ORIGINAL ARTICLE

Dupilumab Efficacy and Safety in Moderate-to-Severe Uncontrolled Asthma

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ABSTRACT

BACKGROUND

Dupilumab is a fully human anti–interleukin-4 receptor α monoclonal antibody that blocks both interleukin-4 and interleukin-13 signaling. We assessed its efficacy and safety in patients with uncontrolled asthma.

METHODS

We randomly assigned 1902 patients 12 years of age or older with uncontrolled asthma in a 2:2:1:1 ratio to receive add-on subcutaneous dupilumab at a dose of 200 or 300 mg every 2 weeks or matched-volume placebos for 52 weeks. The primary end points were the annualized rate of severe asthma exacerbations and the absolute change from baseline to week 12 in the forced expiratory volume in 1 second (FEV_1) before bronchodilator use in the overall trial population. Secondary end points included the exacerbation rate and FEV_1 in patients with a blood eosinophil count of 300 or more per cubic millimeter. Asthma control and dupilumab safety were also assessed.

RESULTS

The annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks and 0.87 (95% CI, 0.72 to 1.05) among those assigned to a matched placebo, for a 47.7% lower rate with dupilumab than with placebo (P<0.001); similar results were seen with the dupilumab dose of 300 mg every 2 weeks. At week 12, the FEV_1 had increased by 0.32 liters in patients assigned to the lower dose of dupilumab (difference vs. matched placebo, 0.14 liters; P<0.001); similar results were seen with the higher dose. Among patients with a blood eosinophil count of 300 or more per cubic millimeter, the annualized rate of severe asthma exacerbations was 0.37 (95% CI, 0.29 to 0.48) among those receiving lower-dose dupilumab and 1.08 (95% CI, 0.85 to 1.38) among those receiving a matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6); similar results were observed with the higher dose. Blood eosinophilia occurred after the start of the intervention in 52 patients (4.1%) who received dupilumab as compared with 4 patients (0.6%) who received placebo.

CONCLUSIONS

In this trial, patients who received dupilumab had significantly lower rates of severe asthma exacerbation than those who received placebo, as well as better lung function and asthma control. Greater benefits were seen in patients with higher baseline levels of eosinophils. Hypereosinophilia was observed in some patients. (Funded by Sanofi and Regeneron Pharmaceuticals; LIBERTY ASTHMA QUEST ClinicalTrials.gov number, NCT02414854.)

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A complete list of investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Approximately 20% of patients with asthma have uncontrolled, moderate-to-severe disease with recurrent exacerbations and persistent symptoms despite maximized standard-of-care controller therapy.[1-3] This population is at an increased risk for illness (especially exacerbations) and accounts for considerable health care resources.[4] Many of these patients have substantially reduced lung function, despite maximum treatment, and face a further loss of lung function over time.[5]

Type 2 inflammation, mediated by cytokines such as interleukin-4, interleukin-5, and interleukin-13, occurs in approximately 50% of patients with asthma.[6] Blood and sputum levels of eosinophils, the fraction of exhaled nitric oxide ($F_{E_{NO}}$), and the serum IgE level have been linked to mechanisms involved in type 2 inflammation.[7,8] Levels of serum IgE and blood eosinophils can be used to guide the use of currently approved biologic agents in the treatment of severe asthma.

Dupilumab is a fully human VelocImmune-derived monoclonal antibody[9] that is directed against the alpha subunit of the interleukin-4 receptor, thereby blocking both interleukin-4 and interleukin-13 signaling and hence type 2 inflammation.[8] It has been approved for the treatment of moderate-to-severe atopic dermatitis.[10-12] This phase 3 trial, LIBERTY ASTHMA QUEST, was designed to confirm earlier findings in patients with severe asthma.[13] A companion article now published in the *Journal* describes the evaluation of dupilumab in patients with oral glucocorticoid–dependent severe asthma.[14]

Methods

Trial Design and Oversight

This randomized, double-blind, placebo-controlled, parallel-group trial assessed the efficacy of dupilumab in patients with uncontrolled moderate-to-severe asthma. Patients completed a screening period of 4 weeks (window, ±1 week), followed by randomization to subcutaneous injections of dupilumab or matched-volume placebo, a 52-week randomized intervention period, and a 12-week postintervention follow-up period (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

The protocol (available at NEJM.org) 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, International Conference on Harmonisation Good Clinical Practice guidelines, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data (details on the committee are available in the Supplementary Appendix). The local institutional review board or ethics committee at each trial center oversaw trial conduct and documentation. All the patients provided written informed consent before participating in the trial. Those 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; provided input into the drafting of the manuscript, critical feedback, and final approval for submission; and vouch for the completeness and accuracy of the data and analyses and for the adherence of the trial to the protocol. All the investigators had confidentiality agreements with the sponsors, Sanofi and Regeneron Pharmaceuticals. The manuscript drafts were prepared with the assistance of a medical writer paid by the sponsors.

