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Original Research

Dupilumab sustains lung function improvements in patients with moderate-to-severe asthma

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ABSTRACT

Background: TRAVERSE (NCT02134028), a phase 3 open-label extension study, assessed dupilumab safety and efficacy in patients with asthma aged ≥12 years who completed a previous dupilumab asthma study. This analysis evaluated changes in multiple lung function parameters in patients with moderate-to-severe asthma with elevated type 2 biomarkers (baseline eosinophils ≥150 cells·μL^{-1} or fractional exhaled nitric oxide ≥25 ppb) who completed QUEST (parent study) and 2 years of dupilumab treatment in TRAVERSE.

Methods: Endpoints analyzed included: pre-bronchodilator forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), forced expiratory flow ($FEF_{25-75\ \%}$), and pre- and post-bronchodilator FEV_1/FVC at parent study baseline (PSBL) at Weeks 0, 2, 48, and 96 in TRAVERSE, as well as pre- and post-bronchodilator FEV_1 slopes in QUEST and TRAVERSE. Statistical analyses were descriptive.

Results: Dupilumab improved pre-bronchodilator FEV_1, FVC, and $FEF_{25–75\ \%}$ in QUEST; these improvements were sustained in TRAVERSE. In QUEST patients who received placebo, dupilumab initiation in TRAVERSE resulted in rapid lung function improvements. Mean (standard deviation) changes from PSBL at TRAVERSE Weeks 48 and 96 in pre-bronchodilator FEV_1 were 0.52 (0.59) and 0.45 (0.49) L in the dupilumab/dupilumab group and 0.47 (0.42) and 0.44 L (0.45) in the placebo/dupilumab group, respectively. Similar trends were observed for FVC and $FEF_{25–75\ \%}$. Dupilumab also improved FEV_1 slopes in QUEST and TRAVERSE.

Conclusion: Dupilumab demonstrated sustained improvements across multiple spirometric lung function measurements for up to 3 years; patients who received placebo in QUEST experienced rapid lung function improvement upon initiation of dupilumab in TRAVERSE.

1. Introduction

Asthma is a common, chronic, inflammatory condition characterised by episodic respiratory symptoms, such as cough, wheeze, shortness of breath and chest tightness, and airflow limitation [1]. With a global prevalence of 262 million cases in 2019, asthma affects 3.5 % of the population [2]. Clinical management of asthma includes both controlling asthma symptoms and reducing the risk of future poor asthma outcomes [1].

Long-term, uncontrolled asthma is linked to a deterioration of lung function over time [3,4], which is in turn associated with poor forced expiratory volume in 1 s (FEV_1) [5–7] and can be accelerated by factors such as recurrent exacerbations [8–10] and systemic inflammation that

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Abbreviations

ACQ-5	5-item Asthma Control Questionnaire
AQLQ	Asthma Quality of Life Questionnaire
CI	confidence interval
$FEF_{25–75\ \%}$	forced expiratory flow at 25–75 % of pulmonary volume
FeNO	fractional exhaled nitric oxide
FEV_1	forced expiratory volume in 1 s
FVC	forced vital capacity
ICS	inhaled corticosteroid(s)
IL	interleukin
IgE	immunoglobulin E
IU	international units
LABA	long-acting beta agonist
LAMA	long-actingmuscarinic antagonist
LS	least squares
ppb	parts per billion
PSBL	parent study baseline
SD	standard deviation
SE	standard error.

can drive airway remodeling [11]. This leads to an increased risk of persistent airflow limitation [10,12,13], which has been associated with an increased burden of disease as well as increased morbidity and mortality [7,12,14,15]. Therefore, preventing loss of lung function in these patients is essential for the management of severe asthma. Current standard-of-care therapies such as inhaled corticosteroids (ICS) or bronchodilators can provide symptomatic relief for shortness of breath, or temporary improvement in FEV_1. Despite the proven value of these agents in improving asthma control, there is less convincing evidence that these therapies sustain long-term, clinically meaningful improvements in FEV_1 or that they prevent lung function decline among patients with moderate-to-severe asthma. There remains an unmet need for therapies that can produce sustained improvements in lung function.

