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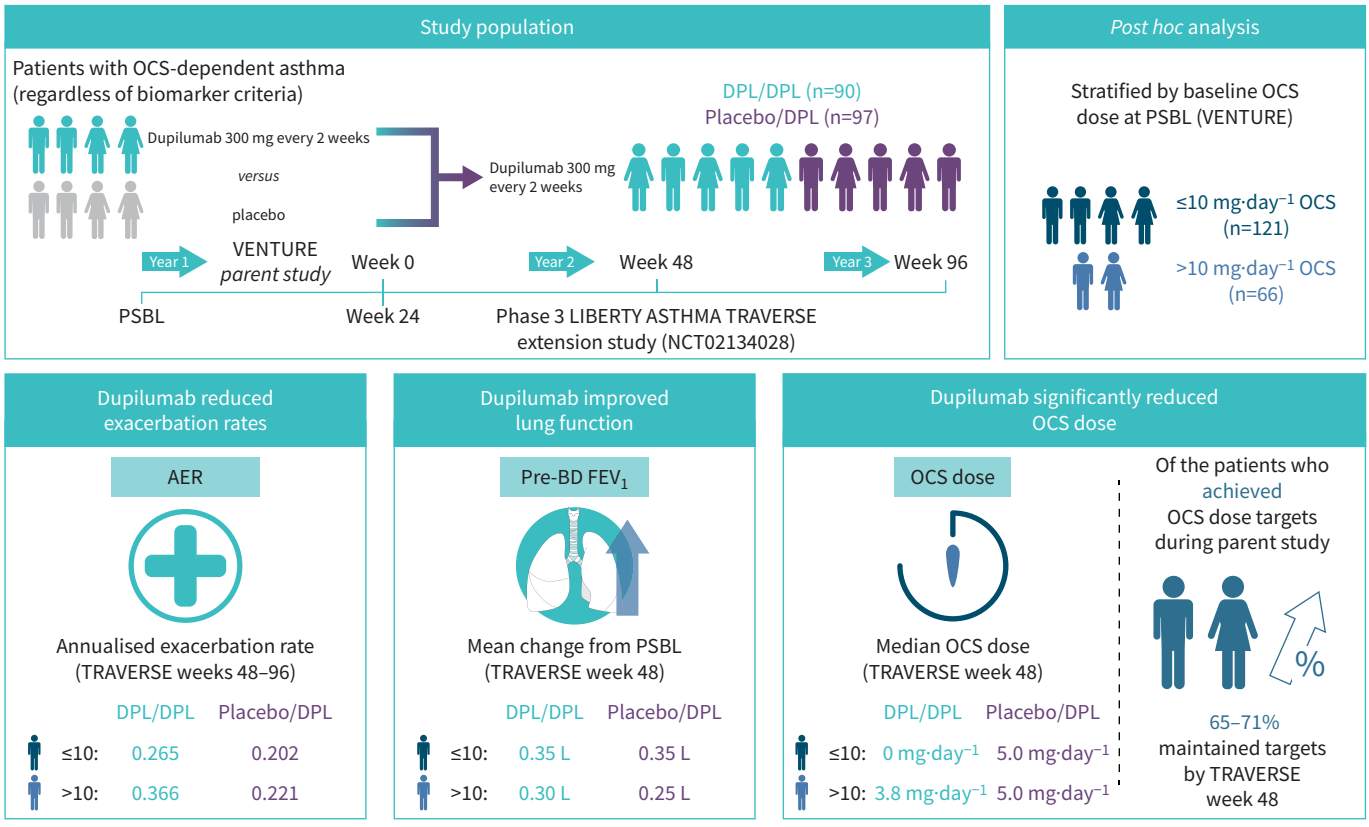

GRAPHICAL ABSTRACT Overview of the study findings. OCS: oral corticosteroid; PSBL: parent study baseline; DPL: dupilumab; AER: annualised severe asthma exacerbation rate; BD: bronchodilator; FEV_1: forced expiratory volume in 1 s.

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Long-term treatment with dupilumab reduces asthma exacerbations, improves lung function, symptom control and quality of life, and reduces oral corticosteroid (OCS) use in patients with OCS-dependent asthma regardless of baseline OCS dose. https://bit.ly/44A7m1k

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Abstract

Background Dupilumab has been shown to improve clinical outcomes long term while reducing oral corticosteroid (OCS) dose in patients with severe OCS-dependent asthma. This *post hoc* analysis assesses the impact of OCS dose at baseline (⩽10 or >10 mg·day^{-1}) on long-term outcomes of dupilumab treatment.

Methods Annualised severe asthma exacerbation rates, forced expiratory volume in 1 s (FEV_1), measures of asthma control and quality of life, and OCS dose were evaluated in patients from the phase 3 VENTURE trial with severe OCS-dependent asthma, further categorised by OCS dose ⩽10 or >10 mg·day^{-1} at parent study baseline (PSBL), who enrolled in TRAVERSE.

Results Dupilumab reduced the annualised exacerbation rate in VENTURE, and it remained low throughout TRAVERSE (0.202–0.265 (OCS ⩽10 mg·day^{-1} at PSBL) and 0.221–0.366 (OCS >10 mg·day^{-1} at PSBL)). Improvements in pre-bronchodilator FEV_1, asthma control and quality of life observed in VENTURE dupilumab patients were sustained throughout TRAVERSE. Patients on placebo during VENTURE showed rapid improvements in FEV_1 upon initiating dupilumab in TRAVERSE, which were sustained to the end of TRAVERSE. Reductions in OCS dose observed in VENTURE were maintained throughout TRAVERSE, with more than two-thirds of patients achieving reductions in OCS doses to ⩽5 mg·day^{-1} by TRAVERSE week 48.

Conclusions Improvements in clinical outcomes and reductions in OCS dose with dupilumab observed in VENTURE were maintained throughout TRAVERSE, regardless of baseline disease severity. Patients who switched from placebo in VENTURE to dupilumab in TRAVERSE had improved clinical outcomes and reductions in OCS dose comparable to those given dupilumab in VENTURE.

Introduction

Oral corticosteroids (OCS) are commonly used for asthma management, particularly in patients with severe or uncontrolled disease [1]. However, OCS use is associated with increased risk of both acute adverse events and chronic adverse effects, including metabolic, bone- and muscle-related, cardiovascular and psychiatric complications [2, 3]. Recent guidelines emphasise prioritising strategies to avoid maintenance OCS use in patients with severe asthma unless all other treatment options have been exhausted [4]. Therapies that improve symptoms while providing durable reductions in OCS dose are therefore required.

Dupilumab, a fully human monoclonal antibody [5, 6], blocks the shared receptor component for interleukin (IL)-4 and IL-13, type 2 inflammatory cytokines implicated in numerous type 2 diseases ranging from asthma to atopic dermatitis [7–9], and thus inhibits their signalling. The OCS-sparing effect of dupilumab added to standard-of-care therapy in adults with OCS-dependent severe asthma was investigated in the phase 3 LIBERTY ASTHMA VENTURE study. At the end of the 24-week study, dupilumab significantly reduced OCS use while also reducing severe asthma exacerbation rates and improving pre-bronchodilator forced expiratory volume in 1 s (FEV_1) [10]. Overall safety was consistent with the known dupilumab safety profile.