A Quick Take is available at NEJM.org

Patients

Patients 12 years of age or older with physician-diagnosed persistent asthma for 12 months or more, according to the Global Initiative for Asthma 2014 guidelines,[15] were eligible to participate if they met the following key criteria: current treatment with a medium-to-high-dose inhaled glucocorticoid (fluticasone propionate at a total daily dose of ≥500 μg or equipotent equivalent) plus up to two additional controllers (e.g., a long-acting β_2-agonist or leukotriene-receptor antagonist); a forced expiratory volume in 1 second (FEV_1) before bronchodilator use of 80% or less of the predicted normal value (or ≤90% of the predicted normal value in those 12 to 17 years of age); FEV_1 reversibility of at least 12% and 200 ml; a score on the 5-item Asthma Control Questionnaire (ACQ-5) of 1.5 or higher (on a scale from 0 [no impairment] to 6 [maximum impairment]; the minimal clinically important difference is 0.5)[16,17]; and a worsening of asthma in the previous year that led to hospital-

ization, emergency medical care, or treatment with systemic glucocorticoids for 3 days or more. Patients were recruited irrespective of a minimum baseline blood eosinophil count or biomarkers of type 2 inflammation. Full inclusion and exclusion criteria are available in the Supplementary Appendix.

INTERVENTIONS AND PROCEDURES

Patients were randomly assigned (in a 2:2:1:1 ratio) to receive 52 weeks of add-on therapy with subcutaneous dupilumab at a dose of 200 mg (loading dose, 400 mg) or 300 mg (loading dose, 600 mg) every 2 weeks or a matched-volume placebo (1.14 ml or 2.00 ml, respectively) for each active dose (supplied in prefilled syringes). Randomization was conducted by means of interactive voice–Web response technology and was stratified according to age (<18 years or ≥18 years), peripheral-blood eosinophil count (<300 or ≥300 per cubic millimeter) at screening, inhaled glucocorticoid dose (medium or high), and country. Background asthma-controller medicines were continued at a stable dose throughout the trial and recorded daily by patients in an electronic diary. Use of long-acting β_2-agonists, long-acting muscarinic antagonists, antileukotriene agents, and methylxanthines was permitted. Throughout the trial, patients were permitted to use a short-acting β_2-adrenergic–receptor agonist as necessary for symptom relief. Biomarkers of type 2 inflammation that were measured included blood eosinophils, $F_{E_{NO}}$, serum IgE, periostin, thymus and activation-regulated chemokine (TARC), eosinophil cationic protein, and plasma eotaxin-3. Full details are available in the protocol.

END POINTS

The primary efficacy end points were the annualized rate of severe exacerbation events (number of severe exacerbations per patient-year) during the 52-week intervention period and the absolute change from baseline in the FEV_1 before bronchodilator use at week 12 in the overall trial population. These end points were also included as secondary trial end points with control for multiplicity in those with a blood eosinophil count of 300 or more per cubic millimeter. Additional secondary trial end points, including the key secondary end point of percentage change from baseline in the FEV_1 before bronchodilator use, are summarized in Table S1 in the Supplementary Appendix. A severe asthma exacerbation was defined as a deterioration of asthma leading to treatment for 3 days or more with systemic glucocorticoids or hospitalization or an emergency department visit leading to treatment with systemic glucocorticoids.[18] The incidence of adverse events and serious adverse events that emerged during the trial period was reported, with the trial period 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 enters the extension study.

STATISTICAL ANALYSIS

On the basis of the previous phase 2b study, we estimated that a sample of approximately 1638 patients would give the trial 99% power (with a two-tailed test at an alpha level of 0.05) to detect a 55% lower rate of severe asthma exacerbations with dupilumab than with placebo — that is, an annualized rate of 0.27 severe exacerbations in each dupilumab group as compared with 0.60 with placebo.[13] This sample was also expected to provide 98% power to detect a between-group difference of 0.15 liters in the change from baseline in the FEV_1 before bronchodilator use at week 12.

Efficacy analyses were performed in the intention-to-treat population, defined as all the patients who underwent randomization; data were analyzed according to the assigned intervention, whether an intervention was received or not. The annualized rate of severe exacerbations was analyzed with the use of a negative binomial regression model, including the four intervention groups, age, geographic region, baseline eosinophil strata, baseline dose of inhaled glucocorticoid, and number of exacerbations in the previous year as covariates. Patients who discontinued the assigned intervention were encouraged to return to the clinic for all remaining trial visits, and all severe exacerbations up to week 52 were included in the primary analysis, regardless of whether the patient was receiving an intervention. The change from baseline in continuous end points such as the FEV_1 and patient-reported outcomes were analyzed with the use of a mixed-effects model with repeated measures, including assigned intervention, age, baseline eosinophil strata, baseline inhaled glucocorticoid dose, visit, intervention-by-visit interaction,

the corresponding baseline value, and baseline-by-visit interaction as covariates. Sex and baseline height were included as covariates only in the models for spirometric values. For patients who discontinued the assigned intervention and remained in the trial, measurements after the intervention was discontinued were included in the primary model.

