ORIGINAL ARTICLE
ASTHMA

Dupilumab improves lung function in patients with uncontrolled, moderate-to-severe asthma

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ABSTRACT

Background: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4 and interleukin-13, key drivers of type 2 inflammation. In the phase 3 LIBERTY ASTHMA QUEST trial (NCT02414854) in patients with uncontrolled, moderate-to-severe asthma, add-on dupilumab 200 mg or 300 mg every 2 weeks reduced exacerbations and improved forced expiratory volume in 1 s (FEV_1) and quality of life over 52 weeks. This analysis evaluates dupilimab's effect on lung function in the overall population, and subgroups with baseline elevated type 2 inflammatory biomarkers.

Methods: Patients were randomised to 52 weeks of subcutaneous dupilumab 200 mg every 2 weeks, 300 mg every 2 weeks, or matched-volume placebos. Lung function outcomes were analysed in the overall population, in patients with ⩾150 eosinophils·μL^{-1}, ⩾300 eosinophils·μL^{-1}, ⩾25 ppb fractional exhaled nitric oxide (F_{eNO}), and both ⩾150 eosinophils·μL^{-1} and ⩾25 ppb F_{eNO}, at baseline.

Results: Dupilumab treatment (200 mg and 300 mg every 2 weeks) resulted in significant improvements *versus* placebo after 52 weeks in pre-bronchodilator FEV_1 (0.20 and 0.13 L, respectively, *versus* placebo) and post-bronchodilator FEV_1 (0.19 and 0.13 L, respectively), forced vital capacity (FVC) (0.20 and 0.14 L, respectively), forced expiratory flow (0.19 and 0.13 L·s^{-1}, respectively) and pre-bronchodilator FEV_1/FVC ratio (1.75% and 1.61%, respectively) in the overall population ($p<0.001$). Difference *versus* placebo in post-bronchodilator FEV_1 slope of change (weeks 4–52) was significant (0.04 L·year^{-1}; $p<0.05$). Greater improvements were achieved in patients with elevated baseline blood eosinophil and/or F_{eNO} levels for most outcomes.

Conclusions: Dupilumab improves lung function outcomes, including large and small airway measurements and fixed airway obstruction, in patients with uncontrolled, moderate-to-severe asthma; particularly in patients with elevated biomarkers of type 2 inflammation.

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Dupilumab is a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, key drivers of type 2 inflammation, improving lung function outcomes in patients with uncontrolled, moderate-to-severe asthma http://bit.ly/2OhKMpi

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This study is registered at www.clinicaltrials.gov with identifier number NCT02414854. Qualified researchers may request access to patient-level data and related study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan and dataset specifications. Patient-level data will be anonymised and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies and process for requesting access can be found at www.clinicalstudydatarequest.com.

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Introduction

A high proportion of asthma patients (23–56.5%) remain uncontrolled despite receiving maximum standard-of-care controller treatment. These patients suffer a significant ongoing disease burden, with poor health-related quality of life and increased risk of developing asthma exacerbations and accelerated decline in lung function [1–6].

Poor lung function as measured by forced expiratory volume in 1 s (FEV_1) is a predictor of risk of asthma exacerbations [7] independent of symptom levels, and all-cause, pulmonary and cardiovascular mortality. Effective new treatments are required to improve lung function for patients with uncontrolled, moderate-to-severe disease.

Asthma is a heterogeneous disease, and type 2 inflammation driven by inflammatory cytokines such as interleukin (IL)-4, IL-5 and IL-13 plays a critical role in >50% of patients with moderate-to-severe asthma [8, 9]. Biomarkers such as blood and sputum eosinophil levels and fractional exhaled nitric oxide (F_{eNO}) are associated with type 2 inflammation [10] and useful for inflammatory phenotyping, which may help guide treatment [11].

Dupilumab, a fully human VelocImmune®-derived [12, 13] monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13, thus inhibiting signalling of both IL-4 and IL-13, cytokines implicated in numerous type 2 inflammatory and allergic diseases including asthma, chronic rhinosinusitis with nasal polyps (CRSwNP), atopic dermatitis and eosinophilic oesophagitis [14].

Dupilumab is approved by the US Food and Drug Administration [15] as an add-on maintenance treatment in patients with moderate-to-severe asthma aged ⩾12 years with an eosinophilic phenotype or oral corticosteroid-dependent asthma; in Japan by the Pharmaceuticals and Medical Devices Agency for patients aged ⩾12 years with severe or refractory asthma whose symptoms are inadequately controlled with existing therapy [16]; and by the European Medicines Agency [17] as an add-on maintenance treatment in patients aged ⩾12 years with type 2 severe asthma characterised by increased blood eosinophils and/or raised F_{eNO} inadequately controlled with high-dose inhaled corticosteroids (ICS) plus another medicinal product for maintenance treatment [18–20]. In addition, dupilumab is approved in the USA as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP [15]; and for the treatment of patients with inadequately controlled, moderate-to-severe atopic dermatitis, aged ⩾12 years in the USA [15] and for adults in the European Union [17] and other countries [21–23].

In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), dupilumab 200 mg and 300 mg every 2 weeks *versus* matched-volume placebo reduced annualised severe exacerbation rates and improved pre-bronchodilator FEV_1, improved asthma control, asthma symptoms and quality-of-life measures, and was generally well tolerated in patients with uncontrolled, moderate-to-severe asthma aged ⩾12 years [19]. The greatest improvements with dupilumab in the phase 3 trial were observed in patients with elevated blood eosinophils or F_{eNO} at baseline [19].

This article presents further pre-specified and *post hoc* analyses from the asthma phase 3 LIBERTY ASTHMA QUEST study that extend the primary study results published by Castro *et al.* [19], assessing the effect of dupilumab on lung function. We analyse additional lung function parameters to look in depth at the impact of dupilumab treatment on small airways and the change in lung function (post-bronchodilator FEV_1) over time in the overall LIBERTY ASTHMA QUEST population and in subgroups of patients with evidence of type 2 inflammation, as reflected by elevated levels of blood eosinophils and F_{eNO} at baseline.

