Impact of exacerbation history on long-term efficacy of dupilumab in patients with asthma

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Dupilumab treatment provides sustained, long-term reduction of exacerbation rates, and improves lung function and asthma control in patients with uncontrolled, moderate-to-severe asthma with a T2 inflammatory phenotype, irrespective of exacerbation history. https://bit.ly/44Di9ZB

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Abstract

Background The phase 3 QUEST (NCT02414854) and TRAVERSE (NCT02134028) studies demonstrated the efficacy of dupilumab 200/300 mg *versus* placebo every 2 weeks for 52 weeks (QUEST) and dupilumab 300 mg up to an additional 96 weeks (TRAVERSE) in patients ⩾12 years of age with uncontrolled, moderate-to-severe asthma. Overall, safety was consistent with the known dupilumab safety profile. This *post hoc* analysis assessed long-term dupilumab efficacy for up to 3 years by exacerbation history.

Patients and methods Unadjusted annualised severe exacerbation rates (AER) and change from parent study baseline (PSBL) in pre-bronchodilator forced expiratory volume in 1 s (FEV_1) and 5-item Asthma Control Questionnaire (ACQ-5) score were assessed in patients with PSBL eosinophils ⩾150 cells·μL^{-1} or fractional exhaled nitric oxide ⩾20 ppb and 1 (n=624), 2 (n=344), or ⩾3 (n=311) exacerbations in the year before enrolment in QUEST.

Results In all three groups, dupilumab treatment progressively reduced AER range to 0.17–0.30 during TRAVERSE (Weeks 48–96), increased pre-bronchodilator FEV_1 range by 0.28–0.49 L by Week 96 and improved asthma control (reduced ACQ-5 score range by 1.51–2.03 by Week 48). For patients who first received dupilumab upon TRAVERSE enrolment, AER decreased, and lung function and asthma control improved rapidly, as was observed upon initiation of dupilumab in QUEST. Dupilumab was efficacious regardless of exacerbation history.

Conclusion For patients with uncontrolled, moderate-to-severe asthma with elevation of at least one type 2 biomarker, dupilumab treatment provides sustained, long-term reduction of exacerbation rates and improvements in lung function and asthma control irrespective of exacerbation history.

Introduction

One of the goals of asthma management is to prevent asthma exacerbations, which have been linked to accelerated lung function decline [1] and negative effects on quality of life [2] and contribute significantly to the economic burden of the disease [3]. Past asthma exacerbations, particularly recent events, significantly and independently predict future risk [4, 5]. Other characteristics, such as elevated type 2 inflammatory biomarkers, also contribute to increased future exacerbation risk [6–10].

Dupilumab, a fully human monoclonal antibody, blocks the shared receptor for interleukin-4 (IL-4) and IL-13, key and central drivers of type 2 inflammation in multiple diseases [11–14]. In the phase 3 LIBERTY ASTHMA QUEST study (NCT02414854) add-on dupilumab *versus* placebo significantly reduced the rate of severe asthma exacerbations and improved pre-bronchodilator forced expiratory volume in 1 s (FEV_1) in patients with uncontrolled, moderate-to-severe asthma [15]. Treatment effects were greater in patients with elevated baseline levels of type 2 biomarkers, including blood eosinophils ⩾150 cells·μL^{-1} and fractional exhaled nitric oxide (F_{ENO}) ⩾20 ppb [15]. Transient elevations in blood eosinophil counts were seen at initiation of dupilumab treatment, with counts decreasing to close to baseline levels by Week 52, while mean F_{ENO} levels declined over the study in patients treated with dupilumab [15]. Blood eosinophils in dupilumab-treated patients continued to gradually decline to below QUEST study baseline levels by Week 4 of the TRAVERSE (NCT02134028) long-term, single-arm, open-label extension study [16]. Safety findings from QUEST were consistent with the known dupilumab safety profile and have been previously reported [15]. A subsequent analysis of QUEST study data showed that dupilumab improves clinical outcomes regardless of exacerbation history [17], but the long-term impact of dupilumab on clinical efficacy in patients with a history of exacerbations is unknown.

The objective of the present analysis was to assess the long-term efficacy of dupilumab in patients with baseline eosinophil counts ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb and categorised by a history of 1, 2 or ⩾3 exacerbations before enrolment in the QUEST study. For this analysis we used data from QUEST and the TRAVERSE study, which evaluated the long-term safety and tolerability of dupilumab added to standard-of-care background controller therapy in adult and adolescent patients with asthma who had participated in a previous dupilumab study [16].