In order to control the family-wise type I error for the primary analyses (two primary end points and two doses) and selected secondary end points, a hierarchical testing procedure was applied at a two-sided 5% significance level. A list of these end points with their testing order is provided in Table S1 in the Supplementary Appendix. The end points after the hierarchy break are presented with 95% confidence intervals. The other efficacy end points that were not listed in the hierarchical testing procedure were not controlled for multiplicity and are also presented with 95% confidence intervals. Full statistical methods are summarized in the Supplementary Appendix and the statistical analysis plan (available with the protocol).

RESULTS

TRIAL PATIENTS

From May 2015 through September 2016, a total of 1902 patients underwent randomization per protocol (intention-to-treat population) (Fig. S2 in the Supplementary Appendix); of these, 1897 received the assigned intervention. As planned, the database was locked for analysis once approximately 1638 patients had completed 52 weeks of the assigned intervention or had discontinued the trial. All 1902 randomly assigned patients were included in the final analysis: 1434 patients completed the 52-week intervention period, 235 had treatment ongoing, and 228 discontinued the intervention (Fig. S2 in the Supplementary Appendix). Baseline demographic and clinical characteristics of the intention-to-treat population were generally similar across the four intervention groups (Table 1, and Table S2 in the Supplementary Appendix).

PRIMARY OUTCOMES

Exacerbations

In the intention-to-treat population (1902 patients), during the 52-week intervention period, the adjusted annualized rate of severe asthma exacerbations was 0.46 (95% confidence interval [CI], 0.39 to 0.53) among patients assigned to 200 mg of dupilumab every 2 weeks versus 0.87 (95% CI, 0.72 to 1.05) among those assigned to matched placebo (47.7% lower rate with dupilumab than with placebo, P<0.001). The rate was 0.52 (95% CI, 0.45 to 0.61) among patients assigned to 300 mg of dupilumab every 2 weeks versus 0.97 (95% CI, 0.81 to 1.16) among those assigned to matched placebo (46.0% lower rate with dupilumab than with placebo, P<0.001) (Fig. 1, and Table S3 in the Supplementary Appendix).

Prespecified subgroup analyses according to baseline blood eosinophil count showed significant differences in exacerbation rates with either dose of dupilumab as compared with matched placebo among patients with an eosinophil count of 300 or more per cubic millimeter. The rate was 0.37 (95% CI, 0.29 to 0.48) with lower-dose dupilumab versus 1.08 (95% CI, 0.85 to 1.38) with matched placebo (65.8% lower rate with dupilumab than with placebo; 95% CI, 52.0 to 75.6), and 0.40 (95% CI, 0.32 to 0.51) with higher-dose dupilumab versus 1.24 (95% CI, 0.97 to 1.57) with matched placebo (67.4% lower rate with dupilumab than with placebo, P<0.001). Among patients with a baseline blood eosinophil count of 150 to less than 300 per cubic millimeter, the exacerbation rate was also lower with dupilumab than with placebo: 0.56 (95% CI, 0.42 to 0.75) with lower-dose dupilumab versus 0.87 (95% CI, 0.59 to 1.27) with matched placebo (35.6% lower rate with dupilumab than with placebo), and 0.47 (95% CI, 0.35 to 0.64) with higher-dose dupilumab versus 0.84 (95% CI, 0.58 to 1.23) with matched placebo (44.3% lower rate with dupilumab than with placebo) (Fig. 1, and Table S5 in the Supplementary Appendix).

Among patients with a baseline blood eosinophil count of less than 150 per cubic millimeter, the exacerbation rate was similar with dupilumab and with placebo: 0.47 (95% CI, 0.36 to 0.62) with lower-dose dupilumab and 0.51 (95% CI, 0.35 to 0.76) with matched placebo, and 0.74 (95% CI, 0.58 to 0.95) with higher-dose dupilumab and 0.64 (95% CI, 0.44 to 0.93) with matched placebo (Fig. 1, and Table S5 in the Supplementary Appendix). Prespecified subgroup analyses according to the baseline Fe_{NO} showed a greater benefit of dupilumab with respect to the exacerbation rate among patients with a

