Original Article

Dupilumab Efficacy in Steroid-Dependent Severe Asthma by Baseline Oral Corticosteroid Dose

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What is already known about this topic? Oral corticosteroids (OCS) are occasionally used to manage severe asthma, but their long-term use is associated with considerable adverse side effects. There is an important clinical need for novel OCS-sparing treatment strategies.

What does this article add to our knowledge? This analysis showed dupilumab significantly reduced the OCS dose, improved the likelihood of no longer requiring OCS, and improved clinical outcomes in patients with OCS-dependent severe asthma receiving a lower or higher OCS dose at baseline.

How does this study impact current management guidelines? The Global Initiative for Asthma (GINA) does not recommend maintenance OCS to manage severe asthma if other options are available. Dupilumab provides an effective OCS-sparing treatment with a demonstrated safety profile for patients taking lower or higher OCS at baseline.

BACKGROUND: Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin-4/-13, key and central drivers of type 2 inflammation in multiple diseases. In the phase 3 LIBERTY ASTHMA VENTURE (VENTURE) study (NCT02528214), dupilumab versus placebo reduced oral corticosteroid (OCS) dose and improved clinical outcomes in patients with OCS-dependent severe asthma. Dupilumab efficacy in patients with varying disease burden (defined by baseline OCS dose) has not been assessed.

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Abbreviations used
ANCOVA- Analysis of covariance
CI- Confidence interval
FEV_1- Forced expiratory volume in 1 second
LS- Least squares
OCS- Oral corticosteroids
OR- Odds ratio
TEAE- Treatment-emergent adverse event
VENTURE- LIBERTY ASTHMA VENTURE

OBJECTIVE: This *post hoc* analysis of VENTURE evaluated dupilumab efficacy across subgroups defined by baseline OCS dose.

METHODS: The OCS dose, proportion no longer needing OCS at week 24, annualized severe exacerbation rate, and least squares mean change from baseline in pre- and post-bronchodilator forced expiratory volume in 1 second at week 24 were evaluated in VENTURE patients with OCS-dependent severe asthma receiving dupilumab 300 mg every 2 weeks versus placebo, categorized by a baseline OCS dose of less than 10 mg/d or 10 or more mg/d.

RESULTS: Dupilumab reduced daily OCS dose from baseline at week 24 in both dose groups. In dupilumab-/placebo-treated patients with a baseline OCS dose of less than 10 mg/d and 10 or more mg/d, 72%/42% and 37%/23% stopped OCS by week 24 ($P < .01$/$P < .05$), respectively. Dupilumab significantly reduced the annualized severe exacerbation rate by 71% and 48% ($P < .01$/$P < .05$). At week 24, dupilumab improved pre- and post-bronchodilator forced expiratory volume in 1 second in patients in both dose groups.

CONCLUSIONS: In patients with OCS-dependent severe asthma receiving lower or higher baseline OCS doses, dupilumab significantly reduced the OCS dose and improved the likelihood of no longer requiring OCS while also reducing exacerbations and improving lung function. **(J Allergy Clin Immunol Pract 2022;10:1835-43)**

Key words: *Asthma; Dupilumab; Exacerbation; Lung function; Chronic oral corticosteroids; Interleukin-4; Interleukin-13*

INTRODUCTION

Patients with severe asthma represent approximately 3% to 10% of the total asthma patient population.[1-3] Severe asthma is a predominantly type 2–driven disease,[4,5] and prior to the era of biologics targeting type 2 inflammation, oral corticosteroids (OCS) were the only therapeutic option for patients with asthma uncontrolled with inhaled therapy alone.[6] It is estimated that 30% to 46% of patients with severe asthma used to receive long-term OCS.[6,7] However, national registry data from several countries still highlight high proportions of patients continuing to be managed with OCS.[3,5] In a retrospective, nationwide study in Spain, 31.2% of patients with severe asthma were OCS-dependent[3] and 51.7% of patients with severe asthma in the U.K. Severe Asthma Registry were on maintenance OCS.[5]

Despite the efficacy of OCS in severe asthma, their use is associated with side effects, including weight gain, metabolic syndrome, type 2 diabetes, bone density loss and fractures, glaucoma, depression, and anxiety.[6,8] In addition, the long-term use of systemic corticosteroids in adults is associated with greater health care costs and health care resource utilization.[9,10] Long-term use of systemic corticosteroids and cumulative exposure to OCS owing to repeated acute bursts are associated with greater health care resource utilization and costs[9,10] as a result of the increase in the incidence of adverse events. Novel OCS-sparing treatment strategies are, therefore, important to help improve patient outcomes.[11]

Several biologics blocking type 2 inflammatory pathways have demonstrated OCS-sparing effect and are approved to treat OCS-dependent severe asthma,[12] including dupilumab.[13,14] Dupilumab is a fully human VelocImmune-derived[15,16] monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation in multiple diseases.[17,18] In the phase 3 LIBERTY ASTHMA VENTURE (VENTURE) study (NCT02528214), add-on dupilumab versus placebo significantly reduced maintenance OCS dose over 24 weeks by 70.1% versus 41.9%.[19] Despite the decreased use of OCS in this population, dupilumab reduced the severe asthma exacerbation rate by 59% and improved pre-bronchodilator forced expiratory volume in 1 second (FEV_1) by 0.22 L compared with placebo; these findings occurred independently of baseline eosinophil levels.[19]

Whereas VENTURE demonstrated the OCS-sparing effect of dupilumab in patients with severe asthma with chronic OCS, the study enrolled patients with a wide range of OCS doses at baseline (5–35 mg/d; median 10 mg/d). It was unknown whether the efficacy of dupilumab was consistent across patients with varying OCS doses at baseline—that is, if the clinical benefit of dupilumab differed in patients receiving lower doses compared with those receiving higher doses of OCS. Therefore, this *post hoc* analysis of VENTURE aimed to evaluate the efficacy of dupilumab in reducing OCS dose and improving clinical outcomes in patients with OCS-dependent severe asthma receiving daily OCS doses less than 10 mg or 10 or more (prednisone or prednisolone or equivalent) at baseline.

