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Dupilumab in Persistent Asthma with Elevated Eosinophil Levels

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ABSTRACT

BACKGROUND

Moderate-to-severe asthma remains poorly treated. We evaluated the efficacy and safety of dupilumab (SAR231893/REGN668), a fully human monoclonal antibody to the alpha subunit of the interleukin-4 receptor, in patients with persistent, moderate-to-severe asthma and elevated eosinophil levels.

METHODS

We enrolled patients with persistent, moderate-to-severe asthma and a blood eosinophil count of at least 300 cells per microliter or a sputum eosinophil level of at least 3% who used medium-dose to high-dose inhaled glucocorticoids plus long-acting beta-agonists (LABAs). We administered dupilumab (300 mg) or placebo subcutaneously once weekly. Patients were instructed to discontinue LABAs at week 4 and to taper and discontinue inhaled glucocorticoids during weeks 6 through 9. Patients received the study drug for 12 weeks or until a protocol-defined asthma exacerbation occurred. The primary end point was the occurrence of an asthma exacerbation; secondary end points included a range of measures of asthma control. Effects on various type 2 helper T-cell (Th2)–associated biomarkers and safety and tolerability were also evaluated.

RESULTS

A total of 52 patients were assigned to the dupilumab group, and 52 patients were assigned to the placebo group. Baseline characteristics were similar in the two groups. Three patients had an asthma exacerbation with dupilumab (6%) versus 23 with placebo (44%), corresponding to an 87% reduction with dupilumab (odds ratio, 0.08; 95% confidence interval, 0.02 to 0.28; P<0.001). Significant improvements were observed for most measures of lung function and asthma control. Dupilumab reduced biomarkers associated with Th2-driven inflammation. Injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo.

CONCLUSIONS

In patients with persistent, moderate-to-severe asthma and elevated eosinophil levels who used inhaled glucocorticoids and LABAs, dupilumab therapy, as compared with placebo, was associated with fewer asthma exacerbations when LABAs and inhaled glucocorticoids were withdrawn, with improved lung function and reduced levels of Th2-associated inflammatory markers. (Funded by Sanofi and Regeneron Pharmaceuticals; ClinicalTrials.gov number, NCT01312961.)

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Recent estimates suggest that 24.6 million people in the United States, or 8.2% of the population, have received a diagnosis of asthma.[1] Despite therapy with inhaled glucocorticoids and long-acting beta-agonists (LABAs), the disease is not adequately controlled in 10 to 20% of patients[2]; these patients are at risk for poor clinical outcomes, and the cost of their care contributes substantially to the economic burden of asthma.[3-5] The mechanisms underlying this inadequate control remain poorly understood.

The clinical syndrome of persistent, moderate-to-severe asthma is increasingly recognized as comprising various phenotypes.[6] Data indicate that inflammatory processes associated with type 2 helper T-cell (Th2) immunity are present in approximately half the population with asthma.[7] For example, clinical trials of antibodies to Th2-associated cytokines consistently show increased efficacy in participants with elevated eosinophil levels or other markers of Th2-pathway activation.[8-14] These cytokines — specifically, interleukin-4 and interleukin-13 — are implicated in asthma and atopic diseases; they signal through two different but overlapping receptors, each containing an alpha subunit of the interleukin-4 receptor.[15-18] The type I receptor, activated only by interleukin-4, is located predominantly on lymphocytes and controls Th2-cell differentiation. The type II receptor, activated by interleukin-4 and interleukin-13, is expressed widely across resident and myeloid cells.[19] Thus, antibodies targeting interleukin-4 receptor α could potentially inhibit downstream pathways engaged by both cytokines.

Dupilumab (SAR231893/REGN668), a fully human monoclonal antibody to the interleukin-4 receptor α subunit that inhibits both interleukin-4 and interleukin-13 signaling, is being evaluated for the treatment of diseases mediated by Th2 pathways. The objective of this study was to assess the efficacy and safety of dupilumab in adults with persistent, moderate-to-severe asthma and elevated eosinophil levels.

METHODS

STUDY DESIGN AND OVERSIGHT

This randomized, double-blind, placebo-controlled, parallel-group phase 2A study was conducted at 28 sites in the United States from March 2011 through October 2012. A 2-week screening period was followed by a 12-week intervention period and an 8-week follow-up period (Fig. 1A).

The protocol (available with the full text of this article at NEJM.org) was developed by the sponsors (Sanofi and Regeneron Pharmaceuticals), with guidance from the first author. Data were collected by the investigators and analyzed by the sponsors. Although the authors were assisted by an independent medical writer paid by the sponsors, the first draft of the manuscript was written by the first author, with input from all other authors and the sponsors. The first and last authors made the decision to submit the manuscript for publication. The academic author and the authors who are employees of the sponsors vouch for the accuracy and completeness of the data, the statistical analysis, and the fidelity of the study to the protocol. During the study, the investigators, participating institutions, and sponsors agreed to maintain data confidentiality. The protocol was approved by the institutional review board of each study site or by a central institutional review board. All patients provided written informed consent.

PATIENTS

Eligible patients were 18 to 65 years old and had persistent, moderate-to-severe asthma, an elevated blood eosinophil count (≥300 cells per microliter) or an elevated sputum eosinophil level (≥3%) at screening, and symptoms that were not well controlled with medium-dose to high-dose inhaled glucocorticoids plus LABAs (fluticasone [≥250 μg] and salmeterol [50 μg] twice daily or the equivalent). Details on sputum induction and analysis are provided in the Assessment Procedures section in the Supplementary Appendix (available at NEJM.org).

