

# The long-term effect of dupilumab on dyspnea, sleep, and activity in oral corticosteroid-dependent severe asthma



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## ARTICLE INFO

### Article history:

Received for publication November 14, 2022.

Accepted for publication December 1, 2022.

## ABSTRACT

**Background:** Severe asthma impacts quality of life (QoL), including dyspnea, sleep, and activity limitation. Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukins-4 and -13, which are key and central drivers of type 2 inflammation. Phase 3 LIBERTY ASTHMA VENTURE (NCT02528214) and LIBERTY ASTHMA TRAVERSE open-label extension (NCT02134028) evaluated dupilumab 300 mg vs placebo every 2 weeks for 24 weeks (VENTURE) and dupilumab only for an additional 48 to 96 weeks (TRAVERSE) in patients with oral corticosteroid (OCS)-dependent severe asthma.

**Objective:** To assess dupilumab's impact on Asthma QoL Questionnaire (AQLQ) items related to breathing symptoms, sleep, and activity limitation, and on OCS reduction.

**Methods:** The proportion of patients with AQLQ scores of 6 or 7 for breathing symptoms-, sleeping-, and activity-related items in VENTURE and TRAVERSE, together with OCS dose reductions in VENTURE.

**Results:** In VENTURE, significantly greater proportions of dupilumab- vs placebo-treated patients achieved scores of 6 or 7 by week 24 in breathing symptoms-related (42.7%-60.2% vs 22.4%-39.3%), sleeping-related (45.6%-65.0% vs 27.1%-47.7%), and activity-related (44.7%-51.5% vs 22.4%-34.6%) AQLQ items. Improvements were maintained through TRAVERSE in the dupilumab/dupilumab group and increased to dupilumab treatment levels in the placebo/dupilumab group. Significant OCS dose reductions were observed in VENTURE; up to 90% and 60% of dupilumab-treated vs 65% and 41% of placebo-treated patients with AQLQ scores of 6 or 7 in breathing symptoms-, sleeping-, and activity-related items achieved greater than or equal to 50% dose reduction and eliminated OCS at week 24, respectively.

**Conclusion:** In patients with severe OCS-dependent asthma, dupilumab improved QoL related to breathing symptoms, sleep, and activity limitation, and reduced OCS use.

**Trial Registration:** ClinicalTrials.gov Identifiers: NCT02528214 and NCT02134028.

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**Disclosures:** Dr Sher is an advisory board member for Aimmune Therapeutics, Optinose, Regeneron Pharmaceuticals, Inc., and Sanofi; reports receiving speaker fees from Regeneron Pharmaceuticals, Inc., and Sanofi; and clinical trials funding from Aimmune Therapeutics, Amgen, AstraZeneca, Circassia, DBV Technologies, Galderma, GSK, Lupin, Merck, Mylan, Novartis, Novo Nordisk, Optinose, Pearl Therapeutics, Pfizer, Pulmagen Therapeutics, Roxane Laboratories, Sanofi, Spirometrix, Teva, Vectura, and Watson Pharmaceuticals. Dr Passalacqua reports receiving speaker fees from AstraZeneca, GSK, Novartis, and Sanofi. Dr Taillé is a

consultant for, and reports research grants and speaker fees from AstraZeneca, GSK, Novartis, and Sanofi. Dr Cohn is an advisory board member for Genentech, GSK, Novartis, Pieris Pharmaceuticals, Regeneron Pharmaceuticals, Inc., and Sanofi; and reports receiving speaker fees from Genentech. Dr Daizadeh is a former employee of Sanofi and may hold stock or stock options in the company. Drs Pandit-Abid, Jacob-Nara, Rowe, and Nag are employees of Sanofi and may hold stock or stock options in the company. Drs Soler, Khodzhaev, Deniz, and Zhang are employees and shareholders of Regeneron Pharmaceuticals, Inc.

**Funding:** This research was sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

<https://doi.org/10.1016/j.annai.2022.12.002>

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## Introduction

Living with severe asthma can have a substantial impact on the patient's quality of life (QoL), which can be diminished by difficulty breathing, sleep impairment, and difficulty performing everyday activities such as household chores or going for a walk.<sup>1–3</sup> These factors are related; patients with asthma often report night-time impaired breathing symptoms, which can disturb sleep.<sup>4</sup> Poor sleep quality in patients with asthma is also associated with reduced QoL<sup>5</sup> and may limit patients' ability to perform activities because of the lack of adequate rest.<sup>4</sup> Some patients avoid physical activity to prevent experiencing impaired breathing symptoms,<sup>2,3</sup> which may further exacerbate poor sleep, as performing regular physical activity may improve nocturnal asthma symptoms.<sup>6</sup>

Patients with severe asthma often require the routine use of oral corticosteroids (OCS) to maintain asthma control,<sup>1</sup> which adds to the symptom burden. Long-term OCS use has been associated with a myriad of adverse effects, and can significantly affect QoL, with an increased risk of mood disorders (eg, depression and anxiety), sleep apnea, and general sleep disturbance.<sup>7–9</sup> There remains, therefore, an urgent clinical need for asthma therapies that reduce the detrimental impact of asthma symptoms on QoL while enabling OCS reduction for patients with severe disease.