Methods

Study design and patients

Detailed descriptions of the study design, inclusion and exclusion criteria and methodology have been reported previously [19, 24]. Briefly, LIBERTY ASTHMA QUEST was a global phase 3, multinational, randomised, double-blind, placebo-controlled, parallel-group trial (NCT02414854) in patients with

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uncontrolled, moderate-to-severe asthma who were receiving continuous treatment with medium-to-high doses of ICS plus one or two additional asthma medications. Patients were enrolled in the study without requirement of minimal levels of any type 2 biomarker such as blood eosinophils, serum total immunoglobulin E or F_{eNO}. Following a 4-week screening period (±1 week), eligible patients were randomised 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) every 2 weeks or matched-volume placebo.

The study was sponsored by Sanofi and Regeneron Pharmaceuticals. Trial data were collected by the study investigators and analysed by the sponsors. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. The appropriate institutional review boards and ethics committees approved the trial procedures and documentation, and written informed consent was obtained from all patients (or their legal guardians) before participation.

This paper contains pre-specified and *post hoc* analyses of outcome measures in the overall intention-to-treat (ITT) population as well as the following "type 2-high" subgroups defined as patients with $\geqslant$150 eosinophils·μL^{-1} at baseline; patients with $\geqslant$300 eosinophils·μL^{-1} at baseline; patients with $\geqslant$25 ppb F_{eNO} at baseline; and patients with elevation of both blood eosinophils ($\geqslant$150 eosinophils·μL^{-1}) and F_{eNO} ($\geqslant$25 ppb) at baseline.

Outcomes

The following pre-specified lung function parameters were assessed at time points up to week 52: change from baseline in pre-bronchodilator FEV_1; change from baseline in pre-bronchodilator forced vital capacity (FVC); change from baseline in forced expiratory flow at 25–75% of FVC ($FEF_{25–75\%}$); and change from baseline in the ratio of pre-bronchodilator FEV_1/FVC ratio. In addition, the slope of change in post-bronchodilator FEV_1 was assessed from week 4 to week 52. Change in post-bronchodilator FEV_1, the number of patients who achieved an improvement in pre-bronchodilator FEV_1 of $\geqslant$200 mL during treatment and all subgroup analyses were assessed *post hoc*.

Statistical analysis

Change from baseline analyses in continuous variables (pre- and post-bronchodilator FEV_1, FVC, pre-bronchodilator FEV_1/FVC ratio and $FEF_{25–75\%}$) were reported as least-square (LS) mean values and analysed using mixed-effects models with repeated-measures (MMRM). The assigned study treatment arm, patient age, sex, height, geographic region, baseline blood eosinophil strata, baseline dose of ICS, visit, treatment-by-visit, corresponding baseline value of lung function measure and baseline-by-visit interaction were included as covariates. The MMRM included changes from baseline values in lung function variables during treatment from week 2 to week 52 as response variables.

The estimated rate of change in post-bronchodilator FEV_1 (post-bronchodilator FEV_1 slope) after week 4 was analysed using MMRM, with repeated post-bronchodilator FEV_1 as the outcome, and treatment arm, age, sex, height, geographic region, baseline blood eosinophil strata, baseline dose of ICS, time since randomisation, treatment-by-time and baseline post-bronchodilator FEV_1 included as covariates.

Results

Baseline characteristics

The ITT population of the LIBERTY ASTHMA QUEST trial comprised 1902 patients. As reported previously, the baseline characteristics of the ITT population were similar across the four treatment groups (table 1).

Pre-bronchodilator FEV_1

In the overall ITT population, the LS mean change from baseline to week 52 in pre-bronchodilator FEV_1 was significantly greater for both doses of dupilumab *versus* the corresponding matched placebo groups ($p<0.0001$), with an LS mean improvement of 0.36 L in patients treated with dupilumab 200 mg every 2 weeks (LS mean difference *versus* placebo 0.20 L, 95% CI 0.14–0.25 L) and an improvement of 0.35 L in patients treated with 300 mg every 2 weeks (LS mean difference *versus* placebo 0.13 L, 95% CI 0.08–0.19 L). Improvements in pre-bronchodilator FEV_1 among patients on dupilumab were rapid and sustained, with substantial changes evident after 2 weeks of treatment, and peak improvements maintained through to week 52 (figure 1a and supplementary table S1). Type 2-high patients, with higher baseline levels of blood eosinophils and/or F_{eNO}, achieved greater benefit with dupilumab treatment *versus* placebo compared with the ITT population, with patients with both $\geqslant$150 eosinophils·μL^{-1} and $\geqslant$25 ppb F_{eNO} at baseline showing an LS mean difference *versus* placebo of 0.33 L (95% CI 0.24–0.43 L) and 0.26 L (95% CI

TABLE 1 Baseline patient demographic and clinical characteristics

	Placebo	Dupilumab 200 mg every 2 weeks	Placebo	Dupilumab 300 mg every 2 weeks	Overall population
Subjects	317	631	321	633	1902
Age years	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
BMI kg·m^{-2}	29.76±7.25	29.05±6.52	29.21±6.95	29.07±6.68	29.20±6.77
Pre-bronchodilator FEV_1 L	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Pre-bronchodilator FEV_1% predicted	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
Exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
High-dose ICS use	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5$^{\#}$ score	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Biomarker levels					
Blood eosinophil count cells·μL^{-1}	370±338	349±345	391±419	351±369	360±366
F_{eNO} ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85

Data are presented as n, mean±SD or n (%). Baseline blood eosinophil data were missing for one randomised patient receiving dupilumab 200 mg every 2 weeks and one randomised patient receiving placebo 2 mL/300 mg every 2 weeks and were excluded from efficacy analyses. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; ACQ-5: five-item Asthma Control Questionnaire; F_{eNO}: fractional exhaled nitric oxide. $^{\#}$: ACQ-5 is a patient-reported measure of the adequacy of asthma control and change in asthma control that occurs either spontaneously or as a result of treatment. Higher scores indicate less control; a global score of 0–6 is calculated.