Dupilumab, a fully human VelocImmune®-derived monoclonal antibody [16,17], blocks the shared receptor component for interleukins (IL)-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases [18,19]. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854), add-on dupilumab 200 or 300 mg every 2 weeks (q2w) vs placebo significantly improved pre-bronchodilator FEV_1 in the overall population of patients with uncontrolled, moderate-to-severe asthma, with greater improvements observed in those with elevated type 2 biomarkers at baseline (blood eosinophils $\geq$150 cells·μL^{-1} or fractional exhaled nitric oxide [FeNO] $\geq$25 ppb) [20,21].

The open-label, single-arm LIBERTY ASTHMA TRAVERSE study (NCT02134028) evaluated the long-term safety and efficacy of add-on dupilumab in adult and adolescent patients who had participated in a previous dupilumab asthma study [22]. TRAVERSE demonstrated that long-term use of dupilumab led to sustained efficacy, with a safety profile consistent with the parent studies [22]. Sustained improvements in pre-bronchodilator FEV_1 were observed in patients who continued receiving dupilumab in TRAVERSE, and rapid and sustained improvements were observed in those patients who initiated dupilumab having received placebo in the parent studies [22].

While QUEST and TRAVERSE demonstrated the rapid and sustained effect that dupilumab has on lung function as measured by pre-bronchodilator FEV_1 [20–22], other spirometric measures assessing aspects of lung physiology such as forced expiratory flow ($FEF_{25-75\ \%}$), forced vital capacity (FVC), and the FEV_1/FVC ratio may provide greater insight into the impact on both small and large airway function, as well as airflow obstruction, and suggest potential improvements in other features impacted by asthma, such as gas trapping.

Here we confirm and expand upon the improvements in pre-bronchodilator FEV_1 previously reported in QUEST and TRAVERSE [20–22] by presenting the analysis of long-term changes in FEV_1, FVC, $FEF_{25–75\ \%}$, and FEV_1/FVC ratio in patients with uncontrolled, moderate-to-severe asthma with elevated type 2 biomarkers at parent study baseline (PSBL) who enrolled in the TRAVERSE open-label extension study from QUEST, receiving up to 3 years of dupilumab treatment.

2. Methods

2.1. Study design

The phase 3 QUEST study (NCT02414854) (parent study) was a randomized controlled trial that evaluated the efficacy and safety of dupilumab in patients aged $\geq$12 years with moderate-to-severe asthma. Full details of the study design have been published previously [20]. Patients (N = 1902) were treated with subcutaneous dupilumab 200 mg or 300 mg or matched placebo q2w for 52 weeks. Patients received medium- or high-dose ICS and at least one other controller medication. Maintenance oral corticosteroid use at baseline was not allowed.

TRAVERSE (NCT02134028), a phase 3 single-arm, open-label extension study, enrolled patients who had previously completed a dupilumab asthma study (N = 2282 patients) and evaluated the long-term safety and efficacy of dupilumab. Full details of the study design have been previously published [22]. The present analysis aimed to evaluate continuous treatment with dupilumab for up to 3 years. Therefore, we only considered patients from the parent study QUEST who enrolled in TRAVERSE because eligible patients from other parent studies such as the dupilumab asthma phase 2b (NCT01854047) had received treatments shorter than 52 weeks and had a treatment gap before enrolling in TRAVERSE [22]. Patients from the phase 3 QUEST study were eligible to enrol in TRAVERSE at the study end-of-treatment visit. In TRAVERSE, all patients received dupilumab 300 mg q2w up to 96 weeks. Patients who were treated with dupilumab during the parent study continued with dupilumab (dupilumab/dupilumab treatment arm); patients who had received placebo during the parent study initiated dupilumab treatment upon entering TRAVERSE (placebo/dupilumab). Following a protocol amendment due to accumulating safety data, the treatment period of TRAVERSE was shortened to 48 weeks [22].

The studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guideline, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. The local institutional review board or ethics committee at each study center oversaw trial conduct and documentation. All patients, or their parents/guardians, provided written informed consent before participating in the trial.