Dupilumab, a fully human<sup>10,11</sup> monoclonal antibody, blocks the shared receptor component for interleukin-4 and 13, cytokines that are key and central drivers of type 2 diseases such as atopic dermatitis (AD), asthma, allergic rhinitis, and food allergies, which are often associated as comorbidities,<sup>12</sup> thus, inhibiting their signaling.<sup>13,14</sup> Dupilumab is approved in the United States as an add-on maintenance treatment in patients with moderate-to-severe asthma aged 12 years and older with an eosinophilic phenotype or with OCS-dependent asthma.<sup>15</sup> In the phase 3 LIBERTY ASTHMA VENTURE study (NCT02528214), add-on dupilumab 300 mg every 2 weeks vs placebo significantly reduced OCS use from baseline over 24 weeks by 70.1% vs 41.9% in adults with OCS-dependent severe asthma. Despite the decreased use of OCS in this population, dupilumab improved clinical outcomes.<sup>16</sup> Patients enrolled in VENTURE had the option to continue treatment as part of the open-label LIBERTY ASTHMA TRAVERSE study (NCT02134028), which investigated the long-term efficacy and safety of dupilumab in patients who had participated in previous dupilumab asthma phase 2B or phase 3 studies.<sup>17</sup> Sustained improvements in clinical outcomes and OCS reduction were observed long term in patients who continued to receive dupilumab.<sup>17,18</sup> The overall safety was consistent with the known dupilumab safety profile.<sup>16,17</sup>

The Asthma QoL Questionnaire (AQLQ) is a health-related questionnaire that measures the impact of asthma on patients, with a score of greater than or equal to 6 indicating minimal negative impact on health-related QoL.<sup>19</sup> The items on the questionnaire related to breathing symptoms, sleep disturbance, and limitation in the ability to perform activities of daily living, assess the impact of asthma on patient health-related QoL from various angles, allowing comprehensive evaluation of the patient experience.

In VENTURE, dupilumab improved total AQLQ scores<sup>20</sup>; however, the specific impact of dupilumab and its long-term effect on breathing symptoms, sleep disturbance, and limitation of activities of daily living-related QoL in patients with OCS-dependent severe asthma has not been assessed. This posthoc analysis of the VENTURE and TRAVERSE studies assessed the long-term effect of dupilumab on patient-reported impacts of asthma on breathing symptoms, sleep disturbance, and limitations in performing activities of daily living in patients with OCS-dependent severe asthma who enrolled in both studies. In addition, we evaluated the ability to reduce OCS dose to clinically relevant thresholds in patients from VENTURE who reported maximal improvement of breathing symptoms, sleep

disturbance, and limitation of activities of daily living as assessed by AQLQ. Some of the results of these studies have been reported previously in the form of abstracts.<sup>21–23</sup>

## Methods

### Study Designs

The VENTURE study was an international, randomized, double-blind, placebo-controlled, phase 3 trial assessing the efficacy and safety of dupilumab in patients with severe OCS-dependent asthma. Full inclusion and exclusion criteria have been published previously.<sup>16</sup> In brief, eligible patients were 12 years of age or older with physician-diagnosed asthma for 1 year or more prior, who had been receiving regular OCS in the previous 6 months and high-dose inhaled corticosteroids with up to 2 controllers for at least 3 months. Patients were randomized 1:1 to receive subcutaneous dupilumab 300 mg every 2 weeks for 24 weeks or matched placebo. During the 24-week treatment period, patients were treated with an optimized OCS dose for 4 weeks. The OCS dose was systematically reduced over the next 16 weeks per a protocol-defined algorithm. Patients then entered a 4-week maintenance phase from weeks 20 to 24.

The TRAVERSE study was an open-label extension study that enrolled patients who had completed a previous phase 2 or 3 dupilumab asthma study.<sup>17</sup> Patients enrolled from VENTURE entered TRAVERSE directly from the VENTURE end-of-treatment visit (VENTURE week 24 = TRAVERSE week 0). All patients received dupilumab 300 mg every 2 weeks for up to an additional 96 weeks in TRAVERSE. Following a protocol amendment in October 2016, the treatment period was reduced from 96 to 48 weeks, after the accumulation of safety data for dupilumab across multiple indications. The dose of OCS was left to the investigator's discretion during TRAVERSE.

The VENTURE and TRAVERSE studies were conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. The appropriate institutional review boards and ethics committees approved the trial procedures and documentation for each participating country and written informed consent was obtained from all patients (or their legal guardians) before participation.