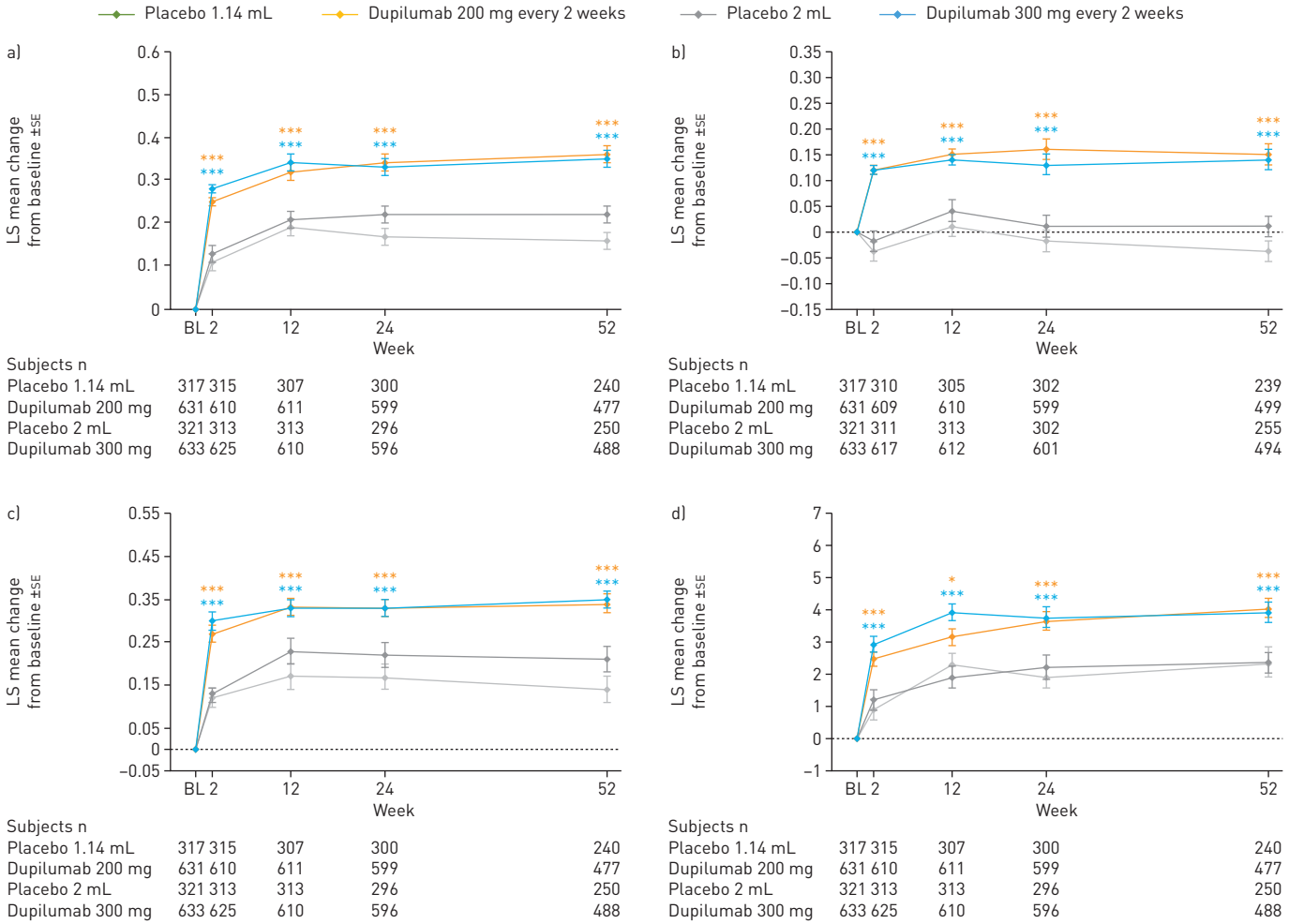


FIGURE 1 Least-square (LS) mean change from baseline (BL) over the 52-week treatment period in the intention-to-treat population in a) pre-bronchodilator forced expiratory volume in 1 s (FEV_1); b) post-bronchodilator FEV_1; c) forced vital capacity (FVC); d) FEV_1/FVC ratio. *: p<0.05, ***: p<0.001.

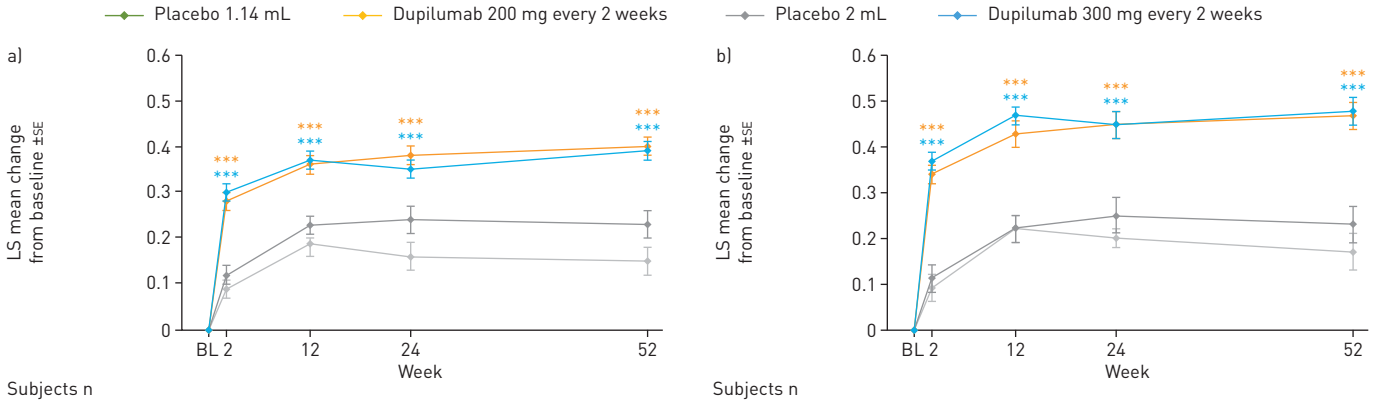
0.17–0.35 L) at week 52 when treated with dupilumab 200 mg or 300 mg every 2 weeks, respectively (figure 2a–d and supplementary table S1).

