**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 (FEV1) 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 $\geq 150$ eosinophils·µL$^{-1}$, $\geq 300$ eosinophils·µL$^{-1}$, $\geq 25$ ppb fractional exhaled nitric oxide (FeNO), and both $\geq 150$ eosinophils·µL$^{-1}$ and $\geq 25$ ppb FeNO, 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 FEV1 (0.20 and 0.13 L, respectively, versus placebo) and post-bronchodilator FEV1 (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 FEV1/FVC ratio (1.75% and 1.61%, respectively) in the overall population ($p<0.001$). Difference versus placebo in post-bronchodilator FEV1 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 FeNO 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 [https://bit.ly/2OhKMpi](https://bit.ly/2OhKMpi)

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This study is registered at [www.clinicaltrials.gov](http://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](http://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 (FEV₁) 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 (FeNO) 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 FeNO 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 FEV₁, 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 FeNO 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 FEV₁) 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 FeNO 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
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 $\geq$150 eosinophils·µL$^{-1}$ at baseline; patients with $\geq$300 eosinophils·µL$^{-1}$ at baseline; patients with
$\geq$25 ppb $F_{ENO}$ at baseline; and patients with elevation of both blood eosinophils ($\geq$150 eosinophils·µL$^{-1}$)
and $F_{ENO}$ ($\geq$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 $\geq$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 $\geq$150 eosinophils·µL$^{-1}$ and $\geq$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

| Subjects | 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 | 29.7±7.25 | 29.0±6.52                       | 31.9±8.59 | 29.0±7.68                     | 29.20±6.77         |
| Pre-bronchodilator FEV₁ L | 1.74±0.61 | 1.78±0.62                       | 1.75±0.57 | 1.78±0.60                     | 1.78±0.60          |
| Pre-bronchodilator FEV₁% predicted | 58.43±13.22 | 58.38±13.52                     | 58.35±13.87 | 58.51±13.52                   | 58.43±13.52        |
| 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-5² score | 2.71±0.73 | 2.76±0.80                       | 2.77±0.77 | 2.77±0.76                     | 2.76±0.77          |
| Blood eosinophil count cells·µL⁻¹ | 370±338 | 349±345                         | 391±419 | 351±369                       | 360±366            |
| FeNO 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; FEV₁: forced expiratory volume in 1 s; ICS: inhaled corticosteroid; ACQ-5: five-item Asthma Control Questionnaire; FeNO: fractional exhaled nitric oxide.²: 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 (FEV₁); b) post-bronchodilator FEV₁; c) forced vital capacity (FVC); d) FEV₁/FVC ratio. *: p<0.05, ***: p<0.001.

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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**

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

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**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 \(\left[F_{eNO}\right]\) at BL; and d) both ≥150 eosinophils·µL\(^{-1}\) and ≥25 ppb \(F_{eNO}\) at BL. ***: p<0.001.

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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 \( \geq 150 \) blood eosinophils·µL\(^{-1}\) and \( F_{\text{eNO}} \geq 25 \) 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<0.0001) 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 \( F_{\text{eNO}} \) (or both elevated eosinophils and \( F_{\text{eNO}} \)) (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
Patients with individual post-bronchodilator FEV₁ slope was calculated as the slope of a linear regression model with the post-bronchodilator FEV₁ (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 FEV₁ as outcome, and treatment, age, sex, height, geographic region, baseline eosinophil counts. Subjects at baseline matched placebo.

Patients with ≥150 blood eosinophils·µL⁻¹ at baseline

Patients with ≥300 blood eosinophils·µL⁻¹ at baseline

Patients with ≥25 ppb FeNO at baseline

Patients with ≥150 blood eosinophils·µL⁻¹ and ≥25 ppb FeNO at baseline

Data are presented as n or mean±sd, unless otherwise stated. ITT: intention-to-treat; LS: least squares; FeNO, fractional exhaled nitric oxide. *: individual post-bronchodilator FEV₁ slope was calculated as the slope of a linear regression model with the post-bronchodilator FEV₁ (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 FEV₁ as outcome, and treatment, age, sex, height, geographic region, baseline eosinophil counts, baseline inhaled corticosteroid dose level, time since randomisation and treatment-by-time interaction and baseline post-bronchodilator as variables.

## TABLE 2 Post-bronchodilator forced expiratory volume in 1 s (FEV₁) 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**   |         |           |         |           |
| Subjects             | 317     | 631       | 321     | 633       |
| Post-bronchodilator FEV₁ 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 FEV₁ 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** |         |           |         |           |
| Subjects             | 232     | 437       | 237     | 452       |
| Post-bronchodilator FEV₁ 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 FEV₁ 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** |         |           |         |           |
| Subjects             | 148     | 264       | 142     | 277       |
| Post-bronchodilator FEV₁ 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 FEV₁ 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 FeNO at baseline** |         |           |         |           |
| Subjects             | 162     | 299       | 172     | 310       |
| Post-bronchodilator FEV₁ 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 FEV₁ 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 FeNO at baseline** |         |           |         |           |
| Subjects             | 134     | 248       | 142     | 258       |
| Post-bronchodilator FEV₁ 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 FEV₁ 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; FeNO, fractional exhaled nitric oxide. *: individual post-bronchodilator FEV₁ slope was calculated as the slope of a linear regression model with the post-bronchodilator FEV₁ (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 FEV₁ as outcome, and treatment, age, sex, height, geographic region, baseline eosinophil counts, 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 FeNO (supplementary table S5).

**Patients with ≥200 mL improvement in pre-bronchodilator FEV₁**

The proportion of patients who attained an improvement of ≥200 mL in pre-bronchodilator FEV₁ 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 FEV₁ 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
A numerically higher proportion of patients achieved a ≥200 mL improvement in pre-bronchodilator FEV1 by week 52 in patients in the dupilumab treatment groups who had both elevated baseline blood eosinophils and elevated FeNO (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 (FEV1, FVC, FEV1/FVC and FEF25–75%) 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 FEV1. A minimal clinically important difference for FEV1 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 FeNO [18, 19].

Greater dupilumab efficacy was observed in patients with elevated baseline levels of either blood eosinophils or FeNO, both biomarkers of type 2 inflammation. A growing body of data suggests that
blood eosinophils and FeNO 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 FeNO 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 FeNO 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 FEV₁ slope from week 4 to week 52. In contrast, the placebo groups experienced an estimated 40 mL-year⁻¹ decline in FEV₁, 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 $F_i_{NO}$, 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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