### Patients

This post hoc analysis included the intention-to-treat patient cohort from VENTURE (210 patients, of whom 103 received dupilumab and 107 received placebo) and patients from VENTURE enrolled in TRAVERSE (187 patients, of whom 90 had previously received dupilumab and 97 had received placebo). Patients in TRAVERSE were categorized into the placebo/dupilumab or dupilumab/dupilumab group, depending on which treatment they received in the parent VENTURE study.

### End Points

Breathing symptoms-related AQLQ items included chest tightness (#6), shortness of breath (#8), wheezing in the chest (#10), chest heaviness (#14), difficulty breathing out (#18), bother because of heavy breathing (#22), and fighting for air (#30). Sleep disturbance-related AQLQ items included a limit in sleep (#5), waking up in the morning with asthma symptoms (#20), being woken by asthma at night (#24), and asthma interfering with sleep (#29). Activities of daily living-related AQLQ items included limitations in performing strenuous (#1), moderate (#2), and work-related (#4) activities, and the overall range of activities (#31).

End points assessed in this analysis included the proportion of patients who reported scores of 6 (“a little limitation” [items #1, #2, #4, #5], “very little” [item #6], “hardly any of the time” [items #8, #10, #14, #18, #20, #22, #24, #29, and #30], or “hardly limited at all” [item #31]), or scores of 7 (“not at all limited” [items #1, #2, #4, and #5], “none” [item #6], “none of the time” [items #8, #10, #14, #18, #20, #22, #24, #29, and #30], or “not limited have done all activities” [item #31]) in breathing symptoms-, sleep disturbance-, and activity limitation-related AQLQ items at baseline and week 24 of VENTURE. In the subset of patients from VENTURE who enrolled in TRAVERSE, the proportion of patients who reported scores of 6 or 7 at VENTURE baseline and week 0 (week 24 of VENTURE), 24, and 48 of TRAVERSE were also analyzed.

The mean OCS dose reduction from baseline, the proportion of patients achieving a 50% or greater OCS dose reduction, and the proportion of patients no longer requiring OCS were assessed at weeks 12 and 24 in VENTURE patients reporting scores of 6 or 7 on breathing symptoms-, sleep disturbance-, and activity limitation-related AQLQ items.

### Statistical Analysis

For the analysis of the proportion of patients reporting AQLQ scores of 6 or 7 in VENTURE and TRAVERSE, responders were defined as patients reporting scores of 6 or 7 for an AQLQ item related to breathing symptoms, sleep disturbance, or activity limitation. Patients reporting other scores or those with a missing value were considered nonresponders. For VENTURE data, odds ratios (OR) were derived from a logistic regression model with treatment group, baseline optimized OCS dose strata, region, baseline eosinophil strata (< 150 cells/ $\mu$ L,  $\geq$  150 cells/ $\mu$ L), and baseline AQLQ item related to

breathing symptoms, sleep disturbance, or activity limitation score as covariates. Statistical testing between groups was not performed in TRAVERSE because of the open-label nature of the study.

Analysis of change from baseline in OCS dose at week 12 was reported as least squares (LS) mean differences, derived from an analysis of covariance model with OCS dose at week 12 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups (< 150 cells/ $\mu$ L,  $\geq$  150 cells/ $\mu$ L) as covariates. Week 24 data were derived from multiple imputed data, followed by an analysis of covariance model with OCS dose at week 24 as the response variable, and the treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups (< 150 cells/ $\mu$ L,  $\geq$  150 cells/ $\mu$ L) as covariates. The LS means obtained from the imputed data were combined by use of Rubin's rule. The adjusted probability of patients achieving a greater than or equal to 50% dose reduction or complete OCS reduction was assessed using a logistic regression model, which used the binary status of whether or not a patient achieved the 50% OCS dose reduction or no longer required OCS as the response variable; treatment groups, optimized OCS dose at baseline, regions, and baseline eosinophil level subgroups (< 150 cells/ $\mu$ L,  $\geq$  150 cells/ $\mu$ L) were used as covariates.

### Results

#### Breathing Symptoms-Related Asthma Quality of Life Questionnaire

In VENTURE, significant improvements in dupilumab vs matched placebo were observed at week 24 in 6 of the 7 breathing symptoms-related AQLQ items assessed, with numerical improvements observed in item #18 “difficulty breathing out”. Across items evaluating breathing symptoms, at baseline, 18.4% to 32.0% of dupilumab-treated patients reported a score of 6 or 7 compared with 14.0% to