A diagnosis of asthma for at least 12 months was substantiated by the reversibility of the forced expiratory volume in 1 second (FEV_1) during screening or earlier or by a positive methacholine challenge within 12 months before screening. Additional inclusion criteria were an FEV_1 that was 50% or more of the predicted value during screening and at randomization, a score on the Asthma Control Questionnaire (five-question version, ACQ5)[20] of 1.5 to 3.0 at screening (scores range from 0 to 6, with lower scores indicating better control of asthma and with 0.5 as the minimal clinically important difference between

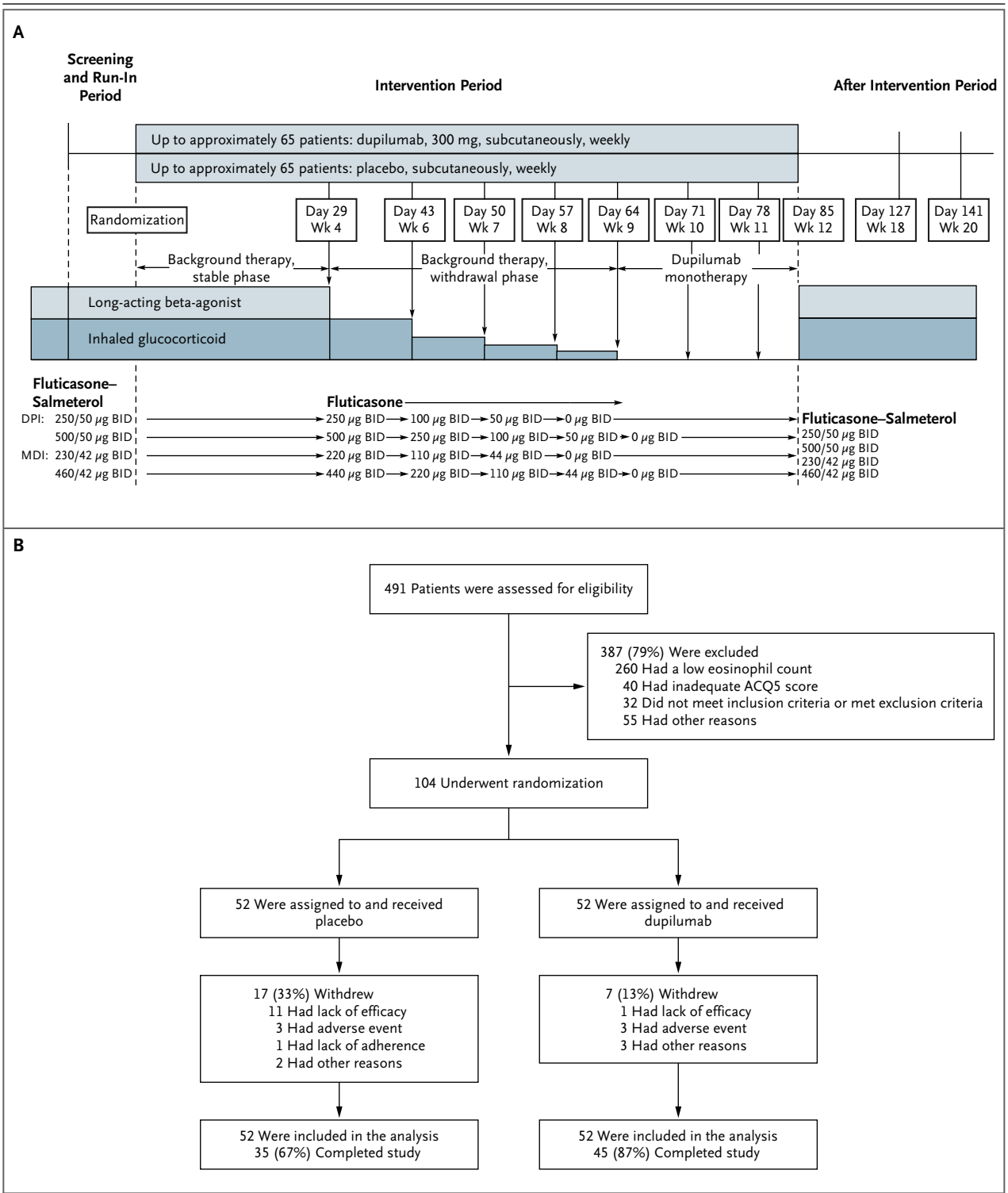

Figure 1. Study Design and Numbers of Patients Enrolled and Included in the Analysis.

Panel A shows the study design, and Panel B the numbers of patients who were assessed, randomly assigned to a study group, and included in the analysis. BID denotes twice daily, DPI dry-powder inhalation, and MDI metered-dose inhalation.

scores), and at least one asthma exacerbation within 2 years before screening (as indicated by treatment with ≥1 systemic glucocorticoid burst, in-patient hospitalization, or an emergency department visit for worsening asthma). For details, see the Study Inclusion and Exclusion Criteria section in the Supplementary Appendix.