Methods

Study design

QUEST was a global, phase 3, multinational, randomised, double-blind, placebo-controlled, parallel-group study that assessed the efficacy and safety of dupilumab in patients aged 12 years and older who had uncontrolled, moderate-to-severe asthma despite treatment with high- or medium-dose inhaled corticosteroids (ICS) in combination with a second controller [15]. Patients were randomised 2:2:1:1 to receive add-on dupilumab 200 mg or 300 mg or matched-volume placebo every 2 weeks for 52 weeks. Enrolment in QUEST did not require minimum levels of type 2 biomarkers. Patients enrolled in QUEST subsequently entered TRAVERSE immediately after the QUEST end-of-treatment visit. All patients enrolled in TRAVERSE received dupilumab 300 mg every 2 weeks for up to an additional 96 weeks [16]. Patients maintained the background asthma therapy dose regimen established and maintained during QUEST (moderate or high-dose ICS with a second controller, *e.g.* long-acting β-agonists, leukotriene receptor antagonists, methylxanthines, *etc.*). Following accumulation of sufficient safety data on dupilumab across multiple indications, the study protocol was amended in October 2016 to reduce the treatment period from 96 to 48 weeks. Full details of both studies have already been published [15, 16].

Both studies were conducted in accordance with the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data. Study conduct and documentation were monitored by local institutional review boards or ethics committees, and all patients provided written informed consent before participating in the trials.

Patients

We present here data from patients who had participated in QUEST and were subsequently enrolled in TRAVERSE, had experienced 1, 2 or ⩾3 exacerbations in the year before enrolment in QUEST, and had baseline blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb at the time of enrolment in QUEST. These cut-off values of eosinophils and F_{ENO} are in line with those suggested as indicative of type 2 asthma [18]. To assess the long-term effect of continuous dupilumab treatment without confounding from dropout due to protocol amendment or different exposure durations, data from the subset of patients who had received 3 full years of treatment (*i.e.* completed the full 96-week treatment period in TRAVERSE, in addition to the 52-week treatment period during QUEST) are presented in the supplementary material.

Outcomes

Demographics, disease characteristics and biomarkers were recorded from all patients at QUEST baseline. Outcomes evaluated over 52 weeks of QUEST followed by up to 96 weeks in TRAVERSE include the unadjusted annualised rates of severe asthma exacerbations and of severe exacerbations requiring hospitalisation or a visit to an emergency department (ED) in QUEST and TRAVERSE; the change from parent study (*i.e.* QUEST) baseline (PSBL) in pre-bronchodilator FEV_1 through Week 96 of TRAVERSE;

and the change from PSBL in the 5-item Asthma Control Questionnaire (ACQ-5) at PSBL through Week 48 of TRAVERSE.

Statistical analysis

Owing to the open-label study design of TRAVERSE, the statistical analyses are descriptive summaries obtained by using observed data only, from the overall exposed population (*i.e.* all patients who had received one or more doses or part-doses of dupilumab), as previously reported [16]. Efficacy end-points are presented as the change from PSBL at several time points during the treatment period, up to a maximum of 96 weeks in TRAVERSE in addition to 52 weeks during QUEST; absolute mean±SD are reported at key time points in the parent study and across treatment groups. For patients who received placebo in the QUEST study and were treated with dupilumab in TRAVERSE, the treatment group is referred to as placebo/dupilumab; for patients who received dupilumab in both studies, the treatment group is referred to as dupilumab/dupilumab.

All analyses were done using SAS version 9.4 or higher (SAS Institute, Cary, NC, USA).

Results

A total of 1279 (83.6%) of 1530 patients from QUEST who enrolled in TRAVERSE were included in this *post hoc* analysis. Further details of both studies and the patient subgroups included in this analysis are found in supplementary figure S1. PSBL characteristics for the patients who had experienced 1 (n=624), 2 (n=344) or ⩾3 (n=311) exacerbations in the year before enrolment in QUEST are shown, by treatment group, in table 1. The equivalent data for patients who had received treatment for a full 3 years are shown

TABLE 1 PSBL characteristics of QUEST patients who had blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb, had experienced 1, 2, or ⩾3 exacerbations in the previous year, and who subsequently enrolled in TRAVERSE