Post-bronchodilator FEV_1

In the overall ITT population, the LS mean change from baseline to week 52 in post-bronchodilator FEV_1 was significantly greater for dupilumab *versus* matched placebo (LS mean difference *versus* placebo 0.19 L (95% CI 0.14–0.24 L) for dupilumab 200 mg every 2 weeks, and 0.13 L (95% CI 0.08–0.18 L) for dupilumab 300 mg every 2 weeks; both p<0.0001). Improvements in patients on dupilumab were observed after 2 weeks of treatment and maintained through to week 52 (figure 1b and supplementary table S2). Significant improvements in post-bronchodilator FEV_1 were also seen in type 2-high subgroups of patients, with greater improvements *versus* placebo observed in all type 2-high subgroups when compared with improvements in the ITT population (figure 3a–d and supplementary table S2).

Post-bronchodilator FEV_1 slope from week 4 to week 52

In the ITT population, rate of change from baseline over time in post-bronchodilator FEV_1 (FEV_1 slope) during the 52-week treatment period after week 4 was significantly different compared with placebo, with an estimated slope±SE of 0.00±0.01 L·year^{-1} for both dupilumab doses, and an estimated negative slope of −0.04±0.02 L·year^{-1} for both matched placebo groups. The LS mean difference in the rate of change from baseline over time in post-bronchodilator FEV_1 *versus* matched placebo was 0.04 L·year^{-1} (95% CI 0.00–0.08 L·year^{-1}; p=0.04) for both 200 mg and 300 mg dupilumab every 2 weeks (table 2). Although the differences *versus* placebo for the type 2-high subgroups of patients were not statistically significant, there



a) Subjects n	BL	2	12	24	52
Placebo 1.14 mL	232	231	224	217	175
Dupilumab 200 mg	437	424	425	419	341
Placebo 2 mL	237	229	229	215	185
Dupilumab 300 mg	452	446	434	426	347

b) Subjects n	BL	2	12	24	52
Placebo 1.14 mL	148	148	144	141	113
Dupilumab 200 mg	264	255	256	252	206
Placebo 2 mL	142	138	139	129	111
Dupilumab 300 mg	277	273	266	259	207

c) Subjects n	BL	2	12	24	52
Placebo 1.14 mL	162	161	157	153	124
Dupilumab 200 mg	299	291	288	286	224
Placebo 2 mL	172	167	167	157	138
Dupilumab 300 mg	310	305	295	293	242

d) Subjects n	BL	2	12	24	52
Placebo 1.14 mL	134	134	130	126	101
Dupilumab 200 mg	248	240	238	238	189
Placebo 2 mL	142	137	137	129	113
Dupilumab 300 mg	258	253	245	244	203

FIGURE 2 Least-square (LS) mean change from baseline (BL) in pre-bronchodilator forced expiratory volume in 1 s over the 52-week treatment period in patients with a) ⩾150 eosinophils·μL^{-1} at BL; b) ⩾300 eosinophils·μL^{-1} at BL; c) ⩾25 ppb fractional exhaled nitric oxide (F_{eNO}) at BL; and d) both ⩾150 eosinophils·μL^{-1} and ⩾25 ppb F_{eNO} at BL. ***: p<0.001.

