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Efficacy and safety of omalizumab in nasal polyposis: two randomized phase III trials

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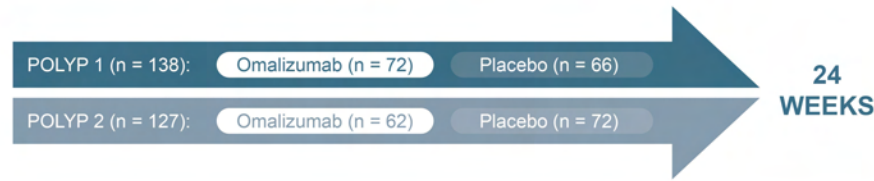
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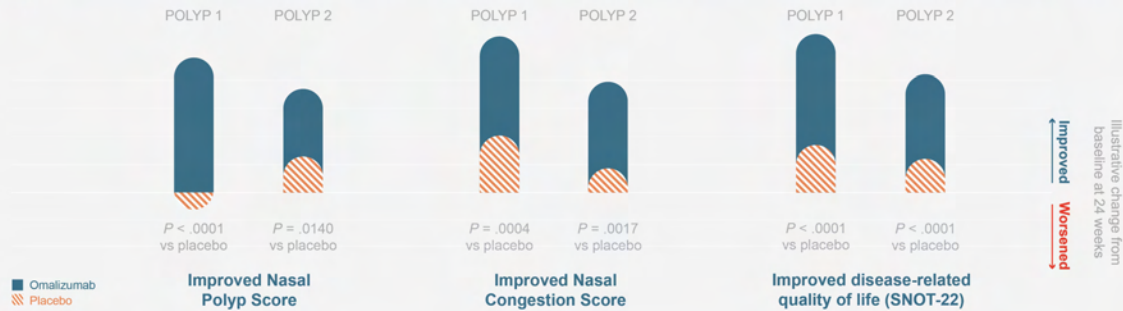
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Omalizumab in patients with nasal polyposis: 2 replicate phase 3 trials



Omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes versus placebo



SNOT-22, Sino-Nasal Outcome Test-22.



Methods E1

Prohibited medications and procedures

The following medications and procedures were prohibited during the study: sinonasal surgical procedures; intranasal corticosteroids (other than required by the protocol); parenteral steroid injections; use of verapamil, cyclosporine, methotrexate, azathioprine, and mycophenolate; chronic use of systemic corticosteroids; changes in or initiation (from within 3 months of screening) of allergen immunotherapy; changes in or initiation (from within 4 months of screening) of aspirin desensitization therapy; use of systemic antibiotics for >14 days; intranasal medication that may interfere with the symptoms of disease, except nasal saline; and nasal decongestants (except administered before endoscopy by study personnel).

Reader reliability

To assess intrareader reliability, a mixed-effects linear model was used on a sample of 199 reads coming from a total of 20 videos (10 videos from each study read twice by each of 5 readers). The estimated intraclass correlation coefficient^{E1,E2} based on the pooled data was 0.88 (95% CI, 0.79-0.94). The interreader reliability was assessed using Fleiss' kappa with linear weights.^{E3} All videos used for analysis of the coprimary end point (including baseline and weeks 4, 8, 16, and 24) were used for calculating kappa by study. The estimates for kappa were 0.61 in POLYP 1 and 0.59 in POLYP 2, which implies moderate to substantial agreement.^{E4}

Type 1 error control

To control the type 1 error $\alpha = 0.05$ in each study, first, the coprimary end points were at critical $P = .05$, and after success in both end points, testing proceeded in sequential order in each study separately:

1. Change from baseline at week 24 in the average daily sense of smell
2. Change from baseline at week 24 in average daily post nasal drip
3. Change from baseline at week 16 in Nasal Polyp Score (NPS)
4. Change from baseline at week 16 in average daily Nasal Congestion Score (NCS)
5. Change from baseline at week 24 in Sino-Nasal Outcome Test-22 (SNOT-22)
6. Change from baseline at week 24 in average daily NCS
7. (Pooled study data): requirement of rescue medication (systemic corticosteroids [SCS] for ≥ 3 consecutive days) through week 24
8. (Pooled study data): having had nasal polypectomy through week 24
9. (Pooled study data): change from baseline at week 24 in Asthma Quality of Life Questionnaire of ≥ 0.5 points (in patients with comorbid asthma only)
10. (Pooled study data): requirement of rescue treatment (SCS or nasal polypectomy) through week 24
11. Reduction in the need for nasal polypectomy by week 24, as defined by an NPS of ≤ 4 (unilateral score of ≤ 2 on each side) and improvement in SNOT-22 score of ≥ 8.9
12. Change from baseline at week 24 in average daily Total Nasal Symptom Score (TNSS)
13. Sense of smell, as assessed by the change from baseline at week 24 in University of Pennsylvania Smell Identification Test (UPSIT)

The following separate sequential testing order was used for the European Medicines Agency only, in each study separately.

1. Change from baseline at week 24 in NPS
2. Change from baseline at week 24 in average daily NCS
3. Change from baseline at week 24 in average daily TNSS
4. Change from baseline at week 24 health-related quality of life, as assessed by total SNOT-22

5. Change from baseline at week 24 in UPSIT
6. Change from baseline at week 16 in NPS
7. Change from baseline at week 16 in average daily NCS

NCS assessment

The day -35 assessment, which was determined at the first screening visit, was the only time point for which nasal congestion was not determined via electronic diary (eDiary). For this assessment, patients were asked to assess their degree of nasal congestion on a 0- to 3-point scale with a 1-week recall. That is, on the day of the first screening visit, patients were asked to report the degree of nasal congestion experienced over the prior week. All subsequent assessments of nasal congestion, including the assessment required for randomization, were done via the eDiary. Specifically, patients completed their eDiary on a daily basis each morning. A score was calculated weekly to determine the weekly average NCS. That is, each score was measured as a weekly average over the latest 7-day interval.

Open-label extension

An open-label extension study will assess consenting patients who received open-label omalizumab for 24 weeks followed by a 24-week off-drug observation period. During this 24-week off-drug observation period, there are continued assessments of NCS, NPS, and other efficacy end points. This study will therefore provide an opportunity to examine recurrence as well as compare recurrence rates among patients who received 6 months versus 12 months of omalizumab.

Data repository

The data were captured using an electronic case report form and entered by the site in a Medidata Rave[®] EDC system (New York, NY). The nasal endoscopy videos were transferred electronically to the

73 central vendor using the Medidata platform. The databases were cleaned centrally and reconciled with
74 source documents locally by the sponsor according to a prespecified risk-based monitoring plan.

