Received: 19 December 2022 | Revised: 28 April 2023 | Accepted: 9 May 2023

DOI: 10.1111/all.15792

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY EAACI WILEY

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Dupilumab sustains efficacy in patients with moderate-to-severe type 2 asthma regardless of inhaled corticosteroids dose

Ian D. Pavord[1] | Arnaud Bourdin[2] | Alberto Papi[3] | Christian Domingo[4] | Jonathan Corren[5] | Arman Altincatal[6] | Amr Radwan[7] | Nami Pandit-Abid[8] | Juby A. Jacob-Nara[8] | Yamo Deniz[7] | Paul J. Rowe[8] | Elizabeth Laws[8] | David J. Lederer[7] | Megan Hardin[6]

[1]NIHR Oxford Biomedical Research Centre, University of Oxford, Oxford, UK

[2]Department of Respiratory Diseases, University of Montpellier, Montpellier, France

[3]Respiratory Medicine Unit, University of Ferrara, S. Anna University Hospital, Ferrara, Italy

[4]Pulmonary Service, Corporació Sanitària Parc Taulí, Sabadell, Autonomous University of Barcelona, Barcelona, Spain

[5]David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[6]Sanofi, Cambridge, Massachusetts, USA

[7]Regeneron Pharmaceuticals, Inc., Tarrytown, New York, USA

[8]Sanofi, Bridgewater, New Jersey, USA

Correspondence
Ian D. Pavord, NDM Research Building, Nuffield Department of Medicine, University of Oxford, Old Road Campus, Roosevelt Drive, Oxford, OX3 7FZ, UK.
Email: ian.pavord@ndm.ox.ac.uk

Funding information
Regeneron Pharmaceuticals Inc.; Sanofi

Abstract

Background: Dupilumab, a human monoclonal antibody, blocks the shared receptor component for interleukins-4/13, key and central drivers of type 2 inflammation. The TRAVERSE (NCT02134028) open-label extension study demonstrated the long-term safety and efficacy of dupilumab in patients ≥12 years who completed a previous dupilumab asthma study. The safety profile was consistent with that observed in the parent studies. Here, we assess whether dupilumab sustains long-term efficacy in patients regardless of inhaled corticosteroid (ICS) dose at parent study baseline (PSBL).

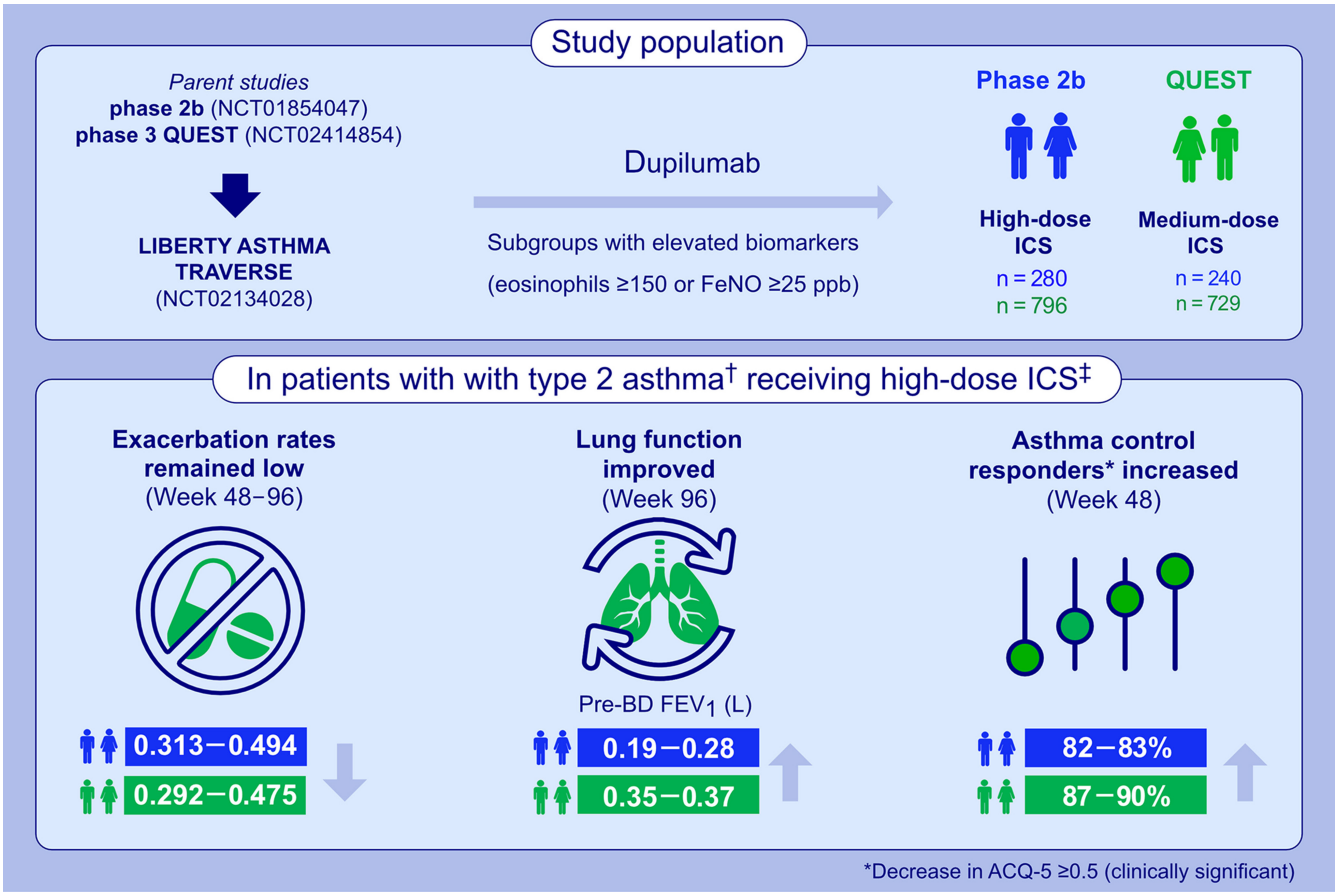
Methods: Patients from phase 2b (NCT01854047) or phase 3 (QUEST; NCT02414854) studies receiving high- or medium-dose ICS at PSBL and enrolled in TRAVERSE were included. We analyzed unadjusted annualized severe exacerbation rates, change from PSBL in pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1), 5-item asthma control questionnaire, and type 2 biomarkers in patients with type 2 asthma at baseline (blood eosinophils ≥150 cells/μL or fractional exhaled nitric oxide [FeNO] ≥25 ppb), and subgroups defined by baseline blood eosinophils or FeNO.

Results: Of patients with type 2 asthma ($n = 1666$), 891 (53.5%) were receiving high-dose ICS at PSBL. In this subgroup, unadjusted exacerbation rates for dupilumab versus placebo were 0.517 versus 1.883 (phase 2b) and 0.571 versus 1.300 (QUEST) over the parent study (52 weeks) and remained low throughout TRAVERSE (0.313–0.494). Improvements in pre-BD FEV_1 were sustained throughout TRAVERSE. Similar clinical efficacy was observed among patients receiving medium-dose ICS at PSBL and biomarker subgroups.

Conclusions: Dupilumab showed sustained efficacy for up to 3 years in patients with uncontrolled, moderate-to-severe type 2 asthma on high- or medium-dose ICS.

Abbreviations: ACQ-5, 5-item asthma control questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; BL, baseline; CI, confidence interval; DPL, dupilumab; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; IgE, immunoglobulin E; ITT, intention-to-treat; NCT, national clinical trial; PBO, placebo; ppb, parts per billion; PSBL, parent study baseline; Q, quartile); q2w, every 2 weeks; SC, subcutaneous).