The single-arm open-label LIBERTY ASTHMA TRAVERSE (www.clinicaltrials.gov identifier: NCT02134028) extension study evaluated the long-term efficacy, safety and tolerability of dupilumab in patients who had participated in a previous dupilumab asthma study, including VENTURE [11, 12]. In TRAVERSE, the safety and efficacy of dupilumab were maintained for up to an additional 96 weeks, and improvements in annualised exacerbation rates, lung function and asthma control were sustained or improved further in patients who received dupilumab during the parent studies and continued into TRAVERSE. Marked and sustained improvements in all outcome measures were observed in patients who received placebo during the parent studies and initiated dupilumab in TRAVERSE [12].

This *post hoc* analysis of TRAVERSE aimed to determine the potential impact of baseline OCS dose on the long-term efficacy of dupilumab, and reduction in OCS use, in patients with severe OCS-dependent asthma who previously participated in VENTURE.

Methods

Study design

Full details of the VENTURE and TRAVERSE studies have been published previously [10, 12]. In brief, VENTURE (www.clinicaltrials.gov identifier: NCT02134028) was an international, randomised, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of dupilumab in patients aged ⩾12 years with OCS-dependent asthma. Patients were randomised 1:1 to subcutaneous dupilumab 300 mg once every 2 weeks for 24 weeks or matched placebo. During the 24-week treatment period, patients received an optimised OCS dose for 4 weeks followed by systematic dose reduction every 4 weeks over the next 16 weeks per protocol-defined algorithm; compliance was monitored at each visit. Further details of the protocol can be found in the primary VENTURE publication [10].

TRAVERSE was a multinational, multicentre, single-arm, open-label extension study that enrolled patients who had completed a previous phase 2 or 3 dupilumab asthma study [12]. All patients received 300 mg once every 2 weeks for up to an additional 96 weeks. Following a protocol amendment due to the accumulation of safety data from clinical trials for dupilumab across multiple indications, the treatment period was reduced from 96 to 48 weeks. Patients enrolled from VENTURE entered TRAVERSE directly from the VENTURE end-of-treatment visit. On enrolment in TRAVERSE, patients were encouraged to continue their background OCS therapy regimen as maintained during VENTURE, and compliance was assessed as part of the efficacy end-points. Modification of daily OCS dose was permitted at the discretion of the study investigator, but changes were not guided by a protocol-defined down-titration algorithm as in VENTURE [10, 12].

VENTURE and TRAVERSE were performed in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonisation and applicable regulatory requirements. Written informed consent was obtained from all patients before enrolment. Patients younger than 18 years of age provided assent according to the ethics committee-approved standard practice for paediatric patients at each participating centre. The protocol and informed consent or assent forms were approved by independent ethics committees and institutional review boards at the study sites.

Study population

Full inclusion and exclusion criteria of VENTURE and TRAVERSE have been published previously [10, 12]. This *post hoc* analysis included patients from VENTURE, stratified according to baseline OCS dose in VENTURE ($\leqslant$10 mg·day^{-1} or >10 mg·day^{-1}), who enrolled in TRAVERSE. A cut-off of 10 mg·day^{-1} was chosen as it was the median optimised OCS dose at VENTURE baseline. Patients who received dupilumab in VENTURE and continued to receive dupilumab in TRAVERSE were classified as the dupilumab/dupilumab group and patients who originally received placebo in VENTURE and received dupilumab in TRAVERSE as the placebo/dupilumab group.

Outcomes

Clinical efficacy end-points included unadjusted annualised severe exacerbation rates over the treatment period (both VENTURE and up to TRAVERSE week 96) and change from parent study baseline (PSBL) in pre-bronchodilator FEV_1, five-item Asthma Control Questionnaire (ACQ-5) scores and Asthma Quality of Life Questionnaire (AQLQ) scores over time up to TRAVERSE week 48.

OCS use assessment included the mean OCS dosage and mean cumulative OCS dose (total cumulative dose/number of days) during VENTURE and over a 48-week TRAVERSE treatment period; the proportions of patients who achieved OCS use targets of <0 mg·day^{-1} (only for eligible patients), $\leqslant 5$ mg·day^{-1} and <10 mg·day^{-1} during VENTURE; and the proportion of these patients who maintained these reductions to TRAVERSE week 48.

Statistical analysis

TRAVERSE was an open-label, single-arm extension study, and statistical analyses are therefore descriptive in nature. Continuous end-points (change in OCS dose, change in pre-bronchodilator FEV_1, ACQ-5 and AQLQ over time) were calculated as mean±SE. The unadjusted annualised exacerbation rates were computed as the total number of events during the observation period divided by the total exposure in patient-years in the observation period. Categorical end-points are presented as percentages, with the number of patients with nonmissing values at any time point as denominators.

Results

Patients

Overall, 121 patients with baseline OCS dose $\leqslant 10$ mg·day^{-1} (dupilumab/dupilumab n=60, placebo/dupilumab n=61) and 66 patients with baseline OCS dose >10 mg·day^{-1} (dupilumab/dupilumab n=30, placebo/dupilumab n=36) were included in this analysis. Baseline characteristics were generally well balanced between groups (table 1).

Annualised rate of severe exacerbations

Dupilumab reduced severe exacerbation rates by 67% and 32% compared with placebo in VENTURE in patients with baseline OCS dose $\leqslant 10$ and >10 mg·day^{-1}, respectively. During the VENTURE study, greater annualised exacerbation rate reductions were seen in the dupilumab group *versus* the placebo group,

TABLE 1 Baseline characteristics, disease characteristics and biomarkers at VENTURE baseline

	VENTURE baseline OCS dose $\leqslant 10$ mg·day^{-1}		VENTURE baseline OCS dose >10 mg·day^{-1}	
	Placebo/DPL	DPL/DPL	Placebo/DPL	DPL/DPL
Patients	61	60	36	30
Age, years	50.9±12.0	53.5±12.0	52.1±13.0	48.0±14.0
Male	26 (42.6)	25 (41.7)	14 (38.9)	12 (40.0)
Ongoing atopic or allergic condition[#]	43 (70.5)	44 (73.3)	28 (77.8)	21 (70.0)
Former smoker	13 (21.3)	16 (26.7)	2 (5.6)	3 (10.0)
OCS dose, mg·day^{-1}	8.07 (2.06)	7.42 (2.16)	17.57 (5.69)	18.08 (5.40)
Number of severe asthma exacerbations in the 1 year prior to parent study	2.30 (2.19)	1.87 (2.17)	1.97 (2.52)	1.97 (1.45)
Pre-bronchodilator FEV_1, L	1.62±0.66	1.50±0.48	1.63±0.57	1.58±0.55
Pre-bronchodilator FEV_1, % predicted	51.6±16.0	51.6±15.2	53.9±14.6	52.1±15.9
FEV_1 reversibility, %	18.6±25.2	22.6±26.4	16.9±20.7	20.2±20.0
ACQ-5 score, scale 0–6	2.54±1.14	2.39±1.18	2.69±1.06	2.53±1.05
AQLQ global score, scale 1–7	4.43±1.11	4.41±1.08	4.19±1.17	4.26±1.26
Blood eosinophils, cells·µL^{-1}	250 (110.0–430.0)	340 (180–545.0)	220 (115.0–430.00)	210 (140.0–320.0)
Total IgE, IU·mL^{-1}	140.0 (36.0–494.5)	185.5 (103.5–484.5)	161.0 (48.0–304.5)	131.0 (40.0–588.0)
F_{ENO}, ppb	21.0 (15.0–44.0)	28.0 (14.0–47.0)	41.0 (26.0–67.0)	26.0 (16.0–42.0)

