Long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma (TRAVERSE): an open-label extension study

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Summary

Background Clinical trials have shown treatment benefits of dupilumab in patients with uncontrolled asthma for up to 1 year. This study aimed to evaluate the long-term safety and efficacy of dupilumab in patients with moderate-to-severe asthma, as data for extended treatment with dupilumab beyond 1 year are not available.

Methods TRAVERSE was an open-label extension study in 362 hospitals and clinical centres across 27 countries that assessed the safety and efficacy of dupilumab 300 mg every 2 weeks up to 96 weeks in adults and adolescents (aged 12–84 years) with moderate-to-severe or oral-corticosteroid-dependent severe asthma who had completed a previous dupilumab asthma study (phase 2A EXPEDITION, phase 2B DRI [P2b], phase 3 QUEST, or VENTURE). The primary endpoint was the number and percentage of patients with any treatment-emergent adverse events. Secondary endpoints included annualised exacerbation rate (AER) over the treatment period and change from parent study baseline in pre-bronchodilator FEV_1, the five-item asthma control questionnaire (ACQ-5), the asthma quality of life questionnaire (AQLQ), type 2 biomarkers (blood eosinophils and serum total IgE), and anti-drug antibodies (ADAs). Statistical analyses were descriptive. We report safety in all enrolled patients, and efficacy in patients with non-oral-corticosteroid-dependent asthma and in subgroups, including patients with a type 2 inflammatory phenotype who received 148 weeks of treatment. This study is registered with ClinicalTrials.gov, NCT02134028.

Findings Between Aug 5, 2014, and Oct 11, 2019, of 2302 patients assessed for eligibility, 2282 adults and adolescents were enrolled (median age 50 years, 62·1% female and 37·9% male). Safety during TRAVERSE was consistent with the known dupilumab safety profile. The proportion of patients reporting treatment-emergent adverse events throughout the study duration was similar to that observed in the parent studies and ranged from 76·3% to 94·7%. The most frequently reported treatment-emergent adverse events were nasopharyngitis (17·5–25·9%), injection-site erythema (2·2–23·4%), and bronchitis (9·3–19·0%). Serious asthma exacerbations (0·5–3·6%) and pneumonia (0·7–2·7%) were the most frequently reported serious adverse events. There were four treatment-emergent adverse events leading to death. Efficacy during TRAVERSE was also consistent with the results of parent studies. In patients who were non-oral-corticosteroid-dependent, AER remained low (0·277–0·327) across parent study and treatment groups, pre-bronchodilator FEV_1 improvements were sustained to the end of treatment at week 96 (mean changes from parent study baseline ranged from 0·22 L [SD 0·44] to 0·33 L [0·44] across parent study and treatment groups), and improvements in ACQ-5 and AQLQ scores were sustained to the last timepoint assessed at week 48. Rapid improvements were observed in pre-bronchodilator FEV_1 and sustained improvements were seen in all outcome measures for patients given dupilumab who previously received placebo in parent studies; further improvements in AER, asthma control, and health-related quality of life were observed in patients who continued receiving dupilumab. Blood eosinophils and serum total IgE decreased progressively. ADA status had no effect on safety or efficacy. In the subgroup of patients with a type 2 inflammatory phenotype followed-up for 148 weeks, AER decreased progressively, and initial lung function improvements were sustained over 148 weeks.

Interpretation Data show that safety and efficacy of dupilumab in adult and adolescent patients with moderate-to-severe asthma are sustained when treatment is extended up to 148 weeks. These findings therefore support the long-term use of dupilumab in this patient population.

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Introduction

Asthma is a chronic lung condition characterised by episodic breathing difficulties, exacerbations, and airflow obstruction. Long-term uncontrolled asthma with associated inflammation increases the risk of exacerbations and leads to lung function deterioration.[1–4] Approximately

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Research in context

Evidence before this study

We searched PubMed on May 4, 2021, for previous studies that assessed the long-term safety and efficacy of dupilumab using multiple search terms including "dupilumab," "anti-interleukin-4," "anti-interleukin-13," "safety," "efficacy," "open-label," "asthma," and "long-term." No language or time restrictions were applied. Our searches revealed studies showing long-term safety and efficacy data for dupilumab in patients with atopic dermatitis, and long-term open-label extension studies of mepolizumab, benralizumab, omalizumab, and reslizumab in patients with asthma, lasting from approximately 1·0 year to 4·5 years. No long-term studies investigating the safety or efficacy of dupilumab in patients with asthma were identified.

Added value of this study

To our knowledge, this study is the first assessment of the long-term safety and efficacy of dupilumab in patients with asthma. To date, safety and efficacy data have been assessed in randomised controlled trials of up to 1 year in duration. The current study is an open-label extension that enrolled patients from phase 2A, phase 2B, and phase 3 studies assessing dupilumab in patients with both oral-corticosteroid-dependent and non-oral-corticosteroid-dependent asthma. We found that the safety profile was acceptable and consistent with that observed in the parent studies, and improvements in exacerbation rates, lung function, asthma control, and quality of life were sustained or improved further over the extended treatment period.

Implications of all the available evidence

This study provides a robust assessment of the safety and efficacy of dupilumab in 2282 patients with asthma up to 148 weeks, and complements the long-term safety profile of dupilumab previously reported in patients with atopic dermatitis. These findings support the long-term use of dupilumab in patients with uncontrolled moderate-to-severe asthma.

80% of patients with asthma have type 2 inflammation-driven disease, characterised by elevated biomarkers including blood eosinophils, fractional exhaled nitric oxide (FeNO), and serum periostin.[5–9] Interleukin (IL)-4 and IL-13 are key and central drivers of type 2 inflammation, and upregulation of these cytokines constitutes an important component of asthma.[10,11] Dupilumab, a fully human VelocImmune-derived[12,13] monoclonal antibody, blocks the shared receptor component for IL-4 and IL-13.[10] In phase 2B DRI (P2b; NCT01854047)[14] and phase 3 LIBERTY ASTHMA QUEST studies (QUEST; NCT02414854),[15] add-on dupilumab 200 mg and 300 mg every 2 weeks versus placebo reduced annualised exacerbation rate (AER) and improved pre-bronchodilator FEV_1 in patients with non-oral corticosteroid (OCS)-dependent, uncontrolled, moderate-to-severe asthma. In the phase 3 LIBERTY ASTHMA VENTURE study (VENTURE; NCT02528214)[16] in patients with OCS-dependent severe asthma, add-on dupilumab 300 mg every 2 weeks versus placebo reduced daily OCS dose while reducing AER and improving pre-bronchodilator FEV_1.

Although these studies show the safety and efficacy of dupilumab up to 1 year, the longer-term effects of dupilumab treatment in patients with asthma have not been assessed. This open-label extension study, LIBERTY ASTHMA TRAVERSE (TRAVERSE), aimed to evaluate the long-term safety and efficacy of dupilumab in patients who had participated in previous dupilumab asthma studies, P2b,[14] phase 3 QUEST,[15] phase 3 VENTURE,[16] and the translational phase 2A EXPEDITION study (NCT02573233). This analysis presents safety data in all patients enrolled in TRAVERSE and efficacy data in patients with non-OCS-dependent asthma from P2b[14] and QUEST.[15]

Methods

Study design and participants

TRAVERSE is a completed, multinational, multicentre, single-arm, open-label extension study in 362 hospitals and clinical centres across 27 countries (appendix p 7), which evaluated dupilumab for up to 96 weeks in patients (aged 12–84 years) with moderate-to-severe or OCS-dependent severe asthma. The study was done in accordance with the Declaration of Helsinki and the principles of Good Clinical Practice. Written informed consent (or assent, where appropriate) was obtained from all patients (or their parents or legal guardians) before enrolment in the study. The protocol and informed consent or assent forms were approved by independent ethics committees and institutional review boards at the study sites.

The trial consisted of a 0–3 week screening period (for patients from P2b[14] only as they had a treatment gap of 16–52 weeks before TRAVERSE), an up to 96 week treatment period, and a 12 week post-treatment period. Following a protocol amendment during the conduct of the study, the treatment period was shortened from 96 weeks to 48 weeks due to accumulating safety data for dupilumab across multiple indications in a clinical trial setting.[17] Further details of the study design and the study protocol are included in the appendix (pp 12, 48).

Patients with asthma who had previously completed the EXPEDITION, P2b,[14] QUEST,[15] or VENTURE[16] studies were eligible for enrolment in TRAVERSE. Briefly, EXPEDITION was an exploratory, randomised, double-blind, placebo-controlled study of the effects of dupilumab 300 mg every 2 weeks subcutaneously for 12 weeks on airway inflammation in adults with uncontrolled persistent asthma; P2b[14] was a randomised, double-blind, placebo-controlled, dose ranging, parallel group study comparing

different doses and regimens of dupilumab subcutaneously for 24 weeks in patients with moderate-to-severe, uncontrolled asthma; QUEST[15] was a phase 3, randomised, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab 200 mg and 300 mg every 2 weeks subcutaneously for 52 weeks in patients with uncontrolled, persistent asthma; and VENTURE[16] was a phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of dupilumab 300 mg every 2 weeks subcutaneously for 24 weeks in patients with severe OCS-dependent asthma. Patients from both placebo and dupilumab treatment arms of the parent studies could enrol, and patients enrolled on a voluntary basis. Further details of parent studies are provided in the appendix (p 13).[14–16]

At enrolment, patients were on background medication as maintained during the parent study, including medium-dose or high-dose inhaled corticosteroids (ICS; fluticasone propionate ≥250 µg twice a day or equivalent) and up to three asthma controllers (in addition to daily OCS for VENTURE[16] patients). During the open-label extension, patients were encouraged to continue their background therapy regimen as maintained during the parent study; daily OCS use could be modified by the investigator. Key exclusion criteria included chronic lung disease, which would impair pulmonary function tests; pregnancy or breastfeeding; active parasitic infection; HIV-positive status or immunosuppression; hypersensitivity to dupilumab; or blood eosinophils of more than 1500 mm³. Full inclusion and exclusion criteria are provided in the appendix (pp 8–9).