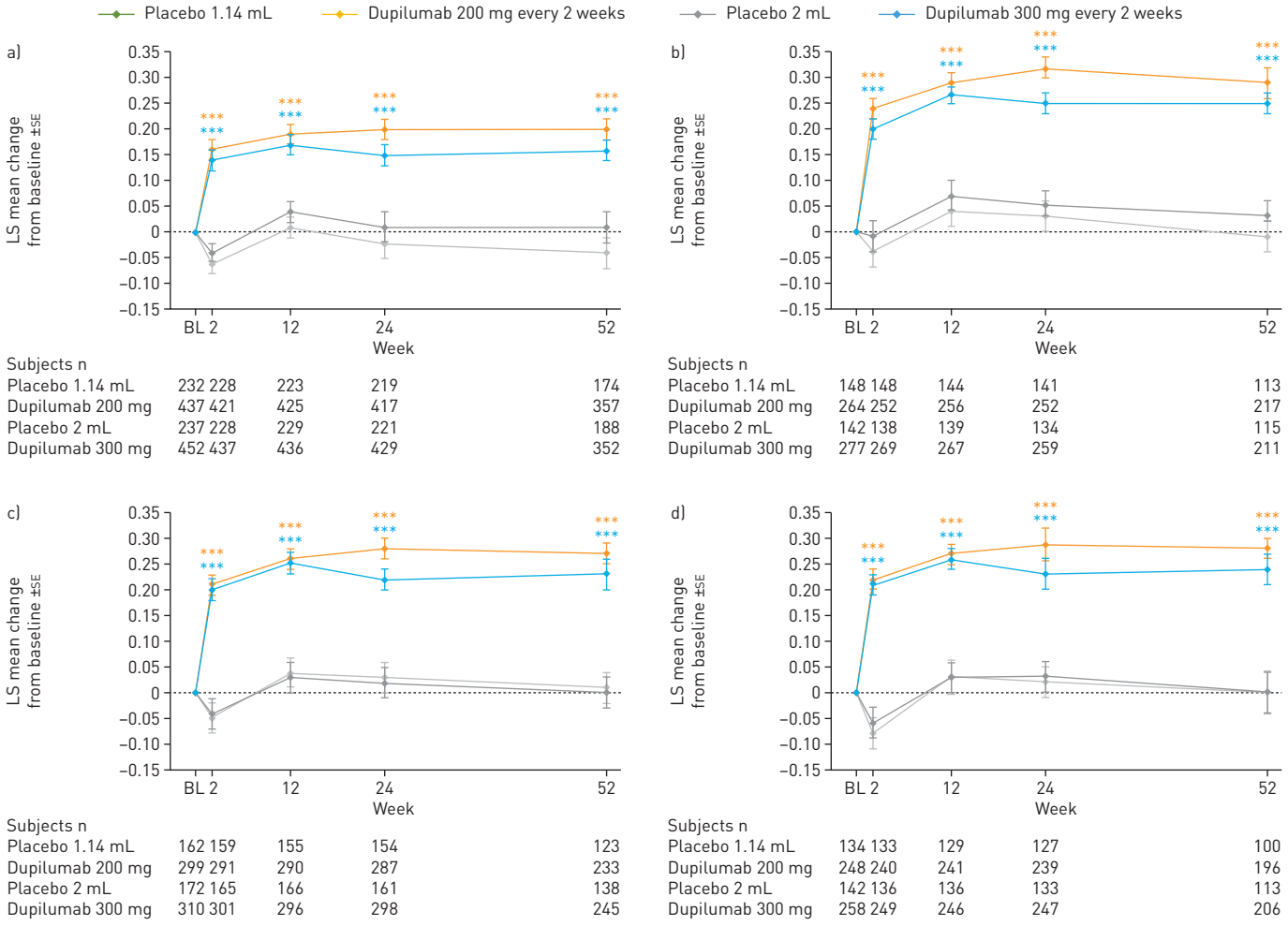


FIGURE 3 Least-square (LS) mean change from baseline (BL) in post-bronchodilator forced expiratory volume in 1 s over the 52-week treatment period in patients with a) ⩾150 eosinophils·μL^{-1} at BL; b) ⩾300 eosinophils·μL^{-1} at BL; c) ⩾25 ppb fractional exhaled nitric oxide (F_{eNO}) at BL; d) both ⩾150 eosinophils·μL^{-1} and ⩾25 ppb F_{eNO} at BL. ***: p<0.001.

was a similar numerical difference *versus* placebo for most comparisons to that seen with the overall ITT population (table 2).

Pre-bronchodilator FVC

The LS mean change from baseline in FVC at week 52 in the ITT population was significantly greater in patients who received dupilumab compared with placebo (p<0.0001) (figure 1c and supplementary table S3). Improvements were rapid and sustained across the 52 weeks of treatment. Patients with both ⩾150 blood eosinophils·μL^{-1} and F_{eNO} ⩾25 ppb at baseline experienced the greatest improvement *versus* placebo in FVC, although a greater improvement *versus* placebo in FVC at week 52 was seen in all the type 2-high subgroups analysed compared with the overall population (figure 4a–d and supplementary table S3). Improvements in FVC *versus* placebo in these patient subgroups were significant from the earliest time point (p<0.01 in both doses for all subgroups).

Pre-bronchodilator FEV_1/FVC ratio

In line with the observed improvements in both FEV_1 and FVC, the ratio of FEV_1/FVC significantly improved (p<0.001) in both dupilumab dose groups compared with respective matched placebo in the overall study population at week 52 (figure 1d and supplementary table S4). Greater improvements at week 52 in the FEV_1/FVC ratio were observed with both dupilumab dose groups *versus* matched placebo (p<0.01) in patients with elevated baseline blood eosinophils or F_{eNO} (or both elevated eosinophils and F_{eNO}) (figure 5a–d and supplementary table S4). As would be expected from the early observed improvement in both FEV_1 and FVC, significant improvements (p<0.05) in the FEV_1/FVC ratio with dupilumab 200 mg or 300 mg every 2 weeks relative to matched placebo occurred from week 2 and were sustained throughout

TABLE 2 Post-bronchodilator forced expiratory volume in 1 s (FEV_1) slope during the 52-week treatment period (after week 4) across different patient subgroups