METHODS

VENTURE study design

The LIBERTY ASTHMA VENTURE study was a phase 3, randomized, double-blind, placebo-controlled trial that assessed the efficacy and safety of dupilumab in patients with OCS-dependent severe asthma. A complete description of the VENTURE study design has been previously published.[19] In short, OCS dose was optimized during screening over 3 to 10 weeks and adjusted to establish the lowest dose required to manage patients' asthma symptoms. Patients were randomized 1:1 to receive subcutaneous dupilumab 300 mg every 2 weeks or matched placebo as an add-on to their adjusted OCS dose for 24 weeks. The treatment period consisted of a 4-week induction phase during which patients were randomized to investigational treatment coadministered with the optimal OCS dose established during screening; a 16-week OCS reduction phase (week 4–20), during which the OCS dose was down-titrated every 4 weeks following a predetermined schedule if the patient did not meet any predefined criteria prohibiting dose reduction; and a 4-week maintenance phase in which patients remained on the OCS dose established at week 20.[19]

VENTURE was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines and was approved by local institutional

review boards and ethics committees. All patients provided written informed consent before participating in the trial.

Patients

Patients aged 12 years or older who had physician-diagnosed asthma for 1 or more years based on the Global Initiative for Asthma (GINA) 2014 definition[20] and who were receiving treatment with regular systemic corticosteroids in the previous 6 months (5−35 mg/d of prednisone or prednisolone or equivalent) participated in VENTURE.[19] In this *post hoc* analysis, patients were divided into subgroups defined by baseline optimized OCS dose less than 10 mg/d and 10 or more mg/d. The rationale for this threshold was based on the median baseline optimized OCS dose of 10 mg/d in VENTURE. The subgroup of patients who were not able to discontinue OCS at week 24 was also analyzed.

Post hoc analysis outcomes

The mean OCS dose at baseline, week 12, and week 24, and reduction from baseline in OCS dose at these times, as well as the proportion of patients who were able to be fully tapered off OCS by week 24, were analyzed in patients receiving less than 10 mg/d and 10 or more mg/d OCS at baseline. Mean OCS dose at baseline, week 12, and week 24 was also assessed in patients who did not discontinue OCS at week 24. Clinical efficacy outcomes included the annualized rate of severe asthma exacerbations during the 24-week treatment period and the change from baseline in pre- and post-bronchodilator FEV_1 (L) over time up to week 24, which were analyzed in all 3 subgroups.

Post hoc statistical analysis

All analyses were *post hoc* and performed on the overall intention-to-treat population separated into subpopulations of patients based on their baseline OCS dose (ie, <10 and ≥10 mg/d) or ability to stop OCS at week 24. Changes in OCS dose were calculated as least squares (LS) mean reduction from baseline. The LS mean differences between the dupilumab and the placebo groups were calculated for both baseline OCS dose subpopulations (<10 and ≥10 mg/d) by combining results from analyzing multiple imputed data using an analysis of covariance (ANCOVA) model by Rubin's rule. The ANCOVA model included treatment group, optimized OCS dose at baseline, study center region, and baseline eosinophil level subgroup (<150 vs ≥150 cells/μL) as covariates. The overall significance of the subpopulation-by-treatment interaction was calculated using an ANCOVA model with treatment group, optimized OCS dose at baseline, study center region, baseline eosinophil level subgroup (<150 vs ≥150 cells/μL), subpopulation, and subpopulation-by-treatment interaction as covariates.

The adjusted annualized rate of severe exacerbations was calculated using a negative binomial model with the total number of events onset from randomization up to visit 11 (week 24) or last contact date (whichever came earlier) as the response variable, and the treatment group, region, number of events within 1 year prior to the study, baseline eosinophils (<150, ≥150 cells/μL), subgroup, and treatment-by-subgroup interaction as covariates. The unadjusted annualized rate of severe exacerbations was calculated for patients who did not reduce OCS dose to 0 mg/d at week 24.

Changes in pre- and post-bronchodilator FEV_1 were calculated as LS mean change from baseline by visit. The LS mean and LS mean difference in dupilumab versus placebo were derived from a mixed-effect model with repeated measures, with the change from baseline in pre- or post-bronchodilator FEV_1 as the response variable, and the treatment group, age, sex, height, region, baseline eosinophils (<150, ≥150 cells/μL), visit, treatment-by-visit interaction, baseline pre- or post-bronchodilator FEV_1, and baseline-by-visit interaction as covariates. Subgroup, subgroup-by-treatment, and subgroup-by-treatment-by-visit interactions were included as additional covariates in the model used to derive interaction *P* values.

Between-treatment differences in the proportion of patients no longer requiring OCS at week 24 were expressed as odds ratios (ORs). The ORs for the proportion of patients no longer requiring OCS at week 24 were calculated by combining results from analyzing multiple imputed data using a logistic regression model by Rubin's rule, with treatment group, optimized OCS dose at baseline, study center region, and baseline eosinophils (<150 vs ≥150 cells/μL) as covariates. The overall significance of the subpopulation-by-treatment interaction was calculated using a logistic regression model, with treatment group, optimized OCS dose at baseline, study center region, baseline eosinophils (<150 vs ≥150 cells/μL), subpopulation, and subpopulation-by-treatment interaction as covariates.

RESULTS

Patients

A total of 210 patients were randomized in LIBERTY ASTHMA VENTURE, 103 to dupilumab and 107 to placebo. At baseline, 82 patients were receiving a daily OCS dose of less than 10 mg (dupilumab n = 46; placebo n = 36), and 128 patients were receiving a daily OCS dose of 10 or more mg (dupilumab n = 57; placebo n = 71). Baseline patient demographics and clinical characteristics were generally consistent between the dupilumab and the placebo groups (Table I). Mean (±SD) patient age was 52.9 ± 12.6 years and 50.3 ± 12.6 years in patients receiving an OCS dose of less than 10 mg/d and 10 or more mg/d at baseline, respectively. The majority of patients (59%−61%) were female. Pre- and post-bronchodilator FEV_1 and 5-item Asthma Control Questionnaire scores were comparable between treatment groups and subpopulations. Differences between the groups receiving an OCS dose of less than 10 mg/d and 10 or more mg/d included a greater exacerbation history and higher fractional exhaled nitric oxide levels in the latter group, which are consistent with more severe disease. The mean (SD) number of severe asthma exacerbations in the past year in the dupilumab and placebo groups was 1.89 ± 1.86 and 1.67 ± 1.22, respectively, in the group receiving an OCS dose of less than 10 mg/d, and 2.11 ± 2.25 and 2.42 ± 2.58, respectively, in the group receiving an OCS dose of 10 or more mg/d. The mean optimized baseline OCS dose in the dupilumab and placebo groups was 6.14 ± 1.26 mg/d and 6.18 ± 1.40 mg/d, respectively, in the group receiving an OCS dose of less than 10 mg/d, and 14.47 ± 5.52 mg/d and 14.58 ± 5.93 mg/d, respectively, in the group receiving an OCS dose of 10 or more mg/d.

