Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: A randomized, placebo-controlled trial

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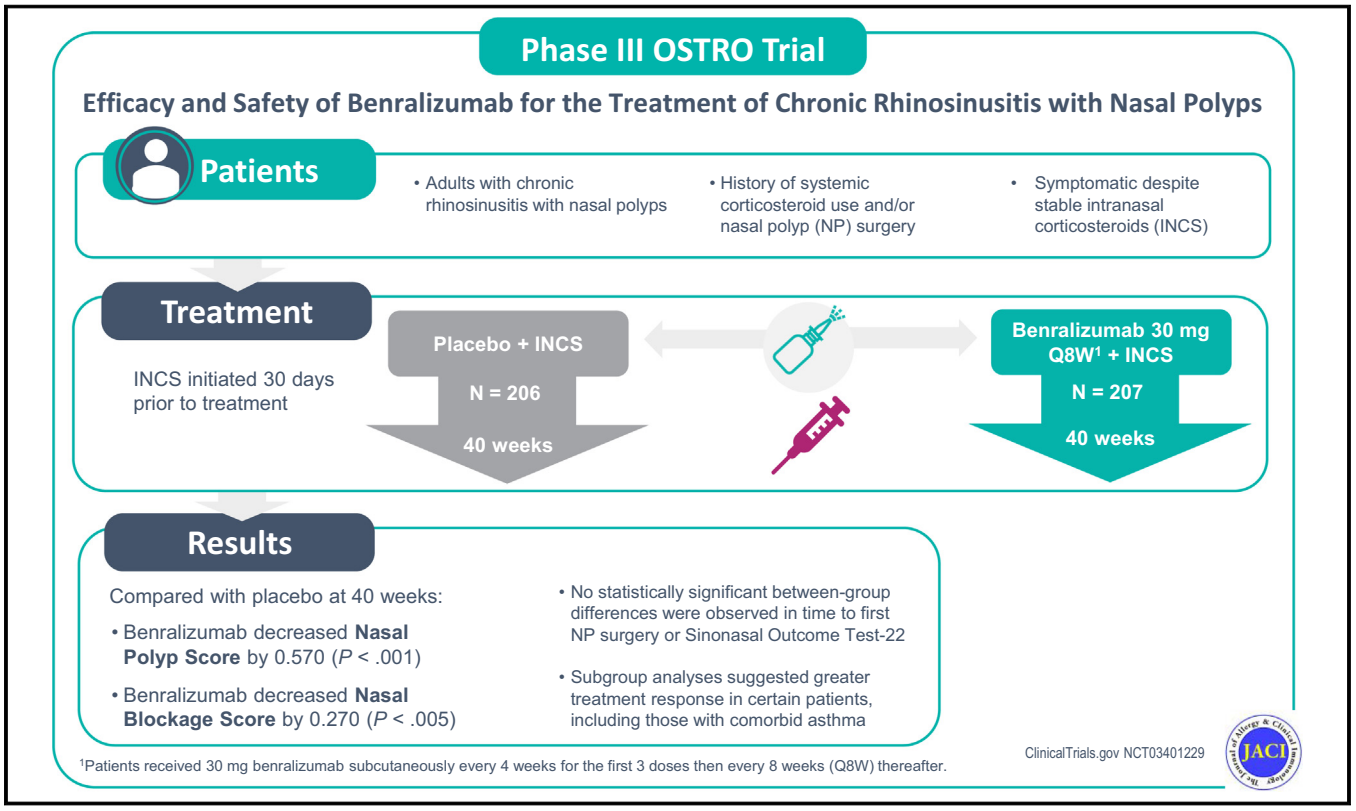
GRAPHICAL ABSTRACT



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Background: Eosinophilic inflammation has been implicated in the pathogenesis, severity, and treatment responsiveness of chronic rhinosinusitis with nasal polyps (CRSwNP).
Objective: We sought to assess the efficacy and safety of benralizumab-mediated eosinophil depletion for treating CRSwNP.
Methods: The phase 3 OSTRO study enrolled patients with severe CRSwNP who were symptomatic despite treatment with intranasal corticosteroids and who had a history of systemic corticosteroid (SCS) use and/or surgery for nasal polyps (NP). Patients were randomized 1:1 to treatment with benralizumab 30 mg or placebo every 4 weeks for the first 3 doses and every 8 weeks thereafter. Coprimary end points were change from baseline to week 40 in NP score (NPS) and patient-reported mean nasal blockage score reported once every 2 weeks.
Results: The study population comprised 413 randomized patients (207 in the benralizumab group and 206 in the placebo group). Benralizumab significantly improved NPS and nasal blockage score compared to placebo at week 40 ($P \leq .005$). Improvements in Sinonasal Outcome Test 22 score at week 40, time to first NP surgery and/or SCS use for NP, and time to first NP surgery were not statistically significant between treatment groups. Nominal significance was obtained for improvement in difficulty in sense of smell score at week 40 ($P = .003$). Subgroup analyses suggested influences of comorbid asthma, number of NP surgeries, sex, body mass index, and baseline blood eosinophil count on treatment effects. Benralizumab was safe and well tolerated.
Conclusion: Benralizumab, when added to standard-of-care therapy, reduced NPS, decreased nasal blockage, and reduced difficulty with sense of smell compared to placebo in patients with CRSwNP. Trial registration: ClinicalTrials.gov NCT03401229 (J Allergy Clin Immunol 2022;149:1309-17.)

