

Original Investigation

Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis

A Randomized Clinical Trial

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IMPORTANCE Dupilumab has demonstrated efficacy in patients with asthma and atopic dermatitis, which are both type 2 helper T-cell-mediated diseases.

OBJECTIVE To assess inhibition of interleukins 4 and 13 with dupilumab in patients with chronic sinusitis and nasal polyposis.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled parallel-group study conducted at 13 sites in the United States and Europe between August 2013 and August 2014 in 60 adults with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids with 16 weeks of follow-up.

INTERVENTIONS Subcutaneous dupilumab (a 600 mg loading dose followed by 300 mg weekly; n = 30) or placebo (n = 30) plus mometasone furoate nasal spray for 16 weeks.

MAIN OUTCOMES AND MEASURES Change in endoscopic nasal polyp score (range, 0-8; higher scores indicate worse status) at 16 weeks (primary end point). Secondary end points included Lund-Mackay computed tomography (CT) score (range, 0-24; higher scores indicate worse status), 22-item SinoNasal Outcome Test score (range, 0-110; higher scores indicating worse quality of life; minimal clinically important difference ≥ 8.90), sense of smell assessed using the University of Pennsylvania Smell Identification Test (UPSIT) score (range, 0-40; higher scores indicate better status), symptoms, and safety.

RESULTS Among the 60 patients who were randomized (mean [SD] age, 48.4 years [9.4 years]; 34 men [56.7%]; 35 with comorbid asthma), 51 completed the study. The least squares (LS) mean change in nasal polyp score was -0.3 (95% CI, -1.0 to 0.4) with placebo and -1.9 (95% CI, -2.5 to -1.2) with dupilumab (LS mean difference, -1.6 [95% CI, -2.4 to -0.7]; $P < .001$). The LS mean difference between the 2 groups for the Lund-Mackay CT total score was -8.8 (95% CI, -11.1 to -6.6; $P < .001$). Significant improvements with dupilumab were also observed for the 22-item SinoNasal Outcome Test (LS mean difference between groups, -18.1 [95% CI, -25.6 to -10.6]; $P < .001$) and sense of smell assessed by UPSIT (LS mean difference, 14.8 [95% CI, 10.9 to 18.7]; $P < .001$). The most common adverse events were nasopharyngitis (33% in the placebo group vs 47% in the dupilumab group), injection site reactions (7% vs 40%, respectively), and headache (17% vs 20%).

CONCLUSIONS AND RELEVANCE Among adults with symptomatic chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids, the addition of subcutaneous dupilumab to mometasone furoate nasal spray compared with mometasone alone reduced endoscopic nasal polyp burden after 16 weeks. Further studies are needed to assess longer treatment duration, larger samples, and direct comparison with other medications.

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Chronic sinusitis, an inflammatory condition of the sinuses, is common with estimates of prevalence as high as 12% in Western populations.^{1,2} It is characterized by specific symptoms often lasting for many years including nasal congestion, discharge and postnasal drip, decreased or lost sense of smell, facial pain and pressure, headache, and the consequences thereof.³ Based on endoscopic findings, the condition can be divided into chronic sinusitis with or without nasal polyposis. Typically observed in the context of eosinophilic inflammation of the upper airways, nasal polyps originate in the sinuses and obstruct the sinus and nasal passages.

Medical management of chronic sinusitis with nasal polyposis focuses on controlling tissue inflammation and, depending on severity, includes use of intranasal corticosteroids, nasal saline irrigation, antibiotics, or short-course oral steroids.³ In patients in whom polyps and symptoms persist despite medical treatment, surgical excision is considered. However, disease recurrence after surgery approaches 50% in patients with tissue eosinophilia,⁴ and resolution of symptoms, including sense of smell loss, is often incomplete.

Epidemiological data from a large European cohort indicate that chronic sinusitis is associated with a 3.5-fold increase in comorbid asthma prevalence.⁵ Although type 2 helper T-cell inflammation is implicated in this association, the mechanisms of this association have not been fully elucidated.⁶⁻⁸

Dupilumab is a fully human monoclonal antibody to the interleukin 4 (IL-4) receptor α subunit, which inhibits signaling of IL-4 and IL-13, 2 cytokines central to type 2 helper T-cell-mediated inflammation. Dupilumab has demonstrated clinical efficacy in the type 2 helper T-cell-mediated diseases of asthma and atopic dermatitis,⁹⁻¹¹ and also improved sino-nasal symptoms in patients with asthma.⁹

We hypothesized that the addition of dupilumab to intranasal corticosteroids would improve endoscopic, radiographic, and patient-reported measures of disease activity in those with chronic sinusitis and nasal polyposis, while also improving lung function and disease control in patients with comorbid asthma.

Methods

Study Design and Participants

This randomized, double-blind, placebo-controlled parallel-group study was conducted at 13 sites in the United States and Europe (Belgium, Spain, and Sweden) between August 2013 and August 2014. A 4-week run-in period was followed by 16 weeks of blinded treatment and 16 weeks of follow-up. The trial protocol (Supplement 1) was approved by the institutional review board at each study site or by a central

institutional review board. All patients provided written informed consent and were given a stipend as governed by local regulations.

Eligible patients were aged 18 to 65 years with bilateral nasal polyposis and chronic symptoms of sinusitis despite intranasal corticosteroid treatment for at least 2 months. Patients were required to have a bilateral endoscopic nasal polyp score of at least 5 (maximum score of 8), with a score of at least 2 for each nostril, and manifest at least 2 of the following symptoms prior to screening: nasal obstruction or discharge, facial pain or pressure, and reduction or lost sense of smell. Patients were excluded if they: (1) had previously participated in any clinical trial of dupilumab; (2) had received corticosteroids (oral or intranasal), monoclonal antibodies, immunosuppressive treatment, or anti-immunoglobulin E (anti-IgE) therapy during the 2 months preceding the screening; (3) had undergone any nasal surgery within 6 months prior to screening or had more than 2 surgeries for nasal polyposis in the past; or (4) had concomitant conditions making them not evaluable for the primary end point.

A prespecified enrollment goal was that 50% of the patients had comorbid asthma. The diagnosis of asthma was based on patient history. The participants with asthma were required to have (1) a forced expiratory volume in the first second of expiration (FEV₁) of more than 60% of predicted, (2) taken daily inhaled corticosteroids of no more than 1000 μ g of fluticasone (or equivalent), and (3) not had an asthma exacerbation requiring systemic corticosteroids or hospitalization within the previous 3 months.

Study Treatments

After a 4-week run-in period of treatment with mometasone furoate nasal spray (100 μ g in each nostril twice daily), patients were randomly allocated (1:1) using an interactive voice or web-response system to add-on therapy with subcutaneous dupilumab (a 600 mg loading dose followed by 15 weekly doses of 300 mg) or matched placebo for 16 weeks. Randomization was performed with the use of a centralized computer-generated, permuted-block schedule with block size of 4 and stratification factors of visit 1 medical history of asthma (yes or no) and visit 2 nasal biopsy (yes or no).