In this report, safety data are presented for all enrolled patients who were exposed to dupilumab from each of the four parent studies. Efficacy data are presented for the non-OCS-dependent populations from P2b[14] and QUEST[15] (90·4% of the total TRAVERSE population) separately. Efficacy for EXPEDITION (1·4%) and VENTURE[16] (8·2%) patients was analysed separately and is not reported here owing to considerable differences in patient characteristics and study designs.

Procedures

Patients from EXPEDITION, QUEST,[15] or VENTURE[16] entered the open-label extension at the end-of-treatment visit of the parent study, whereas patients from P2b[14] completed a 16-week post-treatment follow-up and were off treatment for up to 52 weeks. All patients received subcutaneous dupilumab 300 mg every 2 weeks throughout the open-label extension treatment period. Subcutaneous injection sites (abdomen, thighs, and upper arms) were alternated so that the same site was not used for two consecutive injections. The study assessment schedule involved visits at weeks 2, 4, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72, 84, and end of treatment (week 96), with a post-treatment end-of-study visit scheduled 12 weeks after end of treatment (week 108). Reports of adverse events were collected at all visits and once a month by telephone after week 24. Spirometry was done at weeks 2, 4, 8, 12, 24, 48, 72, 84, end of treatment (week 96), and end of study (week 108). The five-item asthma control questionnaire (ACQ-5) and asthma quality of life questionnaire (AQLQ) were administered at weeks 24 and 48. Clinical laboratory samples were collected at weeks 4, 12, 24, 48, 72, end of treatment (week 96), and end of study (week 108).

Outcomes

The primary endpoint was the number and percentage of patients having any treatment-emergent adverse event up to week 96 (or week 48 for patients enrolled after the protocol amendment). Secondary endpoints included the effects of dupilumab on AER (severe asthma exacerbations requiring systemic corticosteroids for ≥3 days, hospitalisation, or emergency room visit), pre-bronchodilator FEV_1, ACQ-5 (scale 0–6, higher scores indicate lower asthma control), AQLQ (scale 1–7, higher scores indicate less impairment), and biomarkers of type 2 inflammation (blood eosinophils and serum total IgE [assessed in patients from P2b[14] only]). Occurrence of anti-drug antibodies (ADAs) was also assessed. Safety data were collected for the entire treatment-emergent period. For some patients this was 96 weeks and for others this was less (48 weeks, 24–48 weeks, or <24 weeks). Efficacy endpoints for AER, pre-bronchodilator FEV_1, and biomarkers until week 96 are presented. ACQ-5 and AQLQ data are presented until week 48 only as these data were not collected after the protocol amendment to shorten the study from 96 weeks to 48 weeks. Other secondary endpoint data collected for this trial will be reported in separate publications or made publicly available, including safety and tolerability endpoints (vital signs, physical examination, electrocardiogram, and clinical laboratory tests) and efficacy endpoints (five-dimension EuroQol questionnaire [three-level version], health-care resource utilisation questionnaire, morning and evening peak expiratory flow, asthma symptom scores, number of inhalations per day of salbutamol or levosalbutamol for symptom relief, nocturnal awakenings due to asthma requiring use of reliever medication, and prescribed OCS dose for patients from VENTURE[16]).

Statistical analysis

Safety assessments were analysed separately for the following prespecified groups of patients: patients who were non-OCS-dependent from P2b[14] and QUEST,[15] patients who were OCS-dependent from VENTURE,[16] and patients who participated in EXPEDITION. Owing to substantial differences between patients who were OCS-dependent and non-OCS dependent, including differences in disease severity and background controller medication, efficacy assessments were analysed for the prespecified non-OCS-dependent patient populations from P2b[14] and QUEST[15] only.

All statistical analyses are descriptive summaries using observed data only as this study was an open-label, single-group study with no comparator group, and as patients were enrolled from four parent studies with varying duration, dose exposures, enrolment criteria, and background therapies. All statistical analyses were done on the overall exposed populations of each of the individual parent studies. The overall exposed population was defined as all patients who received one or more doses or part-doses of dupilumab. Safety endpoints are presented as the absolute numbers of patients reporting treatment-emergent adverse events and adjusted numbers based on time in the study (incidence per 100 patient-years and number of patients with ≥1 event per 100 years). Efficacy endpoints are presented as change from parent study baseline over the treatment period, with absolute mean and median values at key timepoints across parent study and treatment groups reported. Proportions of patients who showed improvements exceeding the minimal clinically important difference of 0·5 or greater in patient-reported outcomes are also reported. ADA analyses were done on the ADA population, defined as all patients in the overall exposed population who had one or more non-missing functional dupilumab concentration values after the first dose of dupilumab in the TRAVERSE study. No imputations were made for patients with missing data and no sensitivity analyses were done. Treatment in patients who received placebo in the parent study and were exposed to dupilumab in TRAVERSE is referred to as placebo–dupilumab, while treatment in patients who received dupilumab in both studies is referred to as dupilumab–dupilumab. Treatment duration was defined as exposure to dupilumab during the TRAVERSE study unless otherwise stated; owing to an amendment during the conduct of the study, this duration could be up to 48 weeks or 96 weeks.

Subgroup analyses of AER and pre-bronchodilator FEV_1 were done in select populations, including a post-hoc analysis of patients who were non-OCS-dependent with a type 2 inflammatory phenotype (blood eosinophils ≥150 cells per µL or FeNO ≥25 parts per billion [ppb]) at parent study baseline and a prespecified analysis of patients who were non-OCS-dependent and receiving high-dose ICS[18] at parent study baseline.

To assess the long-term effect of continuous dupilumab treatment exposure, without confounding from dropouts or differential exposure duration, an additional post-hoc analysis of AER and pre-bronchodilator FEV_1 was done in patients with a type 2 inflammatory phenotype followed-up for 148 weeks (ie, patients from QUEST[15] with a type 2 inflammatory phenotype defined as above) who received 148 weeks of continuous dupilumab treatment (dupilumab 200 mg or 300 mg every 2 weeks for 52 weeks in QUEST[15] and dupilumab 300 mg every 2 weeks for 96 weeks in TRAVERSE). Efficacy analyses during the QUEST treatment period were pooled across dosing groups due to the similarity in outcomes observed in the parent study.[15] All analyses were done using SAS, version 9.4 or higher.

An independent data monitoring committee commissioned for the dupilumab development programme was used in the study. This study is registered with ClinicalTrials.gov, NCT02134028.

Role of the funding source

The funder of the study had a role in the study design, data collection, data analysis, and data interpretation. The manuscript was written with assistance from an independent medical writing company funded by the study sponsors.