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

Characteristic	Placebo, 1.14 ml (N=317)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=633)	Overall Population (N=1902)
Age — yr	48.2±15.6	47.9±15.3	48.2±14.7	47.7±15.6	47.9±15.3
Female sex — no. (%)	198 (62.5)	387 (61.3)	218 (67.9)	394 (62.2)	1197 (62.9)
Prebronchodilator FEV_1 — liters	1.76±0.61	1.78±0.62	1.75±0.57	1.78±0.60	1.78±0.60
Percent of predicted normal value	58.43±13.22	58.38±13.52	58.35±13.87	58.51±13.52	58.43±13.52
FEV_1 reversibility — %	25.06±18.76	27.39±22.79	26.45±17.65	25.73±23.79	26.29±21.73
No. of exacerbations in past year	2.07±1.58	2.07±2.66	2.31±2.07	2.02±1.86	2.09±2.15
Use of high-dose inhaled glucocorticoid — no. (%)	172 (54.3)	317 (50.2)	167 (52.0)	323 (51.0)	979 (51.5)
ACQ-5 score†	2.71±0.73	2.76±0.80	2.77±0.77	2.77±0.76	2.76±0.77
Ongoing atopic or allergic condition — no. (%)	266 (83.9)	509 (80.7)	266 (82.9)	524 (82.8)	1565 (82.3)
Nasal polyposis or chronic rhinosinusitis — no. (%)	73 (23.0)	141 (22.3)	80 (24.9)	145 (22.9)	439 (23.1)
Former smoker — no. (%)	59 (18.6)	126 (20.0)	67 (20.9)	116 (18.3)	368 (19.3)
No. of pack-yr	3.96±2.81	3.89±2.69	4.07±3.12	4.15±3.04	4.02±2.89
Biomarker levels					
Blood eosinophil count — cells/mm^3					
Mean	370±338	349±345	391±419	351±369	360±366
Median (range)	270 (0–2200)	250 (0–3610)	265 (0–3580)	250 (0–4330)	255 (0–4330)
F_{ENO} — ppb	34.47±28.54	34.45±34.91	38.39±38.00	34.01±29.74	34.97±32.85
Total IgE — IU/ml	394±625	461±818	448±797	415±701	432±747

* Plus–minus values are means ±SD. The intention-to-treat population included all the patients who underwent randomization, regardless of whether an intervention was received. Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. Further information on baseline demographic and clinical characteristics is provided in Table S2 in the Supplementary Appendix. F_{ENO} denotes fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, and ppb parts per billion.

† 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 occurs either spontaneously or as a result of treatment. Scores range from 0 to 6, with higher scores indicating less control. The minimal clinically important difference is 0.5.[17,18]

higher F_{ENO} (≥25 to <50 parts per billion [ppb] or ≥50 ppb) than among those with a lower value (<25 ppb) (Fig. 1, and Table S5 in the Supplementary Appendix).

FEV_1 Outcomes

In the overall trial population, the change from baseline in the FEV_1 before bronchodilator use at week 12 was 0.32 liters with lower-dose dupilumab versus 0.18 liters with matched placebo (difference, 0.14 liters; P<0.001). The change was 0.34 liters with higher-dose dupilumab versus 0.21 liters with matched placebo (difference, 0.13 liters; P<0.001) (Fig. S3 and Table S3 in the Supplementary Appendix).

The benefit of dupilumab with respect to the FEV_1 was greatest among patients with a blood eosinophil count of 300 or more per cubic millimeter at baseline. The change at week 12 was 0.43 liters with lower-dose dupilumab versus 0.21 liters with matched placebo (difference, 0.21 liters; 95% CI, 0.13 to 0.29) and 0.47 liters with higher-dose dupilumab versus 0.22 liters with matched placebo (difference, 0.24 liters; 95% CI, 0.16 to 0.32; P<0.001) (Fig. S3 and Table S5 in the Supplementary Appendix). In patients with a blood eosinophil count of 150 to less than 300 per cubic millimeter at baseline, the change in the FEV_1 at week 12 was 0.28 liters with lower-dose dupilumab and 0.17 liters with matched