2.2. Patients

The primary analysis population comprised patients from QUEST with a type 2 inflammatory phenotype (elevated blood eosinophil counts $\geq$150 cells·μL^{-1} or FeNO $\geq$25 ppb at PSBL) who enrolled in TRAVERSE and received either 3 years of continuous treatment with dupilumab (dupilumab 200 or 300 mg q2w for 1 year in QUEST, and dupilumab 300 mg q2w for 2 years in TRAVERSE; dupilumab/dupilumab treatment arm) or 2 years of continuous treatment with dupilumab (placebo q2w for 1 year in QUEST, and dupilumab 300 mg q2w for 2 years in TRAVERSE; placebo/dupilumab treatment arm). Hereafter, this population is referred to as "patients with a type 2 inflammatory phenotype followed for 3 years." Other populations analyzed and presented in the supplementary appendix were all patients from QUEST with a type 2 inflammatory phenotype who enrolled in TRAVERSE, including those who enrolled in TRAVERSE but did not complete the full 3 years of treatment ("total QUEST type 2 population"), the overall exposed patients from QUEST who enrolled in TRAVERSE, hereafter

Table 1
Demographics, disease characteristics, and biomarkers at parent study baseline in patients with moderate-to-severe asthma with a type 2 inflammatory phenotype, who enrolled in TRAVERSE and received 3 years of treatment.

	Patients with type 2 inflammation[a] followed for 3 years	
	Placebo/dupilumab (n = 185)	Dupilumab/dupilumab (n = 364)
Age, years	50.7 ± 12.9	48.1 ± 13.8
<18 years	3 (1.6)	12 (3.3)
18–64 years	158 (85.4)	309 (84.9)
≥65 years	24 (13.0)	43 (11.8)
Male	72 (38.9)	145 (39.8)
Ongoing atopic or allergic condition	147 (79.5)	300 (82.4)
Former smoker	41 (22.2)	62 (17.0)
High-dose ICS	107 (57.8)	194 (53.3)
Number of severe asthma exacerbations experienced in 1 year before the parent study	2.30 ± 2.08	2.10 ± 1.88
Pre-bronchodilator FEV_1, L	1.74 ± 0.55	1.82 ± 0.59
Pre-bronchodilator $ppFEV_1$, %	57.30 ± 12.90	58.89 ± 12.31
Pre-bronchodilator FVC, L	2.85 ± 0.89	2.90 ± 0.88
Pre-bronchodilator $FEF_{25–75\ \%}$, $L{\cdot}s^{-1}$	1.02 ± 0.54	1.10 ± 0.55
FEV_1 reversibility, %	29.30 ± 18.74	27.12 ± 19.35
ACQ-5 score[b]	2.74 ± 0.77	2.72 ± 0.79
AQLQ global score[c]	4.19 ± 0.99	4.26 ± 1.10
Biomarkers		
Blood eosinophils, $Giga{\cdot}L^{-1}$	0.49 ± 0.42	0.42 ± 0.35
Total IgE, $IU{\cdot}mL^{-1}$	401.03 ± 633.41	502.61 ± 861.32
FeNO, ppb	42.10 ± 36.78	39.56 ± 36.03

Data are presented as n (%) or mean ± SD, unless otherwise stated. Abbreviations: ACQ-5: 5-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; $FEF_{25–75\ \%}$: forced expiratory flow at 25–75 % of pulmonary volume; FeNO: fractional exhaled nitric oxide; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; ICS: inhaled corticosteroid(s); IU: International Units; ppb, parts per billion; $ppFEV_1$; percent predicted FEV_1; PSBL: parent study baseline; SD: standard deviation.

[a] Elevated type 2 biomarkers defined as eosinophils ≥150 $cells{\cdot}\mu L^{-1}$ or FeNO ≥25 ppb at PSBL.

[b] Scores on the ACQ-5 range from 0 (totally controlled) to 6 (severely uncontrolled).

[c] Scores on the AQLQ from 1 to 7, with higher scores indicating better quality of life.

referred to as "total QUEST population," and the overall exposed patients from QUEST who enrolled in TRAVERSE and were followed for 3 years ("QUEST population followed for 3 years").

