Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials

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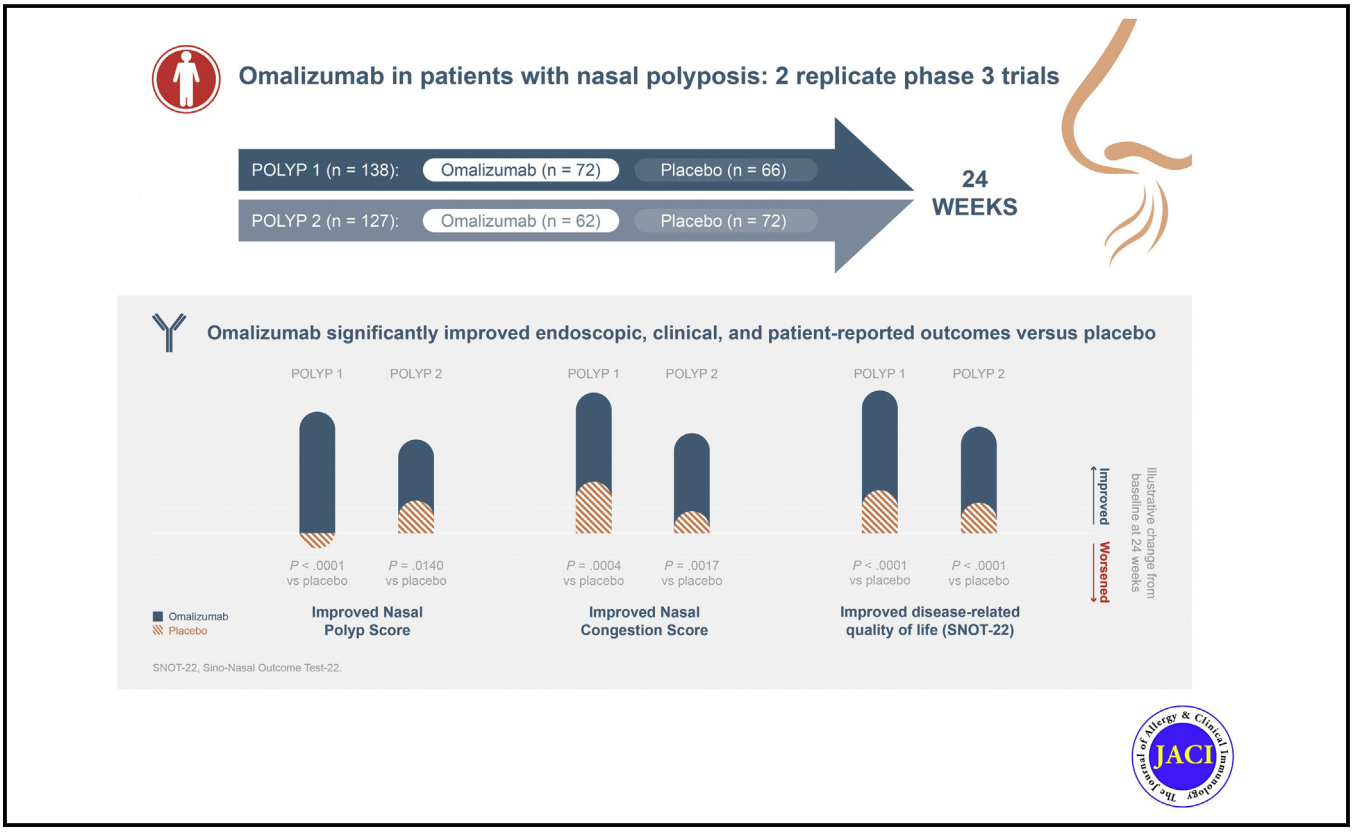
GRAPHICAL ABSTRACT



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Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is characterized by IgE hyperproduction and eosinophilic inflammation. The anti-IgE antibody, omalizumab, has demonstrated efficacy in patients with CRSwNP and comorbid asthma previously.

Objective: Our aim was to determine omalizumab safety and efficacy in CRSwNP in phase 3 trials (POLYP 1 and POLYP 2).

Methods: Adults with CRSwNP with inadequate response to intranasal corticosteroids were randomized (1:1) to omalizumab or placebo and intranasal mometasone for 24 weeks. Coprimary end points included change from baseline to week 24 in Nasal Polyp Score (NPS) and Nasal Congestion Score. Secondary end points included change from baseline to week 24 in Sino-Nasal Outcome Test-22 (SNOT-22) score, University of Pennsylvania Smell Identification Test, sense of smell, postnasal drip, runny nose, and adverse events.

Results: Patients in POLYP 1 (n = 138) and POLYP 2 (n = 127) exhibited severe CRSwNP and substantial quality of life impairment evidenced by a mean NPS higher than 6 and SNOT-22 score of approximately 60. Both studies met both the coprimary end points. SNOT-22 score, University of Pennsylvania Smell Identification Test score, sense of smell, postnasal drip, and runny nose were also significantly improved for omalizumab versus placebo. In POLYP 1 and POLYP 2, the mean changes from baseline at week 24 for omalizumab versus placebo were as follows: NPS, –1.08 versus 0.06 ($P < .0001$) and –0.90 versus –0.31 ($P = .0140$); Nasal Congestion Score, –0.89 versus –0.35 ($P = .0004$) and –0.70 versus –0.20 ($P = .0017$); and SNOT-22 score, –24.7 versus –8.6 ($P < .0001$) and –21.6 versus –6.6 ($P < .0001$). Adverse events were similar between groups.

Conclusion: Omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in severe CRSwNP with inadequate response to intranasal corticosteroids, and it was well tolerated. (J Allergy Clin Immunol 2020;146:595-605.)

Key words: *Nasal polyps, rhinosinusitis, omalizumab, quality of life, nasal obstruction, IgE, allergy, asthma*

Abbreviations used

AE:	Adverse event
AQLQ:	Asthma Quality of Life Questionnaire
CRS:	Chronic rhinosinusitis
CRSwNP:	Chronic rhinosinusitis with nasal polyps
FAS:	Full analysis set
FESS:	Functional endoscopic sinus surgery
HRQoL:	Health-related quality of life
INCS:	Intranasal corticosteroid
LSM:	Least-squares mean
MCID:	Minimal clinically important difference
NCS:	Nasal Congestion Score
NPS:	Nasal Polyp Score
NSAID:	Nonsteroidal anti-inflammatory drug
OR:	Odds ratio
QoL:	Quality of life
SCS:	Systemic corticosteroid
SNOT-22:	Sino-Nasal Outcome Test-22
TNSS:	Total Nasal Symptom Score
UPSIT:	University of Pennsylvania Smell Identification Test