Characteristic	Exacerbations in the previous year, n					
	1		2		⩾3	
	PBO/DPL	DPL/DPL	PBO/DPL	DPL/DPL	PBO/DPL	DPL/DPL
Patients, n	198	426	125	219	116	195
Age years, mean±SD	47.2±15.4	47.3±15.5	48.9±15.4	47.2±14.7	48.4±13.3	48.0±14.8
Female, n (%)	120 (60.6)	248 (58.2)	77 (61.6)	123 (56.2)	76 (65.5)	130 (66.7)
BMI kg·m^{-2}, mean±SD	29.40±6.71	28.33±6.19	29.66±6.61	29.17±6.51	28.97±5.64	29.04±6.61
Pre-bronchodilator FEV_1 L, mean±SD	1.84±0.62	1.85±0.62	1.77±0.58	1.85±0.65	1.69±0.51	1.65±0.58
Pre-bronchodilator FEV_1 % pred, mean±SD	58.48±12.83	59.10±13.44	59.20±13.56	59.36±13.75	57.07±12.80	55.70±13.68
FEV_1 reversibility %, mean±SD	26.89±18.75	27.28±23.93	26.97±19.88	27.72±19.14	24.76±15.13	23.33±18.54
Number of exacerbations in past year, mean±SD	1.00±0.00	1.00±0.00	2.00±0.00	2.00±0.00	4.73±2.46	4.50±2.71
High-dose ICS use, n (%)	99 (50.0)	180 (42.3)	71 (56.8)	123 (56.2)	69 (59.5)	128 (65.6)
ACQ-5 score (range 1–6), mean±SD	2.67±0.71	2.70±0.73	2.76±0.68	2.70±0.73	2.87±0.89	3.00±0.94
AQLQ global score (range 1–7), mean±SD	4.35±0.94	4.44±1.02	4.19±1.07	4.34±1.07	4.02±1.04	3.89±1.13
Ongoing atopic or allergic condition, n (%)	171 (86.4)	360 (84.5)	98 (78.4)	196 (89.5)	97 (83.6)	153 (78.5)
Blood eosinophil count cells·μL^{-1}						
Median (IQR)	330.00 (180.00–500.00)	270.00 (170.00–450.00)	300.00 (200.00–495.00)	330.00 (180.00–550.00)	415.00 (200.00–730.00)	370.00 (200.00–630.00)
Mean±SD	388.38±296.34	356.28±276.45	417.10±397.82	404.66±317.75	566.12±526.60	506.77±522.59
F_{ENO} ppb						
Median (IQR)	31.00 (18.00–53.00)	27.00 (18.00–45.00)	29.00 (18.50–52.00)	29.00 (19.00–51.00)	34.00 (21.00–51.00)	34.50 (21.00–54.00)
Mean±SD	38.15±27.02	37.42±31.56	45.07±51.18	38.56±30.38	41.71±28.10	44.06±40.85
Total IgE IU·mL^{-1}						
Median (IQR)	212.00 (92.00–487.00)	194.00 (69.50–533.00)	197.00 (71.00–489.50)	209.00 (75.00–547.00)	203.00 (76.00–460.00)	157.50 (71.00–491.50)
Mean±SD	466.58±694.17	497.94±831.98	456.05±777.28	529.15±877.05	377.67±560.62	473.06±844.39

PSBL: parent study baseline; PBO: placebo; DPL: dupilumab; BMI: body mass index; FEV_1: fractional exhaled volume in 1 s; ICS: inhaled corticosteroid; ACQ-5: 5-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; F_{ENO}: fractional exhaled nitric oxide; ppb: parts per billion.

in supplementary table S1. Patients' exacerbation history at PSBL was broadly reflective of their disease status, with generally poorer baseline pre-bronchodilator FEV_1, asthma control (as assessed by ACQ-5), and asthma-related quality of life (Asthma Quality of Life Questionnaire) as the number of exacerbations in the year before QUEST increased. Rate of high-dose ICS use and mean eosinophil levels were higher among patients with a history of ⩾3 exacerbations compared with those with a history of 1 or 2 exacerbations. All other characteristics were generally similar across treatment groups and exacerbation history.

Annualised severe exacerbation rate

Patients' unadjusted annualised exacerbation rates by treatment period and exacerbation history are shown in figure 1 (all severe asthma exacerbations) and figure 2 (exacerbations needing hospital admission or an ED visit); the equivalent data for patients who received treatment for 3 full years are shown in supplementary figures S2 and S3. Figure 1 and Figure S2 show progressive reduction in exacerbation rates in both QUEST and TRAVERSE with dupilumab treatment. Patients in the placebo/dupilumab group who first received dupilumab upon enrolment in TRAVERSE had exacerbation rate reductions similar to those seen in patients who received dupilumab during QUEST, and dupilumab was efficacious regardless of exacerbation history. By the last year of TRAVERSE (Weeks 48–96), annualised exacerbation rates decreased from 1.00 (history of 1 exacerbation), 2.00 (history of 2 exacerbations) and 4.50–4.73 (history of ⩾3 exacerbations) to ⩽0.30 irrespective of baseline exacerbation history (figure 1).