KEYWORDS
asthma control, exacerbations, inhaled corticosteroids, moderate-to-severe asthma, pre-bronchodilator FEV_1



GRAPHICAL ABSTRACT

Dupilumab sustained long-term efficacy in patients with type 2 asthma regardless of inhaled corticosteroid (ICS) dose at parent study baseline (PSBL). Similar results were observed in subgroups of patients with elevated type 2 inflammatory biomarkers across ICS dose levels at PSBL. These findings support the long-term use of dupilumab in patients with uncontrolled moderate-to-severe asthma on high- or medium-dose ICS. †Type 2 asthma is defined as blood eosinophils ≥150 cells/μL or FeNO ≥25 ppb. ‡Similar results were observed in patients receiving medium-dose ICS at PSBL and across the remaining subgroups analyzed.
Abbreviations: ACQ-5, 5-item asthma control questionnaire; BD, bronchodilator; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; ppb, parts per billion; NCT, national clinical trial; PSBL, parent study baseline; q2w, every 2 weeks

1 | INTRODUCTION

Asthma severity is largely identified by the therapy required to achieve asthma control.[1,2] While most patients' asthma can be well managed with low-dose inhaled corticosteroids (ICS) and long-acting β_2-agonist (LABA) therapy, 5%–10% of patients have asthma that can be characterized as severe. This includes patients who remain controlled despite maximally tolerated inhaled therapy, e.g., high-dose ICS with additional controllers or maintenance systemic corticosteroids.[1-6] Severe asthma leads to a higher burden of disease, including a greater risk for exacerbations and progressive decline in lung function as well as increased medication burden, poorer asthma control, and a lower quality of life compared with patients with less severe asthma or adults without asthma.[6-9] Frequent exacerbations are often managed by systemic corticosteroids, which can accumulate negative side effects.[10-12] In patients with asthma that is uncontrolled on medium-dose ICS, there are limited data to suggest an added benefit from increasing the background ICS dose.[13] Up to 75% of patients with moderate-to-severe asthma remain uncontrolled despite availability of effective add-on therapies,[14] leaving an unmet and urgent need for more data to support their use in these patients.

Up to 80% of patients with severe asthma present with a phenotype that is driven by type 2 inflammation.[2,15,16,17] Dupilumab, a fully human VelocImmune®-derived monoclonal antibody,[18,19] blocks the shared receptor component for interleukin (IL)-4 and IL-13, type 2

inflammatory cytokines implicated in numerous allergic diseases ranging from asthma to atopic dermatitis,[20,21] thus inhibiting their signaling.

In a previous analysis of the 24-week phase 2b and 52-week phase 3 LIBERTY ASTHMA QUEST studies, dupilumab significantly reduced severe asthma exacerbations and improved asthma control and lung function in patients with type 2 asthma (defined as baseline blood eosinophil count ≥150 or 300 cells/μL and/or fractional exhaled nitric oxide [FeNO] ≥25 parts per billion [ppb]) receiving high-dose ICS at study baseline.[22] However, the long-term impact of dupilumab on patients with moderate-to-severe asthma as identified by baseline high- or medium-dose ICS use has not been reported previously.

The LIBERTY ASTHMA TRAVERSE open-label extension study evaluated the long-term safety and efficacy of dupilumab in patients aged ≥12 years who had participated in previous dupilumab asthma studies.[23] Safety findings were consistent with the known dupilumab safety profile. Improvements in efficacy observed in the parent studies were sustained or increased in patients who had received dupilumab in the parent studies; rapid, sustained improvements were observed in patients who had received placebo and initiated dupilumab in TRAVERSE.[23]

The objective of this analysis of TRAVERSE is to evaluate the long-term efficacy of dupilumab in patients with moderate-to-severe asthma receiving high- or medium-dose ICS at parent study baseline (PSBL).

2 | METHODS

2.1 | Study design and patients

LIBERTY ASTHMA TRAVERSE (NCT02134028) was a multinational, multicenter, single-arm, open-label extension study evaluating the long-term safety and tolerability of subcutaneous dupilumab 300 mg administered every 2 weeks (q2w) for up to 2 years in moderate-to-severe or oral corticosteroid (OCS)-dependent severe asthma patients (Figure S1) who had participated in a previous dupilumab asthma study (phase 2a EXPEDITION [NCT02573233] [Wechsler ME, unpublished data, October 2022], phase 2b [NCT01854047],[24] or QUEST [NCT02414854][25]), or OCS-dependent patients who had participated in the LIBERTY ASTHMA VENTURE (VENTURE; NCT02528214) study,[26] and were eligible for enrollment into TRAVERSE. Patients from EXPEDITION, QUEST, or VENTURE entered the extension study at the end of the parent study treatment period, whereas patients from the phase 2b study had completed a 16-week post-treatment follow-up period and were off treatment for up to 52 weeks. Following a protocol amendment, the treatment period was shortened from 96 to 48 weeks due to accumulating safety data. Full details of the study design have been previously published.[23]

In this predominantly post hoc analysis, only data from patients who had continued from the phase 2b trial and phase 3 QUEST were included (brief descriptions of both studies are available in the Supplemental Material); data from patients from VENTURE and EXPEDITION were not included due to differences in study designs and patient populations. Patients who were treated with dupilumab during the parent study continued with dupilumab for up to 96 weeks (cumulatively up to 3 years of treatment) (dupilumab/dupilumab group); patients who had received placebo during QUEST or the phase 2b trial started dupilumab treatment for up to 96 weeks in TRAVERSE (placebo/dupilumab group). Patients were stratified according to ICS dose at PSBL (high- or medium-dose ICS).

The study was 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 provided written informed consent before participating in the trial.

2.2 | Study endpoints

Annualized severe asthma exacerbation rate, pre-bronchodilator (BD) forced expiratory volume in 1 second (FEV_1), 5-item Asthma Control Questionnaire (ACQ-5;[27] scale 0–6, higher scores indicate lower asthma control), and type 2 inflammatory biomarkers (blood eosinophil count and serum total immunoglobulin E [IgE]) were assessed throughout TRAVERSE. Serum levels for total IgE are only available from patients enrolled from the phase 2b study, and not those coming from QUEST. A responder analysis of ACQ-5 scores reports the proportion of patients who had a response to treatment (responders), defined as those with an improvement from baseline in ACQ-5 score greater than or equal to the threshold of the minimum clinically important difference (MCID) of 0.5.[28]

Efficacy endpoints for annualized severe asthma exacerbation rate, pre-BD FEV_1, and biomarkers are presented until Week 96; ACQ-5 data are presented until Week 48 only, as these data were only collected until Week 48.

2.3 | Statistical analysis

As TRAVERSE is an open-label, single-arm extension study, data were analyzed using descriptive statistics using observed data only, and are presented as absolute mean (standard deviation [SD]) change from PSBL at TRAVERSE Weeks 0, 48, and 96. Efficacy analyses were performed on all patients who received one or more doses of dupilumab (exposed population) and were either on high-dose ICS or medium-dose ICS (defined at PSBL and adapted from the Global Initiative for Asthma [GINA] guidelines; Table S1) plus LABAs and, if required, an additional third controller (patients from QUEST only). Maintenance OCS use at baseline was not allowed. Additionally, analysis was performed on patients who were

on high- or medium-dose ICS at PSBL with type 2 asthma (blood eosinophil count ≥150 cells/μL or FeNO ≥25 ppb). The same analyses were performed on populations with PSBL levels of (1) blood eosinophil count ≥150 cells/μL, (2) blood eosinophil count ≥300 cells/μL, and (3) FeNO ≥25 ppb (Data S1). All analyses were post hoc with the exception of mean change from PSBL in pre-BD FEV_1 and ACQ-5 scores, which were pre-specified for the exposed population. The comparator value for efficacy was the PSBL value.