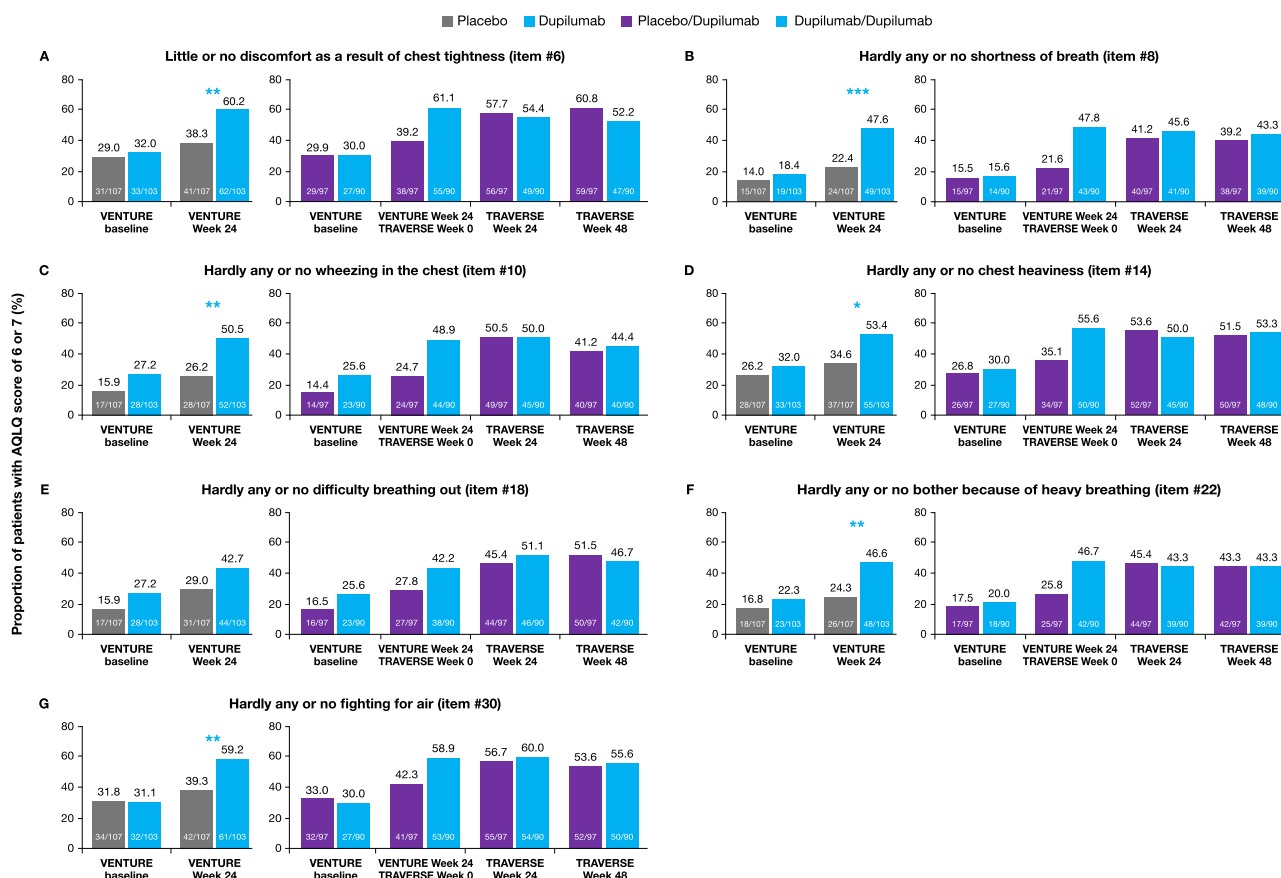


**Figure 1.** The proportion of patients reporting scores of 6 or 7 in AQLQ items related to difficulty in breathing (A-G) in VENTURE (left graphs) and TRAVERSE (right graphs). Asterisk represent  $P < .05$ , double asterisks denotes  $P < .01$ . AQLQ, Asthma Quality of Life Questionnaire.

