ORIGINAL ARTICLE

Dupilumab for COPD with Blood Eosinophil Evidence of Type 2 Inflammation

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ABSTRACT

BACKGROUND

Dupilumab, a fully human monoclonal antibody that blocks the shared receptor component for interleukin-4 and interleukin-13, key and central drivers of type 2 inflammation, has shown efficacy and safety in a phase 3 trial involving patients with chronic obstructive pulmonary disease (COPD) and type 2 inflammation and an elevated risk of exacerbation. Whether the findings would be confirmed in a second phase 3 trial was unclear.

METHODS

In a phase 3, double-blind, randomized trial, we assigned patients with COPD who had a blood eosinophil count of 300 cells per microliter or higher to receive subcutaneous dupilumab (300 mg) or placebo every 2 weeks. The primary end point was the annualized rate of moderate or severe exacerbations. Key secondary end points, analyzed in a hierarchical manner to adjust for multiplicity, included the changes from baseline in the prebronchodilator forced expiratory volume in 1 second (FEV_1) at weeks 12 and 52 and in the St. George's Respiratory Questionnaire (SGRQ; scores range from 0 to 100, with lower scores indicating better quality of life) total score at week 52.

RESULTS

A total of 935 patients underwent randomization: 470 were assigned to the dupilumab group and 465 to the placebo group. As prespecified, the primary analysis was performed after a positive interim analysis and included all available data for the 935 participants, 721 of whom were included in the analysis at week 52. The annualized rate of moderate or severe exacerbations was 0.86 (95% confidence interval [CI], 0.70 to 1.06) with dupilumab and 1.30 (95% CI, 1.05 to 1.60) with placebo; the rate ratio as compared with placebo was 0.66 (95% CI, 0.54 to 0.82; P<0.001). The prebronchodilator FEV_1 increased from baseline to week 12 with dupilumab (least-squares mean change, 139 ml [95% CI, 105 to 173]) as compared with placebo (least-squares mean change, 57 ml [95% CI, 23 to 91]), with a significant least-squares mean difference at week 12 of 82 ml (P<0.001) and at week 52 of 62 ml (P=0.02). No significant between-group difference was observed in the change in SGRQ scores from baseline to 52 weeks. The incidence of adverse events was similar in the two groups and consistent with the established profile of dupilumab.

CONCLUSIONS

In patients with COPD and type 2 inflammation as indicated by elevated blood eosinophil counts, dupilumab was associated with fewer exacerbations and better lung function than placebo. (Funded by Sanofi and Regeneron Pharmaceuticals; NOTUS ClinicalTrials.gov number, NCT04456673.)

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*A list of the investigators in the NOTUS Study group is provided in the Supplementary Appendix, available at NEJM.org.

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Chronic obstructive pulmonary disease (COPD) is a progressive condition that represents a major public health issue owing to its high prevalence and associated high morbidity and mortality.[1] Exacerbations of COPD are clinically important events that may accelerate disease progression.[2-4] Approximately half of patients with COPD continue to have exacerbations despite maximal standard care with inhaled triple therapy consisting of a glucocorticoid agent, a long-acting muscarinic antagonist (LAMA), and a long-acting β-agonist (LABA).[5,6] Thus, prevention of exacerbations is an important goal for new COPD therapeutics, alongside improvement in lung function and health-related quality of life.

A subgroup of patients with COPD is characterized by evidence of local and systemic type 2 inflammation.[7-16] Type 2 inflammation is regulated by type 2 helper T cells and innate lymphoid cells and driven by inflammatory cytokines, including interleukin-4, interleukin-5, and interleukin-13.[14]

Dupilumab is a fully human monoclonal antibody that blocks the interleukin-4 and interleukin-13[17,18] pathways and is approved for multiple diseases marked by type 2 inflammation worldwide (indications are country-dependent),[19,20] which raises the possibility that it could be effective therapy in patients with COPD characterized by type 2 inflammation. In a previous phase 3 trial, dupilumab was effective in treating patients with COPD and type 2 inflammation; it was associated with a reduction in moderate or severe exacerbations, improvements in lung function and patient-reported health-related quality of life, and a lessening of the severity of symptoms.[7] The results of safety analyses were consistent with the known safety profile of dupilumab. We designed the NOTUS trial to confirm the efficacy and safety of dupilumab in patients with COPD and evidence of type 2 inflammation indicated by blood eosinophil count and high exacerbation risk despite the use of inhaled triple therapy.