75 **REFERENCES**

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1 **ONLINE REPOSITORY**

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2 **TABLE E1.** Omalizumab dosing table

Baseline IgE (IU/mL) (day -35)	Body weight (kg)							
	>30-40	>40-50	>50-60	>60-70	>70-80	>80-90	>90-125	>125-150
≥30-100	75 mg	150 mg	150 mg	150 mg	150 mg	150 mg	300 mg	300 mg
	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W
>100-200	150 mg	300 mg	300 mg	300 mg	300 mg	300 mg	450 mg	600 mg
	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W
>200-300	225 mg	300 mg	300 mg	450 mg	450 mg	450 mg	600 mg	375 mg
	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q2W
>300-400	300 mg	450 mg	450 mg	450 mg	600 mg	600 mg	450 mg	525 mg
	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q2W	Q2W
>400-500	450 mg	450 mg	600 mg	600 mg	375 mg	375 mg	525 mg	600 mg
	Q4W	Q4W	Q4W	Q4W	Q2W	Q2W	Q2W	Q2W
>500-600	450 mg	600 mg	600 mg	375 mg	450 mg	450 mg	600 mg	
	Q4W	Q4W	Q4W	Q2W	Q2W	Q2W	Q2W	
>600-700	450 mg	600 mg	375 mg	450 mg	450 mg	525 mg		
	Q4W	Q4W	Q2W	Q2W	Q2W	Q2W		

>700-800	300 mg	375 mg	450 mg	450 mg	525 mg	600 mg	
	Q2W	Q2W	Q2W	Q2W	Q2W	Q2W	
>800-900	300 mg	375 mg	450 mg	525 mg	600 mg		
	Q2W	Q2W	Q2W	Q2W	Q2W		
>900-1,000	375 mg	450 mg	525 mg	600 mg			
	Q2W	Q2W	Q2W	Q2W			
>1,000-1,100	375 mg	450 mg	600 mg	STUDY DRUG NOT ADMINISTERED			
	Q2W	Q2W	Q2W				
>1,100-1,200	450 mg	525 mg	600 mg				
	Q2W	Q2W	Q2W				
>1,200-1,300	450 mg	525 mg					
	Q2W	Q2W					
>1,300-1,500	525 mg	600 mg					
	Q2W	Q2W					

3 Q2W, Every 2 weeks; Q4W, every 4 weeks.

- 4 Lighter gray shading with black text indicates doses to be administered by subcutaneous injection Q4W. Darker gray shading with white text
- 5 indicates doses to be administered by subcutaneous injection Q2W. Injections were administered at a concentration of 150 mg/mL with either
- 6 1-mL or 0.5-mL injections (eg, for patients receiving 375 mg, receiving two 1-mL injections and one 0.5-mL injection).

7 **TABLE E2.** Nasal polyposis scoring system

Nasal Polyp Score	Nasal polyp size
0	No nasal polyps
1	Small nasal polyps in the middle meatus not reaching below the inferior border of the middle turbinate
2	Nasal polyps reaching below the lower border of the middle turbinate*
3	Large nasal polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate
4	Large nasal polyps causing complete obstruction of the inferior nasal cavity

8 Scoring system used to evaluate nasal polyp size in each nasal passage by means of video nasal
9 endoscopy by central readers. Total Nasal Polyp Score is the sum of unilateral polyp scores for each
10 nasal passage. The intraclass correlation coefficient of 0.88 (95% CI, 0.79-0.94), based on 20 videos (10
11 from POLYP 1 and 10 from POLYP 2), demonstrates high intrareader reliability. Reliability of score
12 assessments between readers was assessed on all pooled data from POLYP 1 and POLYP 2, assessed
13 separately for each planned nasal endoscopic assessment in each arm and overall. The interreader
14 reliability between the central readers, expressed as weighted kappas, was fair to moderate (range,
15 0.56-0.66).

16 *The scoring is modified to accommodate patients who have had a middle turbinectomy, such that the
17 polyp must reach the top of the inferior turbinate to be graded as score 2.

18 **TABLE E3.** Nasal symptoms assessed daily via electronic diary

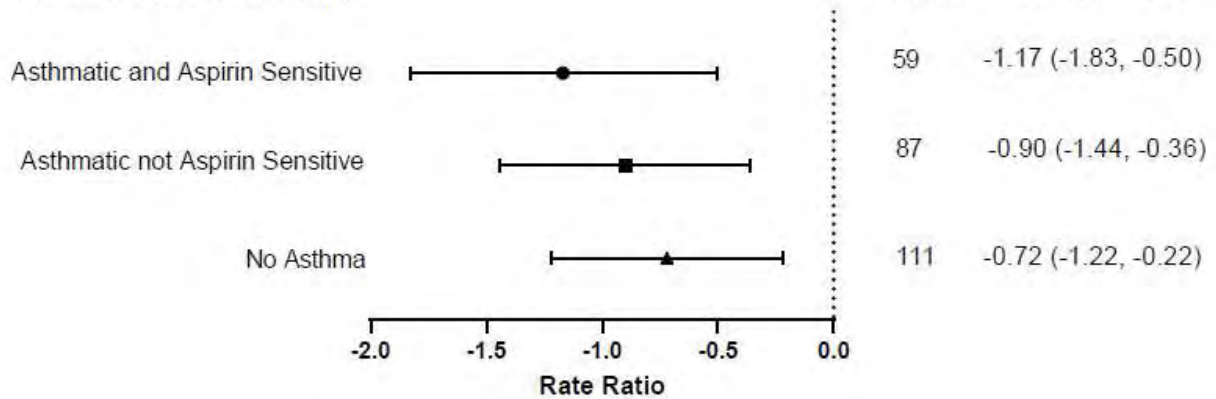
1. Is your nose blocked?*				
	0 = Not at all	1 = Mild	2 = Moderate	3 = Severe
2. Is your sense of smell reduced?				
	0 = Not at all	1 = Mild	2 = Moderate	3 = Severe
3. Do you have a runny nose (anterior rhinorrhea)?				
	0 = Not at all	1 = Mild	2 = Moderate	3 = Severe
4. Do you feel dripping at the back of the nose (posterior rhinorrhea)?				
	0 = Not at all	1 = Mild	2 = Moderate	3 = Severe

19 *Question 1 represents the Nasal Congestion Score.

20 **FIGURE E1.** Improvements in NPS and NCS (pooled results from POLYP 1 and POLYP 2) at Week 24 by
 21 Asthma Subtype