Data are presented as n, mean±SD, n (%) or median (interquartile range). OCS: oral corticosteroids; DPL: dupilumab; FEV_1: forced expiratory volume in 1 s; ACQ-5: five-item Asthma Control Questionnaire; AQLQ: Asthma Quality of Life Questionnaire; IgE: immunoglobulin E; F_{ENO}: fractional exhaled nitric oxide. [#]: a patient who has any of the following diseases: atopic dermatitis, allergic conjunctivitis or rhinitis, eosinophilic oesophagitis, food allergy or hives, or if baseline total IgE $\geqslant 100$ IU·mL^{-1} and at least one aeroantigen-specific IgE is positive ($\geqslant 0.35$ IU·mL^{-1}) at baseline.

irrespective of baseline OCS dose group (figure 1). The annualised exacerbation rate continued to progressively decrease in both OCS dose subgroups during TRAVERSE, with the dupilumab/dupilumab and placebo/dupilumab groups achieving comparable outcomes over the treatment period in patients with OCS $\leqslant$10 mg·day^{-1} at PSBL. In the subgroup of patients with OCS >10 mg·day^{-1} at PSBL, dupilumab also further reduced the annualised exacerbation rate compared with the parent study, although reductions in the placebo/dupilumab group were greater than those observed in the dupilumab/dupilumab group, which may be attributable in part to small patient numbers (figure 1).

Pre-bronchodilator FEV_1

The overall improvement in pre-bronchodilator FEV_1 seen with dupilumab in VENTURE was sustained during TRAVERSE irrespective of the baseline OCS dose, while patients switching from placebo to dupilumab showed rapid and marked improvements in FEV_1 during TRAVERSE (figure 2). By week 48 of TRAVERSE, mean±SD change from baseline in FEV_1 in patients with PSBL OCS dose $\leqslant$10 mg·day^{-1} was 0.35±0.53 L in the dupilumab/dupilumab group and 0.35±0.52 L in the placebo/dupilumab group (figure 2a). In patients with PBSL OCS dose >10 mg·day^{-1}, mean±SD change in FEV_1 from baseline to week 48 of TRAVERSE was 0.30±0.55 L in the dupilumab/dupilumab group and 0.25±0.45 L in the placebo/dupilumab group (figure 2b).

Asthma control

ACQ-5 showed an overall improvement from VENTURE baseline, with sustained reductions throughout the TRAVERSE study regardless of baseline OCS dose (figure 3a).

In patients with PSBL OCS dose $\leqslant$10 mg·day^{-1}, mean±SD total ACQ-5 scores at VENTURE baseline were 2.39±1.18 in the dupilumab/dupilumab group and 2.54±1.14 in the placebo/dupilumab group. In patients with PSBL OCS dose >10 mg·day^{-1}, mean±SD total ACQ-5 scores at VENTURE baseline were 2.53±1.05 in the dupilumab/dupilumab group and 2.69±1.06 in the placebo/dupilumab group. At week 0 of TRAVERSE, there was a greater improvement in mean (95% CI) change from baseline in ACQ-5 in the dupilumab/dupilumab group (−1.05, −1.34 to −0.750) compared with the placebo/dupilumab group (−0.44, −0.76 to −0.110) in patients with PSBL OCS dose $\leqslant$10 mg·day^{-1}; asthma control had improved in both treatment arms in patients with PSBL OCS dose >10 mg·day^{-1} (figure 3a). These improvements were maintained in the dupilumab/dupilumab group in both OCS dose subgroups, with additional improvements seen in the placebo/dupilumab group, by week 48 of TRAVERSE.

Asthma-related quality of life

Overall, improvements in AQLQ scores seen during VENTURE were maintained through TRAVERSE regardless of baseline OCS dose (figure 3b). In patients with PSBL OCS dose $\leqslant$10 mg·day^{-1}, mean±SD AQLQ score at VENTURE baseline was 4.41±1.08 in the dupilumab/dupilumab group and 4.43±1.11 in the placebo/dupilumab group; in patients with PSBL OCS dose >10 mg·day^{-1} the scores were 4.26±1.26

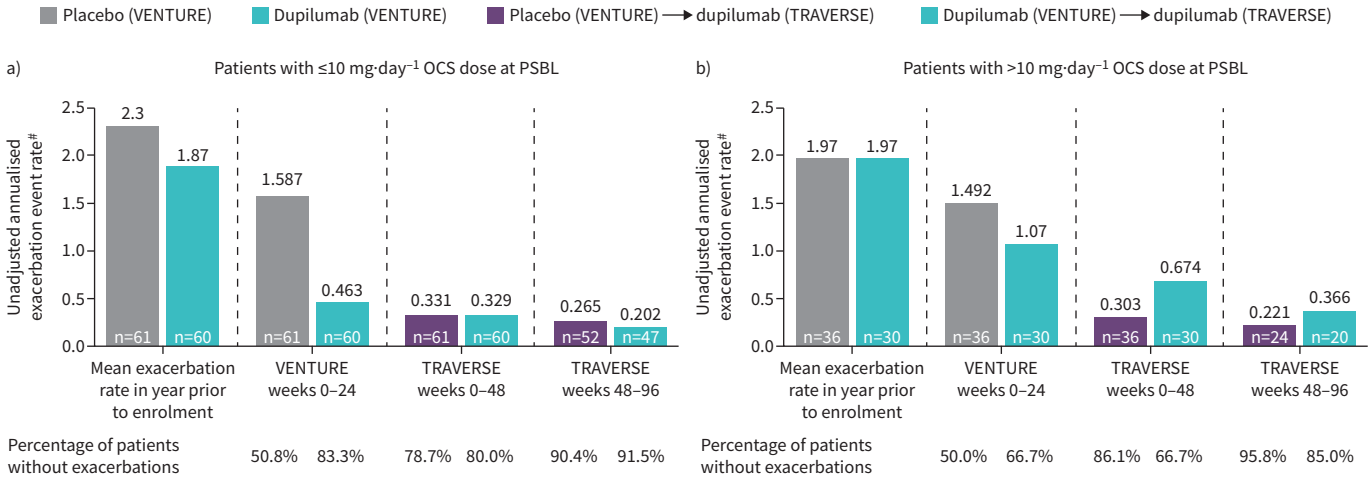

FIGURE 1 Unadjusted annualised rate of severe asthma exacerbations in the patients with oral corticosteroid (OCS) dose a) $\leqslant$10 mg·day^{-1} and b) >10 mg·day^{-1} at VENTURE baseline. PSBL: parent study baseline. #: the total number of events that occurred during the treatment period divided by the total number of patient-years followed in the treatment period.

