

## ORIGINAL ARTICLE

# Efficacy and Safety of Dupilumab in Glucocorticoid-Dependent Severe Asthma

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## ABSTRACT

**BACKGROUND**

Dupilumab is a fully human anti-interleukin-4 receptor  $\alpha$  monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. Its effectiveness in reducing oral glucocorticoid use in patients with severe asthma while maintaining asthma control is unknown.

**METHODS**

We randomly assigned 210 patients with oral glucocorticoid-treated asthma to receive add-on dupilumab (at a dose of 300 mg) or placebo every 2 weeks for 24 weeks. After a glucocorticoid dose-adjustment period before randomization, glucocorticoid doses were adjusted in a downward trend from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The primary end point was the percentage reduction in the glucocorticoid dose at week 24. Key secondary end points were the proportion of patients at week 24 with a reduction of at least 50% in the glucocorticoid dose and the proportion of patients with a reduction to a glucocorticoid dose of less than 5 mg per day. Severe exacerbation rates and the forced expiratory volume in 1 second (FEV<sub>1</sub>) before bronchodilator use were also assessed.

**RESULTS**

The percentage change in the glucocorticoid dose was -70.1% in the dupilumab group, as compared with -41.9% in the placebo group ( $P < 0.001$ ); 80% versus 50% of the patients had a dose reduction of at least 50%, 69% versus 33% had a dose reduction to less than 5 mg per day, and 48% versus 25% completely discontinued oral glucocorticoid use. Despite reductions in the glucocorticoid dose, in the overall population, dupilumab treatment resulted in a severe exacerbation rate that was 59% (95% confidence interval [CI], 37 to 74) lower than that in the placebo group and resulted in an FEV<sub>1</sub> that was 0.22 liters (95% CI, 0.09 to 0.34) higher. Injection-site reactions were more common with dupilumab than with placebo (9% vs. 4%). Transient blood eosinophilia was observed in more patients in the dupilumab group than in the placebo group (14% vs. 1%).

**CONCLUSIONS**

In patients with glucocorticoid-dependent severe asthma, dupilumab treatment reduced oral glucocorticoid use while decreasing the rate of severe exacerbations and increasing the FEV<sub>1</sub>. Transient eosinophilia was observed in approximately 1 in 7 dupilumab-treated patients. (Funded by Sanofi and Regeneron Pharmaceuticals; LIBERTY ASTHMA VENTURE ClinicalTrials.gov number, NCT02528214.)

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**A**N ESTIMATED 45% OF PATIENTS WITH severe asthma use systemic glucocorticoids to control the disease and prevent exacerbations.<sup>1,3</sup> However, systemic glucocorticoids act nonselectively and are associated with considerable multiorgan toxic effects and broad immunosuppression.<sup>4,5</sup> The use of the currently approved biologic agents mepolizumab and benralizumab with anti-interleukin-5 mechanisms has shown oral glucocorticoid-sparing effects in patients with severe asthma.<sup>6,7</sup> Biologic agents targeting other cytokines may also be oral glucocorticoid-sparing while providing a favorable safety profile and further improvement in lung function and control of exacerbations and asthma symptoms.

Patients with glucocorticoid-dependent asthma may present with type 2 inflammatory disease, as shown by elevated levels in the fraction of exhaled nitric oxide (Fe<sub>NO</sub>), IgE, and other type 2 inflammation biomarkers.<sup>8</sup> Dupilumab is a fully human, VelocImmune-derived monoclonal antibody directed against the alpha subunit of the interleukin-4-receptor component that is common to signal transduction for both interleukin-4 and interleukin-13, and dupilumab treatment has the capacity to reduce type 2 inflammation.<sup>9</sup> Dupilumab treatment has been shown to reduce the rate of exacerbations and improve lung function in patients with uncontrolled moderate-to-severe asthma.<sup>10,11</sup> In this phase 3 trial, LIBERTY ASTHMA VENTURE, we assessed the efficacy and safety of dupilumab, as compared with placebo, in reducing the maintenance dose of oral glucocorticoids in patients with glucocorticoid-dependent severe asthma.

## METHODS

### TRIAL DESIGN AND OVERSIGHT

In this international, randomized, double-blind, placebo-controlled, phase 3 trial, we assessed the efficacy and safety of dupilumab in patients with oral glucocorticoid-dependent severe asthma. Patients completed an oral glucocorticoid dose-adjustment period lasting 3 to 10 weeks, followed by 1:1 randomization to receive dupilumab or placebo for a 24-week intervention period. The 24-week intervention period consisted of a 4-week induction period, during which the adjusted oral glucocorticoid dose was continued; a 16-week period of reduction in oral glucocorticoid use (weeks 4 to 20),

during which the glucocorticoid dose was adjusted down every 4 weeks according to a protocol-prespecified algorithm; and a 4-week maintenance period, during which patients continued the glucocorticoid dose that was established at week 20; the 24-week intervention period was followed by a 12-week evaluation period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Full details regarding the trial design are provided in Section 2 in the Supplementary Appendix; the protocol (with the statistical analysis plan) is also available at NEJM.org. Eligible patients who completed the trial regimen were permitted to enter a long-term, open-label extension study.