STUDY INTERVENTIONS

Patients were randomly assigned in a 1:1 ratio by means of a centralized system to receive once-weekly subcutaneous injections of dupilumab (300 mg) or placebo for 12 weeks. Injections were administered by investigators or other site personnel who were unaware of the study-group assignments. In addition, patients received fluticasone (250 or 500 μg) and salmeterol (50 μg) twice daily (on the basis of the pretrial doses of inhaled glucocorticoids and LABAs) for 4 weeks. Patients were instructed to discontinue LABAs at week 4 and to taper and discontinue inhaled glucocorticoids during weeks 6 through 9. This approach enabled us to observe the effects of dupilumab when added to background therapy, after LABA discontinuation, during the tapering of inhaled glucocorticoids, and as monotherapy.

Patients received the study drug for 12 weeks or until a protocol-defined asthma exacerbation occurred. For the purposes of this medication-withdrawal study, an exacerbation was defined as the occurrence of any one of the following: a reduction of 30% or more in morning peak expiratory flow (PEF) from baseline on 2 consecutive days, at least six additional reliever inhalations of albuterol or levalbuterol in a 24-hour period relative to baseline on 2 consecutive days, or an exacerbation of asthma requiring systemic glucocorticoid treatment, an increase in inhaled glucocorticoids of at least four times the most recent dose, or hospitalization for asthma, as determined by the investigator.

OUTCOMES

The primary efficacy end point was the occurrence of an asthma exacerbation, as previously defined, during the 12-week intervention period. Secondary end points were the time to an asthma exacerbation and the change from baseline at each visit and at week 12 in FEV_1, morning and evening PEF, ACQ5 score, morning and evening asthma-symptom scores (ranging from 0 to 4, with higher scores indicating more severe symptoms), nocturnal awakenings, and the number of albuterol or levalbuterol inhalations per day. All outcomes except for FEV_1 were recorded in an electronic diary and used for the assessment of lower-airway symptoms. Participants completed the 22-item Sinonasal Outcome Test (SNOT-22 [scores range from 0 to 110, with higher scores indicating poorer outcomes and with 8.9 as the minimal clinically important difference between scores])[21] at baseline and at the end of the intervention period (week 12). Details are provided in the Assessment Procedures section and Table S1 in the Supplementary Appendix.

Pharmacodynamic measurements, including Th2-associated biomarkers, were assessed at multiple time points. These were the fraction of exhaled nitric oxide (FE_{NO}), serum biomarkers (thymus and activation-regulated chemokine [TARC, or CCL17], IgE, YKL-40, and carcinoembryonic antigen [CEA]), plasma eotaxin-3 (CCL26), and peripheral-blood eosinophil levels. Details are provided in the Assessment Procedures section in the Supplementary Appendix.

Safety and tolerability were evaluated on the basis of the incidence of adverse events and serious adverse events, as well as vital signs and findings on physical examination, clinical laboratory testing, and 12-lead electrocardiography (ECG).

STATISTICAL ANALYSIS

Efficacy analyses were performed in the intention-to-treat population, defined as all randomly assigned patients who received at least one dose of the study drug. Approximately 50 patients per group were needed to detect an absolute difference of 30 percentage points in asthma exacerbations between the two groups, with 80% power (two-tailed alpha level of 0.05) and an assumed 10% dropout rate.

For the primary end point, a logistic-regression model was used to compare the two study groups, with study drug and stratification factor (prior dose of inhaled glucocorticoids and LABAs) included as covariates. The secondary end point of the time to an asthma exacerbation was analyzed with the use of a log-rank test for comparison of survival distributions between groups. For other secondary end points (except the SNOT-22 score), the change from baseline was evaluated with the use of a mixed-effects model with repeated measures. The model included change from baseline

values up to week 12 as response variables and included factors (fixed effects) for study drug, stratification factor, visit, interaction between study drug and visit, baseline value, and interaction between baseline value and visit. Statistical inferences on study-drug comparisons for changes from baseline at week 12 were derived from the mixed-effects model. No imputations for missing data were performed. The change from baseline in the SNOT-22 score was analyzed with the use of an analysis of covariance (ANCOVA), with measurements at the end of the intervention period used to impute missing data. Pharmacodynamic effects were evaluated with the use of mixed-effects models with repeated measures in a post hoc fashion. No adjustments were made for multiple comparisons because there was only one primary end point and analysis.

Descriptive statistics were used for demographic and clinical characteristics and for safety variables, including adverse events, vital signs, and findings on physical examination, clinical laboratory testing, and ECG.

Plots of secondary and pharmacodynamic variables are presented as the mean (±SE) change or percent change from baseline over time. Comparisons of treatment effects from the mixed-effects model with repeated measures are based on the least-square mean change (95% confidence intervals) from baseline at week 12.

RESULTS

PATIENTS

A total of 104 patients (from 491 screened) underwent randomization, with 52 assigned to each study group (Fig. 1B). Three patients qualified only on the basis of elevated sputum eosinophil levels, and the remainder were eligible on the basis of elevated blood eosinophil levels. All randomly assigned patients received at least one dose of the study drug and were therefore included in the intention-to-treat population.

Demographic and clinical characteristics were similar in the two groups (Table 1). The intervention period was completed by 87% of patients in the dupilumab group and 67% of patients in the placebo group (Fig. 1B). The most common cause of discontinuation of the study drug was lack of efficacy, which was more frequent with placebo (11 patients, 21%) than with dupilumab (1 patient, 2%).