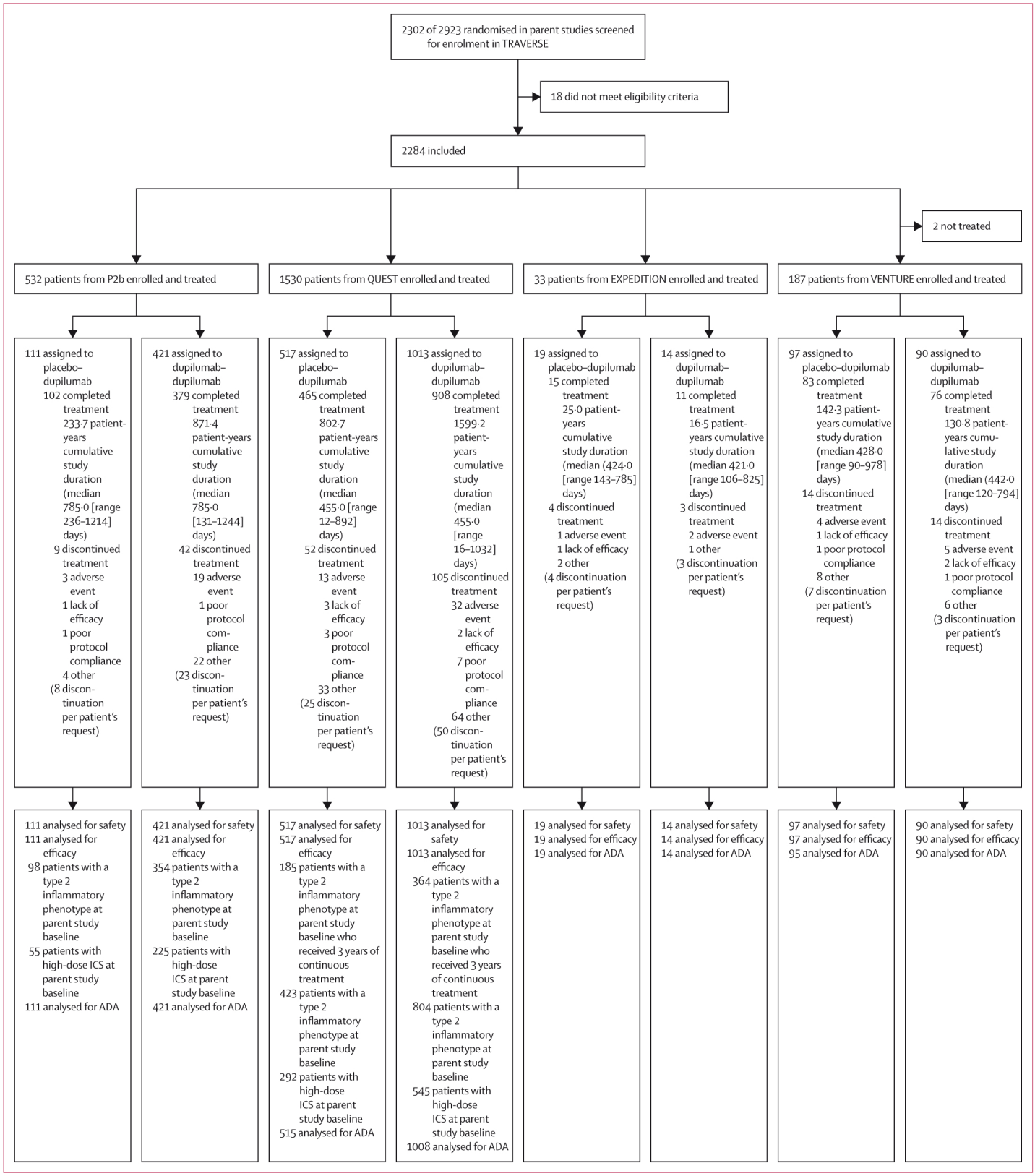
Results

The TRAVERSE study took place between Aug 5, 2014, and Oct 11, 2019. Of the 2923 patients randomly assigned in the parent studies, 2302 were screened and 2282 (78·1%; median age 50 years, 62·1% female and 37·9% male) participated and were exposed to dupilumab in TRAVERSE: 2062 patients with non-OCS-dependent moderate-to-severe asthma from P2b (placebo–dupilumab, 111 of 158 included in the parent study; dupilumab–dupilumab, 421 of 611) and QUEST (placebo–dupilumab, 517 of 638; dupilumab–dupilumab, 1013 of 1264); 33 patients with moderate-to-severe asthma from EXPEDITION (placebo–dupilumab, 19 of 22; dupilumab–dupilumab, 14 of 20); and 187 patients with OCS-dependent severe asthma from VENTURE (placebo–dupilumab, 97 of 107; dupilumab–dupilumab, 90 of 103; figure 1). 18 patients from P2b were considered ineligible for enrolment into TRAVERSE as per the inclusion or exclusion criteria. Two patients from the VENTURE study were enrolled in error and were prematurely discontinued from the study without exposure to dupilumab. Overall, 2182 (95·6%) of 2282 patients completed TRAVERSE to week 48 and 1240 (54·3%) patients to week 96, with a cumulative study duration of 3507 patient-years (figure 1).

Baseline demographics and clinical characteristics at parent study baseline are shown in table 1, and the appendix (p 14). Demographics were similar across non-OCS-dependent patient populations in the P2b and QUEST studies. There were 87 adolescents (<18 years) among the patients who were non-OCS-dependent included from QUEST. Patients who were OCS-dependent from VENTURE were typically older and had lower FEV_1 values and higher IgE concentrations than

Figure 1: **Trial profile**

Study duration included the duration from enrolment to the end of participation in the TRAVERSE study. A screening period was applicable for patients enrolling from P2b only, as they had a treatment gap of between 16 and 52 weeks before TRAVERSE. Discontinuation per patient's request and discontinued treatment are not mutually exclusive. ICS=inhaled corticosteroid. ADA=anti-drug antibodies. P2b=phase 2B DRI.


2302 of 2923 randomised in parent studies screened for enrolment in TRAVERSE
18 did not meet eligibility criteria
2284 included
2 not treated
532 patients from P2b enrolled and treated
1530 patients from QUEST enrolled and treated
33 patients from EXPEDITION enrolled and treated
187 patients from VENTURE enrolled and treated
111 assigned to placebo–dupilumab
102 completed treatment
233·7 patient-years cumulative study duration (median 785·0 [range 236–1214] days)
9 discontinued treatment
3 adverse event
1 lack of efficacy
1 poor protocol compliance
4 other
(8 discontinuation per patient's request)
421 assigned to dupilumab–dupilumab
379 completed treatment
871·4 patient-years cumulative study duration (median 785·0 [131–1244] days)
42 discontinued treatment
19 adverse event
1 poor protocol compliance
22 other
(23 discontinuation per patient's request)
517 assigned to placebo–dupilumab
465 completed treatment
802·7 patient-years cumulative study duration (median 455·0 [range 12–892] days)
52 discontinued treatment
13 adverse event
3 lack of efficacy
3 poor protocol compliance
33 other
(25 discontinuation per patient's request)
1013 assigned to dupilumab–dupilumab
908 completed treatment
1599·2 patient-years cumulative study duration (median 455·0 [range 16–1032] days)
105 discontinued treatment
32 adverse event
2 lack of efficacy
7 poor protocol compliance
64 other
(50 discontinuation per patient's request)
19 assigned to placebo–dupilumab
15 completed treatment
25·0 patient-years cumulative study duration (median (424·0 [range 143–785] days)
4 discontinued treatment
1 adverse event
1 lack of efficacy
2 other
(4 discontinuation per patient's request)
14 assigned to dupilumab–dupilumab
11 completed treatment
16·5 patient-years cumulative study duration (median 421·0 [range 106–825] days)
3 discontinued treatment
2 adverse event
1 other
(3 discontinuation per patient's request)
97 assigned to placebo–dupilumab
83 completed treatment
142·3 patient-years cumulative study duration (median 428·0 [range 90–978] days)
14 discontinued treatment
4 adverse event
1 lack of efficacy
1 poor protocol compliance
8 other
(7 discontinuation per patient's request)
90 assigned to dupilumab–dupilumab
76 completed treatment
130·8 patient-years cumulative study duration (median (442·0 [range 120–794] days)
14 discontinued treatment
5 adverse event
2 lack of efficacy
1 poor protocol compliance
6 other
(3 discontinuation per patient's request)
111 analysed for safety
111 analysed for efficacy
98 patients with a type 2 inflammatory phenotype at parent study baseline
55 patients with high-dose ICS at parent study baseline
111 analysed for ADA
421 analysed for safety
421 analysed for efficacy
354 patients with a type 2 inflammatory phenotype at parent study baseline
225 patients with high-dose ICS at parent study baseline
421 analysed for ADA
517 analysed for safety
517 analysed for efficacy
185 patients with a type 2 inflammatory phenotype at parent study baseline who received 3 years of continuous treatment
423 patients with a type 2 inflammatory phenotype at parent study baseline
292 patients with high-dose ICS at parent study baseline
515 analysed for ADA
1013 analysed for safety
1013 analysed for efficacy
364 patients with a type 2 inflammatory phenotype at parent study baseline who received 3 years of continuous treatment
804 patients with a type 2 inflammatory phenotype at parent study baseline
545 patients with high-dose ICS at parent study baseline
1008 analysed for ADA
19 analysed for safety
19 analysed for efficacy
19 analysed for ADA
14 analysed for safety
14 analysed for efficacy
14 analysed for ADA
97 analysed for safety
97 analysed for efficacy
95 analysed for ADA
90 analysed for safety
90 analysed for efficacy
90 analysed for ADA

	Patients from P2b		Patients from QUEST		Patients from VENTURE	
	Placebo–dupilumab (n=111)	Dupilumab–dupilumab (n=421)	Placebo–dupilumab (n=517)	Dupilumab–dupilumab (n=1013)	Placebo–dupilumab (n=97)	Dupilumab–dupilumab (n=90)
Age, years	49·1 (12·3)	49·8 (12·5)	48·2 (15·1)	47·9 (15·2)	51·3 (12·4)	51·7 (12·9)
<18	0	0	32 (6·2%)	55 (5·4%)	1 (1·0%)	1 (1·1%)
18–64	101 (91·0%)	374 (88·8%)	422 (81·6%)	826 (81·5%)	81 (83·5%)	80 (88·9%)
≥65	10 (9·0%)	47 (11·2%)	63 (12·2%)	132 (13·0%)	15 (15·5%)	9 (10·0%)
Sex						
Female	69 (62·2%)	259 (61·5%)	335 (64·8%)	618 (61·0%)	57 (58·8%)	53 (58·9%)
Male	42 (37·8%)	162 (38·5%)	182 (35·2%)	395 (39·0%)	40 (41·2%)	37 (41·1%)
Ongoing atopic or allergic condition	88/110 (80·0%)	333/420 (79·3%)	426 (82·4%)	839 (82·8%)	71 (73·2%)	65 (72·2%)
Former smoker	28 (25·2%)	93 (22·1%)	98 (19·0%)	195 (19·2%)	15 (15·5%)	19 (21·1%)
Number of severe asthma exacerbations in the year before the parent study	2·37 (2·49)	2·27 (2·22)	2·22 (1·87)	2·09 (2·00)	2·18 (2·31)	1·90 (1·95)
Pre-bronchodilator FEV_1, L	1·80 (0·53)	1·82 (0·54)	1·77 (0·58)	1·79 (0·62)	1·62 (0·62)	1·53 (0·50)
Pre-bronchodilator FEV_1, % predicted	59·78 (10·75)	60·71 (11·00)	58·39 (13·25)	58·48 (13·51)	52·47 (15·46)	51·76 (15·37)
FEV_1 reversibility, %	28·51 (14·31)	26·75 (16·80)	25·79 (18·16)	26·35 (22·95)	17·96 (23·47)	21·79 (24·34)
ACQ-5 score, scale 0–6	2·63 (0·77)	2·74 (0·80)	2·73 (0·74)	2·76 (0·79)	2·60 (1·11)	2·43 (1·14)
AQLQ global score, scale 1–7	4·27 (1·12)	3·98 (1·10)	4·25 (1·01)	4·29 (1·08)	4·34 (1·13)	4·36 (1·14)
High-dose inhaled corticosteroids	55/109 (50·5%)	225/411 (54·7%)	292 (56·5%)	545 (53·8%)	88 (90·7%)	81/89 (91·0%)
Blood eosinophils, Giga/L	0·33 (0·29)	0·37 (0·52)	0·39 (0·39)	0·35 (0·35)	0·32 (0·29)	0·38 (0·33)
Total IgE, IU/mL	423·6 (700·1)	441·2 (767·3)	407·1 (672·3)	453·9 (796·3)	450·6 (920·8)	452·4 (689·7)
FeNO, parts per billion	37·63 (33·54)	40·16 (35·94)	36·78 (34·70)	34·70 (32·38)	38·98 (33·09)	35·20 (29·48)

Data are mean (SD) or n (%). The patients from P2b and QUEST were non-OCS dependent and the patients from VENTURE were OCS-dependent. An atopic medical history or ongoing atopic disease was considered to be present if the patient had or has any of the following diseases: atopic dermatitis, allergic conjunctivitis or allergic rhinitis, chronic rhinosinusitis, nasal polyposis, food allergy, or hives. Asthma exacerbation before the study was defined as any treatment with one systemic (oral or parenteral) steroid burst or more for worsening asthma, or hospital admission or an emergency or urgent medical care visit for worsening asthma. Owing to substantial differences in study design and sample size, EXPEDITION data are presented in the appendix (p 14). P2b=phase 2B DRI. OCS=oral corticosteroid. FeNO=fractional exhaled nitric oxide. ACQ-5=five-item asthma control questionnaire. AQLQ=asthma quality of life questionnaire.