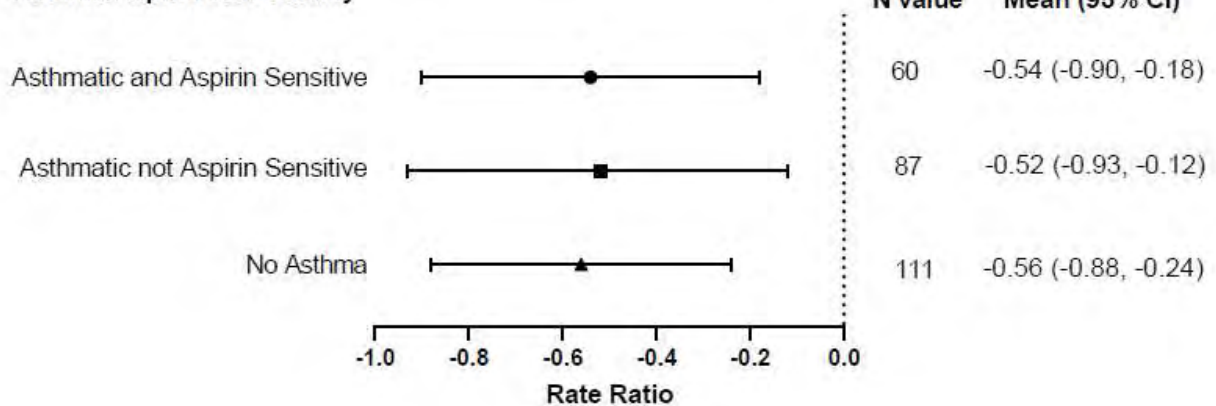
NPS

Asthma/Aspirin Comorbidity



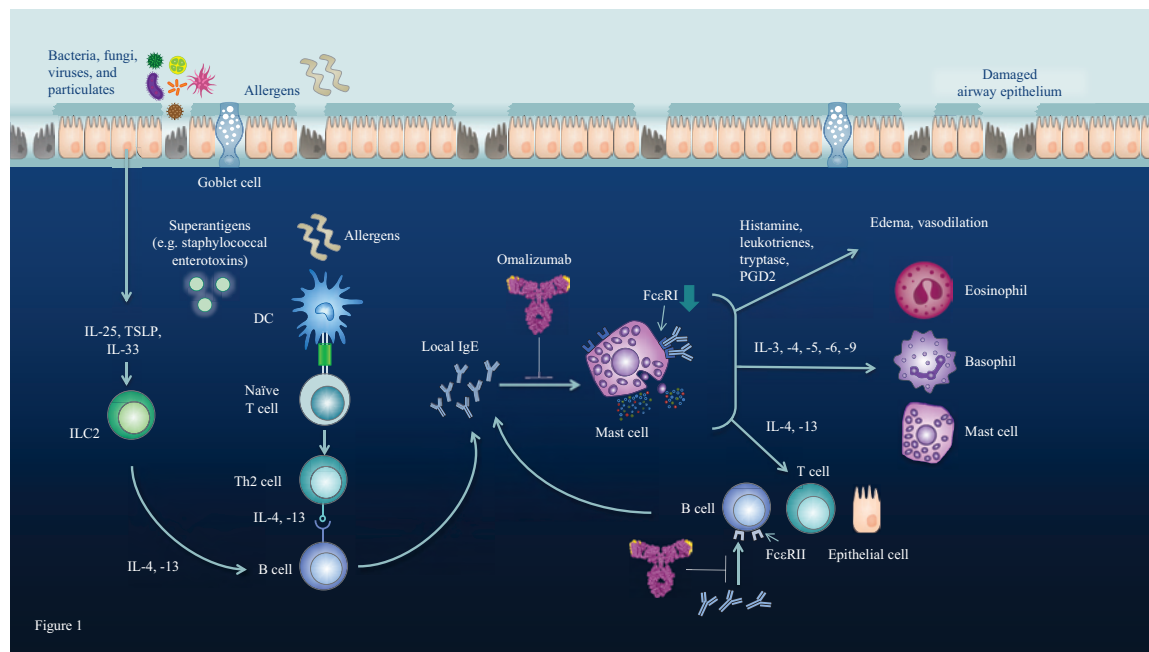
NCS

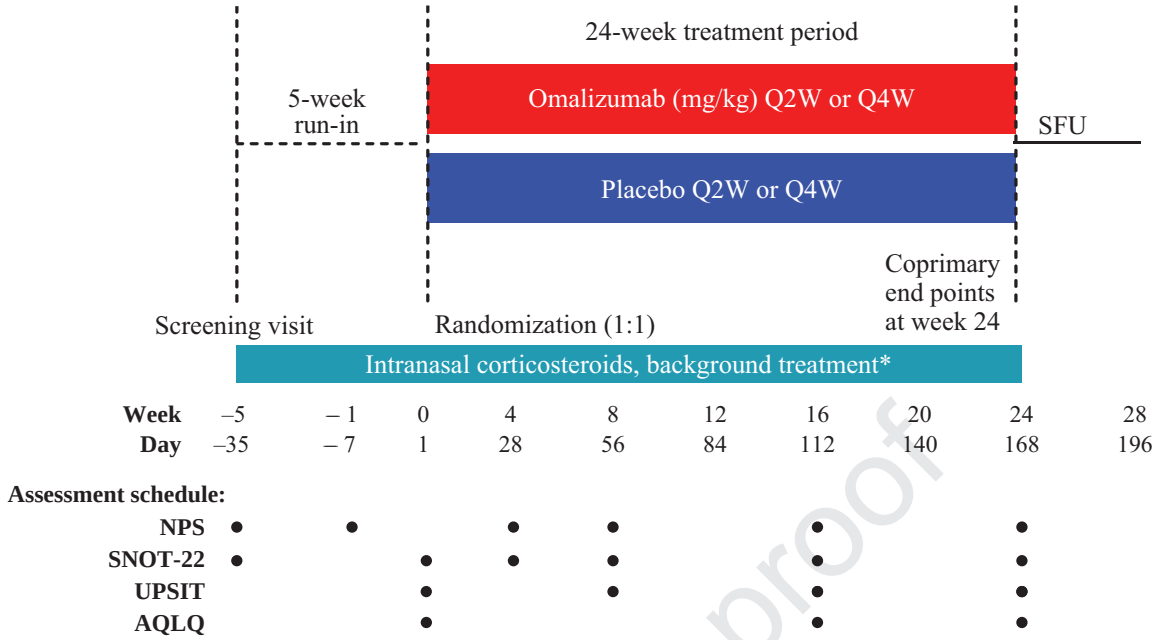
Asthma/Aspirin Comorbidity

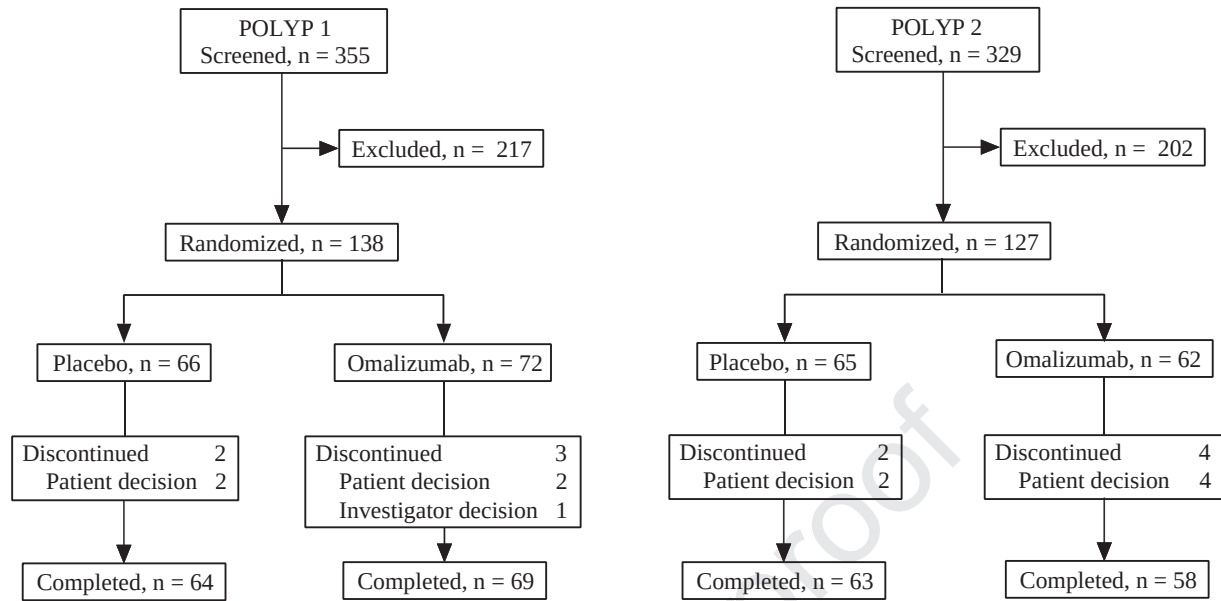


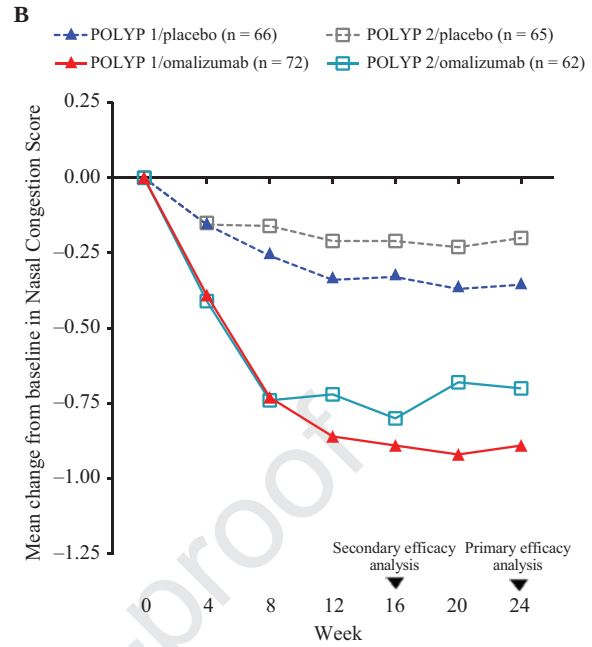