2.3. Endpoints

The following endpoints were included in this analysis: change from QUEST baseline in pre-bronchodilator FEV_1, FVC, and forced expiratory flow ($FEF_{25–75\ \%}$), and pre-bronchodilator FEV_1/FVC during the 52-week treatment period of QUEST and TRAVERSE. Change from PSBL at Week 0 of TRAVERSE was also assessed for post-bronchodilator FEV_1/FVC. Outcomes analyzed in a slope analysis were pre- and post-bronchodilator FEV_1 in QUEST after Week 4 of the 52-week treatment period of QUEST, and pre-bronchodilator FEV_1 after Week 4 of TRAVERSE. Post-bronchodilator FEV_1 was analyzed only for QUEST as post-bronchodilator spirometry was not collected in TRAVERSE.

2.4. Statistical analysis

Due to the open-label nature of TRAVERSE, data were analyzed using descriptive statistics and presented as mean (standard deviation [SD]) change from PSBL at TRAVERSE Weeks 0, 2, 48, and 96, key timepoints of the open-label extension study. For the slope analysis, individual pre- and post-bronchodilator FEV_1 slopes were calculated as the slope of a linear regression model with the pre- and post-bronchodilator FEV_1, respectively, at each visit as the response variable and the time since randomization as the independent variable. Data after TRAVERSE Week 4 to Week 96 were included in the analysis. The estimated pre- and post-bronchodilator FEV_1 slopes in QUEST were calculated from a mixed-effects model with repeated pre- or post-bronchodilator FEV_1 as the outcome, and the 2 pooled treatment groups, age, sex, height, region (pooled country), baseline eosinophil strata, baseline ICS dose level, time since randomization, treatment-by-time interaction, and baseline relevant spirometric variable as covariates. Intercept and time since randomization are random effects. Data after QUEST Week 4 to Week 52 were included in the analysis.

3. Results

3.1. Patients

Demographics, disease characteristics, and biomarkers at PSBL in patients with a type 2 inflammatory phenotype who were followed for 3 years were similar across the treatment arms (Table 1).

Furthermore, baseline characteristics across the different subgroups analyzed were generally similar to the primary analysis population (Table S1). For the population of QUEST patients with a type 2 inflammatory phenotype, controller medications used at PSBL and baseline characteristics at entry into TRAVERSE are shown in the supplementary appendix (Table S2 and Table S3, respectively).

3.2. Lung function

In patients with a type 2 inflammatory phenotype who were followed for 3 years, the improvements observed for pre-bronchodilator FEV_1, FVC, and $FEF_{25–75\ \%}$ during QUEST were sustained in TRAVERSE for patients in the dupilumab/dupilumab group (Fig. 1a–c, respectively). Across all 3 measurements, rapid improvements were observed as early as Week 2 after initiation of dupilumab in TRAVERSE in those patients who had received placebo during QUEST (Fig. 1a–c). At Week 0 of TRAVERSE, dupilumab improved pre-bronchodilator FEV_1 (mean [SD]) over the PSBL by 0.35 L (0.45 L), which was sustained up to Week 96 of TRAVERSE (0.35 L [0.48 L]) in the dupilumab/dupilumab group. In the placebo/dupilumab group, pre-bronchodilator FEV_1 (mean [SD]) over the PSBL was improved by 0.19 L (0.39 L) at Week 0 of TRAVERSE, with a rapid improvement by TRAVERSE Week 2 of 0.34 L (0.42 L), which was sustained to Week 96 (0.37 L [0.44 L]) (Fig. 1a).