Figure 2 and Figure S3 show how treatment with dupilumab *versus* placebo resulted in consistently lower rates of asthma exacerbations requiring hospitalisation or an ED visit in QUEST, regardless of exacerbation history. Annualised rates of asthma exacerbations requiring hospitalisation or ED visit in patients in the placebo/dupilumab group with a history of ⩾3 exacerbations, who first received dupilumab in TRAVERSE, were halved during the first year of TRAVERSE; exacerbations for all patients remained low through the second year of TRAVERSE (annualised exacerbation rate range: 0–0.10). Sample size reduction due to the protocol amendment did not appear to affect the results, as similar efficacy was observed in patients who completed 3 full years of treatment (supplementary figures S2 and S3).

Pre-bronchodilator FEV_1

The change from PSBL in pre-bronchodilator FEV_1 is shown in figure 3; the equivalent data for patients who received 3 full years of treatment are shown in supplementary figure S4. Whether patients had

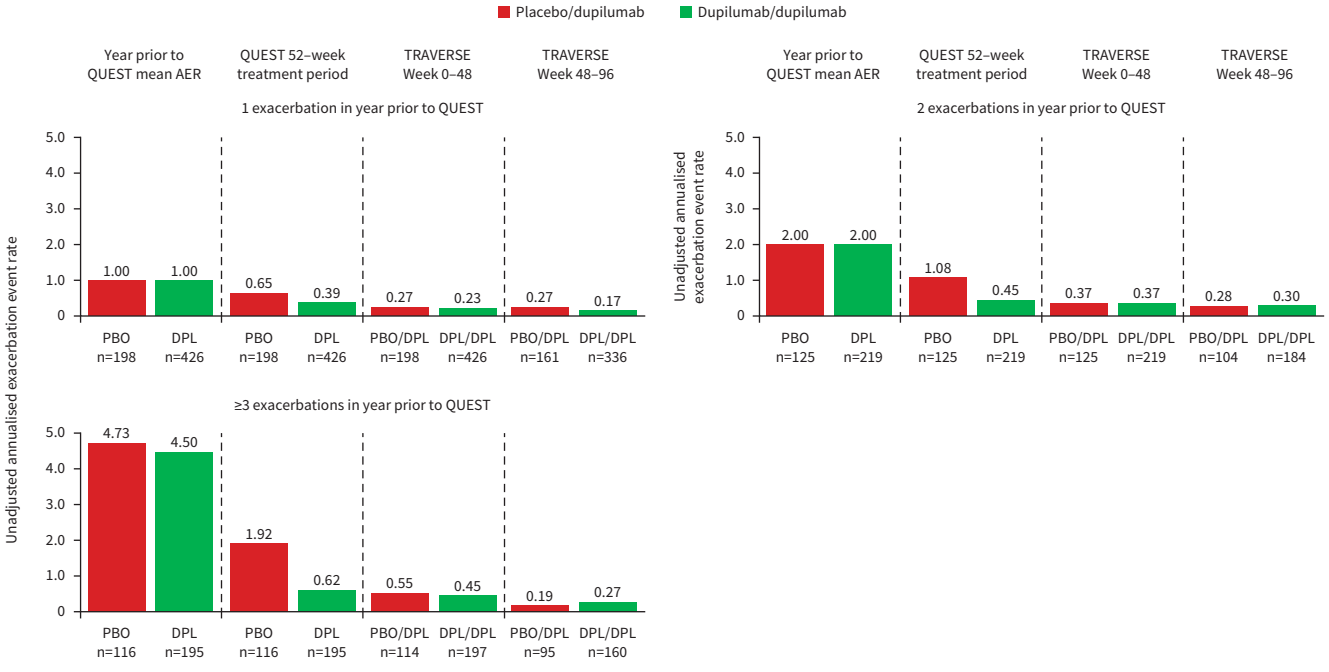

FIGURE 1 Unadjusted annualised exacerbation rates by exacerbation history and treatment period in patients enrolled in TRAVERSE who began QUEST with blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb. F_{ENO}: fractional exhaled nitric oxide; AER: annualised severe exacerbation rate; PBO: placebo; DPL: dupilumab; ppb: parts per billion.