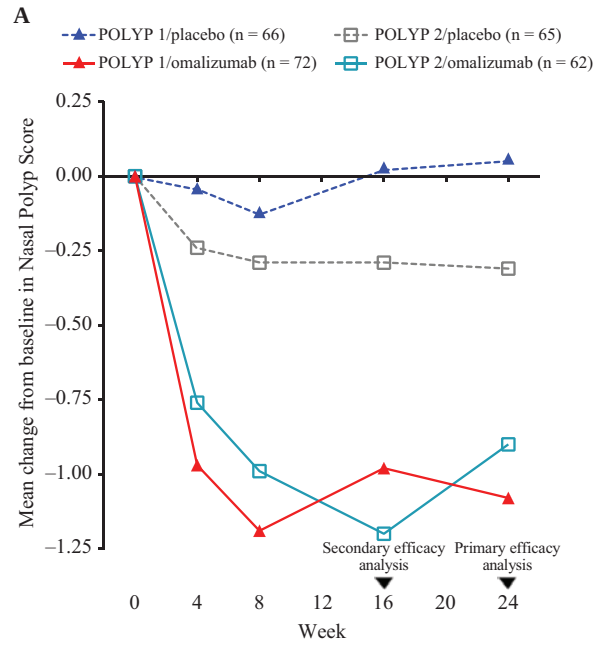
22
 23 *NCS*, Nasal Congestion Score; *NPS*, Nasal Polyp Score.

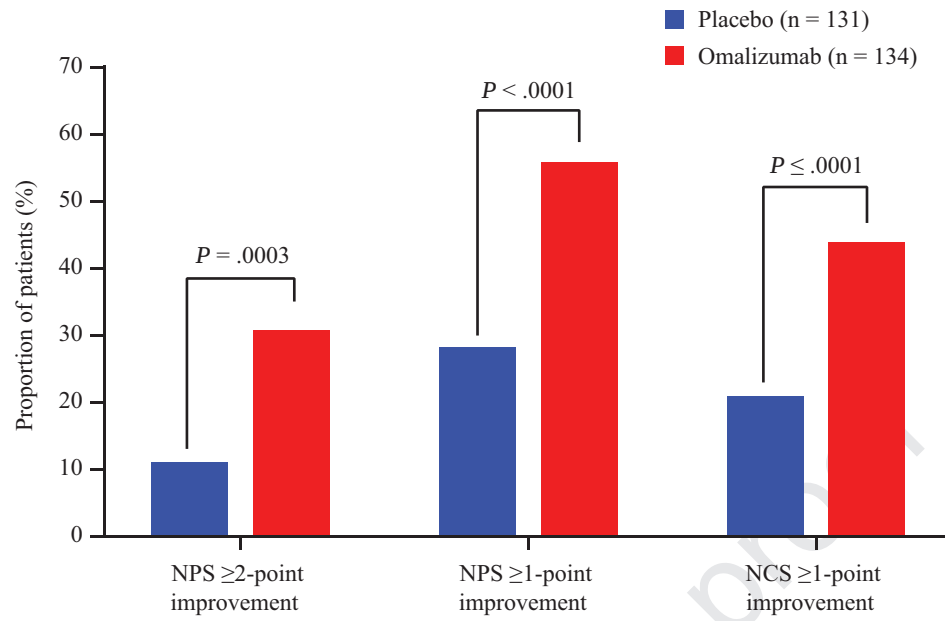
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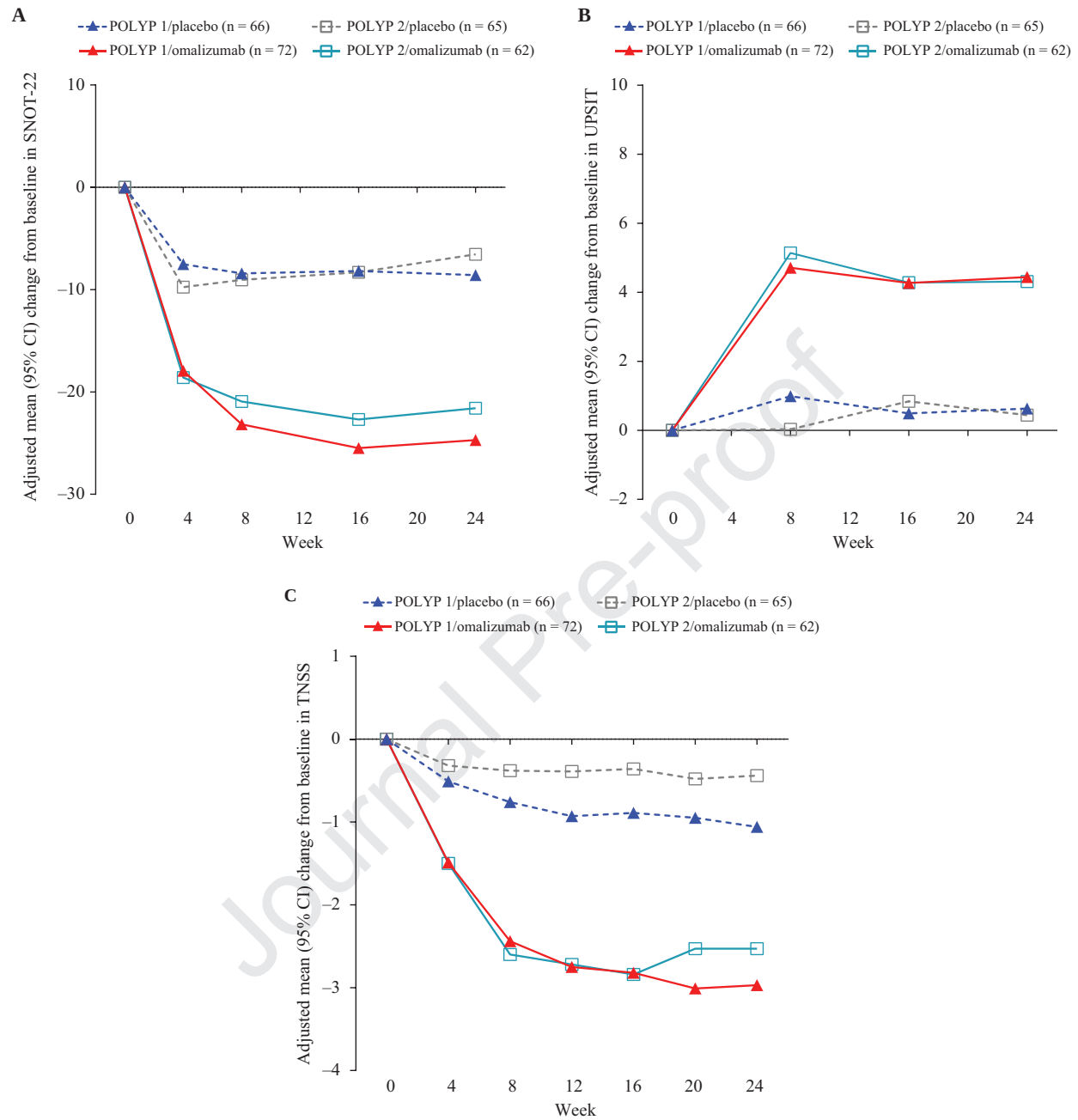