Similarly, improvements observed during QUEST in pre-bronchodilator FVC were sustained during TRAVERSE. In the placebo/dupilumab group, pre-bronchodilator FVC (mean [SD]) over the PSBL

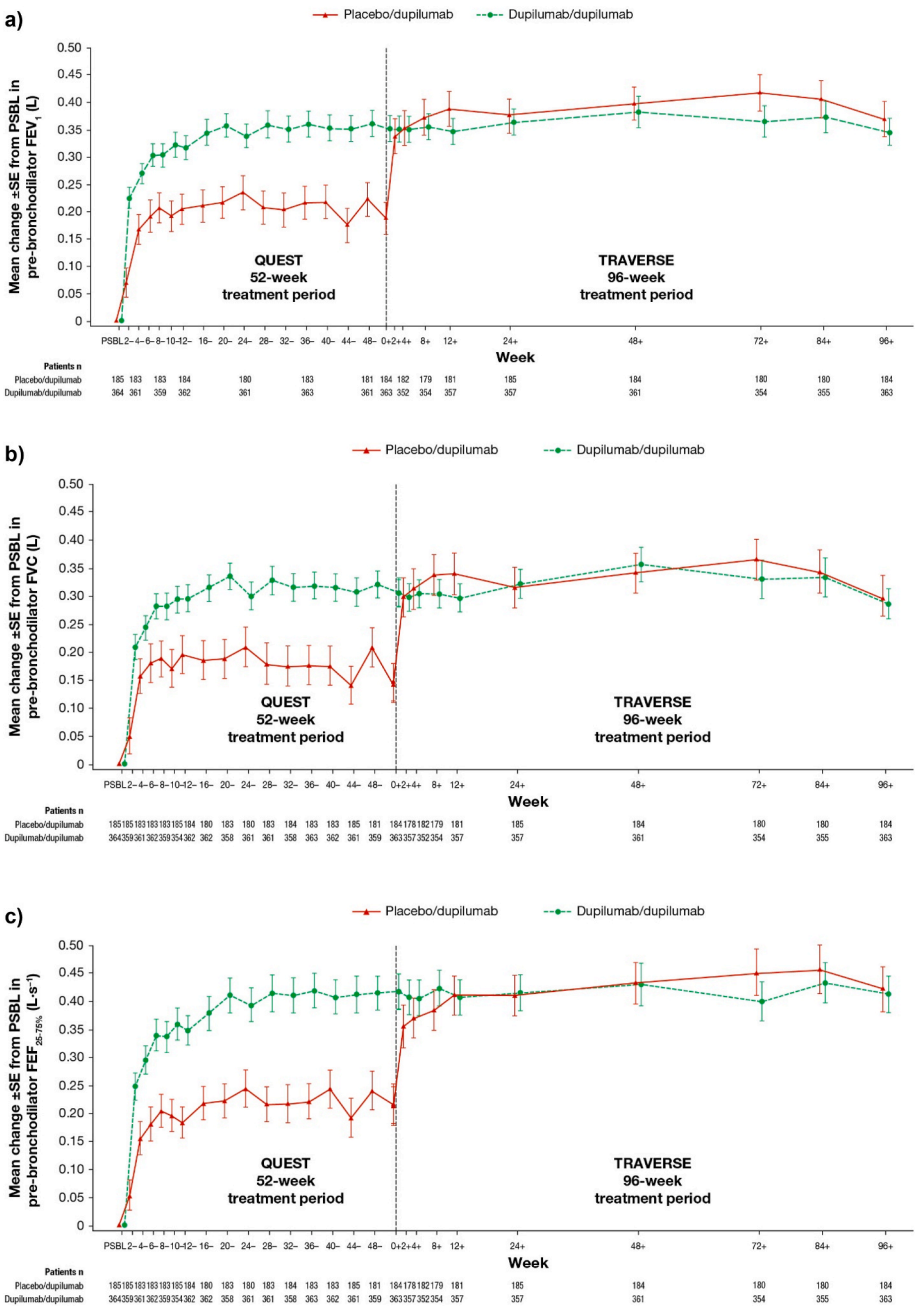

Fig. 1. Mean change from QUEST baseline in pre-bronchodilator a) FEV_1, b) FVC, and c) $FEF_{25–75\ \%}$ in patients with a type 2 inflammatory phenotype followed for 3 years. Abbreviations: $FEF_{25–75\ \%}$: forced expiratory flow at 25–75 % of pulmonary volume;FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PSBL, parent study baseline; SE, standard error.

was improved by 0.15 L (0.46 L) at Week 0 of TRAVERSE, with a rapid improvement by TRAVERSE Week 2 of 0.30 L (0.47 L), which was sustained to Week 96 (0.30 L [0.49 L]) (Fig. 1b).