Methods

Trial Design and Oversight

We conducted the NOTUS trial, a 52-week phase 3, international, double-blind, randomized, placebo-controlled trial, at 329 sites in 29 countries. Eligible patients who were receiving triple inhaler therapy were randomly assigned, in a 1:1 ratio, to receive add-on subcutaneous dupilumab at a dose of 300 mg or matched placebo every 2 weeks (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Randomization was stratified according to country, the dose of inhaled glucocorticoid in use at baseline (Table S1), and smoking status at the time of screening. Enrollment of current smokers was capped at 30%.

Owing to the positive results of the first phase 3 trial and the high unmet medical need among patients with COPD, we conducted a prespecified interim analysis of the primary end point with the use of all available participant data. The statistical analysis plan (available with the protocol at NEJM.org) prespecified that when the results of the interim analysis were positive, the primary analysis would be performed and the remaining end points would be analyzed in a hierarchical manner to adjust for multiplicity.

The trial was approved by the appropriate regulatory authorities and ethics committees. All patients provided written informed consent. Oversight of the trial was provided by an external independent data and safety monitoring committee, the members of which were unaware of group assignments (see the Supplementary Appendix).

The sponsors, Sanofi and Regeneron Pharmaceuticals, designed the trial and collected and analyzed the data. All the authors had access to the data, contributed to interpretation of the data, and provided input into the drafting of the manuscript and final approval of the manuscript for submission. Medical writing and editorial assistance with an earlier version of the manuscript were provided by a medical writer, in accordance with Good Publication Practice guidelines, who was funded by the sponsors. The authors vouch for the completeness and accuracy of the data and for the fidelity of the trial to the protocol.

Patients

Patients 40 to 85 years of age were eligible if they had had physician-diagnosed COPD for at least 12 months and had been receiving background triple inhaler therapy (an inhaled glucocorticoid agent plus LAMA–LABA or LAMA–LABA alone if inhaled glucocorticoid agents were contraindicated) for at least 3 months and at a stable dose for at least 1 month. In the year before screening for eligibility, patients must have had at least two moderate or one severe exacerbation;

at least one moderate exacerbation must have resulted in treatment with systemic glucocorticoids, and at least one exacerbation had to occur while the patient was receiving background triple inhaler therapy.

Patients were current or former tobacco smokers with a smoking history of at least 10 pack-years. At screening, patients had to have a postbronchodilator ratio of the forced expiratory volume in 1 second (FEV_1) to the forced vital capacity (FVC) of less than 0.70 and a postbronchodilator FEV_1 of more than 30% and up to 70% of the predicted normal value. Patients had symptomatic COPD, as indicated by a dyspnea score of at least 2 on the Medical Research Council dyspnea scale (scores ranges from 1 to 5, with higher scores indicating more severe dyspnea), and reported symptoms of chronic bronchitis (chronic productive cough) for 3 months in the year before screening, in the absence of other known causes of chronic cough. Patients with symptomatic COPD are at increased risk for exacerbations and encompass both the chronic bronchitis and emphysema phenotypes.[21,22] Patients with investigator-reported emphysema were not excluded.

Patients had an absolute blood eosinophil count of at least 300 cells per microliter on at least one analysis during the screening period before randomization. A current diagnosis or a history of asthma was an exclusion criterion. A complete list of inclusion and exclusion criteria are provided in the Supplementary Appendix.

END POINTS

The primary end point was the annualized rate of moderate or severe exacerbations of COPD during the 52-week trial period. Moderate exacerbations were defined as exacerbations that resulted in treatment with a systemic glucocorticoid, antibiotic agent, or both. Severe exacerbations were defined as exacerbations that led to hospitalization or an emergency medical care visit (with observation lasting >24 hours) or that resulted in death.