PRIMARY END POINT

Asthma exacerbations occurred in 26 patients: 3 receiving dupilumab (6%) and 23 receiving placebo (44%) (odds ratio with dupilumab, 0.08; 95% confidence interval [CI], 0.02 to 0.28; P<0.001) (Table 2 and Fig. 2A). No patients were hospitalized for asthma exacerbations. The most frequent events qualifying as an asthma exacerbation were a reduction in morning PEF and increased use of reliever medication, each reported in 2% and 19% of patients in the dupilumab and placebo groups, respectively (Table 2).

SECONDARY END POINTS

The time to an asthma exacerbation was longer (Fig. 2B) and the risk of exacerbation was reduced with dupilumab as compared with placebo (hazard ratio, 0.10; 95% CI, 0.03 to 0.34; P<0.001). For all secondary end points, week-12 measurements favored dupilumab and the between-group differences were significant except for evening PEF, nocturnal awakenings, and some SNOT-22 items (Table 2, and Table S2 in the Supplementary Appendix).

Lung Function over Time

Dupilumab was associated with a significant increase from baseline in percent of predicted FEV_1 and actual FEV_1 at week 2, which was maintained through week 12 (Fig. 2C, and Table S3 in the Supplementary Appendix) despite discontinuation of LABAs and inhaled glucocorticoids, with a small decrease in FEV_1 at week 5 coinciding with discontinuation of LABAs. Similar improvements were observed in morning PEF with dupilumab, but the improvement in evening PEF was smaller (Fig. S1 in the Supplementary Appendix).

Asthma Symptoms and Beta-Agonist Use over Time

The ACQ5 score was improved in both study groups at week 1 (Fig. S2 in the Supplementary Appendix). Subsequently, the ACQ5 score in the dupilumab group continued to improve, whereas the placebo effect stabilized, with a significant between-group difference by week 3 (Table S3 in the Supplementary Appendix) that was maintained through week 12.

Morning asthma-symptom scores increased from baseline to week 12 with placebo. With dupilumab, there was an initial decrease, with scores remaining below the baseline score through week 12 (Fig. S3A and S3B in the Supplementary

Table 1. Baseline Demographic and Clinical Characteristics of the Participants.*

Characteristic	Placebo (N=52)	Dupilumab (N=52)
Age — yr	41.6±13.1	37.8±13.2
Male sex — no. (%)	26 (50)	26 (50)
Race — no. (%)†		
White	38 (73)	45 (87)
Black	9 (17)	5 (10)
Asian	3 (6)	1 (2)
Other	2 (4)	1 (2)
Body-mass index‡		
Mean	31.7±7.0	31.3±8.0
≥30 — no. (%)	25 (48)	24 (46)
Duration of asthma — yr	26.9±14.8	24.2±12.6
No. of asthma exacerbations in previous 2 yr	1.4±1.3	1.4±1.0
Combination therapy with inhaled glucocorticoids and LABAs — no. (%)§		
High dose	41 (79)	42 (81)
Medium dose	11 (21)	10 (19)
Blood eosinophils — $\times 10^{-9}$/liter	0.47±0.21	0.55±0.19
FEV_1		
Value — liters	2.54±0.66	2.47±0.65
Percent of predicted value	72.0±12.7	72.0±12.6
PEF — liters/min		
Morning	406.9±110.7	393.0±101.1
Evening	416.6±116.8	414.6±102.3
ACQ5 score¶	2.1±0.5	2.1±0.5
Asthma-symptom score‖		
Morning	0.7±0.6	0.8±0.8
Evening	1.1±0.7	0.9±0.7
No. of nocturnal awakenings per day	0.2±0.5	0.4±0.8
SNOT-22 score**	26.2±15.6	30.9±14.8
No. of inhalations of albuterol or levalbuterol per 24-hr period	2.0±1.8	2.2±2.4
FE_{NO} — ppb	35.0±27.1	37.6±28.1
TARC — pg/ml	470.5±204.7	496.1±342.4
Eotaxin-3 — pg/ml	117.3±349.2	75.4±44.0
IgE — IU/ml	694.7±1837.8	657.7±1482.3

* Plus–minus values are means ±SD. There were no significant between-group differences at baseline with the exception of the blood eosinophil level (P=0.04). FE_{NO} denotes fraction of exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, LABAs long-acting beta-agonists, PEF peak expiratory flow, and TARC thymus and activation-regulated chemokine.
† Race was self-reported.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ High-dose combination therapy was defined as fluticasone (≥500 μg) and salmeterol (50 μg) twice daily or the equivalent. Medium-dose combination therapy was defined as fluticasone (250–499 μg) and salmeterol (50 μg) twice daily or the equivalent.
¶ Scores on the Asthma Control Questionnaire (five-question version, ACQ5) range from 0 to 6, with lower scores indicating better control of asthma and with 0.5 as the minimal clinically important difference between scores.
‖ Asthma-symptom scores range from 0 to 4, with higher scores indicating more severe symptoms.
** Scores on the 22-item Sinonasal Outcome Test (SNOT-22) range from 0 to 110, with higher scores indicating poorer outcomes and with 8.9 as the minimal clinically important difference between scores.