Reduction in OCS dose over time

Compared with placebo, dupilumab reduced the mean OCS dose over time in both subpopulations (*P* value for interaction at week 12 = .59; *P* value for interaction at week 24 = .54) (Figure 1). In the subgroup receiving an OCS dose of less than 10 mg/d, the mean daily OCS dose was 6.1 mg at baseline and 1.3 mg (78% reduction) and 1.2 mg (80% reduction) at weeks 12 and 24, respectively, in patients receiving dupilumab. For patients receiving placebo, the mean daily OCS dose was 6.2 mg at baseline and 3.2 mg (47% reduction) and 3.5 mg (44%

TABLE I. Baseline demographics and clinical characteristics

	Baseline OCS dose < 10 mg/d		Baseline OCS dose ≥ 10 mg/d	
Characteristic	**Placebo (n = 36)**	**Dupilumab (n = 46)**	**Placebo (n = 71)**	**Dupilumab (n = 57)**
Age (y), mean (SD)	49.8 (13.6)	55.4 (11.2)	51.2 (12.5)	49.1 (12.8)
Male, n (%)	14 (38.9)	19 (41.3)	28 (39.4)	22 (38.6)
BMI (kg/m^2), mean (SD)	29.1 (6.1)	28.0 (5.4)	30.1 (6.0)	29.6 (6.3)
Age at asthma onset (y), mean (SD)	31.5 (17.6)	34.0 (21.3)	31.6 (15.9)	28.9 (16.5)
Time since asthma diagnosis (y), mean (SD)	18.27 (13.25)	21.42 (17.89)	19.63 (12.90)	20.22 (11.91)
Number of severe asthma exacerbations experienced in the past year, mean (SD)	1.67 (1.22)	1.89 (1.86)	2.42 (2.58)	2.11 (2.25)
Preoptimized daily OCS dose (mg/d), mean (SD)	7.03 (2.31)	7.76 (3.21)	14.26 (5.86)	15.04 (6.50)
Optimized daily OCS dose (mg/d), mean (SD)	6.18 (1.40)	6.14 (1.26)	14.58 (5.93)	14.47 (5.52)
Preoptimized daily OCS dose (mg/d), median	5.00	7.50	10.00	12.50
Optimized daily OCS dose (mg/d), median	6.25	5.00	12.50	12.50
Ongoing atopic condition,* n (%)	25 (69.4)	31 (67.4)	52 (73.2)	43 (75.4)
Atopic dermatitis, n (%)	3 (8.3)	3 (6.5)	5 (7.0)	5 (8.8)
Chronic rhinosinusitis, n (%)	11 (30.6)	10 (21.7)	17 (23.9)	12 (21.1)
Nasal polyposis, n (%)	9 (25.0)	11 (23.9)	12 (16.9)	12 (21.1)
Former smoker, n (%)	7 (19.4)	14 (30.4)	10 (14.1)	10 (17.5)
Pre-bronchodilator FEV_1 (L), mean (SD)	1.62 (0.60)	1.49 (0.57)	1.63 (0.62)	1.57 (0.49)
Post-bronchodilator FEV_1 (L), mean (SD)	1.93 (0.80)	1.79 (0.60)	1.87 (0.70)	1.86 (0.60)
FEV_1 reversibility (%), mean (SD)	21.24 (31.69)	22.49 (29.83)	17.03 (17.45)	19.07 (17.31)
ACQ-5 score (scale 0−6), mean (SD)	2.57 (1.04)	2.27 (1.28)	2.59 (1.12)	2.53 (1.21)
Blood eosinophils (Giga/L), median (IQR)	0.27 (0.15−0.47)	0.33 (0.16−0.51)	0.22 (0.11−0.41)	0.26 (0.17−0.52)
Total IgE, median (IU/mL), (IQR)	143.00 (74.00−397.00)	179.00 (96.00−389.00)	135.00 (36.00−307.00)	201.00 (84.00−611.00)
FeNO (ppb), median (IQR)	23.00 (15.00−52.00)	27.00 (14.00−46.00)	30.00 (18.00−58.00)	35.50 (16.50−51.00)

ACQ-5, 5-Item Asthma Control Questionnaire; *BMI,* body mass index; *FeNO,* fractional exhaled nitric oxide; *IgE,* immunoglobulin E; *IQR,* interquartile range; *ppb,* parts per billion.

*A patient is considered to have an ongoing atopic medical condition if he or she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives; or has baseline total IgE ≥ 100 IU/mL and ≥ 1 aeroantigen-specific IgE (≥0.35 IU/mL) at baseline.

reduction) at weeks 12 and 24, respectively. The LS mean difference in reduction from baseline between dupilumab and placebo was 1.8 mg at week 12 (95% CI 0.65−2.85; P =.0017) and 2.1 mg at week 24 (95% CI 0.84−3.32; P = .001) (Figure 1, *A*). In the subgroup receiving an OCS dose of 10 or more mg/d, the mean daily OCS dose was 14.5 mg at baseline and 6.3 mg (58% reduction) at week 12 and 4.7 mg (69% reduction) at week 24 in patients receiving dupilumab. For patients treated with placebo, the mean daily OCS dose was 14.6 mg at baseline and, at weeks 12 and 24, respectively, 7.3 mg (51% reduction) and 7.8 mg (46% reduction). The LS mean difference in reduction from baseline between dupilumab and placebo was 1.2 mg at week 12 (95% CI −0.61 to 3.01; P = 0.19) and 3.3 mg at week 24 (95% CI 0.96−5.54; P = .005) (Figure 1, *B*).