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP), also referred to as nasal polyposis, is a severe form of CRS. CRS is common and is estimated to affect up to 15% of the population based on a symptomatic definition[1] and 3% to 6.7% of the population based on symptoms combined with endoscopic evaluation.[2] A recent large single-center study from the United States reported that approximately 18% of patients with CRS have CRSwNP.[3] CRSwNP is associated with adult-onset asthma, significant morbidity, decreased health-related quality of life (HRQoL),[4-8] and substantial economic burden (amounting to more than $22 billion for CRS in the United States in 2014).[9,10] Quality of life (QoL) impairment is comparable with that experienced by patients with chronic lower back pain.[11] Many patients with CRSwNP have uncontrolled symptoms despite use of intranasal corticosteroids (INCS) or systemic corticosteroids (SCS), use of doxycycline to reduce inflammation or infection, or functional endoscopic sinus surgery (FESS).[4,12] Furthermore, disease control is poor, with 20% to 80% of patients experiencing recurrence depending on follow-up duration.[13-15]

IgE is thought to play a central role in CRSwNP pathogenesis by activating type 2 inflammatory cells such as mast cells, basophils, and eosinophils (Fig 1).[16] Local IgE class switching by B cells and IgE production is well documented in tissue from patients with CRSwNP.[17-19] Within the sinonasal mucosa, *Staphylococcal* enterotoxin–specific IgE and polyclonal IgE for inhalant allergens, as well as colonization by microbial agents including *Staphylococcus aureus*, are associated with CRSwNP irrespective of atopic status.[20] Locally produced IgE appears to be functional and involved in regulating chronic inflammation.[21]

In real-world and randomized clinical studies, patients treated with the anti-IgE mAb, omalizumab, demonstrated reductions in CRS-related symptoms, endoscopic Nasal Polyp Score (NPS), and need for INCS use.[22-24] Improvements were observed by week 4 and were similar to those observed in patients receiving FESS.[23] In a randomized controlled trial of 24 patients with CRSwNP with comorbid asthma, omalizumab significantly improved endoscopic NPS, Lund-Mackay score (a validated measure of paranasal sinus occupation severity), and patient-reported outcomes irrespective of atopic status.[24]

On the basis of these proof-of-concept studies,[22-24] 2 phase 3 studies (POLYP 1 and POLYP 2) were conducted to evaluate the efficacy and safety of omalizumab versus placebo in adult patients with CRSwNP with inadequate response to INCS therapy.

METHODS

Study design and patient population

POLYP 1 (NCT03280550) and POLYP 2 (NCT03280537) were replicate (identical), phase 3, randomized, multicenter, double-blind, placebo-controlled studies evaluating the efficacy and safety of omalizumab in patients with inadequately controlled CRSwNP despite daily INCS therapy. They were conducted across 82 centers in North America and Europe between November 15, 2017, and March 11, 2019 (POLYP 1) and November 21, 2017, and March 7, 2019 (POLYP 2).

Patients aged 18-75 years with persistent bilateral nasal polyps, nasal congestion, impaired HRQoL, and weight and serum IgE level permitting omalizumab dosing per Table E1 (in this article's Online Repository at www.jacionline.org) (ie, weight of 30-50 kg and serum IgE level of 30-1500 IU/mL) were eligible. Patients were required to have received at least 4 weeks of INCS therapy before screening visit 1 and have a total NPS of 5 or higher (NPS ≥2 for each nostril) at screening visit 1 (day –35). Patients were further required to have an NPS of 5 or higher at screening visit 2 (day –7), after 4 weeks of

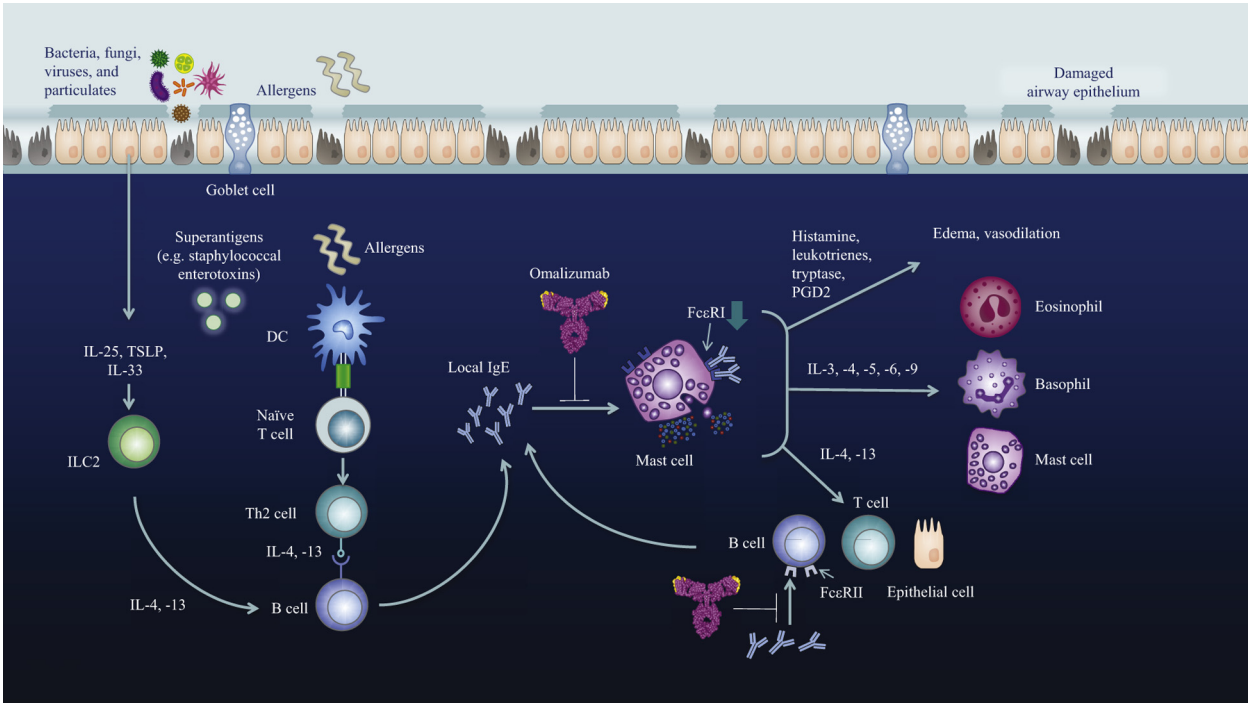

FIG 1. Role of IgE and proposed mechanism of action in chronic rhinosinusitis with nasal polyps. *DC*, Dendritic cell; *FcεRI*, high-affinity IgE receptor; *ILC2*, type 2 innate lymphoid cell; *PGD2*, prostaglandin D_2; *TSLP*, thymic stroma–derived lymphopoietin.

intranasal mometasone during run-in (200 μg twice daily or 200 μg daily if unable to tolerate 200 μg twice daily). A Nasal Congestion Score (NCS) of 2 or higher (with additional symptoms of postnasal drip, runny nose, and/or loss of sense of smell) at day –35 (1-week recall) and a weekly mean NCS higher than 1 at randomization (assessed every morning via an eDiary) were required (see the section Methods E1 in this article's Online Repository at www.jacionline.org). Patients were required to have a Sino-Nasal Outcome Test-22 (SNOT-22) score of 20 or higher at day –35 and randomization.