Table 1: **Baseline characteristics**

patients who were non-OCS-dependent. Two of the patients who were OCS-dependent included from VENTURE were adolescents. Nearly all patients who were OCS-dependent were on high-dose ICS (169 [90·9%] of 186) compared with 50·5–56·5% across the groups of patients who were non-OCS-dependent.

An overview of the incidence of treatment-emergent adverse events during TRAVERSE is provided in table 2. In patients who were non-OCS-dependent, one or more treatment-emergent adverse events were seen in 88 (79·3%) of 111 patients given placebo–dupilumab and 369 (87·6%) of 421 given dupilumab–dupilumab from P2b and 414 (80·1%) of 517 patients given placebo–dupilumab and 789 (77·9%) of 1013 given dupilumab–dupilumab from QUEST (table 2). The most frequently reported treatment-emergent adverse events were nasopharyngitis, bronchitis, and injection-site erythema, with similar incidence between patients given placebo–dupilumab and dupilumab–dupilumab (appendix pp 15–19). Incidence of treatment-emergent serious adverse events was low (table 2), with serious asthma exacerbations (0·5–3·6%) and pneumonia (0·7–2·7%) being the most frequently reported treatment-emergent serious adverse events (appendix pp 20–28). Four patients had treatment-emergent adverse events leading to death, all of whom had received dupilumab in the parent study: three were enrolled from P2b (with the treatment-emergent adverse events of metastatic lung cancer, gastric adenocarcinoma, and craniocerebral injury) and one from QUEST (respiratory failure). Patient narratives for these cases are provided in the appendix (pp 9–10). The incidence of treatment-emergent adverse events leading to permanent treatment discontinuation was low (table 2); no differences were observed between treatment groups for patients enrolled from either study (appendix pp 29–32). Eosinophilia treatment-emergent adverse events were reported in 29 (1·4%) of 2062 patients from P2b and QUEST. In most cases, these were laboratory findings without associated clinical symptoms. Three cases of treatment-emergent eosinophilic granulomatosis with polyangiitis were reported (all patients given dupilumab–dupilumab). Patient narratives for these cases are provided in the appendix (pp 10–11).

In patients from P2b, incidence rates of treatment-emergent adverse events adjusted on the basis of time in the study were higher in patients given dupilumab–dupilumab compared with patients given placebo–dupilumab (table 2). In patients from QUEST, incidence rates of treatment-emergent adverse events in the dupilumab–dupilumab group were lower than those observed in the placebo–dupilumab group (table 2). The safety profile of dupilumab in adolescents enrolled from

	Patients from P2b		Patients from QUEST		Patients from VENTURE	
	Placebo–dupilumab (n=111)	Dupilumab–dupilumab (n=421)	Placebo–dupilumab (n=517)	Dupilumab–dupilumab (n=1013)	Placebo–dupilumab (n=97)	Dupilumab–dupilumab (n=90)
Patients with any treatment-emergent adverse event	88 (79·3%)	369 (87·6%)	414 (80·1%)	789 (77·9%)	74 (76·3%)	70 (77·8%)
Per patient-year (per 100 patient-years)*	88/72·5 (121·4)	369/228·7 (161·4)	414/293·6 (141·0)	789/613·6 (128·6)	74/57·0 (129·8)	70/53·8 (130·0)
Patients with any treatment-emergent serious adverse event	14 (12·6%)	42 (10·0%)	48 (9·3%)	106 (10·5%)	12 (12·4%)	10 (11·1%)
Per patient-year (per 100 patient-years)*	14/207·0 (6·8)	42/794·2 (5·3)	48/747·9 (6·4)	106/1457·6 (7·3)	12/125·3 (9·6)	10/119·4 (8·4)
Patients with any treatment-emergent adverse event leading to death†	0	3 (0·7%)	0	1 (0·1%)	0	0
Per patient-year (per 100 patient-years)*	0/222·3	3/827·6 (0·4)	0/780·5	1/1543·4 (<0·1)	0/137·6	0/124·8
Patients with any treatment-emergent adverse event leading to permanent treatment discontinuation	3 (2·7%)	19 (4·5%)	12 (2·3%)	31 (3·1%)	4 (4·1%)	5 (5·6%)
Per patient-year (per 100 patient-years)*	3/221·5 (1·4)	19/822·4 (2·3)	12/777·1 (1·5)	31/1534·4 (2·0)	4/136·4 (2·9)	5/123·5 (4·0)
Treatment-emergent adverse events occurring in ≥10% in any treatment group by preferred term‡						
Nasopharyngitis	27 (24·3%)	109 (25·9%)	99 (19·1%)	191 (18·9%)	17 (17·5%)	16 (17·8%)
Bronchitis	15 (13·5%)	80 (19·0%)	63 (12·2%)	118 (11·6%)	9 (9·3%)	14 (15·6%)
Upper respiratory tract infection	18 (16·2%)	60 (14·3%)	65 (12·6%)	130 (12·8%)	8 (8·2%)	6 (6·7%)
Influenza	5 (4·5%)	45 (10·7%)	30 (5·8%)	69 (6·8%)	9 (9·3%)	7 (7·8%)
Pharyngitis	16 (14·4%)	37 (8·8%)	26 (5·0%)	59 (5·8%)	1 (1·0%)	4 (4·4%)
Headache	13 (11·7%)	47 (11·2%)	47 (9·1%)	74 (7·3%)	4 (4·1%)	5 (5·6%)
Injection-site erythema	26 (23·4%)	55 (13·1%)	35 (6·8%)	50 (4·9%)	5 (5·2%)	2 (2·2%)
Injection-site pruritus	12 (10·8%)	16 (3·8%)	15 (2·9%)	7 (0·7%)	2 (2·1%)	0

Data are n (%) of patients with one or more treatment-emergent adverse event (MedDRA preferred term). The patients from P2b and QUEST were non-OCS-dependent and the patients from VENTURE were OCS-dependent. All safety results were summarised with descriptive statistics using data from the overall exposed population, defined as patients who received one or more doses or part of a dose of dupilumab in the open-label extension. For patients with an event, patient-years are calculated up to the date of the first incidence; for patients without an event, patient-years correspond to the length of study observation period. Owing to substantial differences in study design and sample size, EXPEDITION data are presented in the appendix (p 33). MedDRA=Medical Dictionary for Regulatory Activities. OCS=oral corticosteroid. P2b=phase 2B DRI. *Data are number of patients with any event per patient-year (number of patients with one or more event per 100 patient-years). †Causes of death were metastatic lung cancer, gastric adenocarcinoma, craniocerebral injury, and respiratory failure. ‡Adverse events in this category were reported according to the preferred terms in MedDRA version 22.0.

***Table 2*: Overview of treatment-emergent adverse events in the overall exposed populations of non-OCS-dependent and OCS-dependent patients from P2b, QUEST, and VENTURE during the open-label extension**

QUEST will be presented in a separate publication.

In patients enrolled from EXPEDITION, 18 (94·7%) of 19 patients given placebo–dupilumab and 13 (92·9%) of 14 given dupilumab–dupilumab had one or more treatment-emergent adverse events (appendix p 33). Most frequently reported were nasopharyngitis, influenza, headache, diarrhoea, nausea, vomiting, back pain, injection-site erythema, and injection-site oedema (appendix pp 34–40). Four (12·1%) of the 33 patients from EXPEDITION reported one or more treatment-emergent serious adverse events (appendix p 41) and three (9·1%) of 33 patients had treatment-emergent adverse events leading to permanent treatment discontinuation (appendix p 42).

In patients who were OCS-dependent from VENTURE, during TRAVERSE, 74 (76·3%) of 97 patients given placebo–dupilumab and 70 (77·8%) of 90 given dupilumab–dupilumab had one or more treatment-emergent adverse events (table 2). The most frequently reported treatment-emergent adverse events were nasopharyngitis and bronchitis (appendix pp 15–19). Low proportions of patients had one or more treatment-emergent serious adverse events (table 2; appendix pp 20–28). No treatment-emergent adverse events led to death. The number of patients with a treatment-emergent adverse event leading to permanent treatment discontinuation was low and similar to rates in patients who were non-OCS-dependent (appendix pp 29–32). Eosinophilia treatment-emergent adverse events were reported by 12 (6·4%) of 187 patients, including two cases of treatment-emergent eosinophilic granulomatosis with polyangiitis, which led to treatment discontinuation (one case in the group given placebo–dupilumab, one in the group given dupilumab–dupilumab; appendix p 11).

Efficacy results are presented in patients who were non-OCS-dependent for each study separately. Efficacy results from the 87 adolescent patients enrolled from QUEST will be presented in a separate publication.