Table 2. Primary and Secondary Efficacy Outcomes.*

Outcome	Dupilumab (N=52)	Placebo (N=52)	Difference, Dupilumab vs. Placebo (95% CI)†	P Value
Primary end point: occurrence of asthma exacerbation during 12-wk intervention period — no. (%)	3 (6)	23 (44)	0.08 (0.02 to 0.28)	<0.001
≥30% Reduction in morning PEF from baseline on 2 consecutive days	1 (2)	10 (19)‡		
≥6 Additional inhalations of albuterol or levalbuterol in a 24-hr period relative to baseline on 2 consecutive days	1 (2)	10 (19)		
Systemic glucocorticoid treatment	1 (2)	5 (10)		
Dose of inhaled glucocorticoids ≥4 times the previous dose	0	3 (6)		
Hospitalization for asthma	0	0		
Secondary end points				
Kaplan–Meier estimate for probability of asthma exacerbation at 12 wk (95% CI)	0.06 (0.00 to 0.12)	0.46 (0.32 to 0.60)	0.10 (0.03 to 0.34)	<0.001
Change in FEV_1, baseline to wk 12 — liters	0.05±0.06	−0.22±0.06	0.27 (0.11 to 0.42)	<0.001
Change in morning PEF, baseline to wk 12 — liters/min	13.9±8.8§	−20.7±9.1	34.6 (10.6 to 58.5)	0.005
Change in evening PEF, baseline to wk 12 — liters/min	4.3±8.5	−18.4±8.9§	22.7 (−0.7 to 46.0)	0.06
Change in ACQ5 score, baseline to wk 12	−1.00±0.16	−0.27±0.16	−0.73 (−1.15 to −0.30)	0.001
Change in morning asthma-symptom score, baseline to wk 12	−0.4±0.1	0.3±0.1	−0.7 (−0.9 to −0.4)	<0.001
Change in evening asthma-symptom score, baseline to wk 12	−0.6±0.1	0.1±0.1	−0.7 (−0.9 to −0.4)	<0.001
Change in no. of nocturnal awakenings, baseline to wk 12	−0.2±0.1	0.1±0.1	−0.2 (−0.5 to 0.0)	0.05
Change in SNOT-22 score, baseline to wk 12	−8.26±2.20¶	0.23±2.15§	−8.49 (−13.96 to −3.03)	0.003
Change in no. of inhalations of albuterol or levalbuterol in 24-hr period, baseline to wk 12	−1.3±0.3¶	0.7±0.3	−2.0 (−2.9 to −1.2)	<0.001

* Plus–minus values are least-square means ±SD. CI denotes confidence interval.
† For the proportion of patients with an asthma exacerbation, the difference is expressed as the odds ratio with dupilumab. For the Kaplan–Meier estimate, the difference is expressed as the hazard ratio with dupilumab. For all other outcomes, the differences are absolute differences (the least-square mean value in the dupilumab group minus the mean value in the placebo group).
‡ Four patients in the placebo group met the criteria for reduced PEF and initiation of systemic glucocorticoid treatment, and one patient in the placebo group met the criteria for reduced PEF and additional inhalations of albuterol or levalbuterol.
§ These values reflect data from 51 patients with at least one postbaseline assessment.
¶ These values reflect data from 50 patients with at least one postbaseline assessment.

Appendix). A similar pattern (but with greater variability) was observed for evening asthma-symptom scores (Fig. S3C and S3D in the Supplementary Appendix).

Nocturnal awakenings were stable with placebo through week 6, then increased between weeks 6 and 12. In contrast, nocturnal awakenings decreased with dupilumab by week 1, and the reduction was maintained and awakenings remained less frequent versus baseline through week 12 (Fig. 2D).

Changes in the use of albuterol or levalbuterol (Fig. S4 in the Supplementary Appendix) were similar to those in other secondary end points: an initial decrease, followed by a return toward baseline, with placebo and an initial decrease that was maintained over time with dupilumab.

PHARMACODYNAMIC AND TH2-ASSOCIATED BIOMARKERS

With placebo, FE_{NO} values remained stable through week 8, followed by an increase at week 12 that coincided with discontinuation of inhaled glucocorticoids (Fig. 3A). With dupilumab, FE_{NO} values were markedly decreased at week 4 and remained below baseline values through week 12, despite discontinuation of inhaled glucocorticoids. Improvement in FEV_1 correlated with the reduced