3 | RESULTS

3.1 | Patients

A total of 520 patients from the phase 2b trial ($n=411$ and $n=109$ patients in the dupilumab/dupilumab and placebo/dupilumab groups, respectively) and 1525 patients from QUEST ($n=1007$ and $n=518$ patients in the dupilumab/dupilumab and placebo/dupilumab groups, respectively) rolled over into TRAVERSE ($n=2045$). Of those, 225/411 (54.7%) and 55/109 (50.5%) patients who rolled over from the phase 2b study were on high-dose ICS in the dupilumab/dupilumab and placebo/dupilumab groups, respectively, as were 513/1007 (50.9%) and 283/518 (54.6%) patients, respectively, of those who rolled over from QUEST (Table 1).

There were 1076 participants in TRAVERSE on high-dose ICS and 969 on medium-dose ICS at PSBL. Baseline data were generally similar between treatment arms (Table 1).

3.2 | Annualized rate of severe asthma exacerbations

Unadjusted annualized exacerbation rates by treatment period for patients with type 2 asthma and high- or medium-dose ICS at PSBL are shown in Figure 1. In patients with type 2 asthma and high-dose ICS at PSBL, dupilumab versus placebo reduced adjusted severe exacerbation rates by 74% from the phase 2b trial and by 52% from QUEST, with unadjusted exacerbation rates of 0.517 (phase 2b) and 0.571 (QUEST) for dupilumab-treated patients and 1.883 (phase 2b) and 1.300 (QUEST) for patients receiving placebo. The reductions in exacerbation rates observed in the parent studies (both phase 2b and QUEST) remained low during TRAVERSE (unadjusted annualized exacerbation rates during TRAVERSE Week 48–96; phase 2b, 0.313–0.327; QUEST, 0.313–0.373) for those patients who had previously received dupilumab (dupilumab/dupilumab group; Figure 1A). Patients who had received placebo during the parent studies showed reductions in severe exacerbation rates upon initiating dupilumab in TRAVERSE, which were sustained through end of treatment (TRAVERSE Week 48–96; phase 2b, 0.402–0.494; QUEST, 0.292–0.475).

Similar trends were observed in patients with type 2 asthma receiving medium-dose ICS at PSBL (Figure 1B) and the remaining subgroups analyzed in patients receiving high- and medium-dose ICS at PSBL (Figures S2 and S3). The reduction in severe exacerbations (%) from PSBL at Week 52 of QUEST for multiple other subgroups analyzed within the intention-to-treat (ITT) and high-dose ICS populations are shown in Figure S4.

3.3 | Pre-bronchodilator FEV_1

In patients with type 2 asthma receiving high-dose ICS, pre-BD FEV_1 measurements at PSBL (mean [SD]) were 1.66 (0.49) L to 1.77 (0.49) L in patients from the phase 2b study and 1.68 (0.57) L to 1.73 (0.53) L in patients from QUEST, across treatment arms. By TRAVERSE Week 0, dupilumab improved pre-BD FEV_1 with mean (SD) changes over baseline of 0.13 (0.36) L in the phase 2b study and 0.36 (0.46) L in QUEST in the dupilumab/dupilumab group (Figure 2A). Improvements observed in the parent studies were sustained in TRAVERSE for patients in the dupilumab/dupilumab group (mean [SD] at Week 96 of TRAVERSE over PSBL from phase 2b study 0.28 [0.42] L and from QUEST 0.35 [0.47] L). Rapid improvements as early as Week 2 after initiation of dupilumab in TRAVERSE were observed (mean [SD] at Week 2 of TRAVERSE over PSBL from phase 2b study 0.27 [0.43] L and from QUEST 0.33 [0.43] L) in patients who had received placebo during the parent studies. These improvements were sustained through Week 96 of TRAVERSE (mean [SD] over PSBL from phase 2b study 0.19 [0.41] L; QUEST 0.37 [0.45] L) (Figure 2A). Similar trends were observed in patients with type 2 asthma receiving medium-dose ICS at PSBL (Figure 2B) and in the remaining subgroups analyzed in patients receiving high- and medium-dose ICS at PSBL (Figures S5 and S6). Improvements in pre-BD FEV_1 (L) from PSBL during the phase 2b study and QUEST are shown for the ITT population in Table S2, and improvements at Week 52 of QUEST and Week 96 of TRAVERSE for multiple other subgroups analyzed within the ITT (QUEST), exposed (TRAVERSE), and high-dose ICS populations (QUEST and TRAVERSE) are shown in Figure S7.

3.4 | Asthma control (ACQ-5 scores)

In patients with type 2 asthma and high-dose ICS at PSBL, asthma control scores ranged from 2.76 (0.78) to 2.85 (0.79) in patients from the phase 2b study and from 2.86 (0.77) to 2.92 (0.88) in patients from QUEST, across treatment arms. By TRAVERSE Week 0, dupilumab reduced ACQ-5 scores by a mean (SD) change over baseline of −0.96 (1.11) in the phase 2b study and −1.69 (1.13) in QUEST. Improvements observed in the parent studies were sustained in TRAVERSE for patients in the dupilumab/dupilumab group (mean [SD] at Week 48 of TRAVERSE over PSBL from phase 2b study: −1.63 [1.13]; QUEST: −1.85 [1.13]). Improvements were observed by the first assessment after initiation of dupilumab at Week 24 in TRAVERSE (mean [SD] over PSBL from phase 2b study: −1.42 [0.93]; QUEST: −1.73 [1.10]) in patients who had received placebo during the parent studies. These

TABLE 1 Demographic and disease characteristics at PSBL of patients in TRAVERSE from phase 2b and QUEST studies by baseline ICS dose.

	Exposed population			
	Patients rolled over from phase 2b trial		Patients rolled over from QUEST	
	Placebo/dupilumab	Dupilumab/dupilumab	Placebo/dupilumab	Dupilumab/dupilumab
High-dose ICS at PSBL				
n	55	225	283	513
Age, mean (SD), years	50.7 (10.5)	50.7 (12.0)	49.4 (13.6)	49.6 (14.0)
Female sex, *n* (%)	37 (67.3)	135 (60.0)	192 (67.8)	322 (62.8)
Pre-BD FEV_1, mean (SD), L	1.68 (0.50)	1.78 (0.51)	1.71 (0.53)	1.69 (0.59)
Percent predicted pre-BD FEV_1, mean (SD)	58.15 (10.97)	60.28 (11.35)	57.55 (12.76)	56.45 (14.04)
FEV_1 reversibility, mean (SD), %	27.10 (13.15)	26.07 (15.74)	24.31 (15.37)	27.91 (24.85)
Severe asthma exacerbations in past year, mean (SD)	2.64 (2.98)	2.63 (2.60)	2.44 (2.13)	2.34 (2.04)
ACQ-5 score, mean (SD)	2.83 (0.84)	2.89 (0.81)	2.85 (0.77)	2.92 (0.85)
AQLQ global score, mean (SD)	3.93 (1.08)	3.72 (1.07)	4.07 (1.02)	4.09 (1.06)
Number of puffs of albuterol or levalbuterol in a 24-h period	2.94 (2.33)	3.86 (3.30)	3.57 (4.15)	4.02 (4.56)
Biomarkers				
Blood eosinophil count, cells/μL	*n* = 55	*n* = 225	*n* = 283	*n* = 512
Median (Q1–Q3)	290.0 (210.0–450.0)	270.0 (160.0–470.0)	280.0 (130.0–510.0)	250.0 (130.0–470.0)
Total serum IgE, IU/mL	*n* = 55	*n* = 225	*n* = 281	*n* = 510
Median (Q1–Q3)	236.0 (94.0–484.0)	163.0 (76.0–404.0)	181.0 (63.0–406.0)	162.5 (59.0–459.0)
FeNO, ppb	*n* = 50	*n* = 200	*n* = 278	*n* = 511
Median (Q1–Q3)	30.0 (20.0–40.0)	29.5 (17.0–55.0)	25.0 (15.0–42.0)	24.0 (14.0–41.0)
Medium-dose ICS at PSBL				
n	54	186	235	494
Age, mean (SD), years	47.3 (13.5)	48.6 (13.2)	46.6 (16.6)	46.3 (16.2)
Female sex, *n* (%)	31 (57.4)	115 (61.8)	142 (60.4)	292 (59.1)
Pre-BD FEV_1, mean (SD), L	1.92 (0.55)	1.87 (0.59)	1.84 (0.64)	1.89 (0.64)
Percent predicted, mean (SD), %	61.48 (10.55)	61.03 (10.66)	59.37 (13.77)	60.55 (12.66)
FEV_1 reversibility, mean (SD), %	30.02 (15.62)	27.39 (18.18)	27.54 (20.90)	24.81 (20.81)
Severe asthma exacerbations in past year, mean (SD)	2.07 (1.91)	1.82 (1.60)	2.01 (1.60)	1.82 (1.89)
ACQ-5 score, mean (SD)	2.46 (0.65)	2.52 (0.73)	2.59 (0.69)	2.61 (0.68)
AQLQ global score, mean (SD)	4.58 (1.08)	4.30 (1.06)	4.45 (0.98)	4.49 (1.05)
Number of puffs of albuterol or levalbuterol in a 24-h period	2.15 (2.61)	2.22 (2.71)	2.78 (3.73)	2.84 (3.29)
Biomarkers				
Blood eosinophil count, cells/μL, median (Q1–Q3)	*n* = 54 215.0 (140.0–360.0)	*n* = 186 250.0 (140.0–380.0)	*n* = 235 260.0 (130.0–440.0)	*n* = 494 250.0 (120.0–460.0)

