ORIGINAL ARTICLE

Dupilumab in Children with Uncontrolled Moderate-to-Severe Asthma

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ABSTRACT

BACKGROUND

Children with moderate-to-severe asthma continue to have disease complications despite the receipt of standard-of-care therapy. The monoclonal antibody dupilumab has been approved for the treatment of adults and adolescents with asthma as well as with other type 2 inflammatory diseases.

METHODS

In this 52-week phase 3, randomized, double-blind, placebo-controlled trial, we assigned 408 children between the ages of 6 and 11 years who had uncontrolled moderate-to-severe asthma to receive a subcutaneous injection of dupilumab (at a dose of 100 mg for those weighing ≤30 kg and 200 mg for those weighing >30 kg) or matched placebo every 2 weeks. All the children continued to receive a stable dose of standard background therapy. The primary end point was the annualized rate of severe asthma exacerbations. Secondary end points included the change from baseline in the percentage of predicted prebronchodilator forced expiratory volume in 1 second ($ppFEV_1$) at week 12 and in the score on the Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) at week 24. End points were evaluated in the two primary efficacy populations who had either a type 2 inflammatory asthma phenotype (≥150 blood eosinophils per cubic millimeter or a fraction of exhaled nitric oxide of ≥20 ppb at baseline) or a blood eosinophil count of at least 300 cells per cubic millimeter at baseline.

RESULTS

In patients with the type 2 inflammatory phenotype, the annualized rate of severe asthma exacerbations was 0.31 (95% confidence interval [CI], 0.22 to 0.42) with dupilumab and 0.75 (95% CI, 0.54 to 1.03) with placebo (relative risk reduction in the dupilumab group, 59.3%; 95% CI, 39.5 to 72.6; P<0.001). The mean (±SE) change from baseline in the $ppFEV_1$ was 10.5±1.0 percentage points with dupilumab and 5.3±1.4 percentage points with placebo (mean difference, 5.2 percentage points; 95% CI, 2.1 to 8.3; P<0.001). Dupilumab also resulted in significantly better asthma control than placebo (P<0.001). Similar results were observed in the patients with an eosinophil count of at least 300 cells per cubic millimeter at baseline. The incidence of serious adverse events was similar in the two groups.

CONCLUSIONS

Among children with uncontrolled moderate-to-severe asthma, those who received add-on dupilumab had fewer asthma exacerbations and better lung function and asthma control than those who received placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; Liberty Asthma VOYAGE ClinicalTrials.gov number, NCT02948959.)

Asthma affects 1 in 12 children in the United States.[1] Approximately 5 to 10% of all children with asthma have disease that is characterized as severe,[2,3] with increasing severity associated with substantial health care costs, caregiver burden, impaired quality of life, and loss of school days.[4-8] Children with moderate-to-severe asthma can have reduced lung function and are at increased risk for abnormal patterns of lung growth and decline, including an increased risk of chronic obstructive pulmonary disease (COPD) in adulthood.[9-13]

Type 2 inflammation is the predominant driver of asthma in children and is characterized by the release of signature cytokines interleukin-4, interleukin-5, and interleukin-13, which leads to the downstream activation of eosinophils, the production of IgE, and increased levels of fraction of exhaled nitric oxide (F_ENO) and mucus production.[14] To identify adolescent and adult patients with severe, uncontrolled asthma who may benefit from biologic therapies targeting type 2 inflammation, the Global Initiative for Asthma (GINA) recommends the use of an elevated peripheral-blood eosinophil count (≥150 cells per cubic millimeter), an elevated F_ENO (≥20 parts per billion [ppb]), or both as cutoff values.[15]

Dupilumab, a fully human monoclonal antibody, blocks the alpha subunit of the interleukin-4 receptor and inhibits signaling by interleukin-4 and interleukin-13.[16,17] It is approved for the treatment of adults and adolescents with asthma as well as other type 2 inflammatory diseases, including atopic dermatitis and chronic rhinosinusitis with nasal polyposis. We designed a multinational, randomized, placebo-controlled, phase 3 trial, Liberty Asthma VOYAGE (Evaluation of Dupilumab in Children with Uncontrolled Asthma), to assess the efficacy and safety of dupilumab in children between the ages of 6 and 11 years with moderate-to-severe asthma.

Methods

Trial Design and Oversight

Full details regarding the trial design are provided in Figure S1 and Section 2 in the Supplementary Appendix, available with the full text of this article at NEJM.org. The protocol (also available at NEJM.org) was developed by the sponsors, Sanofi and Regeneron Pharmaceuticals. Data were collected by the investigators and were analyzed by the sponsors according to a predefined statistical analysis plan.