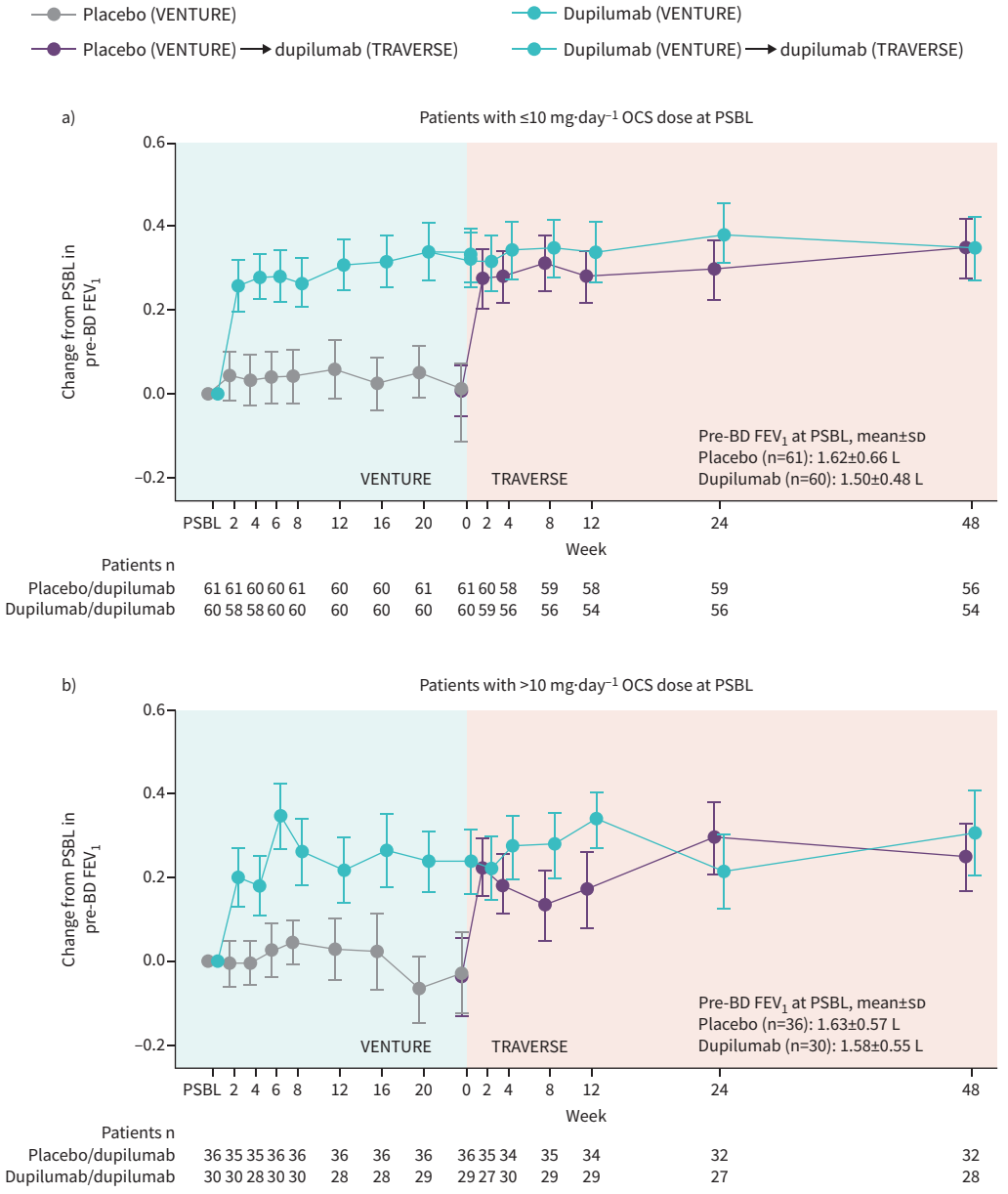

FIGURE 2 Change over time in mean±SE pre-bronchodilator (BD) forced expiratory volume in 1 s (FEV_1) from parent study baseline (PSBL) in patients with oral corticosteroid (OCS) dose a) ⩽10 mg·day^{-1} and b) >10 mg·day^{-1} at PSBL.

in the dupilumab/dupilumab group and 4.19±1.17 in the placebo/dupilumab group. By the end of VENTURE, mean (95% CI) change from baseline in AQLQ in the dupilumab/dupilumab group (1.05, 0.73–1.36) was greater than in the placebo/dupilumab group (0.42, 0.17–0.68) in patients with PSBL OCS dose ⩽10 mg·day^{-1}, and mean AQLQ score had improved in both treatment arms in patients with PSBL OCS dose >10 mg·day^{-1} (figure 3b). These improvements were sustained in the dupilumab/dupilumab group, in both OCS dose subgroups, while further improvements were seen in the placebo/dupilumab groups, through to week 48 of TRAVERSE.

OCS use

Over the course of the VENTURE study, mean OCS use decreased in both the dupilumab and placebo arms, following study protocol, with a significantly greater percentage reduction in the dupilumab group irrespective of baseline OCS dose (figure 4). Reduction in OCS use with dupilumab persisted through TRAVERSE in both the dupilumab/dupilumab and placebo/dupilumab groups, across the two baseline