Dupilumab and placebo were provided in identical and indistinguishable treatment kits, and study patients, investigators, and site personnel were blinded to study treatment. Mometasone furoate nasal spray was continued at a stable dose throughout the treatment period. Inhaled asthma controller therapies could be continued.

Outcomes

The primary efficacy end point was mean change in bilateral endoscopic nasal polyp score from baseline to week 16. This score is graded based on polyp size (recorded as the sum of the right and left nostril scores with a range of 0-8; higher scores indicate worse status).¹² Video recordings of endoscopies were sent to an independent reviewer for centralized blinded data assessment.

Secondary end points included change in the Lund-Mackay computed tomography (CT) score, percentage of max-

illary sinus volume occupied by disease, 22-item SinoNasal Outcome Test (SNOT-22) score, University of Pennsylvania Smell Identification Test (UPSIT) score, and peak nasal inspiratory flow. The secondary end points also included patient-rated nasal congestion or obstruction, anterior and posterior rhinorrhea, loss in sense of smell, nocturnal awakenings, and overall symptom severity. In patients with asthma, nasal polyp score was also a predefined secondary end point.

The Lund-Mackay CT score evaluates the patency of each sinus using a 0 to 2 scale (0 = normal; 2 = total opacification) and has a total score range from 0 to 24 (higher scores indicate more opacification).^{13,14} The 22-question SNOT-22 is scored as 0 (no problem) to 5 (problem as bad as it can be) with a total range from 0 to 110 (higher scores indicate poorer outcomes); a minimally clinically important difference (MCID) of 8.90 has been established.¹⁵ The UPSIT was administered every 8 weeks; scores range from 0 to 40 (higher scores of 35-40 indicate normal sense of smell and lower scores of 0-18 indicate anosmia).^{16,17}

Individual signs and symptoms were captured daily (AM and PM) by patients using an electronic diary and a categorical scale (0 = no symptoms; 3 = severe symptoms).¹⁸ Peak nasal inspiratory flow was also measured daily (AM and PM). A visual analog scale was used every 4 weeks to measure symptom severity, ranging from 0 (not troublesome) to 10 (worst thinkable), with total scores of 0 to 3 indicating presence of mild symptoms, greater than 3 to 7 indicating moderate symptoms, and greater than 7 to 10 indicating severe symptoms.¹⁸

Exploratory end points in patients with asthma were changes in FEV₁ (measured in liters) and FEV₁ percent predicted; the 5-question Asthma Control Questionnaire assessed asthma control.¹⁹ The 5-question Asthma Control Questionnaire is scored on a 7-point scale (0 = no impairment; 6 = maximum impairment) with an MCID of 0.5.²⁰ Further details on outcomes appear in eTable 1 in Supplement 2.

Pharmacodynamic measurements included total serum IgE, blood eosinophil count, serum thymus and activation-regulated chemokine (TARC) level, and plasma eotaxin-3 level; the latter 2 are involved in the chemotaxis of type 2 helper T-cells and eosinophils, respectively. These pharmacodynamic measurements were collected at weeks 2, 4, 8, 12, and 16. Safety and tolerability assessments were based on the incidence of adverse events and serious adverse events, as well as vital signs, physical examination, clinical laboratory evaluation, and 12-lead electrocardiogram findings.

Statistical Analysis

Efficacy analyses were performed using the intent-to-treat (ITT) population, which was predefined as all patients who were randomized. The safety data set comprised all randomized patients exposed to study medication. Statistical analyses were conducted using SAS nQuery Advisor version 6.01 (SAS Institute Inc).

The primary efficacy variable in the ITT population was analyzed using a mixed-effect model with repeated measures (MMRM) approach. The model included change while receiving treatment from baseline to follow-up time

points every 4 weeks through week 16 as response variables, fixed-effects factors for treatment, stratification (comorbid asthma, biopsy performed), visit, treatment × visit interaction, nasal polyp score baseline value, and baseline × visit interaction. The model did not impute missing data points. An unstructured correlation matrix was used to model the within-patient errors. Parameters were estimated using the restricted maximum likelihood method with the Newton-Raphson algorithm.

With approximately 28 patients per group, the study was predicted to have 80% power to detect a between-group difference of 1.3 in reduction of nasal polyp score from baseline using a 2-sided *t* test at the .05 significance level, and assuming a common standard deviation of 1.5 and a dropout rate of 20%. A sensitivity analysis also was performed using multiple imputation based on the placebo group to fill in the missing data, and an MMRM model was then built for the primary efficacy variable. Missing data that were not in a monotonic pattern were first imputed using a Markov-chain Monte Carlo method.

The rest of the missing data in both treatment groups were sequentially imputed by visit based only on the observed data of patients in the placebo group. This method should be considered as a conservative approach for a sensitivity analysis. The change from baseline to week 16 in percentage of maxillary sinus volume occupied by disease and Lund-Mackay score were analyzed using analysis of covariance models. The models include change from baseline as the response variable, and treatment, stratification factors, and baseline value as covariates. The change from baseline for other continuous end points was analyzed using an MMRM, which was the same analysis as described for the primary end point.

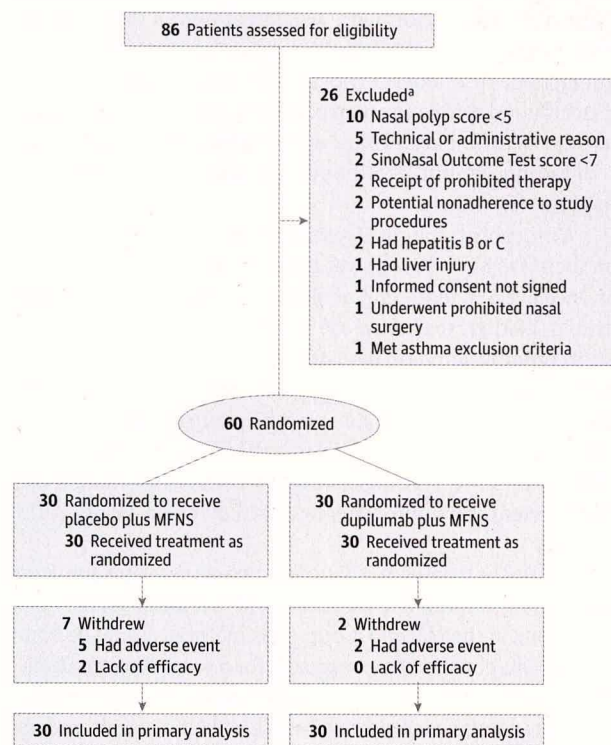
A prespecified responder analysis of patients with a reduction in nasal polyp score of at least 1.0 from baseline to week 16 was performed using logistic regression, including terms for treatment, stratification, and treatment × stratification interaction. An analysis of covariance model was used for the CT scan end points of Lund-Mackay total score and percentage of maxillary sinus volume occupied by disease. The factors in the model include treatment, stratification factors, and baseline values.