Clinical outcomes

Dupilumab reduced the adjusted annualized rate of severe asthma exacerbations compared with placebo, irrespective of the baseline OCS dose (P value for interaction = .19) (Figure 2). In the subgroups of patients who received less than 10 mg/d and 10 or more mg/d OCS at study baseline, dupilumab significantly reduced the adjusted annualized rate of severe exacerbations compared with placebo by 71% (relative risk 0.29; 95% CI 0.13−0.64; P = .003) and 48% (relative risk 0.52; 95% CI 0.31−0.86; P = .01), respectively (Figure 2).

Dupilumab improved pre- and post-bronchodilator FEV_1 at week 24 compared with placebo, and improvements from baseline FEV_1 were sustained and comparable between both subgroups (P value for interaction: pre-bronchodilator FEV_1 = .54; post-bronchodilator FEV_1 = .85) (Figure 3). In the subpopulation of patients who received a baseline OCS dose of less than 10 mg/d, LS mean (standard error) change from baseline at week 24 in pre-bronchodilator FEV_1 was 0.26 L (0.07) in the dupilumab group, and 0.11 L (0.08) in the placebo group (LS mean difference between dupilumab and placebo: 0.15 L; 95% CI −0.04 to 0.33; P = .13) (Figure 3, *A*). Dupilumab improved pre-bronchodilator FEV_1 from baseline at week 24 in the subgroup of patients who received an OCS dose of 10 or more mg/d to a similar magnitude as the low-dose subgroup (0.23 L [0.07]), while pre-bronchodilator FEV_1

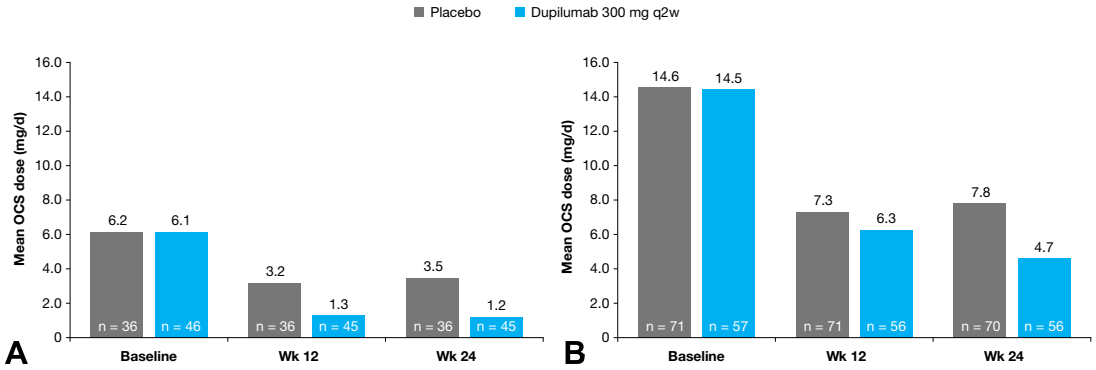

FIGURE 1. Mean OCS dose at baseline, wk 12, and wk 24 in patients receiving (**A**) OCS dose < 10 mg/d and (**B**) OCS dose ≥10 mg/d at baseline. *q2w,* Every 2 wk.

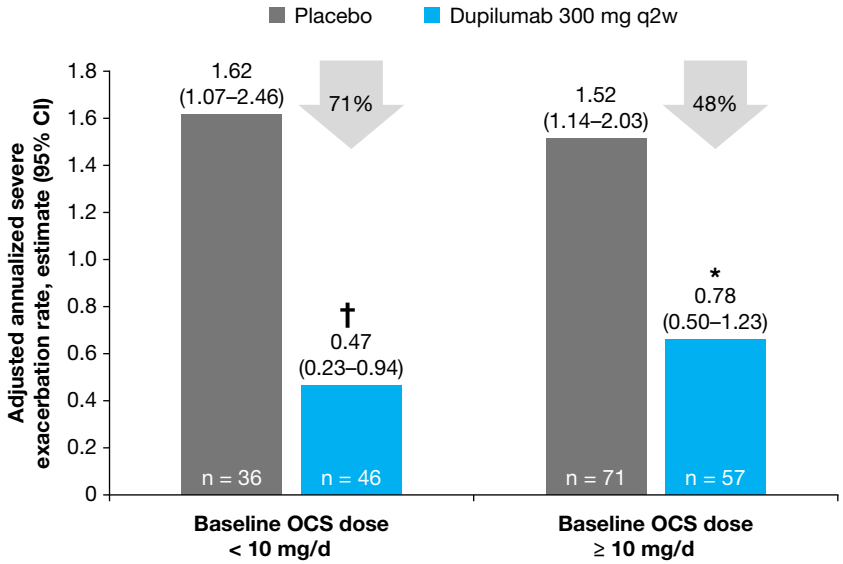

FIGURE 2. Adjusted annualized rate of severe exacerbations. *q2w,* Every 2 wk. *$P < .05$; †$P < .01$; vs placebo.

decreased by 0.03 L (0.06) in placebo-treated patients (LS mean difference between dupilumab and placebo, 0.26 L; 95% CI 0.09−0.43; $P = .003$) (Figure 3, *B*).

In patients with an OCS dose of less than 10 mg/d at baseline, post-bronchodilator FEV_1 at week 24 improved by 0.15 L (0.06) from baseline in patients treated with dupilumab and decreased by 0.05 L (0.06) in patients treated with placebo (LS mean difference between dupilumab and placebo 0.20 L; 95% CI 0.05−0.35; $P = .01$) (Figure 3, *C*). Similar results were observed in the subgroup of patients receiving 10 or more mg/d OCS at baseline. At week 24, post-bronchodilator FEV_1 improved by 0.13 L (0.06) from baseline in patients receiving dupilumab and decreased by 0.05 L (0.05) in patients receiving placebo (LS mean difference between dupilumab and placebo 0.18 L; 95% CI 0.02−0.34; $P = .03$) (Figure 3, *D*).