Patients were excluded if they had other sinonasal or pulmonary disorders (except asthma), including the following: current upper respiratory tract infection, cystic fibrosis, or other dyskinetic ciliary syndrome; past or current malignancy; a cardiac condition; hepatitis; liver cirrhosis; recent or current infection requiring hospitalization (≤4 weeks), antibiotic (≤2 weeks) or antifungal treatment, or parasitic infection (≤6 months); recent use of an SCS (≤2 months), immunosuppressant, biologic, or leukotriene antagonist or modifier; recent nasal surgery (≤6 months); known allergy to omalizumab; or those who were immunocompromised.

Patients were randomized (1:1) to omalizumab or placebo and background intranasal mometasone for 24 weeks (Fig 2). The protocol specified study dosing of 75 to 600 mg by subcutaneous injection every 2 or 4 weeks, depending on the pretreatment serum total IgE level and body weight (see Table E1). Permuted block randomization (block size 4) was performed by using an interactive web-based response system within strata defined by comorbid asthma/aspirin sensitivity and geographic region. The investigator, investigational site staff, central image readers, sponsor and sponsor's representatives, and patients were blinded to treatment allocation.

Saline nasal lavages were permitted during the study. However, because antibiotics are often used to treat CRSwNP, systemic antibiotic therapy for more than 14 days was not permitted during the study. A complete list of prohibited medications and procedures are in the section Methods E1.

The protocol was approved by the studies' respective institutional review boards or ethics committees. All patients provided written informed consent. The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice,[25] the Declaration of Helsinki,[26] and all applicable laws and regulations.

Assessments

Demographic data and medical history were collected during screening visit 1. Blood samples were collected at screening and at weeks 16, 24, and 28 for routine analyses. Serum IgE levels were determined at baseline. NPS (point range, 0-8 [see Table E2 in this article's Online Repository at www.jacionline.org]) was determined for each nasal passage at screening and at weeks 4, 8, 16, and 24. Endoscopic videos were scored at a central reading center by 2 blinded independent trained otolaryngologists. Discrepancies were adjudicated by a third blinded otolaryngologist. Nasal symptoms were recorded daily with the use of an eDiary (with nasal congestion, sense of smell, postnasal drip, and runny nose each assigned a score ranging from 0 [not at all] to 3 [severe]); each component was analyzed separately and in a combined summed Total Nasal Symptom Score (TNSS) (point range, 0-12 [see Table E3 in this article's Online Repository at www.jacionline.org]). The nasal congestion question forms the NCS. The University of Pennsylvania Smell Identification Test (UPSIT) was performed at day 1 and at weeks 8, 16, and 24 (point range, 0-40, with higher scores indicating better smell). SNOT-22 score was measured at screening; on day 1; and at weeks 4, 8, 16, and 24 (point range, 0-110, with lower scores indicating better disease control and QoL). In patients with comorbid asthma, the Asthma Quality of Life Questionnaire (AQLQ) was administered at day 1 and at weeks 16 and 24 (point range, 1-7, with higher scores indicating better QoL). Adverse events (AEs) and concomitant medications were monitored throughout treatment and safety follow-up.

An open-label extension study will assess patients who received 24 weeks of open-label omalizumab followed by a 24-week off-drug observation period (see the section Methods E1).

Outcomes

The coprimary end points were change from baseline to week 24 in endoscopic NPS[24] and mean daily NCS. Secondary end points included change from baseline at week 24 in SNOT-22 score, UPSIT (a widely used measure recommended by British Medical Journal Best Practice Guidelines to assess olfactory function in nasal polyps[27]) score, mean daily sense of smell,

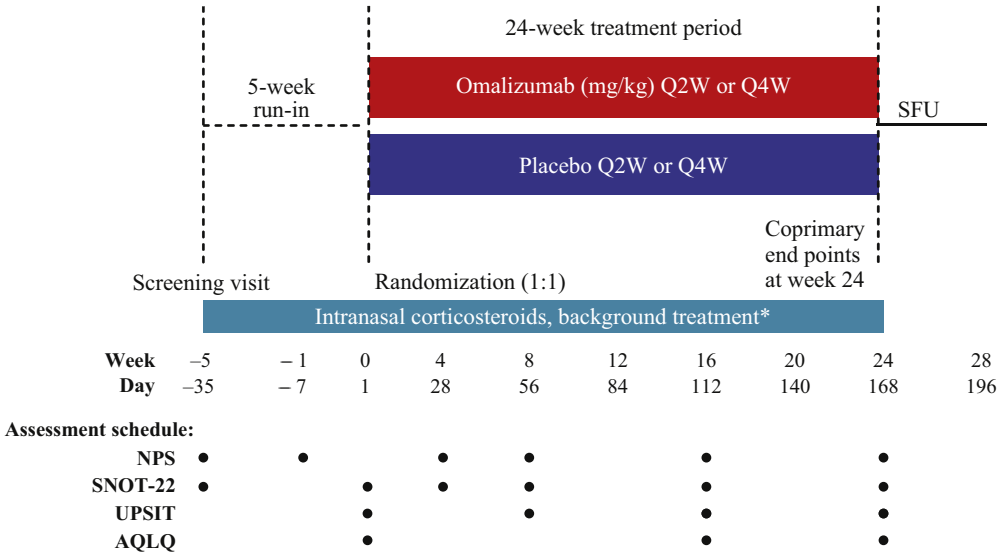

FIG 2. Study design for POLYP 1 and POLYP 2. *All patients received intranasal corticosteroids (mometasone nasal spray) as background therapy. *Q2W*, Every 2 weeks; *Q4W*, every 4 weeks; *SFU*, safety follow-up.

postnasal drip, runny nose, and TNSS; change from baseline at week 16 in NPS and NCS; and percentage of patients requiring rescue therapy (an SCS for ≥3 consecutive days and/or nasal polypectomy) by week 24. Reduction in need for surgery through week 24 was predefined as achievement of an NPS of 4 or lower (≤2 for each nostril) and an improvement of at least the minimal clinically important difference (MCID[28];≥8.9 points) in SNOT-22 score. The percentage of patients with comorbid asthma demonstrating an MCID in improvement (≥0.5 points) in AQLQ score through week 24 was also assessed. Exploratory end points included percentage of patients in the pooled population achieving at least a 2-point or at least a 1-point improvement in NPS and at least a 1-point improvement in NCS.

AEs were assessed for severity and potential causal relationship to the study drug. Patients were monitored to week 28 as a safety follow-up. AEs were reported for the pooled POLYP 1 and POLYP 2 population.