A Quick Take is available at NEJM.org

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable regulatory requirements. An independent data and safety monitoring committee conducted blinded monitoring of patient safety data (as outlined in Section 3 in the Supplementary Appendix). The local institutional review board or ethics committee at each trial center oversaw the conduct and documentation of the trial. Parents or guardians of patients provided written informed consent. The children provided assent according to the standard practice for pediatric patients that had been approved by the ethics committee at each participating center.

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

Patients

Children between the ages of 6 and 11 years were eligible to participate if they had physician-diagnosed moderate-to-severe asthma according to GINA guidelines.[18] Patients completed a screening period of 4 weeks (±1 week) followed by randomization. At screening, patients were required to have at least a 3-month history of receiving either a medium-dose inhaled glucocorticoid in combination with a second controller or a high-dose inhaled glucocorticoid alone or in combination with a second controller at a dose that had been stable for at least 1 month before screening (Table S1). Additional key inclusion criteria included at least one severe exacerbation (defined as leading to the use of systemic glucocorticoids, hospitalization, or emergency department visit for worsening asthma) within the past year, a prebronchodilator forced expiratory volume in 1 second (FEV_1) of 95% or less of the predicted value at screening and baseline

visits, and FEV_1 reversibility of 10% or more. The enrollment of patients with a baseline blood eosinophil count of less than 150 cells per cubic millimeter was limited to 20% of the total population. A complete list of inclusion and exclusion criteria is provided in Section 3 of the Supplementary Appendix.

There were two primary efficacy populations: patients with the type 2 inflammatory asthma phenotype (defined as a blood eosinophil count of ≥150 cells per cubic millimeter or a FeNO of ≥20 ppb at baseline) and patients with a blood eosinophil count of at least 300 cells per cubic millimeter at baseline. The selection of these populations was based on efficacy findings in studies of dupilumab involving adults and adolescents with asthma,[19,20] which suggested that either the blood eosinophil count or FeNO could be used to identify patients with type 2 inflammatory asthma. Additional efficacy populations in the multiplicity-controlled testing hierarchy included patients with a baseline blood eosinophil count of at least 150 cells per cubic millimeter, those with a baseline FeNO of 20 ppb or more, and all the patients who had undergone randomization.

The safety population consisted of all the patients who had received at least one dose or part of a dose of dupilumab or placebo. The safety analysis was performed according to the intervention that the patients actually received.

TRIAL REGIMENS

Eligible patients were randomly assigned to receive subcutaneous dupilumab or volume-matched placebo every 2 weeks for 52 weeks. Patients with a body weight of 30 kg or less at randomization received 100 mg of dupilumab or matching placebo, and those with a body weight of more than 30 kg received 200 mg of dupilumab or matching placebo. Home administration of the trial regimen was permitted after week 12.

END POINTS

The primary end point was the annualized rate of severe asthma exacerbations during the 52-week treatment period. A severe asthma exacerbation was defined as a deterioration of asthma control leading to treatment with systemic glucocorticoids for at least 3 days, hospitalization, or an emergency department visit leading to the systemic administration of glucocorticoids. Two exacerbations within a 28-day period were considered to be a single exacerbation.

The key secondary end point was the change from baseline at week 12 in the percentage of predicted prebronchodilator FEV_1 ($ppFEV_1$). Additional multiplicity-controlled end points included the change from baseline to week 24 in asthma control (as assessed with the Asthma Control Questionnaire 7 Interviewer-Administered [ACQ-7-IA]) and the change from baseline to week 12 in the FeNO level (Table S2 in the Supplementary Appendix). ACQ-7-IA scores range from 0 (totally controlled asthma) to 6 (severely uncontrolled); a change of 0.5 is considered to be clinically important. Additional efficacy end points are presented in Section 3 in the Supplementary Appendix. Biomarkers in the dupilumab and placebo groups during the 52-week period were evaluated in prespecified and descriptive exploratory analyses.

STATISTICAL ANALYSIS

The trial was sufficiently powered to detect a reduction in asthma exacerbations in the two primary efficacy populations. The estimated sample size was based on the observed effect sizes for these populations in the phase 3 trial involving adults and adolescents.[19] We determined that a sample of approximately 345 and 255 patients would have approximately 94% and 96% power to detect a 54% and 60% relative reduction in the annualized rate of severe exacerbations in the two primary efficacy populations, respectively, assuming a randomization ratio of 2:1 and annualized rates of severe exacerbation of 0.7 and 0.8 in the placebo group, with a two-tailed significance level of 0.05. These calculations assumed an average exposure duration of 0.9 years and a dispersion measure of 1.5 for the negative binomial distribution assumed for the exacerbation count.