	1.14 mL/200 mg every 2 weeks		2 mL/300 mg every 2 weeks	
	Placebo	Dupilumab	Placebo	Dupilumab
ITT population	317	631	321	633
Subjects	311	622	319	626
Post-bronchodilator FEV_1 slope after week 4[#] L·year^{-1}	−0.038±0.453	0.001±0.393	−0.075±0.737	0.009±0.442
Estimated post-bronchodilator FEV_1 slope[¶] ±SE	−0.04±0.02	−0.00±0.01	−0.04±0.02	−0.00±0.01
LS mean difference *versus* matched placebo (95% CI)		0.04 (0.00–0.08)		0.04 (0.00–0.08)
p-value *versus* matched placebo		0.04		0.04
Patients with ⩾150 blood eosinophils·μL^{-1} at baseline	232	437	237	452
Subjects	228	432	235	447
Post-bronchodilator FEV_1 slope after week 4[#] L·year^{-1}	−0.038±0.487	−0.003±0.350	−0.086±0.842	−0.006±0.447
Estimated post-bronchodilator FEV_1 slope[¶] ±SE	−0.04±0.02	0.00±0.01	−0.04±0.02	−0.01±0.01
LS mean difference *versus* matched placebo (95% CI)		0.04 (−0.01–0.09)		0.03 (−0.02–0.08)
p-value *versus* matched placebo		0.08		0.18
Patients with ⩾300 blood eosinophils·μL^{-1} at baseline	148	264	142	277
Subjects	146	261	142	274
Post-bronchodilator FEV_1 slope after week 4[#] L·year^{-1}	−0.025±0.525	−0.008±0.355	−0.160±1.006	−0.012±0.533
Estimated post-bronchodilator FEV_1 slope[¶] ±SE	−0.05±0.03	−0.02±0.02	−0.07±0.03	−0.01±0.02
LS mean difference *versus* matched placebo (95% CI)		0.03 (−0.03–0.09)		0.06 (−0.01–0.12)
p-value *versus* matched placebo		0.37		0.09
Patients with ⩾25 ppb F_{eNO} at baseline	162	299	172	310
Subjects	159	295	171	306
Post-bronchodilator FEV_1 slope after week 4[#] L·year^{-1}	−0.019±0.530	0.016±0.446	−0.098±0.958	−0.007±0.405
Estimated post-bronchodilator FEV_1 slope[¶] ±SE	−0.02±0.03	0.00±0.02	−0.06±0.03	−0.01±0.02
LS mean difference *versus* matched placebo (95% CI)		0.03 (−0.04–0.09)		0.05 (−0.02–0.11)
p-value *versus* matched placebo		0.42		0.14
Patients with ⩾150 blood eosinophils·μL^{-1} and ⩾25 ppb F_{eNO} at baseline	134	248	142	258
Subjects	132	245	141	255
Post-bronchodilator FEV_1 slope after week 4[#] L·year^{-1}	−0.002±0.562	0.008±0.347	−0.102±1.043	−0.014±0.413
Estimated post-bronchodilator FEV_1 slope[¶] ±SE	−0.01±0.03	0.00±0.02	−0.05±0.03	−0.02±0.02
LS mean difference *versus* matched placebo (95% CI)		0.01 (−0.06–0.08)		0.03 (−0.04–0.10)
p-value *versus* matched placebo		0.71		0.36

Data are presented as n or mean±SD, unless otherwise stated. ITT: intention-to-treat; LS: least squares; F_{eNO}, fractional exhaled nitric oxide. [#]: individual post-bronchodilator FEV_1 slope was calculated as the slope of a linear regression model with the post-bronchodilator FEV_1 (L) at each visit as the response variable and the time since randomisation as the independent variable; [¶]: estimated from a mixed-effects model with repeated measure with post-bronchodilator FEV_1 as outcome, and treatment, age, sex, height, geographic region, baseline eosinophil strata, baseline inhaled corticosteroid dose level, time since randomisation and treatment-by-time interaction and baseline post-bronchodilator as variables.

the treatment period to week 52 in the ITT population and in patients with elevated type 2 biomarkers (figures 1d and 5a–d and supplementary table S4).

Pre-bronchodilator $FEF_{25–75\%}$

$FEF_{25–75\%}$ was significantly improved in both the dupilumab 200 mg and 300 mg every 2 weeks dose groups compared with matched-volume placebo throughout the treatment period in the overall population and the type 2-high subgroups analysed ($p<0.01$) (supplementary table S5). The largest improvements in $FEF_{25–75\%}$ with dupilumab *versus* placebo were seen in those type 2-high patients with elevated baseline eosinophils and/or F_{eNO} (supplementary table S5).

Patients with ⩾200 mL improvement in pre-bronchodilator FEV_1

The proportion of patients who attained an improvement of ⩾200 mL in pre-bronchodilator FEV_1 during the 52-week treatment period in the overall population and each of the type 2-high biomarker subgroups is summarised in supplementary table S6. In the overall population, the proportion of patients who achieved a ⩾200 mL improvement in pre-bronchodilator FEV_1 by week 52 of treatment was higher in each of the dupilumab treatment groups (50.5% and 54.5% for the 200 mg and 300 mg every 2 weeks dose groups, respectively) than the matched placebo groups (37.1% and 44.0% for the respective placebo