(Continues)

TABLE 1 (Continued)

	Exposed population			
	Patients rolled over from phase 2b trial		Patients rolled over from QUEST	
	Placebo/dupilumab	Dupilumab/dupilumab	Placebo/dupilumab	Dupilumab/dupilumab
Total serum IgE, IU/mL, median (Q1–Q3)	*n* = 53 200.0 (94.0–381.0)	*n* = 186 195.0 (77.0–472.0)	*n* = 233 184.0 (64.0–447.0)	*n* = 492 178.5 (67.0–455.5)
FeNO, ppb, median (Q1–Q3)	*n* = 51 25.0 (15.0–53.0)	*n* = 162 29.5 (16.0–51.0)	*n* = 233 27.0 (16.0–51.0)	*n* = 493 25.0 (15.0–46.0)

Note: *n*, number of patients assessed. Percentages are calculated using number of patients assessed as denominator.

Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BD, bronchodilator; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); IgE, immunoglobulin E; ppb, parts per billion; PSBL, parent study baseline; Q, quartile; SD, standard deviation.

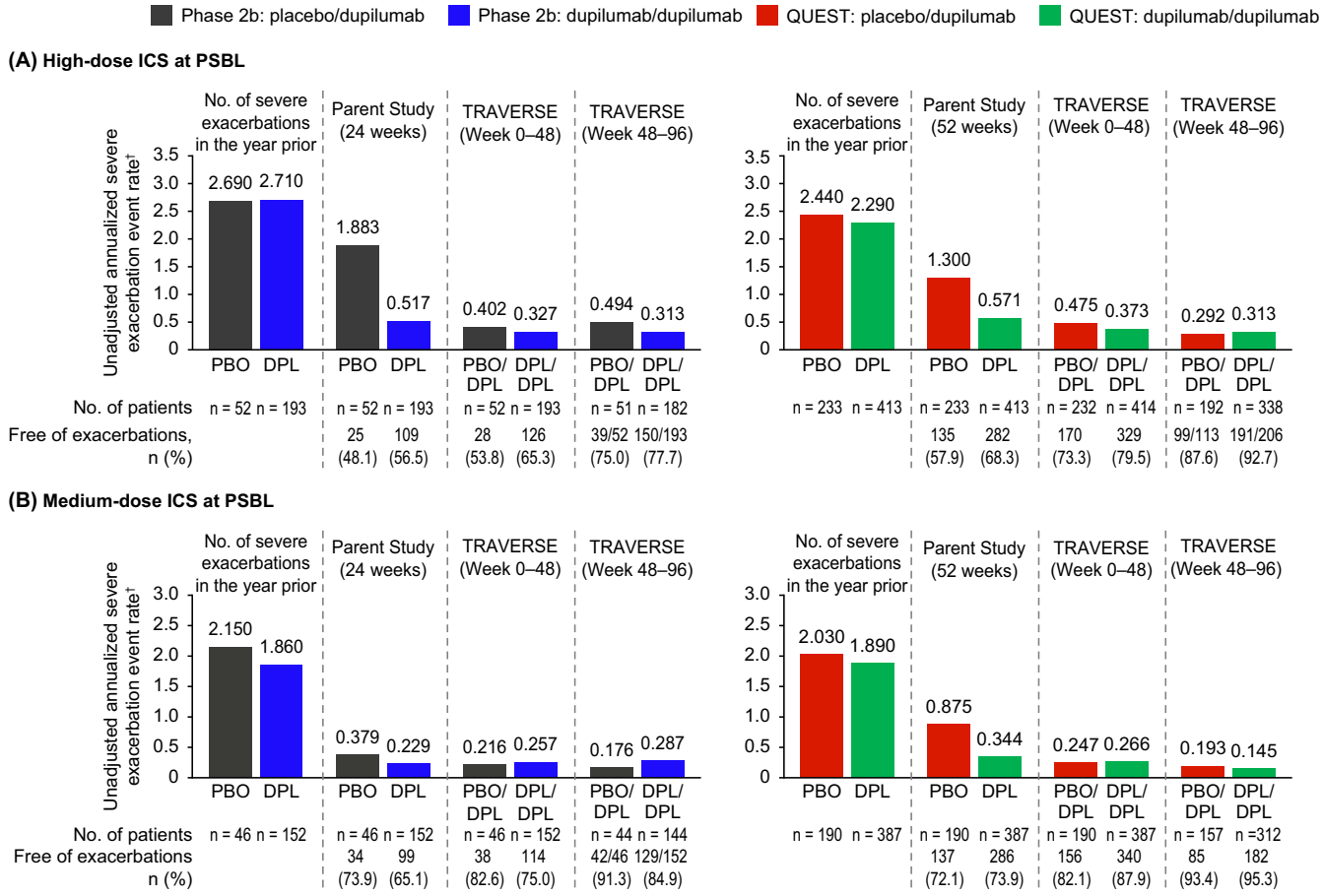


FIGURE 1 Unadjusted annualized rate of severe exacerbations† in patients receiving (A) high- and (B) medium-dose ICS at baseline—type 2 population. Patient is said to be free of exacerbations if there are no exacerbation events during the study period at a corresponding time point. If any patient has events with a missing end date, then those events are considered as ongoing events, and therefore, the patient is not considered to be free of exacerbations. For the analysis of free-of-exacerbation patients at the end of Week 96, only patients enrolled for 2 years in TRAVERSE study are considered. †The total number of events that occurred during the observational period divided by the total patient-years followed in the observational period. DPL, dupilumab; ICS, inhaled corticosteroid(s); PBO, placebo; PSBL, parent study baseline.

improvements were sustained through Week 48 of TRAVERSE (mean [SD] at Week 48 of TRAVERSE over PSBL from phase 2b study: −1.36 [1.10]; QUEST: −1.73 [1.13]) (Figure 3A). Similar trends were observed in patients with type 2 asthma receiving medium-dose ICS at PSBL (Figure 3B) and in patients receiving high- and medium-dose ICS at PSBL across the remaining subgroups analyzed (Figures S8 and S9).