The following end points were corrected for multiplicity in order of hierarchical testing: the change from baseline in the prebronchodilator FEV_1 at weeks 12 and 52, the change from baseline in the prebronchodilator FEV_1 at weeks 12 and 52 among the patients who had a fractional exhaled nitric oxide (F_ENO) level at baseline of 20 parts per billion (ppb) or higher, the change from baseline to week 52 in the total score on the St. George's Respiratory Questionnaire (SGRQ; scores range from 0 to 100, with lower scores indicating a better quality of life; minimum clinically important difference [MCID], 4 points),[23] the percentage of patients with a change of 4 points (the MCID) in the SGRQ total score at week 52, the change from baseline to week 52 in the Evaluating Respiratory Symptoms in COPD (E-RS–COPD) total score (scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms), and the annualized rate of moderate or severe COPD exacerbations among the patients who had a F_ENO level of 20 ppb or higher. The key safety end points were adverse events and serious adverse events that occurred after initiation of dupilumab or placebo.

STATISTICAL ANALYSIS

Efficacy for the primary and week 12 end points was evaluated in the intention-to-treat population (i.e., all the patients who underwent randomization). The week 52 efficacy end points (continuous and proportion types) were analyzed in the intention-to-treat population among the patients who reached trial week 52 at the time of the primary analysis. Safety was evaluated in the safety population (which included all patients who received at least one full or partial dose of dupilumab or placebo) on the basis of all available data at the cutoff date for the primary analysis.

We estimated that a sample of 924 patients (462 in each trial group) would provide the trial with 90% power to detect a between-group difference in the annualized rate of moderate or severe exacerbations of 25% at week 52 at a two-sided alpha level of 0.05. Additional details are provided in the Supplementary Appendix.

The primary end point was analyzed with the use of a negative binomial regression model, with the total number of events occurring during the 52-week trial period as the response variable. Covariates were trial group, geographic region, dose of inhaled glucocorticoid at baseline, smoking status at screening, disease severity at baseline, and number of moderate or severe exacerbation events of COPD within 1 year before trial screening. The natural log of the 52-week duration of follow-up was used as an offset variable.

The key secondary end points were evaluated with the use of a mixed-effect model for repeated measures that included the trial group, geograph-

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

Characteristic	Placebo (N=465)	Dupilumab (N=470)	Total (N=935)
Age — yr	64.9±8.5	65.2±8.1	65.0±8.3
Male sex — no. (%)	312 (67.1)	320 (68.1)	632 (67.6)
Race or ethnic group — no. (%)†			
White	416 (89.5)	422 (89.8)	838 (89.6)
Black	8 (1.7)	4 (0.9)	12 (1.3)
Asian	3 (0.6)	7 (1.5)	10 (1.1)
American Indian or Alaska Native	26 (5.6)	22 (4.7)	48 (5.1)
Native Hawaiian or Pacific Islander	0	1 (0.2)	1 (0.1)
Multiple	8 (1.7)	12 (2.6)	20 (2.1)
Not reported	4 (0.9)	2 (0.4)	6 (0.6)
Hispanic or Latino ethnic group — no. (%)			
Hispanic or Latino	149 (32.0)	151 (32.1)	300 (32.1)
Non-Hispanic or non-Latino	308 (66.2)	315 (67.0)	623 (66.6)
Unknown	2 (0.4)	0	2 (0.2)
Not reported	6 (1.3)	4 (0.9)	10 (1.1)
Smoking status — no. (%)			
Former smoker	331 (71.2)	328 (69.8)	659 (70.5)
Current smoker	134 (28.8)	142 (30.2)	276 (29.5)
Smoking history — pack-yr	42.1±30.2	38.6±23.7	40.3±27.2
Emphysema — no. (%)‡	150 (32.3)	134 (28.5)	284 (30.4)
Body-mass index§	27.8±5.6	28.1±5.3	27.9±5.4
Background medication — no. (%)			
Inhaled triple therapy¶	458 (98.5)	466 (99.1)	924 (98.8)
Inhaled high-dose glucocorticoid	134 (28.8)	127 (27.0)	261 (27.9)
Biomarkers of type 2 inflammation			
Blood eosinophil count at randomization — per μl			
Mean	402±314	412±357	407±336
Median (interquartile range)	330 (220–470)	340 (230–460)	330 (220–460)
Category at randomization — no. (%)			
<300 cells/μl	188/465 (40.4)	184/469 (39.2)	372/934 (39.8)
≥300 cells/μl	277/469 (59.6)	285/469 (60.8)	562/934 (60.1)
Postbronchodilator FeNO — ppb			
Mean	24.4±23.4	24.8±28.3	24.6±26.0
Median (interquartile range)	16 (10–30)	16 (10–27)	16 (10–29)
FeNO — no./total no. (%)			
<20 ppb	240/423 (56.7)	257/429 (59.9)	497/852 (58.3)
≥20 ppb	183/423 (43.3)	172/429 (40.1)	355/852 (41.7)
No. of moderate or severe COPD exacerbations in previous yr	2.1±0.7	2.2±1.0	2.1±0.9

Table 1. (Continued.)