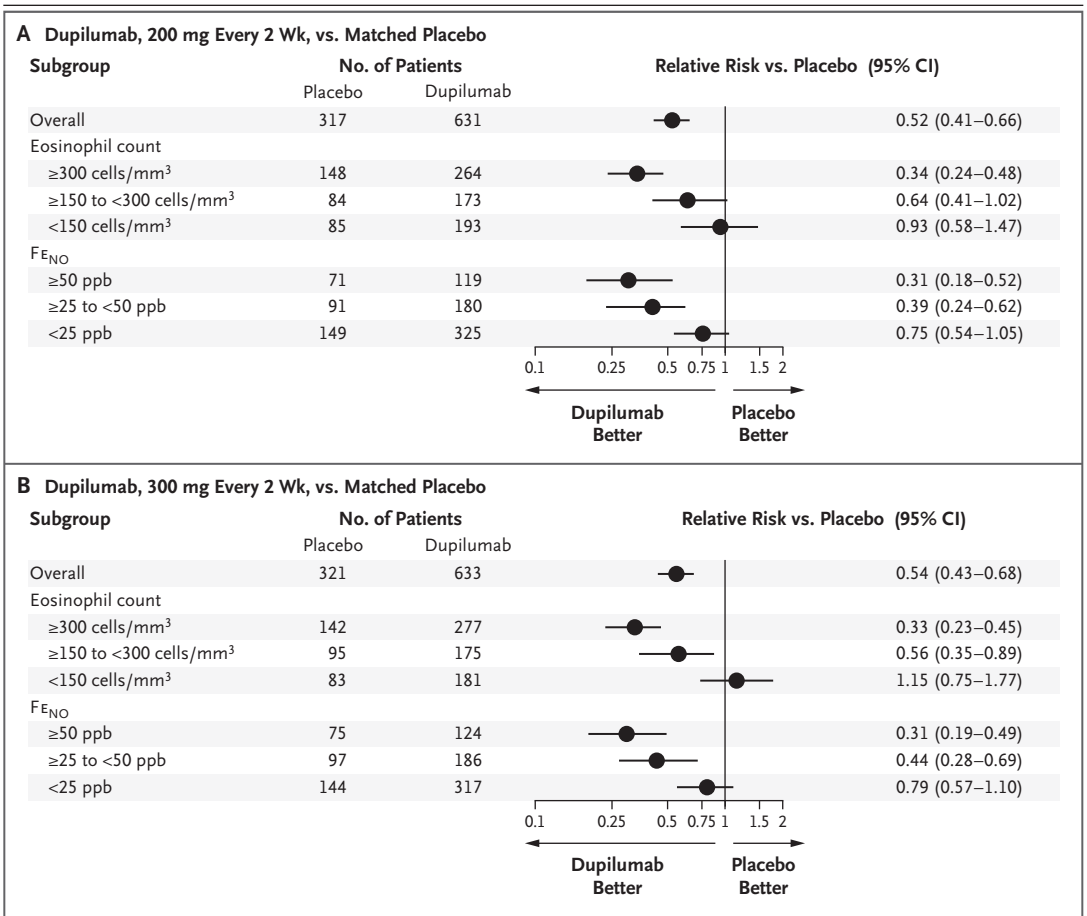


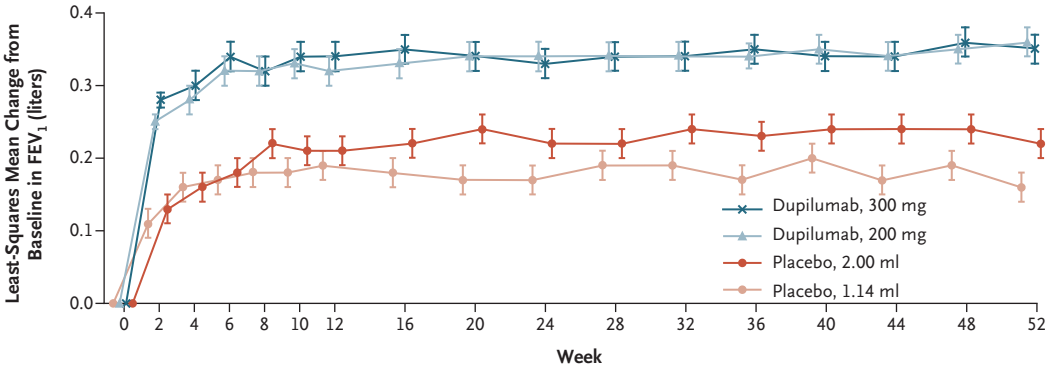
Figure 1. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FE_{NO}.

FE_{NO} denotes fraction of exhaled nitric oxide, and ppb parts per billion.

placebo (difference, 0.11 liters; 95% CI, 0.01 to 0.21) and 0.25 liters with higher-dose dupilumab and 0.25 liters with matched placebo (difference, 0.00 liters; 95% CI, −0.10 to 0.10). In patients with a blood eosinophil count of less than 150 per cubic millimeter at baseline, the change in the FEV_1 at week 12 was 0.19 liters with lower-dose dupilumab and 0.13 liters with matched placebo (difference, 0.06 liters; 95% CI, −0.04 to 0.15) and 0.20 liters with higher-dose dupilumab and 0.11 liters with matched placebo (difference, 0.09 liters; 95% CI, −0.01 to 0.18).