Proportion of patients who no longer required OCS at week 24

A greater proportion of patients treated with dupilumab were able to eliminate OCS by week 24, irrespective of the OCS dose at the start of the trial (P value for interaction = .36) (Figure 4). In patients who received less than 10 mg/d OCS at study baseline, 72.3% treated with dupilumab versus 41.7% treated with placebo no longer required OCS by week 24 (OR dupilumab vs placebo 3.75; 95% CI 1.40−10.01; $P = .008$) (Figure 4). In patients with an OCS dose of 10 or more mg/d at study baseline, 37.0% receiving dupilumab versus 22.5% receiving placebo no longer required OCS by week 24 (OR dupilumab vs placebo 2.32; 95% CI 1.00−5.38; $P = .05$) (Figure 4).

Outcomes in patients who did not eliminate OCS by week 24

Baseline patient demographics and clinical characteristics of patients who required OCS at week 24 were generally consistent between treatment arms (Table II). The mean daily OCS dose at baseline and week 24 was 13.4 mg and 6.7 mg (44% reduction), respectively, in patients treated with dupilumab, and 12.8 mg and 8.9 mg (23% reduction), respectively, in patients treated with placebo (Figure 5).

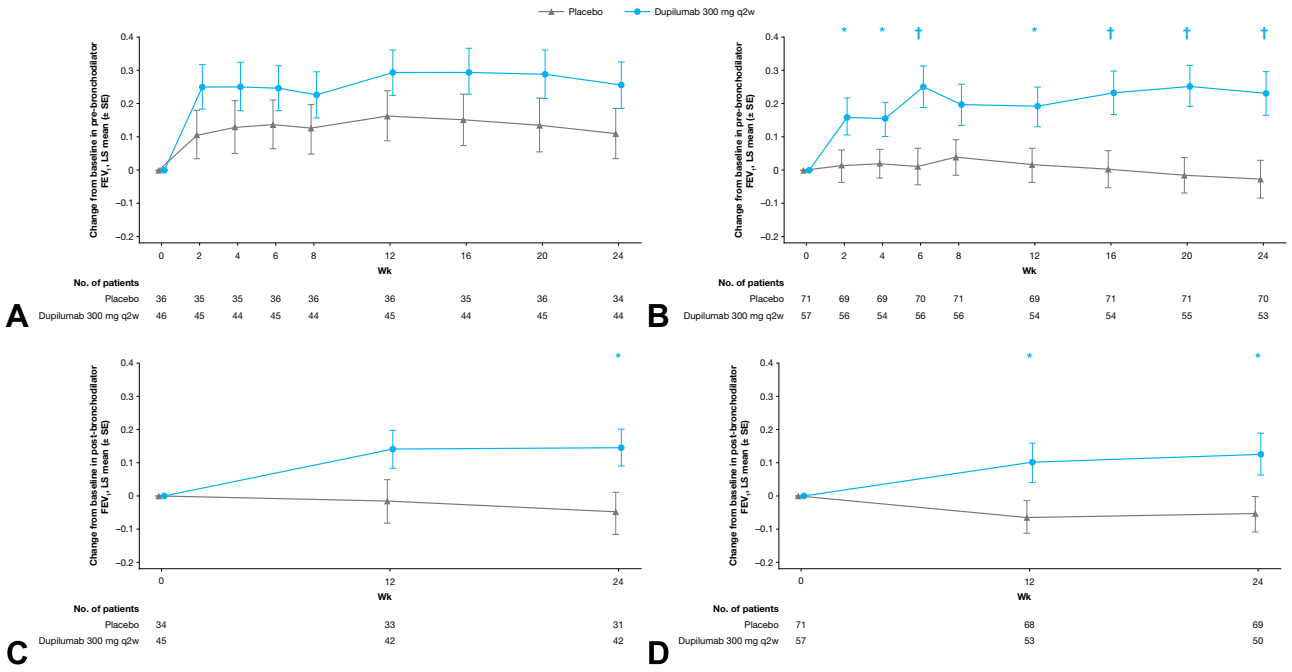

FIGURE 3. LS mean change from baseline in pre-bronchodilator FEV_1 in patients receiving (**A**) OCS < 10 mg/d and (**B**) OCS ≥ 10 mg/d and in post-bronchodilator FEV_1 in patients receiving (**C**) OCS < 10 mg/d and (**D**) OCS ≥ 10 mg/d. *q2w,* Every 2 wk; *SE,* standard error. **P* < .05; †*P* < .01; vs placebo.

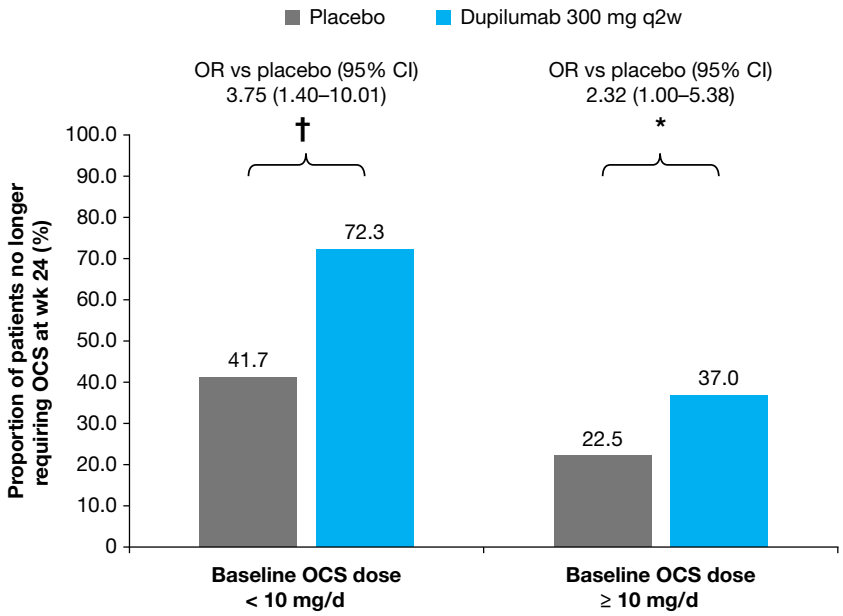

FIGURE 4. Proportion of patients who no longer required OCS at wk 24. *q2w,* Every 2 wk. **P* < .05; †*P* < .01; vs placebo.