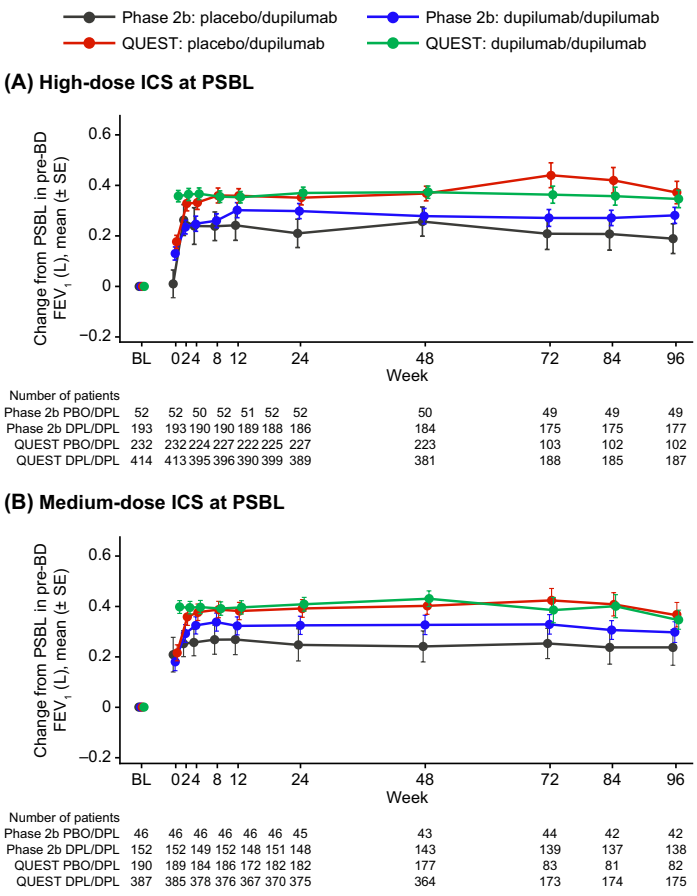


FIGURE 2 Mean change from PSBL in pre-BD FEV_1 (L) over time in patients with (A) high- and (B) medium-dose ICS at baseline—type 2 population. The baseline values are from the baseline of the parent study. Week 0 represents the start of TRAVERSE. Pre-BD FEV_1 was assessed using descriptive statistics. BD, bronchodilator; BL, baseline; DPL, dupilumab; FEV_1, forced expiratory volume in 1 second; ICS, inhaled corticosteroid(s); PBO, placebo; PSBL, parent study baseline; SE, standard error.

3.5 | ACQ-5 responder analysis

Many patients showed clinically significant improvements in asthma control, as evidenced by reductions versus PSBL in ACQ-5 scores reaching or exceeding the MCID of 0.5. In patients with type 2 asthma on high-dose ICS at PSBL, 81.3% and 82.4% of patients from the phase 2b trial and 88.0% and 87.0% of patients from QUEST (in the dupilumab/dupilumab and placebo/dupilumab groups, respectively) were identified as responders at TRAVERSE Week 24. Furthermore, 82.7% and 82.0% of patients from the phase 2b study and 89.6% and 86.9% from QUEST (in the dupilumab/dupilumab and placebo/dupilumab groups, respectively) achieved or exceeded the MCID at TRAVERSE Week 48 (Figure 4A). Similar results were observed in patients with type 2 asthma receiving medium-dose ICS at PSBL (Figure 4B) and for patients receiving high- and medium-dose ICS at PSBL across all subgroups analyzed (Figures S10 and S11).

3.6 | Biomarkers

Patients from QUEST on high-dose ICS at PSBL who received dupilumab in the parent study showed a continuous decline in blood eosinophil counts over time, and patients who received placebo in the parent study showed an attenuated initial rise followed by continued decline over time. Similar trends were observed in patients from the phase 2b study and also in patients on medium-dose ICS at PSBL (Figure 5A).

Serum levels for total IgE in TRAVERSE are only available from patients enrolled from the phase 2b study, and not those coming from QUEST. In patients rolled over from the phase 2b trial, long-term dupilumab treatment resulted in a progressive, continued reduction in serum total IgE levels in patients on high-dose ICS at PSBL (Figure 5B). Similar results were observed in patients on medium-dose ICS at PSBL (Figure 5B).

4 | DISCUSSION

This analysis of data from the TRAVERSE single-arm, open-label extension study demonstrated that patients exposed to dupilumab for up to 3 years experienced sustained reductions in severe exacerbation rates and improvements in lung function, asthma control, and rate of response (difference in ACQ-5 score ≥0.5 over baseline) for up to 96 weeks in patients on either high- or medium-dose ICS at PSBL. These results are consistent with the observations from the previously published data of the phase 2b and QUEST parent studies[24,25] and with further investigations into dupilumab's efficacy across subgroups of patients from these studies with a type 2 inflammatory phenotype receiving high- or medium-ICS dose at PSBL.[22,29] In TRAVERSE, dupilumab was well tolerated and had an acceptable safety profile during long-term treatment.[23]