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This analysis was funded by Genentech, Inc., a member of the Roche Group, and Novartis Pharma AG.

CONFLICT OF INTEREST

P. Gevaert is a speaker and advisory board member for Ablynx, ALK, Argenx, Genentech, Inc., Hal Allergy, Novartis, Regeneron, Roche, Sanofi, and Stallergenes. T. A. Omachi, D. Kaufman, M. Howard, R. Zhu, R. Owen, and K. Wong are employees of Genentech, Inc., a member of the Roche Group. J. Corren is a consultant for AstraZeneca, Genentech, Inc., Novartis, Regeneron, and Sanofi; speaker bureau member for AstraZeneca and Genentech, Inc.; and has received grants to his institution from Genentech, Inc., Regeneron, and Sanofi. J. Mullol is a speaker, advisory board member, and received research grants from ALK-Abelló, AstraZeneca, Genentech, Inc., GlaxoSmithKline, Menarini, Mitsubishi-Tanabe, MSD, Mylan, Novartis, Sanofi-Regeneron, and the Uriach Group. J. Han is an advisory board member for Genentech, Inc. and Sanofi-Regeneron, and investigator for Amgen, AstraZeneca, GlaxoSmithKline, Novartis, and Sanofi-Regeneron. S. E. Lee has been an investigator for AstraZeneca, Genentech, Inc., GlaxoSmithKline, Regeneron, and Sanofi, and advisory board member for AstraZeneca, Genentech, Inc., GlaxoSmithKline, Sanofi, and Regeneron. M. Ligueros-Saylan is an employee of Novartis Pharmaceuticals Corporation. L. Islam is an employee of Roche. C. Bachert is a speaker and advisory board member for ALK, ASIT Biotech, AstraZeneca, GlaxoSmithKline, Mylan, Novartis, Sanofi, and Stallergenes.

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49 **Specifications:**

50 **Word count:** 3491 (limit: 3500 words)

51 **Abstract word count:** 247 (limit: 250 words [Background, Objective, Methods, Results, Conclusion, NCT
52 numbers])

53 **Figure legends:** 60 words

54 **Tables/Figures:** 3 tables/6 figures (limit: 8 total)

55 **Supplementary Material:** 5 tables, Methods section

ABSTRACT (247/250 words)

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: To determine omalizumab safety/efficacy in CRSwNP in phase 3 trials (POLYP 1, 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 (NCS). Secondary end points included change from baseline to week 24 in Sino-Nasal Outcome Test-22 (SNOT-22), University of Pennsylvania Smell Identification Test (UPSIT), sense of smell, postnasal drip, runny nose, and adverse events (AEs).

RESULTS: Patients in POLYP 1 (n=138) and POLYP 2 (n=127) exhibited severe CRSwNP and substantial quality-of-life impairment evidenced by mean NPS >6 and SNOT-22 of ~60. Both studies met both coprimary end points. SNOT-22, UPSIT, sense of smell, postnasal drip and runny nose were also significantly improved for omalizumab versus placebo. In POLYP 1 and POLYP 2, mean changes from baseline at week 24 for omalizumab versus placebo were: NPS, -1.08 versus 0.06 ($P<.0001$) and -0.90 versus -0.31 ($P=.0140$); NCS, -0.89 versus -0.35 ($P=.0004$) and -0.70 versus -0.20 ($P=.0017$); SNOT-22, -24.7 versus -8.6 ($P<.0001$) and -21.6 versus -6.6 ($P<.0001$). AEs were similar between groups.

CONCLUSION: Omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in severe CRSwNP with inadequate response to intranasal corticosteroids, and was well tolerated.

TRIAL REGISTRATION: NCT03280550 (POLYP 1), NCT03280537 (POLYP 2)

CLINICAL IMPLICATIONS (29/30 WORDS)

The results from these 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.

CAPSULE SUMMARY (32/35 WORDS)

In two replicate, randomized placebo-controlled trials, POLYP 1 and POLYP 2, omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in severe CRSwNP with inadequate response to intranasal corticosteroids, and was well tolerated.

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

OCS: Oral corticosteroid

- 105 OR: Odds ratio
- 106 Q4W: Every 4 weeks
- 107 SCS: Systemic corticosteroid
- 108 SNOT-22: Sino-Nasal Outcome Test-22
- 109 TNSS: Total Nasal Symptom Score
- 110 UPSIT: University of Pennsylvania Smell Identification Test

INTRODUCTION

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 definition¹ and 3%-6.7% of the population as defined by symptoms combined with endoscopic evaluation.² Of patients with CRS, a recent large single-center study from the United States reported that ~18% of patients 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} QoL impairment is comparable with that experienced by patients with chronic lower back pain.¹¹ Many patients with CRSwNP have uncontrolled symptoms despite intranasal (INCS) or systemic corticosteroids (SCS), doxycycline to reduce inflammation or infection, or functional endoscopic sinus surgery (FESS).^{4,12} Furthermore, disease control is poor, with 20%-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 (Figure 1).¹⁶ Local IgE class switching by B cells and IgE production is well documented in CRSwNP tissues.¹⁷⁻¹⁹ Within the sinonasal mucosa, *Staphylococcal* enterotoxin-specific IgE and polyclonal IgE for inhalant allergens, and 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 monoclonal antibody, omalizumab, demonstrated reductions in CRS-related symptoms, endoscopic Nasal Polyp Score (NPS), and need for INCS.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 scores (a validated

135 measure of paranasal sinus occupation severity), and patient-reported outcomes irrespective of atopic
136 status.²⁴

137 Based on these proof-of-concept studies,²²⁻²⁴ 2 phase 3 studies (POLYP 1, POLYP 2) were
138 conducted to evaluate efficacy and safety of omalizumab versus placebo in adult patients with CRSwNP
139 with inadequate response to INCS.