The reductions in AER observed during the parent studies[14–16] were sustained and showed additional reductions during TRAVERSE (figure 2A). At parent study baseline, the mean number of exacerbations in the year before the parent study was 2·37 (SD 2·49) in patients given placebo–dupilumab and 2·27 (2·22) in patients given dupilumab–dupilumab from P2b, and 2·22 (1·87) in patients given placebo–dupilumab and

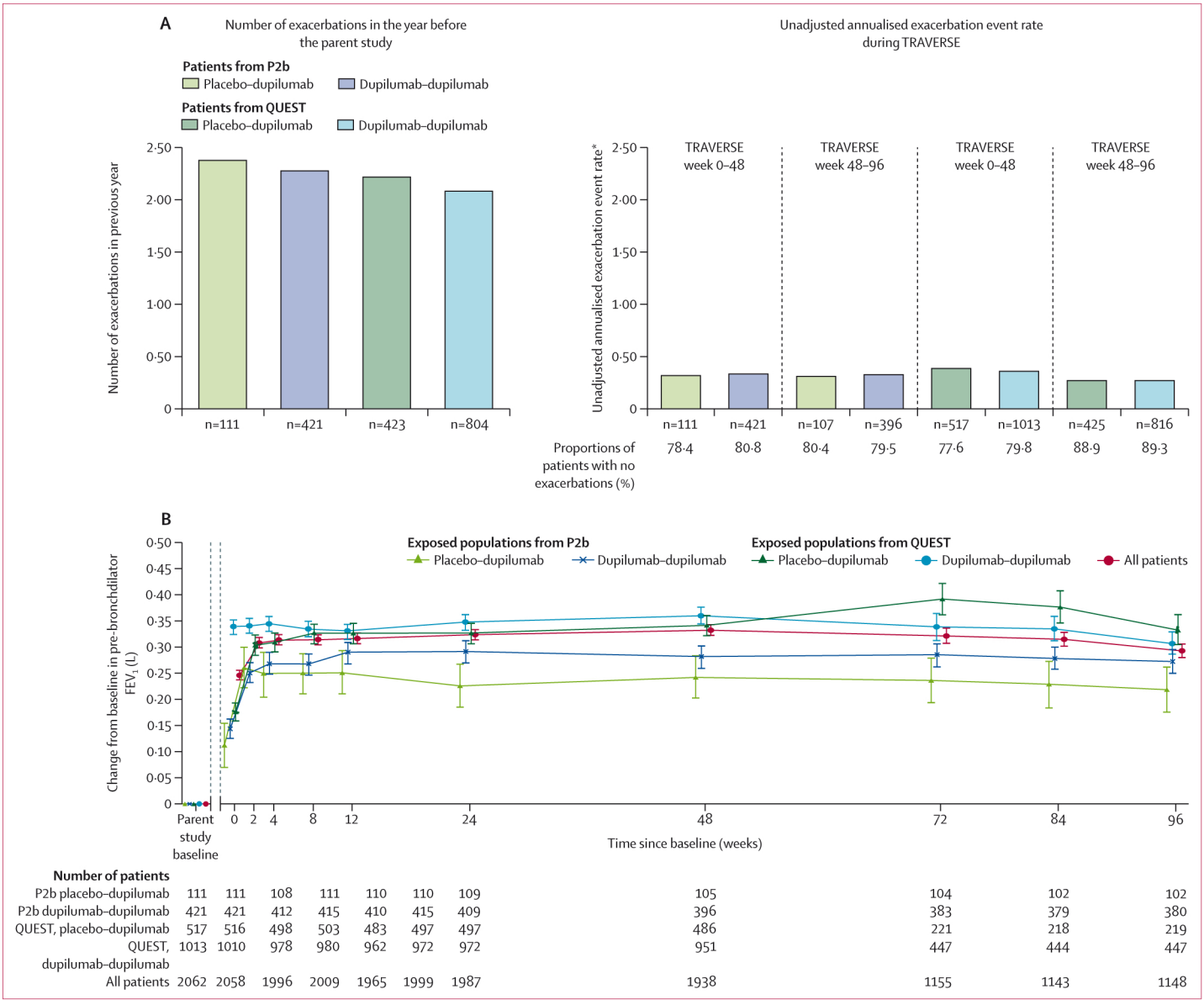


Figure 2: **Exacerbation rates and lung function in non-oral-corticosteroid-dependent patients from P2b and QUEST**

(A) Number of exacerbations in the year before the parent study and AER during the open-label extension treatment period and (B) change from parent study baseline in pre-bronchodilator FEV_1 in the overall exposed populations from P2b and QUEST (mean [SE]). AER was assessed in the overall exposed population (observed cases). Pre-bronchodilator FEV_1 was assessed in the overall exposed population (observed cases) using descriptive statistics. Week 0 represents the start of the open-label extension. Patients from P2b had a treatment gap of between 16 and 52 weeks before enrolment in TRAVERSE. AER=annualised exacerbation rate. P2b=phase 2B DRI. *The total number of events that occurred during the treatment period divided by the total number of patient-years followed-up in the treatment period.

2·09 (2·00) in patients given dupilumab–dupilumab from QUEST (table 1, figure 2A). Between weeks 0 and 48 of TRAVERSE, the unadjusted AER was 0·319 in patients given placebo–dupilumab and 0·333 in patients given dupilumab–dupilumab from P2b, and 0·385 in patients given placebo–dupilumab and 0·357 in patients given dupilumab–dupilumab from QUEST. Between weeks 48 and 96, the unadjusted AER was 0·310 in patients given placebo–dupilumab and 0·327 in patients given dupilumab–dupilumab from P2b, and 0·278 in patients given placebo–dupilumab and 0·277 in patients given dupilumab–dupilumab from QUEST (figure 2A).

Pre-bronchodilator FEV_1 improvements observed during the parent studies[14–16] were sustained during TRAVERSE (figure 2B). At parent study baseline, we observed a mean pre-bronchodilator FEV_1 of 1·80 L (SD 0·53) in patients given placebo–dupilumab and 1·82 L (0·54) in patients given dupilumab–dupilumab from P2b, and 1·77 L (0·58) in patients given placebo–dupilumab and 1·79 L (0·62) in patients given

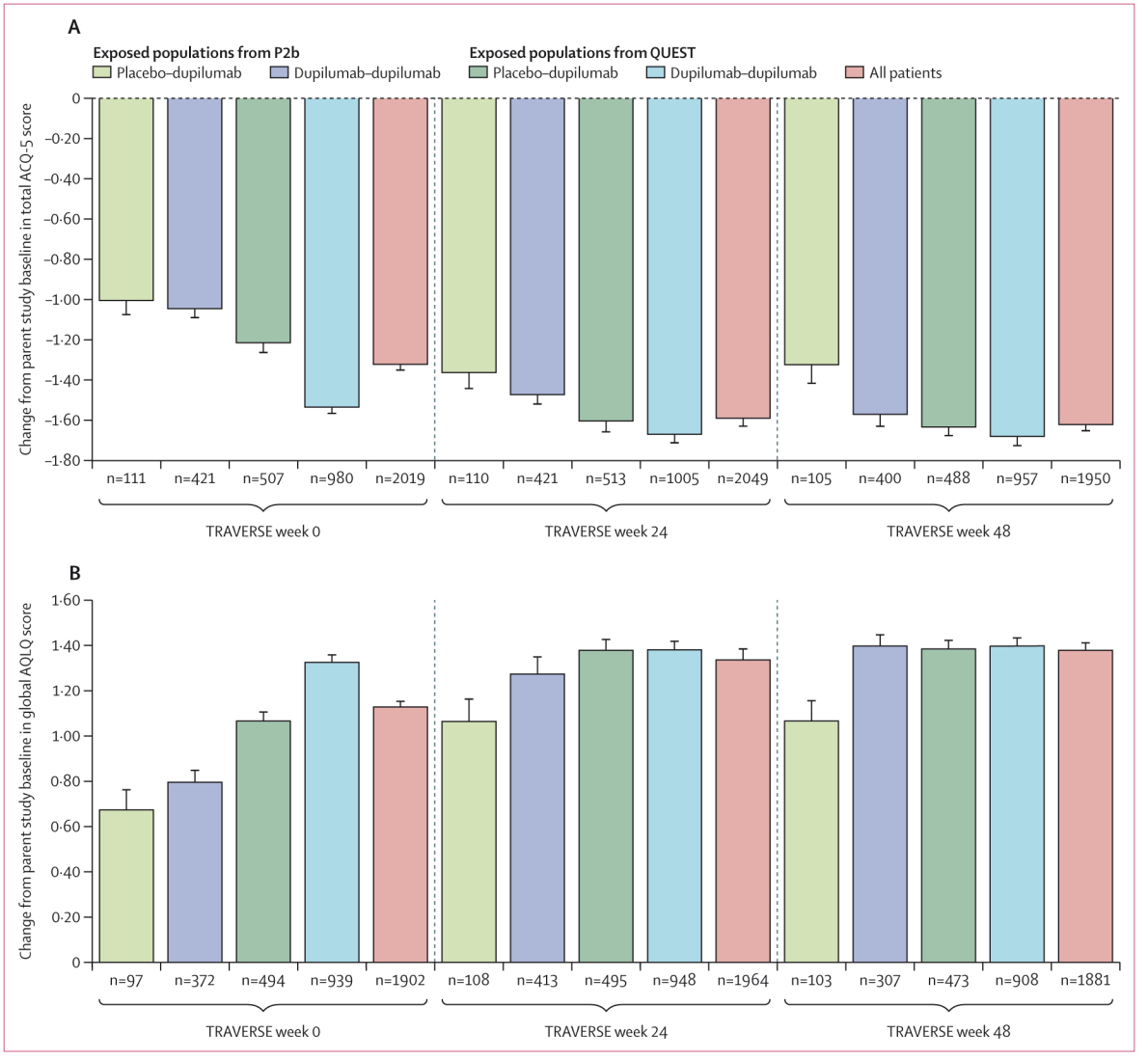


Figure 3: **Asthma control and health-related quality of life in non-oral-corticosteroid-dependent patients from P2b and QUEST**
Data are mean (SE). (A) Change from parent study baseline in total ACQ-5 score at weeks 0, 24, and 48 of the open-label extension and (B) change from parent study baseline in global AQLQ score at weeks 0, 24, and 48 of the open-label extension in overall exposed populations from P2b and QUEST. Patients from P2b had a treatment gap of between 16 and 52 weeks before enrolment in TRAVERSE. ACQ-5 and AQLQ were assessed up to week 48 only owing to the protocol amendment. Data were not available for all patients at all timepoints. ACQ-5=five-item asthma control questionnaire. AQLQ=asthma quality of life questionnaire. P2b=phase 2B DRI.

dupilumab–dupilumab from QUEST (table 1). In patients given placebo–dupilumab from P2b and QUEST, rapid improvements in pre-bronchodilator FEV_1 were observed by TRAVERSE week 2 (mean pre-bronchodilator FEV_1 changes from parent study baseline 0·26 L [SD 0·40] for P2b and 0·30 L [0·44] for QUEST; figure 2B). Pre-bronchodilator FEV_1 improvements observed in patients given dupilumab in the parent studies[14–16] were sustained during TRAVERSE. By week 96 of TRAVERSE, mean changes from parent study baseline in pre-bronchodilator FEV_1 were 0·22 L (SD 0·44) for P2b and 0·33 L (0·44) for QUEST in patients given placebo–dupilumab, and 0·27 L (0·46) for P2b and 0·31 L (0·47) for QUEST in patients given dupilumab–dupilumab (figure 2B). Absolute mean (SD) and median (IQR) values are reported in the appendix (pp 44–45).