A benefit of dupilumab over matched placebo with respect to the change in the FEV_1 from baseline was evident by the first evaluation at week 2 and was sustained throughout the 52-week intervention period (difference vs. matched placebo at 52 weeks, 0.20 liters [95% CI, 0.14 to 0.25] with the lower dose and 0.13 liters [95% CI, 0.08 to 0.19] with the higher dose) (Fig. 2). In addition, a prespecified analysis of the rate of change in the postbronchodilator FEV_1 (FEV_1 slope after week 4 to week 52) showed a loss of lung function of 40 ml per year with placebo and no loss with either dupilumab dose (Table S4 in the Supplementary Appendix).

Dupilumab had a greater benefit with respect to the change from baseline in the FEV_1 at week 12 among patients with a higher FE_{NO} (≥25 to <50 ppb or ≥50 ppb) than among those with a lower value (<25 ppb) (Fig. S3 and Table S5 in the Supplementary Appendix). In patients with a FE_{NO} of 25 to less than 50 ppb, the difference as compared with matched placebo was 0.19 liters



No. at Risk

Dupilumab, 300 mg	633	625	614	612	609	598	610	611	593	596	586	579	584	584	570	562	488
Dupilumab, 200 mg	631	610	613	615	604	607	611	605	601	599	589	585	590	577	581	570	477
Placebo, 2.00 ml	321	313	311	313	311	309	313	310	304	296	304	301	301	297	292	290	250
Placebo, 1.14 ml	317	315	307	301	305	301	307	300	303	300	290	286	289	287	288	281	240

Figure 2. Change in the Prebronchodilator FEV_1 from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population.
Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. P<0.001 for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV_1 denotes forced expiratory volume in 1 second.

(95% CI, 0.09 to 0.28) with lower-dose dupilumab and 0.12 liters (95% CI, 0.03 to 0.21) with higher-dose dupilumab. In patients with a FE_{NO} of 50 ppb or more, the difference as compared with matched placebo was 0.30 liters (95% CI, 0.17 to 0.44) with lower-dose dupilumab and 0.39 liters (95% CI, 0.26 to 0.52) with higher-dose dupilumab.

ADDITIONAL SECONDARY OUTCOMES

The percentage change from baseline to week 12 in the FEV_1 before bronchodilator use was greater with dupilumab than with placebo. The difference as compared with matched placebo was 9.2 percentage points (95% CI, 5.5 to 12.9) with lower-dose dupilumab and 9.4 percentage points (95% CI, 5.7 to 13.1) with higher-dose dupilumab (P<0.001 for higher-dose dupilumab vs. matched placebo) (Table S3 in the Supplementary Appendix).

ACQ-5 scores were lower (indicating better asthma control) with dupilumab than with placebo as early as week 2, and the effect was sustained over the 52-week intervention period (Table S6 in the Supplementary Appendix). Similarly, dupilumab showed benefits over matched placebo with respect to the global score on the Asthma Quality of Life Questionnaire (standardized),[17] morning and evening asthma symptom scores, and morning and evening peak expiratory flow at weeks 24 and 52 (Table S6 in the Supplementary Appendix).

The rate of severe exacerbation events resulting in hospitalization or an emergency department visit during the 52-week intervention period was 0.035 (95% CI, 0.025 to 0.048) in the combined dupilumab groups and 0.065 (95% CI, 0.047 to 0.090) in the combined placebo groups (Table S6 in the Supplementary Appendix). This produced a 46.8% lower rate with dupilumab than with placebo.

EXPLORATORY OUTCOMES

Patients who received dupilumab had greater reductions from baseline over the course of the intervention period in the FE_{NO} and levels of total IgE, periostin, eotaxin-3, and TARC than did patients who received matched placebo (Table S7 in the Supplementary Appendix). Transient elevations in blood eosinophil counts were observed in both dupilumab groups; the counts decreased to close to baseline levels by week 52 (Fig. S4 and Table S7 in the Supplementary Appendix). Transient increases were also observed

Table 2. Adverse Events That Emerged during the Intervention Period (Safety Population).*