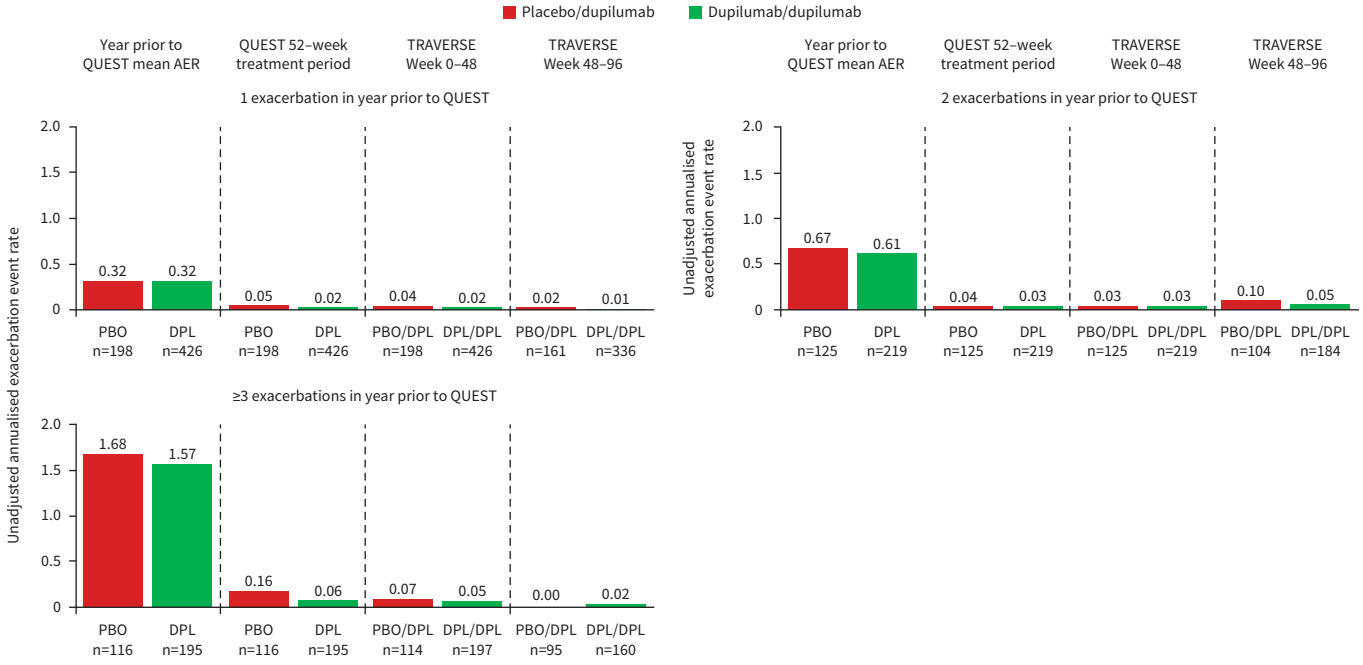

FIGURE 2 Unadjusted annualised exacerbation rates by exacerbation history and treatment period in patients enrolled in TRAVERSE who began QUEST with blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb and required hospitalisation or an emergency department visit. F_{ENO}: fractional exhaled nitric oxide; AER: annualised severe exacerbation rate; ppb: parts per billion; PBO: placebo; DPL: dupilumab.

experienced 1, 2 or ⩾3 exacerbations in the year before enrolment in QUEST, treatment with dupilumab resulted in a sustained increase in pre-bronchodilator FEV_1 over time in both QUEST and TRAVERSE. For those who had received placebo in QUEST, lung function improved rapidly upon initiation of dupilumab in TRAVERSE. Mean±SD changes from PSBL in the placebo/dupilumab and dupilumab/dupilumab groups, respectively, in patients with 1 exacerbation in the previous year were 0.19±0.42 and 0.33±0.47 L at TRAVERSE Week 0, 0.33±0.42 and 0.34±0.52 L at Week 48 and 0.28±0.44 and 0.31±0.46 L at Week 96. The respective changes for patients with a history of 2 exacerbations were 0.18±0.40 and 0.39±0.44 L at Week 0, 0.40±0.47 and 0.43±0.58 L at Week 48 and 0.39±0.38 and 0.31±0.44 L at Week 96. Similar results were observed in patients with ⩾3 exacerbations in the previous year, with those in the placebo/dupilumab and dupilumab/dupilumab groups achieving pre-bronchodilator FEV_1 improvements of 0.20±0.41 and 0.44±0.52 L at TRAVERSE Week 0, 0.43±0.44 and 0.49±0.51 L at Week 48 and 0.49±0.47 and 0.45±0.52 L at Week 96, respectively.

Overall, exacerbation history did not influence pre-bronchodilator FEV_1 improvements. Consistent with the annualised rate of severe exacerbations outcome, data from patients who were treated for 3 full years suggest that sample size reduction due to the protocol amendment did not appear to affect the results (supplementary figure S4).