The protocol was developed by the sponsors (Sanofi and Regeneron Pharmaceuticals). Data were collected by the investigators and analyzed by the sponsors. The trial was conducted in accordance with the Declaration of Helsinki, with the Good Clinical Practice guidelines of the International Conference on Harmonisation, and with applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patients' safety data (Section 2 in the Supplementary Appendix). The local institutional review board or ethics committee at each center oversaw trial conduct and documentation. All the patients provided written informed consent before participating in the trial. Patients younger than 18 years of age provided assent according to the ethics committee-approved standard practice for pediatric patients at each participating center.

All the authors participated in the interpretation of the data and provided input into the drafting of the manuscript, critical feedback, and final approval for submission of the manuscript for publication. The authors take responsibility for the accuracy and completeness of the data and analyses and vouch for the fidelity of the trial to the protocol. All the investigators had confidentiality agreements with the sponsors. The drafts of the manuscript were prepared with the assistance of a medical writer paid by the sponsors.

### PATIENTS

Patients 12 years of age or older who had had physician-diagnosed asthma for 1 year or more according to the Global Initiative for Asthma 2014 guidelines<sup>12</sup> and who had been receiving treatment with regular systemic glucocorticoids in the pre-

vious 6 months (5 to 35 mg per day of prednisone or prednisolone or equivalent) were eligible to participate. During the 4 weeks before screening, their treatment had to also include a high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of  $>500\text{ }\mu\text{g}$  or equipotent equivalent) in combination with up to two controllers (i.e., a long-acting  $\beta_2$ -agonist or leukotriene-receptor antagonist) for at least 3 months. Eligible patients had to have a forced expiratory volume in 1 second ( $\text{FEV}_1$ ) before bronchodilator use of 80% or less of the predicted normal value (or  $\leq 90\%$  of the predicted normal value in adolescents),<sup>13</sup>  $\text{FEV}_1$  reversibility of at least 12% and 200 ml, or airway hyperresponsiveness documented in the 12 months before screening visit 1. Patients were recruited with no minimum requirement regarding a baseline blood or sputum eosinophil count or any other type 2 biomarkers (i.e.,  $\text{Fe}_{\text{NO}}$  or IgE). A complete list of the inclusion and exclusion criteria is provided in Section 3 in the Supplementary Appendix.

#### TRIAL REGIMENS AND PROCEDURES

Patients were randomly assigned in a 1:1 ratio to receive subcutaneous dupilumab (at a dose of 300 mg, after the receipt of a 600-mg loading dose on day 1) as add-on therapy or matched placebo every 2 weeks. Randomization was conducted by means of interactive voice–Web response technology, and patients were stratified according to the adjusted oral glucocorticoid dose ( $\leq 10$  mg per day vs.  $>10$  mg per day of prednisone or prednisolone) and country. In patients who had been using other oral glucocorticoids, these agents were switched to a clinically comparable dose of prednisone or prednisolone during the screening period.

The adjusted oral glucocorticoid dose was defined as the lowest dose that a patient could receive without having an increase of 0.5 (i.e., the minimal clinically important difference) or more in the 5-item Asthma Control Questionnaire (ACQ-5) score (global scores range from 0 to 6, with higher scores indicating less asthma control),<sup>14,15</sup> a severe exacerbation, or any clinically significant event leading to an upward adjustment in the oral glucocorticoid dose. During the dose-reduction phase, the oral glucocorticoid dose was reduced every 4 weeks to minimize the risk of clinically significant events and carryover effects from the previous dose. No dose adjustments were allowed beyond

week 20 except for safety reasons. Background asthma controllers were continued at a stable dose, and the use of a short-acting  $\beta_2$ -agonist was permitted as needed for asthma symptoms. Full details of the methods are provided in the protocol.

#### END POINTS

The primary efficacy end point was the percentage reduction in the oral glucocorticoid dose from baseline to week 24 while asthma control was maintained. Between weeks 20 and 24 asthma control was considered to be maintained if no clinically significant event (on the basis of investigator judgment) leading to an upward adjustment in the oral glucocorticoid dose occurred. For patients who had an exacerbation, the final oral glucocorticoid dose was considered to be one step higher than the dose they had been receiving at the time of the exacerbation.