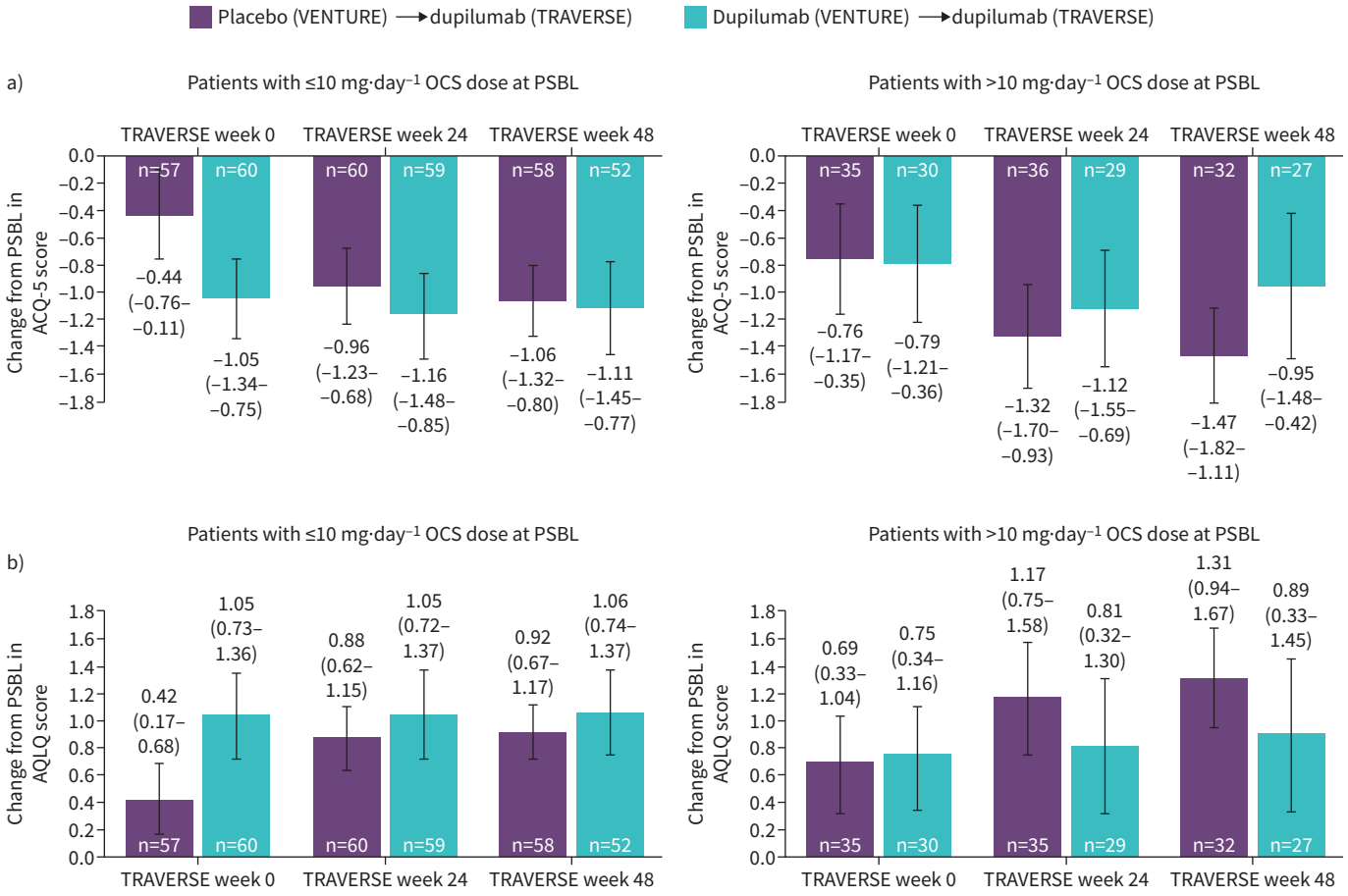

FIGURE 3 Mean (95% CI) change in a) asthma control (as measured by the five-item Asthma Control Questionnaire (ACQ-5) scores) and b) asthma-related quality of life (as measured by Asthma Quality of Life Questionnaire (AQLQ) scores) during TRAVERSE in patients with oral corticosteroid (OCS) dose ⩽10 mg·day^{-1} and >10 mg·day^{-1} at parent study baseline (PSBL).

OCS dose groups, where no OCS-sparing protocol was provided and the decision to reduce OCS was at the treating physician's discretion.

In patients with PSBL OCS dose ⩽10 mg·day^{-1}, mean±SD daily OCS dose was 1.60±2.85 mg·day^{-1} in the dupilumab/dupilumab group and 4.80±4.50 mg·day^{-1} in the placebo/dupilumab group at TRAVERSE week 0, falling to 1.06±1.87 and 4.35±3.98 mg·day^{-1}, respectively, at week 48 (figure 4). In patients with PSBL OCS dose >10 mg·day^{-1}, mean±SD daily OCS dose was 6.17±7.95 mg·day^{-1} in the dupilumab/dupilumab group and 9.10±9.18 mg·day^{-1} in the placebo/dupilumab group at TRAVERSE week 0, and 4.58±4.72 and 6.06±6.49 mg·day^{-1}, respectively, at week 48 (figure 4). Overall OCS dose reductions from PSBL were 83% and 50% in patients with PSBL OCS dose ⩽10 mg·day^{-1}, and 75% and 66% in patients with PSBL OCS dose >10 mg·day^{-1}, in the dupilumab/dupilumab and placebo/dupilumab groups, respectively, by TRAVERSE week 48 (figure 4).

Mean cumulative OCS dose and mean daily dose were markedly higher in placebo/dupilumab-treated patients compared with dupilumab/dupilumab-treated patients regardless of OCS dose subgroup in both VENTURE and TRAVERSE (table 2).

Mean±SD daily dose in patients with PSBL OCS ⩽10 mg·day^{-1}, who had week 48 data available, was 3.14±1.56 mg in the dupilumab/dupilumab group and 5.37±2.35 mg in the placebo/dupilumab group during VENTURE, and 1.15±2.25 mg *versus* 4.42±3.94 mg, respectively, during TRAVERSE. In patients with PSBL OCS >10 mg·day^{-1} who had week 48 data available, mean±SD daily OCS dose was 10.78±4.70 mg in the dupilumab/dupilumab group and 11.34±5.39 mg in the placebo/dupilumab group during VENTURE, and 4.94±5.32 mg *versus* 6.10±6.54 mg, respectively, during TRAVERSE.