Event	Placebo, 1.14 ml (N=313)	Dupilumab, 200 mg (N=631)	Placebo, 2.00 ml (N=321)	Dupilumab, 300 mg (N=632)	Combined Placebo (N=634)	Combined Dupilumab (N=1263)
	number of patients (percent)					
Any adverse event	257 (82.1)	508 (80.5)	270 (84.1)	515 (81.5)	527 (83.1)	1023 (81.0)
Any serious adverse event	26 (8.3)	49 (7.8)	27 (8.4)	55 (8.7)	53 (8.4)	104 (8.2)
Any adverse event leading to death†	3 (1.0)	1 (0.2)	0	4 (0.6)	3 (0.5)	5 (0.4)
Any adverse event leading to permanent discontinuation of the intervention	19 (6.1)	19 (3.0)	10 (3.1)	44 (7.0)	29 (4.6)	63 (5.0)
Adverse events occurring in ≥5% of patients in any group‡						
Viral upper respiratory tract infection	60 (19.2)	119 (18.9)	64 (19.9)	111 (17.6)	124 (19.6)	230 (18.2)
Upper respiratory tract infection	37 (11.8)	69 (10.9)	49 (15.3)	77 (12.2)	86 (13.6)	146 (11.6)
Bronchitis	47 (15.0)	73 (11.6)	42 (13.1)	71 (11.2)	89 (14.0)	144 (11.4)
Influenza	29 (9.3)	36 (5.7)	22 (6.9)	38 (6.0)	51 (8.0)	74 (5.9)
Sinusitis	27 (8.6)	36 (5.7)	29 (9.0)	26 (4.1)	56 (8.8)	62 (4.9)
Urinary tract infection	17 (5.4)	17 (2.7)	12 (3.7)	19 (3.0)	29 (4.6)	36 (2.9)
Headache	26 (8.3)	46 (7.3)	25 (7.8)	40 (6.3)	51 (8.0)	86 (6.8)
Rhinitis allergic	16 (5.1)	21 (3.3)	15 (4.7)	18 (2.8)	31 (4.9)	39 (3.1)
Back pain	16 (5.1)	30 (4.8)	7 (2.2)	25 (4.0)	23 (3.6)	55 (4.4)
Accidental overdose§	16 (5.1)	33 (5.2)	16 (5.0)	33 (5.2)	32 (5.0)	66 (5.2)
Injection-site reaction¶	17 (5.4)	96 (15.2)	33 (10.3)	116 (18.4)	50 (7.9)	212 (16.8)

* The safety population included all the patients who received at least one dose or part of a dose, and data were analyzed according to the intervention received. Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo.

† Causes of death in the dupilumab groups were pulmonary embolism, cardiopulmonary arrest in a patient with paraplegia due to spinal cord injury and multiple vertebral fractures due to osteoporosis, respiratory depression with cardiorespiratory arrest and ischemic encephalopathy, unwitnessed death attributed to myocardial infarction, and cardiac congestive failure with ventricular tachycardia in an obese patient with a history of obstructive sleep apnea. In the placebo groups, deaths were attributed to recurrence of thyroid cancer, postoperative pulmonary embolism after knee arthroplasty, and suicide.

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

§ Accidental overdose is coded in MedDRA as an overdose arising from a medication error (e.g., drug reconstitution error, incorrect dose, or incorrect dosing interval) and that was not associated with clinical symptoms.

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

in serum concentrations of eosinophil cationic protein in all intervention groups (Table S7 in the Supplementary Appendix). Eosinophilia is discussed further in the safety section below.

After a post hoc interaction analysis of biomarkers with the primary efficacy end points (Table S8 in the Supplementary Appendix), an analysis of the effect of dupilumab on exacerbations and the FEV_1 was conducted on the basis of both the baseline blood eosinophil count and the baseline $F_{E_{NO}}$ (Fig. S5 in the Supplementary Appendix). The greatest treatment benefit as compared with placebo was observed in patients with elevated type 2 biomarkers (both baseline blood eosinophil count of ≥150 per cubic millimeter and baseline $F_{E_{NO}}$ of ≥25 ppb).

SAFETY

The incidence of adverse events that emerged during the trial period was similar across intervention groups (81.0% in the combined dupilumab groups and 83.1% in the combined placebo groups) in the safety population (Table 2). The most frequent adverse event, occurring in 5% or

more of the patients and at higher rates among patients who received dupilumab than among those who received placebo, was injection-site reaction (in 15.2% of patients who received lower-dose dupilumab vs. 5.4% of those who received matched placebo, and in 18.4% of patients who received higher-dose dupilumab vs. 10.3% of those who received matched placebo), reported as a high-level term in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 20.0. Eosinophilia was reported as an adverse event that emerged during the trial period in 52 patients (4.1%) who received dupilumab versus 4 patients (0.6%) who received placebo; in 0.2% of the total patient population, these adverse events were accompanied by clinical symptoms. Increased blood eosinophil levels (Fig. S4 and Table S7 in the Supplementary Appendix) were associated with symptoms in 4 patients who received dupilumab, and two of these events were reported as serious adverse events (worsening of hypereosinophilia and chronic eosinophilic pneumonia; patient narratives are provided in the Supplementary Appendix). A total of eight adverse events of eosinophilia (seven in patients who received dupilumab and one in a patient who received placebo) resulted in permanent discontinuation of the assigned intervention.

Per the trial protocol, all cases of an eosinophil count of more than 3000 per cubic millimeter during the 52-week intervention period were reported as adverse events. This event occurred in 1.2% of the patients in the combined dupilumab groups and 0.3% of those in the combined placebo groups.