Data were analyzed in the intention-to-treat population according to the assigned intervention, regardless of whether the intervention was received. All analyses were prespecified unless specifically stated otherwise. The annualized rate of severe exacerbations was analyzed with the use of a negative binominal regression model that included the total number of events that were observed from randomization until week 52 or the last trial contact date (whichever occurred earlier) as the response variable and included as covariates the trial group, age, base-

line weight (≤30 kg or >30 kg), geographic region, baseline eosinophil level (<300 cells or ≥300 cells per cubic millimeter), baseline FeNO (<20 ppb or ≥20 ppb), baseline dose of inhaled glucocorticoid (medium or high), and the number of severe exacerbation events within 1 year before the initiation of the trial; the log-transformed standardized observation duration was included as an offset variable. The change from baseline in the prebronchodilator ppFEV$_1$ was analyzed with the use of a mixed-effects model with a repeated-measures approach, including trial group, baseline weight, geographic region, race or ethnic group, baseline eosinophil count, baseline FeNO, baseline dose of inhaled glucocorticoid, visit, treatment-by-visit interaction, baseline ppFEV$_1$, and a baseline-by-visit interaction term as covariates. Changes from baseline in biomarker levels are presented with the use of descriptive statistics unless otherwise specified.

To control the family-wise type I error for the statistical analyses of the primary and selected secondary efficacy end points, a step-down hierarchical testing procedure was applied at a two-sided significance level of 0.05. Two separate testing orders were prespecified and reflected regional differences in the dupilumab indication label for adults and adolescents with asthma (Table S2). Additional details regarding the statistical methods, including a description of how missing data were handled, are summarized in the Supplementary Appendix.

RESULTS

PATIENTS

A total of 408 patients underwent randomization: 273 to the dupilumab group and 135 to the placebo group (Table S6). In the dupilumab group, 3 patients did not receive the assigned intervention (Fig. S4). The demographic and clinical characteristics of the patients in the two groups were similar at baseline, and the treatment assignments were balanced between the two primary efficacy populations (Table 1 and Table S7). The median follow-up duration was 365 days.

PRIMARY END POINT

In the population with the type 2 inflammatory phenotype, the adjusted annualized rate of severe asthma exacerbations was 0.31 (95% confidence interval [CI], 0.22 to 0.42) in the dupilumab group and 0.75 (95% CI, 0.54 to 1.03) in the placebo group (relative risk reduction in the dupilumab group, 59.3%; 95% CI, 39.5 to 72.6; P<0.001) (Fig. 1A). Among the patients with at least 300 eosinophils per cubic millimeter at baseline, the adjusted annualized rate of severe asthma exacerbations was 0.24 (95% CI, 0.16 to 0.35) in the dupilumab group and 0.67 (95% CI, 0.47 to 0.95) in the placebo group (relative risk reduction, 64.7%; 95% CI, 43.8 to 77.8; P<0.001).

The relative reduction in the risk of severe exacerbations with dupilumab, as compared with placebo, was 61.0% (95% CI, 41.7 to 73.9) among the patients with at least 150 eosinophils per cubic millimeter at baseline, 61.6% (95% CI, 35.1 to 77.3) among those with a FeNO of at least 20 ppb at baseline, and 54.2% (95% CI, 32.9 to 68.7) among all the patients who had undergone randomization (Fig. 1A). Similar findings to those in the above-mentioned groups were observed in patients who were receiving high-dose inhaled glucocorticoids at baseline (Fig. S5).

ADDITIONAL EXACERBATION-RELATED END POINTS

The percentage of patients who had no exacerbations during the 52-week treatment period was 77.1% in the dupilumab group and 59.6% in the placebo group among the patients with the type 2 phenotype; among those with at least 300 eosinophils per cubic millimeter at baseline, the percentage was 79.0% and 58.3% in the two groups, respectively. Patients in the dupilumab group had a longer time until the first severe exacerbation than those in the placebo group, both among those with the type 2 phenotype (hazard ratio, 0.44; 95% CI, 0.29 to 0.67) and among those with at least 300 eosinophils per cubic millimeter at baseline (hazard ratio, 0.38; 95% CI, 0.23 to 0.63).

Patients in the dupilumab group also had a lower risk of loss of asthma control than those in the placebo group among the patients with the type 2 phenotype (hazard ratio, 0.69; 95% CI, 0.52 to 0.9) and among those with at least 300 eosinophils per cubic millimeter at baseline (hazard ratio, 0.66; 95% CI, 0.48 to 0.90) (Figs. S4 and S5). In the dupilumab group, the annualized number of treatment courses with systemic glucocorticoids was lower than that in the placebo group by 59.3% (95% CI, 39.1 to 72.8) among patients with the type 2 phenotype and

Table 1. Demographic and Clinical Characteristics of the Patients in the Two Primary Efficacy Populations at Baseline.*