Statistical analyses

A sample size of 120 patients was calculated to provide at least 85% power to detect a 0.56-point between−treatment group difference in change from baseline to week 24 in mean daily NCS and a 1.50-point between−treatment group difference in mean change from baseline to week 24 in NPS. The corresponding assumed SDs were 0.83 and 2.2.[24,29,30]

The full analysis set (FAS) included all randomized patients who received at least 1 dose of study drug according to assigned treatment group. The safety analysis set included all patients who received at least 1 dose of study drug according to treatment received. Randomized patients were treated with the study drug; both analysis sets were identical in POLYP 1 and differed by 1 patient in POLYP 2. Safety and tolerability results were described for the FAS by using summary statistics. Patient demographic and clinical characteristics and efficacy end points were evaluated by using the FAS. Sequential testing type 1 error control procedures are described in the section Methods E1. All 95% CIs are unadjusted for multiplicity. The within-group means and between-group differences in absolute change from baseline to week 24 were the estimated least squares means (LSMs) obtained by using a mixed-effect model with repeated measures with unstructured covariance matrix, adjusted for comorbid asthma/aspirin sensitivity, geographic region, time point per schedule of assessments, baseline outcome score, treatment by time point interaction, and baseline outcome score by time point interaction for NCS, UPSIT score, SNOT-22 score, and TNSS. *P* values were derived from a *t* test of difference in LSMs.

The between-group difference in the proportion of patients at week 24 with reduced need for surgery was estimated by using a logistic regression model analysis adjusted for the aforementioned baseline covariates, baseline NPS, and SNOT-22 score. The between-group difference in the proportion of patients requiring rescue treatment by week 24 was estimated by using a logistic regression model analysis for oral corticosteroid use for 3 or more consecutive days and/or sinus surgery adjusted for baseline covariates (see earlier). The between-group differences in the proportion of patients with comorbid asthma by week 24 was estimated by using a logistic regression model analysis adjusted for baseline covariates (see earlier) and baseline AQLQ score. *P* values for between-group differences in proportions were derived from a Wald chi-square test of the treatment effect coefficient in the logistic regression model.

RESULTS

Study disposition, baseline demographics, and clinical characteristics of patients

In POLYP 1, 138 of 355 screened patients were randomized. In POLYP 2, 127 of 329 screened patients were randomized (Fig 3). In POLYP 1, 95.8% of patients treated with omalizumab (69 of 72) and 97.0% of patients in the placebo group (64 of 66) completed the study. In POLYP 2, 93.5% of patients treated with omalizumab (58 of 62) and 96.9% of those in the placebo group (63 of 65) completed the study. Five patients (3 who received omalizumab and 2 who received placebo) in POLYP 1 and 6 patients (4 who received omalizumab and 2 who received placebo) in POLYP 2 discontinued the study. Reasons for discontinuation included patient decision (2 patients in POLYP 1 and 4 in POLYP 2) and investigator decision (1 patient in POLYP 1) for the omalizumab groups and patient decision for the placebo groups (2 patients in POLYP 1 and 2 in POLYP 2).

Demographics and clinical characteristics were similar between treatment groups and across the studies (Table I). Patients had severe nasal polyps and/or symptoms at baseline (mean NPS >6), significant loss of smell (mean UPSIT score, 12.8-13.9 [81.5% of patients had anosmia]), and substantial CRSwNP-related HRQoL impairment (mean SNOT-22 score, 59.2-60.5). Across the studies, 48.5% to 61.3% of patients had comorbid asthma; most had mild (35.1%) or moderate (58.3%) physician-assessed asthma severity. Nonsteroidal

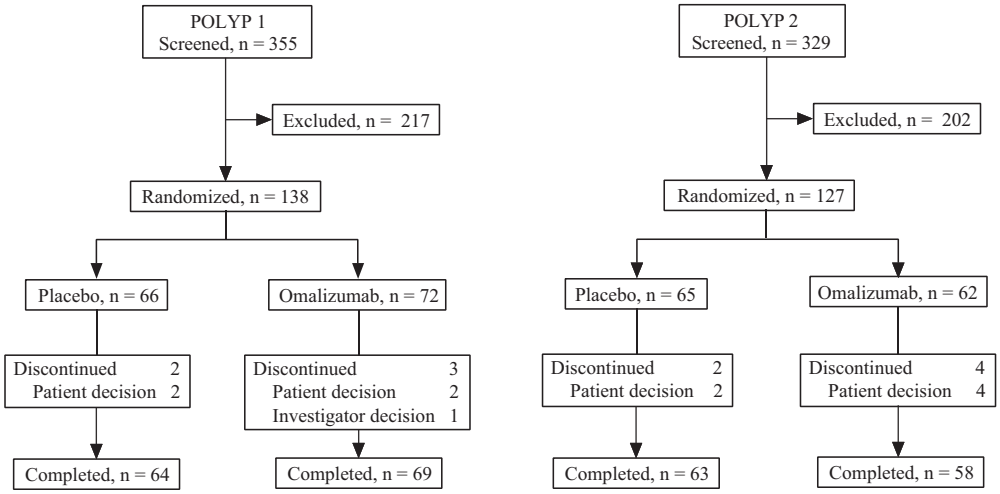

FIG 3. Patient disposition (Consolidated Standards of Reporting Trials flow diagram).

anti-inflammatory drug (NSAID)-exacerbated respiratory disease (or aspirin-exacerbated respiratory disease) was present in 27.2% of patients.

Across the studies, 12.1% to 29.0% of patients used an SCS in the prior year and 59.6% of patients had undergone prior sinonasal surgery. Most patients (92.3%-96.8%) received the maximum allowed mometasone dosag during run-in and treatment. Most patients (90.4% in the pooled omalizumab arms and 86.9% in the pooled placebo arms) were assigned to receive omalizumab or placebo every 4 weeks, with similar dose and dosing frequency across the studies and between treatment groups (Table I).

Changes in NPS and NCS

Both studies met their coprimary end points, with omalizumab-treated patients achieving statistically significant improvements in mean NPS and daily NCS at week 24 versus placebo. The mean changes in NPS for omalizumab versus placebo from baseline at week 24 were –1.08 versus +0.06 (treatment arm difference, –1.14 [95% CI = –1.59 to –0.69; $P < .0001$]) in POLYP 1 and –0.90 versus –0.31 (treatment arm difference, –0.59 [95% CI = –1.05 to –0.12; $P = .0140$]) in POLYP 2. The mean changes for omalizumab versus placebo in NCS from baseline to week 24 were –0.89 versus –0.35 (treatment arm difference, –0.55 [95% CI = –0.84 to –0.25; $P = .0004$]) in POLYP 1 and –0.70 versus –0.20 (treatment arm difference, –0.50 [95% CI = –0.80 to –0.19; $P = .0017$]) in POLYP 2, respectively (Table II). The between-treatment group differences at week 16 were similar to those at week 24 for NPS and NCS (Table II). Greater improvements in NPS and NCS for omalizumab versus placebo were observed as early as week 4 (first assessment) in both studies (Fig 4, *A* and *B*). The mean changes from baseline at week 4 in NPS for omalizumab versus placebo were –0.92 (95% CI = –1.37 to –0.48) in POLYP 1 and –0.52 (95% CI = –0.94 to –0.11) in POLYP 2. The mean changes from baseline at week 4 in NCS for omalizumab versus placebo were –0.25 (95% CI = –0.46 to –0.04) in POLYP 1 and –0.26 (95% CI = –0.45 to –0.07) in POLYP 2.