The rate of persistent antidrug antibody responses was 4.2% with lower-dose dupilumab and 2.1% with higher-dose dupilumab, as compared with 1.1% in the combined placebo groups, and had no meaningful effect on efficacy or safety. A numerical imbalance in serious adverse events that were categorized as cardiac disorders in the MedDRA system organ class was noted. After assessment by an expert panel whose members were unaware of the intervention assignments, no imbalances in rates of major adverse cardiac events were observed (Table S9 in the Supplementary Appendix), and none of the events were associated with increased eosinophil levels (Table S10 in the Supplementary Appendix). During the 52-week intervention period, there were no meaningful between-group differences in adverse events of conjunctivitis, observed in 2.3% of the patients receiving dupilumab and 3.3% of those receiving placebo.

Serious adverse events that emerged during the trial period were reported in 104 patients (8.2%) who received dupilumab and 53 patients (8.4%) who received placebo (Table 2). The most frequent serious adverse event was pneumonia, observed in 4 patients (0.3%) who received dupilumab and 2 patients (0.3%) who received placebo. A total of 5 patients (0.4%) who received dupilumab (1 patient received the lower dose, and 4 received the higher dose) and 3 patients (0.5%) who received placebo (all 3 were in the 1.14-ml group) had an adverse event leading to death. All deaths were considered by the investigator to be unrelated to the intervention (detailed narratives are provided in the Supplementary Appendix).

DISCUSSION

The annualized rate of severe asthma exacerbations was significantly lower with either dose of dupilumab than with matched placebo in the intention-to-treat population, with greater treatment effects observed with increasing baseline levels of blood eosinophils and $F_{E_{NO}}$. The rate of the most severe asthma exacerbations, those leading to hospitalization or emergency department visits, was also significantly lower with dupilumab than with placebo. Assessment of the FEV_1 and asthma control over time showed that dupilumab efficacy was rapid, with significant differences versus placebo seen at the first evaluation at week 2 and maintained throughout the 52-week intervention period for both dose regimens. In the overall population, increases in the FEV_1 of 0.32 to 0.34 liters were observed at week 12, with even larger increases in patients with a baseline blood eosinophil count of 300 or more per cubic millimeter and in those with a baseline $F_{E_{NO}}$ of 25 ppb or more.

Furthermore, an analysis of the postbronchodilator FEV_1 slope showed a loss of lung function in patients who received placebo and no loss in those who received dupilumab, findings that suggest a potential effect of dupilumab on airway remodeling. The slope analysis showed that patients who received placebo lost, on average, ap-

proximately 40 ml annually, which is consistent with data from other cohorts of patients with asthma.[19]

The results of this trial confirm that interleukin-4 and interleukin-13 are key proximal drivers of type 2 inflammation in asthma. Dupilumab significantly reduced the $F_{E_{NO}}$, in addition to other biomarkers of systemic type 2 inflammation such as IgE, confirming its biologic activity on airway inflammation. A higher baseline $F_{E_{NO}}$ was also predictive of greater response to dupilumab with respect to both exacerbations and the FEV_1, findings that suggest the importance of other biomarkers of type 2 inflammation beyond blood eosinophils. The mechanism of action of dupilumab, with dual blockade of interleukin-4 and interleukin-13 signaling, may explain why dupilumab had a significant treatment effect in a broad patient population with a type 2 phenotype, as compared with the targeted use of anti–interleukin-5 agents in populations with eosinophilia. In the accompanying trial, LIBERTY ASTHMA VENTURE, add-on therapy with dupilumab significantly reduced the use of oral glucocorticoids, while simultaneously reducing severe exacerbations and improving lung function (FEV_1), in patients with glucocorticoid-dependent severe asthma, irrespective of baseline blood eosinophil count.[14]

In our trial, patients who received dupilumab had a greater mean transient increase from baseline in blood eosinophil counts than did patients who received placebo. Per trial protocol, all cases of eosinophil counts of more than 3000 per cubic millimeter during the intervention period were to be reported as adverse events in this trial. Most of the observed elevations in eosinophil counts were laboratory findings without clinical consequences or associated adverse events. The increase in blood eosinophil counts is consistent with the hypothesis that dupilumab blocks interleukin-4 and interleukin-13 function in eosinophil survival, activation, and recruitment to tissues but not egress from bone marrow, which is influenced by interleukin-5. As a result, it has been speculated that initial treatment with dupilumab may result in a transient increase in circulating blood eosinophil counts.[20] No meaningful differences in adverse events of conjunctivitis were observed between the dupilumab and placebo groups, in contrast to the findings of studies of dupilumab involving patients with atopic dermatitis.[10-12]

In conclusion, we found that dupilumab effectively treated patients with moderate-to-severe asthma, providing a significant reduction in the rate of severe exacerbations, rapid and sustained improvement in lung function and asthma control, and symptom relief. The most robust results were observed in patients with elevated type 2 immune characteristics, including eosinophil counts and $F_{E_{NO}}$.

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APPENDIX

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