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 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 (30-150 kg) and serum IgE (30-1,500 IU/mL) permitting omalizumab dosing per Table E1 were eligible. Patients were required to have received ≥ 4 weeks of INCS before screening visit 1 and have total NPS ≥ 5 (NPS ≥ 2 for each nostril) at screening visit 1 (day -35). Patients were further required to have NPS ≥ 5 at screening visit 2 (day -7), after 4 weeks of intranasal mometasone during run-in (200 μ g twice daily, or 200 μ g daily if unable to tolerate 200 μ g twice daily). Nasal Congestion Score (NCS) ≥ 2 (with additional symptoms of postnasal drip, runny nose, and/or loss of sense of smell) at day -35 (1-week recall) and weekly mean NCS > 1 at randomization (assessed every morning via an eDiary) were required (Methods E1). Patients were required to have Sino-Nasal Outcome Test-22 (SNOT-22) score ≥ 20 at day -35 and randomization.

Patients were excluded if they had other sinonasal or pulmonary disorders (except asthma), including current upper respiratory tract infection, cystic fibrosis, or other dyskinetic ciliary syndrome; past/current malignancy; cardiac conditions; hepatitis; liver cirrhosis; recent/current infection requiring hospitalization (≤ 4 weeks), antibiotics (≤ 2 weeks) or antifungal treatment, or parasitic infection (≤ 6 months); recent SCS (≤ 2 months), immunosuppressants, biologics, or leukotriene antagonists/modifiers; recent nasal surgery (≤ 6 months); known allergy to omalizumab; or who were immunocompromised.

Patients were randomized (1:1) to omalizumab or placebo and background intranasal mometasone for 24 weeks (Figure 2). The protocol specified study dosing of 75-600 mg by subcutaneous injection every 2 or 4 (Q4W) weeks, based on pretreatment serum total IgE level and body weight (Table E1). Permuted block randomization (block size 4) was performed 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 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 >14 days was not permitted during the study. A complete list of prohibited medications and procedures are in Methods E1.

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

Assessments

Demographic data and medical history were collected during screening visit 1. Blood samples were collected at screening and weeks 16, 24, and 28 for routine analyses. Serum IgE levels were determined at baseline. NPS (range, 0-8; Table E2) was determined for each nasal passage at screening and 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 using an eDiary (nasal congestion, sense of smell, postnasal drip, runny nose; range, 0 [not at all] to 3 [severe] for each) and analyzed separately and in a combined summed Total Nasal Symptom Score (TNSS; range, 0-12; Table E3). The nasal congestion

question forms the NCS. University of Pennsylvania Smell Identification Test (UPSIT) was performed at day 1 and weeks 8, 16, and 24 (range, 0-40; higher scores indicate better smell). SNOT-22 was measured at screening, day 1, and weeks 4, 8, 16, and 24 (range, 0-110; lower scores indicate better disease control and QoL). In patients with comorbid asthma, Asthma Quality of Life Questionnaire (AQLQ) was administered at day 1 and weeks 16 and 24 (range, 1-7; higher scores indicate 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 (Methods E1).

Outcomes

Coprimary end points were change from baseline to week 24 in endoscopic NPS²⁴ and mean daily NCS. Secondary end points included change from baseline at week 24 in SNOT-22, UPSIT (widely used measure recommended by BMJ Best Practice Guidelines to assess olfactory function in nasal polyps²⁷), mean daily sense of smell, postnasal drip, runny nose, and TNSS; change from baseline at week 16 in NPS and NCS; and percentage of patients requiring rescue therapy (SCS for ≥ 3 consecutive days and/or nasal polypectomy) by week 24. Reduction in need for surgery through week 24 was predefined as patients achieving NPS of ≤ 4 (≤ 2 for each nostril) and at least minimal clinically important difference (MCID)²⁸ improvement (≥ 8.9 points) in SNOT-22. Percentage of patients with comorbid asthma demonstrating MCID improvement (≥ 0.5 points) in AQLQ through week 24 was also assessed. Exploratory end points included percentage of patients in the pooled population achieving ≥ 2 -point and ≥ 1 -point improvement in NPS and ≥ 1 -point improvement in NCS.

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

Statistical analyses

Sample size of 120 patients was calculated to provide $\geq 85\%$ 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.

Corresponding assumed SDs were 0.83 and 2.2.^{24,29,30}

The full analysis set (FAS) included all randomized patients who received ≥ 1 dose of study drug according to assigned treatment group. The safety analysis set included all patients who received ≥ 1 dose of study drug according to treatment received. Randomized patients were treated with 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 using summary statistics. Patient demographic and clinical characteristics and efficacy end points were evaluated using the FAS. Sequential testing type 1 error control procedures are described in Appendix E1. 95% CIs are unadjusted for multiplicity. Within-group means and between-group differences in absolute change from baseline to week 24 were estimated least-squares means (LSMs) 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, SNOT-22, and TNSS. *P* values are derived from a *t* test of difference in LSMs.

Between-group difference in proportion of patients at week 24 with reduced need for surgery was estimated using a logistic regression model analysis adjusted for baseline covariates as above, baseline NPS, and SNOT-22. Between-group differences in proportion of patients requiring rescue treatment by week 24 was estimated using a logistic regression model analysis for oral corticosteroid (OCS) use for ≥ 3 consecutive days and/or sinus surgery adjusted for baseline covariates (above).

235 Between-group differences in proportion of patients with comorbid asthma by week 24 was estimated
236 using a logistic regression model analysis adjusted for baseline covariates (above) and baseline AQLQ. *P*
237 values for between-group differences in proportions are derived from Wald chi-square test of the
238 treatment effect coefficient in the logistic regression model.

RESULTS

Study disposition, baseline demographics, and clinical characteristics of patients

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

Demographics and clinical characteristics were similar between treatment groups and across studies (Table I). Patients had severe nasal polyps/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 studies, 48.5%-61.3% of patients had comorbid asthma; most had mild (35.1%) or moderate (58.3%) physician-assessed asthma severity. Nonsteroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD or AERD) was present in 27.2% of patients.