Dupilumab- versus placebo-treated patients who did not completely discontinue OCS at week 24 also experienced improvements in clinical outcomes. The unadjusted annualized rate of severe asthma exacerbations was numerically lower in the dupilumab (1.27) versus placebo (2.10) groups. At week 24, pre-bronchodilator FEV_1 significantly improved by 0.20 L (0.06) from baseline in the dupilumab group and decreased by 0.01 L (0.05) in the placebo group (LS mean difference between dupilumab and placebo 0.21 L; 95% CI 0.05−0.36; $P = .01$) (Figure 6, *A*). Similarly, post-bronchodilator FEV_1 improved by 0.12 L (0.06) from baseline in the dupilumab group and decreased by 0.06 L (0.05) in the placebo group (LS mean difference between dupilumab and placebo 0.18 L; 95% CI 0.03-0.34; $P = .02$) (Figure 6, *B*).

TABLE II. Baseline demographics and clinical characteristics of patients who did not reduce their OCS dose to 0 mg/d at wk 24

	ITT	
Characteristic	**Placebo (n = 75)**	**Dupilumab (n = 47)**
Age (y), mean (SD)	50.8 (12.7)	49.7 (11.7)
Male, n (%)	25 (33.3)	16 (34.0)
BMI (kg/m^2), mean (SD)	29.79 (5.82)	29.48 (6.37)
Age at asthma onset (y), mean (SD)	29.9 (16.1)	27.9 (17.4)
Time since asthma diagnosis (y), mean (SD)	20.94 (13.30)	21.84 (14.76)
Number of severe asthma exacerbations experienced in the past year, mean (SD)	2.47 (2.32)	2.34 (2.40)
Preoptimized daily OCS dose (mg/d), mean (SD)	12.71 (6.17)	14.28 (7.20)
Optimized daily OCS dose (mg/d), mean (SD)	12.77 (6.75)	13.35 (6.72)
Preoptimized daily OCS dose (mg/d), median	10.00	12.50
Optimized daily OCS dose (mg/d), median	10.00	12.50
Ongoing atopic condition,* n (%)	52 (69.3)	31 (66.0)
Atopic dermatitis, n (%)	6 (8.0)	3 (6.4)
Chronic rhinosinusitis, n (%)	20 (26.7)	13 (27.7)
Nasal polyposis, n (%)	14 (18.7)	11 (23.4)
Former smoker, n (%)	11 (14.7)	14 (29.8)
Pre-bronchodilator FEV_1 (L), mean (SD)	1.52 (0.56)	1.49 (0.55)
Post-bronchodilator FEV_1 (L), mean (SD)	1.75 (0.69)	1.75 (0.65)
FEV_1 reversibility (%), mean (SD)	16.88 (17.18)	17.57 (14.92)
ACQ-5 score (scale 0−6), mean (SD)	2.59 (1.06)	2.35 (1.24)
Blood eosinophils (Giga/L), median (IQR)	0.23 (0.11−0.47)	0.24 (0.16−0.54)
Total IgE (IU/mL), median (IQR)	135.00 (40.00−302.00)	169.00 (50.00−498.00)
FeNO (ppb), median (IQR)	32.00 (18.00−56.00)	32.50 (14.00−53.00)

ACQ-5, 5-Item Asthma Control Questionnaire; *BMI,* body mass index; *FeNO,* fractional exhaled nitric oxide; *IgE,* immunoglobulin E; *IQR,* interquartile range; *ITT,* intention-to-treat; *ppb,* parts per billion.

*A patient is considered to have an ongoing atopic medical condition if he or she has any of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives; or has baseline total IgE ≥ 100 IU/mL and ≥ 1 aeroantigen-specific IgE (≥0.35 IU/mL) at baseline.

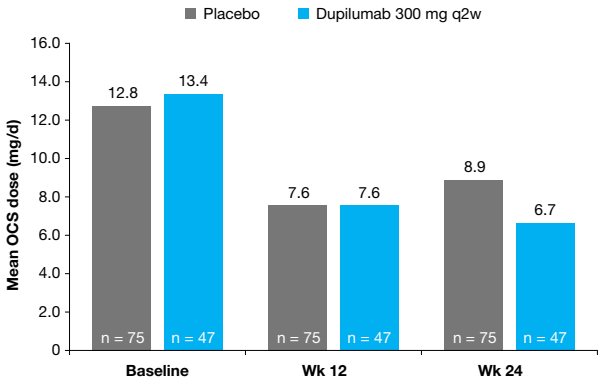

FIGURE 5. Mean OCS dose at baseline, wk 12, and wk 24 in patients who did not reduce OCS dose to 0 mg/d at wk 24. *q2w,* Every 2 wk.

Safety

Dupilumab was generally well tolerated in VENTURE. In the overall safety population, the incidence of treatment-emergent adverse events was similar across treatment groups, and the most common treatment-emergent adverse events reported in the dupilumab versus placebo groups, respectively, were transient blood eosinophilia (14% vs 1%) and injection-site reactions (9% vs 4%). The reported adverse events of eosinophilia were laboratory findings without clinical consequence, and associated adverse events were not reported.

DISCUSSION

In the LIBERTY ASTHMA VENTURE study, subcutaneous dupilumab 300 mg every 2 weeks reduced OCS dose and improved clinical outcomes in patients aged 12 years or older with OCS-dependent severe asthma.[19] In this *post hoc* analysis of VENTURE, which assessed whether subpopulations of patients with OCS-dependent severe asthma responded differently to dupilumab based on their OCS dose at baseline, dupilumab demonstrated consistent efficacy in patients receiving a lower or higher OCS dose at baseline. Dupilumab significantly reduced the mean OCS dose over time from a mean daily dose at baseline of 6.1 mg to 1.2 mg at week 24 in patients receiving a baseline OCS dose of less than 10 mg/d, and from 14.5 mg to 4.7 mg in patients receiving a baseline OCS dose of 10 or more mg/d. Dupilumab also significantly improved the odds of no longer requiring OCS at week 24 versus placebo (72.3% vs 41.7% and 37.0% vs 22.5% of patients receiving a baseline OCS dose of less than 10 mg/d and 10 or more mg/d, respectively).