Key secondary efficacy end points that were assessed in patients with maintained asthma control were the proportion of patients with a reduction from baseline of at least 50% in the oral glucocorticoid dose and the proportion of patients who had a reduction in the oral glucocorticoid dose to less than 5 mg per day. Other secondary end points included the proportion of patients who had the maximum possible reduction in the oral glucocorticoid dose (in patients who began the trial while they were taking a glucocorticoid dose of 35 mg per day, the dose could not be reduced to  $<2.5$  mg per day), the proportion of patients who no longer used oral glucocorticoids, and the absolute reduction in the oral glucocorticoid dose.

Other efficacy end points included the annualized rate of severe exacerbation events (defined as events leading to hospitalization, an emergency department visit, or treatment for  $\geq 3$  days with systemic glucocorticoids at  $\geq 2$  times the current dose of oral glucocorticoid) during the 24-week intervention period; the absolute change from baseline in the  $\text{FEV}_1$  before bronchodilator use at weeks 2, 4, 8, 12, 16, 20, and 24; and the change from baseline in the ACQ-5 score at week 24.

An exploratory end point of the absolute change from baseline in the  $\text{Fe}_{\text{NO}}$  level (assessed in parts per billion [ppb]) was assessed with the use of a NIOX (Aerocrine) or similar instrument at weeks 2, 4, 8, 12, 16, 20, and 24. The full list of prespecified end points is provided in the protocol.

**STATISTICAL ANALYSIS**

We estimated that 90 patients randomly assigned to each group would provide the trial with 94% power (with a two-tailed test at an alpha level of 0.05) to detect a between-group difference of 27 percentage points in the percentage reduction in daily glucocorticoid dose,<sup>16</sup> assuming a common standard deviation of 50%. The primary end point was assessed with the use of an analysis of covariance model. The model included the percentage reduction in the oral glucocorticoid dose at week 24 as the response variable, with trial group, adjusted oral glucocorticoid dose at baseline, geographic region (pooled countries), and baseline eosinophil subgroups ( $\geq 150$  or  $< 150$  cells per cubic millimeter) as covariates. The between-group difference was tested at the two-sided alpha level of 0.05. For patients who discontinued the trial or had missing data regarding the oral glucocorticoid dose at week 24 in the primary analysis, the missing data were handled with the use of a pattern-mixture model by multiple imputations.

The key secondary and other binary secondary end points were analyzed with the use of logistic-regression models. The annualized rate of severe exacerbations during the 24-week intervention period was analyzed with the use of a negative binomial regression model. A mixed-effects model with a repeated-measures approach was used to analyze the changes from baseline in the FEV<sub>1</sub> before bronchodilator use at various time points during the 24-week intervention period and the change from baseline in the ACQ-5 score at week 24. To control the overall type I error rate among the primary, key secondary, and the other binary secondary end points, multiple comparisons were controlled with the use of a prespecified hierarchical test procedure (Section 4 in the Supplementary Appendix). The other efficacy end points and exploratory end points were not controlled for multiple comparisons and are presented with 95% confidence intervals.

Efficacy analyses were performed in the intention-to-treat population, which included all the patients who underwent randomization; data were analyzed according to the assigned trial group, regardless of the trial regimen received. Primary and key secondary end points, FEV<sub>1</sub>, and rates of severe asthma exacerbations were also analyzed in subgroups of patients according to baseline blood eosinophil levels ( $\geq 300$  or  $< 300$

cells per cubic millimeter and  $\geq 150$  or  $< 150$  cells per cubic millimeter) and baseline Fe<sub>NO</sub> level ( $< 25$  ppb or  $\geq 25$  to  $< 50$  ppb or  $\geq 50$  ppb) to assess consistency in effects across the different subgroups. The safety population included all the patients who received at least one dose or a partial dose of dupilumab or placebo; data were analyzed according to the regimen received. Adverse events were assessed during the trial period, which was defined as the time from the first administration of the trial regimen to the last administration of the trial regimen plus 98 days or until the patient entered the extension study.

All the analyses were conducted with the use of SAS software, version 9.4 (SAS Institute). The statistical methods are summarized in Section 4 in the Supplementary Appendix.

**RESULTS****PATIENTS**

From December 2015 through September 2017, a total of 210 patients underwent randomization and received dupilumab (103 patients) or placebo (107) (Fig. S2 in the Supplementary Appendix). A total of 203 patients (101 patients in the dupilumab group and 102 in the placebo group) completed the 24-week intervention period, and 189 patients (93%) entered the long-term, open-label extension study. Two patients in the dupilumab group and one in the placebo group discontinued the trial or had missing data regarding the oral glucocorticoid dose at week 24. The mean duration of the trial was similar in the two groups (176.8 days in the dupilumab group and 176.0 days in the placebo group). The demographic and baseline clinical characteristics of the patients in the intention-to-treat population are shown in Table 1, and in Table S2 in the Supplementary Appendix.