Characteristic	Placebo (N=465)	Dupilumab (N=470)	Total (N=935)
Lung function			
Prebronchodilator FEV_1 — liters	1.38±0.50	1.35±0.49	1.36±0.50
Postbronchodilator FEV_1			
Volume — liters	1.46±0.50	1.43±0.49	1.45±0.49
Percent of predicted value	50.7±12.6	49.5±12.6	50.1±12.6
Postbronchodilator FEV_1:FVC	0.5±0.1	0.5±0.1	0.5±0.1
SGRQ total score‖	51.1±16.5	52.0±17.5	51.5±17.0
E-RS–COPD total score**	13.3±7.2	13.4±6.7	13.3±7.0

* Plus–minus values are means ±SD. The intention-to-treat population included all patients who underwent randomization, with data analyzed according to group assignment. Percentages may not total 100 because of rounding. Additional data on baseline characteristics and characteristics of patients who reached the 52-week assessments (721 patients) are provided in the Supplementary Appendix. COPD denotes chronic obstructive pulmonary disease, FeNO fractional exhaled nitric oxide, FEV_1 forced expiratory volume in 1 second, FVC forced vital capacity, and ppb parts per billion.

† Race and ethnic group were reported by the patient.

‡ Emphysema was reported by the investigator.

§ The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶ Patients were receiving triple therapy consisting of an inhaled glucocorticoid, a long-acting muscarinic antagonist (LAMA), and a long-acting β2-agonist (LABA) unless inhaled glucocorticoid was contraindicated, in which case therapy included only LAMA and LABA.

‖ The St. George's Respiratory Questionnaire (SGRQ) is a 50-item questionnaire designed to measure and quantify health status in adult patients with chronic airflow limitation. Total scores range from 0 to 100, with lower scores indicating a better quality of life; the minimum clinically important difference is 4 points.

** The Evaluating Respiratory Symptoms in COPD (E-RS–COPD) instrument is an 11-item derivative tool used to measure the effect of a treatment on the severity of respiratory symptoms in patients with stable COPD. Total scores range from 0 to 40, with lower scores indicating less severe respiratory symptoms.

ic region, the dose of inhaled glucocorticoid at baseline, smoking status at screening, visit, trial group–by–visit interaction, baseline value, baseline value–by–visit interaction, and other model-specific factors as covariates. If the primary end point met statistical significance, a hierarchical testing procedure would be used. Additional details of the hierarchical testing procedure and sensitivity and tipping-point analyses are provided in the Supplementary Appendix. The 95% confidence intervals have not been adjusted for multiplicity and should not be used in place of hypothesis testing.

RESULTS

PATIENTS

From July 2020 through May 2023, a total of 935 patients underwent randomization: 470 to the dupilumab group and 465 to the placebo group (Fig. S2). The demographic and clinical characteristics of the patients at baseline were similar in the two groups (Table 1). The mean (±SD) age of the patients was 65.0±8.3 years, and 29.5% were current smokers. Nearly all the patients (98.8%) were receiving an inhaled glucocorticoid plus LAMA–LABA. The mean number of moderate or severe exacerbation events in the year before screening was 2.1±0.9. The mean percent of predicted values at baseline for prebronchodilator and postbronchodilator FEV_1 were 47.2±13.0% and 50.1±12.6%, respectively.

The mean blood eosinophil count at baseline was 407±336 cells per microliter, and 39.8% of the patients had a blood eosinophil count of less than 300 cells per microliter at randomization. The mean FeNO level at baseline was 24.6±26.0 ppb, and 41.7% of the patients had a FeNO level of 20 ppb or higher at baseline (Tables 1 and S2). The representativeness of the trial population is shown in Table S3.

PRIMARY END POINT

The annualized rate of moderate or severe exacerbations of COPD was lower in the dupilumab group (0.86; 95% confidence interval [CI], 0.70

Table 2. Summary of End Points Included in the Hierarchical Testing Procedure.

