.0) <i>P</i> = 0.039	1.0 (−19.0 to 14.0)	−167.5 (−277.0 to −116.0) <i>P</i> < 0.0001
Blood eosinophil count (cells/μL) at Week 52, mean (SD)	n = 9 273.3 (273.1)	n = 16 143.8 (129.8)	n = 9 131.1 (117.9)	n = 19 152.1 (137.5)	n = 18 202.2 (216.8)	n = 35 148.3 (132.1)
Blood eosinophil count (cells/μL) at Week 52, median (95% CI)	230.0 (50.0–490.0)	125.0 (50.0–190.0)	100.0 (60.0–250.0)	100.0 (60.0–240.0)	105.0 (60.0–330.0)	120.0 (60.0–170.0)
Median change from baseline (95% CI) <i>P</i> -value vs matching placebo	50.0 (−120.0 to 310.0)	0.0 (−40.0 to 110.0) <i>P</i> = 0.91	40.0 (−90.0 to 110.0)	−10.0 (−60.0 to 90.0) <i>P</i> = 0.10	45.0 (−90.0 to 120.0)	−10.0 (−40.0 to 60.0) <i>P</i> = 0.86
Japanese patients with FeNO < 25 ppb at baseline						
Annualized event rate of severe exacerbation (95% CI)	n = 9 0.197 (0.032–1.232)	n = 13 0.566 (0.151–2.125)	n = 4 0.645 (0.057–7.280)	n = 17 0.372 (0.102–1.358)	n = 13 0.293 (0.061–1.404)	n = 30 0.445 (0.159–1.249)
Relative risk reduction vs placebo (95% CI)	–	2.870 (0.391–21.072) <i>P</i> = 0.29	–	0.578 (0.047–7.123) <i>P</i> = 0.66	–	1.520 (0.356–6.495) <i>P</i> = 0.56
Change from baseline in pre-BD FEV ₁ (L) at Week 12, LS mean (SE)	n = 9 0.18 (0.12)	n = 13 0.30 (0.11)	n = 4 0.19 (0.18)	n = 17 0.13 (0.10)	n = 13 0.19 (0.10)	n = 30 0.20 (0.07)
LS mean difference vs matching placebo (95% CI)	–	0.12 (−0.20 to 0.45) <i>P</i> = 0.45	–	−0.06 (−0.45 to 0.33) <i>P</i> = 0.74	–	0.01 (−0.22 to 0.24) <i>P</i> = 0.94
Change from baseline in pre-BD FEV ₁ (L) at Week 52, LS mean (SE)	n = 8 0.13 (0.15)	n = 12 0.45 (0.12)	n = 4 0.20 (0.22)	n = 13 0.15 (0.11)	n = 12 0.16 (0.12)	n = 25 0.28 (0.09)
LS mean difference vs matching placebo (95% CI)	–	0.32 (−0.07 to 0.71) <i>P</i> = 0.11	–	−0.05 (−0.53 to 0.42) <i>P</i> = 0.82	–	0.12 (−0.16 to 0.40) <i>P</i> = 0.40
Change from baseline in ACQ-5 [†] total score at Week 12, LS mean (SE)	n = 9 −0.83 (0.21)	n = 13 −1.07 (0.18)	n = 4 −1.09 (0.32)	n = 16 −1.29 (0.16)	n = 13 −0.93 (0.18)	n = 29 −1.20 (0.13)
LS mean difference vs matching placebo (95% CI)	–	−0.24 (−0.78 to 0.31) <i>P</i> = 0.39	–	−0.20 (−0.89 to 0.49) <i>P</i> = 0.55	–	−0.27 (−0.68 to 0.14) <i>P</i> = 0.19
Change from baseline in ACQ-5 [†] total score at Week 52, LS mean (SE)	n = 8 −1.07 (0.35)	n = 12 −1.21 (0.30)	n = 4 −1.36 (0.53)	n = 12 −1.04 (0.28)	n = 12 −1.17 (0.29)	n = 24 −1.12 (0.20)
LS mean difference vs matching placebo (95% CI)	–	−0.14 (−1.06 to 0.78) <i>P</i> = 0.76	–	0.32 (−0.86 to 1.50) <i>P</i> = 0.59	–	0.05 (−0.64 to 0.74) <i>P</i> = 0.88