**PRIMARY OUTCOME**

In the intention-to-treat population, the least-squares mean ( $\pm$ SE) percentage change in the oral glucocorticoid dose from baseline to week 24, while asthma control was maintained, was  $-70.1 \pm 4.9\%$  in the dupilumab group, as compared with  $-41.9 \pm 4.6\%$  in the placebo group ( $P < 0.001$ ) (Fig. 1A, and Table S3 in the Supplementary Appendix). The observed median change in the oral glucocorticoid dose from baseline to week 24 was  $-100\%$  (interquartile range,  $-100$  to  $-62.5$ ) in the dupilumab group, as compared with  $-50\%$

**Table 1. Demographic and Clinical Characteristics of the Patients at Baseline (Intention-to-Treat Population).\***

| Characteristic                                            | Placebo Group<br>(N = 107) | Dupilumab Group<br>(N = 103) | Total<br>(N = 210) |
|-----------------------------------------------------------|----------------------------|------------------------------|--------------------|
| Age — yr                                                  | 50.7±12.8                  | 51.9±12.5                    | 51.3±12.6          |
| Male sex — no. (%)                                        | 42 (39)                    | 41 (40)                      | 83 (40)            |
| No. of severe asthma exacerbations in previous year       | 2.17±2.24                  | 2.01±2.08                    | 2.09±2.16          |
| Time since first oral glucocorticoid prescription — yr    | 1.64±3.54                  | 1.77±3.52                    | 1.70±3.52          |
| Daily oral glucocorticoid dose — mg/day                   |                            |                              |                    |
| Dose before adjustment phase                              | 11.83±6.02                 | 11.79±6.40                   | 11.81±6.20         |
| Adjusted dose                                             | 11.75±6.31                 | 10.75±5.90                   | 11.26±6.12         |
| Prebronchodilator FEV <sub>1</sub> — liters               | 1.63±0.61                  | 1.53±0.53                    | 1.58±0.57          |
| Prebronchodilator FEV <sub>1</sub> — % of predicted value | 52.69±15.14                | 51.64±15.28                  | 52.18±15.18        |
| FEV <sub>1</sub> reversibility — liters†                  | 0.28±0.32                  | 0.29±0.31                    | 0.28±0.31          |
| Any relevant medical history — no. (%)‡                   | 86 (80)                    | 76 (74)                      | 162 (77)           |
| Nasal polyposis                                           | 38 (36)                    | 33 (32)                      | 71 (34)            |
| Food allergy                                              | 10 (9)                     | 10 (10)                      | 20 (10)            |
| Former smoker — no. (%)                                   | 17 (16)                    | 24 (23)                      | 41 (20)            |
| Time since cessation of smoking — yr                      | 16.98±11.01                | 13.99±10.96                  | 15.23±10.94        |
| ACQ-5 score§                                              | 2.58±1.09                  | 2.42±1.24                    | 2.50±1.16          |
| Blood eosinophil count — cells/mm <sup>3</sup>            | 325±298                    | 370±316                      | 347±307            |
| F <sub>ENO</sub> — ppb                                    | 39.62±34.12                | 35.55±28.34                  | 37.61±31.38        |

\* Plus–minus values are means ±SD. Patients received dupilumab (at a dose of 300 mg) or matching placebo every 2 weeks. There were no significant between-group differences in the characteristics at baseline. F<sub>ENO</sub> denotes fraction of exhaled nitric oxide, FEV<sub>1</sub> forced expiratory volume in 1 second, and ppb parts per billion.

† FEV<sub>1</sub> reversibility indicates the change (measured in liters) between an FEV<sub>1</sub> value obtained before bronchodilator use and an FEV<sub>1</sub> value obtained after bronchodilator use.

‡ Patients were considered to have a relevant medical history if they had had any of the following diseases: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, eosinophilic esophagitis, food allergy, or hives.

§ The 5-item Asthma Control Questionnaire (ACQ-5) is a patient-reported measure of the adequacy of asthma control and change in asthma control that occur either spontaneously or as a result of treatment. Global scores range from 0 to 6, with higher scores indicating less asthma control; the minimal clinically important difference is 0.5.<sup>14,15</sup>