A greater percentage of omalizumab-treated patients had improved NPS and NCS at week 24 versus placebo in the pooled population. One-point or greater and 2-point or greater improvements in NPS were observed in 56.3% (72 of 128) and 31.3% (40 of 128) of omalizumab-treated patients and 28.7% (37 of 129) and 11.6% (15 of 129) of placebo-treated patients, respectively. A 1-point or greater improvement in NCS was observed in 56 of 126 omalizumab-treated patients (44.4%) and in 27 of 126 placebo-treated patients (21.4%) (Fig 5).

Patients with comorbid asthma and NSAID-exacerbated respiratory disease in the pooled population had similar mean improvements in NPS and NCS at week 24 compared with patients without NSAID-exacerbated respiratory disease (see Fig E1 in this article's Online Repository at www.jacionline.org).

Secondary efficacy end points

Statistically significant improvements favoring omalizumab were observed in both studies for SNOT-22 score, UPSIT score, TNSS, and individual nasal symptoms (sense of smell, postnasal drip, runny nose) from baseline at week 24 (Table II and Fig 6, *A-C*). In an exploratory analysis of prior time points, effects were observed as early as the first time point assessed (week 4 for most end points, week 8 for UPSIT score). The LSM difference in change from baseline at week 4 in SNOT-22 score with omalizumab versus placebo was –10.43 (95% CI = –15.08 to –5.79) in POLYP 1 and –8.84 (95% CI = –13.84 to –3.84) in POLYP 2. The LSM difference in change from baseline at week 8 in UPSIT score for omalizumab versus placebo was 3.78 (95% CI = 1.56-6.00) in POLYP 1 and 3.44 (95% CI = 1.03-5.85) in POLYP 2.

The odds of achieving at least a 0.5-point improvement in AQLQ score (MCID) were approximately 4 times higher for omalizumab- versus placebo-treated patients with comorbid asthma (for POLYP 1, odds ratio [OR] = 3.7 [95% CI = 1.0-13.7; $P = .0492$]; for POLYP 2, OR = 4.0 [95% CI = 1.1-15.3; $P = .0396$]) (Table III).

Rescue SCS therapy was required in 8 of 129 placebo-treated patients (6.2%) and 3 of 129 omalizumab-treated patients (2.3%) from the pooled population during the study, favoring omalizumab with a 62.5% relative reduction (a 3.9% absolute difference) in rescue steroid use ($P = .16$). No sinus surgeries or polypectomies were recorded. A reduced need for surgery by week 24 was observed in 2 of 65 placebo-treated patients (3.1%) and 13 of 69 omalizumab-treated patients (18.8%) from POLYP 1

TABLE I. Baseline characteristics of randomized patients

Characteristic	POLYP 1		POLYP 2	
	Placebo (n = 66)	Omalizumab (n = 72)	Placebo (n = 65)	Omalizumab (n = 62)
Age (y), mean (SD)*	52.2 (11.6)	50.0 (14.5)	51.0 (12.0)	49.0 (11.9)
Male, no. (%)*	41 (62.1)	47 (65.3)	44 (67.7)	39 (62.9)
BMI (mg/kg^2), mean (SD)	27.7 (5.3)	27.4 (4.8)	28.1 (5.0)	26.9 (4.1)
Geographic region, no. (%)				
North America	19 (28.8)	23 (31.9)	14 (21.5)	12 (19.4)
Europe	47 (71.2)	49 (68.1)	51 (78.5)	50 (80.6)
Tobacco use, no. (%)				
Current smoker	6 (9.1)	6 (8.3)	8 (12.3)	7 (11.3)
Former smoker	13 (19.7)	11 (15.3)	18 (27.7)	15 (24.2)
NPS (range, 0-8), mean (SD)†	6.3 (0.9)	6.2 (1.0)	6.1 (0.9)	6.4 (0.9)
NCS (range, 0-3), mean (SD)†	2.5 (0.6)	2.4 (0.7)	2.3 (0.6)	2.3 (0.7)
Sense of smell score (range, 0-3), mean (SD)†	2.8 (0.4)	2.5 (0.8)	2.8 (0.6)	2.6 (0.8)
Postnasal drip score (range, 0-3), mean (SD)†	2.0 (0.9)	1.7 (0.9)	1.8 (0.9)	1.6 (0.9)
Runny nose score (range, 0-3), mean (SD)†	2.1 (0.8)	1.9 (0.8)	1.9 (0.8)	1.9 (0.9)
TNSS (range, 0-12), mean (SD)†	9.3 (1.9)	8.6 (2.5)	8.7 (2.3)	8.4 (2.6)
UPSIT score (range, 0-40), mean (SD)‡	13.9 (7.4)	12.8 (7.9)	13.1 (7.3)	12.8 (7.6)
SNOT-22 score (range, 0-110), mean (SD)†	60.5 (15.3)	59.8 (19.7)	59.8 (18.2)	59.2 (20.5)
Comorbid asthma, no. (%)	32 (48.5)	42 (58.3)	39 (60.0)	38 (61.3)
Physician-assessed asthma severity, no. (%)				
Mild	15 (46.9)	13 (31.0)	13 (33.3)	12 (31.6)
Moderate	16 (50.0)	27 (64.3)	25 (64.1)	20 (52.6)
Severe	1 (3.1)	2 (4.8)	1 (2.6)	6 (15.8)
AQLQ score, mean (SD)*	4.8 (1.3)	4.5 (1.5)	5.2 (1.3)	4.9 (1.2)
NSAID-exacerbated respiratory disease (AERD), no. (%)	11 (16.7)	16 (22.2)	21 (32.3)	24 (38.7)
Serum total IgE (IU/mL), mean (SD)	162.0 (141.2)	159.9 (139.0)	196.1 (200.6)	184.1 (201.9)
Blood eosinophils (cells/μL), mean (SD)	358.6 (305.2)	334.4 (264.7)	357.4 (196.2)	310.8 (176.6)
SCS use in past year, no. (%)	8 (12.1)	18 (25.0)	15 (23.1)	18 (29.0)
Courses of SCS, no. (%)				
1	5 (62.5)	9 (50.0)	6 (40.0)	11 (61.6)
≥2	2 (25.0)	7 (38.9)	9 (60.0)	5 (27.8)
Unknown	1 (12.5)	2 (11.1)	0 (0.0)	2 (11.1)
Previous NP surgery, no. (%)	40 (60.6)	39 (54.2)	40 (61.5)	39 (62.9)
No. of previous NP surgeries, no. (%)				
1	24 (36.4)	23 (31.9)	15 (23.1)	22 (35.5)
≥2	16 (24.2)	16 (22.2)	25 (38.5)	17 (27.4)
Time since last NP surgery, no. (%)				
>12 mo to 5 y	13 (32.5)	9 (23.1)	12 (30.0)	9 (24.3)
>5 y	27 (67.5)	30 (76.9)	28 (70.0)	28 (75.7)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	2 (5.1)
Mometasone dose prescribed, no. (%)				
200 μg daily	4 (6.1)	4 (5.6)	5 (7.7)	2 (3.2)
200 μg twice daily	62 (93.9)	68 (94.4)	60 (92.3)	60 (96.8)
Planned dosing schedule for study drug, no. (%)				
Every 4 weeks	61 (92.4)	67 (93.1)	52 (81.3)	55 (87.3)
Every 2 weeks	5 (7.6)	5 (6.9)	12 (18.8)	8 (12.7)

AERD, Aspirin-exacerbated respiratory disease; *BMI*, body mass index; *NP*, nasal polyp.
*In POLYP 2: placebo, n = 64.
†Higher scores indicate worse health status.
‡Higher scores indicate better sense of smell; UPSIT score of 0 to 18 indicates a total loss of smell/anosmia.