End Point*	Placebo (N=465)	Dupilumab (N=470)	P Value
Primary end point			
Annualized rate of moderate or severe exacerbations of COPD			
Adjusted annualized rate of moderate or severe exacerbations — no. of events/yr (95% CI)	1.30 (1.05 to 1.60)	0.86 (0.70 to 1.06)	
Rate ratio vs. placebo (95% CI)	—	0.66 (0.54 to 0.82)	<0.001
Secondary and other end points			
Change in prebronchodilator FEV_1 from baseline to wk 12			
Least-squares mean change (95% CI) — liters	0.057 (0.023 to 0.091)	0.139 (0.105 to 0.173)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.082 (0.040 to 0.124)	<0.001
Change in prebronchodilator FEV_1 from baseline to wk 52†			
No. of patients	359	362	
Least-squares mean change (95% CI) — liters	0.054 (0.014 to 0.093)	0.115 (0.075 to 0.156)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.062 (0.011 to 0.113)	0.02
Change in prebronchodilator FEV_1 from baseline to wk 12 among patients with a baseline FeNO level ≥20 ppb			
No. of patients	183	172	
Least-squares mean change (95% CI) — liters	0.081 (0.008 to 0.153)	0.221 (0.148 to 0.294)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.141 (0.058 to 0.223)	0.001
Change in prebronchodilator FEV_1 from baseline to wk 52 among patients with a baseline FeNO level ≥20 ppb†			
No. of patients	132	132	
Least-squares mean change (95% CI) — liters	0.095 (0.011 to 0.179)	0.176 (0.091 to 0.261)	
Least-squares mean difference vs. placebo (95% CI) — liters	—	0.081 (–0.019 to 0.181)	0.11
Change in SGRQ total score from baseline to wk 52†			
No. of patients	359	362	
Least-squares mean change (95% CI)	–6.4 (–8.3 to –4.6)	–9.8 (–11.6 to –8.0)	
Least-squares mean difference vs. placebo (95% CI)‡	—	–3.4 (–5.8 to –0.9)	
SGRQ total score improvement ≥4 points at wk 52†			
No. of patients	359	362	
Percentage of patients (95% CI)	46.5 (41.3 to 51.8)	51.4 (46.1 to 56.6)	
Odds ratio vs. placebo (95% CI)‡	—	1.2 (0.9 to 1.6)	
Change in E-RS:COPD total score from baseline to wk 52†			
No. of patients	359	362	
Least-squares mean change (95% CI)	–1.8 (–2.4 to –1.2)	–2.4 (–3.0 to –1.8)	
Least-squares mean difference vs. placebo (95% CI)‡	—	–0.6 (–1.4 to 0.2)	
Annualized rate of moderate or severe exacerbations of COPD among patients with a baseline FeNO level ≥20 ppb			
No. of patients	183	172	
Adjusted annualized rate of moderate or severe exacerbations — no. of events/yr (95% CI)	1.57 (1.12 to 2.21)	0.74 (0.53 to 1.03)	
Rate ratio vs. placebo (95% CI)‡	—	0.47 (0.33 to 0.68)	

* End points are listed in the order in which they were hierarchically tested.
† Only data from patients who reached the week 52 assessments were analyzed for the continuous- and proportion-type end points at week 52.
‡ The 95% confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing.

to 1.06) than in the placebo group (1.30; 95% CI, 1.05 to 1.60), resulting in a rate ratio of 0.66 (95% CI, 0.54 to 0.82; P<0.001) (Table 2 and Fig. 1). Results were similar in prespecified demographic and disease subgroups and in control-based pattern-mixture–model-multiple imputation and tipping-point sensitivity analyses (Tables S4 and S5 and Fig. S3).

SECONDARY AND OTHER END POINTS

Lung Function

Changes from baseline in the prebronchodilator FEV_1 during the 52-week trial period are shown in Figure 2. At week 12, the least-squares mean change in the prebronchodilator FEV_1 was 139 ml (95% CI, 105 to 173) in the dupilumab group as compared with 57 ml (95% CI, 23 to 91) in the placebo group (least-squares mean difference, 82 ml; 95% CI, 40 to 124; P<0.001). This improvement was sustained through week 52 (least-squares mean difference, 62 ml; 95% CI, 11 to 113; P=0.02) (Table 2 and Fig. 2). The results were similar to those in prespecified subgroups and in sensitivity analyses (Tables S6 and S7 and Fig. S4). Changes in other variables of lung function are shown in Figure S5.