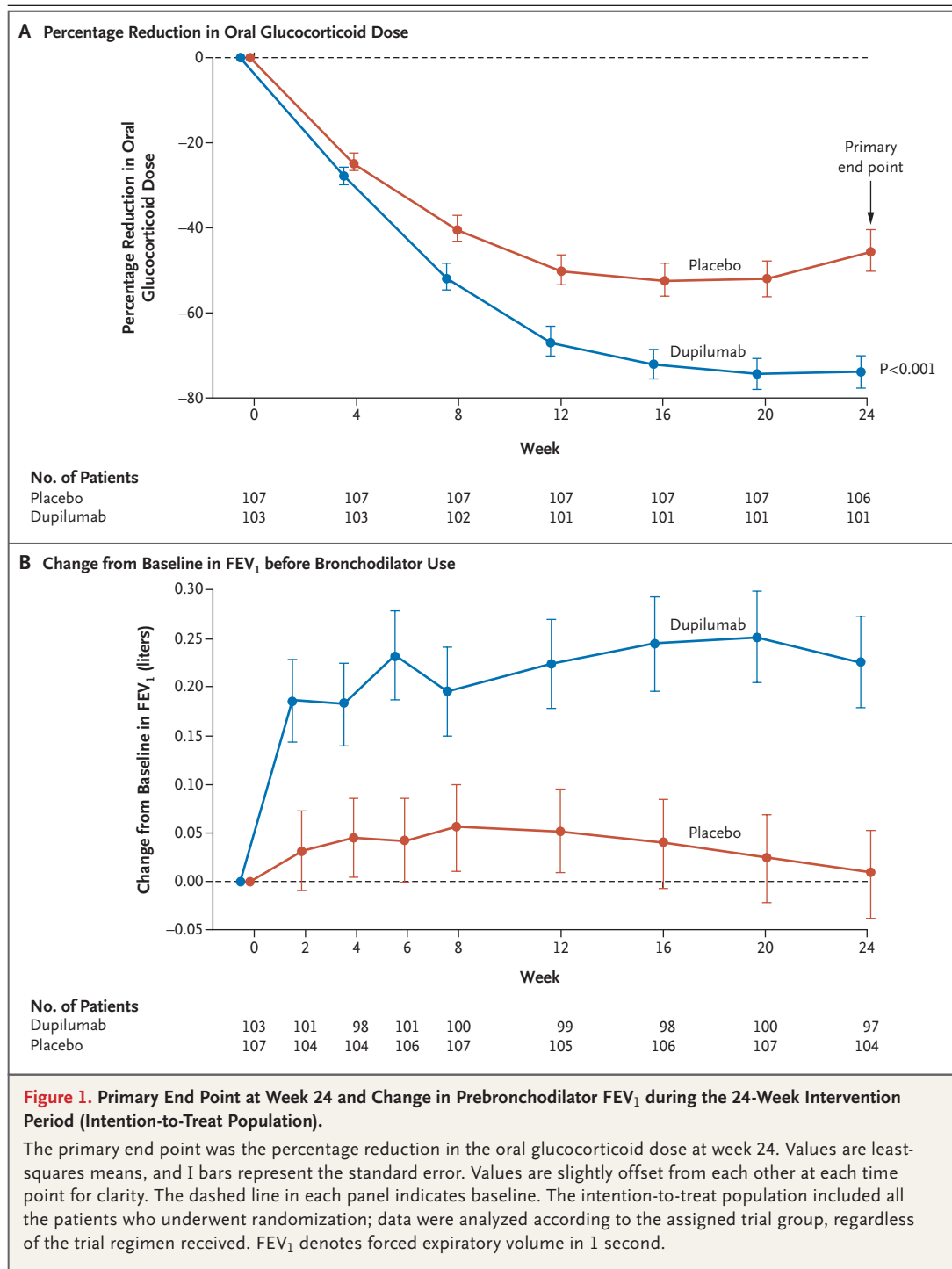
(interquartile range, –100 to 0) in the placebo group.