(OR = 6.3 [95% CI = 1.3-29.6; P = .0209]) and in 2 of 63 placebo-treated patients (3.2%) and 10 of 59 omalizumab-treated patients (16.9%) from POLYP 2 (OR = 6.2 [95% CI = 1.2-60.2; P = .0139]) (Table III).

Safety and tolerability

The proportions of patients who experienced at least 1 treatment-emergent AE were 58.5% in placebo-treated patients and 50.4% in omalizumab-treated patients. The number of AEs was greater in placebo-treated patients than in omalizumab-treated patients. Most events across both studies were of mild to moderate intensity. Two serious AEs were reported in placebo-treated patients (1.5% [1 case of myocardial infarction and 1 case of pneumonia]) and 3 were reported in omalizumab-treated patients (2.2% [1 case of snake bite, 1 hand fracture, and 1 case of asthma exacerbation/worsening]). The proportion of patients experiencing at least 1 AE suspected by the investigator to be omalizumab related was 3.8% in placebo-treated patients versus 6.7% in omalizumab-treated patients. These AEs were mild to

TABLE II. Primary and secondary efficacy end points

End point	POLYP 1				POLYP 2			
	Placebo (n = 66)*	Omalizumab (n = 72)*	Treatment arm differences†	*P* value	Placebo (n = 65)*	Omalizumab (n = 62)*	Treatment arm differences†	*P* value
Primary end point at week 24								
NPS (range, 0-8)	0.06 (0.16)	−1.08 (0.16)	−1.14 (−1.59 to −0.69)	<.0001	−0.31 (0.16)	−0.90 (0.17)	−0.59 (−1.05 to −0.12)	.0140
NCS (range, 0-3)	−0.35 (0.11)	−0.89 (0.10)	−0.55 (−0.84 to −0.25)	.0004	−0.20 (0.11)	−0.70 (0.11)	−0.50 (−0.80 to −0.19)	.0017
Secondary end point at week 16								
NPS (range, 0-8)	0.03 (0.15)	−0.98 (0.14)	−1.01 (−1.43 to −0.60)	<.0001	−0.29 (0.16)	−1.20 (0.17)	−0.91 (−1.39 to −0.44)	.0002
NCS (range, 0-3)	−0.32 (0.10)	−0.89 (0.09)	−0.57 (−0.83 to −0.31)	<.0001	−0.21 (0.10)	−0.80 (0.10)	−0.59 (−0.87 to −0.30)	<.0001
Secondary end point at week 24								
SNOT-22 score (range, 0-110)	−8.58 (2.08)	−24.70 (2.01)	−16.12 (−21.86 to −10.38)	<.0001	−6.55 (2.19)	−21.59 (2.25)	−15.04 (−21.26 to −8.82)	<.0001
UPSIT score (range, 0-40)	0.63 (0.90)	4.44 (0.84)	3.81 (1.38-6.24)	.0024	0.44 (0.81)	4.31 (0.83)	3.86 (1.57-6.15)	.0011
TNSS (range, 0-12)	−1.06 (0.34)	−2.97 (0.33)	−1.91 (−2.85 to −0.96)	.0001	−0.44 (0.32)	−2.53 (0.33)	−2.09 (−3.00 to −1.18)	<.0001
Loss of smell score (range, 0-3)	−0.23 (0.10)	−0.56 (0.09)	−0.33 (−0.60 to −0.06)	.0161	−0.13 (0.10)	−0.58 (0.10)	−0.45 (−0.73 to −0.16)	.0024
Postnasal drip score (range, 0-3)	−0.16 (0.10)	−0.72 (0.10)	−0.56 (−0.84 to −0.28)	.0001	−0.00 (0.10)	−0.55 (0.10)	−0.54 (−0.81 to −0.27)	.0001
Runny nose score (range, 0-3)	−0.34 (0.10)	−0.77 (0.10)	−0.43 (−0.70 to −0.16)	.0023	−0.08 (0.10)	−0.70 (0.10)	−0.63 (−0.90 to −0.35)	<.0001

Pooled analysis of data from POLYP 1 and POLYP 2.
*Data expressed as adjusted means (SEs), with *P* values unadjusted for multiplicity.
†Data expressed as treatment arm differences (95% CIs), with *P* values unadjusted for multiplicity.

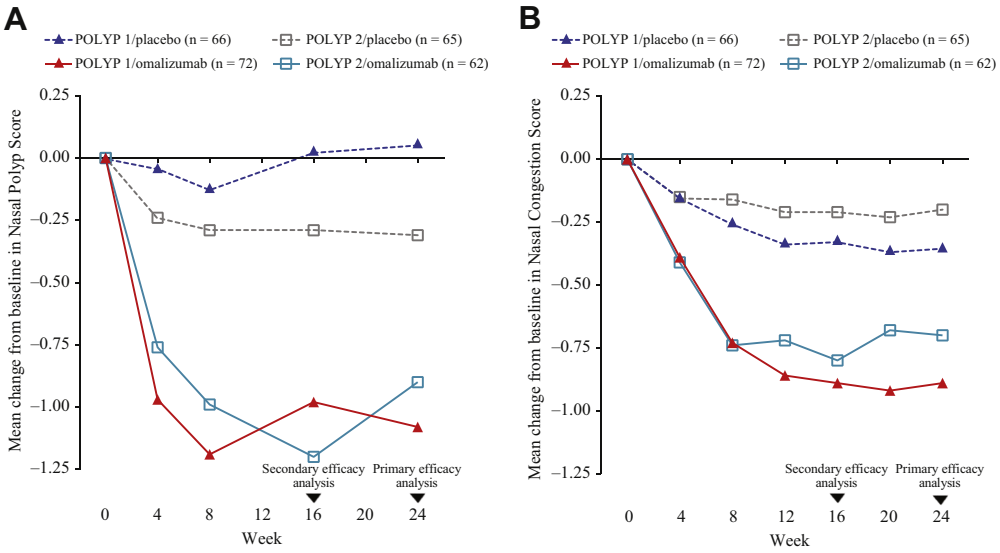

FIG 4. Mean change from baseline in NPS (**A**) and NCS (**B**) in POLYP 1 and POLYP 2.

moderate in intensity, and most occurred within 24 hours of administration of the study drug. An episode of anaphylaxis, later adjudicated as not meeting the Sampson criteria by an independent anaphylaxis adjudication committee, led to discontinuation in the placebo-treated patients. No AEs were reported as omalizumab-associated risks (Table IV).