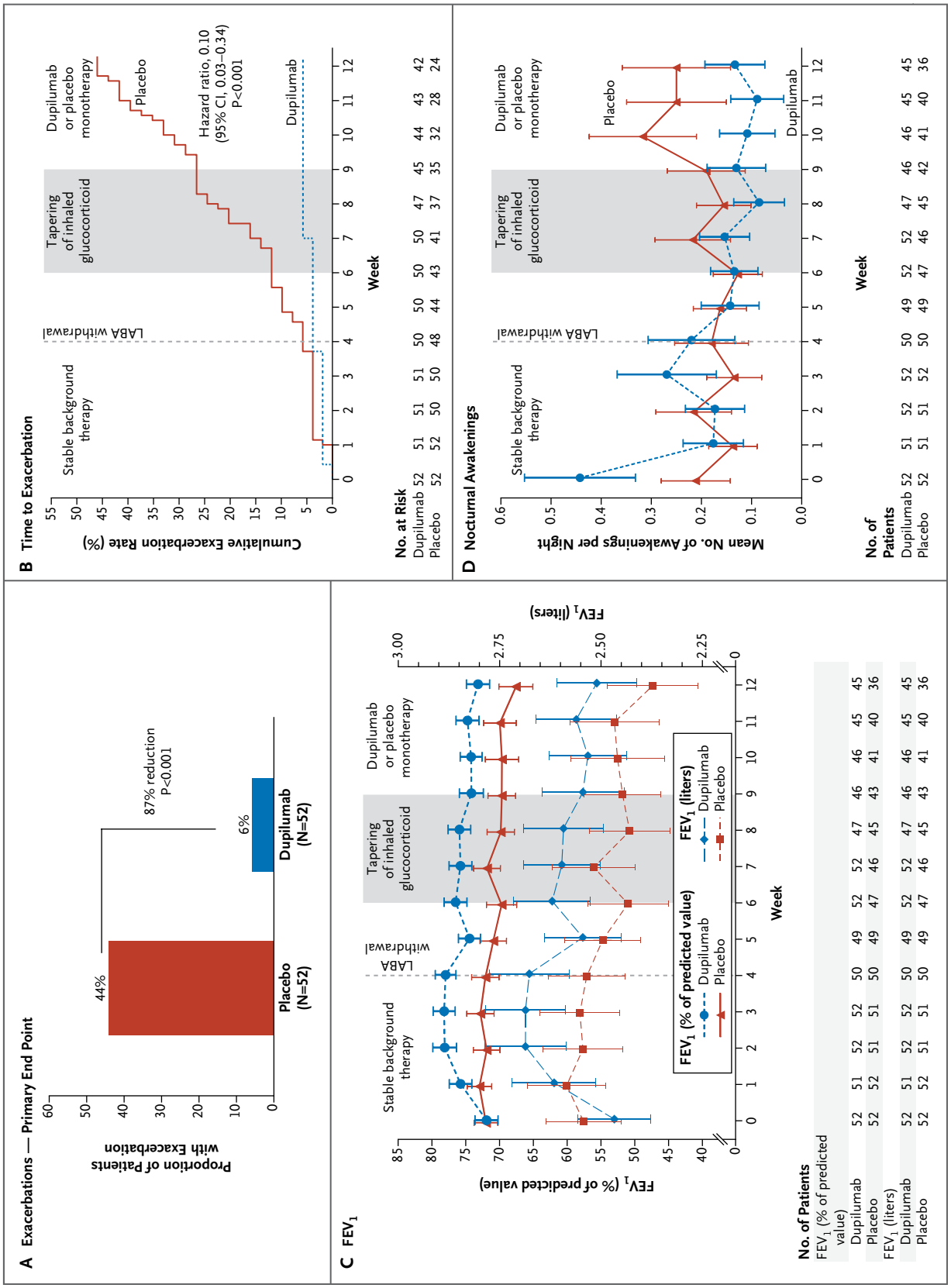

Figure 2 (facing page). Primary and Key Secondary Efficacy End Points (Intention-to-Treat Population).

As compared with placebo, dupilumab therapy was associated with an 87% relative reduction in the proportion of patients with an asthma exacerbation during the 12-week intervention period (the primary end point) (odds ratio, 0.08; 95% confidence interval [CI], 0.02 to 0.28; P<0.001) (Panel A) and a significantly longer time to an asthma exacerbation (hazard ratio, 0.10; 95% CI, 0.03 to 0.34; P<0.001) (Panel B). The forced expiratory volume in 1 second (FEV_1) and the percent of predicted FEV_1 were higher with dupilumab than with placebo over the duration of the study (Panel C), and the number of nocturnal awakenings was lower (Panel D). The I bars indicate standard errors.

Fe_{NO} value at week 12 (Pearson's r=−0.408, P=0.009); correlations of other biomarkers with FEV_1 were not significant (Table S4 in the Supplementary Appendix).

Levels of TARC, eotaxin-3, and IgE (Fig. 3B, 3C, and 3D) remained unchanged with placebo. In contrast, with dupilumab, TARC and eotaxin-3 levels were decreased at week 1 and remained lower than baseline values through week 12. With dupilumab, the IgE level was also lower than the baseline value at week 4, diverging from the value with placebo (Fig. 3D), and was further decreased at week 12. Changes from baseline at week 12 for Fe_{NO}, TARC, eotaxin-3, and IgE levels all favored dupilumab (P<0.001 for all comparisons) (Table S5 and Fig. S5 through S8 in the Supplementary Appendix). No significant differences from baseline or between study groups were observed in YKL-40 or CEA levels (Fig. S9 and S10 in the Supplementary Appendix).

Peripheral-blood eosinophil levels were unchanged with placebo throughout the intervention period. With dupilumab, the majority of patients had little or no change in eosinophil levels; 4 patients had large increases, but no specific trend toward improvement in lung function was observed in these patients (Fig. S11 and Table S6 in the Supplementary Appendix). Results for the 15 patients for whom data on sputum eosinophil levels were available are shown in Table S7 in the Supplementary Appendix.