While reducing OCS dose, dupilumab improved clinical outcomes across patients receiving a lower or higher OCS dose at baseline, regardless of their ability to completely stop using OCS at week 24. Dupilumab significantly reduced the adjusted annualized rate of severe asthma exacerbations by 71% and 48% versus placebo in patients receiving a baseline OCS dose of less than 10 mg/d and 10 or more mg/d, respectively. Consistent with the overall population, a numerical reduction in severe exacerbation rate was observed in dupilumab-treated patients who did not discontinue OCS at week 24. Dupilumab also improved lung

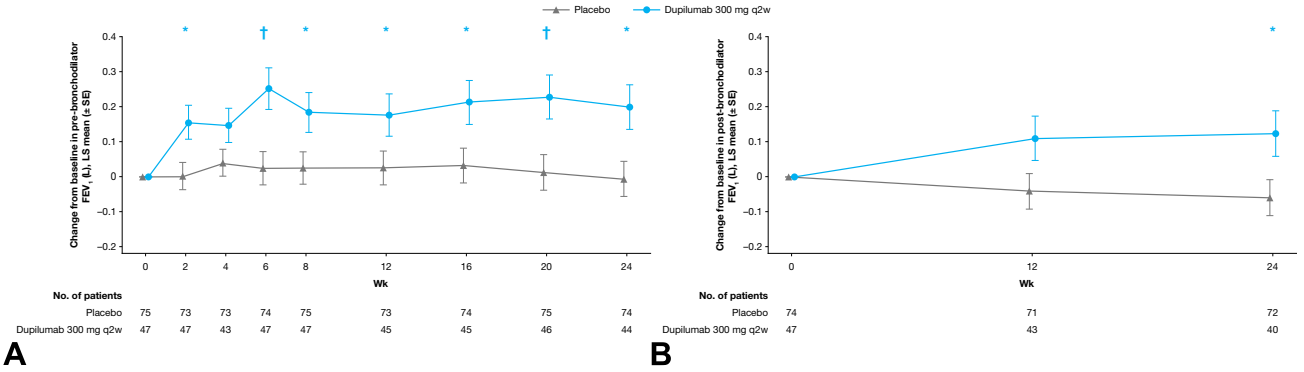

FIGURE 6. LS mean change from baseline in (**A**) pre-bronchodilator FEV_1 and (**B**) post-bronchodilator FEV_1 in patients who did not reduce OCS dose to 0 mg/d at wk 24. *q2w,* Every 2 wk; *SE,* standard error. $*P < .05$; $\dagger P < .01$; vs placebo.

function in the subgroups of patients defined by baseline OCS dose and in those who did not reduce daily OCS dose to 0 mg at week 24. Pre-bronchodilator and post-bronchodilator FEV_1 were improved over time with dupilumab treatment consistently in patients who received an OCS dose of less than 10 mg/d or 10 or more mg/d at baseline, despite the high placebo response for pre-bronchodilator FEV_1 in patients with a baseline OCS dose of less than 10 mg/d. A decline in post-bronchodilator FEV_1 values over time was observed in patients treated with placebo. Dupilumab therefore appears to preserve and improve lung function despite a reduction in OCS dose.

Although, in some cases, the effect of dupilumab was greater in the subgroup of patients receiving less than 10 mg/d OCS at baseline, this trend was not consistent across clinical outcomes, and no significant interaction effects were observed for any outcome assessed. Therefore, efficacy of dupilumab in OCS dose reduction and clinical outcome improvement is independent of baseline OCS dose category.

OCS-sparing treatment strategies are increasingly important in improving patient outcomes,[11,12,21] due to the well-known toxicity and morbidity burden associated with long-term OCS use,[6,8,12,22] in addition to the greater health care costs and health care resource utilization connected with their use.[9,10,22] GINA 2020 recommended that, whereas add-on maintenance OCS of 7.5 or more mg/d prednisone equivalent may be needed for some patients with severe asthma, because of serious side effects, maintenance OCS should be avoided if other options are available for the management of severe asthma.[2] In addition to dupilumab, several targeted biologic therapies have been tested for the treatment of severe asthma, including benralizumab, mepolizumab, omalizumab, and tezepelumab.[12,23] Compared with placebo, tezepelumab failed to demonstrate an OCS-sparing effect in a phase 3 clinical trial testing efficacy in patients with severe asthma.[23] Benralizumab and mepolizumab have been shown in double-blind, placebo-controlled trials to reduce the dose of OCS and the exacerbation rate in patients with severe asthma.[12,24,25] Although omalizumab demonstrated no OCS dose reduction in double-blind, randomized, controlled clinical trials, an OCS-sparing effect was observed in a randomized open-label study[26] and in a meta-analysis of real-world evidence.[12,27] Whereas these other biologics enabled patients with severe asthma to taper OCS over time, the reduction of OCS was not systematically accompanied by the statistically significant improvement in lung function[24-26,28,29] demonstrated by dupilumab in both VENTURE[30] and the *post hoc* analysis presented here.

The limitations of this study are inherent to its design, as all the analyses were *post hoc*. It is possible that the 1:1 dupilumab:placebo randomization in the VENTURE primary study may not be maintained in this *post hoc* analysis. The limited 24-week study duration and titration protocol of VENTURE did not allow for down-titration of the OCS dose to 0 mg in patients receiving an optimized OCS dose of 35 mg/d at baseline. Furthermore, it is possible that some patients could not reduce OCS to 0 mg/d owing to adrenal insufficiency.

In conclusion, this *post hoc* analysis shows that dupilumab significantly reduced the OCS dose, improved the likelihood of no longer requiring OCS, and improved clinical outcomes in patients with OCS-dependent severe asthma receiving a lower or higher OCS dose at baseline.