DISCUSSION

CRSwNP is a chronic, debilitating condition associated with high symptom burden and substantial impact on QoL, as well as with allergic comorbidities, including asthma and NSAID-exacerbated respiratory disease (aspirin-exacerbated respiratory disease).[12,31,32] Many patients fail to achieve sufficient benefit from INCS therapy and require repeated courses of an SCS and/or sinus surgeries.[12,13] Although sinus surgeries may be successful initially, relapse occurs in approximately 20% of patients after 12 months,[14] in 40% after 18 months,[13] and in 80% after 12 years[15] despite ongoing INCS therapy.[15] Novel treatments for CRSwNP are therefore needed. In these replicate, randomized, pivotal, phase 3 studies of omalizumab in patients with CRSwNP, both co-primary end points were met, with statistically significant improvements from baseline to week 24 in mean daily NCS and NPS.

Improvements in NPS and NCS were accompanied by significant improvements in patient-reported symptoms and disease-related QoL (TNSS, SNOT-22 score, sense of smell,

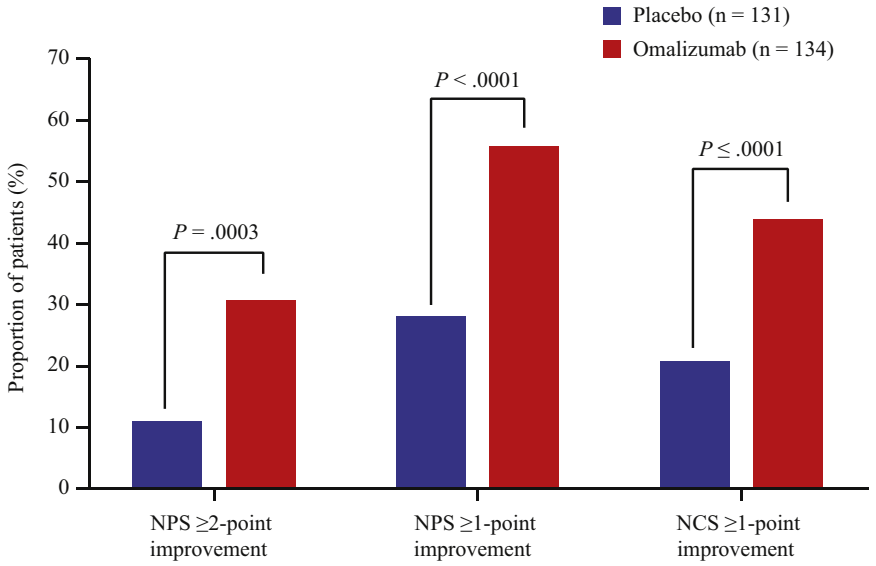

FIG 5. Proportion of patients reporting at least a 1-point improvement in NPS and NCS and at least a 2-point improvement in NPS in POLYP 1 and POLYP 2 (pooled data).

postnasal drip, runny nose) and smell test (UPSIT score). These results may be more intuitively appreciated through the responder analyses, which demonstrated a greater proportion of omalizumab- versus placebo-treated patients achieving at least a 1-point (56.3% vs 28.7%) and at least a 2-point (31.3% vs 11.6%) improvement in NPS and at least a 1-point improvement in NCS (44.4% vs 21.4%). Asthma-related QoL was also significantly improved, as was demonstrated by the percentage of patients with comorbid asthma achieving at least a 0.5-point improvement in AQLQ score. Improvements above placebo were evident as early as week 4 for most metrics (week 8 for UPSIT) and were maintained over the 24-week treatment period, suggesting a rapid and sustained effect of omalizumab. These data support the findings of previous studies showing significant improvements in CRSwNP with omalizumab when similar outcome measures were used.[23]

In addition to significant improvements in nasal polyp and nasal symptom scores, omalizumab led to significant and substantial improvements in nasal polyp−related QoL in both studies. In the pooled analysis, omalizumab treatment resulted in a 23.1-point improvement in SNOT-22 score versus a 7.7-point improvement in the placebo-treated arm. Placebo-corrected improvements exceeded the commonly accepted MCID of 8.9 points.[28,33] Interestingly, the improvements observed here with omalizumab were similar to those reported for FESS in a recent systematic review and meta-analysis of 15 studies (mean change, 23.0 [95% CI = 20.2-25.8]), which included 3048 patients.[34] These findings thus support those by Bidder et al,[23] who demonstrated similar improvements in SNOT-22 score in omalizumab- and surgically treated patients with CRSwNP.

Patients with asthma are more likely to develop CRSwNP than are those without asthma, and they are more likely to have severe disease, receive more oral corticosteroid courses, and experience relapse requiring multiple endoscopic surgeries.[3,35] In the pooled population, most patients with comorbid asthma had physician-assessed mild to moderate disease (93.4%). Nonetheless, improvements in AQLQ score were similar to a previous study in a population with more severe asthma.[24] In these studies, omalizumab-treated patients were 4 times more likely than placebo-treated patients to achieve an MCID (by ≥0.5 points) in improvement in AQLQ score. Omalizumab may therefore offer a viable treatment to simultaneously control asthma and CRSwNP symptoms.

Omalizumab numerically reduced rescue medication use by approximately two-thirds versus placebo, but the number of events related to rescue medication was low, making it difficult to draw conclusions. These steroid-sparing results are similar to those previously reported in omalizumab studies in patients with asthma.[36,37]

Omalizumab was well tolerated, with no new or unexpected safety concerns identified in the pooled data. The most common AEs observed (headache, injection site reactions, arthralgia, dizziness, and upper abdominal pain) have been previously reported with omalizumab.[38-40] The safety profile of omalizumab is well established in patients with allergic asthma and chronic idiopathic urticaria,[41] with a cumulative exposure of more than 16,000 patient-years in clinical trials and an estimated cumulative patient exposure of more than 1.3 million patient-years to date in the postmarketing setting (omalizumab periodic safety update report, unpublished data, Novartis). Rare events such as anaphylaxis (occurring in 0.1%-0.2% of patients with asthma according to clinical and postmarketing data)[42,43] were not observed in these trials.

These results are strengthened by the study design with sufficient power to meet the coprimary end points. The baseline patient characteristics were well balanced between studies and within treatment arms.