In prespecified analyses involving patients with FeNO levels at baseline of 20 ppb or higher, the least-squares mean change from baseline in the prebronchodilator FEV_1 at week 12 was 221 ml (95% CI, 148 to 294) with dupilumab as compared with 81 ml (95% CI, 8 to 153) with placebo (least-squares mean difference, 141 ml; 95% CI, 58 to 223; P=0.001). There was no significant difference between the groups at 52 weeks, and no further statistical testing was performed according to the hierarchical testing procedure (Table 2).

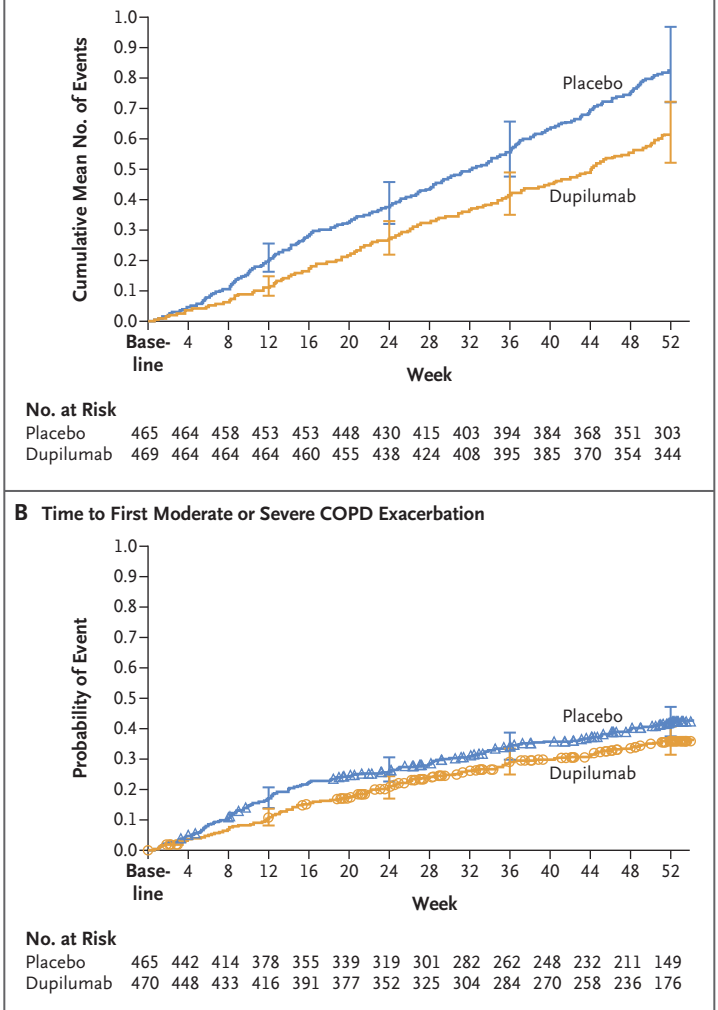

Figure 1. Cumulative Moderate or Severe COPD Exacerbations and Time to the First Moderate or Severe COPD Exacerbation Event during the 52-Week Trial Period.

I bars indicate 95% confidence intervals. Triangles and circles indicate censored data. COPD denotes chronic obstructive pulmonary disease.

Patient-Reported Outcomes

At week 52, the decrease from baseline in SGRQ total score (indicating improvement) was −9.8 points (95% CI, −11.6 to −8.0) in the dupilumab group and −6.4 points (95% CI, −8.3 to −4.6) in the placebo group (least-squares mean difference, −3.4 points; 95% CI, −5.8 to −0.9) (Table 2 and Fig. S6). SGRQ scores according to domain and from baseline through week 52 are presented in Table S8. At week 52, improvement in the SGRQ total score by at least 4 points (the MCID) occurred in 51.4% of the patients in the dupilumab group and in 46.5% of the patients in the placebo group (odds ratio, 1.16; 95% CI, 0.86 to 1.58) (Table 2). The change from baseline in E-RS–COPD total score at week 52 was −2.4 points (95% CI, −3.0 to −1.8) and −1.8 points (95% CI, −2.4 to −1.2) in the dupilumab and placebo groups, respectively (least-squares mean difference, −0.6 points; 95% CI, −1.4 to 0.2) (Table 2 and Fig. S6).