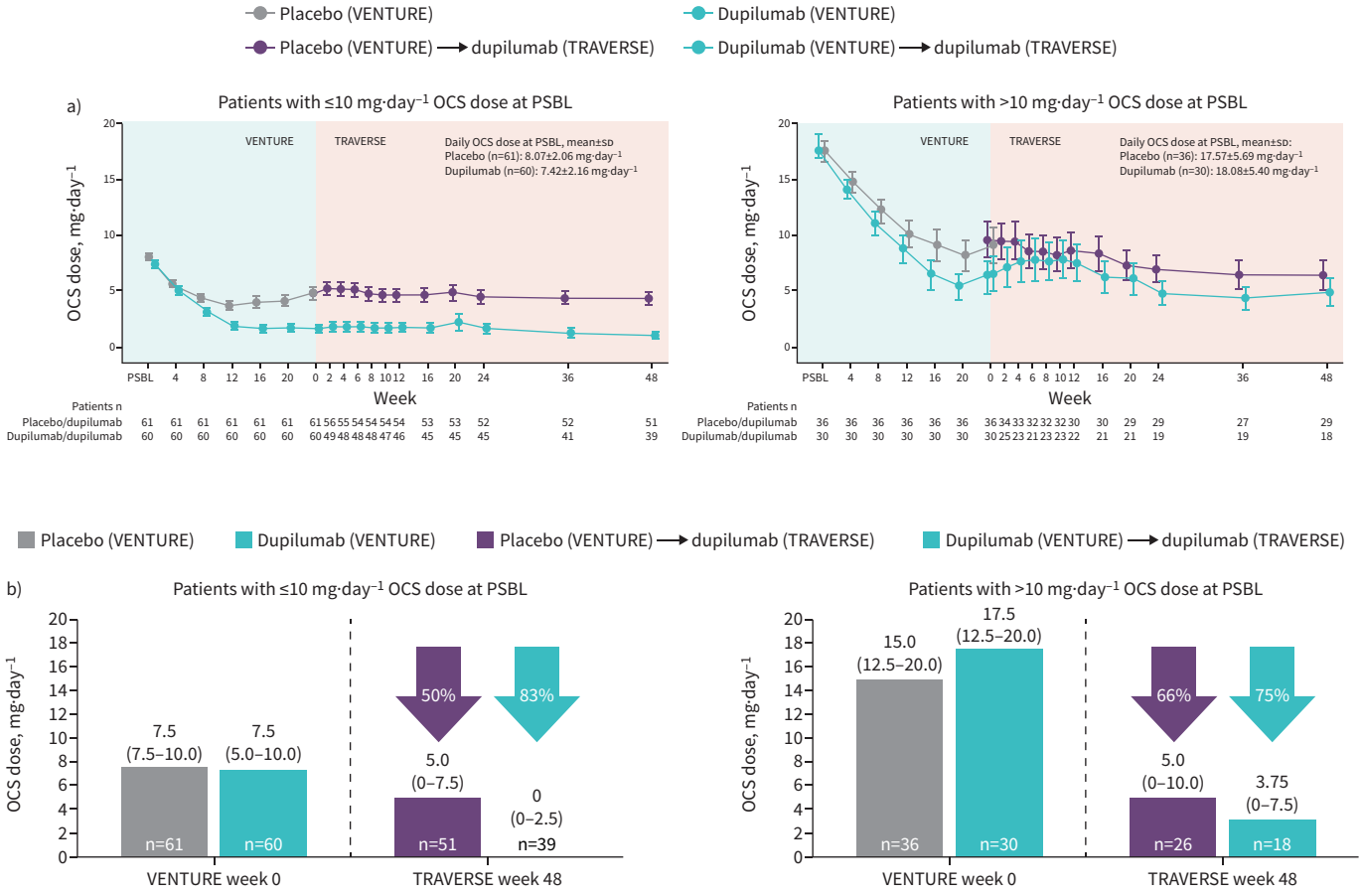

FIGURE 4 a) Change from parent study baseline (PSBL) in mean±SE oral corticosteroid (OCS) dose and b) median (interquartile range) change of OCS dose at week 48 of TRAVERSE in patients with OCS dose ⩽10 mg·day^{-1} and >10 mg·day^{-1} at PSBL.

Similar reductions were observed in median OCS dose (figure 4b). In line with the observation for the daily mean OCS dose, median OCS dose was also markedly lower in the dupilumab/dupilumab group compared with the placebo/dupilumab group regardless of OCS dose subgroup in both VENTURE and TRAVERSE.

The proportion of all patients achieving clinically relevant OCS dose thresholds of 0 mg·day^{-1}, ⩽5 mg·day^{-1} and <10 mg·day^{-1} during VENTURE and TRAVERSE are shown in figure 5. The analysis of patients who achieved the 0 mg·day^{-1} OCS threshold in VENTURE (figure 5a) included only those

TABLE 2 Mean cumulative oral corticosteroid (OCS) dose and mean daily OCS dose in patients with OCS dose ⩽10 mg·day^{-1} and >10 mg·day^{-1} at VENTURE baseline who have week 48 OCS data available

	VENTURE baseline OCS dose ⩽10 mg·day^{-1}		VENTURE baseline OCS dose >10 mg·day^{-1}	
	Placebo/DPL	DPL/DPL	Placebo/DPL	DPL/DPL
Patients	51	39	26	18
Cumulative OCS dose, mg				
VENTURE (weeks 0–24)	911.4±397.99	532.1±259.53	1920.3±911.91	1839.2±797.39
TRAVERSE (weeks 0–48)	2388.5±2037.25	584.9±1118.65	3119.0±3242.56	2463.3±2631.92
Daily OCS dose, mg				
VENTURE (weeks 0–24)	5.37±2.35	3.14±1.55	11.34±5.39	10.78±4.70
TRAVERSE (weeks 0–48)	4.42±3.94	1.15±2.25	6.10±6.54	4.94±5.32

Data are presented as n or mean±SD. DPL: dupilumab.

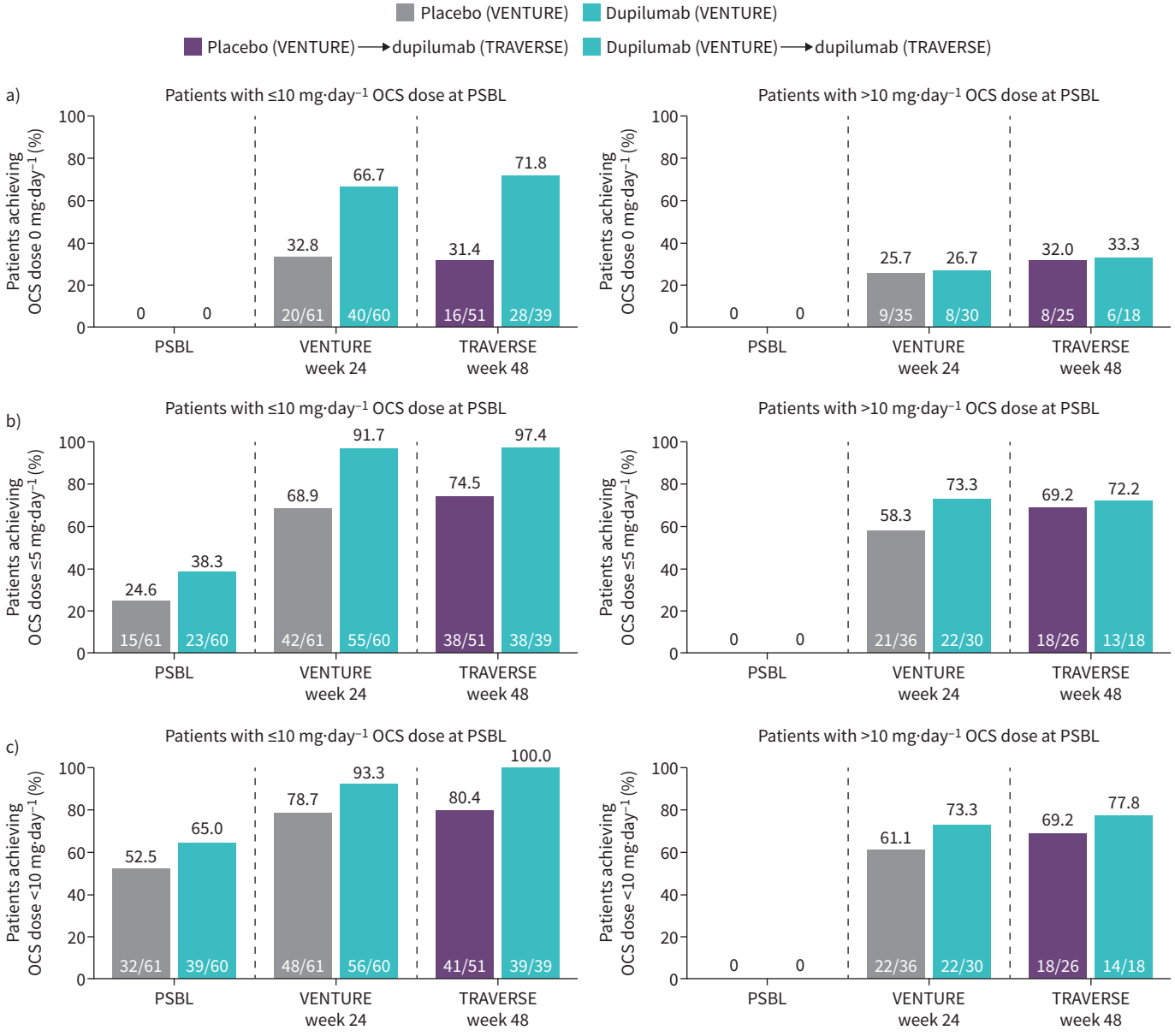

FIGURE 5 Proportion of patients who achieved oral corticosteroid (OCS) dose targets during VENTURE and TRAVERSE by VENTURE baseline OCS dose a) 0 mg·day^{-1}, b) ⩽5 mg·day^{-1} and c) <10 mg·day^{-1}. Analysis of patients who achieved the 0 mg·day^{-1} OCS threshold in VENTURE included only those who were eligible to achieve this during the study using the down-titration protocol in the time specified. PSBL: parent study baseline.