ACQ-5 score

Change from PSBL in patients' ACQ-5 scores are shown in figure 4; the equivalent data for patients who received 3 full years of treatment are shown in supplementary figure S5. Similar to other outcomes analysed, dupilumab treatment resulted in a sustained decrease in ACQ-5 scores (*i.e.* improvement in asthma control) over time in both QUEST and TRAVERSE irrespective of whether patients had experienced 1, 2 or ⩾3 exacerbations in the year before enrolment in QUEST. Patients who had received placebo in QUEST experienced improvement in asthma control upon initiation of dupilumab in TRAVERSE that was similar to that experienced by patients who had initially received dupilumab in QUEST. Mean±SD changes from PSBL in ACQ-5 scores in the placebo/dupilumab and dupilumab/dupilumab groups, respectively, of patients with 1 exacerbation in the previous year were −1.16±0.99 and −1.51±1.03 at TRAVERSE Week 0, and −1.51±1.01 and −1.66±1.03 at Week 48. The respective changes for patients with a history of 2 exacerbations were −1.29±1.03 and −1.58±0.99 at Week 0, and

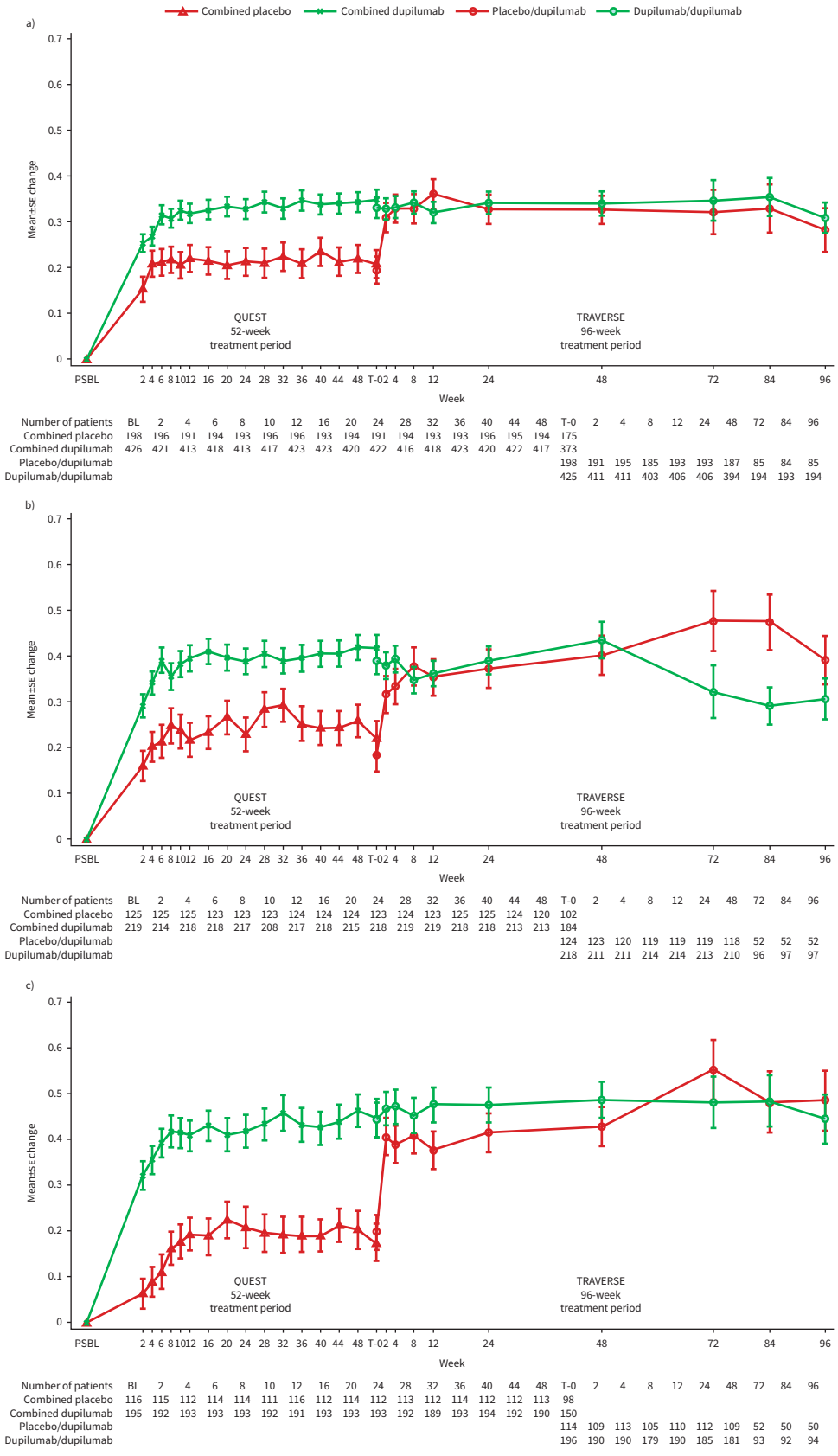

FIGURE 3 Change from PSBL in pre-bronchodilator FEV_1 in patients enrolled in TRAVERSE who began QUEST with blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb and had experienced a) 1, b) 2 or c) ⩾3 exacerbations in the previous year. BL: baseline; ppb: parts per billion; PSBL: parent study baseline; FEV_1: forced expiratory volume in 1 s; F_{ENO}: fractional exhaled nitric oxide; SE: standard error.