Descriptive statistics were used for demographics, baseline characteristics, and safety variables. Plots of secondary and pharmacodynamic variables are presented as mean or percentage change from baseline over time. Comparison of treatment effects from the MMRM analyses are based on the least squares mean change (with 95% confidence intervals and *P* values) from baseline to week 16. A 2-sided *t* test with a .05 significance level was used.

Results

Of 86 patients screened, 60 patients with chronic sinusitis and nasal polyposis were randomized (Figure 1). Among the 60 patients who were randomized (mean [SD] age, 48.4 years [9.4 years]; 34 men [56.7%]; 35 with comorbid asthma), 51 completed the study. Thirty patients were assigned to each treat-

Figure 1. Patients Enrolled and Included in the Analysis



MFNS indicates mometasone furoate nasal spray.

^a A patient could have more than 1 reason for exclusion.

ment group (ITT population). All patients received at least 1 dose of the study drug.

Demographic and baseline clinical characteristics were similar between the 2 groups (Table 1). There were 23 patients in the placebo group who completed the 16-week treatment period and 28 in the dupilumab group. Of the 7 patients in the placebo group who prematurely withdrew study treatment, 5 prematurely discontinued the study due to experiencing an adverse event and 2 due to lack of efficacy (Figure 1). Two patients in the dupilumab group did not complete treatment due to experiencing an adverse event.

Primary End Point

The least squares mean change in bilateral endoscopic nasal polyp score between baseline and week 16 was -0.3 (95% CI, -1.0 to 0.4) in the placebo plus mometasone furoate nasal spray group and -1.9 (95% CI, -2.5 to -1.2) in the dupilumab plus mometasone furoate nasal spray group (least squares mean difference, -1.6 [95% CI, -2.4 to -0.7], $P < .001$; Table 2 and Figure 2A). A sensitivity analysis using multiple imputation resulted in a least squares mean change in bilateral endoscopic nasal polyp score between baseline and week 16 of -0.4 (95% CI, -1.1 to 0.3) in the placebo plus mometasone furoate nasal spray group and -1.8 (95% CI, -2.5 to -1.2) in the dupilumab plus mometasone furoate nasal spray group (least squares mean difference, -1.5 [95% CI, -2.4 to -0.5]; $P = .002$).

In an additional analysis of this end point, improvement of at least 1 point in the nasal polyp score was observed in 20%

of the patients who received placebo vs 70% of those who received dupilumab (odds ratio [OR], 9.5 [95% CI, 2.8 to 31.8], $P < .001$). Furthermore, the improvement in nasal polyp score with dupilumab vs placebo was observed at week 4, which was the first postbaseline assessment (least squares mean difference, -1.03 [95% CI, -1.58 to -0.49]; $P < .001$).

Secondary End Points

Radiographic and Inspiratory Flow

The least squares mean change from baseline to week 16 for the Lund-Mackay CT total score was -0.2 (95% CI, -2.1 to 1.7) with placebo plus mometasone furoate nasal spray and -9.1 (95% CI, -10.7 to -7.5) with dupilumab plus mometasone furoate nasal spray (least squares mean difference, -8.8 [95% CI, -11.1 to -6.6], $P < .001$; Table 2). The least squares mean change in percentage of maxillary sinus volume occupied by disease was -4.2 (95% CI, -13.5 to 5.2) with placebo and -36.4 (95% CI, -44.4 to -28.4) with dupilumab (least squares mean difference, -32.2 [95% CI, -43.1 to -21.4]; $P < .001$).

The least squares mean change from baseline to week 16 for morning peak nasal inspiratory flow was 27.1 L/min (95% CI, 12.1–42.1 L/min) with placebo plus mometasone furoate nasal spray and 60.2 L/min (95% CI, 45.6–74.7 L/min) with dupilumab plus mometasone furoate nasal spray (least squares mean difference, 33.1 L/min [95% CI, 12.7–53.5 L/min], $P = .002$; Table 2 and Figure 2B).

Quality of Life and Daily Symptoms

There was improvement from baseline to week 16 for the SNOT-22 total score in patients treated with dupilumab plus mometasone furoate nasal spray vs those treated with placebo plus mometasone furoate nasal spray (least squares mean difference, -18.1 [95% CI, -25.6 to -10.6], $P < .001$; Table 2 and Figure 3A). This effect exceeded the MCID of 8.90.¹⁵

Significant improvements favoring dupilumab were observed with improved UPSIT scores for sense of smell, decreases in morning posterior rhinorrhea (Figure 3B–C), decreases in morning symptoms of nasal congestion or obstruction (Table 2), decreases in morning anterior rhinorrhea, increases in subjective sense of smell, decreases in evening symptoms, and decreases in nocturnal awakenings (eTable 2 in Supplement 2).

Nasal Polyp Score in Patients With Comorbid Asthma

In the subset of patients with comorbid asthma ($n = 35$), the least squares mean change in nasal polyp score was -0.02 (95% CI, -0.9 to 0.8) with placebo plus mometasone furoate nasal spray and -2.3 (95% CI, -3.2 to -1.4) with dupilumab plus mometasone furoate nasal spray (least squares mean difference, -2.3 [95% CI, -3.4 to -1.2], $P < .001$; Figure 4A). An improvement of at least 1 point in nasal polyp score was observed in 10.5% of patients who received placebo vs 75.0% of those who received dupilumab (OR, 26.1 [95% CI, 3.8 to 179.3]; $P < .001$).

Exploratory Analyses

Evaluations From Baseline to Week 32

Compared with patients who received placebo, reductions in nasal polyp score and improvements in peak nasal inspira-