Key words: *Eosinophils, eosinophilia, type 2 inflammation, nasal polyposis, biologic, IL-5 receptor, sinonasal polyposis, systemic corticosteroids, intranasal corticosteroids, nasal blockage*

Abbreviations used

ACQ-6:	Asthma Control Questionnaire 6
ADA:	Antidrug antibody
AE:	Adverse event
ANCOVA:	Analysis of covariance
BMI:	Body mass index
CI:	Confidence interval
COVID-19:	Coronavirus disease 2019
CRS:	Chronic rhinosinusitis
CRSwNP:	CRS with NPs
CT:	Computed tomography
DSS:	Difficulty with sense of smell
IL-5Rα:	Alpha subunit of the IL-5 receptor
INCS:	Intranasal corticosteroid
LMS:	Lund-MacKay score
NBS:	Nasal blockage score
NP:	Nasal polyp
NPS:	Nasal polyp score
SCS:	Systemic corticosteroid
SNOT-22:	Sinonasal Outcome Test 22
UPSIT:	University of Pennsylvania Smell Identification Test

Chronic rhinosinusitis with nasal polyps (CRSwNP) is an inflammatory condition associated with symptoms that may be severe, including rhinorrhea, nasal blockage/congestion, hyposmia or anosmia, and facial pressure or pain.[1,2] Symptoms of CRSwNP are often insufficiently managed by currently available pharmacologic therapies (eg, intranasal corticosteroids [INCS] and systemic corticosteroids [SCS]), resulting in significantly impaired health-related quality of life and considerable health care resource utilization.[3,4] Furthermore, patients with CRSwNP often require surgery and frequently experience postsurgical disease recurrence.[5,6]

The etiology of CRSwNP remains incompletely understood, although several immunologic mechanisms—type 1, type 2, and type 3 immune reactions marked by the involvement of T helper cells and corresponding innate lymphocytes—have been implicated in disease pathogenesis.[7] The diversity of cytokine profiles[8-10] that present with a common symptomology indicates heterogeneous pathways lead to a shared clinical expression. CRSwNP associated with type 2 inflammation, the most common endotype in Western populations,[8,9] has a strong connection with tissue eosinophilia,[11] suggesting that eosinophils may play a mechanistic role in the pathogenesis of CRSwNP. Supporting this putative etiologic link are the observations that marked eosinophilic inflammation within polyp tissue and elevations in blood eosinophil counts correlate with greater disease severity, risk of recurrence, and likelihood for refractory disease.[12-15] Nonetheless, a clear definition for the role of eosinophils in type 2 inflammation has yet to be elucidated. Moreover, there is currently no biomarker, demographic parameter, or clinical finding that predicts patient-specific treatment response to biologic therapies,[16] each of which suppresses inflammation through targeting distinct aspects of the immunologic pathways implicated in CRSwNP.

Benralizumab is a humanized afucosylated monoclonal antibody that is produced in Chinese hamster ovary cells.[17] The antibody is directed against the alpha subunit of the IL-5 receptor (IL-5Rα), which is primarily expressed by human eosinophils and basophils.[18,19] Benralizumab binds to IL-5Rα–expressing cells, blocking IL-5 signaling and targeting them for enhanced antibody-dependent cellular cytotoxicity, resulting in rapid, near-complete depletion of blood eosinophils and a reduction in basophil counts.[18,19] Profound depletion of eosinophils by benralizumab provides a unique opportunity to explore the role of eosinophils in CRSwNP. Previous clinical trials, observational studies, and case series have shown improvements with benralizumab in nasal polyp score (NPS), symptoms, and health-related quality of life in patients with severe asthma and comorbid CRSwNP.[20-22] In a small proof-of-concept study, benralizumab reduced NPS from baseline and improved symptoms and sense of smell in patients with severe CRSwNP.[23] The phase 3 OSTRO study expands on these data and contributes to our understanding of CRSwNP pathophysiology by evaluating the efficacy and safety of benralizumab versus placebo and identifying demographic, laboratory, and clinical characteristics that predict response to benralizumab therapy in a population of patients with severe, symptomatic CRSwNP despite standard-of-care therapy.