#### KEY SECONDARY OUTCOMES

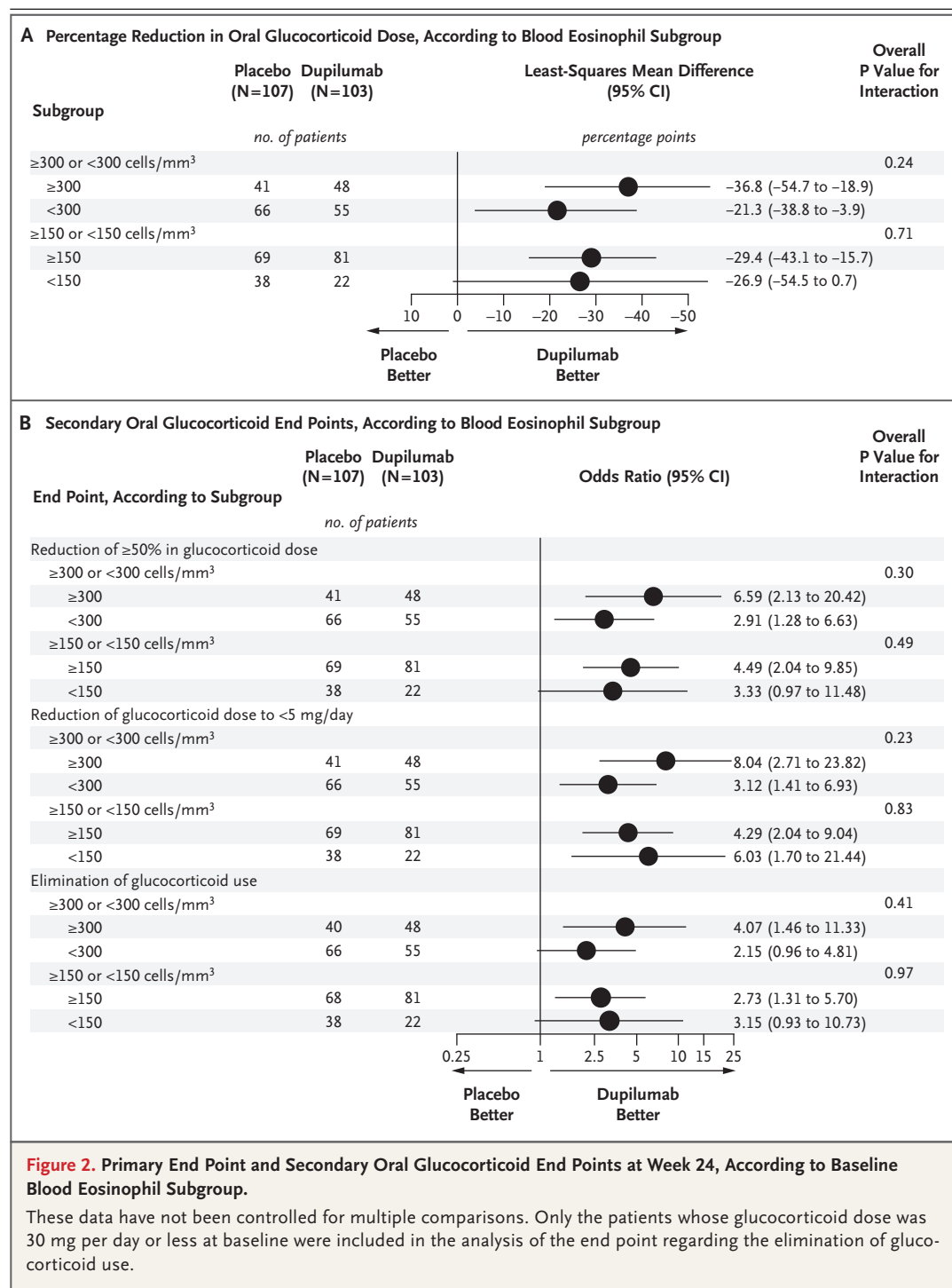
All the binary secondary end points regarding reduction in the oral glucocorticoid dose, including the key secondary and other secondary end points, reached statistical significance according to the control hierarchy for multiple comparisons. The model-adjusted percentage of patients who had a reduction from baseline of at least 50% in the oral glucocorticoid dose at week 24 was 80% in the dupilumab group versus 50% in the placebo group (P<0.001) (Table S3 in the Supplementary Appendix). Sensitivity analyses also showed that the proportions of patients with reductions in the oral glucocorticoid dose of at least 50%,

at least 75%, and at least 90% were greater with dupilumab than with placebo (Table S4 in the Supplementary Appendix). The percentage of patients who had a reduction in the oral glucocorticoid dose to less than 5 mg per day was 69% in the dupilumab group, as compared with 33% in the placebo group (P<0.001) (Table S3 in the Supplementary Appendix).

Although there was a change in the magnitude of the outcome according to the blood eosinophil count, dupilumab treatment was associated with a greater reduction in the dose of oral glucocorticoid than was placebo, regardless of the baseline blood eosinophil count (Fig. 2, and Table S5 in the Supplementary Appendix). The magnitude of the effect was largest in patients with a higher eosinophil count at baseline; among the



patients who had a reduction of at least 50% in the oral glucocorticoid dose, the odds ratios for dupilumab versus placebo were 6.59 (95% confidence interval [CI], 2.13 to 20.42) among patients with 300 or more cells per cubic millimeter at baseline and 2.91 (95% CI, 1.28 to 6.63) among those with less than 300 cells per cubic millimeter at baseline.



#### GLUCOCORTICOID-REDUCTION OUTCOMES

A total of 52% of the patients in the dupilumab group no longer used oral glucocorticoids at week 24, as compared with 29% of those in the

placebo group. After model adjustment, the corresponding values were 48% versus 25% (P=0.002) (Table S3 in the Supplementary Appendix).

**EXACERBATIONS, LUNG FUNCTION, AND ASTHMA CONTROL**

In addition to significant reductions in oral glucocorticoid use during the 24-week intervention period, dupilumab treatment resulted in a 59% (95% CI, 37 to 74) lower rate of severe asthma exacerbations than placebo in the overall population (Fig. S3 and Table S3 in the Supplementary Appendix). In the overall population, the FEV<sub>1</sub> was higher in the dupilumab group than in the placebo group at week 24 by a least-squares mean value of 0.22 liters (95% CI, 0.09 to 0.34) (Fig. 1B, and Table S3 in the Supplementary Appendix).