Table 1. Baseline Demographic and Clinical Characteristics of the Patients

	Placebo Plus MFNS (n = 30)	Dupilumab Plus MFNS (n = 30)
Age, mean (SD), y	49.3 (9.1)	47.4 (9.8)
Male sex, No. (%)	16 (53.3)	18 (60.0)
Body mass index, mean (SD) ^a	26.8 (3.9)	28.1 (4.2)
Body mass index <30, No. (%)	24 (80.0)	22 (73.3)
White race, No. (%)	30 (100)	29 (96.7)
Bilateral endoscopic nasal polyp score, mean (SD) ^b	5.7 (0.9)	5.9 (1.0)
Assessed with computed tomography, mean (SD)		
Lund-Mackay total score ^c	18.7 (5.5)	18.6 (5.0)
Percentage of maxillary sinus volume occupied by disease	76.3 (23.9)	71.0 (26.2)
Peak nasal inspiratory flow in morning, mean (SD), L/min	109.2 (46.8)	98.4 (48.5)
SNOT-22 total score, mean (SD) ^d	40.6 (19.9)	41.4 (18.2)
Sinusitis symptom severity assessed on visual analog scale, mean (SD), cm ^e	6.4 (2.7)	6.4 (2.7)
Sense of smell assessed by UPSIT, mean (SD) ^f	15.6 (7.9)	12.8 (8.3)
Nasal congestion or obstruction, mean (SD) ^g		
AM	1.7 (0.7)	1.7 (0.7)
PM	1.6 (0.7)	1.6 (0.8)
Sense of smell loss, mean (SD) ^g		
AM	2.8 (0.5)	2.4 (0.9)
PM	2.8 (0.5)	2.4 (0.9)
Anterior rhinorrhea, mean (SD) ^g		
AM	1.1 (0.8)	1.0 (0.9)
PM	1.2 (0.7)	1.0 (0.9)
Posterior rhinorrhea, mean (SD) ^g		
AM	1.4 (0.8)	1.1 (0.9)
PM	1.4 (0.8)	1.0 (0.9)
Nocturnal awakenings, mean (SD) ^g	1.0 (1.2)	0.9 (1.1)
≥1 Prior surgery for nasal polyposis, No. (%)	19 (63.3)	16 (53.3)
Duration of nasal polyposis, mean (SD), y	11.5 (8.7)	7.6 (6.1)
Aspirin sensitivity, No. (%)	9 (30.0)	6 (20.0)
≥1 Positive antigen-specific IgE, No./total (%)	20/28 (71.4)	18/26 (69.2)
Comorbid asthma, No. (%)	19 (63.3)	16 (53.3)
Duration of asthma, mean (SD), y	20.2 (17.4)	15.5 (12.1)
FEV ₁ for all patients, mean (SD), L	3.0 (0.9)	3.2 (0.9)
FEV ₁ percent predicted for all patients, mean (SD)	86.5 (18.4)	87.9 (18.9)
FEV ₁ for patients with asthma, mean (SD), L	2.7 (0.8)	2.7 (0.7)
FEV ₁ percent predicted for patients with asthma, mean (SD)	79.8 (14.6)	82.2 (17.7)
ACQ5 score in patients with asthma, mean (SD) ^h	1.5 (0.9)	1.6 (1.1)
Total serum IgE, IU/mL		
Mean (SD)	195.3 (251.5)	139.7 (136.3)
Median (IQR)	101 (37-254)	87 (47-185)
Serum thymus and activation-regulated chemokine, mean (SD), pg/mL	449.3 (376.8)	469.7 (298.0)
Plasma eotaxin-3, mean (SD), pg/mL	61.6 (48.4)	64.0 (29.8)
Blood eosinophil count, ×10 ⁹ /L		
Mean (SD)	0.45 (0.67)	0.41 (0.24)
Median (IQR)	0.32 (0.18-0.49)	0.36 (0.25-0.47)

Abbreviations: ACQ5, 5-question Asthma Control Questionnaire; FEV₁, forced expiratory volume in the first second of expiration; IgE, immunoglobulin E; IQR, interquartile range; MFNS, mometasone furoate nasal spray; SNOT-22, 22-item SinoNasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.

^a Calculated as weight in kilograms divided by height in meters squared.

^b Range of 0 to 8 (higher scores indicate worse outcomes).¹²

^c Range of 0 to 24 (higher scores indicate more opacification).¹³

^d Range of 0 to 110 (higher scores indicate poorer outcomes) and a minimally clinically important difference of 8.90.¹⁵

^e Range of 0 (not troublesome) to 10 (worst thinkable).¹⁸

^f Range of 0 to 40 (higher scores of 35-40 indicate normal sense of smell).¹⁷

^g Symptoms were captured using a categorical scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms).¹⁸

^h Range from 0 to 6 (lower scores indicate better control of asthma) and a minimally clinically important difference of 0.5.²⁰

tory flow, SNOT-22, and symptom-based end points were sustained throughout the 16-week follow-up period in patients who received dupilumab plus mometasone furoate nasal spray; patients only received mometasone furoate nasal spray during follow-up (eTable 3 in Supplement 2).

Other End Points by Asthma Status

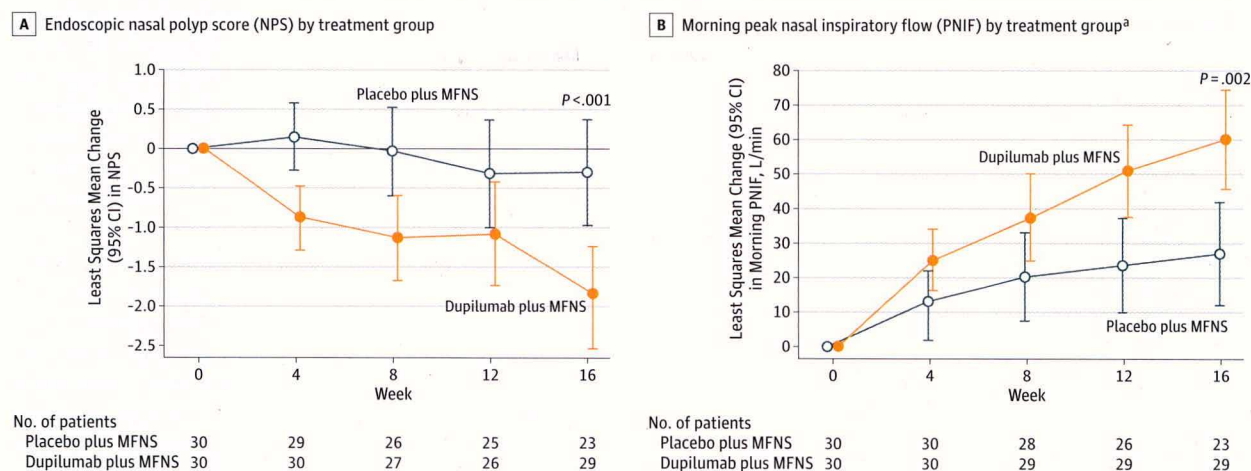
In the subset of patients with comorbid asthma (n = 35) and compared with patients who received placebo plus mometasone furoate nasal spray, dupilumab plus mometasone furoate nasal spray improved lung function and asthma control when assessed

Table 2. Change From Baseline to Week 16 in Primary, Secondary, and Exploratory End Points and in Pharmacodynamic and Type 2 Helper T-cell-Associated Biomarkers