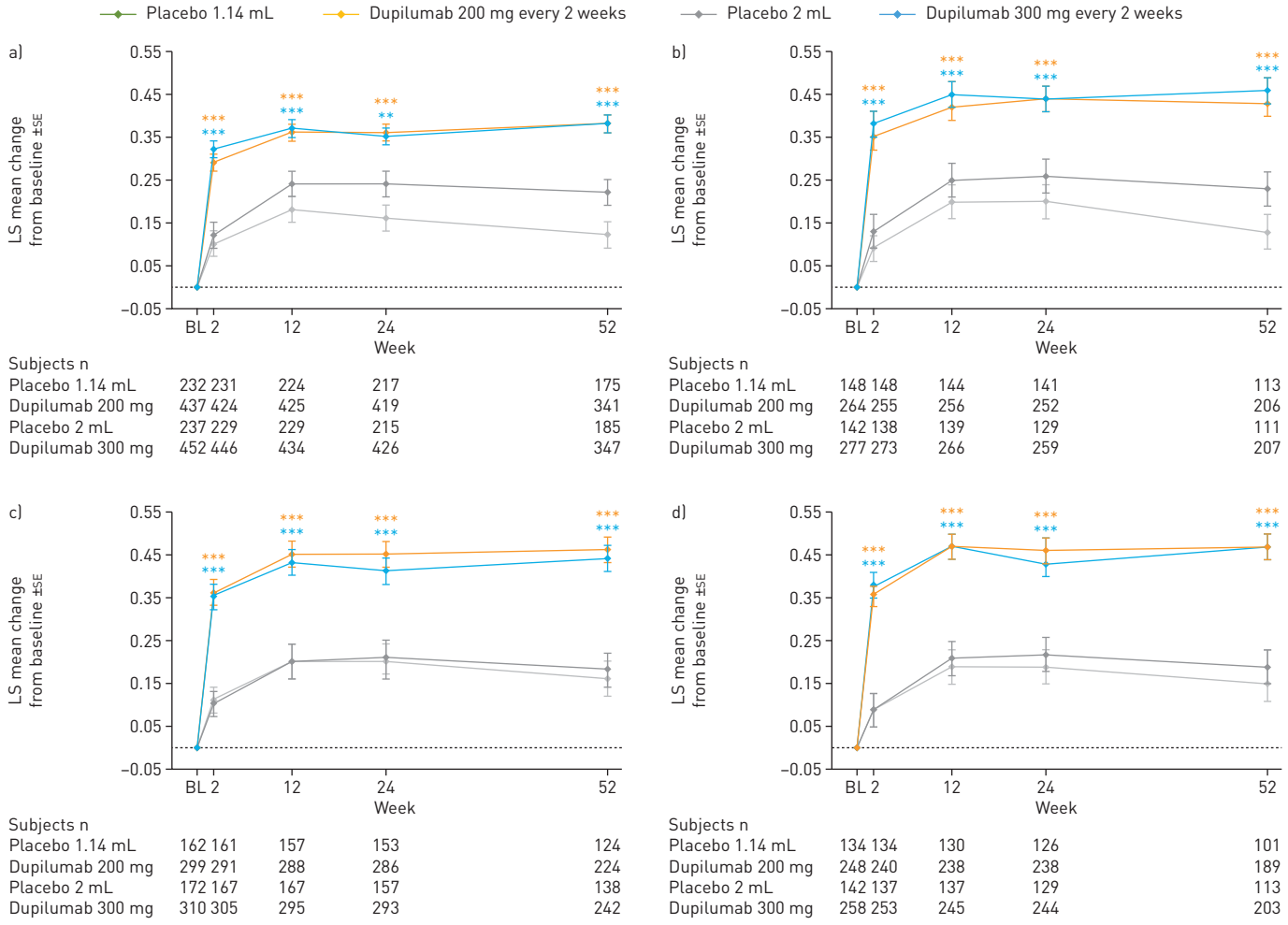


FIGURE 4 Least-square (LS) mean change from baseline (BL) in pre-bronchodilator forced vital capacity over the 52-week treatment period in patients with a) ⩾150 eosinophils·μL^{-1} at BL; b) ⩾300 eosinophils·μL^{-1} at BL; c) ⩾25 ppb fractional exhaled nitric oxide (F_{eNO}) at BL; d) both ⩾150 eosinophils·μL^{-1} and ⩾25 ppb F_{eNO} at BL. **: p<0.01, ***: p<0.001.

groups). A numerically higher proportion of patients achieved a ⩾200 mL improvement in pre-bronchodilator FEV_1 by week 52 in patients in the dupilumab treatment groups who had both elevated baseline blood eosinophils and elevated F_{eNO} (70.4% and 66.0% in the dupilumab 200 mg and 300 mg every 2 weeks groups, respectively, compared with 43.6% and 43.4% in the matched placebo groups), not assessed for statistical significance.

Discussion

This analysis of pre-specified secondary and *post hoc* results from patients with uncontrolled, moderate-to-severe asthma enrolled in the LIBERTY ASTHMA QUEST phase 3 trial showed that lung function across large and small airway outcome measures (FEV_1, FVC, FEV_1/FVC and $FEF_{25–75\%}$) showed significant improvements for patients treated with dupilumab compared with placebo in the overall ITT population. Improvements in these lung function parameters were rapid (noted at the first assessment time point) and sustained over a 52-week treatment period. A higher number of patients treated with dupilumab achieved a ⩾200 mL improvement in pre-bronchodilator FEV_1. A minimal clinically important difference for FEV_1 has not been established for asthma, but it is thought that an improvement of 100–200 mL would be clinically important [25, 26].

These data support previously reported findings that add-on dupilumab treatment reduces the number of severe asthma exacerbations and improves lung function compared with placebo, particularly in patients with higher baseline levels of blood eosinophils or F_{eNO} [18, 19].

Greater dupilumab efficacy was observed in patients with elevated baseline levels of either blood eosinophils or F_{eNO}, both biomarkers of type 2 inflammation. A growing body of data suggests that