METHODS

Patients

Eligible patients were 18 to 75 years of age with bilateral NP and a total NPS of ≥5 (with unilateral scores of ≥2) despite maintenance treatment with

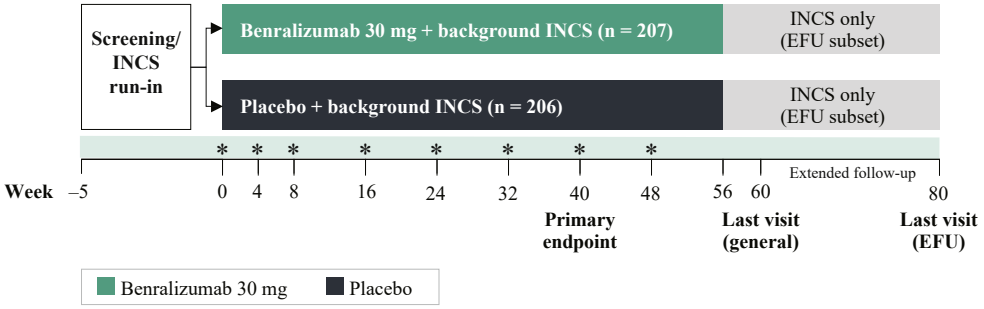

FIG 1. Study design. *Asterisks* indicate study drug dose administration visits. *EFU,* Extended follow-up population. Study-provided mometasone furoate nasal spray was maintained throughout the study.

INCS for at least 4 weeks before enrollment and a history of SCS use and/or surgery for NP. In addition, patients were required to have ongoing NP symptoms for ≥12 weeks, moderate to severe nasal blockage (nasal blockage score [NBS] ≥2, captured electronically in the Nasal Polyposis Symptom Diary), and Sinonasal Outcome Test 22 (SNOT-22) total score ≥30 at enrollment. Patients were excluded if they had nasal/sinus surgery in the previous 3 months, had an asthma exacerbation within 4 weeks of enrollment, or were deemed ineligible because of clinically significant concurrent disease. Full inclusion and exclusion criteria are included in this article's Online Repository at www.jacionline.org.

Study design

This phase 3, randomized, double-blind, placebo-controlled study (ClinicalTrials.gov NCT03401229) was conducted at 102 sites in Europe and the United States from January 2018 to July 2020. To ensure consistency of background INCS, during the 5-week screening/run-in period, patients transitioned from their existing INCS regimen to a stable dose of study-provided mometasone furoate nasal spray (total daily dose, 400 μg), which was maintained throughout the study (Fig 1). Patients who continued to meet eligibility criteria were randomized 1:1 to treatment with benralizumab 30 mg or placebo administered subcutaneously every 4 weeks for the first 3 doses and every 8 weeks thereafter. Randomization was stratified by region and comorbid asthma status. SCS use was only permitted in the short term (≤14 days) for treatment of NP worsening or asthma exacerbations.

The last study drug dose was administered at week 48, and the end-of-treatment visit occurred at week 56. The first 185 patients who completed the 56-week treatment period entered a 24-week extended follow-up period, during which background INCS usage continued. The study protocol was amended in August 2020 to change the primary assessment time point from week 56 to week 40 due to the coronavirus disease 2019 (COVID-19) global pandemic. Week 40 was the latest study visit not substantially affected by COVID-19–related missing data or missed doses (see Table E1 in the Online Repository available at www.jacionline.org).

The study protocol received independent ethics committee approval at each study site, and the clinical trial was conducted in accordance with the principles of good clinical practice. All patients provided written informed consent.

Assessments and end points

The coprimary end points were change from baseline to week 40 in total NPS and in biweekly mean NBS. Total NPS was determined from bilateral nasal endoscopy and rated on a scale of 0 (no polyps) to 4 (large polyps completely obstructing the inferior nasal cavity) for each nostril (total score range, 0-8). NPS was scored centrally by 2 expert physicians unrelated to the study sites using video image data captured during endoscopy; a third physician adjudicated discrepancies (Parexel, Newton, Mass). All reviewers were unaware of the study treatment assignment. Patients rated NBS daily on the basis of their perceived nasal blockage severity over the past 24 hours on a scale of 0 (none) to 3 (severe).

Key secondary efficacy end points included change from baseline in NPS and biweekly mean NBS at week 56, change from baseline in SNOT-22 total score at weeks 40 and 56, time to first NP surgery and/or SCS use for NP, time to first NP surgery, change from baseline in biweekly mean difficulty with sense of smell (DSS) score at weeks 40 and 56, and change from baseline in sinus opacification as measured by computed tomography (CT)-derived Lund-Mackay score (LMS) at end of treatment. SNOT-22 quantified chronic rhinosinusitis (CRS)-specific quality-of-life impairments on a scale from 0 (no problem) to 5 (problem as bad as can be), for a maximum score of 110.[24] The DSS score was derived from daily Nasal Polyposis Symptom Diary entries in which patients rated their worst difficulty in sense of smell over the past 24 hours on a scale of 0 (none) to 3 (severe). LMS was scored by a central reader, with higher scores indicating a greater degree of sinus opacification (range, 0-24).[25]

Additional efficacy measures included SCS use, University of Pennsylvania Smell Identification Test (UPSIT) score, sinus severity score, and asthma-specific measures. UPSIT, a quantitative test of olfactory function, was used to gauge the ability of patients to correctly identify odors using a 40-sample testing panel with forced choice among 4 options for each sample.[26] UPSIT total scores range from 0 to 40, with anosmia defined for this study as a score of 0 to 18. Sinus severity score was measured in the CT subset and was defined as the percentage of sinus volume occupied by the mucosa. For patients with comorbid asthma, asthma control was evaluated through the occurrence of exacerbations and change in Asthma Control Questionnaire 6 (ACQ-6) score. An exacerbation was defined as use of SCS for the treatment of asthma or hospitalization due to asthma. ACQ-6 measures asthma symptom control on the basis of 5 symptom questions and 1 bronchodilator use question, each rated on a scale from 0 (no impairment) to 6 (maximum impairment).[27] Mean ACQ-6 score is the average of the 6 individual question scores, and a score of ≥1.5 indicates poor asthma control.