Additional End Points

The time to the first moderate or severe exacerbation event for dupilumab as compared with placebo is shown in Figure 1B (hazard ratio, 0.71;

Table 3. Adverse Events (Safety Population).*

Event	Placebo (N=464)	Dupilumab (N=469)
	no. of patients (%)	
Any adverse event	306 (65.9)	313 (66.7)
Any serious adverse event	74 (15.9)	61 (13.0)
Any adverse event leading to death	7 (1.5)	12 (2.6)
Any adverse event leading to permanent discontinuation of trial intervention	12 (2.6)	18 (3.8)
Adverse events occurring in ≥5% of patients in either group		
Coronavirus disease 2019	38 (8.2)	44 (9.4)
Headache	30 (6.5)	35 (7.5)
COPD	36 (7.8)	23 (4.9)
Nasopharyngitis	24 (5.2)	29 (6.2)
Major adverse cardiovascular event†	7 (1.5)	3 (0.6)

* The safety population consisted of all the patients who received at least one full or partial dose of dupilumab or placebo; the analysis was performed according to the treatment each patient received.
† Major adverse cardiovascular events (adjudicated) included cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke.

95% CI, 0.57 to 0.89). The time to a first severe exacerbation event with dupilumab as compared with placebo (hazard ratio, 0.51; 95% CI, 0.29 to 0.90) as well as other end-point analyses are shown in Tables S9 and S10. The annualized rate of severe exacerbations was 0.07 (95% CI, 0.04 to 0.12) in the dupilumab group and 0.12 (95% CI, 0.07 to 0.22) in the placebo group (rate ratio vs. placebo, 0.56; 95% CI, 0.31 to 1.02). A summary of missing data in end-point analyses that were included in the hierarchical testing procedure is shown in Table S11.

Biomarkers of Type 2 Inflammation

In the dupilumab group, levels of IgE and FeNO decreased during the 52-week study. Changes from baseline in FeNO, total IgE, and blood eosinophil count are shown in Table S12 and Figure S7.

SAFETY

The percentage of patients who had adverse events during the 52-week trial period was similar in the two groups (66.7% in the dupilumab group and 65.9% in the placebo group) (Table 3). The most common adverse events were coronavirus disease 2019 (Covid-19), nasopharyngitis, headache, and COPD. Serious adverse events were reported in 13.0% and 15.9% of the patients in the dupilumab and placebo groups, respectively. Adverse events that resulted in death occurred in 2.6% and 1.5% of the patients in the dupilumab and placebo groups, respectively. Adjudicated death from cardiovascular causes occurred in one patient in each group. Adverse events that were classified as major adverse cardiovascular events occurred in 0.6% and 1.5% of the patients in the dupilumab and placebo groups, respectively. Adverse events according to system organ class are shown in Table S13. Persistent antidrug antibody responses were observed in 14 patients (3.0%) in the dupilumab group and in 3 patients (0.7%) in the placebo group.

DISCUSSION

The NOTUS trial showed that dupilumab, when added to background triple inhaler therapy, reduced the annualized rate of moderate or severe exacerbations and improved lung function in patients with COPD and type 2 inflammation. These results further confirm the role of type 2 inflammation in the pathobiologic disease mechanisms in a subgroup of patients with COPD and the role of dupilumab in treating this distinct COPD endotype.

The current trial, combined with the findings in the BOREAS trial,[7] confirms the importance of interleukin-4 and interleukin-13 in driving the inflammatory process in a subgroup of patients with COPD. Although blood eosinophil counts serve as practical and accessible markers of type 2 inflammation, type 2 inflammatory pathways are not necessarily driven solely by blood eosinophils. Previous completed phase 3 trials of biologic agents that specifically target blood eosinophils (e.g., anti–interleukin-5) showed inconsistent reduction in frequency of exacerbation events and lacked evidence of improvement in lung function or quality of life.[24,25] In the BOREAS[7] and NOTUS trials, we observed robust and consistent clinical efficacy of interleukin-4 and interleukin-13 blockade in patients with COPD with evidence of type 2 inflammation (guided by blood eosinophil counts of ≥300 cells per microliter at screening). The efficacy that was observed in the these trials is supported by the central role of interleukin-4 and interleukin-13 in driving airway epithelial-barrier dysfunction, airway remodeling, and, more specifically for interleukin-13, goblet-cell hyper-