Dupilumab improved pre-bronchodilator $FEF_{25–75\ \%}$ over PSBL in the dupilumab/dupilumab group by 0.42 $L{\cdot}s^{-1}$ (0.60 $L{\cdot}s^{-1}$) at Week 0 of TRAVERSE, and this was sustained to Week 96 (0.41 $L{\cdot}s^{-1}$ [0.64 $L{\cdot}s^{-1}$]). In the placebo/dupilumab group, change in pre-bronchodilator $FEF_{25–75\ \%}$ over PSBL at TRAVERSE Week 0 was 0.22 $L{\cdot}s^{-1}$ (0.47 $L{\cdot}s^{-1}$). At Week 2 of TRAVERSE, after initiation of dupilumab treatment, a rapid improvement in pre-bronchodilator $FEF_{25–75\ \%}$ over PSBL was observed to 0.36 $L{\cdot}s^{-1}$ (0.50 $L{\cdot}s^{-1}$), which continued to improve to Week 96 (0.42 $L{\cdot}s^{-1}$ [0.54 $L{\cdot}s^{-1}$]) (Fig. 1c).

Consistent with these findings, pre-bronchodilator FEV_1, FVC, and $FEF_{25–75\ \%}$ improvements in TRAVERSE were observed in patients from QUEST with a type 2 inflammatory phenotype (Figs. S1a–c, respectively), the total QUEST population (Fig. S2a–c, respectively), and the overall QUEST population followed for 3 years (Figs. S3a–c, respectively).

3.3. *Pre- and post-bronchodilator FEV_1/FVC ratio*

In line with the improvements observed in both pre-bronchodilator FEV_1 and FVC, improvements in the ratio of FEV_1/FVC observed during QUEST were sustained throughout TRAVERSE in the dupilumab/dupilumab group, and improvements over PSBL were observed as early as TRAVERSE Week 2 in the placebo/dupilumab group, which were sustained throughout TRAVERSE. While both pre-bronchodilator FEV_1 and FVC improved over the course of QUEST and TRAVERSE, the ratio

Table 2
FEV_1/FVC ratio in patients with moderate-to-severe asthma and a type 2 inflammatory phenotype at parent study baseline followed for 3 years.

	Patients with a type 2 inflammatory phenotype followed for 3 years	
	Placebo/dupilumab (n = 185)	Dupilumab/dupilumab (n = 364)
Pre-bronchodilator FEV_1/FVC, %		
PSBL	61.6 ± 9.6	62.9 ± 9.8
TRAVERSE Week 0	64.6 ± 10.2	67.6 ± 9.6
TRAVERSE Week 2	66.2 ± 9.6	67.7 ± 9.4
TRAVERSE Week 48	67.3 ± 9.5	67.2 ± 10.0
TRAVERSE Week 96	67.3 ± 9.5	67.6 ± 9.8
Post-bronchodilator FEV_1/FVC, %		
PSBL	66.6 ± 10.2	66.8 ± 10.3
QUEST Week 52	66.5 ± 10.2	69.9 ± 10.2

Data are presented as mean ± SD. Abbreviations: FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; PSBL: parent study baseline; SD: standard deviation.

Table 3
FEV_1 slope during QUEST and TRAVERSE in patients with moderate-to-severe asthma and a type 2 inflammatory phenotype at parent study baseline followed for 3 years.