	Placebo Plus MFNS (n = 30)		Dupilumab Plus MFNS (n = 30)		Absolute Difference for Dupilumab vs Placebo, LS Mean (95% CI)	P Value		
	Baseline, Mean (SD)	Week 16, Mean (SD)	Baseline, Mean (SD)	Week 16, Mean (SD)				
Primary End Point								
Nasal polyp score ^a	5.7 (0.9)	5.4 (1.5)	5.9 (1.0)	4.0 (1.9)	-1.9 (-2.5 to -1.2)	<.001		
Secondary End Points								
Lund-Mackay total score ^{b,c}	18.7 (5.5)	17.9 (5.7)	18.6 (5.0)	9.4 (5.1)	-9.1 (-10.7 to -7.5)	<.001		
Percentage of maxillary sinus volume occupied by disease ^c	76.3 (23.9)	69.8 (25.1)	71.0 (26.2)	34.9 (21.9)	-36.4 (-44.4 to -28.4)	<.001		
Peak nasal inspiratory flow in morning, L/min ^d	109.2 (46.8)	135.7 (58.2)	98.4 (48.5)	162.0 (51.7)	60.2 (45.6 to 74.7)	.002		
SNOT-22 total score ^e	40.6 (19.9)	30.2 (19.6)	41.4 (18.2)	12.8 (11.0)	-27.3 (-32.7 to -21.9)	<.001		
Sinusitis symptom severity assessed on visual analog scale, cm ^f	6.4 (2.7)	4.3 (3.1)	6.4 (2.7)	2.2 (2.7)	-4.3 (-5.4 to -3.2)	.008		
Sense of smell assessed by UPSIT ^g	15.6 (7.9)	16.2 (8.7)	12.8 (8.3)	28.7 (8.2)	14.1 (11.4 to 16.8)	<.001		
Nasal congestion or obstruction in the morning ^{g,h}	1.7 (0.7)	1.4 (0.7)	1.7 (0.7)	0.7 (0.7)	-0.9 (-1.2 to -0.7)	<.001		
Posterior rhinorrhea in the morning ^{g,h}	1.4 (0.8)	1.3 (0.9)	1.1 (0.9)	0.6 (0.6)	-0.5 (-0.8 to -0.3)	.002		
Exploratory End Points in Patients With Asthma								
FEV ₁ , L	2.7 (0.8)	2.8 (0.9)	2.7 (0.7)	3.1 (0.6)	0.3 (0.1 to 0.5)	.07		
FEV ₁ percent predicted	79.8 (14.6)	84.5 (13.7)	82.2 (17.7)	93.1 (12.6)	9.0 (3.0 to 15.1)	.04		
ACQ5 score ⁱ	1.6 (0.9)	1.4 (1.0)	1.6 (1.1)	0.3 (0.5)	-1.2 (-1.6 to -0.8)	<.001		
Pharmacodynamic and Type 2 Helper T-cell-Associated Biomarkers								
	Baseline, Mean (SD)	Week 16, Mean (SD)	% Change From Baseline, LS Mean (95% CI)	Baseline, Mean (SD)	Week 16, Mean (SD)	% Change From Baseline, LS Mean (95% CI)	Difference in % Change for Dupilumab vs Placebo, LS Mean (95% CI)	P Value
Total serum immunoglobulin E, IU/mL	195.3 (251.5)	122.8 (131.4)	7.9 (-1.2 to 17.0) ^j	139.7 (136.3)	79.5 (97.3)	-48.4 (-56.9 to -40.0) ^k	-56.3 (-68.2 to -44.4)	<.001
Serum thymus and activation-regulated chemokine, pg/mL	449.3 (376.8)	369.8 (222.8)	0.66 (-20.0 to 21.3)	469.7 (298.0)	312.2 (168.2)	-20.5 (-39.3 to -1.6)	-21.1 (-48.6 to 6.3)	.13
Plasma eotaxin-3, pg/mL	61.6 (48.4)	52.9 (26.7)	10.0 (0.4 to 19.5)	64.0 (29.8)	34.5 (14.2)	-35.5 (-44.3 to -26.7)	-45.5 (-57.6 to -33.3)	<.001
Blood eosinophil count, ×10 ⁹ /L	0.45 (0.67)	0.32 (0.20)	-2.9 (-29.2 to 23.4)	0.41 (0.24)	0.39 (0.34)	-7.3 (-29.2 to 14.6)	-4.4 (-36.1 to 27.2)	.78
Abbreviations: ACQ5, 5-question Asthma Control Questionnaire; FEV ₁ , forced expiratory volume in the first second of expiration; LS, least squares; MFNS, mometasone furoate nasal spray; SNOT-22, 22-item SinoNasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.								
Range of 0 to 8 (higher scores indicate worse outcomes). ¹²								
Range of 0 to 24 (higher scores indicate more opacification). ¹³								
Assessed with computed tomography.								
Change from baseline averaged over 4 weeks prior to each time point.								
Range of 0 to 110 (higher scores indicate poorer outcomes) and a minimally clinically important difference of 8.90. ¹⁵								

Abbreviations: ACQ5, 5-question Asthma Control Questionnaire; FEV₁, forced expiratory volume in the first second of expiration; LS, least squares; MFNS, mometasone furoate nasal spray; SNOT-22, 22-item SinoNasal Outcome Test; UPSIT, University of Pennsylvania Smell Identification Test.^a Range of 0 to 8 (higher scores indicate worse outcomes).¹²^b Range of 0 to 24 (higher scores indicate more opacification).¹³^c Assessed with computed tomography.^d Change from baseline averaged over 4 weeks prior to each time point.^e Range of 0 to 110 (higher scores indicate poorer outcomes) and a minimally clinically important difference of 8.90.¹⁵^f Range of 0 (not troublesome) to 10 (worst thinkable).¹⁸^g Range of 0 to 40 (higher scores of 35-40 indicate normal sense of smell).¹⁷^h Symptoms were captured using a categorical scale (0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms).¹⁸ⁱ Range from 0 to 6 (lower scores indicate better control of asthma) and a minimally clinically important difference of 0.5.²⁰^j Absolute change is 7.9.^k Absolute change is -48.4.

Figure 2. Primary and Secondary End Points for All Patients



The *P* value comparisons are for week 16. Compared with placebo plus mometasone furoate nasal spray (MFNS), dupilumab plus MFNS significantly improved the endoscopic NPS (maximum score = 8) and morning PNIF. Error bars indicate 95% CIs.

^a Assessed as change from baseline averaged over 4 weeks prior to each time point.

by the FEV₁ percent predicted (least squares mean difference, 7.2 [95% CI, 0.4 to 13.9], *P* = .04; Table 2 and Figure 4B-D). The least squares mean change from baseline to week 16 in scores on the 5-question Asthma Control Questionnaire was -0.1 (95% CI, -0.5 to 0.3) in the placebo group and -1.2 (95% CI, -1.6 to -0.8) in the dupilumab group (least squares mean difference, -1.1 [95% CI, -1.5 to -0.6]; *P* < .001), which exceeded the MCID of 0.5. Patients with asthma also experienced improvements with dupilumab in UPSIT score, SNOT-22 total score, and symptoms of congestion (eTable 4 in Supplement 2).