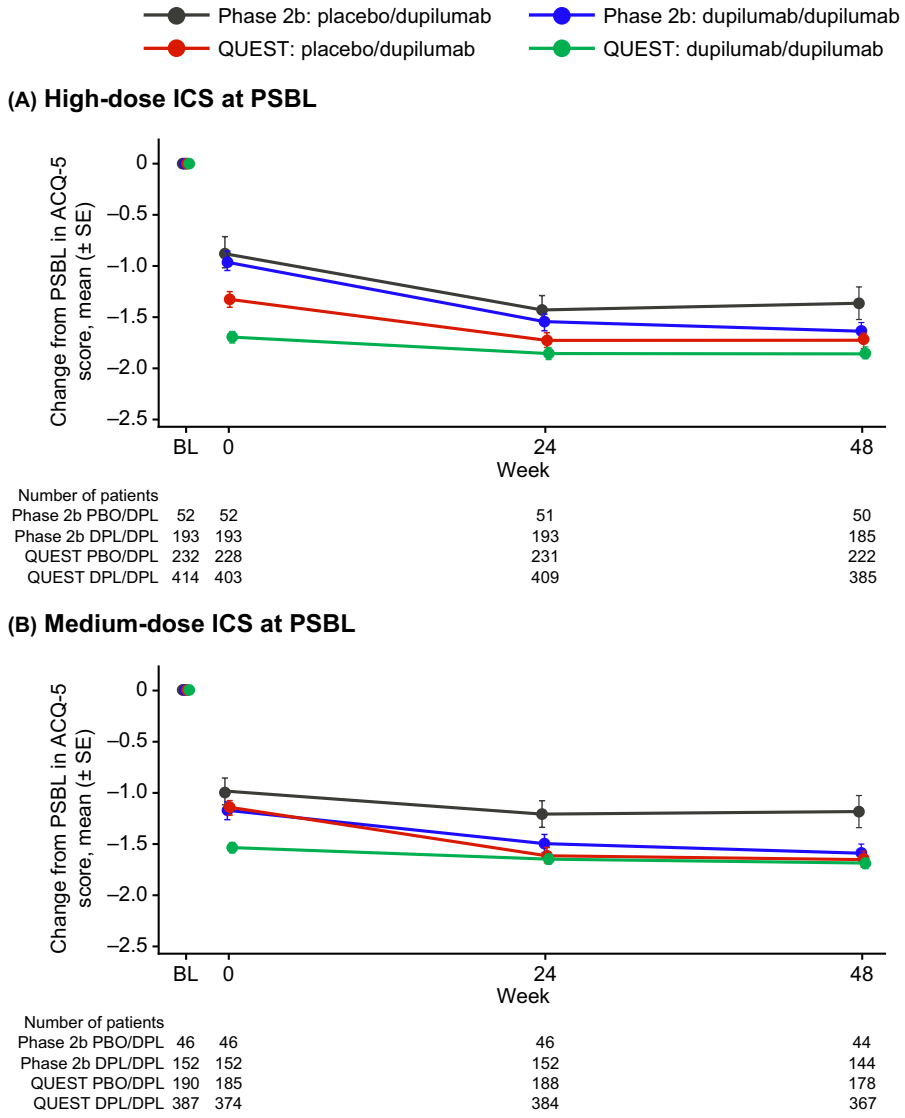


FIGURE 3 Mean change from baseline in ACQ-5 scores over time in patients receiving (A) high- and (B) medium-dose ICS—type 2 population. The baseline values are from the baseline of the parent study. Week 0 represents the start of TRAVERSE. ACQ-5 scores were assessed using descriptive statistics. ACQ-5, 5-item Asthma Control Questionnaire; BL, baseline; DPL, dupilumab; ICS, inhaled corticosteroid(s); PBO, placebo; PBSL, parent study baseline; SE, standard error.

Furthermore, similar to previously published dupilumab studies,[22,23,24,25,26,29] a greater magnitude of efficacy was observed in patients with elevated type 2 biomarkers at PSBL (defined as blood eosinophil count ≥150 cells/μL or FeNO ≥25 ppb), as well as in populations with elevated eosinophils ([1] blood eosinophils ≥150 cells/μL, [2] blood eosinophils ≥300 cells/μL), and elevated FeNO ([3] FeNO ≥25 ppb).

We observed similar efficacy with dupilumab treatment regardless of the dose of ICS that patients were using at PSBL, indicating that dupilumab is equally efficacious regardless of background ICS dose, and across patients with both moderate or severe uncontrolled asthma. Patients with moderate uncontrolled asthma receive minimal benefit from increasing to high-dose ICS,[13] and this analysis shows that a clear sustained benefit is seen with long-term dupilumab use.

As observed in the parent studies, a downward trend in blood eosinophils was seen in patients on either high- or medium-dose ICS at PSBL.[24,25] The precise mechanism for this effect is yet to be explained in full; however, dupilumab binds to IL-4Rα, thus blocking IL-4 and IL-13 signaling and reducing proinflammatory cytokine expression, as well as eosinophilic inflammation.[30]

It has been shown previously that eosinophil levels in peripheral blood can be significantly influenced by the use of ICS.[31,32] Here, we show that long-term dupilumab treatment leads to a decline in blood eosinophils, irrespective of whether patients were receiving high- or medium-dose ICS at PSBL.

Furthermore, consistent with observations made in the parent study,[24] dupilumab further reduced serum total IgE levels in patients who had previously participated in the phase 2b study; unfortunately, no IgE measurements were available from patients who enrolled from QUEST. In addition, further studies will be needed to examine long-term change in type 2 biomarkers when dupilumab treatment is halted (e.g., in patients who had a treatment gap between the end of treatment in the parent study and the beginning of TRAVERSE, as with the phase 2b study).

The strength of this analysis includes its long-term observation across multiple efficacy endpoints for up to 96 weeks. The limitations of this study are inherent to its design: analyses were

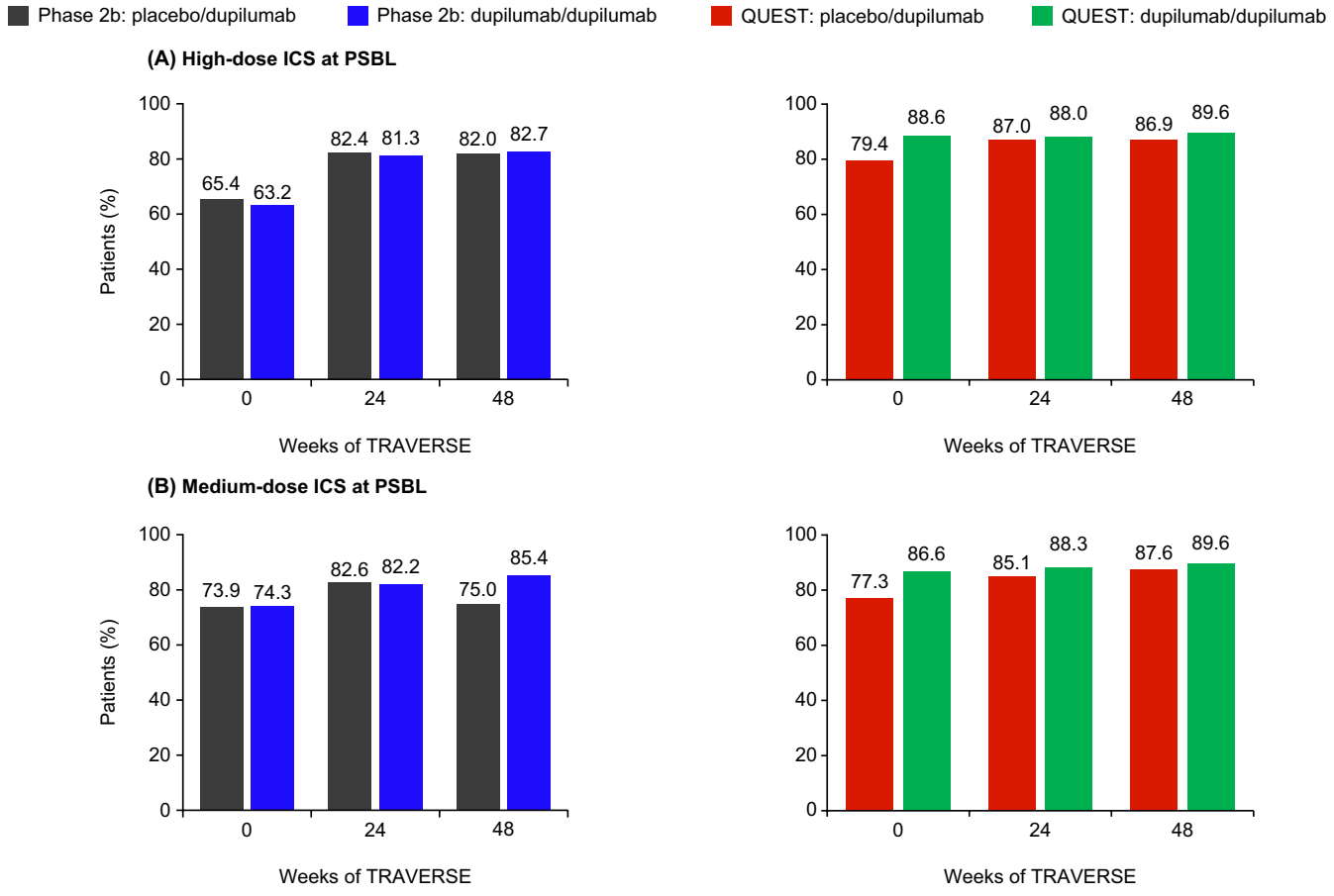


FIGURE 4 Proportion of patients requiring (A) high- and (B) medium-dose ICS at baseline who reached clinically significant improvements (MCID ≥0.5) in ACQ-5 scores—type 2 population. Responders are defined as patients with improvement from baseline in ACQ-5 ≥ 0.5. Patients with improvement from baseline in ACQ-5 < 0.5 at the time point are considered as non-responders. Abbreviations: ACQ-5, 5-item Asthma Control Questionnaire; ICS, inhaled corticosteroid(s); MCID, minimally clinically important difference; PSBL, parent study baseline.

primarily post hoc, and, as TRAVERSE was a single-arm open-label study, statistical analyses were descriptive only. Additionally, only patients who completed the parent study were eligible to participate, which could potentially have introduced a treatment bias towards patients who received active treatment during the parent study over those on placebo. Furthermore, the findings are constrained by the low sample sizes in some of the subgroups, as these were not defined a priori in the parent studies and were not powered to investigate differences between patients with asthma on high- or medium-dose ICS and by baseline levels of type 2 inflammatory biomarkers (eosinophil count ≥150 cells/μL or ≥ 300 cells/μL, FeNO ≥25 ppb, or eosinophil count ≥150 cells/μL or FeNO ≥25 ppb). Also, following a protocol amendment, the treatment period was reduced from 96 to 48 weeks, and therefore, for some analyses only 48-week data were available.