Characteristic	Patients with Type 2 Inflammatory Phenotype		Patients with ≥300 Blood Eosinophils per mm³	
	Placebo (N=114)	Dupilumab (N=236)	Placebo (N=84)	Dupilumab (N=175)
Age — yr	9.0±1.6	8.9±1.6	9.0±1.5	8.9±1.6
Male sex — no. (%)	78 (68.4)	152 (64.4)	58 (69.0)	116 (66.3)
Race or ethnic group — no. (%)†				
White	102 (89.5)	208 (88.1)	75 (89.3)	151 (86.3)
Black	5 (4.4)	9 (3.8)	5 (6.0)	8 (4.6)
Asian	0	2 (0.8)	0	2 (1.1)
American Indian or Alaska Native	0	1 (0.4)	0	1 (0.6)
Other	7 (6.1)	16 (6.8)	4 (4.8)	13 (7.4)
Weight — kg	37.1±11.6	35.6±10.0	37.0±11.7	35.4±10.0
Use of high-dose inhaled glucocorticoid — no. (%)	50 (43.9)	102 (43.2)	41 (48.8)	74 (42.3)
No. of severe asthma exacerbations in past year	2.2±1.6	2.6±2.6	2.4±1.7	2.8±2.9
Asthma exacerbations in past year — no. (%)				
1	47 (41.2)	85 (36.0)	32 (38.1)	64 (36.6)
2	32 (28.1)	75 (31.8)	20 (23.8)	53 (30.3)
3	21 (18.4)	29 (12.3)	19 (22.6)	17 (9.7)
≥4	14 (12.3)	47 (19.9)	13 (15.5)	41 (23.4)
Atopic medical condition — no. (%)‡	103 (90.4)	226 (95.8)	79 (94.0)	171 (97.7)
Prebronchodilator FEV_1				
Mean volume — liter	1.53±0.46	1.48±0.39	1.52±0.48	1.45±0.39
Mean percent of predicted value	78.4±14.5	77.7±14.4	77.9±15.2	76.4±14.6
FEV_1 reversibility — %	15.8±16.4	21.5±21.4	16.2±15.8	22.9±23.2
Score on ACQ-7-IA§	2.1±0.8	2.2±0.7	2.2±0.8	2.2±0.7
Blood eosinophil count				
Mean — cells/mm³	520±360	600±390	640±350	740±360
Median (IQR) — cells/mm³	440 (280–660)	510 (290–780)	530 (420–730)	660 (480–910)
≥150 cells/mm³ — no. (%)	108 (94.7)	223 (94.5)	84 (100)	175 (100)
Median total IgE (IQR) — IU/ml	397 (144–862)	530 (213–1268)	554 (215–1101)	600 (331–1470)
Fractional exhaled nitric oxide				
Mean — ppb	28.4±23.4	31.8±24.9	31.3±23.5	34.5±25.8
≥20 ppb — no. (%)	62 (54.4)	141 (59.7)	52 (61.9)	114 (65.1)
Serum thymus and activation-regulated chemokine — pg/ml	568.0±666.3	525.6±511.8	579.3±728.5	573.8±573.8

* Plus–minus values are means ±SD. The two primary efficacy populations included patients who had a type 2 inflammatory asthma phenotype (≥150 blood eosinophils per cubic millimeter or a fraction of exhaled nitric oxide of ≥20 ppb at baseline) and those who had at least 300 eosinophils per cubic millimeter at baseline. Percentages may not total 100 because of rounding. FEV_1 denotes forced expiratory volume in 1 second, IQR interquartile range, and ppb parts per billion.

† Race or ethnic group was reported by the patients' parents or guardians.

‡ An atopic medical condition was defined as the presence of one or more of the following ongoing conditions: atopic dermatitis, allergic conjunctivitis, allergic rhinitis, eosinophilic esophagitis, food allergy, or hives or a baseline total IgE level of at least 100 IU per milliliter and positivity (≥0.35 IU/ml) for at least one aeroallergen-specific IgE at baseline.

§ Scores on the Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) range from 0 (totally controlled) to 6 (severely uncontrolled); a change of 0.5 is considered to be clinically important.