SAFETY

Adverse events were reported by a similar proportion of patients in the two groups (77% in the placebo group and 81% in the dupilumab group) (Table 3). The events were generally nonspecific and of mild-to-moderate intensity. Four patients had a serious adverse event: three in the placebo group (gunshot, with pneumothorax; ankle fracture; and asthma exacerbation, with pneumonia) and one in the dupilumab group (worsening of bipolar disorder); no serious adverse events were considered by the investigator to be related to the study drug. There were no deaths.

Three adverse events in the placebo group led to discontinuation of the study drug (psoriasis, asthma exacerbation, and an upper respiratory tract infection), as did three adverse events in the dupilumab group (worsening of bipolar disorder, angioedema, and an increase in asthma symptoms). The adverse event reported as angioedema and deemed to be related to the study drug occurred in a 42-year-old woman after receipt of the ninth dose of the study drug. It was manifested as a progressive papular rash, urticaria, and edema at, and distant to, the injection site; it persisted for 1 week and resolved after nonurgent symptomatic treatment (prednisone and diphenhydramine) and early discontinuation of the study drug. This adverse event was preceded by milder rashes at the injection site after receipt of the first and sixth doses of the study drug.

Among the most common adverse events occurring in at least three patients in either study group (Table 3), injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo. No clinically significant changes in vital signs or findings on physical examination, clinical laboratory testing, or ECG were reported in either group.

DISCUSSION

Previous studies have suggested that the Th2 cytokines interleukin-4 and interleukin-13 have a role in asthma.[17,22,23] Data from our study of dupilumab support their pathogenic role in patients with persistent, moderate-to-severe asthma and elevated eosinophil levels. Our data and those from prior studies suggest that blocking both cytokines may be more effective than targeting either alone.[10,24] The efficacy of dupilumab was observed in patients treated with medium-dose to high-dose inhaled glucocorticoids (80% of patients used high-dose inhaled glucocorticoids) in combination with LABAs, a finding that suggests that in patients with residual airway inflammation, interleukin-4 and interleukin-13 are present

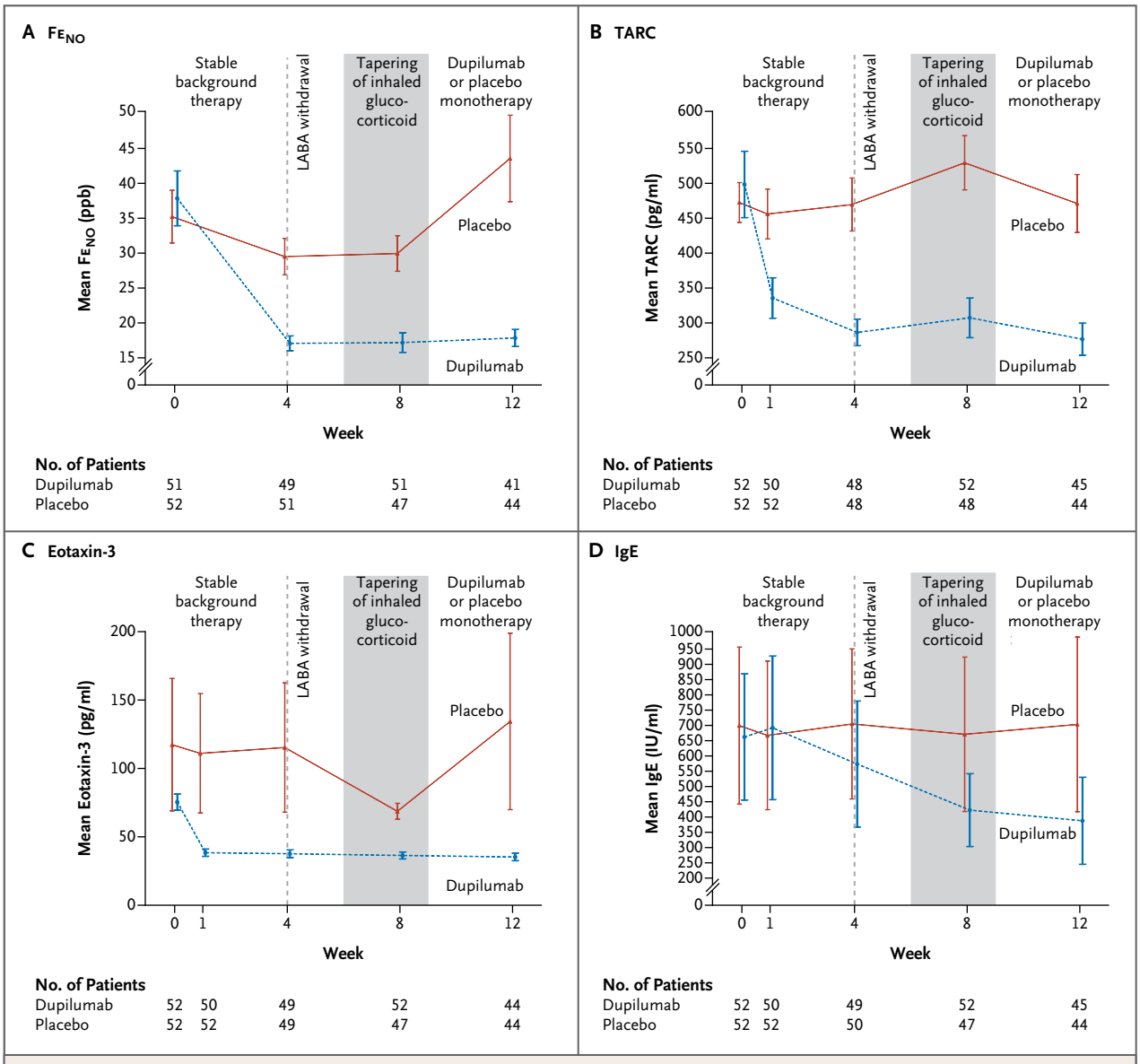

Figure 3. Values for Key Pharmacodynamic Markers over the Duration of the Study (Intention-to-Treat Population).