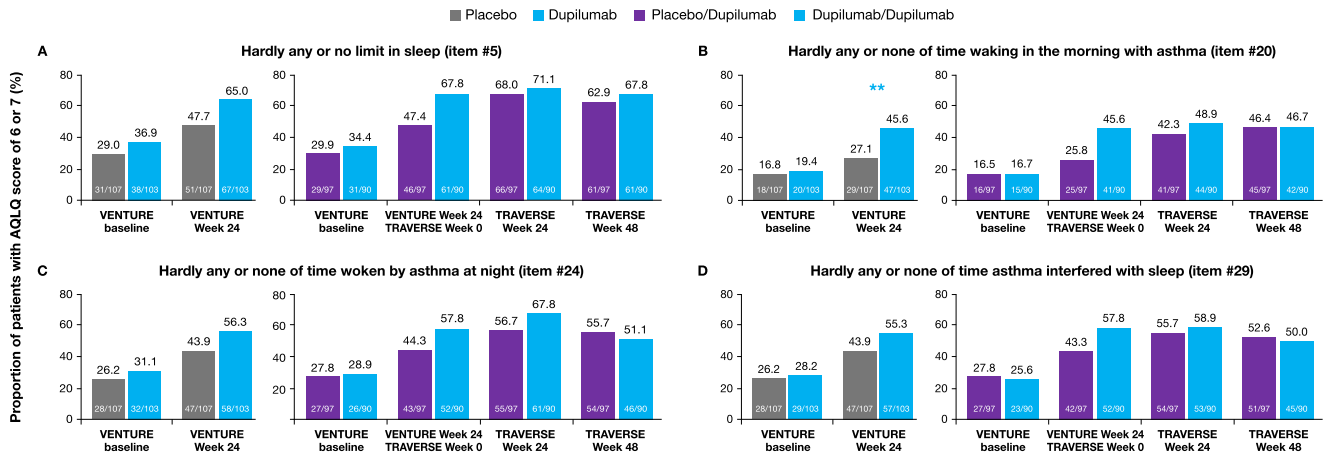


**Figure 2.** The proportion of patients reporting scores of 6 or 7 in AQLQ items related to sleep disturbance (A-D) in VENTURE (left graphs) and TRAVERSE (right graphs). Double asterisks denote  $P < .01$ . AQLQ, Asthma Quality of Life Questionnaire.

31.8% of placebo recipients; by week 24, these percentages had increased to 42.7% to 60.2% and 22.4% to 39.3% for dupilumab and placebo, respectively (Fig 1).

In VENTURE patients enrolled in TRAVERSE, differences in scores between placebo/dupilumab and dupilumab/dupilumab groups observed at TRAVERSE week 0 (ie, week 24 of VENTURE) were no longer evident at weeks 24 and 48 of TRAVERSE. Across the breathing symptoms-related AQLQ items, the improvements observed during VENTURE were maintained in the dupilumab/dupilumab group, with 43.3% to 55.6% of patients reporting a score of 6 or 7 by week 48 of TRAVERSE. In the placebo/dupilumab group, these percentages had also increased from 39.2% to 60.8% of patients across items by week 48 (Fig 1).

#### Sleep Disturbance-Related Asthma Quality of Life Questionnaire

In VENTURE, there was a trend toward improvement in sleep disturbance-related AQLQ item scores during the study. Across the 4 items evaluating sleep impairment, the proportion of patients reporting a score of 6 or 7 was 16.8% to 36.9% at baseline, suggesting that most patients experienced reduced sleep-related QoL. A numerically greater proportion of dupilumab-treated patients (45.6%–65.0%) compared with placebo-treated patients (27.1%–47.7%) reported little or no impact of asthma on sleep disturbance at week 24 (Fig 2), with significant improvement vs placebo observed for the proportion of patients reporting minimal waking up in the morning with asthma ( $P = .008$ ) (Fig 2B).

In patients from VENTURE enrolled in TRAVERSE, improvements in sleep disturbance-related items observed in the dupilumab group during VENTURE were maintained through week 48 in patients in the dupilumab/dupilumab group. By week 48, 46.7% to 67.8% of patients in the dupilumab/dupilumab group reported a score of 6 or 7 across the 4 sleeping-related items. As with breathing symptoms-related items, by week 48, patients in the placebo/dupilumab group had achieved similar results to those observed in the dupilumab/dupilumab group (46.4% to 62.9% reporting a score of 6 or 7 across items) (Fig 2).

#### Limitation of Activities of Daily Living-Related Asthma Quality of Life Questionnaire

In VENTURE, significant improvements vs placebo were seen in dupilumab-treated patients in all 4 AQLQ items related to the limitation in performing physical and work-related activities (activities of daily living). By week 24, the proportion of dupilumab-treated patients reporting a score of 6 or 7 had increased from 13.6% to 23.3% at baseline to 44.7% to 51.5% across items. In the placebo group, there were also small increases from 15.9% to 24.3% at baseline to 22.4% to 34.6% by week 24, although the magnitude of improvement was higher in dupilumab-treated patients (Fig 3).

In patients from VENTURE enrolled in TRAVERSE, as with the breathing symptoms- and sleep disturbance-related items, changes in the dupilumab group observed during VENTURE were maintained. A similar proportion of patients who had received a placebo in