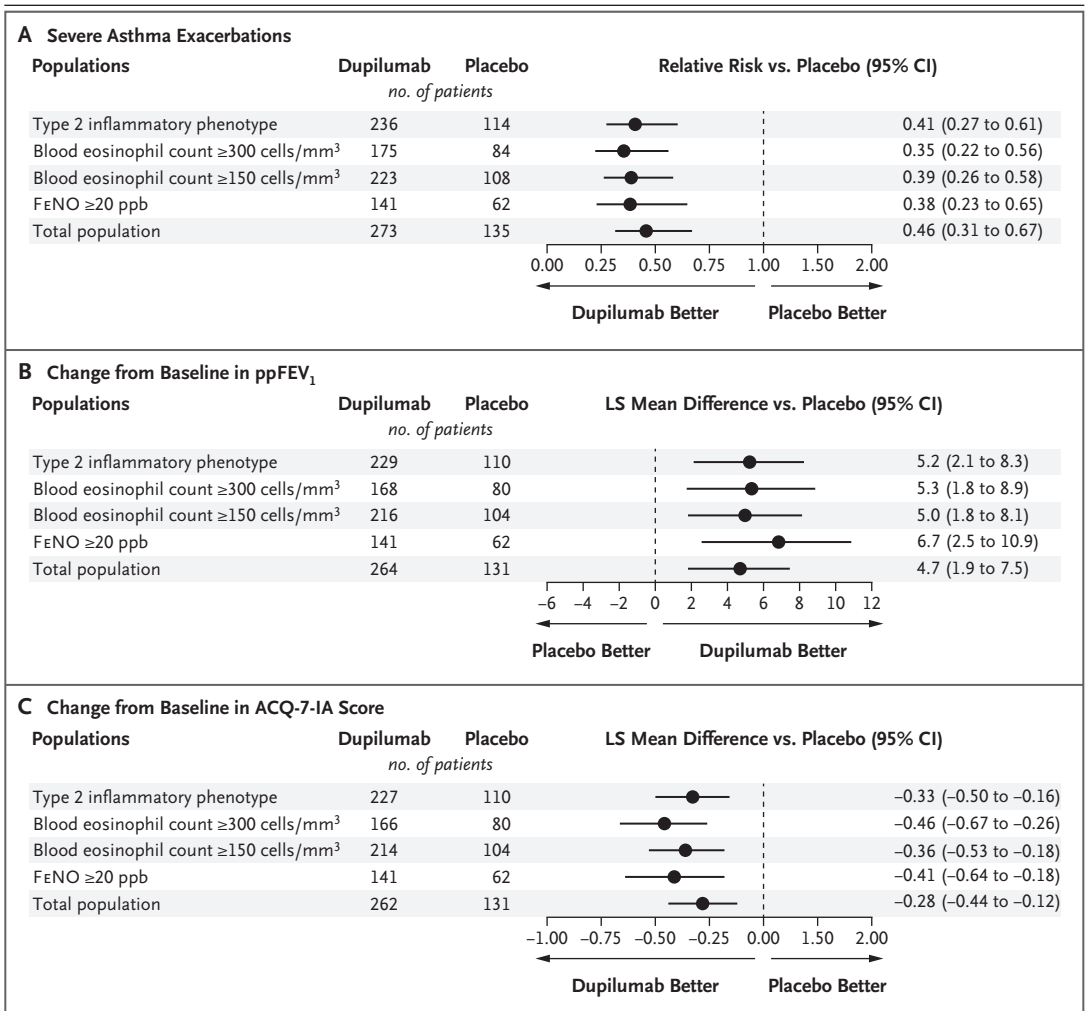

Figure 1. Key End Points in Children with Moderate-to-Severe Asthma.

Among the children with uncontrolled moderate-to-severe asthma who received either dupilumab or placebo in the trial, Panel A shows a forest plot of the relative risk of severe asthma exacerbations, Panel B shows the least-squares (LS) mean difference in the change from baseline (measured in percentage points) in the percentage of the predicted prebronchodilator forced expiratory volume in 1 second ($ppFEV_1$) at week 12, and Panel C shows the LS mean difference in the change from baseline in the Asthma Control Questionnaire 7 Interviewer-Administered (ACQ-7-IA) score at week 24. These key end points were evaluated in the two primary efficacy populations — patients who had a type 2 inflammatory asthma phenotype (≥150 blood eosinophils per cubic millimeter or a fraction of exhaled nitric oxide [FeNO] of ≥20 ppb at baseline) and those who had at least 300 blood eosinophils per cubic millimeter at baseline — and in the patients who had at least 150 eosinophils per cubic millimeter at baseline, in those who had a FeNO of at least 20 ppb at baseline, and in the total population.

by 66.0% (95% CI, 45.5 to 78.8) among those with at least 300 eosinophils per cubic millimeter at baseline (Table S8).