Although dupilumab treatment resulted in a lower annualized rate of severe asthma exacerbations and a higher FEV<sub>1</sub> than placebo, regardless of the baseline blood eosinophil count (Fig. S4 and Table S6 in the Supplementary Appendix), these benefits were more pronounced in patients with a higher baseline blood eosinophil count and in those with a higher FE<sub>NO</sub> level at baseline (Table S7 in the Supplementary Appendix). For example, among patients with a baseline blood eosinophil count of 300 or more cells per cubic millimeter, dupilumab treatment resulted in a rate of severe asthma exacerbations that was 71% (95% CI, 40 to 86) lower than the rate in the placebo group and in an FEV<sub>1</sub> that was higher by a least-squares mean value of 0.32 liters (95% CI, 0.10 to 0.54). Among patients with a baseline blood eosinophil count of less than 150 cells per cubic millimeter, dupilumab treatment resulted in a rate of severe asthma exacerbations that was 60% (95% CI, 5 to 83) lower than the rate with placebo and in an FEV<sub>1</sub> that was higher by a least-squares mean value of 0.24 liters (95% CI, 0.05 to 0.44). Increases in the FEV<sub>1</sub> in patients treated with dupilumab were noted as early as week 2 (least-squares mean change, 0.15 liters; 95% CI, 0.04 to 0.26) and showed a further increase through week 24 (Fig. 1B, and Table S3 in the Supplementary Appendix).

The ACQ-5 scores at week 24 indicated an improvement in asthma control with dupilumab, as compared with placebo. The least-squares mean difference between the dupilumab group and the placebo group in the score change from baseline was -0.47 (95% CI, -0.76 to -0.18).

**EXPLORATORY OUTCOME OF FE<sub>NO</sub> LEVEL**

Dupilumab treatment resulted in a suppression in the FE<sub>NO</sub> level by week 2, which was sustained dur-

ing the 24-week intervention period (Fig. S5 in the Supplementary Appendix). The percentage of patients with an FE<sub>NO</sub> level of less than 25 ppb (the upper limit of the normal range)<sup>17</sup> increased from 44% at baseline to 84% at week 24 in the dupilumab group, whereas no meaningful change was observed in the placebo group (45% at both time points) (Table S8 in the Supplementary Appendix).

**SAFETY**

In the safety population, the incidence of adverse events during the trial period was similar in the two groups (62% in the dupilumab group and 64% in the placebo group) (Table 2). According to the preferred terms in the Medical Dictionary for Regulatory Activities, version 20.0, the most frequent adverse events (i.e., those occurring in at least 5% of the patients in either group) were viral upper respiratory tract infection (9% of the patients in the dupilumab group vs. 18% of those in the placebo group), bronchitis (7% vs. 6%), sinusitis (7% vs. 4%), influenza (3% vs. 6%), and the laboratory measure of eosinophilia (grouped as the preferred terms of eosinophil count increase and eosinophilia) (14% vs. 1%). Injection-site reactions were observed in 9% of the patients in the dupilumab group and in 4% of those in the placebo group. Per the trial protocol, all cases of an eosinophil count of more than 3000 cells per cubic millimeter during the trial period were reported as adverse events; this event occurred in 13% of the patients in the dupilumab group versus 1% of those in the placebo group. The reported adverse events of eosinophilia were all exclusively laboratory findings without any clinical consequences or associated adverse events.

Serious adverse events during the trial period were reported in nine patients (9%) in the dupilumab group and in six (6%) in the placebo group. There were no deaths during the trial. Antidrug-antibody responses during the trial period were observed in five patients in each group (5% of the patients in the dupilumab group and 5% of those in the placebo group) and had no meaningful effect on efficacy or safety. During the trial period, no adverse events of conjunctivitis were observed in either group.

**DISCUSSION**

This trial showed that dupilumab as an add-on therapy significantly reduced oral glucocorticoid

**Table 2. Overview of Adverse Events during 24-Week Intervention Period and Injection-Site Reactions (Safety Population).\***

| Event                                                                   | Placebo Group<br>(N = 107) | Dupilumab Group<br>(N = 103) |
|-------------------------------------------------------------------------|----------------------------|------------------------------|
|                                                                         | number (percent)           |                              |
| Any adverse event                                                       | 69 (64)                    | 64 (62)                      |
| Any serious adverse event                                               | 6 (6)                      | 9 (9)                        |
| Any adverse event leading to death                                      | 0                          | 0                            |
| Any adverse event leading to permanent discontinuation of trial regimen | 4 (4)                      | 1 (1)                        |
| Adverse event occurring in ≥5% of patients in either group†             |                            |                              |
| Viral upper respiratory tract infection                                 | 19 (18)                    | 9 (9)                        |
| Bronchitis                                                              | 6 (6)                      | 7 (7)                        |
| Sinusitis                                                               | 4 (4)                      | 7 (7)                        |
| Influenza                                                               | 6 (6)                      | 3 (3)                        |
| Eosinophilia‡                                                           | 1 (1)                      | 14 (14)                      |
| Injection-site reaction§                                                | 4 (4)                      | 9 (9)                        |
| ≥1 measurement of blood eosinophil count >3000 cells/mm <sup>3</sup>    | 1 (1)                      | 13 (13)                      |

\* The safety population included all the patients who received at least one dose or a partial dose of dupilumab or placebo; data were analyzed according to the regimen received.