Shown are the fraction of exhaled nitric oxide (FE_{NO}) (Panel A) and levels of thymus and activation-regulated chemokine (TARC) (Panel B), eotaxin-3 (Panel C), and IgE (Panel D). The I bars indicate standard errors.

and contribute to disease despite glucocorticoid therapy.

Dupilumab reduced the proportion of patients with asthma-exacerbation events, as defined by our protocol, by 87% relative to placebo. Intriguingly, dupilumab showed substantial efficacy with regard to both objective and patient-reported end points even when added to inhaled glucocorticoids and LABAs, with efficacy maintained despite the discontinuation of background therapy. FEV_1 improved by more than 200 ml when dupilumab, as compared with placebo, was added to inhaled glucocorticoids and LABAs, an increase sustained during their tapering and discontinuation. This is especially notable because patients entering the study had an FEV_1 of approximately 70% of the predicted value and, despite background therapy, would not have been considered to have well-controlled asthma according to standard criteria (baseline ACQ5 score of 2.1). Rapid,

sustained improvements over the duration of the study were also observed in symptoms, beta-agonist use, and ACQ5 score. For the ACQ5 score, the between-group difference in the change from baseline was 0.73 points, which is greater than the 0.5-point change considered to be clinically significant.[20] Notably, the improvement in the ACQ5 score with dupilumab was accompanied by an improvement in the SNOT-22 total score at week 12, but this difference did not reach the level considered to be clinically significant.

Levels of the biomarkers FE_{NO}, serum IgE, eotaxin-3, and TARC decreased with dupilumab, confirming the biologic activity of the drug.[25,26] The degree of reduction in the FE_{NO} level corresponded with the improvement in FEV_1, a finding that suggests that the degree of inhibition of Th2 biologic activity is also relevant. There was no clear pattern of change in blood eosinophil levels with dupilumab. Future studies of dupilumab should include observations of eosinophil levels.

The magnitude and breadth of efficacy that we observed exceed those in other studies of Th2 cytokine inhibtion.[8-11,13,14] Our data contrast with those in studies of lebrikizumab and tralokinumab, both monoclonal antibodies targeting interleukin-13 without effects on interleukin-4.[11,14] Those agents improved lung function, but asthma symptoms, beta-agonist use, and quality of life were not affected, even with stratification according to status with respect to "Th2-like" inflammation. In addition, three studies evaluating monoclonal antibodies to the Th2 cytokine interleukin-5 in patients with eosinophilia showed reductions in asthma exacerbations and eosinophil levels, with little effect on lung function or symptoms.[8,12,13] Indeed, efficacy in the current study may exceed that shown in previous studies involving patients with Th2-associated phenotypes of asthma.

Injection-site reactions, nasopharyngitis, nausea, and headache occurred more frequently with dupilumab than with placebo, and a progressive papular rash, urticaria, and edema developed in 1 patient, leading to nonurgent symptomatic treatment and early discontinuation of dupilumab. Because only 52 patients received dupilumab in our study, the spectrum of potential adverse events is unknown; patients will continue to be monitored closely for such events.

In conclusion, our 12-week study showed that in a subpopulation of patients with persistent asthma, dupilumab therapy, as compared with placebo, was associated with fewer exacerbations induced by medication withdrawal; the benefit was primarily identified by changes in peak flow and beta-agonist use. The short study period and the definition used for exacerbation may not reflect real-world asthma exacerbations. Further studies are needed to confirm these observations and better define the target population, dosing regimen, and long-term efficacy and safety.

Table 3. Adverse Events.

Event	Placebo (N=52)	Dupilumab (N=52)
	no. of patients (%)	
Any adverse event	40 (77)	42 (81)
Any serious adverse event	3 (6)	1 (2)
Study discontinuation owing to adverse event	3 (6)	3 (6)
Death	0	0
Most common adverse events*		
Injection-site reactions†	5 (10)	15 (29)
Nasopharyngitis	2 (4)	7 (13)
Upper respiratory tract infection	9 (17)	7 (13)
Headache	3 (6)	6 (12)
Nausea	1 (2)	4 (8)
Arthropod bite	0	3 (6)
Muscle spasms	0	3 (6)
Nasal congestion	1 (2)	3 (6)
Rash	1 (2)	3 (6)
Viral upper respiratory tract infection	0	3 (6)
Urticaria	0	3 (6)
Sinusitis	5 (10)	1 (2)
Gastroenteritis, viral	3 (6)	0
Rhinitis, seasonal	3 (6)	0

* Shown are events that occurred in at least three patients in either study group, according to the preferred term in the *Medical Dictionary for Regulatory Activities*.

† This category includes events reported as pain, reaction, erythema, rash, hematoma, urticaria, dermatitis, inflammation, nodule, pruritus, or swelling at the injection site.

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