PREBRONCHODILATOR PPFEV$_1$

In the type 2 phenotype population, the least-squares mean (±SE) change in the $ppFEV_1$ from baseline to week 12 was 10.5±1.01 percentage points in the dupilumab group and 5.3±1.4 percentage points in the placebo group (mean difference, 5.2 percentage points; 95% CI, 2.1 to 8.3; P<0.001). The mean (±SD) $ppFEV_1$ at baseline was 77.7±14.4 in the dupilumab group and 78.4±14.5 in the placebo group, values that in-

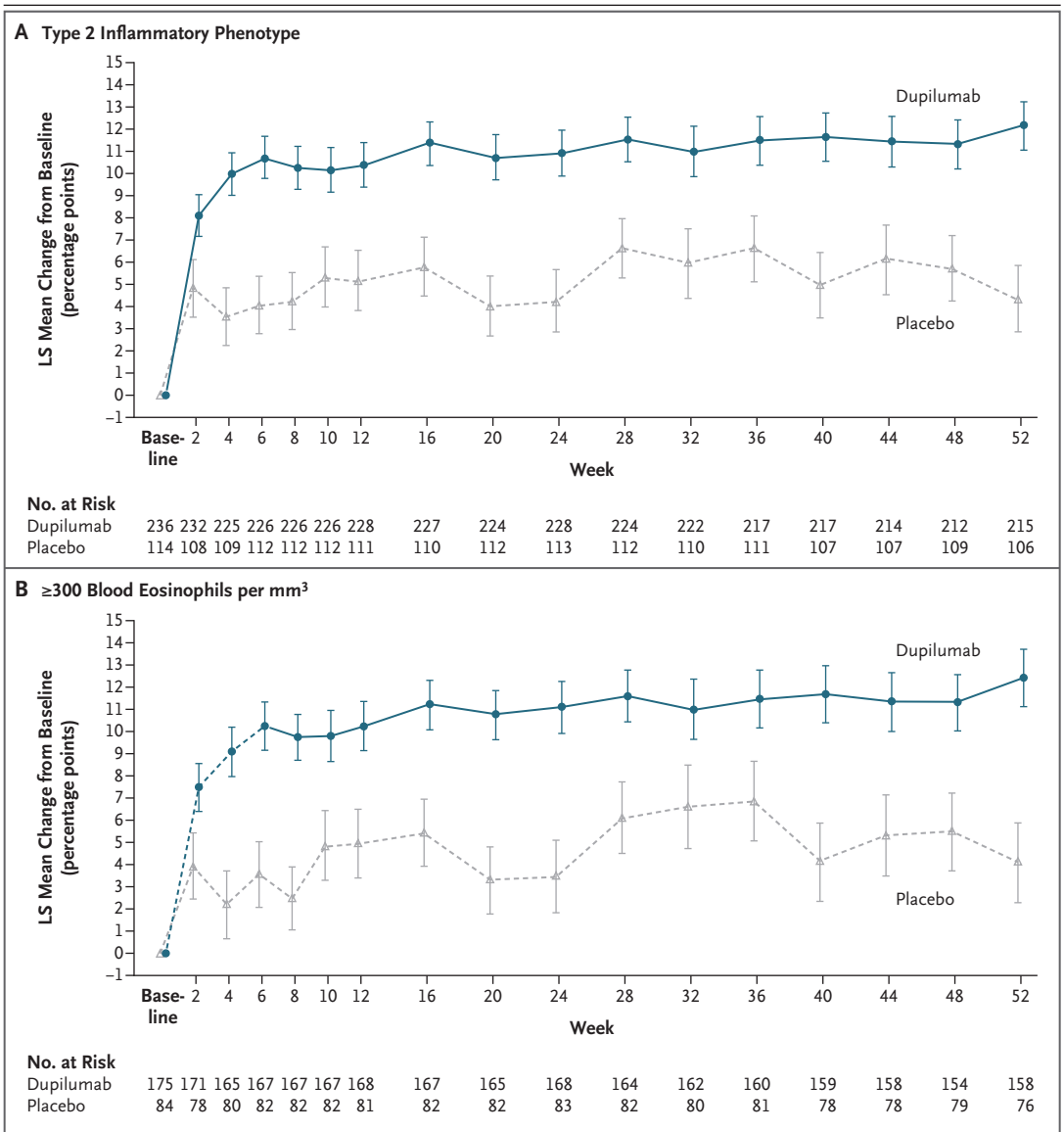

Figure 2. Change in ppFEV$_1$ during the 52-Week Trial Period, According to Primary Efficacy Population.

Shown is the LS mean change from baseline in the ppFEV$_1$ in patients with the type 2 inflammatory phenotype (Panel A) and in those with at least 300 blood eosinophils per cubic millimeter at baseline (Panel B). The I bars indicate standard errors.

creased to 87.8±14.6 and 83.2±15.5 at week 12, respectively. Similar findings were observed in the patients with at least 300 eosinophils per cubic millimeter at baseline and in all multiplicity-controlled populations (Figs. 1B, 2, and S8). The results for additional lung-function end points are provided in Tables S9 and S10.