Safety assessments included treatment-emergent adverse events (AEs), laboratory variables, and antidrug antibody (ADA) assays. The final safety assessment occurred at week 80 for patients in the extended follow-up population and week 60 for all others.

Statistical analysis

A sample size of 400 randomized patients (200 assigned to benralizumab and 200 to placebo) was calculated to provide ≥95% power to detect a treatment difference of 1.2 units in total NPS and 0.6 units in biweekly mean NBS at a 2-sided alpha level of 0.01, assuming population standard deviations of 2 for NPS and 1 for NBS.

Efficacy analyses included all randomized patients who received ≥1 dose of study drug, except where limited by evaluation (CT subset) or presence of comorbidity (asthma subset). For NPS, NBS, SNOT-22, and DSS, treatment effects were measured using a primary estimand method with a hybrid of worst possible score (for patients who underwent NP surgery)/worst observation carried forward (for patients receiving SCS for NP worsening) and multiple imputation followed by analysis of covariance (ANCOVA). Treatment group, baseline scores, region, and baseline comorbid asthma status were covariates. Between-group comparisons are reported as point estimates and 95%

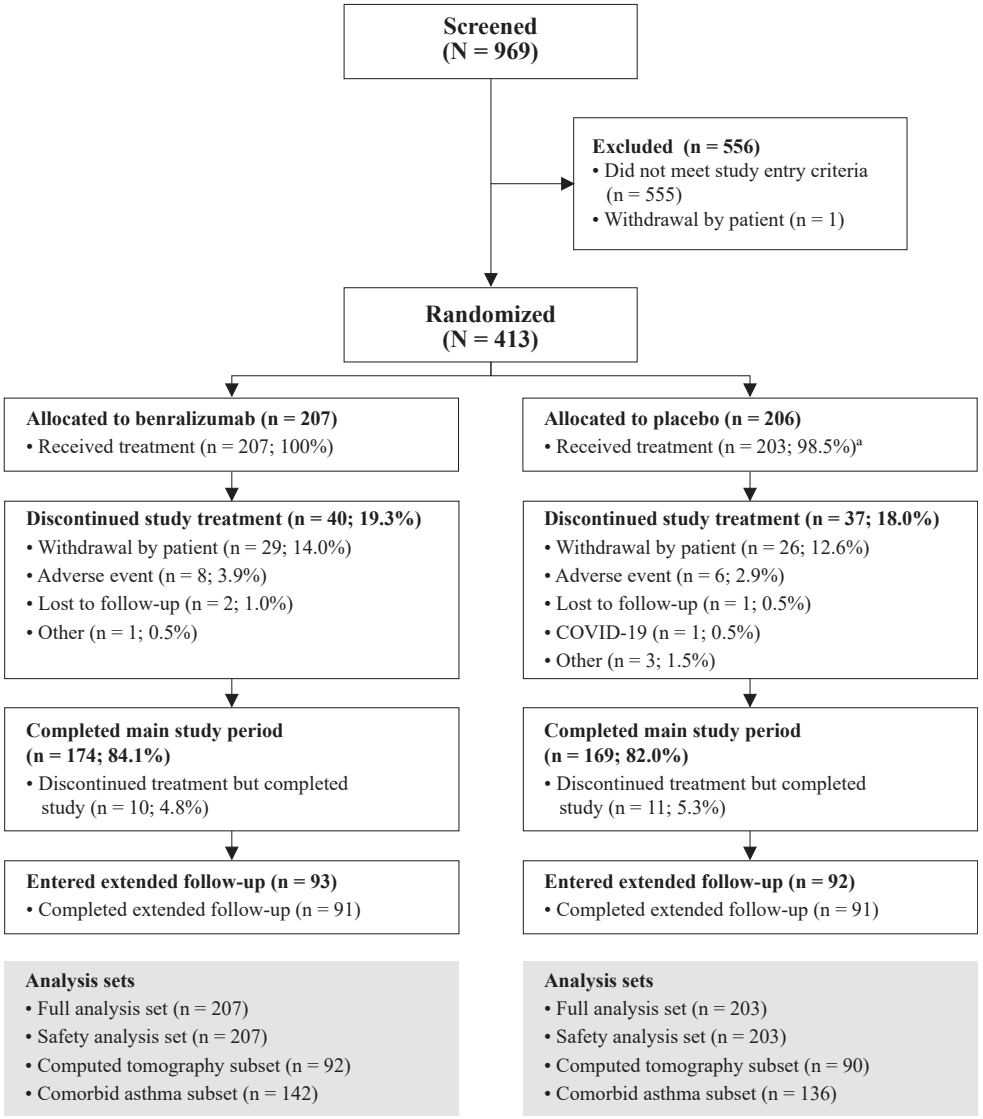

FIG 2. Patient disposition. [a]Three patients in the placebo group were randomized in error and did not receive any dose of the study drug.