In patients without asthma, a dupilumab-specific effect was observed for the Lund-Mackay total score, UPSIT score, SNOT-22 total score, self-reported sense of smell loss, and other clinical end points; however, dupilumab did not lead to a significant reduction in endoscopic nasal polyp score (eTable 5 in Supplement 2).

Pharmacodynamic and Type 2 Helper T-cell-Associated Biomarkers

Levels of total serum IgE, serum TARC, and plasma eotaxin-3 expressed as least squares mean percentage changes from baseline decreased with dupilumab plus mometasone furoate nasal spray vs placebo plus mometasone furoate nasal spray (Table 2 and Figure 5A-C). Relative reductions in IgE with dupilumab progressed over the 16-week treatment period (*P* = .05 vs placebo at week 4 and *P* < .001 at each remaining assessment).

Levels of eotaxin-3 decreased significantly with dupilumab plus mometasone furoate nasal spray vs placebo by week 2 and remained reduced throughout the treatment period (all *P* ≤ .001 vs placebo). Levels of TARC decreased significantly with dupilumab vs placebo by week 2 (*P* < .001 vs placebo), remained significantly reduced through week 12 (*P* < .001), and tended to remain decreased at week 16 (*P* = .13). Transient increases in blood eosinophil count occurred in some patients

after initiation of dupilumab treatment; however, the mean blood eosinophil count was unchanged in both groups at week 16 (Figure 5D).

Safety

Adverse events were reported by 25 of 30 patients in the placebo group and 30 of 30 in the dupilumab group (eTable 6 in Supplement 2). Mild-to-moderate nasopharyngitis (33% in the placebo group vs 47% in the dupilumab group), injection site reactions (7% vs 40%, respectively), and headache (17% vs 20%) were the most frequent adverse events.

Six patients had serious adverse events: 4 in the placebo group (uterine cancer, transient ischemic attack, asthma, and nasal polyp) and 2 in the dupilumab group (one with herpes zoster and the other with arrhythmia and upper extremity pain or numbness). No serious adverse events were considered to be related to dupilumab.

Five patients in the placebo group experienced an adverse event that led to discontinuation of study drug (otitis media, bronchitis, hypersensitivity, headache, hypertension, asthma, and abdominal pain), as did 2 in the dupilumab group (constipation and injection site reaction). No clinically deleterious changes in vital signs, physical examination, laboratory testing, or electrocardiogram were observed with dupilumab compared with placebo.

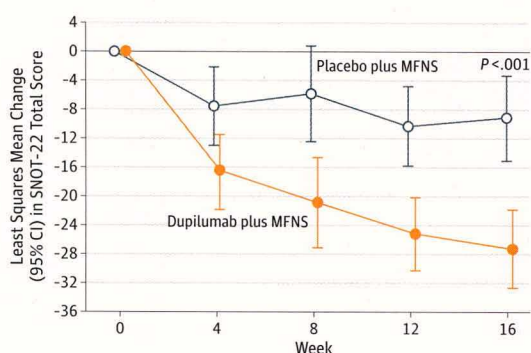
There were no deaths during the active treatment period. One patient died of a ruptured aortic aneurysm during the screening period prior to having been randomized to active treatment.

Discussion

In this proof-of-concept trial of dupilumab vs placebo added to standard-of-care intranasal corticosteroids in patients

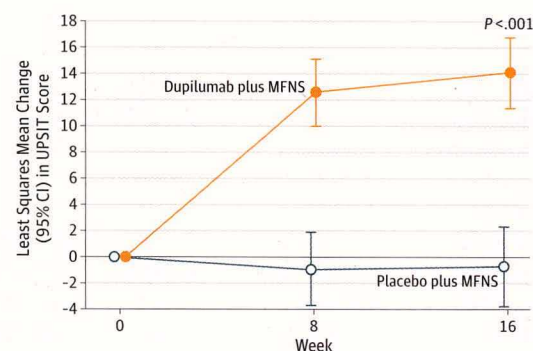
Figure 3. Quality-of-Life and Symptom-Based Secondary End Points

A 22-Item SinoNasal Outcome Test (SNOT-22) total score by treatment group

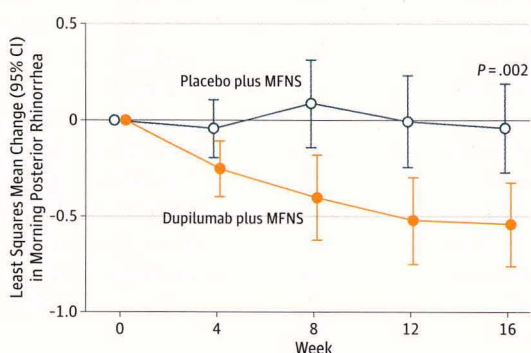


No. of patients					
Placebo plus MFNS	30	29	27	24	23
Dupilumab plus MFNS	30	30	29	29	29

B University of Pennsylvania Smell Identification Test (UPSIT) score by treatment group



No. of patients			
Placebo plus MFNS	30	28	23
Dupilumab plus MFNS	30	30	28

C Morning posterior rhinorrhea by treatment group^a

No. of patients					
Placebo plus MFNS	30	30	28	26	23
Dupilumab plus MFNS	30	30	29	29	29

The *P* value comparisons are for week 16. Compared with placebo plus mometasone furoate nasal spray (MFNS), dupilumab plus MFNS was associated with a significant improvement in the SNOT-22 total score, sense of smell (assessed by the UPSIT), and self-reported morning posterior rhinorrhea. Error bars indicate 95% CIs.

^a Assessed as change from baseline averaged over 4 weeks prior to each time point.

with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids alone, dupilumab treatment was associated with significant improvements in endoscopic, clinical, radiographic, and pharmacodynamic end points after 16 weeks. Although an MCID for nasal polyp score has not yet been established, the observed effect exceeded that of other approved treatments²¹ and was supported by meaningful changes in several other objective clinical and radiographic parameters, including significant improvement in CT scores.

Furthermore, significant improvements in quality of life (assessed by SNOT-22) and in major symptoms, such as subjective sense of smell, nasal obstruction or congestion, and nocturnal awakenings, were reported. Dupilumab was generally well tolerated, and no serious adverse events were considered to be related to dupilumab. Although injection site reactions were more frequent in patients treated with dupilumab vs placebo, there was no safety signal that contributed to excess study discontinuations in the dupilumab group.

Surgery is recommended as the next treatment option for patients who experience medical therapy failure³; however, a substantial proportion of patients experience post-surgical recurrence and require additional surgery.^{4,22} Although this trial was not designed to determine if dupilumab could delay or reduce surgical intervention, 58% of the study population had undergone prior surgery for nasal polyps, suggesting a potential role for dupilumab in this patient population.