Asthma is driven by type 2 inflammation in a large proportion of patients with an uncontrolled, severe phenotype.[2,15,16,17] The results presented here provide further confirmation of and insights into dupilumab's dual mode of action of blocking the signaling of IL-4/IL-13, key and central drivers of type 2 inflammatory diseases.[20,21] Taken together, the results presented here provide important insights into the continued use of dupilumab over time in the moderate-to-severe asthma population requiring either high- or medium-dose ICS, including evidence of long-term efficacy of dupilumab in these populations. In addition, the results from this analysis suggest that the benefits of dupilumab may accumulate, with observed concordance between sustained reduction in type 2 biomarkers and sustained clinical efficacy over time across multiple assessments (severe exacerbation rates, pre-BD FEV_1, and ACQ-5).

5 | CONCLUSIONS

Treatment with dupilumab treatment for up to 3 years demonstrated sustained long-term efficacy in patients with uncontrolled, moderate-to-severe asthma, among those with evidence of type 2 inflammation and requiring either high- or medium-dose ICS. Reductions in severe exacerbation rates and improvements in lung function and asthma control were sustained in patients who were treated with dupilumab during the parent studies, and were

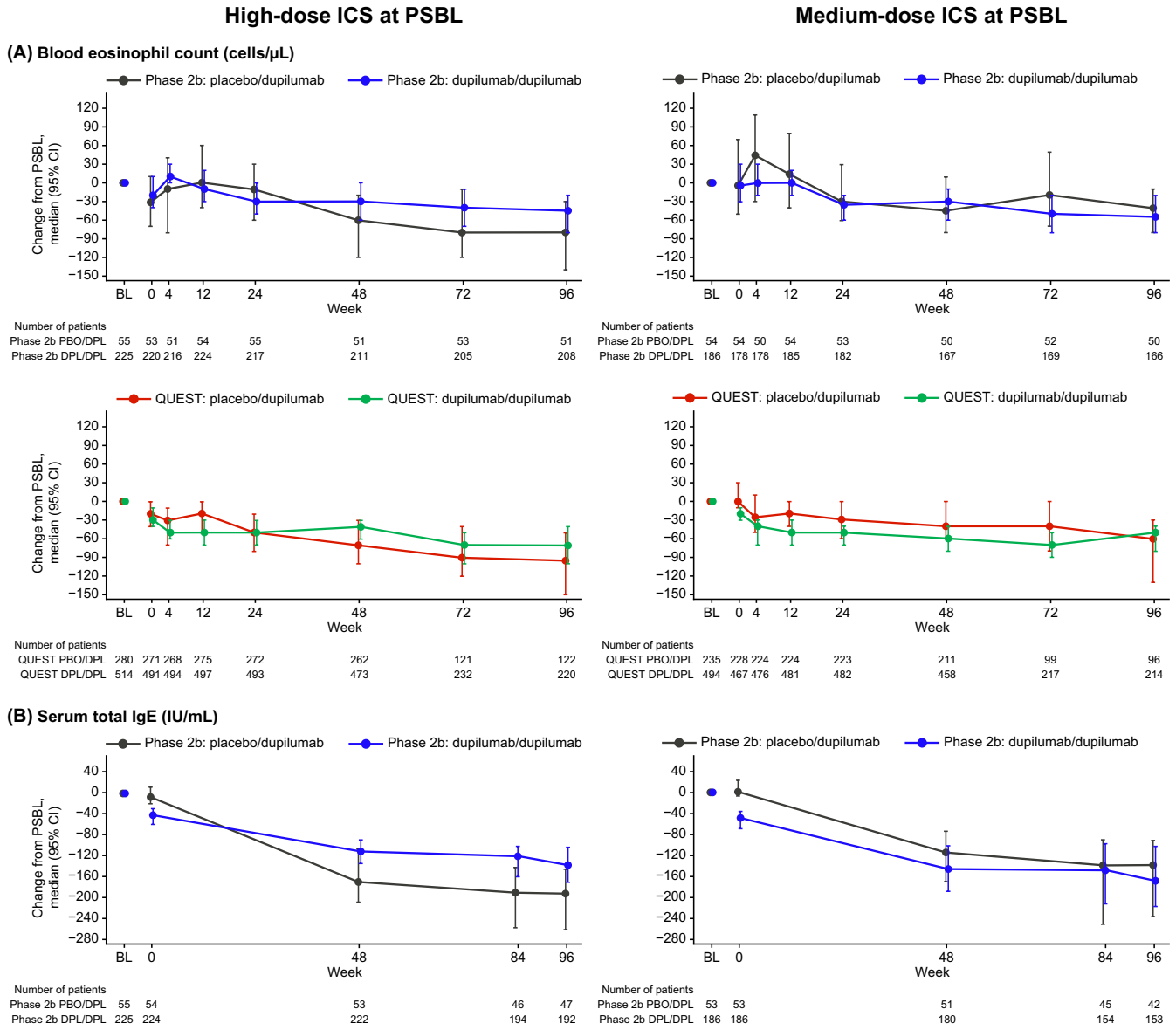


FIGURE 5 Median (95% CI) change from PSBL in (A) blood eosinophil count and (B) total serum IgE† in patients receiving high- (left) and medium-dose (right) ICS at PSBL—exposed population. The baseline values are from the baseline of the parent study. Week 0 represents the start of TRAVERSE. †Serum levels for total IgE in TRAVERSE are only available from patients enrolled from the phase 2b study, not those coming from QUEST. CI, confidence interval; DPL, dupilumab; ICS, inhaled corticosteroid(s); IgE, immunoglobulin E; PBO, placebo; PSBL, parent study baseline.

generally of greater magnitude in patients with the type 2 inflammatory asthma phenotype or in subgroups identified by elevations in either type 2 biomarker, regardless of ICS dose at PSBL. Furthermore, rapid improvements upon initiation of dupilumab in TRAVERSE were observed in patients who had received placebo during the parent study; these improvements were generally sustained until the end of treatment. These data provide added evidence supporting the use of dupilumab as an add-on therapy for patients who remain uncontrolled despite medium- or high-dose ICS use.

AUTHOR CONTRIBUTIONS

IDP, AB, AP, CD, and JC contributed to the data collection, data analysis, data interpretation, and writing of this manuscript. AA, AR, NP-A, JAJ-N, YD, PJR, EL, DJL, and MH contributed to the study design, data analysis, data interpretation, and writing of this manuscript. AA accessed and verified the data and did statistical analyses. All authors interpreted the data, provided critical feedback on the manuscript, approved the final manuscript for submission, and were accountable for the accuracy and integrity of the manuscript.

ACKNOWLEDGMENTS

Research sponsored by Sanofi and Regeneron Pharmaceuticals Inc. ClinicalTrials.gov identifier: NCT02134028. Medical writing/editorial assistance was provided by Éilis Sutton, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals Inc., according to the Good Publication Practice guideline.