confidence intervals (CIs). Time to first NP surgery and/or SCS use for NP and time to first NP surgery were analyzed using a Cox proportional hazard model, with treatment group, region, and baseline comorbid asthma status as covariates. Mean biweekly values for variables derived from the Nasal Polyposis Symptom Diary (NBS and DSS) were calculated by summing daily entries at 2-week intervals and dividing by the number of nonmissing days, if at least 8 days in the interval had evaluable data.

To account for multiplicity in testing, both coprimary end points were tested at the .01 level (2 sided), and the key secondary end points were tested hierarchically at the .05 level (2 sided). Coprimary end points were required to obtain significance at the .01 level with treatment effects in favor of benralizumab before testing the 9 key secondary end points in a fixed-sequence testing approach.

Additional prespecified analyses included treatment effects by baseline demographic and clinical characteristic subgroups for NPS and NBS at weeks 40 and 56 and responder analyses for NPS at weeks 24, 40, and 56. Safety analyses included all randomized patients who received ≥1 dose of study drug and were reported using descriptive statistics. All analyses were performed by SAS 9.4 software (SAS Institute, Cary, NC). Additional details of the analysis's methodology are provided in the Online Repository available at www.jacionline.org.

RESULTS

A total of 413 patients were randomized, 207 to benralizumab and 206 to placebo (Fig 2). Three patients in the placebo group were randomized in error and did not receive any dose of study drug. The majority of randomized patients (80.6%) completed the study treatment, and 83.1% completed the main study period. Rates of discontinuation were similar between treatment groups (benralizumab, 19.3%; placebo, 18.0%), with patient withdrawal (14.0% and 12.6%) and AEs (3.9% and 2.9%) as the predominant reasons for discontinuation. A subset of 185 patients (benralizumab, 93; placebo, 92) continued into the extended follow-up period.

Demographics were generally balanced between treatment groups, although a greater proportion of men were randomized to benralizumab versus placebo (Table I). There were also fewer patients with a body mass index (BMI) of >30 kg/m^2 in the benralizumab group compared with the placebo group. In the overall population, female predominance was observed in patients with comorbid asthma (see Table E2 in the Online

TABLE I. Demographics and baseline characteristics, full analysis set

Parameter	Benralizumab 30 mg (n = 207)	Placebo (n = 203)
Age (years), mean ± SD	50.1 ± 12.4	50.2 ± 13.9
Male sex	142 (68.6)	121 (59.6)
Race		
White	197 (95.2)	190 (93.6)
Black	4 (1.9)	8 (3.9)
Asian	3 (1.4)	1 (0.5)
Other	3 (1.4)	4 (2.0)
BMI (kg/m^2), mean ± SD	27.4 ± 5.1	28.5 ± 6.4
BMI category		
Normal (≤25 kg/m^2)	73 (35.3)	59 (29.1)
Overweight (>25 to ≤30 kg/m^2)	87 (42.0)	77 (37.9)
Obese (>30 to ≤35 kg/m^2)	29 (14.0)	45 (22.2)
Morbidly obese (>35 kg/m^2)	18 (8.7)	22 (10.8)
Comorbid asthma	142 (68.6)	136 (67.0)
ACQ-6 score, mean ± SD†	1.92 ± 1.27	2.05 ± 1.20
≥1 exacerbation in past 12 months	26 (18.3)	23 (16.9)
Anosmia*†	147 (82.6)	152 (84.4)
AERD	62 (30.0)	59 (29.1)
Prior NP surgery	151 (72.9)	149 (73.4)
No. of surgeries, median (range)	2 (1, 40)	2 (1, 15)
Years since surgery	6.93 ± 6.45	6.95 ± 5.46
History of SCS use for NP	161 (77.8)	146 (71.9)
No. of courses in past 12 months, median (range)	1 (0, 10)	1 (0, 7)
NPS, mean ± SD†	6.15 ± 1.19	6.13 ± 1.13
NBS, mean ± SD	2.62 ± 0.46	2.59 ± 0.46
SNOT-22 total score, mean ± SD†	69.3 ± 19.77	69.0 ± 19.03
Baseline IgE (IU/mL), mean ± SD†	214 ± 344	251 ± 549
Baseline blood eosinophil count (cells/μL)†		
Mean ± SD	448.3 ± 364.6	445.7 ± 245.1
Median (range)	375.0 (40, 3670)	400.0 (80, 1710)
Atopic by Phadiatop†	111 (55.8)	102 (52.8)
Region		
United States	39 (18.8)	39 (19.2)
Rest of world	168 (81.2)	164 (80.8)

Data are presented as no. (%) unless otherwise indicated.
AERD, Aspirin-exacerbated respiratory disease.
*Anosmia was defined as an UPSIT score of ≤18.
†Baseline data were available for in the benralizumab and placebo groups for 140 and 135 patients (ACQ-6), 178 and 180 patients (anosmia), 204 and 198 patients (NPS), 205 and 199 patients (SNOT-22), 204 and 201 patients (IgE), 206 and 202 patients (eosinophil count), and 199 and 193 patients (atopic status).