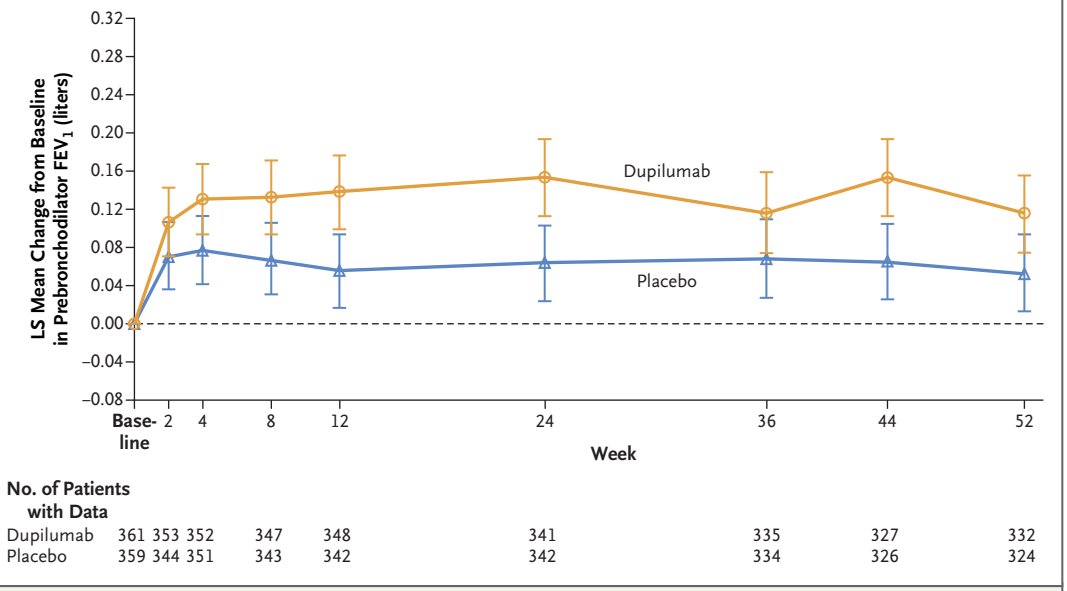

Figure 2. Change in Prebronchodilator FEV_1 over Time.

I bars indicate 95% confidence intervals. FEV_1 denotes forced expiratory volume in 1 second, and LS denotes least squares.

plasia and mucus secretion in type 2 mediated airway diseases.[12,13,26] Collectively, these findings highlight the importance of targeting interleukin-4 and interleukin-13 as drivers of type 2 inflammation in COPD.

Changes that were observed with dupilumab appeared to be similar across multiple subgroups defined according to demographic and disease characteristics. Of note, reductions in the frequency of moderate or severe exacerbations appeared to be similar in all prespecified subgroups, including subgroups defined according to age, sex, smoking status, lung function at baseline, history of exacerbations, and absence of emphysema.

The strengths of our trial include that it was an adequately powered, large, international trial in a patient population without other clinically significant pulmonary disease (notably asthma). A 34% relative reduction in moderate or severe exacerbations with dupilumab as compared with placebo observed in this trial is clinically significant.[27,28]

This trial also has limitations. The sample size for the week-52 end points was reduced owing to the early primary analysis, which reduced the statistical power for some week-52 end points. In addition, this trial was limited by the enrollment of a predominantly White population despite efforts to enroll a diverse patient population. Finally, the trial was conducted during the global Covid-19 pandemic, which led to disruptions in health care and changes in behaviors that, at times, led to decreased exposure to viral respiratory infections. Although the trial included patients who were enrolled at a time when the interruptions and effects of Covid-19 were less pronounced (e.g., 2022 and 2023), the Covid-19 pandemic and related behavioral changes could affect the generalizability of the results.

Our trial confirmed that add-on dupilumab treatment reduced the rate of exacerbations and increased lung function in patients with COPD with type 2 inflammation as indicated by elevated blood eosinophil counts.

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APPENDIX

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