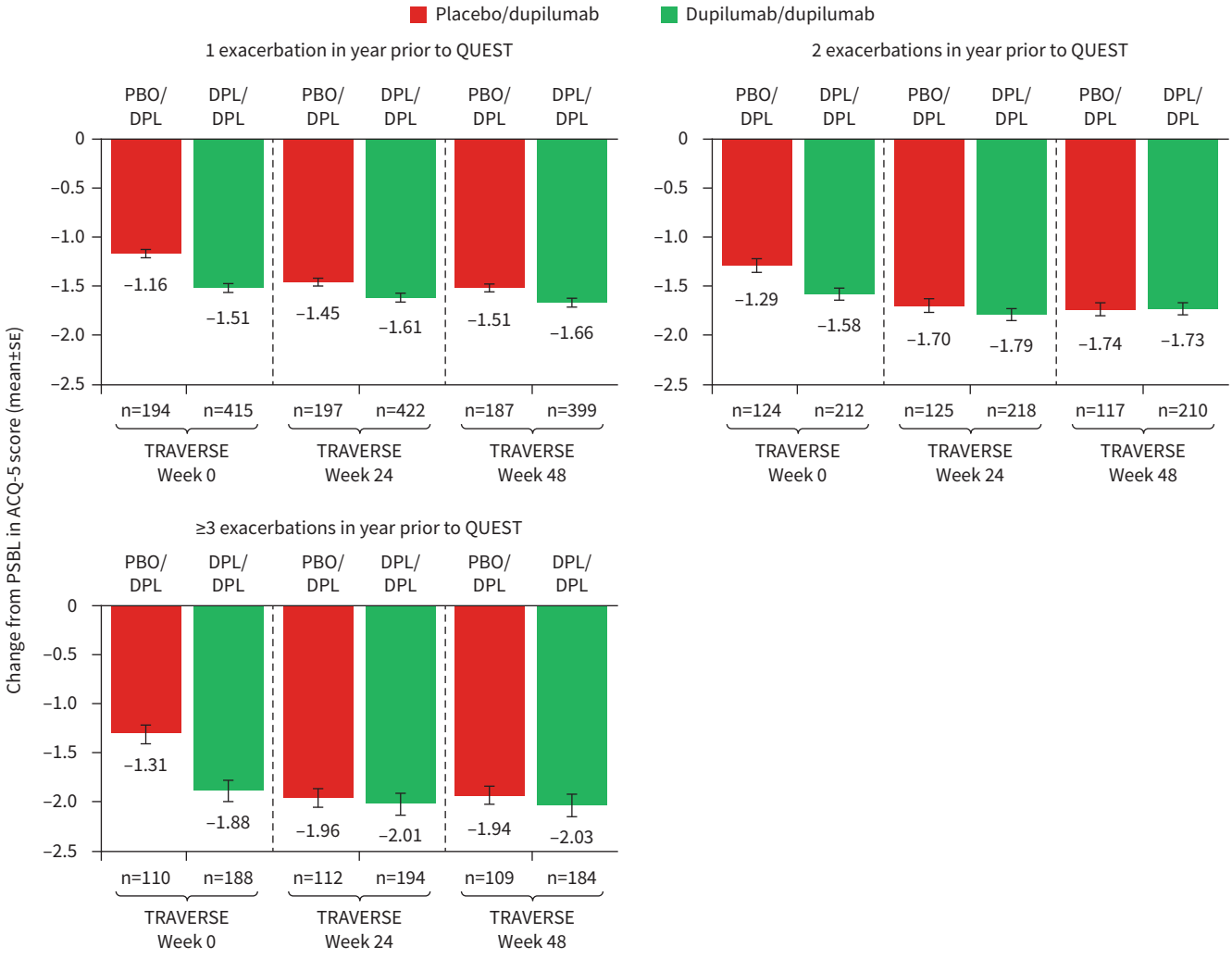

FIGURE 4 Change from PSBL in ACQ-5 scores in patients enrolled in TRAVERSE who began QUEST with blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb and had experienced 1, 2 or ⩾3 exacerbations in the previous year. PSBL: parent study baseline; ACQ-5: 5-item Asthma Control Questionnaire; F_{ENO}: fractional exhaled nitric oxide; ppb: parts per billion; SE: standard error; PBO: placebo; DPL: dupilumab.