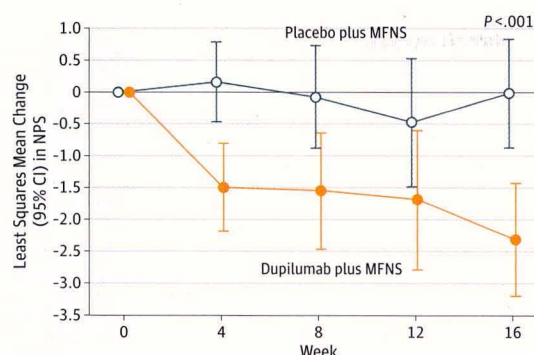
The clinical improvements observed with dupilumab treatment throughout the study appeared to be similar to that of the anti-IL-5 monoclonal antibody mepolizumab²³ (another biological therapy) in the ITT population and to that of the anti-IgE monoclonal antibody omalizumab¹² in the subgroup of patients with concomitant asthma; however, head-to-head studies are needed to draw conclusions.

These data suggest that signaling pathways mediated by IL-4 and IL-13 are important to the pathogenesis of chronic sinusitis with nasal polyposis, and that blocking these pathways leads to significant clinical benefit.

The improvements observed in patients with nasal polyposis and comorbid asthma are in line with data from patients with severe asthma observed in phase 2 studies of dupilumab, which suggest that dupilumab treatment improves both upper and lower airway inflammation. In the present trial, improvements were observed in endoscopic nasal polyp scores (a prespecified secondary end point) and in asthma control and lung function (exploratory end points) in patients with asthma. Mechanistically, these clinical observations support earlier reports^{7,8} suggesting that nasal polyposis and asthma share the same underlying type 2 helper T-cell inflammation.⁹ Elevations in levels of biomarkers associated with type 2 helper T cells (relative to controls), including eotaxin-3, TARC, and IgE, and their reduction by dupilumab herein, as well as in studies of patients with asthma⁹ and atopic dermatitis,¹¹ further support a common set of underlying type 2 helper T-cell inflammatory mechanisms in these diseases.

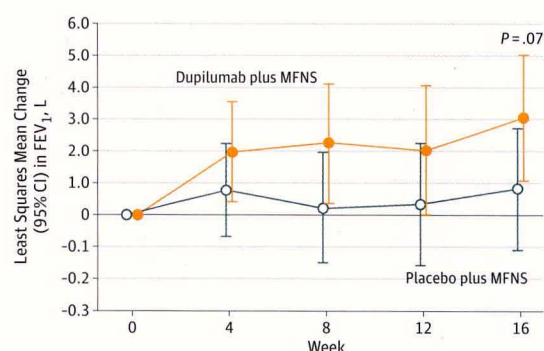
Figure 4. End Points in Patients With Comorbid Asthma

A Endoscopic nasal polyp score (NPS) by treatment group



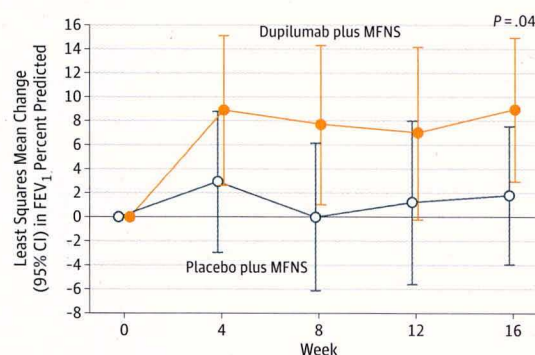
No. of patients

Placebo plus MFNS	19	19	18	17	15
Dupilumab plus MFNS	16	16	14	15	15

B Forced expiratory volume in the first second of expiration (FEV₁) by treatment group

No. of patients

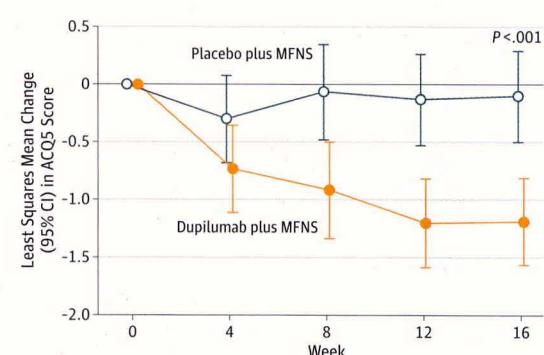
Placebo plus MFNS	17	17	17	16	14
Dupilumab plus MFNS	16	16	15	15	15

C FEV₁ percent predicted by treatment group

No. of patients

Placebo plus MFNS	17	17	17	16	14
Dupilumab plus MFNS	16	16	15	15	15

D 5-Question Asthma Control Questionnaire (ACQ5) score by treatment group



No. of patients

Placebo plus MFNS	16	16	16	13	12
Dupilumab plus MFNS	16	16	15	15	15

The *P* value comparisons are for week 16. Compared with placebo plus mometasone furoate nasal spray (MFNS), dupilumab plus MFNS was associated with improvements in endoscopic NPS (maximum score = 8), FEV₁, FEV₁

percent predicted, and ACQ5 score compared with placebo plus MFNS. Error bars indicate 95% CIs.

As a proof-of-concept trial, this study had some limitations. The number of participants (60 patients) was small, although this sample size was based on calculations identifying it as adequate to test the central hypothesis. The study duration was 16 weeks, limiting our ability to comment on the effect of dupilumab during long-term treatment.