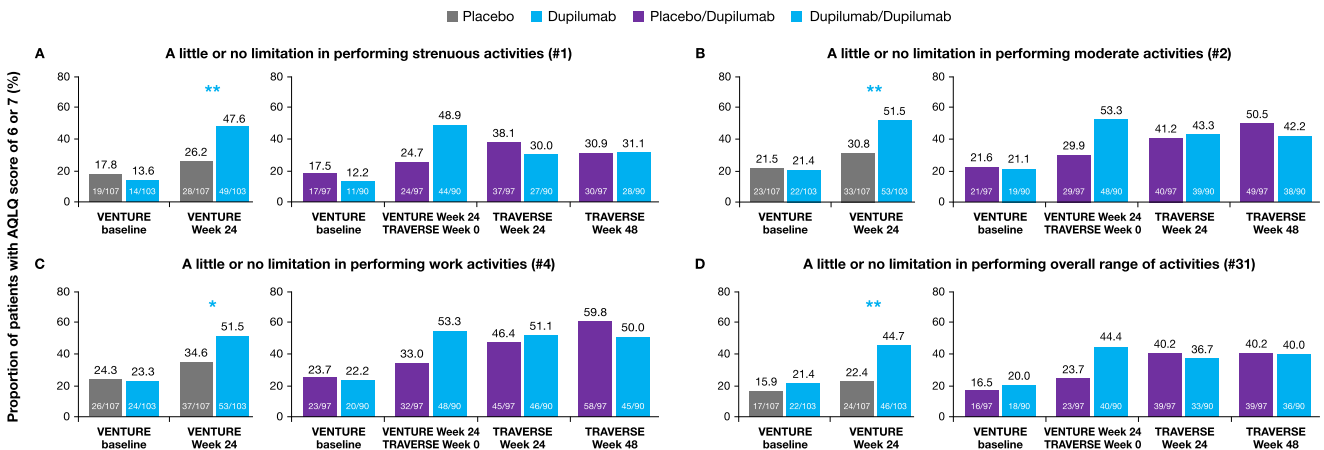


**Figure 3.** The proportion of patients reporting scores of 6 or 7 in AQLQ items related to limitation of activities of daily living (A-D) in VENTURE (left graphs) and TRAVERSE (right graphs). Asterisk denotes  $P < .05$ ; double asterisks denote  $P < .01$ . AQLQ, Asthma Quality of Life Questionnaire.

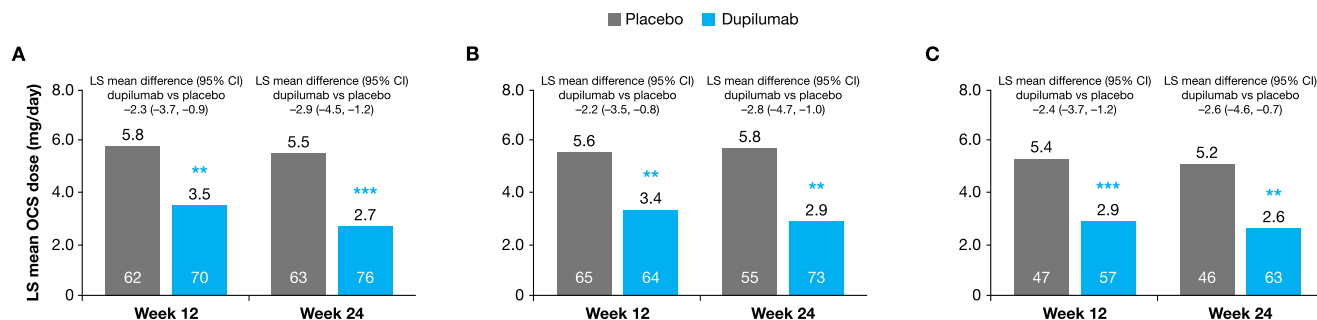


**Figure 4.** Change from baseline in OCS dose during VENTURE in patients reporting scores of 6 or 7 in (A) breathing symptoms-related, (B) sleep disturbance-related, and (C) limitation of activities of daily living-related AQLQ items. Double asterisks denote  $P < .01$ , triple asterisks denote  $P < .001$ . AQLQ, Asthma Quality of Life Questionnaire; CI, confidence interval; LS, least squares; OCS, oral corticosteroids.