who were eligible to achieve this during the study using the down-titration protocol in the time specified. Overall, data from TRAVERSE are consistent with those from VENTURE, in which patients reduced OCS dose according to a protocol-defined algorithm.

Of patients who had achieved an OCS dose threshold at the end of VENTURE, a majority maintained it through to week 48 of TRAVERSE (figure 6).

Effect of OCS dose on clinical efficacy

In all patients from VENTURE who enrolled in TRAVERSE (*i.e.* patients with PSBL OCS ⩽10 mg·day^{-1} and patients with PSBL OCS >10 mg·day^{-1}) the interaction between treatment and VENTURE baseline OCS dose across the clinical efficacy outcomes analysed (annualised severe asthma exacerbation rates and change from PSBL in FEV_1, ACQ-5, AQLQ and OCS dose) was not significant (p-value for interaction >0.05) up to TRAVERSE week 96.

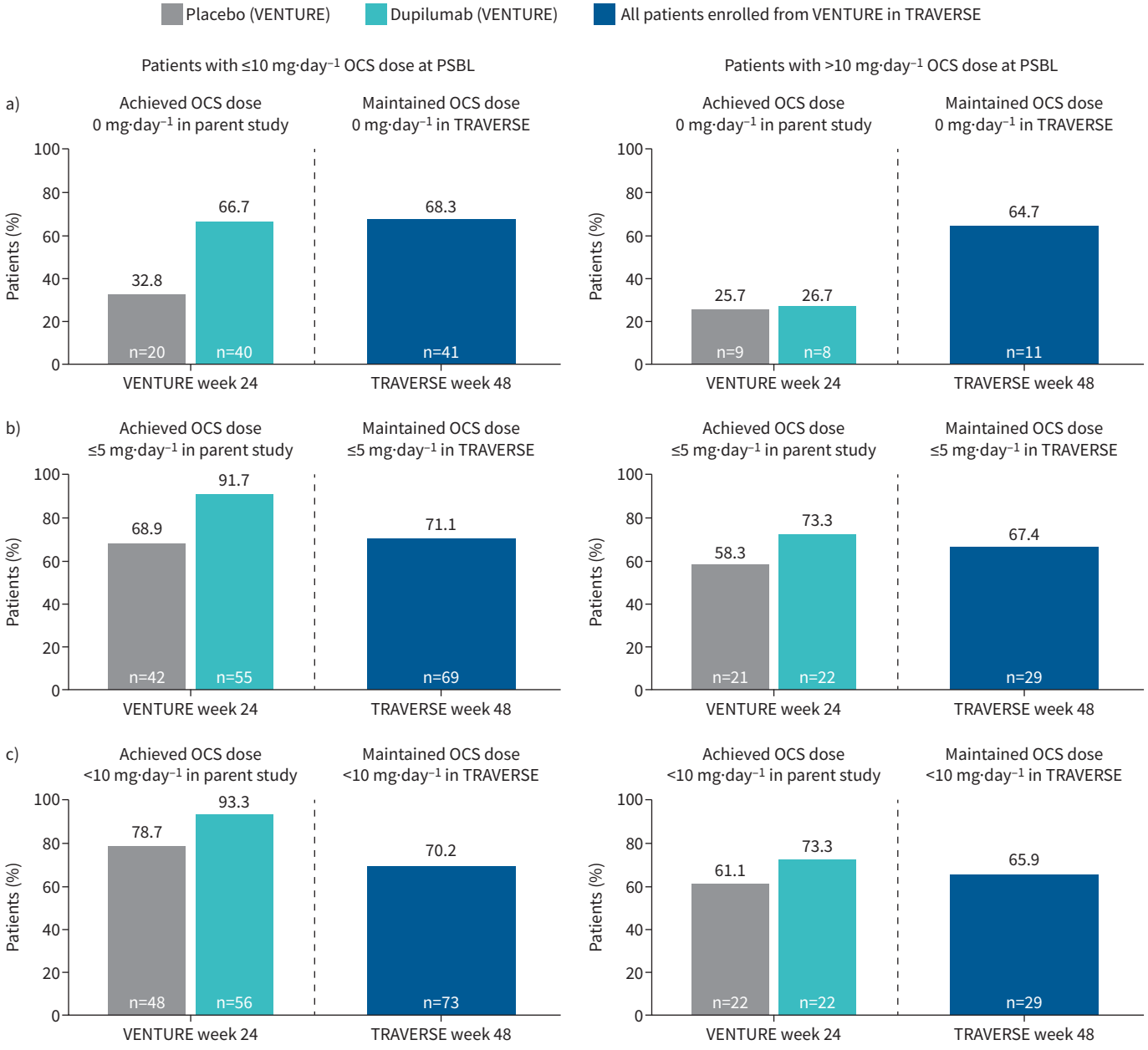

FIGURE 6 Proportion of patients who achieved oral corticosteroid (OCS) dose targets during VENTURE and maintained targets during TRAVERSE by VENTURE baseline OCS dose a) 0 mg·day^{-1}, b) ⩽5 mg·day^{-1} and c) <10 mg·day^{-1}. Analysis of patients who achieved the 0 mg·day^{-1} OCS threshold in VENTURE included only those who were eligible to achieve this during the study using the down-titration protocol in the time specified. PSBL: parent study baseline.

Discussion

This analysis demonstrated that reductions in annualised exacerbation rates and lung function improvements seen with dupilumab in VENTURE [10, 13] continued through TRAVERSE and were consistent in patients who received an OCS dose ⩽10 mg·day^{-1} or >10 mg·day^{-1} at baseline, with patients in the placebo/dupilumab group (who first initiated dupilumab in TRAVERSE) achieving improvements in both clinical measures comparable with the dupilumab/dupilumab group, irrespective of baseline OCS dose. Dupilumab also maintained improvements in asthma control and quality of life in VENTURE through TRAVERSE regardless of baseline OCS dose. Assessment of dupilumab's effectiveness across OCS dose levels at PSBL showed similar treatment effects across the end-points included in this analysis, suggesting that OCS dose level does not have an impact on dupilumab's efficacy.