† Adverse events in this category were reported according to preferred terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0.

‡ The adverse event of eosinophilia in this table is a combination of the preferred terms of eosinophil count increase (in 7% of the patients in the dupilumab group vs. no patients in the placebo group) and eosinophilia (in 7% vs. 1%).

§ Injection-site reaction is a high-level term in MedDRA.

use in patients with oral glucocorticoid-dependent severe asthma. In the overall population, dupilumab treatment resulted in a rate of severe asthma exacerbations that was 59% lower than that in the placebo group and in an FEV<sub>1</sub> that was 0.22 liters higher. Among patients with a baseline blood eosinophil count of 300 or more cells per cubic millimeter, dupilumab treatment led to a 71% lower rate of exacerbations than placebo and an FEV<sub>1</sub> that was 0.32 liters higher. In this trial, patients in the placebo group also had a 41.9% reduction in the oral glucocorticoid dose. Better adherence to drug regimens in the context of a clinical trial may have contributed to this observation, but even with this level of placebo effect, patients in the dupilumab group had a significant additional benefit regarding multiple measures of asthma control.

Dupilumab treatment showed positive efficacy on the basis of multiple asthma-outcome measures in the overall trial population regardless of the baseline blood eosinophil count. Among patients with a baseline blood eosinophil count of

less than 150 cells per cubic millimeter, 75% of the patients in the dupilumab group had a reduction in their oral glucocorticoid dose of 50%, and 62% of the patients had a reduction in the oral glucocorticoid dose to less than 5 mg per day. In the large, phase 3 LIBERTY ASTHMA QUEST trial, which studied the efficacy and safety of dupilumab and the results of which are now reported in the *Journal*, treatment with dupilumab also reduced the rate of severe exacerbations and showed a rapid and sustained improvement in lung function.<sup>18</sup> In both the LIBERTY ASTHMA VENTURE trial and the LIBERTY ASTHMA QUEST trial, as well as in the earlier pivotal study,<sup>10</sup> the most robust results were observed in patients with heightened type 2 immune activity, including elevated blood eosinophil counts and FE<sub>NO</sub> level.

Dupilumab treatment reduced FE<sub>NO</sub> levels concurrent with a significant reduction in oral glucocorticoid use. Unlike with anti-interleukin-5 therapies,<sup>19</sup> a reduction in the FE<sub>NO</sub> level has been observed in all previous trials of dupilumab in patients with asthma,<sup>10,11</sup> a finding that is con-

sistent with the mechanism of action of dupilumab. These findings suggest that dupilumab inhibits type 2 inflammation more broadly than targeting eosinophils alone.

Dupilumab treatment was associated with transient eosinophilia, which was observed in 14% of the patients in the dupilumab group. Patients in the dupilumab group had a greater mean transient increase from baseline in blood eosinophil counts than those in the placebo group, with a higher percentage of patients (13%) having an eosinophil count of more than 3000 cells per cubic millimeter. The high blood eosinophil counts returned to baseline levels by the end of the dupilumab treatment period. Patients with transient elevations in the blood eosinophil counts did not have concomitant clinical adverse events or consequences. The increase in the blood eosinophil counts is consistent with the hypothesis that dupilumab blocks the migration of eosinophils into tissue by inhibiting interleukin-4- and interleukin-13-mediated production of eotaxins (as suggested by a reduction in the serum eotaxin-3 level<sup>18</sup>) and vascular-cell adhesion molecule 1<sup>20,21</sup> but not eosinophil production or egress from bone

marrow. This action results in a transient increase in circulating eosinophil counts — a finding consistent with other clinical studies of dupilumab.<sup>22</sup> Since glucocorticoids suppress circulating eosinophils, the greater reduction in the oral glucocorticoid dose in the dupilumab group than in the placebo group could also have contributed to the elevations in the eosinophil counts. No adverse events of conjunctivitis during the 24-week intervention period were observed in either group, in contrast to findings in studies of dupilumab in patients with atopic dermatitis.<sup>23-25</sup>

In conclusion, add-on therapy with dupilumab significantly reduced the oral glucocorticoid dose while simultaneously reducing the rate of severe exacerbations and improving lung function (FEV<sub>1</sub>) in patients with glucocorticoid-dependent severe asthma.

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