Across studies, 12.1%-29.0% of patients used 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 dosage during run-in and treatment. Most patients (pooled omalizumab arms, 90.4%; pooled placebo arms, 86.9%) were assigned omalizumab or placebo Q4W, with similar dose/dosing frequency across 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. For omalizumab versus placebo, mean change in NPS from baseline at week 24 was -1.08 versus $+0.06$ (treatment arm differences [95% CI], -1.14 [-1.59 , -0.69]; $P < .0001$) in POLYP 1 and -0.90 versus -0.31 (treatment arm differences [95% CI], -0.59 [-1.05 , -0.12]; $P = .0140$) in POLYP 2. Mean change in NCS from baseline to week 24 was -0.89 versus -0.35 (treatment arm differences [95% CI], -0.55 [-0.84 , -0.25]; $P = .0004$) for omalizumab versus placebo in POLYP 1 and -0.70 versus -0.20 (treatment arm differences [95% CI], -0.50 [-0.80 , -0.19]; $P = .0017$) in POLYP 2, respectively (Table II). 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 (Figure 4). Mean change from baseline at week 4 in NPS for omalizumab versus placebo was -0.92 (95% CI, -1.37 , -0.48) in POLYP 1 and -0.52 (95% CI, -0.94 , -0.11) in POLYP 2. Mean change from baseline at week 4 in NCS for omalizumab versus placebo was -0.25 (95% CI, -0.46 , -0.04) in POLYP 1 and -0.26 (95% CI, -0.45 , -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 more and ≥ 2 -point NPS improvements were observed in 56.3% (72/128) and 31.3% (40/128) of omalizumab-treated patients and 28.7% (37/129) and 11.6% (15/129) of placebo-treated patients, respectively. One-point or more NCS improvements were observed in 56/126 (44.4%) omalizumab-treated patients and 27/126 (21.4%) placebo-treated patients (Figure 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 (Figure E1).

Secondary efficacy end points

Statistically significant improvements favoring omalizumab were observed in both studies for SNOT-22, UPSIT, TNSS, and individual nasal symptoms (sense of smell, postnasal drip, runny nose) from baseline at week 24 (Table II; Figure 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). LSM difference (95% CI) in change from baseline at week 4 in SNOT-22 with omalizumab versus placebo was -10.43 (-15.08, -5.79) in POLYP 1 and -8.84 (-13.84, -3.84) in POLYP 2. LSM difference (95% CI) in change from baseline at week 8 in UPSIT for omalizumab versus placebo was 3.78 (1.56-6.00) in POLYP 1 and 3.44 (1.03-5.85) in POLYP 2.

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

Rescue SCS therapy was required in 8/129 (6.2%) placebo-treated patients and 3/129 (2.3%) omalizumab-treated patients from the pooled population during the study, favoring omalizumab with a 62.5% relative reduction (3.9% absolute difference) in rescue steroid use ($P = .16$). No sinus surgeries/polypectomies were recorded. Reduced need for surgery by week 24 was observed in 2/65 (3.1%) placebo-treated and 13/69 (18.8%) omalizumab-treated patients from POLYP 1 (OR, 6.3; 95% CI, 1.3-29.6; $P = .0209$) and in 2/63 (3.2%) placebo-treated patients and 10/59 (16.9%) omalizumab-treated patients from POLYP 2 (OR, 6.2; 95% CI, 1.2-60.2; $P = .0139$).

Safety and tolerability

The proportion of patients who experienced ≥ 1 treatment-emergent AE was 58.5% in placebo-treated patients and 50.4% in omalizumab-treated patients. Number of AEs was greater in placebo-

310 treated versus omalizumab-treated patients. Most events across both studies were of mild-to-moderate
311 intensity. Two serious AEs were reported in placebo-treated patients (1.5%; myocardial infarction, n = 1;
312 pneumonia, n = 1) and 3 in omalizumab-treated patients (2.2%; snake bite, n = 1; hand fracture, n = 1;
313 asthma exacerbation/worsening, n = 1). The proportion of patients experiencing ≥ 1 AE suspected to be
314 omalizumab related by the investigator was 3.8% in placebo-treated patients and 6.7% in omalizumab-
315 treated patients. These AEs were mild-to-moderate in intensity and most occurred within 24 hours of
316 study drug administration. An episode of anaphylaxis, later adjudicated as not meeting Sampson's
317 criteria by an independent anaphylaxis adjudication committee, led to discontinuation in placebo-
318 treated patients. No AEs were reported as omalizumab-associated risks (Table III).

DISCUSSION

CRSwNP is a chronic, debilitating condition associated with high symptom burden and substantial impact on QoL, and with allergic comorbidities, including asthma and NSAID-exacerbated respiratory disease (N-ERD or AERD).^{12,31,32} Many patients fail to achieve sufficient benefit from INCS and require repeated courses of SCS and/or sinus surgeries.^{12,13} Although sinus surgeries may be successful initially, relapse occurs in ~20% of patients after 12 months,¹⁴ 40% after 18 months,¹³ and 80% after 12 years¹⁵ despite ongoing INCS.¹⁵ Novel treatments for CRSwNP are therefore needed. In these replicate, randomized, pivotal, phase 3 studies of omalizumab in patients with CRSwNP, both coprimary 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, sense of smell, postnasal drip, runny nose) and smell test (UPSIT). These results may be more intuitively appreciated through the responder analyses, which demonstrated a greater proportion of omalizumab- versus placebo-treated patients achieving ≥ 1 -point (56.3% vs 28.7%) and ≥ 2 -point (31.3% vs 11.6%) NPS improvements and ≥ 1 -point NCS improvements (44.4% vs 21.4%). Asthma-related QoL was also significantly improved based on the percentage of patients with comorbid asthma achieving ≥ 0.5 -point AQLQ improvements. 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 previous studies showing significant improvements in CRSwNP with omalizumab using similar outcome measures.²³

In addition to significant improvements in NP and nasal symptom scores, omalizumab led to significant and substantial improvements in nasal polyps-related QoL in both studies. In the pooled analysis, omalizumab treatment resulted in a 23.1-point improvement in SNOT-22 versus 7.7 points in

the placebo-treated arm. Placebo-corrected improvements exceeded the commonly accepted MCID of 8.9 points.^{28,33} Interestingly, the improvements observed with omalizumab here 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 3,048 patients.³⁴ These findings thus support those by Bidder et al,²³ who demonstrated similar SNOT-22 improvements in omalizumab- and surgically treated patients with CRSwNP.

Patients with asthma are more likely to develop CRSwNP than nonasthmatics, and are more likely to have severe disease, receive more OCS 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, AQLQ improvements were similar to a previous study in a more severely asthmatic population.²⁴ In these studies, omalizumab-treated patients were 4 times more likely than placebo-treated patients to achieve MCID (≥ 0.5 points) AQLQ improvement. 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, 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 >16,000 patient-years in clinical trials and an estimated cumulative patient exposure of >1,300,000 patient-years to date in the postmarketing setting (omalizumab periodic safety

update report, unpublished data, Novartis). Rare events such as anaphylaxis (0.1%-0.2% in patients with asthma based on 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. Baseline patient characteristics were well balanced between studies and within treatment arms.

However, limitations of the present analysis included 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-to-moderate asthma, in contrast to those in the proof-of-concept study,¹⁷ all of whom had severe asthma meeting criteria for omalizumab treatment. While 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 symptoms severity 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 illustrate the impact on patient QoL and place the results into 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.