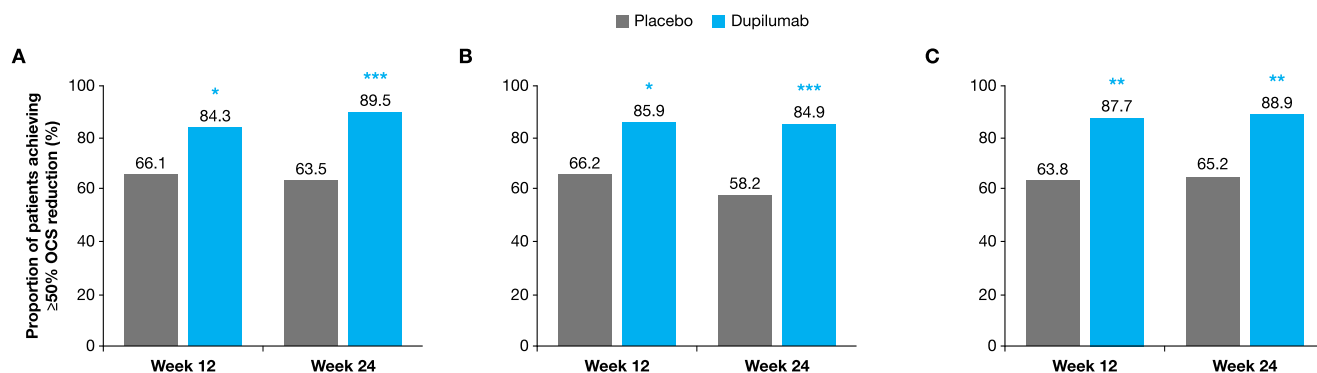


**Figure 5.** The proportion of patients achieving 50% or greater OCS dose reduction in VENTURE reporting scores of 6 or 7 in (A) breathing symptoms-related, (B) sleep disturbance-related, and (C) limitation of activities of daily living-related AQLQ items. Asterisk denotes  $P < .05$ , double asterisks denote  $P < .01$ , triple asterisks denote  $P < .001$ . AQLQ, Asthma Quality of Life Questionnaire; OCS, oral corticosteroids.

VENTURE and patients from the dupilumab/dupilumab group reported a score of 6 or 7 for activities of daily living-related items from week 24 onwards in TRAVERSE. Overall, proportions ranged from 31.1% to 50.0% in dupilumab/dupilumab and 30.9% to 59.8% in placebo/dupilumab groups across items by week 48 (Fig 3).

#### Oral Corticosteroid Dose Reduction

In patients from VENTURE who reported little to no difficulty in any breathing symptoms-related AQLQ items, the mean (SD) OCS dose was reduced from baseline to week 24 from 10.1 (5.6) mg/day to 2.3 (4.1) mg/day in dupilumab recipients, and from 11.8 (6.2) mg/day to 5.2 (6.5) mg/day in placebo recipients. Significantly greater reductions in OCS dose were observed at weeks 12 and 24 for dupilumab vs placebo, with LS mean differences of  $-2.30$  (95% confidence interval [CI],  $-3.70$  to  $-0.90$ ;  $P = .001$ ) at week 12 and  $-2.85$  ( $-4.47$  to  $-1.24$ ;  $P < .001$ ) at week 24 (Fig 4A). Similar findings were

observed in patients from VENTURE with little to no sleeping impairment (Fig 4B) and little or no limitation in activities of daily living (Fig 4C).

The proportion of patients achieving a 50% or greater reduction in OCS dose was also significantly higher in the dupilumab vs the placebo group. In patients with little to no breathing symptoms, the OR for dupilumab vs placebo was 2.79 (1.16–6.73;  $P = .02$ ) by week 12 and 5.74 (2.19–15.07;  $P < .001$ ) by week 24, with 89.5% of dupilumab recipients achieving at least 50% reduction in OCS at week 24 compared with 63.5% for placebo (Fig 5A). Similar trends were observed in patients with little to no difficulty sleeping (Fig 5B) and little to no limitation in activities of daily living (Fig 5C).

A significantly higher proportion of dupilumab- vs placebo-treated patients completely stopped OCS by week 24 of VENTURE. In patients with little to no breathing symptoms, 38.6% and 14.5% of dupilumab- and placebo-treated patients, respectively, no longer

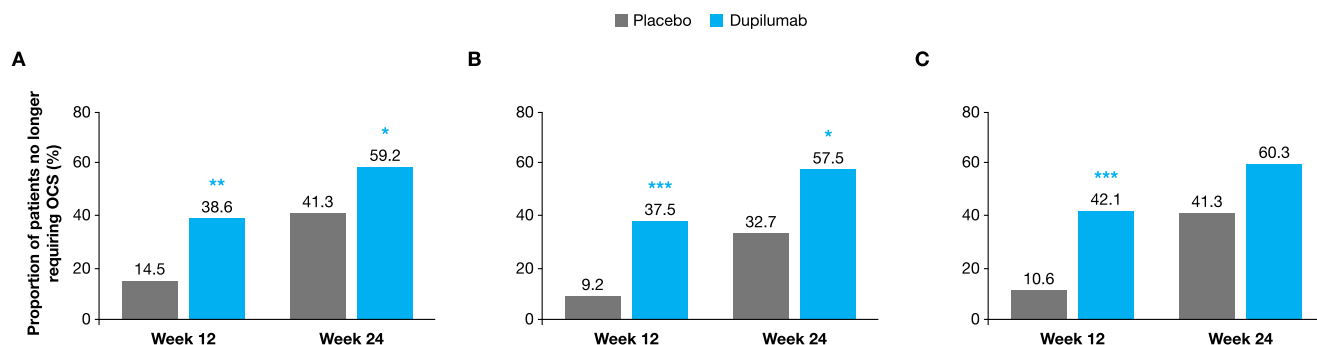


**Figure 6.** The proportion of patients no longer requiring OCS in VENTURE reporting scores of 6 or 7 in (A) breathing symptoms-related, (B) sleep disturbance-related, and (C) limitation of activities of daily living-related AQLQ items. Asterisk denotes  $P < .05$ , double asterisks denote  $P < .01$ , triple asterisks denote  $P < .001$ . AQLQ, Asthma Quality of Life Questionnaire; OCS, oral corticosteroids.

required OCS by week 12 (OR, 6.19 [2.04–18.76];  $P = .001$ ), and 59.2% and 41.3%, respectively, by week 24 (OR, 2.16 [1.01–4.64];  $P = .048$ ) (Fig 6A). Consistent with the breathing symptoms-related AQLQ items, approximately 60% of dupilumab-treated patients reported little or no sleep disturbance and little to no limitation in activities of daily living and no longer required OCS by week 24 (Fig 6B–C).