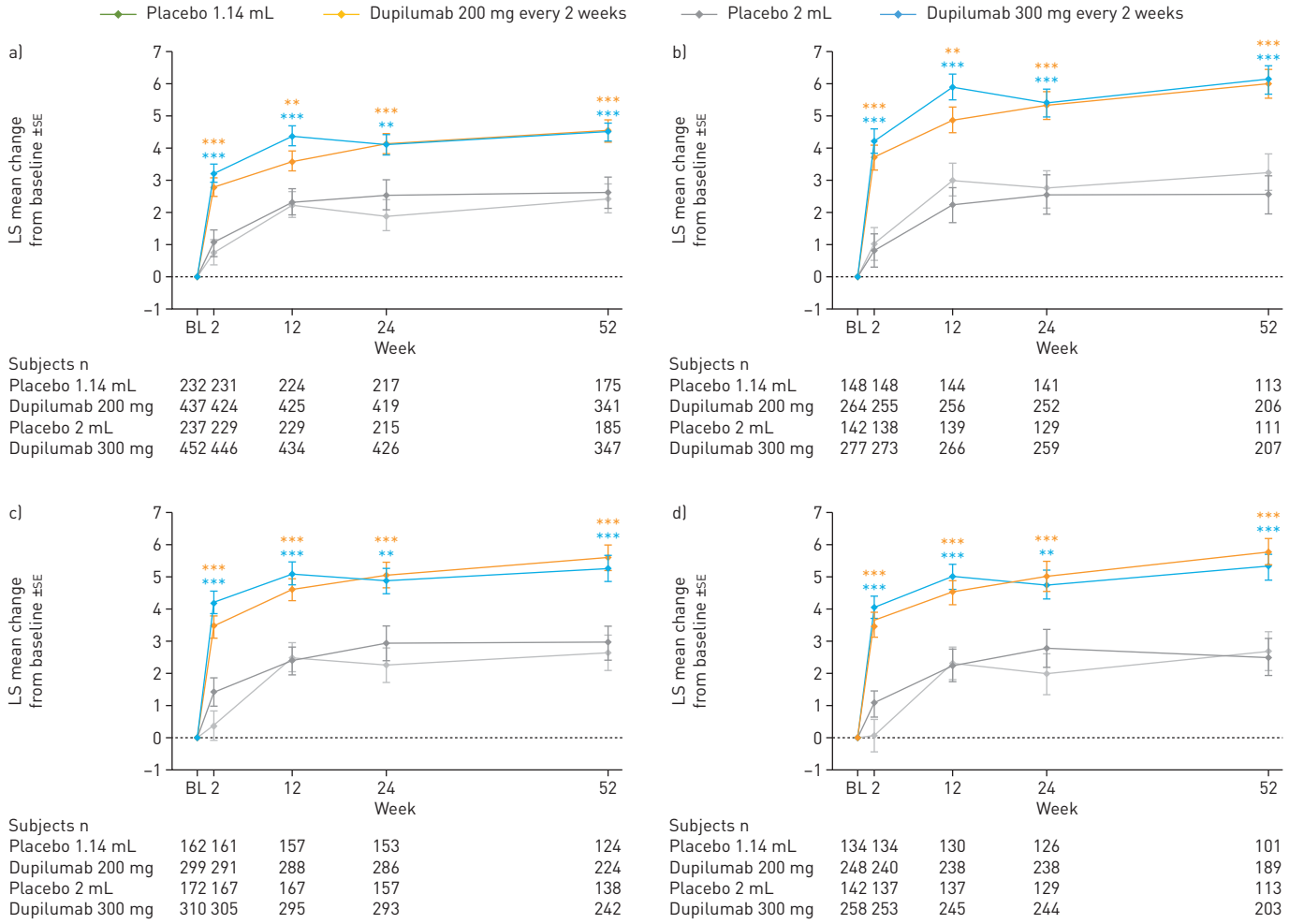


FIGURE 5 Least-square (LS) mean change from baseline (BL) in pre-bronchodilator forced expiratory volume in 1 s/forced vital capacity ratio over the 52-week treatment period in patients with a) ⩾150 eosinophils·μL^{-1} at BL; b) ⩾300 eosinophils·μL^{-1} at BL; c) ⩾25 ppb fractional exhaled nitric oxide (F_{eNO}) at BL; d) both ⩾150 eosinophils·μL^{-1} and ⩾25 ppb F_{eNO} at BL. *: p<0.05, **: p<0.01, ***: p<0.001.

blood eosinophils and F_{eNO} are good markers of type 2 inflammation in asthmatic airways, and that blood eosinophilia reflects airway eosinophilia in asthma [27, 28]. IL-13 plays a predominant role in the production of F_{eNO} by upregulating epithelial cell inducible nitric oxide synthase [10]. Taken together, these data are in line with the mechanism of action of dupilumab, which provides dual blockade targeting both IL-4 and IL-13 signalling pathways. The positive effect seen across several lung function parameters in patients with high baseline levels of either blood eosinophils or F_{eNO} or both supports the broad efficacy of dupilumab.

Post-bronchodilator airway function correlates with aspects of airway remodelling [29, 30]. In the overall QUEST treatment population, there was no observed decline in lung function with dupilumab treatment as measured by post-bronchodilator FEV_1 slope from week 4 to week 52. In contrast, the placebo groups experienced an estimated 40 mL·year^{-1} decline in FEV_1, a rate of decline reported/expected in patients with moderate-to-severe uncontrolled asthma [31]. Mucus plugging is a potential mechanism for airflow obstruction and lung function decline in severe asthma, furthered by involvement of type 2 inflammation of the airways [32]. Reversal of the mucus plugging by dupilumab could be a potential explanation of why the expected lung function decline in these patients was not seen on treatment. Lung function decline in both placebo and dupilumab-treated patients was greatest in the subgroup of patients with ⩾300 eosinophils·μL^{-1} at baseline, indicating a role of type 2 inflammation in contributing to the pathophysiology of lung function decline. A study with a longer-term observation period using imaging will be required to confirm this finding.

As reported in detail previously [20], dupilumab treatment was well tolerated (data not shown). The proportion of patients with serious treatment-emergent adverse events related to dupilumab was low (8.2%) and similar to that reported with combined placebo (8.4%).

A potential limitation of these findings was our reliance on spirometry ($FEF_{25–75\%}$) to assess small airways function. This technique is regarded by some to be less than optimal, as measurements can be influenced by large airway obstruction [33]. While a reliable, non-invasive index for diagnosis and monitoring of small airways disease remains elusive, other techniques such as imaging with computed tomography or magnetic resonance imaging, plethysmography and impulse oscillometry have proven valuable in some studies [34].

In conclusion, these further observations from the phase 3 LIBERTY ASTHMA QUEST trial show that add-on therapy with dupilumab 200 mg or 300 mg every 2 weeks compared with matched placebo significantly improves outcomes across a range of lung function measures, including those of large and small airways and fixed airway obstruction, in patients with uncontrolled, moderate-to-severe asthma. The observed improvements in lung function were rapid and sustained throughout the treatment period. Greater improvements in lung function were observed in patients with higher baseline levels of blood eosinophils and F_{eNO}, markers of type 2 inflammation. The positive effect of dupilumab on lung function and the protective effect against asthma exacerbations should be further investigated long-term to better understand the implications of these benefits.

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