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DATA SHARING STATEMENT

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available here (<https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx>). For further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents, see here (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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515 **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 (score, 0-8), mean (SD) †	6.3 (0.9)	6.2 (1.0)	6.1 (0.9)	6.4 (0.9)
NCS (score, 0-3), mean (SD)†	2.5 (0.6)	2.4 (0.7)	2.3 (0.6)	2.3 (0.7)
Sense of smell (score, 0-3), mean (SD)†	2.8 (0.4)	2.5 (0.8)	2.8 (0.6)	2.6 (0.8)
Postnasal drip (score, 0-3), mean (SD)†	2.0 (0.9)	1.7 (0.9)	1.8 (0.9)	1.6 (0.9)
Runny nose (score, 0-3), mean (SD)†	2.1 (0.8)	1.9 (0.8)	1.9 (0.8)	1.9 (0.9)
TNSS (score, 0-12), mean (SD)†	9.3 (1.9)	8.6 (2.5)	8.7 (2.3)	8.4 (2.6)
UPSIT (score, 0-40), mean (SD)‡	13.9 (7.4)	12.8 (7.9)	13.1 (7.3)	12.8 (7.6)
SNOT-22 (score, 0-110), mean	60.5 (15.3)	59.8 (19.7)	59.8 (18.2)	59.2 (20.5)

(SD)[†]

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/ μ L) 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)
No. of 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 BID	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)

516 *AERD*, Aspirin-exacerbated respiratory disease; *AQLQ*, Asthma Quality of Life Questionnaire; *BID*, twice
 517 daily; *BMI*, body mass index; *NCS*, Nasal Congestion Score; *NP*, nasal polyp; *NPS*, Nasal Polyp Score;
 518 *NSAID*, nonsteroidal anti-inflammatory drug; *SCS*, systemic corticosteroid; *SNOT-22*, Sino-Nasal Outcome
 519 Test-22; *TNSS*, Total Nasal Symptom Score; *UPSIT*, University of Pennsylvania Smell Identification Test.
 520 *POLYP 2: placebo, n = 64.
 521 †Higher scores indicate worse health status.
 522 ‡Higher scores indicate better sense of smell; UPSIT score of 0-18 indicates “total loss of
 523 smell/anosmia.”

524 **TABLE II.** Primary and secondary efficacy end points*

	POLYP 1				POLYP 2			
	Placebo	Omalizumab	Treatment arm	<i>P</i> value	Placebo	Omalizumab	Treatment arm	<i>P</i> value
	(n = 66)†	(n = 72)†	differences‡		(n = 65)†	(n = 62)†	differences‡	
Primary end point at week 24								
NPS (score range, 0-8)	0.06	−1.08	−1.14	<.0001	−0.31	−0.90	−0.59	.0140
	(0.16)	(0.16)	(−1.59, −0.69)		(0.16)	(0.17)	(−1.05, −0.12)	
NCS (score range, 0-3)	−0.35	−0.89	−0.55	.0004	−0.20	−0.70	−0.50	.0017
	(0.11)	(0.10)	(−0.84, −0.25)		(0.11)	(0.11)	(−0.80, −0.19)	
Secondary end point at week 16								
NPS (score range, 0-8)	0.03	−0.98	−1.01	<.0001	−0.29	−1.20	−0.91	.0002
	(0.15)	(0.14)	(−1.43, −0.60)		(0.16)	(0.17)	(−1.39, −0.44)	
NCS (score range, 0-3)	−0.32	−0.89	−0.57	<.0001	−0.21	−0.80	−0.59	<.0001
	(0.10)	(0.09)	(−0.83, −0.31)		(0.10)	(0.10)	(−0.87, −0.30)	
Secondary end point at week 24								
SNOT-22 (score range, 0-110)	−8.58	−24.70	−16.12	<.0001	−6.55	−21.59	−15.04	<.0001
	(2.08)	(2.01)	(−21.86, −10.38)		(2.19)	(2.25)	(−21.26, −8.82)	

UPSIT (score range, 0-40)	0.63	4.44	3.81	.0024	0.44	4.31	3.86	.0011
	(0.90)	(0.84)	(1.38-6.24)		(0.81)	(0.83)	(1.57- 6.15)	
TNSS (score range, 0-12)	-1.06	-2.97	-1.91	.0001	-0.44	-2.53	-2.09	<.0001
	(0.34)	(0.33)	(-2.85, -0.96)		(0.32)	(0.33)	(-3.00, -1.18)	
Loss of smell score (score range, 0-3)	-0.23	-0.56	-0.33	.0161	-0.13	-0.58	-0.45	.0024
	(0.10)	(0.09)	(-0.60, -0.06)		(0.10)	(0.10)	(-0.73, -0.16)	
Postnasal drip (score range, 0-3)	-0.16	-0.72	-0.56	.0001	-0.00	-0.55	-0.54	.0001
	(0.10)	(0.10)	(-0.84, -0.28)		(0.10)	(0.10)	(-0.81, -0.27)	
Runny nose (score range, 0-3)	-0.34	-0.77	-0.43	.0023	-0.08	-0.70	-0.63	<.0001
	(0.10)	(0.10)	(-0.70, -0.16)		(0.10)	(0.10)	(-0.90, -0.35)	
	OR (95% CI)			P value	OR (95% CI)			P value
AQLQ, OR of MCID	3.71			.0492	4.04			.0396
(≥0.5-point improvement)	(1.00-13.71)				(1.07-15.25)			
Reduction in need for surgery,	6.3			.0209	6.2			.0139
NPS ≤4 (unilateral score ≤2 on each side) and SNOT-22 improvement ≥8.9	(1.3-29.6)				(1.2-60.2)			

AQLQ, Asthma Quality of Life Questionnaire; MCID, minimal clinically important difference; NCS, Nasal Congestion Score; NPS, Nasal Polyp Score; OR, odds

ratio; SNOT-22, Sino-Nasal Outcome Test-22; TNSS, Total Nasal Symptom Score; UPSIT, University of Pennsylvania Smell Identification Test.

527 *Pooled analysis of data from POLYP 1 and POLYP 2.

528 Data are expressed as †adjusted mean (SE) or ‡treatment arm differences (95% CI). *P* values are unadjusted for multiplicity.

529 **TABLE III.** AEs (safety population)

	Pooled data	
	Placebo	Omalizumab
	(n = 130)	(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 polyangitis/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)

530 AE, Adverse event; SAE, serious adverse event.

531 *SAEs in the omalizumab arm were hand fracture, snake bite, and asthma.

532 †Includes injection site reaction, injection-related reaction, and injection site pain.

533 ‡1 patient experienced 1 event of injection site reaction and 1 event of injection site pain.

FIGURE 1. Role of IgE and proposed mechanism of action in chronic rhinosinusitis with nasal polyps.

FIGURE 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.

FIGURE 3. Patient disposition (consort flow diagram).

FIGURE 4. Mean change from baseline in **(A)** Nasal Polyp Score and **(B)** Nasal Congestion Score in POLYP 1 and POLYP 2.

FIGURE 5. Proportion of patients reporting ≥ 1 -point Nasal Polyp Score (NPS) and Nasal Congestion Score (NCS) and ≥ 2 -point NPS improvement in POLYP 1 and POLYP 2 (pooled data).

FIGURE 6. Change from baseline in **(A)** Sino-Nasal Outcome Test-22 (SNOT-22), **(B)** University of Pennsylvania Smell Identification Test (UPSIT), and **(C)** Total Nasal Symptom Score (TNSS) scores in POLYP 1 and POLYP 2.