Repository available at www.jacionline.org). Baseline characteristics were reflective of a population with severe CRSwNP, with a high mean NPS (6.1) and SNOT-22 total score (69), and large proportions of patients with anosmia (83.5%) and a history of NP surgery (73.2%). Comorbid asthma was present in 67.8% of patients (mean baseline ACQ-6 score, 1.98), and 54.3% of patients were atopic by Phadiatop test. Mean blood eosinophil counts were elevated and were similar in the benralizumab and placebo groups (448.3 ± 364.6 and 445.7 ± 245.1 cells/μL, respectively).

NPS and NBS

Benralizumab treatment resulted in significantly greater improvements compared with placebo in the coprimary end points of change from baseline in total mean NPS (between-group difference, −0.570 [95% CI, −0.852 to −0.289]; $P < .001$) and

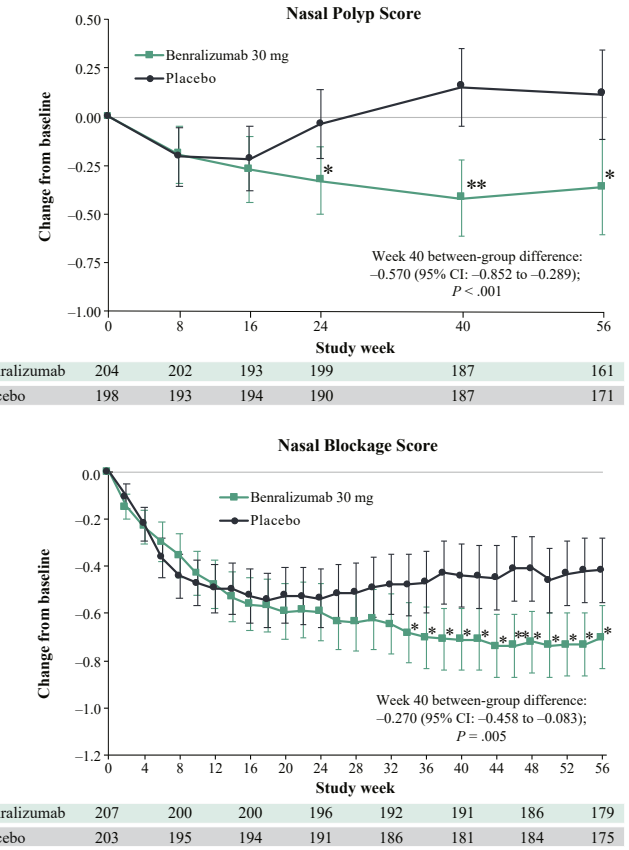

FIG 3. Changes from baseline in NPS and NBS during the main study period. Data are least-squares means ± 95% CIs for the full analysis set. NPS range, 0-8. NBS range, 0-3. *$P < .05$; **$P < .001$ for the comparison of benralizumab and placebo.

biweekly mean NBS (between-group difference, −0.270 [95% CI, −0.458 to −0.083]; $P = .005$) at week 40 (Fig 3). Reductions in NPS and NBS with benralizumab were maintained through week 56.

At week 40, a greater proportion of patients who received benralizumab (35.3%) versus placebo (19.2%) experienced at least a 1-point improvement in NPS from baseline (odds ratio, 2.30 [95% CI, 1.46 to 3.64]; $P < .001$). Nominally significant differences between groups were also observed at week 24 (odds ratio, 1.67 [95% CI, 1.07 to 2.60]; $P = .02$) and week 56 (odds ratio, 1.93 [95% CI, 1.18 to 3.18]; $P = .009$]). Notably, patients with missing data at a given time point were conservatively considered non-responders, and fewer patients had NPS data at week 56 (332 patients) compared to week 40 (374 patients).

Secondary end points

Change from baseline in SNOT-22 total score at week 40, the first key secondary end point, was numerically greater with benralizumab versus placebo (least-squares mean changes, −16.23 vs −11.02); however, the between-group difference did not achieve statistical significance (Table II). Therefore, statistical significance cannot be claimed for subsequent end points in the hierarchy. Results for secondary end points are