	Japanese ITT population					
Assessment	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined	
	Placebo	Dupilumab	Placebo	Dupilumab	Placebo	Dupilumab
Change from baseline in AQLQ(S) [‡] global score at Week 12, LS mean (SE)	n = 9 0.82 (0.28)	n = 13 0.52 (0.24)	n = 4 0.52 (0.43)	n = 17 0.70 (0.22)	n = 13 0.74 (0.24)	n = 30 0.64 (0.17)
LS mean difference vs matching placebo (95% CI)	–	–0.30 (–1.02 to 0.42) P = 0.41	–	0.18 (–0.71 to 1.07) P = 0.69	–	–0.10 (–0.63 to 0.44) P = 0.72
Change from baseline in AQLQ(S) [‡] global score at Week 52, LS mean (SE)	n = 9 0.90 (0.31)	n = 12 0.75 (0.27)	n = 4 0.44 (0.47)	n = 12 0.64 (0.24)	n = 13 0.76 (0.26)	n = 24 0.72 (0.19)
LS mean difference vs matching placebo (95% CI)	–	–0.14 (–0.94 to 0.66) P = 0.72	–	0.20 (–0.79 to 1.20) P = 0.68	–	–0.04 (–0.63 to 0.55) P = 0.89
FeNO (ppb) at Week 52, mean (SD)	n = 8 16.4 (4.1)	n = 12 14.3 (9.8)	n = 3 23.3 (18.9)	n = 12 12.6 (3.2)	n = 11 18.3 (9.7)	n = 24 13.5 (7.2)
FeNO (ppb) at Week 52, median (95% CI)	17.5 (11.0–20.0)	12.5 (8.0–14.0)	19.0 (7.0–44.0)	13.0 (11.0–15.0)	19.0 (11.0–20.0)	13.0 (12.0–14.0)
Median change from baseline (95% CI) P-value vs matching placebo	0.0 (–3.0 to 8.0)	–2.0 (–7.0 to 0.0) P = 0.47	–2.0 (–4.0 to 21.0)	–4.0 (–8.0 to 2.0) P = 0.30	–1.0 (–3.0 to 8.0)	–3.0 (–6.0 to 0.0) P = 0.11
Serum total IgE (IU/mL) at Week 52, mean (SD)	n = 9 344.8 (242.7)	n = 12 117.8 (241.1)	n = 3 41.0 (28.2)	n = 13 59.9 (43.8)	n = 12 268.8 (248.7)	n = 25 87.7 (168.7)
Serum total IgE (IU/mL) at Week 52, median (95% CI)	263.0 (107.0–643.0)	37.5 (16.0–77.0)	34.0 (17.0–72.0)	69.0 (17.0–75.0)	215.5 (72.0–416.0)	42.0 (20.0–70.0)
Median change from baseline (95% CI) P-value vs matching placebo	8.0 (–80.0 to 49.0)	–115.0 (–217.0 to –54.0) P = 0.001	–12.0 (–13.0 to –6.0)	–228.0 (–369.0 to –34.0) P = 0.10	–9.0 (–25.0 to 27.0)	–119.0 (–227.0 to –82.0) P < 0.0001
Blood eosinophil count (cells/μL) at Week 52, mean (SD)	n = 8 325.0 (258.5)	n = 12 213.3 (212.3)	n = 4 77.5 (54.4)	n = 13 168.5 (109.4)	n = 12 242.5 (241.2)	n = 25 190.0 (164.8)
Blood eosinophil count (cells/μL) at Week 52, median (95% CI)	305.0 (70.0–860.0)	130.0 (50.0–380.0)	95.0 (0.0–120.0)	150.0 (70.0–260.0)	175.0 (70.0–340.0)	130.0 (90.0–250.0)
Median change from baseline (95% CI) P-value vs matching placebo	15.0 (–90.0 to 680.0)	–25.0 (–160.0 to 70.0) P = 0.53	–15.0 (–120.0 to 110.0)	0.0 (–110.0 to 100.0) P = 0.18	10.0 (–90.0 to 120.0)	–10.0 (–110.0 to 60.0) P = 0.43

[†]ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or because of treatment. Higher scores indicate less control; a total score is calculated ranging from 0 to 6; the minimal clinically important difference is 0.5.

[‡]AQLQ(S) is a patient-reported measure of the impact of asthma on quality of life. Higher scores indicate better quality of life; a global score is calculated ranging from 1 to 7; the minimal clinically important difference is 0.5.

ACQ-5, 5-item Asthma Control Questionnaire; AQLQ(S), Standardized Asthma Quality of Life Questionnaire; BD, bronchodilator; CI, confidence interval; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in 1 second; IgE, immunoglobulin E; ITT, intention-to-treat; LS, least squares; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation; SE, standard error.

Supplementary Table 3 Type 2 inflammatory biomarkers at baseline in the Japanese ITT population.

	Japanese ITT population						
	1.14 mL/200 mg q2w		2 mL/300 mg q2w		Combined		Overall (N = 114)
	Placebo (n = 19)	Dupilumab (n = 37)	Placebo (n = 17)	Dupilumab (n = 41)	Placebo (n = 36)	Dupilumab (n = 78)	
Type 2 inflammatory biomarkers at baseline							
FeNO (ppb), mean (SD)	36.47 (27.10)	37.43 (26.98)	52.94 (33.47)	40.49 (30.37)	44.25 (30.97)	39.04 (28.67)	40.68 (29.38)
FeNO (ppb), median (Q1–Q3)	25.0 (15.0–51.0)	28.0 (19.0–49.0)	41.0 (25.0–84.0)	37.0 (17.0–53.0)	35.0 (19.0–67.5)	29.0 (18.0–53.0)	29.5 (18.0–54.0)
Serum total IgE (IU/mL), mean (SD)	725.63 (795.85)	930.05 (1333.91)	371.65 (666.35)	481.78 (838.93)	558.47 (748.90)	694.42 (1117.25)	651.49 (1014.06)
Serum total IgE (IU/mL), median (Q1–Q3)	456 (189–924)	331 (124–1043)	200 (78–248)	323 (139–504)	240 (136–595)	326 (124–606)	303 (124–606)
Blood eosinophil count (cells/ μ L), mean (SD)	522.63 (494.25)	447.30 (464.67)	485.88 (469.95)	444.15 (694.60)	505.28 (476.38)	445.64 (592.95)	464.47 (557.35)
Blood eosinophil count (cells/ μ L), median (Q1–Q3)	280 (150–1040)	250 (100–670)	280 (120–800)	250 (110–490)	280 (135–840)	250 (100–600)	250 (110–690)
FeNO, fractional exhaled nitric oxide; IgE, immunoglobulin E; ITT, intention-to-treat; ppb, parts per billion; q2w, every 2 weeks; SD, standard deviation.							