	Patients with a type 2 inflammatory phenotype followed for 3 years	
	Placebo/dupilumab (n = 185)	Dupilumab/dupilumab (n = 364)
Pre-bronchodilator FEV_1 slope during the QUEST 52-week treatment period after Week 4, mL·year^{-1}	−4 ± 334	55 ± 252
Estimated pre-bronchodilator FEV_1±SE	−0.3 ± 20	60 ± 20
LS mean difference vs matching placebo (95 % CI)		60 (5–110)
P value vs matching placebo		0.0316
Post-bronchodilator FEV_1 slope during QUEST 52-week treatment period after Week 4, mL·year^{-1}	−67 ± 368	2 ± 241
Estimated post-bronchodilator FEV_1±SE	−60 ± 20	2 ± 20
LS mean difference vs matching placebo (95 % CI)		60 (10–120)
P value vs matching placebo		0.0160
Pre-bronchodilator FEV_1 slope during TRAVERSE 96-week treatment after Week 4, mL·year^{-1}	9 ± 156	2 ± 177

Data are presented as mean ± SD unless otherwise stated. Abbreviations: CI: confidence interval; FEV_1: forced expiratory volume in 1 s; LS: least squares, SD: standard deviation; SE: standard error.

remained balanced (Table 2).

Post-bronchodilator measurements were taken only during QUEST, not TRAVERSE. In QUEST, dupilumab significantly improved the post-bronchodilator FEV_1/FVC ratio vs placebo at Week 52 ($P < 0.0001$) and by mean (SD) 3.41 (7.01) percentage points over PSBL vs −0.11 (7.71) percentage points over PSBL in the placebo group.

Similar results were observed in the total QUEST population both overall and with elevated type 2 biomarkers, and in the overall QUEST population followed for 3 years (Table S4).

3.4. *Pre- and post-bronchodilator FEV_1 slope*

In patients with a type 2 inflammatory phenotype followed for 3 years, the rate of change from baseline over time in pre-bronchodilator FEV_1 (FEV_1 slope [mean ± SD]) from Week 4 to Week 52 of QUEST was −4 ± 334 for placebo/dupilumab and 55 ± 252 for dupilumab/dupilumab. The least squares (LS) mean difference in pre-bronchodilator FEV_1 slope vs placebo was 60 mL ·year^{-1} (95 % confidence interval [CI] 5–110 mL ·year^{-1}; $P = 0.032$) (Table 3). During Weeks 4–96 in the TRAVERSE study, the pre-bronchodilator FEV_1 slope between Weeks 4 and 96 was stable and similar for both treatment groups exposed to dupilumab (Table 3).

In addition, the estimated post-bronchodilator FEV_1 slope from Week 4 to Week 52 of QUEST was −67 ± 368 in the placebo/dupilumab group and 2 ± 241 in the dupilumab/dupilumab group with an LS mean difference vs placebo of 60 mL ·year^{-1} (95 % CI 10–120 mL ·year^{-1}; $P = 0.016$) (Table 3).

4. Discussion

These results extend the previous comprehensive analysis from QUEST that have shown that the improvements observed with dupilumab in pre-bronchodilator FEV_1 extend to other measures of lung function [21]. The results presented here show that dupilumab led to sustained improvement for up to 3 years across multiple lung function parameters (FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75\ \%}$) in patients with uncontrolled, moderate-to-severe asthma with a type 2 inflammatory phenotype who completed the 52-week placebo-controlled QUEST study and were subsequently enrolled in the TRAVERSE open-label extension study. In line with previous observations [22], dupilumab demonstrated a rapid onset of action across these lung function parameters in patients who received placebo during the parent study and initiated dupilumab treatment in TRAVERSE.

Analyses of the pre-bronchodilator FEV_1 slopes in QUEST and TRAVERSE also support previously published data from the QUEST study [21], suggesting that dupilumab may prevent loss of lung function over time. This stability in lung function persisted throughout TRAVERSE, as demonstrated by the pre-bronchodilator FEV_1 slope analyses.