Asthma control and health-related quality-of-life improvements observed during the parent studies[14–16] were sustained during TRAVERSE (figure 3). At parent study baseline, mean total ACQ-5 scores were 2·63 (SD 0·77) in patients given placebo–dupilumab and 2·74 (0·80) in patients given dupilumab–dupilumab from P2b, and 2·73 (0·74) in patients given placebo–dupilumab and 2·76 (0·79) in patients given dupilumab–dupilumab from QUEST, indicative of uncontrolled asthma (table 1). At TRAVERSE week 48, mean total ACQ-5 scores had improved from parent study baseline (P2b, placebo–

dupilumab –1·33 [SD 1·07], dupilumab–dupilumab –1·57 [1·11]; QUEST, placebo–dupilumab –1·64 [1·08], dupilumab–dupilumab –1·69 [1·08]; figure 3A). At week 0, 79 (71·2%) of 111 patients given placebo–dupilumab and 284 (67·5%) of 421 patients given dupilumab–dupilumab from P2b, and 390 (76·9%) of 507 patients with available data given placebo–dupilumab and 818 (83·5%) of 980 patients with available data given dupilumab–dupilumab from QUEST, showed an ACQ-5 improvement from parent study baseline that exceeded the minimal clinically important difference of 0·5 or greater. These proportions increased to 83 (79·0%) of 105 patients (placebo–dupilumab) and 329 (82·3%) of 400 patients (dupilumab–dupilumab) from P2b, and 418 (85·7%) of 488 patients (placebo–dupilumab) and 830 (86·7%) of 957 patients (dupilumab–dupilumab) from QUEST at week 48, indicating an increase in patients responding to treatment over time, as assessed by total ACQ-5 scores.

At parent study baseline, mean global AQLQ scores were 4·27 (SD 1·12) for patients given placebo–dupilumab and 3·98 (1·10) for patients given dupilumab–dupilumab from P2b, and 4·25 (1·01) for patients given placebo–dupilumab and 4·29 (1·08) for patients given dupilumab–dupilumab from QUEST (table 1). At week 48, mean global AQLQ scores had improved from parent study baseline (P2b, placebo–dupilumab 1·07 [SD 1·13], dupilumab–dupilumab 1·40 [1·19]; QUEST, placebo–dupilumab 1·39 [1·17], dupilumab–dupilumab 1·40 [1·18]; figure 3B). At week 0, 49 (50·5%) of 97 patients given placebo–dupilumab and 221 (59·4%) of 372 patients given dupilumab–dupilumab from P2b, and 340 (68·8%) of 494 patients given placebo–dupilumab and 716 (76·3%) of 939 patients given dupilumab–dupilumab from QUEST had an AQLQ improvement from parent study baseline that exceeded the minimal clinically important difference of 0·5 or greater. These proportions increased to 67 (65·0%) of 103 patients (placebo–dupilumab) and 303 (76·3%) of 397 patients (dupilumab–dupilumab) from P2b, and 366 (77·4%) of 473 patients (placebo–dupilumab) and 712 (78·4%) of 908 patients (dupilumab–dupilumab) from QUEST at week 48, indicating an increase in patients responding to treatment over time, as assessed by global AQLQ scores.

Absolute mean (SD) and median (IQR) values for lung function, asthma control, and health-related quality of life outcomes in non-OCS-dependent patients from P2b and QUEST are reported in the appendix (pp 44–45).

At parent study baseline, mean blood eosinophil counts were 0·33 Giga/L (SD 0·29) for patients given placebo–dupilumab and 0·37 Giga/L (0·52) for patients given dupilumab–dupilumab from P2b, and 0·39 Giga/L (0·39) for patients given placebo–dupilumab and 0·35 Giga/L (0·35) for patients given dupilumab–dupilumab from QUEST (table 1). For patients from the P2b study, mean changes in blood eosinophil counts from parent study baseline to week 96 were –0·07 Giga/L (SD 0·25; mean percentage change from parent study baseline 2·15%; median change –0·06 [IQR –0·18 to 0·03]) for the placebo–dupilumab group and –0·08 Giga/L (0·56; 8·20%; –0·05 [–0·17 to 0·05]) for the dupilumab–dupilumab group. For patients from the QUEST study, mean changes to week 96 were –0·16 Giga/L (SD 0·39; mean percentage change from parent study baseline 5·54%; median change –0·08 [IQR –0·27 to 0·01]) for patients given placebo–dupilumab and –0·11 Giga/L (0·35; 25·63%; –0·06 [–0·23 to 0·03]) for patients given dupilumab–dupilumab (figure 4A). As in the parent studies, a transient increase in blood eosinophils was observed after dupilumab initiation in patients given placebo–dupilumab. In patients from QUEST given placebo–dupilumab, blood eosinophil counts peaked at week 12 (mean percentage change from parent study baseline 61·3%; median change –11·11 [IQR –44·66 to 50·00]); in patients from P2b, whose treatment was interrupted before the open-label extension, a transient increase was seen in both treatment groups and counts peaked at week 4 (mean percentage change from parent study baseline 74·1%; median change 8·89 [IQR –35·90 to 114·29] in patients given placebo–dupilumab and 38·2%; 2·80 [–31·23 to 53·75] in patients given dupilumab–dupilumab). By week 96, mean blood eosinophil counts had decreased to below parent study baseline concentrations for all groups (figure 4A). Median blood eosinophil counts remained unchanged throughout the treatment period.

In patients from P2b, mean serum total IgE at parent study baseline was 423·6 IU/mL (SD 700·1) in patients given placebo–dupilumab and 441·2 IU/mL (767·3) in patients given dupilumab–dupilumab (table 1). During TRAVERSE, absolute mean serum total IgE decreased to 75·5 IU/mL (SD 111·4) at week 96 (absolute median 42·0 [IQR 14·0–82·0]; mean percentage change from parent study baseline –77·03% [SD 18·01]; median percentage change –81·65% [IQR –87·88 to –73·04]) in patients given placebo–dupilumab. Corresponding values for patients given dupilumab–dupilumab were 95·7 IU/mL (SD 315·9; 29·0 [IQR 2·0–70·0]; –79·07% [14·88]; –82·35% [–88·46 to –72·90]; figure 4B). Full details of efficacy findings in patients who were OCS-dependent will be published separately.

At parent study baseline, 32 (1·6%) of 2055 patients who were non-OCS-dependent from QUEST and P2b had pre-existing immunoreactivity. Treatment-emergent ADA responses (defined as a positive ADA response after the first dose in the current study, when baseline status in the parent study was negative or missing) were observed in 157 (7·6%) of 2055 patients who were non-OCS-dependent. Regardless of previous treatment in the parent study, most patients from P2b and QUEST (134 of 157) with a positive ADA assay response during the open-label extension study had low ADA titres (median titre 120), and eight patients had ADA responses of high titres (>10 000). 77 (3·7%) of 2055 patients who

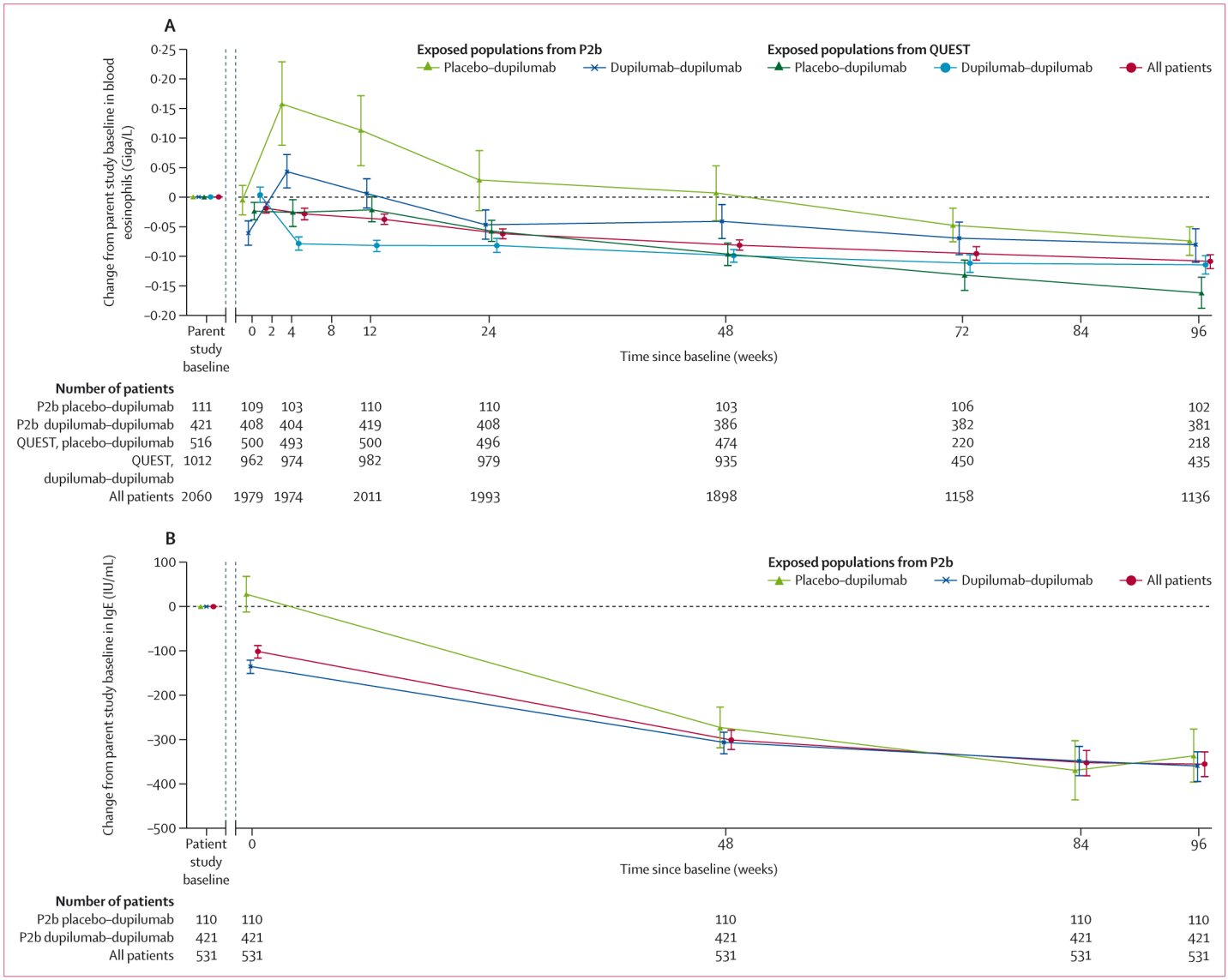


Figure 4: **Type 2 inflammatory biomarkers in non-oral-corticosteroid-dependent patients from P2b and QUEST**