## Discussion

In this posthoc analysis of patients with OCS-dependent severe asthma from the phase 3 VENTURE OCS reduction and TRAVERSE open-label extension trials, dupilumab improved key symptoms and reduced the impact of asthma on breathing symptoms, sleep disturbance, and limitation in performing activities of daily living compared with placebo. Breathing better, sleeping better, and waking up refreshed can lead to an overall better patient experience and improvement in the ability to perform activities of daily living. This holistic improvement was exhibited with patients experiencing sustained, long-term improvements in health-related QoL after treatment with dupilumab. In addition, nearly all patients who reported little or no impact of asthma on breathing symptoms, sleep disturbance, or limitation in activities of daily living-related AQLQ items achieved a 50% or higher OCS dose reduction, with more than half of these patients no longer requiring OCS by the end of VENTURE.

A large proportion of patients included in this analysis experienced a significant burden of asthma on breathing symptoms, sleep disturbance, and limitation in performing activities of daily living at baseline, despite being treated with OCS. Considering that OCS use is associated with sleep disturbance,<sup>7</sup> which also impacts breathing and activity levels,<sup>24</sup> a treatment that improves sleep quality while reducing OCS dependence is of substantial potential benefit for patients. Many patients with severe asthma have worse symptoms at night, which also impacts the quality of sleep and, thus, daytime activity.<sup>4</sup> Patients with comorbidities, such as chronic rhinosinusitis with nasal polyps, tend to have poor sleep quality.<sup>25</sup> Although not assessed in this analysis, dupilumab may have improved sleep quality in these patients by reducing nasal obstruction, as has been exhibited previously in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma.<sup>26</sup>

In this analysis, a significantly greater proportion of patients stated that they woke up with asthma in the morning “hardly any of the time” or “none of the time” after treatment with dupilumab, with trends toward improvements vs placebo in the other 3 AQLQ sleeping-related items. These findings were potentially confounded by the small sample size together with improvements observed in the placebo group, which may explain why only numerical differences in the proportion of patients achieving improvement in sleep disturbance-related AQLQ items were observed in 3 of the 4 items. This placebo effect could potentially be related to the reductions in OCS dose, which were also observed in the placebo group, as the long-term use of OCS has been associated with sleep disruption.<sup>7</sup> Robust interpretation of this placebo effect is difficult because of the interrelationship between AQLQ items, particularly the effect of poor sleep, together with differences in individual patient experiences.

Data from TRAVERSE revealed how the improvements in AQLQ were maintained for at least up to 18 months in patients who had received dupilumab in the 6-month parent VENTURE study. In addition, the effects of dupilumab on AQLQ items observed in VENTURE were mirrored in patients in TRAVERSE who had previously received a placebo during the VENTURE study. As many of these patients had also reduced OCS dose during VENTURE, this provides some insight into the action of dupilumab on asthma symptom relief that is independent of the contribution of reducing OCS adverse effects.

As with all post hoc analyses, this evaluation had several limitations. As the studies were not specifically designed to assess the impact of dupilumab on individual AQLQ items, sample sizes were small for some of the assessed treatment groups, although the numbers of patients included in each group in this analysis were relatively well-balanced across treatments. Despite these limitations, the analysis provides valuable evidence of the long-term effects of dupilumab on health-related QoL in patients with OCS-dependent severe asthma.

In summary, dupilumab reduced the impact of asthma on breathing symptoms, sleep disturbance, and limitation in performing activities of daily living while reducing reliance on OCS in patients with OCS-dependent severe asthma. The effects were maintained long term, with similar improvements observed in patients who had previously received a placebo in VENTURE and started dupilumab during the open-label TRAVERSE study. Overall, the findings from this analysis indicate that dupilumab has a significant impact on patient-reported health-related QoL in addition to OCS dose reduction in patients with severe asthma.

## Acknowledgments

The authors thank Nora Crikelair of Regeneron Pharmaceuticals, Inc, and Arman Altincatal and Colin Mitchell of Sanofi. Medical writing and editorial assistance was provided by Erin McClure Carroll, PhD, of Excerpta Medica, and was funded by Sanofi and Regeneron Pharmaceuticals, Inc, according to the [GoodPublicationPracticeguide line](#).

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