Given the potential for dupilumab to act on parameters related to peripheral airways where remodeling processes mostly occur, it is relevant to expand previous analyses to include other lung function measurements that may provide information on small and large airway function, as well as on airflow obstruction, such as the ones included in this study. A key, novel finding in this study is the fact that pre-bronchodilator FVC improved in the long term to the same extent as pre-bronchodilator FEV_1 did; in fact, the FEV_1/FVC ratio remained notably constant throughout TRAVERSE. Similarly, $FEF_{25–75\ \%}$ showed sustained improvements through Week 96 of TRAVERSE. Although indicative of lung function improvements, these results need to be interpreted with caution because changes in FEV_1, FVC, or $FEF_{25–75\ \%}$ values might be affected by potential concomitant changes in lung residual volume (due to changes in bronchial diameter, for instance) or total lung capacity [23–25]. Unfortunately, lung volume measurements were not collected during QUEST or TRAVERSE and hence were not included in this analysis; however a study is currently underway that will account for lung and airway volume measurements during

dupilumab treatment (see discussion further down).

In addition, the response to dupilumab treatment was favorable in the population with evidence of type 2 inflammation as defined by elevated blood eosinophil ($\geq$150 cells·μL^{-1}) or FeNO ($\geq$25 ppb) levels at PSBL. This is consistent with the dupilumab mechanism of action, which blocks signaling of IL-4 and IL-13, key and central drivers of type 2 inflammatory diseases [18,19].

While the strength of this evaluation includes the long-term observation across multiple spirometric endpoints for up to 3 years, the analysis has limitations. As a single-arm, open-label extension study, it was not designed for comparisons between treatment arms (dupilumab/dupilumab and placebo/dupilumab). In addition, patients were enrolled on a voluntary basis and only those who completed the parent study were eligible to participate. Potentially, this could have introduced a treatment bias towards patients who received active treatment during the parent study over those on placebo. In addition, while we used several spirometric measures to evaluate lung function, post-bronchodilator measurements were not available for TRAVERSE, and therefore only pre-bronchodilator measurements could be evaluated in the long term.

While these assessments may provide some insights into the physiological impact that dupilumab may have on lung function, future studies assessing the role of dupilumab in lung remodeling and the impact on long-term lung function decline are required to better understand the long-term improvement in lung function consistently observed in TRAVERSE. Ultimately, these indicators may suggest durable changes in lung physiology, which can be evaluated in targeted clinical trials. Two such studies to explore how dupilumab achieves these durable spirometric changes are currently underway. The ongoing phase 4 VESTIGE study (NCT04400318) is using functional respiratory imaging to assess the effects of dupilumab on lung function and airway volume changes in patients with moderate-to-severe asthma [26]. The phase 3b/4 placebo-controlled ATLAS study (NCT05097287) is currently recruiting and will evaluate lung function decline in patients with elevated baseline FeNO levels, primarily through post-bronchodilator FEV_1 measurements.

In conclusion, the results presented here show that the benefits of dupilumab observed in QUEST patients with uncontrolled, moderate-to-severe asthma were sustained across multiple lung function parameters, including large and small airways and fixed airway obstruction for up to 3 years in TRAVERSE. Furthermore, in patients who received placebo in QUEST and initiated dupilumab after enrolling in TRAVERSE, the observed improvements were rapid and sustained over the treatment period. Further studies are underway to better understand the positive and protective effects of dupilumab on lung function.

CRediT authorship contribution statement

Alberto Papi: contributed to data collection. Mario Castro: contributed to data collection. Jonathan Corren: contributed to data collection. Ian D. Pavord: contributed to data collection. Arman Altincatal: contributed to project concept, study design, and study implementation; contributed to data and statistical analysis. Nami Pandit-Abid: contributed to project concept, study design, and study implementation. Elizabeth Laws: contributed to project concept, study design, and study implementation. Bolanle Akinlade: contributed to project concept, study design, and study implementation. Leda P. Mannent: contributed to project concept, study design, and study implementation. Rebecca Gall: contributed to project concept, study design, and study implementation. Juby A. Jacob-Nara: contributed to project concept, study design, and study implementation. Yamo Deniz: contributed to project concept, study design, and study implementation. Paul J. Rowe: contributed to project concept, study design, and study implementation. David J. Lederer: contributed to project concept, study design, and study implementation. Megan Hardin: contributed to project, concept, study design, and study implementation. All authors, including Yuji Tohda, contributed to data analysis and interpretation and manuscript editing. All authors critically reviewed and approved the final version of the manuscript.

Declaration of competing interest

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Appendix A. Supplementary data

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