CONFLICT OF INTEREST STATEMENT

IDP has received speaker fees from Aerocrine, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline (GSK), Novartis, and Teva; reports payments for organizing educational events for AstraZeneca and Teva; consultant fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, Merck Sharp & Dohme, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals Inc., RespiVert, Sanofi, Schering-Plough, and Teva; international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp Pharmaceuticals, and Teva; and has received a research grant from Chiesi. AB reports non-financial support during the conduct of the study for GSK; other support from Acceleron Pharma, Actelion, Galapagos, Merck Sharp & Dohme, Nuvaira, Pulmonx, United Therapeutics, and Vertex Pharmaceuticals; grants and personal fees from Boehringer Ingelheim; and personal fees from AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals Inc., and Sanofi. AP reports grants, personal fees, non-financial support, and other from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, and Teva; personal fees and non-financial support from Menarini, Novartis, and Zambon; and grants (all outside the submitted work) from Sanofi. CD has received travel and speaker fees from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer Pharma, GSK, HAL Allergy, Inmunotek, Menarini, Novartis, Pfizer, sanofi-aventis, Stallergenes Greer, Takeda, and Teva. JC reports research grants and consultancy for AstraZeneca, Genentech, Novartis, Regeneron Pharmaceuticals Inc., and Sanofi; and speaker fees from AstraZeneca, Genentech, and Novartis. AA, NP-A, JAJ-N, PJR, EL, and MH are employees of Sanofi, and may hold stock and/or stock options in the company. AR, YD, and DJL are employees and shareholders of Regeneron Pharmaceuticals Inc.

DATA AVAILABILITY STATEMENT

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 anonymized, 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: http://www.vivli.org/.

ORCID

Ian D. Pavord https://orcid.org/0000-0002-4288-5973
Arnaud Bourdin https://orcid.org/0000-0002-4645-5209
Alberto Papi https://orcid.org/0000-0002-6924-4500
Christian Domingo https://orcid.org/0000-0001-8358-773X
Jonathan Corren https://orcid.org/0000-0001-5951-3239
Arman Altincatal https://orcid.org/0009-0003-6666-6227
Amr Radwan https://orcid.org/0000-0003-1658-5229
Nami Pandit-Abid https://orcid.org/0000-0002-1072-2897
Juby A. Jacob-Nara https://orcid.org/0000-0002-5372-8762
David J. Lederer https://orcid.org/0000-0001-5258-0228
Megan Hardin https://orcid.org/0000-0001-7622-9598

REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma [published correction appears in *Eur Respir J*. 2014;43(2):1216. Dosage error in article text] [published correction appears in *Eur Respir J*. 2018;52(1):1352020]. *Eur Respir J*. 2014;43(2):343-373.
2. Global Initiative for Asthma. GINA Report, Global Strategy for Asthma Management and Prevention. 2022 www.ginasthma.org/gina-reports
3. Bateman ED, Boushey HA, Bousquet J, et al. Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am J Respir Crit Care Med*. 2004;170(8):836-844.
4. Hekking PW, Wener RR, Amelink M, Zwinderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol*. 2015;135(4):896-902.
5. Most JF, Ambrose CS, Chung Y, et al. Real-world assessment of asthma specialist visits among U.S. patients with severe asthma. *J Allergy Clin Immunol Pract*. 2021;9(10):3662-3671.e1.
6. Rönnebjerg L, Axelsson M, Kankaanranta H, et al. Severe asthma in a general population study: prevalence and clinical characteristics. *J Asthma Allergy*. 2021;14:1105-1115.
7. Reed CE. The natural history of asthma. *J Allergy Clin Immunol*. 2006;118(3):543-548.
8. Lange P, Çolak Y, Ingebrigtsen TS, Vesbo J, Marott JL. Long-term prognosis of asthma, chronic obstructive pulmonary disease, and asthma-chronic obstructive pulmonary disease overlap in the Copenhagen City Heart study: a prospective population-based analysis. *Lancet Respir Med*. 2016;4(6):454-462.
9. Busse WW, Kraft M. Current unmet needs and potential solutions to uncontrolled asthma. *Eur Respir Rev*. 2022;31(163):210176.
10. Sweeney J, Patterson CC, Menzies-Gow A, et al. Comorbidity in severe asthma requiring systemic corticosteroid therapy: cross-sectional data from the Optimum Patient Care Research Database and the British Thoracic Difficult Asthma Registry. *Thorax*. 2016;71(4):339-346.
11. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. *J Allergy Clin Immunol*. 2018;141(1):110-116.e117.
12. Al Efraij K, Johnson KM, Wiebe D, Sadatsafavi M, FitzGerald JM. A systematic review of the adverse events and economic impact associated with oral corticosteroids in asthma. *J Asthma*. 2019;56(12):1334-1346.
13. Vähätalo I, Ilmarinen P, Tuomisto LE, Niemelä O, Kankaanranta H. Inhaled corticosteroids and asthma control in adult-onset asthma: 12-year follow-up study. *Respir Med*. 2018;137:70-76.
14. Czira A, Turner M, Martin A, et al. A systematic literature review of burden of illness in adults with uncontrolled moderate/severe asthma. *Respir Med*. 2022;191:106670.
15. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380(9842):651-659.

16. Fahy JV. Type 2 inflammation in asthma—present in most, absent in many. *Nat Rev Immunol*. 2015;15(1):57-65.
17. Kaur R, Chupp G. Phenotypes and endotypes of adult asthma: moving toward precision medicine. *J Allergy Clin Immunol*. 2019;144(1):1-12.
18. Macdonald LE, Karow M, Stevens S, et al. Precise and in situ genetic humanization of 6 Mb of mouse immunoglobulin genes. *Proc Natl Acad Sci USA*. 2014;111(14):5147-5152.
19. Murphy AJ, Macdonald LE, Stevens S, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. *Proc Natl Acad Sci USA*. 2014;111(14):5153-5158.
20. Gandhi NA, Bennett BL, Graham NM, Pirozzi G, Stahl N, Yancopoulos GD. Targeting key proximal drivers of type 2 inflammation in disease. *Nat Rev Drug Discov*. 2016;15(1):35-50.
21. Le Floc'h A, Allinne J, Nagashima K, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. *Allergy*. 2020;75(5):1188-1204.
22. Bourdin A, Papi AA, Corren J, et al. Dupilumab is effective in type 2-high asthma patients receiving high-dose inhaled corticosteroids at baseline. *Allergy*. 2021;76(1):269-280.
23. Wechsler ME, Ford LB, Maspero JF, et al. Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study. *Lancet Respir Med*. 2022;10(1):11-25.
24. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388(10039):31-44.
25. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496.
26. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485.
27. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47(2):76-83.
28. Juniper EF, Svensson K, Mörk AC, Ståhl E. Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med*. 2005;99(5):553-558.
29. Bourdin A, Virchow JC, Papi A, et al. Dupilumab efficacy in subgroups of type 2 asthma with high-dose inhaled corticosteroids at baseline. *Respir Med*. 2022;202:106938.
30. Harb H, Chatila TA. Mechanisms of dupilumab. *Clin Exp Allergy*. 2020;50(1):5-14.
31. Demarche SF, Schleich FN, Henket MA, Paulus VA, Van Hees TJ, Louis RE. Effectiveness of inhaled corticosteroids in real life on clinical outcomes, sputum cells and systemic inflammation in asthmatics: a retrospective cohort study in a secondary care centre. *BMJ Open*. 2017;7(11):e018186.
32. Lommatzsch M, Klein M, Stoll P, Virchow JC. Impact of an increase in the inhaled corticosteroid dose on blood eosinophils in asthma. *Thorax*. 2019;74(4):417-418.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Pavord ID, Bourdin A, Papi A, et al. Dupilumab sustains efficacy in patients with moderate-to-severe type 2 asthma regardless of inhaled corticosteroids dose. *Allergy*. 2023;78:2921-2932. doi:10.1111/all.15792