PATIENT-REPORTED END POINTS

The least-squares mean (±SE) change from baseline in the ACQ-7-IA score at week 24 (with greater reductions indicating better asthma control) was –1.33±0.05 in the dupilumab group and –1.00±0.07 in the placebo group among the patients with the type 2 phenotype and –1.34±0.06 and –0.88±0.09, respectively, among those with at least 300 eosinophils per cubic millimeter at baseline (P<0.001 for both comparisons). Similar changes were observed across all multiplicity-controlled populations (Fig. 1C) and were sustained up to week 52 in all populations (Figs. S9 and S10). The results for other patient-

reported end points are provided in Tables S11 and S12.

BIOMARKER END POINTS

In a multiplicity-controlled analysis, the decrease from baseline to week 12 in the FeNO was significantly greater in the dupilumab group than in the placebo group in the two primary efficacy populations (P<0.001 for both comparisons) (Table S13). In prespecified exploratory analyses in the safety population, numerically greater reductions in the mean FeNO, total serum IgE, and serum thymus and activation-regulated chemokine (TARC) were observed during the 52-week treatment period with dupilumab than with placebo (Fig. S11). In the dupilumab group, a transient increase from baseline in the mean blood eosinophil count was observed at the first postbaseline assessment at week 12, with mean counts returning to baseline levels by week 36 (Fig. S11B). The median eosinophil counts remained stable across 52 weeks in the two treatment groups (Fig. S12B).

SAFETY

The frequencies of adverse events during the 52-week trial period were similar across trial groups in the safety population (83.0% with dupilumab and 79.9% with placebo) (Table 2). The most common adverse event that occurred in at least 5% of the patients and at a higher frequency in the dupilumab group was viral infection of the upper respiratory tract (12.2% with dupilumab and 9.7% with placebo). Discontinuation of a trial intervention owing to adverse events occurred in 1.8% of the patients in the dupilumab group and in 1.5% of those in the placebo group. Serious adverse events were reported in 13 patients (4.8%) in the dupilumab group and in 6 (4.5%) in the placebo group. Eosinophilia occurred in 5.9% and 0.7% of the patients in the dupilumab and placebo groups, respectively. Most episodes of eosinophilia were self-limited laboratory findings without any associated symptoms. A single case of eosinophilia was associated with clinical symptoms that included hospitalization and permanent discontinuation of dupilumab (Section 3 in the Supplementary Appendix).

Parasitic infections were reported in 7 patients (2.6%) in the dupilumab group. All cases of parasitic infections were mild, and all the patients recovered after treatment with anthelmintic therapy with no permanent discontinuation of dupilumab or placebo (Table 2 and Section 3.4 of the Supplementary Appendix). Asthma exacerbations leading to hospitalization were reported in 4 of 271 patients (1.5%) in the dupilumab group and in no patients in the placebo group (Section 3.5 in the Supplementary Appendix). The incidence of conjunctivitis was low in both groups; one case of keratitis was reported in each group. There were no deaths during the trial. Antidrug antibody responses were observed in 6.3% of the patients in the dupilumab group and in 3.0% of those in the placebo group (Table S14).

DISCUSSION

Among the children between the ages of 6 and 11 years in our trial who had uncontrolled moderate-to-severe asthma, those who added dupilumab to their standard therapy had a significantly lower rate of severe asthma exacerbations and had better lung function and asthma control than those who received placebo. Few randomized trials of add-on biologic therapy have been conducted in this age group, and we found that add-on dupilumab provided a clinically meaningful effect on lung function. Furthermore, we determined the utility of a biomarker-driven approach to phenotyping and treating children with uncontrolled asthma.

Dupilumab treatment led to significant improvements in all end points in the testing hierarchy. Even though the number of asthma exacerbations had averaged at least two in the previous year, the percentage of children who remained exacerbation-free during the 52-week treatment period was almost 78% in the dupilumab group and 60% in the placebo group. Children in the dupilumab group also had a lower exposure to systemic glucocorticoids than those who received placebo, a finding that is especially important in this population. The efficacy of dupilumab was rapid, with observably higher values in the $ppFEV_1$ than with placebo by the first on-treatment assessment at week 2 and with a longer time until the first exacerbation by week 4, with sustained benefits during the 52-week treatment period.