Data are mean (SE). (A) Change from parent study baseline in blood eosinophils up to week 96 of the open-label extension in overall exposed patients from P2b and QUEST and (B) change from parent study baseline in serum total IgE up to week 96 of the open-label extension in overall exposed population patients from P2b. Week 0 represents the start of the open-label extension. Patients from P2b had a treatment gap of between 16 and 52 weeks before enrolment in TRAVERSE. P2b=phase 2B DRI.

were non-OCS-dependent had pre-existing neutralising antibodies. ADA status had no clinically significant impact on the overall incidence or type of treatment-emergent adverse events or on efficacy parameters (appendix pp 46–47).

Similar results for both AER and lung function were observed in the subgroups of patients who were non-OCS-dependent with a type 2 inflammatory phenotype and in those with high-dose ICS at parent study baseline, as compared with the overall study populations from QUEST and P2b (appendix p 43).

In patients from QUEST with a type 2 inflammatory phenotype followed-up for 148 weeks, the mean number of exacerbations in the year before the parent study was 2·30 (SD 2·08) in patients given placebo–dupilumab and 2·10 (1·88) in patients given dupilumab–dupilumab (figure 5A). Dupilumab showed efficacy that was sustained over the subsequent 148 weeks in these patients. In patients given dupilumab–dupilumab, AER progressively reduced from 0·42 during the first 52 weeks of dupilumab exposure in the parent study, to 0·31 during weeks 52–100 of exposure (weeks 0–48 in TRAVERSE), and to 0·23 during weeks 100–148 of exposure (weeks 48–96 in TRAVERSE; figure 5A). Similar reductions were observed in patients given placebo–dupilumab after dupilumab initiation in TRAVERSE: during QUEST,

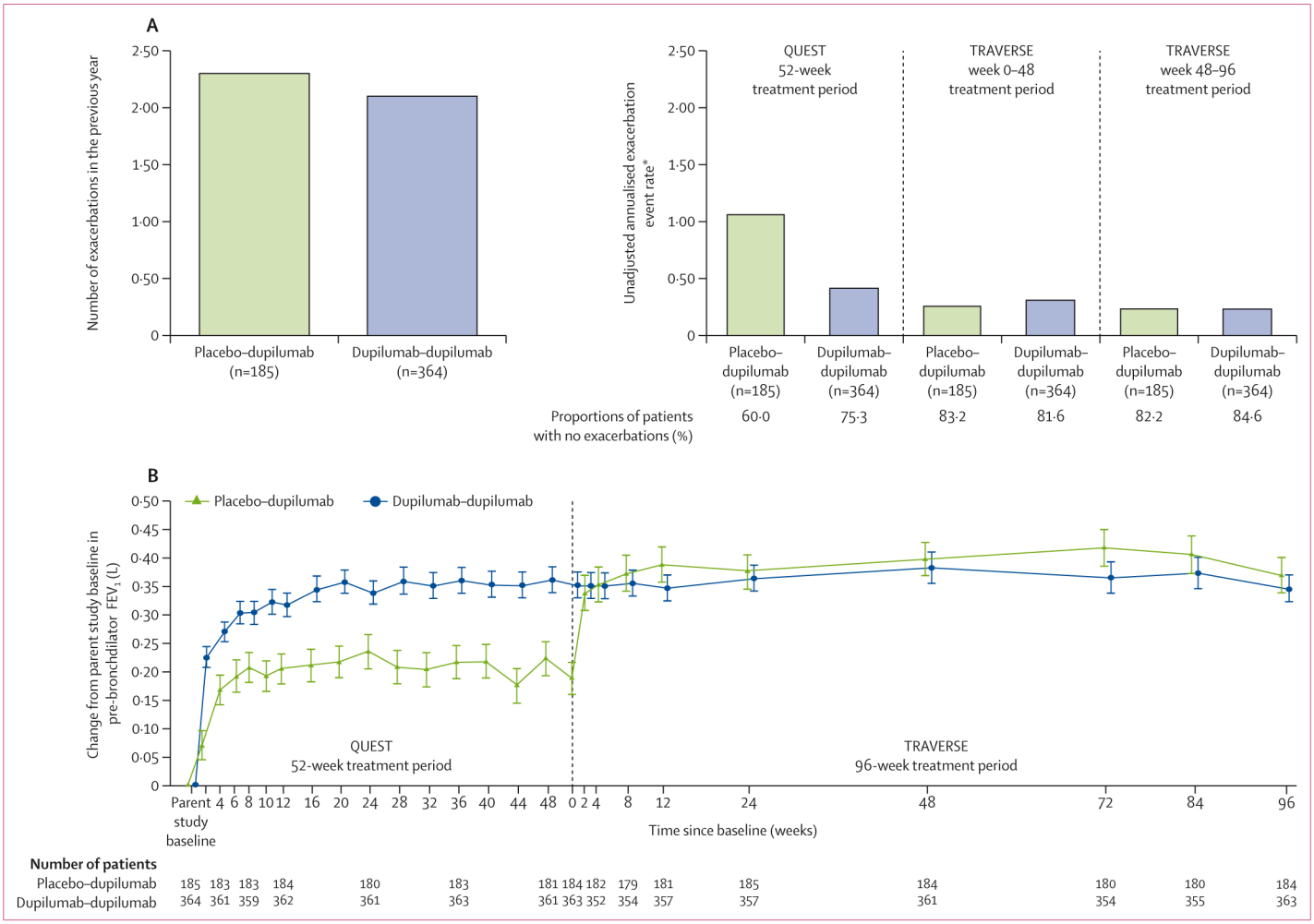


Figure 5: **Exacerbation rates and lung function in patients from QUEST with a type 2 inflammatory phenotype followed-up for 148 weeks**

(A) Number of exacerbations in the year before the parent study and AER during the parent and open-label extension treatment periods (mean [SD]) and (B) change from parent study baseline in pre-bronchodilator FEV_1 in patients from QUEST with a type 2 inflammatory phenotype followed-up for 148 weeks (ie, given dupilumab for 52 weeks during QUEST and an additional 96 weeks during TRAVERSE; mean [SE]). A type 2 inflammatory phenotype was defined as blood eosinophils 150 cells per µL or more or FeNO 25 ppb or more. AER was assessed in the overall exposed population (observed cases). Pre-bronchodilator FEV_1 was assessed in the overall exposed population (observed cases) using descriptive statistics. Week 0 represents the start of the open-label extension. AER=annualised exacerbation rate. FeNO=fractional exhaled nitric oxide. ppb=parts per billion. *The total number of events that occurred during the treatment period divided by the total number of patient-years followed-up in the treatment period.

AER was 1·06, which reduced to 0·26 during weeks 0–48 of dupilumab exposure in TRAVERSE, and to 0·24 during weeks 48–96 of exposure in TRAVERSE.

Improvements in pre-bronchodilator FEV_1 observed during the parent study were sustained in patients from QUEST with a type 2 inflammatory phenotype given dupilumab–dupilumab followed-up for 148 weeks, with mean changes from parent study baseline of 0·35 L (SD 0·45) after the first 52 weeks of dupilumab exposure in QUEST, 0·38 L (0·55) after 100 weeks of treatment (week 48 in TRAVERSE), and 0·35 L (0·48) after 148 weeks (week 96 in TRAVERSE; figure 5B). Similar findings were observed in patients given placebo–dupilumab after dupilumab initiation in TRAVERSE: mean changes from parent study baseline were 0·19 L (SD 0·39) at TRAVERSE week 0; 0·40 L (0·41) after 48 weeks of treatment in TRAVERSE; and 0·37 L (0·44) after 96 weeks of treatment in TRAVERSE.

Discussion

The TRAVERSE study has shown that long-term dupilumab 300 mg every 2 weeks is well tolerated and can provide sustained improvements in clinical efficacy up to 148 weeks in adult and adolescent patients with moderate-to-severe asthma enrolled from phase 2B and phase 3 studies.

Long-term dupilumab exposure was well tolerated with an acceptable safety profile. The number and percentage of patients with any treatment-emergent adverse events in TRAVERSE were similar to those observed in the parent studies, with safety consistent with the known dupilumab safety profile.[14–16] Treatment-emergent adverse

event incidence rates were higher in P2b patients given dupilumab–dupilumab versus patients given placebo–dupilumab; however, caution should be exercised in comparing results from these groups because of the 4:1 randomisation imbalance in patients previously given dupilumab in the parent study versus those who previously received placebo. Incidence rates of treatment-emergent adverse events in QUEST patients given dupilumab–dupilumab were lower than those observed in patients given placebo–dupilumab. The percentage of patients in the dupilumab–dupilumab groups reporting treatment-emergent adverse events was similar between studies (ranging from 77·8% in the dupilumab-dupilumab group from VENTURE to 87·6% in the dupilumab-dupilumab group from P2b) and was not affected by ADA status.