−1.74±1.06 and −1.73±1.05 at Week 48; those for patients with a history of ⩾3 exacerbations were −1.31±1.08 and −1.88±1.19 at Week 0, and −1.94±1.14 and −2.03±1.13 at Week 48.

The observed improvements in asthma control were, like the gains in lung function, not influenced by exacerbation history. Sample size reduction due to dropout did not appear to affect the results (supplementary figure S5).

Discussion

This analysis of the long-term efficacy of dupilumab in patients with uncontrolled, moderate-to-severe asthma and baseline blood eosinophils ⩾150 cells·μL^{-1} or F_{ENO} ⩾20 ppb showed that treatment with dupilumab progressively reduced patients' exacerbation rates and improved their lung function (as shown by a sustained increase in pre-bronchodilator FEV_1) and asthma control (as shown by a sustained decrease in ACQ-5 scores), regardless of their exacerbation history in the year before enrolment in QUEST. Overall, improvements in ACQ-5 across all subgroups exceeded 0.5, considered to represent a clinically meaningful change [19]. These findings support previous work [16, 17] demonstrating that the efficacy of dupilumab is sustained for at least 3 years. Our study builds on these data by demonstrating that similar benefits of treatment are seen irrespective of asthma exacerbations history. This provides important information to clinicians who treat patients with a high disease burden as indicated by frequent exacerbations who are at increased risk of accelerated lung function decline [1], poorer quality of life [2] and future exacerbation risk [4].

The beneficial effects of dupilumab were seen across the range of exacerbation histories studied, and the findings demonstrate that even patients who experience several (at least three) exacerbations each year can benefit from long-term treatment with dupilumab. The magnitude of improvement in clinical outcomes including lung function and patient-related outcomes was comparable to or even exceeded that of patients with a history of fewer exacerbations. Importantly, these patients had not only a high burden of exacerbations but also high baseline levels of type 2 biomarkers. Type 2 inflammation is successfully targeted by dupilumab owing to its blockade of IL-4 and IL-13, key and central drivers of type 2 inflammation in multiple diseases.

While the data were collected from large phase 3 clinical trials spanning a period of up to 3 years, exacerbation history subgroups were not pre-specified in QUEST and TRAVERSE. Therefore, a limitation of this analysis is its *post hoc* nature. Further discussion of limitations can be found in previous work [17].

In summary, this analysis of patients with uncontrolled, moderate-to-severe asthma with a type 2 inflammatory phenotype showed that treatment with dupilumab can provide sustained, long-term reduction of exacerbation rates and improvements in lung function and asthma control irrespective of exacerbation history.

Provenance: Submitted article, peer reviewed.

This study is registered at www.clinicaltrials.gov with identifier numbers NCT02414854 and NCT02134028. 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 https://www.vivli.org/.

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Conflict of interest: J. Corren reports research grants from and is a consultant for AstraZeneca, Genentech, Novartis, Regeneron Pharmaceuticals Inc. and Sanofi; and speaker fees from AstraZeneca, Genentech and Novartis. C.H. Katelaris is a Principal Investigator of the dupilumab asthma phase 2b (NCT01854047) and phase 3 (NCT02414854) studies for Regeneron Pharmaceuticals Inc. and Sanofi. M. Castro reports research support from the American Lung Association, AstraZeneca, GlaxoSmithKline, NIH, Novartis, PCORI, Pulmatrix, Sanofi-Aventis and Shionogi; is a consultant for Genentech, Novartis, Sanofi-Aventis and Teva; reports speaker fees from AstraZeneca, Genentech, GlaxoSmithKline, Regeneron Pharmaceuticals Inc., Sanofi and Teva; and royalties from Elsevier. J.F. Maspero is a consultant for AstraZeneca and Sanofi; reports speaker fees from GlaxoSmithKline, Menarini, Novartis and Uriach; and research grants from Novartis. M. Humbert reports consultant and speaker fees from AstraZeneca, Chiesi, GlaxoSmithKlein, Novartis and Sanofi. D.M.G. Halpin reports advisory board membership, speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, CSL Behring, GlaxoSmithKline, Novartis, Pfizer, Sandoz and Sanofi. A. Altincatal, N. Pandit-Abid, J.A. Jacob-Nara and P.J. Rowe are employees of Sanofi, and may hold stock and/or stock options in the company. X. Soler, A. Radwan and Y. Deniz are employees and shareholders of Regeneron Pharmaceuticals Inc.

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