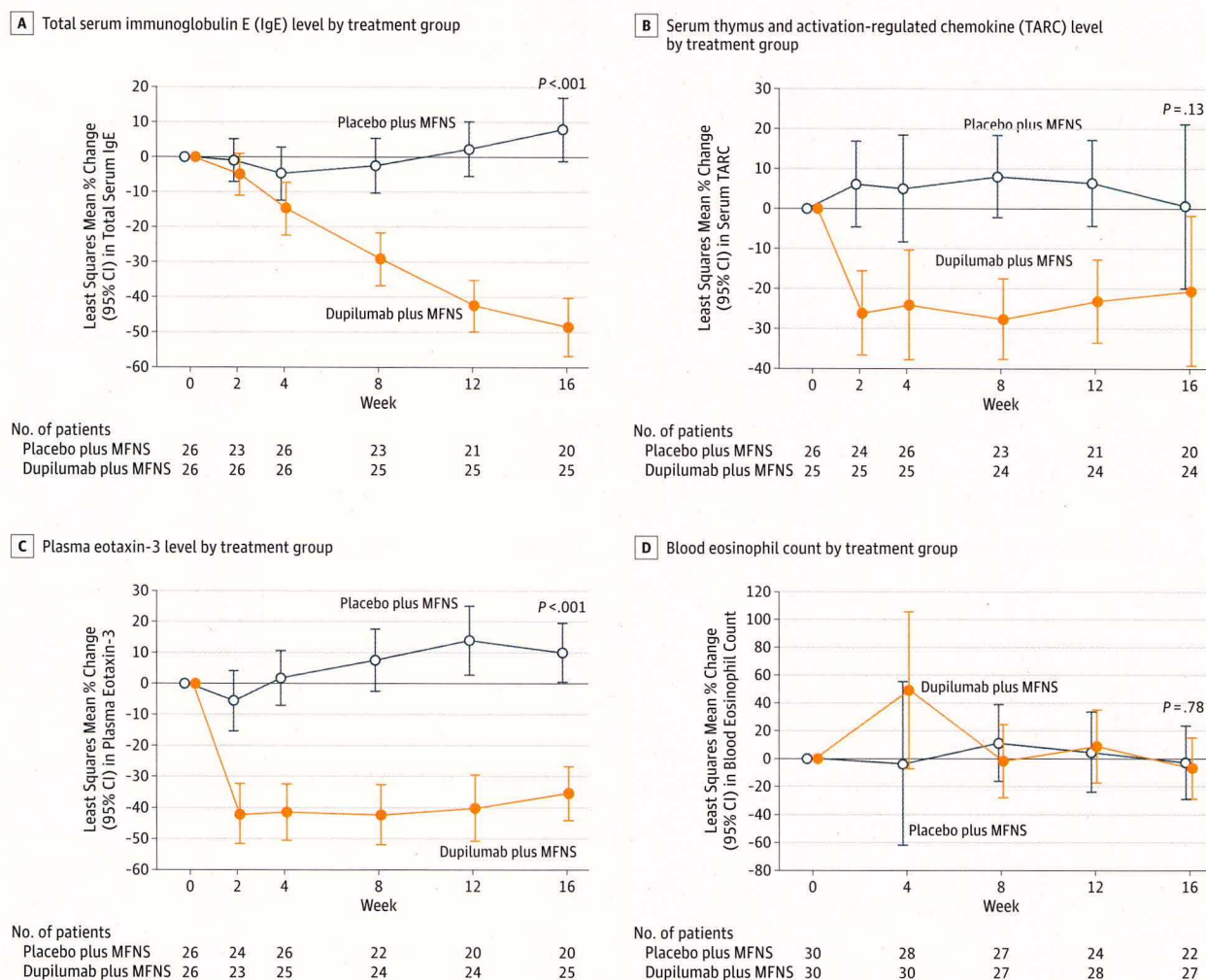
In addition, the absence of an established MCID for nasal polyp score presents a challenge for interpreting the clinical effect of dupilumab on the primary end point of the study. The least squares mean change from baseline at week 16 was -0.30 (SE, 0.34) in the placebo group and -1.85 (SE, 0.30) in the dupilumab group (least squares mean difference, -1.55 [95% CI, -2.43 to -0.67]; $P < .001$).

A previous study using a nasal polyp score with a narrower range (0-6 as opposed to 0-8 for the score in the current study) showed that intranasal corticosteroid treatment

(a standard therapy for nasal polyposis) led to a mean change of -0.5 vs placebo. A study²¹ using the same nasal polyp score as the current study showed a peak difference vs placebo of approximately -2.2 for systemic corticosteroids alone, without intranasal corticosteroids, in patients with nasal polyposis.

Because intranasal corticosteroids are the only approved treatment for nasal polyps, there is currently no suitable comparator drug available for long-term treatment. Further studies will be needed to investigate the potential use of dupilumab as adjunct therapy or in direct comparison with other medications or surgery.²⁴ In addition, 25% of participants (7/30) in the placebo group discontinued therapy. However, a sensitivity analysis using multiple imputation found similar results, suggesting that this dropout rate is unlikely to have biased the study findings.

Figure 5. Pharmacodynamic and Type 2 Helper T-cell-Associated Biomarkers



The *P* value comparisons are for week 16. Compared with placebo plus mometasone furoate nasal spray (MFNS), dupilumab plus MFNS was associated

with a significant improvement in pharmacodynamic and type 2 helper T-cell-associated biomarkers. Error bars indicate 95% CIs.

Conclusions

Among adults with symptomatic chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids, the addi-

tion of subcutaneous dupilumab to mometasone furoate nasal spray compared with mometasone alone reduced endoscopic nasal polyp burden after 16 weeks. Further studies are needed to assess longer treatment duration, larger samples, and direct comparison with other medications.

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Author Contributions: Dr Bachert had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Acquisition, analysis, or interpretation of data: Bachert, Mannent, Naclerio, Mullol, Ferguson, Gevaert, Jiao, Wang, Evans, Pirozzi, Graham, Swanson, Hamilton, Radin, Stahl, Yancopoulos, Sutherland.

Drafting of the manuscript: Bachert, Mannent, Gevaert, Wang, Evans, Hamilton, Sutherland. **Critical revision of the manuscript for important intellectual content:** Bachert, Mannent, Naclerio, Mullol, Ferguson, Gevaert, Hellings, Jiao, Evans, Pirozzi, Graham, Swanson, Hamilton, Radin, Gandhi, Stahl, Yancopoulos, Sutherland.

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Obtained funding: Pirozzi, Gandhi.

Administrative, technical, or material support: Ferguson, Evans, Swanson, Hamilton, Radin, Sutherland.

Study supervision: Bachert, Mannent, Gevaert, Hellings, Evans, Pirozzi, Graham, Stahl, Yancopoulos, Sutherland.

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Dr Bachert reported serving on advisory boards for and receiving personal fees from Sanofi and Novartis. Drs Mannent, Jiao, Wang, Pirozzi, Swanson, and Sutherland reported being employees and shareholders of Sanofi. Dr Naclerio reported receiving grant support from Meda Pharmaceuticals Inc, Merck, Nasaleze, Teva Pharmaceutical Industries Ltd, and Kalypsys Inc; and personal fees from Meda AB, Merck, GlaxoSmithKline, Teva Pharmaceutical Industries Ltd, and Sanofi. Dr Mullol reported receiving grant support from the Uriach Group, Meda Pharma, Faes Farma, Merck Sharp Dohme, and GlaxoSmithKline; and personal fees from Sanofi, the Uriach Group, Meda Pharma, ALK-Abelló A/S, Faes Farma, Hartington Pharmaceutical SL, Johnson & Johnson, the Menarini Group, Merck Sharp Dohme, GlaxoSmithKline, Crucell, Novartis, Pierre Fabre, and UCB. Dr Ferguson reported receiving consulting fees and travel reimbursement from Sanofi; and support for the conduct of studies from Meda Pharmaceuticals Inc, Teva Pharmaceutical Industries Ltd, Sanofi, and Knopp Biosciences. Dr Gevaert reported receiving grant support from Sanofi. Dr Hellings reported receiving grant support from Meda Pharma, GlaxoSmithKline, Merck, and ALK-Abelló. Drs Evans, Graham, Hamilton, Radin, Gandhi, Stahl, and Yancopoulos reported being employees and shareholders of Regeneron Pharmaceuticals Inc.

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