TABLE II. Primary and key secondary efficacy parameters, full analysis set*

Characteristic	Benralizumab 30 mg No.	Benralizumab 30 mg LS mean change	Placebo No.	Placebo LS mean change	Between-group comparison†	95% CI	*P* value
NPS at week 40 (scale, 0-8)	187	−0.418	187	0.153	−0.570	−0.852, −0.289	< .001
Biweekly mean NBS at week 40 (scale, 0-3)	191	−0.711	181	−0.441	−0.270	−0.458, −0.083	.005
SNOT-22 total score at week 40 (scale, 0-110)	193	−16.23	190	−11.02	−5.21	−11.09, 0.66	.08
Time to first NP surgery and/or SCS use for NP	207	72 (34.8)‡	203	91 (44.8)‡	0.75	0.55, 1.02	.07
Time to first NP surgery	207	33 (15.9)§	203	37 (18.2)§	0.85	0.53, 1.36	.50
Biweekly mean DSS score at week 40 (scale, 0-3)	191	−0.383	181	−0.165	−0.218	−0.361, −0.074	.003
NPS at week 56 (scale, 0-8)	161	−0.361	171	0.114	−0.475	−0.810, −0.141	.005
Biweekly mean NBS at week 56 (scale, 0-3)	179	−0.703	175	−0.416	−0.287	−0.477, −0.096	.003
SNOT-22 total score at week 56 (scale, 0-110)	190	−16.25	184	−8.75	−7.49	−13.74, −1.24	.02
Biweekly mean DSS score at week 56 (scale, 0-3)	179	−0.423	175	−0.187	−0.237	−0.389, −0.084	.002
LMS at end of treatment/discontinuation (scale, 0-24)	81	−0.993	84	−0.138	−0.856	−2.281, 0.570	.24

End points are shown in hierarchical analysis order. The number of patients in each category reflects those with evaluable data at the time point, which includes patients with imputed values for worst possible value/worst observation carried forward after NP surgery and/or use of SCS for NP.

LS, Least-squares.

*LMS data are for the CT subset.

†Data are LS mean differences, except for time to event analyses, which are shown as hazard ratios.

‡No. (%) of patients with ≥1 NP surgery and/or SCS use for NP.

§No. (%) of patients with ≥1 NP surgery.

presented with unadjusted *P* values; differences with $P < .05$ are referred to as nominally significant.

Surgery for NP and/or use of SCS for NP was reported for 34.8% and 44.8% of patients in the benralizumab and placebo groups, respectively. A trend was observed toward a longer time to first NP surgery and/or first SCS use for NP with benralizumab versus placebo (Table II; see Fig E1 in the Online Repository available at www.jacionline.org). The apparent divergence was primarily driven by differences in SCS use, as time to first NP surgery was similar between treatment groups. During the study, 25.1% and 32.5% of patients in the benralizumab and placebo groups were prescribed SCS for NP, respectively (odds ratio, 0.69 [95% CI, 0.44 to 1.06]; $P = .09$). Kaplan-Meier curves of time to first SCS use for NP began to diverge at week 24, with greater utilization in the placebo group continuing through week 56 (Fig E1).

Nominal significance was obtained for improvements in the key secondary end points of change from baseline in NPS and biweekly mean NBS at week 56 ($P = .005$ and $P = .003$), DSS at weeks 40 and 56 ($P = .003$ and $P = .002$), and SNOT-22 total score at week 56 ($P = .02$) (Table II; see Figs E2 and E3 in the Online Repository available at www.jacionline.org). Change in the ability to identify odors, as measured by UPSIT, was not appreciably different between treatment groups at weeks 40 or 56.

In the subset of patients who underwent sinus evaluation by CT, reduction in LMS at end of treatment/discontinuation was numerically greater with benralizumab (−0.993) versus placebo (−0.138), but the difference between groups did not achieve nominal significance. Improvement from baseline in aeration of nasal sinuses, as assessed by sinus severity score, similarly favored benralizumab versus placebo (between-group difference, −5.057 [95% CI, −11.129 to 1.015]; $P = .10$).

Results of sensitivity analyses for NPS, NBS, SNOT-22, and DSS were broadly consistent with primary analyses across multiple imputation methods (see Fig E4 in the Online Repository available at www.jacionline.org). Although the shape of the curves over time was affected by the analysis method, the magnitude of difference between benralizumab and placebo and the qualitative conclusions from the different estimand approaches were consistent.

Subgroup analyses

In prespecified subgroup analyses, NPS treatment effect at week 40 differed by asthma status ($P = .01$) and number of prior NP surgeries ($P = .02$) (Fig 4). There was some evidence of differential effects on NPS and NBS based on sex, BMI, and baseline blood eosinophil counts, but the interaction tests did not reach nominal significance. Similar trends continued at week 56 (data not shown). Subgroup analyses for SNOT-22 total score and DSS were generally directionally consistent with NPS and NBS findings (data not shown).

Asthma control in patients with comorbid asthma

At week 40, a decrease from baseline in ACQ-6 score was observed in patients with comorbid asthma who received benralizumab (−0.195) that was not observed in the placebo group (0.135). Improvements in ACQ-6 score favored benralizumab versus placebo at week 40 (between-group difference, −0.330 [95% CI, −0.748 to 0.089]; $P = .12$) and week 56 (−0.331 [95% CI, −0.795 to 0.133]; $P = .16$). The annualized exacerbation rate was 47% lower with benralizumab than placebo (0.06 and 0.12 events per year, respectively; rate ratio, 0.53 [95% CI, 0.17 to 1.63]).