Significant reductions in severe exacerbations and improvement in lung function are clinically relevant, since uncontrolled asthma in childhood can lead to reduced lung function, irreversible airflow limitation, and COPD in adulthood.[11,12]

Table 2. Adverse Events and Injection-Site Reactions (Safety Population).*

Event	Placebo (N = 134)	Dupilumab (N = 271)
	number of patients (percent)	
Adverse events		
Any	107 (79.9)	225 (83.0)
Leading to permanent discontinuation	2 (1.5)	5 (1.8)
Serious adverse events	6 (4.5)	13 (4.8)
Adverse events in ≥5% of patients in either group†		
Nasopharyngitis	29 (21.6)	50 (18.5)
Upper respiratory tract infection		
Any	18 (13.4)	35 (12.9)
Viral	13 (9.7)	33 (12.2)
Pharyngitis	14 (10.4)	24 (8.9)
Influenza	12 (9.0)	20 (7.4)
Bronchitis	14 (10.4)	17 (6.3)
Sinusitis	7 (5.2)	9 (3.3)
Eosinophilia‡	1 (0.7)	16 (5.9)
Headache	10 (7.5)	19 (7.0)
Allergic rhinitis	16 (11.9)	16 (5.9)
Cough	9 (6.7)	15 (5.5)
Accidental overdose§	7 (5.2)	3 (1.1)
Injection-site reaction¶		
Erythema	13 (9.7)	35 (12.9)
Edema	7 (5.2)	28 (10.3)
Nodule	3 (2.2)	17 (6.3)
Adverse events of special interest		
Parasitic infection		
Any‖	0	7 (2.6)
Enterobiasis	0	5 (1.8)
Ascariasis	0	1 (0.4)
Lice infestation	0	1 (0.4)
Conjunctivitis		
Narrow custom MedDRA query	9 (6.7)	7 (2.6)
Broad custom MedDRA query	10 (7.5)	8 (3.0)

* The safety population consisted of all the patients who had received at least one dose or part of a dose of dupilumab or placebo. No deaths were reported in either group during the trial. MedDRA denotes *Medical Dictionary for Regulatory Activities*.
† Adverse events are reported at the preferred-term level of the MedDRA hierarchy.
‡ Eosinophilia was defined as a peripheral-blood eosinophil count at least 3000 cells per cubic millimeter.
§ Overdose was defined as at least twice the standard dose of either dupilumab or placebo during an interval of less than 11 days.
¶ Descriptions of injection-site reactions include MedDRA high-level terms.
‖ One additional patient in the placebo group had parasitic gastroenteritis that was erroneously not recorded as a parasitic infection and therefore was not identified as an adverse event of special interest.

Longer-term studies are needed to determine whether dupilumab leads to sustained improvements in lung function and whether it can restore normal patterns of lung growth.

Efficacy was observed among the patients with the type 2 phenotype and in populations defined by individual type 2 inflammatory biomarkers. These findings support a biomarker-driven approach to the treatment of children with uncontrolled asthma in which clinicians would use peripheral-blood eosinophil counts, FeNO, or both to identify patients who are likely to have a response to treatments such as dupilumab that target type 2 inflammatory pathways.[16,17]

In our trial, dupilumab also provided rapid and sustained decreases in markers of type 2 inflammation in airways (FeNO) and circulation (serum total IgE and TARC), findings that were consistent with results in adults and adolescents.[19-21] These data strengthen the clinical understanding of the dupilumab mechanism of action, with effective blockade of signaling mediated by interleukin-4 and interleukin-13 that leads to broad suppression of type 2 inflammation. In contrast, median blood eosinophil counts remained stable during 52 weeks, with a transient early increase in mean levels similar to findings in adults and adolescents.[19] This result was consistent with the hypothesis that dupilumab blocks the migration of eosinophils into tissue by inhibiting the production of eotaxin and vascular-cell adhesion molecule mediated by interleukin-4 and interleukin-13[19,22,23] but not eosinophil production or egress from bone marrow.[17]

Dupilumab had a generally acceptable adverse-event profile in this pediatric asthma population, with safety findings similar to those in adult and adolescent patients.[19-21] One case of symptomatic eosinophilia associated with headache and dizziness was reported, which involved hospitalization and cessation of dupilumab, after which the condition resolved. Instances of parasitic infections were not serious and were not considered by trial investigators to be related to dupilumab.

Our trial has several limitations. Although the trial patients reflected the demographic makeup of the geographic regions, the limited ethnic diversity in the trial population, particularly the low number of Black children who were enrolled, should be considered when generalizing findings to the wider population of children with asthma. The inclusion of these underrepresented populations in future studies is needed. The rapid decrease in the FeNO among the children receiving dupilumab could have given investigators a suspicion of trial-group assignment that could have had an effect on treatment decisions. However, we note that data regarding the effect of dupilumab on FeNO levels in adolescents and adults[19] were not available until midway through the trial, and multiple objective measures of efficacy, such as the clear improvement in lung function, support the overall efficacy of dupilumab in this population.

Dupilumab therapy led to meaningful improvements through reductions in asthma exacerbations and rapid improvements in lung function and asthma control during the 52-week trial period. The treatment also had an acceptable side-effect profile in patients between the ages of 6 and 11 years with uncontrolled moderate-to-severe asthma and a type 2 inflammatory asthma phenotype.

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APPENDIX

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