However, the limitations of the present analysis include the number of patients requiring rescue medication and sinonasal surgery, which was too low in the pooled population to draw meaningful conclusions about the benefit of omalizumab in these areas. Additionally, most patients in the studies had mild

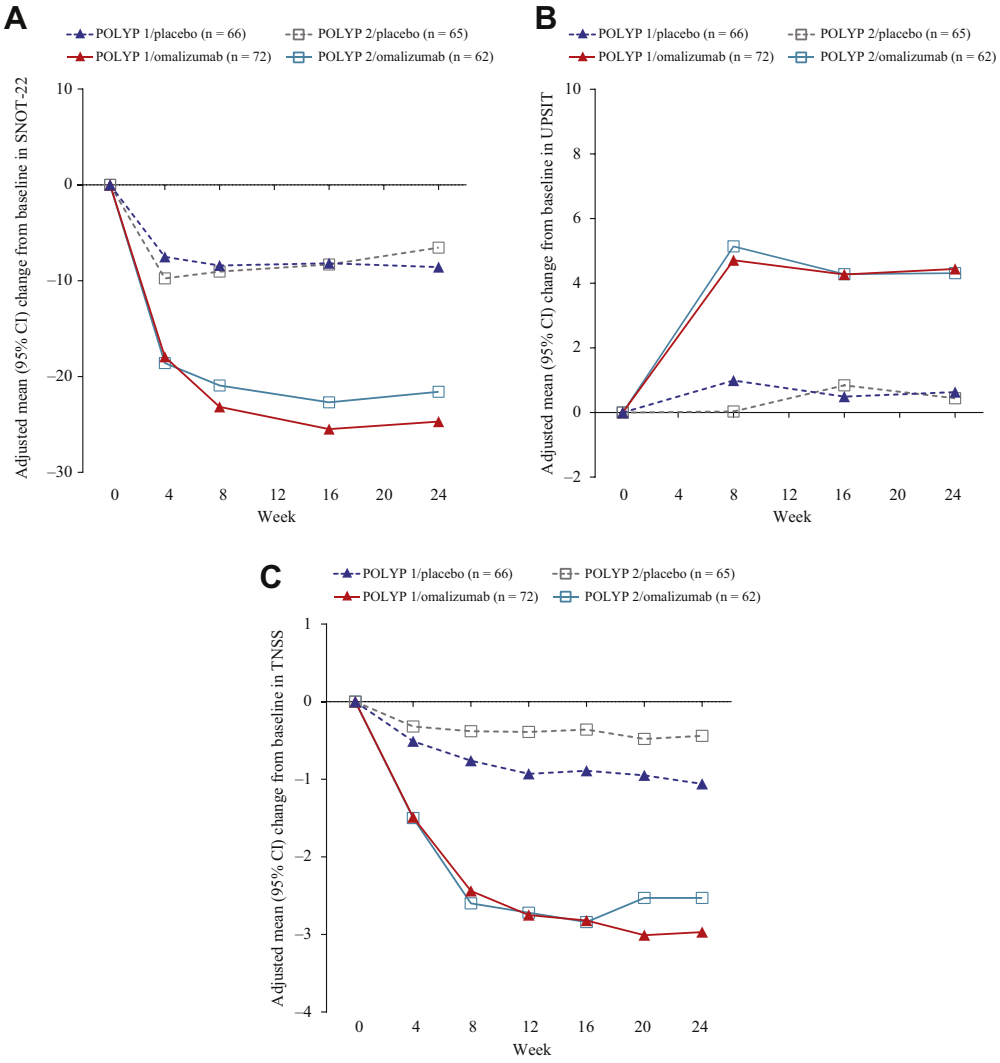

FIG 6. Change from baseline in SNOT-22 score (**A**), UPSIT score (**B**), and TNSS (**C**) in POLYP 1 and POLYP 2.

TABLE III. Secondary efficacy end points

	POLYP 1		POLYP 2	
End point	**OR (95% CI)**	***P* value**	**OR (95% CI)**	***P* value**
AQLQ score, OR of MCID (≥0.5-point improvement)	3.71 (1.00-13.71)	.0492	4.04 (1.07-15.25)	.0396
Reduction in need for surgery, NPS ≤4 (unilateral score ≤2 on each side) and SNOT-22 score improvement ≥8.9	6.3 (1.3-29.6)	.0209	6.2 (1.2-60.2)	.0139

to moderate asthma, in contrast to patients in the proof-of-concept study,[17] all of whom had severe asthma meeting the criteria for omalizumab treatment. Although the relative efficacy in more severe asthma cannot be established, asthma comorbidity did not appear to be a significant predictor of response.

In conclusion, the global, replicate, phase 3 studies, POLYP 1 and POLYP 2, met both coprimary end points, demonstrating statistically significant improvements in NPS and mean daily NCS as well as patient-reported assessments of severity of symptoms in response to omalizumab versus placebo, on a background of intranasal mometasone, at week 24. Multiple secondary outcomes were also met. The improvements in SNOT-22 score illustrate the impact on patient QoL and place the results into an important context relative to other therapies such as SCS and surgery. Omalizumab was well tolerated, and AEs were consistent with those previously reported. Omalizumab represents a promising new treatment option for patients with refractory CRSwNP, for whom there is a substantial unmet need for effective therapies.

TABLE IV. AEs (safety population)

Event	Pooled data	
	Placebo (n = 130)	Omalizumab (n = 135)
Total no. of AEs	210	178
Total no. of SAEs*	2	3
Patients with		
≥1 AE, no. (%)	76 (58.5)	68 (50.4)
≥1 SAE, no. (%)	2 (1.5)	3 (2.2)
Treatment-related AE, no. (%)	5 (3.8)	9 (6.7)
≥1 AE leading to discontinuation of study drug, no. (%)	1 (0.8)	0 (0.0)
AEs occurring in ≥3% of patients		
Headache	7 (5.4)	11 (8.1)
Nasopharyngitis	11 (8.5)	8 (5.9)
Injection site terms†	2 (1.5)	7 (5.2)‡
Asthma exacerbation/worsening	15 (11.5)	5 (3.7)
Upper abdominal pain	1 (0.8)	4 (3.0)
Arthralgia	2 (1.5)	4 (3.0)
Back pain	5 (3.8)	4 (3.0)
Dizziness	1 (0.8)	4 (3.0)
Epistaxis	4 (3.1)	4 (3.0)
Rhinitis	4 (3.1)	4 (3.0)
Sinusitis	3 (2.3)	4 (3.0)
Nasal polyps	4 (3.1)	3 (2.2)
Nasal congestion	4 (3.1)	0 (0.0)
AEs identified as risks associated with omalizumab		
Serum sickness syndrome/serum sickness–like disease	0 (0.0)	0 (0.0)
Anti-omalizumab antibodies	0 (0.0)	0 (0.0)
Eosinophilic granulomatosis with polyangiitis/Churg-Strauss syndrome/hypereosinophilic syndrome	0 (0.0)	0 (0.0)
Thrombocytopenia	0 (0.0)	0 (0.0)
Arterial thrombotic events	1 (0.8)	0 (0.0)
Malignant neoplasms	1 (0.8)	0 (0.0)
Parasitic infections	0 (0.0)	0 (0.0)

SAE, Serious adverse event.
*The SAEs in the omalizumab arm were hand fracture, snake bite, and asthma.
†Includes injection site reaction, injection-related reaction, and injection site pain.
‡One patient experienced 1 event of injection site reaction and 1 event of injection site pain.

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Clinical implications: The results from the POLYP 1 and POLYP 2 trials reinforce the findings of previous trials showing that omalizumab is a viable alternative treatment for patients with CRSwNP with inadequate response to intranasal corticosteroids.

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