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REFERENCES

1. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. Eur Respir J 2014;43:343-73.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Updated 2020. Accessed September 21, 2021. https://ginasthma.org/wp-content/uploads/2020/06/GINA-2020-report_20_06_04-1-wms.pdf.
3. Domingo Ribas C, Sogo Sagardia A, Prina E, Mainar AS, Navarro AS, Engroba Teijeiro C. Prevalence, characterization and costs of severe asthma in Spain (BRAVO 1). Eur Respir J 2020;56:4639.
4. Heaney LG, Perez de Llano L, Al-Ahmad M, Backer V, Busby J, Canonica GW, et al. Eosinophilic and noneosinophilic asthma: an expert consensus framework to characterize phenotypes in a global real-life severe asthma cohort. Chest 2021;160:814-30.
5. Jackson DJ, Busby J, Pfeffer PE, Menzies-Gow A, Brown T, Gore R, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. Thorax 2021;76:220-7.

6. Ramsahai JM, Wark PA. Appropriate use of oral corticosteroids for severe asthma. Med J Aust 2018;209:S18-21.
7. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J 2015;46:1308-21.
8. Price DB, Trudo F, Voorham J, Xu X, Kerkhof M, Ling Zhi Jie J, et al. Adverse outcomes from initiation of systemic corticosteroids for asthma: long-term observational study. J Asthma Allergy 2018;11:193-204.
9. Voorham J, Xu X, Price DB, Golam S, Davis J, Ling Zhi Jie J, et al. Healthcare resource utilization and costs associated with incremental systemic corticosteroid exposure in asthma. Allergy 2019;74:273-83.
10. Zeiger R, Sullivan P, Chung Y, Kreindler JL, Zimmerman NM, Tkacz J. Systemic corticosteroid-related complications and costs in adults with persistent asthma. J Allergy Clin Immunol Pract 2020;8:3455-3465.e13.
11. Sullivan PW, Ghushchyan VH, Globe G, Schatz M. Oral corticosteroid exposure and adverse effects in asthmatic patients. J Allergy Clin Immunol 2018;141:110-116.e7.
12. Cataldo D, Louis R, Michils A, Peché R, Pilette C, Schleich F, et al. Severe asthma: oral corticosteroid alternatives and the need for optimal referral pathways. J Asthma 2021;58:448-58.
13. European Medicines Agency. Dupixent (dupilumab). Summary of Product Characteristics. Accessed September 21, 2021. https://ec.europa.eu/health/documents/community-register/2019/20190801145601/anx_145601_en.pdf.
14. U.S. Food and Drug Administration. 2019. Dupixent (dupilumab). Highlights of Prescribing Information. Accessed September 21, 2021. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761055s014lbl.pdf.
15. Macdonald LE, Karow M, Stevens S, Auerbach W, Poueymirou WT, Yasenchak J, et al. Precise and *in situ* genetic humanization of 6 Mb of mouse immunoglobulin genes. Proc Natl Acad Sci U S A 2014;111:5147-52.
16. Murphy AJ, Macdonald LE, Stevens S, Karow M, Dore AT, Pobursky K, et al. Mice with megabase humanization of their immunoglobulin genes generate antibodies as efficiently as normal mice. Proc Natl Acad Sci U S A 2014;111:5153-8.
17. Gandhi NA, Pirozzi G, Graham NMH. Commonality of the IL-4/IL-13 pathway in atopic diseases. Expert Rev Clin Immunol 2017;13:425-37.
18. Le Floc'h A, Allinne J, Nagashima K, Scott G, Birchard D, Asrat S, et al. Dual blockade of IL-4 and IL-13 with dupilumab, an IL-4Rα antibody, is required to broadly inhibit type 2 inflammation. Allergy 2020;75:1188-204.
19. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. N Engl J Med 2018;378:2475-85.
20. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention. Revised 2014. Accessed September 21, 2021. https://ginasthma.org/wp-content/uploads/2019/01/2014-GINA.pdf.
21. Gurnell M, Heaney LG, Price D, Menzies-Gow A. Long-term corticosteroid use, adrenal insufficiency and the need for steroid-sparing treatment in adult severe asthma. J Intern Med 2021;290:240-56.
22. Volmer T, Effenberger T, Trautner C, Buhl R. Consequences of long-term oral corticosteroid therapy and its side-effects in severe asthma in adults: a focused review of the impact data in the literature. Eur Respir J 2018;52:1800703.
23. Update on SOURCE Phase III Trial for Tezepelumab in Patients with Severe, Oral Corticosteroid-Dependent Asthma. Accessed September 21, 2021. https://www.astrazeneca.com/media-centre/press-releases/2020/update-on-source-phase-iii-trial-for-tezepelumab-in-patients-with-severe-oral-corticosteroid-dependent-asthma.html.
24. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid−sparing effect of benralizumab in severe asthma. N Engl J Med 2017;376:2448-58.
25. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. N Engl J Med 2014;371:1189-97.
26. Siergiejko Z, Świebocka E, Smith N, Peckitt C, Leo J, Peachey G, et al. Oral corticosteroid sparing with omalizumab in severe allergic (IgE-mediated) asthma patients. Curr Med Res Opin 2011;27:2223-8.
27. Bousquet J, Humbert M, Gibson PG, Kostikas K, Jaumont X, Pfister P, et al. Real-world effectiveness of omalizumab in severe allergic asthma: a meta-analysis of observational studies. J Allergy Clin Immunol Pract 2021;9:2702-14.
28. Domingo C, Moreno A, Jose Amengual M, Montón C, Suarez D, Pomares X. Omalizumab in the management of oral corticosteroid−dependent IGE-mediated asthma patients. Curr Med Res Opin 2011;27:45-53.
29. Bjerrum AS, Skjold T, Schmid JM. Oral corticosteroid sparing effects of anti-IL5/anti-IL5 receptor treatment after 2 years of treatment. Respir Med 2021;176:106260.
30. Rabe KF, Nair P, Maspero JF, Castro M, Rice MS, Deniz Y, et al. The effect of dupilumab on lung function parameters in patients with oral corticosteroid-dependent severe asthma. Respir Med X 2020;2:100010.