The transient increase in mean blood eosinophils that was observed in a subset of patients after initiating treatment in the parent studies was again noted in the open-label extension in patients from the parent study placebo groups.[15] However, blood eosinophil counts gradually decreased during the study to below parent study baseline amounts by week 72. Blood eosinophil counts of more than 3 Giga/L during the open-label extension were reported as a treatment-emergent adverse event even in the absence of symptoms; 29 (1·4%) patients from P2b and QUEST and 12 (6·4%) patients from VENTURE reported eosinophilia treatment-emergent adverse events. Most of these patients did not have associated clinical symptoms and did not have treatment interruptions or discontinuations. In five patients, eosinophilia was associated with eosinophilic granulomatosis with polyangiitis; these patients had a clinical history suggestive of pre-existing systemic eosinophilic conditions or received cycles of tapering doses of steroids before the occurrence of the adverse event. A causal association between dupilumab and these underlying conditions has not been established. Similar cases have been described with other approved anti-inflammatory asthma therapies,[19] whereby patients with asthma might present with serious systemic eosinophilic syndromes usually, but not always, associated with reduction in OCS therapy.

Long-term dupilumab exposure in patients who were non-OCS-dependent from P2b and QUEST showed maintenance of the clinical efficacy observed in the parent studies, including sustained improvements in lung function, and additional improvements over the open-label extension treatment period in AER, asthma control, and health-related quality of life.[14–16] These improvements resulted in large proportions of patients having no exacerbations and normal pre-bronchodilator FEV_1. ADA status had no clinically significant effect on efficacy parameters.

In addition to the gradual reduction in blood eosinophils observed, long-term dupilumab exposure in patients who were non-OCS-dependent from P2b resulted in a progressive, continued reduction in serum total IgE concentrations, consistent with observations in atopic dermatitis.[17] Previous studies suggest that dupilumab is efficacious in patients with asthma with an allergic phenotype.[20] These findings support the concept that dupilumab gradually suppresses B-cell class switching and IgE production.[11]

Efficacy was maintained in the subgroups of non-OCS-dependent patients with a type 2 inflammatory phenotype (blood eosinophils ≥150 cells per µL or FeNO ≥25 ppb) and in those receiving high-dose ICS[18] at parent study baseline, a population with uncontrolled and severe disease. As in the parent studies, the magnitude of efficacy improvements was greatest in patients with a type 2 inflammatory phenotype.[15] Higher amounts of type 2 inflammatory asthma biomarkers have previously been associated with increased rates of exacerbation in patients with uncontrolled, persistent asthma,[21,22] and our findings add to the body of knowledge showing that treatment targeting underlying type 2 inflammation might play a key role in blunting its clinical consequences.

Efficacy during the parent study and the open-label extension was also evaluated in patients with a type 2 inflammatory phenotype followed-up for 148 weeks, defined as patients from QUEST with a type 2 inflammatory phenotype (defined as above) who received 148 weeks of continuous dupilumab treatment. This subpopulation provides the opportunity to evaluate long-term dupilumab exposure without confounding from dropouts or differential exposure duration. Furthermore, by focusing on patients with evidence of type 2 inflammation, this analysis enabled assessment of long-term dupilumab in the population that had greatest efficacy in the parent study.[15] Long-term dupilumab showed a continued reduction in AER with each year of treatment, suggesting a cumulative effect on inflammation and exacerbation susceptibility with increasing exposure duration. The initial rapid improvements in pre-bronchodilator FEV_1 observed within 2 weeks of dupilumab treatment initiation in the QUEST study[15] were stable over the 148 weeks of treatment duration.

Safety was consistent between patients given placebo–dupilumab and dupilumab–dupilumab, including those from P2b who had a treatment gap of 16 weeks or longer suggesting that re-treatment of adult and adolescent patients with moderate-to-severe asthma with dupilumab is not associated with additional safety issues. Furthermore, rapid and sustained clinical efficacy responses, like those seen in the parent studies,[14–16] were observed irrespective of whether patients initiated dupilumab in the open-label extension or re-initiated dupilumab after P2b.

This study has some limitations. TRAVERSE was designed as a single-arm, open-label extension to evaluate long-term safety and efficacy of dupilumab in patients with asthma. All patients in the open-label extension

received 300 mg every 2 weeks, whereas dosing of 200 mg and 300 mg every 2 weeks or every 4 weeks was used in the parent studies. Given the fact that no major differences in safety or efficacy were observed between doses in the parent studies,[14,15] the higher dose was chosen for the open-label extension to simplify procedures and interpretation of results. Exposure to this dose provides the most robust safety assessment. TRAVERSE was not designed to allow for comparisons between patients from different parent studies. Common to any extension study, patients entered TRAVERSE on a voluntary basis, and only patients who completed the parent study were eligible for participation. This voluntary enrolment potentially introduced a treatment bias, as those responding to active treatment in the parent study were considered more likely to agree to continue in the extension study than those on placebo. In addition, there were some differences in the numbers of patients assessed for safety and efficacy outcomes and, for some analyses, only 48-week data were available.

The TRAVERSE open-label extension study shows that long-term dupilumab treatment for up to 96 weeks is well tolerated, with a safety profile consistent with results from shorter-term, placebo-controlled dupilumab asthma studies. In summary, dupilumab treatment for up to 148 weeks continues to provide sustained efficacy in adult and adolescent patients with moderate-to-severe asthma.

Contributors

MEW, LBF, JFM, IDP, AP, AB, HW, MC, NMN, YT, DL, GC, CD, HSP, and KRC acquired data. XM and MH accessed and verified the data. XM did statistical analyses. YZ, AHK, YD, PJR, UK, FAK, LPM, MR, EL, NA, and MH contributed to the conception and design of the study. All authors participated in the interpretation of the data, provided critical feedback and final approval for submission, and took responsibility for the accuracy, completeness, and protocol adherence of data and analyses. All authors had full access to all of the data and took final responsibility to submit for publication. All investigators had confidentiality agreements with the sponsors.

Declaration of interests

MEW reports personal fees from AstraZeneca, Boehringer Ingelheim, Equillium, Gala Therapeutics, Genentech, Genzyme, Mylan, Novartis, Pulmatrix, ResTORbio, Regeneron Pharmaceuticals, Sentien Biotechnologies, and Teva; and grants and personal fees from GSK and Sanofi. LBF reports grant support through the Asthma & Allergy Center, Bellevue, NE, USA, from 3M, Aimmune, AstraZeneca, DBV Technologies, Genentech, Glenmark, GSK, Hoffmann-La Roche, Novartis, Pearl, Sanofi, and Teva; and has served as a national consultant for Sanofi. JFM has served as a consultant for AstraZeneca and Sanofi; received speaker fees from Boehringer Ingelheim, GSK, Menarini, Novartis, and Uriach; and received research grants from Novartis. IDP reports speaker fees from Aerocrine AB, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Regeneron Pharmaceuticals, Sanofi, and Teva; payments for organisation of educational events from AstraZeneca, GSK, Regeneron Pharmaceuticals, Sanofi, and Teva; consultant fees from Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Dey Pharma, Genentech, GSK, Knopp Biosciences, Merck, MSD, Napp Pharmaceuticals, Novartis, Regeneron Pharmaceuticals, RespiVert, Sanofi, Schering-Plough, and Teva; international scientific meeting sponsorship from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Napp Pharmaceuticals, Regeneron Pharmaceuticals, Sanofi, and Teva; and a research grant from Chiesi. AP reports grants, personal fees, and non-financial support from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, and Teva; personal fees and non-financial support from Menarini, Novartis, and Zambon; and grants from Sanofi. AB reports non-financial support during the conduct of the study from GSK; serving as an investigator on clinical trials promoted by Acceleron Pharma, Actelion, Galapagos, MSD, Nuvaira, Pulmonx, United Therapeutic, and Vertex Pharmaceuticals; grants and personal fees from Boehringer Ingelheim; and personal fees from AstraZeneca, Chiesi, GSK, Regeneron Pharmaceuticals, and Sanofi. HW reports serving as a consultant and receiving travel and speaker fees from AstraZeneca, Bayer, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi, and Takeda. MC reports research support from the American Lung Association, AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, Patient-Centered Outcomes Research Institute, and Sanofi; serving as a consultant for 4D Pharma, Aviragen Therapeutics, Boston Scientific, Genentech, Nuvaira, Sanofi, Teva, Therabron Therapeutics, Theravance Biopharma, Vectura, and Vida Pharma; speaker fees from AstraZeneca, Boehringer Ingelheim, Boston Scientific, Genentech, Regeneron Pharmaceuticals, Sanofi, and Teva; and royalties from Elsevier. NMN reports speaker fees from ALK, AstraZeneca, Boehringer Ingelheim, Glenmark, MSD, Novartis, Sanofi, Stallergenes Greer, and Teva. YT has served as a consultant for AstraZeneca, Kyorin Pharmaceuticals, and Sanofi. DL has received research funding from Sanofi. CD reports travel and speaker fees from Allergy Therapeutics, ALK, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, Esteve, Ferrer, GSK, HAL Allergy, Inmunotek, Menarini, Novartis, Pfizer, Sanofi-Aventis, Stallergenes Greer, Takeda, and Teva. KRC reports grants and personal fees from AstraZeneca, Boehringer Ingelheim, CSL Behring, Genentech, Grifols, Kamada, Mereo BioPharma, Novartis, Roche, and Sanofi; grants from Amgen, Baxter, and GSK; and personal fees from the GSK-Canadian Institutes of Health Research chair in Respiratory Health Care Delivery at the University Health Network, and Merck. XM, AHK, PJR, UK, LPM, EL, and MH are Sanofi employees and hold stock or stock options in the company. YZ, YD, FAK, MR, and NA are employees and shareholders at Regeneron Pharmaceuticals. All other authors declare no competing interests.

Data sharing

Qualified researchers can request access to patient-level data and related study documents after publication, 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 online.

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