These clinical improvements were seen despite persistent reductions in OCS use, which were greater in the dupilumab/dupilumab group compared to the placebo/dupilumab group by the end of TRAVERSE, both in patients with baseline OCS dose above and below the median. This demonstrates the persistent and incremental benefit of OCS dose reduction when maintaining dupilumab treatment over time. For the dupilumab group during VENTURE, approximately two-thirds of patients with baseline OCS dose $\leqslant$10 mg·day^{-1} and over a quarter of patients with baseline OCS dose >10 mg·day^{-1} were able to completely discontinue OCS use following the OCS-sparing strategy as per study protocol [10]. Modification of OCS dose was not mandated in the TRAVERSE protocol, but at the investigators' discretion, which is reflective of the real-world scenario. Despite this there were, for the most part, incremental improvements in the percentage of patients achieving 0, $\leqslant$5 and <10 mg·day^{-1} OCS dose by week 48 of TRAVERSE in both OCS dose subgroups within each treatment arm.

When interpreting these data, it should be noted that investigators may have concerns regarding adrenal insufficiency [14, 15] and there is currently no consensus on whether to reduce maintenance OCS dose in this context. However, there is consensus that OCS doses $\leqslant$5 mg·day^{-1} are acceptable (in situations where OCS maintenance treatment is required, *e.g.* uncontrolled asthma despite optimised Global Initiative for Asthma 5 treatment steps), but annual cumulative OCS doses should be closely monitored as a marker for asthma control [16].

There are increasing risks of acute and chronic complications with cumulative OCS exposure (including bone, respiratory, cardiovascular, renal, eye and neurological disorders) [1], with a clear dose–response relationship between outcomes and cumulative OCS exposure [17]. Importantly, onset of some outcomes is seen with a cumulative OCS dose exposure of between 500 and <1000 mg, with risk increasing substantially >1000 mg [17]. In TRAVERSE, we have demonstrated that delaying treatment can result in cumulative doses up to four times greater, as seen in the placebo/dupilumab group when compared with the dupilumab/dupilumab group. Thus, in this patient population earlier treatment with dupilumab is warranted to reduce overall OCS dose exposure and the resulting side-effects.

Our findings suggest that active, guided management of OCS dose may be required to encourage OCS dose reductions if goals of "oral steroid stewardship" [18, 19] or complete avoidance of OCS in patients with asthma are to be achieved [4, 16, 20, 21]. A lack of asthma-specific algorithms for OCS dose reduction and guidelines for systematic screening of adverse events have been cited as potential barriers to reducing OCS exposure [20]. Hesitancy to reduce OCS dose in patients with severe asthma may mean that the opportunity to improve outcomes by reducing the risk of OCS-related adverse events is missed. Clinical studies of biologics in asthma have used different tapering algorithms for OCS-sparing regimens [10, 22–25], emphasising a need for clinical guidelines in routine practice.

The limitations of this study are inherent to its design. All analyses were *post hoc*, and as TRAVERSE was a single-arm open-label study, statistical analyses were descriptive only. Furthermore, as is common with extension studies, patients were enrolled on a voluntary basis and only patients who completed the parent study were eligible to participate. This could potentially have introduced a treatment bias towards patients who received active treatment during the parent study. In addition, following a protocol amendment the treatment period was reduced from 96 to 48 weeks; therefore, for some analyses only 48-week data were available. The optimal OCS dose cut-off for subgroup stratification could be debated; we chose the median optimised baseline dose of 10 mg·day^{-1} at VENTURE baseline. Rheumatology guidelines propose a cut-off of 7.5 mg daily OCS dose to optimise antiresorptive treatment [26, 27]. Thus, a cut-off of 10 mg was justifiable from a clinical standpoint. Finally, the extent to which adrenal suppression influenced patients' ability to reduce their OCS dose is unclear.

An evaluation of the VENTURE and TRAVERSE studies combined has shown that long-term dupilumab treatment provided sustained efficacy in adult and adolescent patients with OCS-dependent severe asthma while allowing for significant reductions in OCS dose, regardless of baseline OCS starting dose.

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Ethics approval: VENTURE and TRAVERSE were performed in accordance with the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Conference on Harmonisation, and applicable regulatory requirements. Written informed consent was obtained from all patients before enrolment. Patients younger than 18 years of age provided assent according to the ethics committee-approved standard practice for paediatric patients at each participating centre. The protocol and informed consent or assent forms were approved by independent ethics committees and institutional review boards at the study sites.

The TRAVERSE and VENTURE studies are registered at www.clinicaltrials.gov with identifier numbers NCT0213402 and NCT02528214, respectively. 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.

Conflict of interest: C. Domingo reports travel and speaker fees from ALK, Allergy Therapeutics, Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, HAL Allergy, ImmunoTek, Menarini, Novartis, Pfizer, Sanofi-Aventis, Stallergenes Greer and Teva. K.F. Rabe reports consultant and speaker fees from AstraZeneca, Boehringer Ingelheim, Novartis, Sanofi and Teva. D. Price reports advisory board membership with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mundipharma, Novartis, Regeneron Pharmaceuticals Inc., Sanofi, Teva Pharmaceuticals, Thermo Fisher Scientific and Viatris; consultancy agreements with Amgen, AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Mundipharma, Novartis, Pfizer, Teva Pharmaceuticals, Theravance Biopharma and Viatris; grants and unrestricted funding for investigator-initiated studies (conducted through Observational and Pragmatic Research Institute) from AstraZeneca, Boehringer Ingelheim, Chiesi, Circassia, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Teva Pharmaceuticals, Theravance Biopharma, UK National Health Service and Viatris; payment for lectures/speaking engagements from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, GSK, Mundipharma, Novartis, Pfizer, Regeneron Pharmaceuticals Inc., Sanofi, Teva Pharmaceuticals and Viatris; payment for travel/accommodation/meeting expenses from AstraZeneca, Boehringer Ingelheim, Circassia, Mundipharma, Novartis, Teva Pharmaceuticals and Thermo Fisher Scientific; funding for patient enrolment or completion of research from Novartis; stock or stock options from AKL Research and Development and Timestamp; owns 74% of Optimum Patient Care (Australia and UK) and 74% of Observational and Pragmatic Research Institute (Singapore); is a peer reviewer for grant committees of the UK Efficacy and Mechanism Evaluation programme and Health Technology Assessment; and was an expert witness for GSK. G. Brusselle reports consultant and speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GSK, Novartis, Sanofi and Teva. M.E. Wechsler reports personal fees from Amgen, AstraZeneca, Boehringer Ingelheim, CytoReason, Equillium, Genentech, Genzyme, Novartis, Pulmatrix, Regeneron Pharmaceuticals Inc., resTORbio, Sentien Biotechnologies and Teva; and grants and personal fees from GSK and Sanofi. C. Xia, R. Gall, Y. Deniz and A. Radwan are employees of and shareholders in Regeneron Pharmaceuticals Inc. N. Pandit-Abid, P.J. Rowe and J.A. Jacob-Nara are employees of Sanofi, and may hold stock and/or stock options in the company.

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