Safety and tolerability

During the main study period, 77.3% and 78.8% of patients in the benralizumab and placebo groups, respectively, experienced ≥1 AE (Table III). AEs were predominantly mild to moderate in intensity. The most commonly reported AEs were nasopharyngitis, asthma, headache, and viral upper respiratory tract infection, none of which occurred more frequently in the benralizumab group compared with placebo. Serious AEs occurred at a similar frequency between treatment groups. Only 2 serious AEs occurred in more than 1 patient: pericarditis and gastritis were reported for 2 patients each in the benralizumab group; no events were considered related to the study treatment by the investigator.

Injection site reactions were transient, mild to moderate in intensity, and occurred at a low rate in both treatment groups

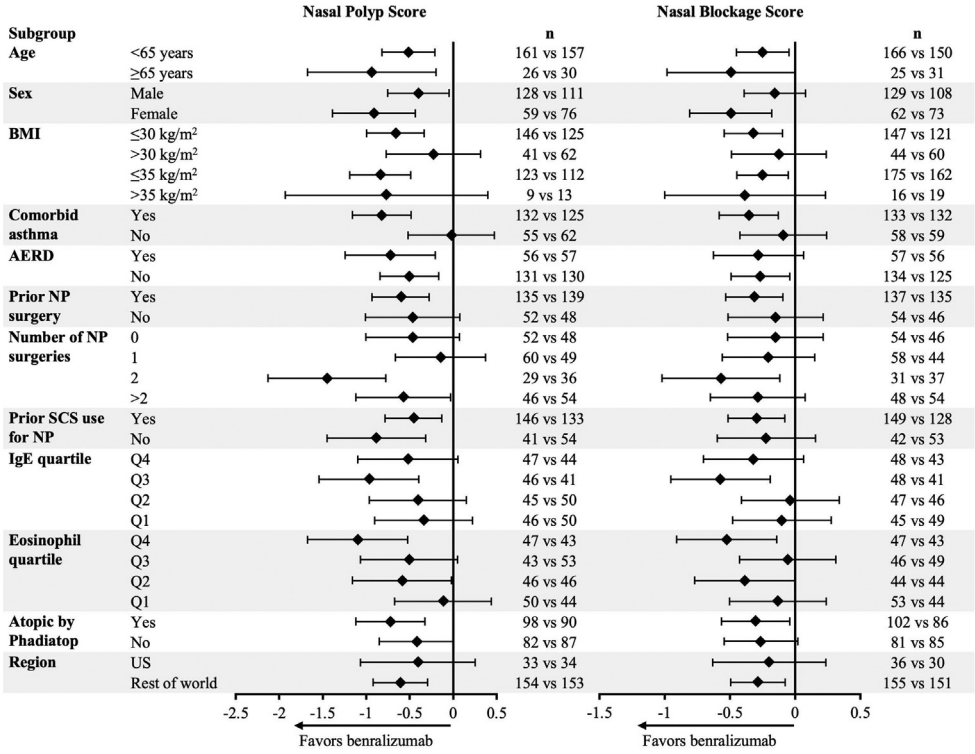

FIG 4. Between-group differences in NPS and NBS improvement at week 40 by subgroup. Data are point estimates and 95% CIs. Number of patients shown as benralizumab versus placebo. Quartiles of baseline IgE (IU/mL): Q1, ≤38.7; Q2, >38.7 to ≤93.4; Q3, >93.4 to ≤294.1; Q4, >294.1. Quartiles of blood eosinophil counts (cells/μL): Q1, ≤260; Q2, >260 to ≤385; Q3, >385 to ≤560; Q4, >560. *P* values for tests of interaction were <.05 for number of NP surgeries and comorbid asthma (NPS), <.1 for sex (NPS and NBS), and <.2 for BMI ≤30 versus >30 kg/m^2 (NPS), eosinophil quartiles (NPS), comorbid asthma (NBS), and IgE quartiles (NBS). *AERD,* Aspirin-exacerbated respiratory disease.

(benralizumab, 1.9%; placebo, 2.0%). The prevalence of neutralizing antibodies was 10.0% in the benralizumab group and were not associated with AEs. No placebo patients were neutralizing antibody positive. Additional information is provided in the Online Repository available at www.jacionline.org.

As expected on the basis of the mechanism of action of benralizumab, blood eosinophils were nearly completely depleted and basophil counts were reduced in the benralizumab group. No other clinically meaningful changes in laboratory parameters or vital signs were observed.

Extended follow-up population

For the subset of 185 patients who entered the extended follow-up period (up to 32 weeks after last dose administration), there was no clear loss of efficacy in patient-reported outcome measures (NBS, SNOT-22, DSS) for benralizumab compared with placebo from week 56 through week 80. Mean NPS in patients who had formerly received benralizumab increased slowly from week 56 (−0.49 [SD, 1.74]) to week 80 (−0.17 [SD, 1.71]), indicating loss of efficacy after treatment discontinuation. Notably, fewer patients had evaluable NPS at week 80 (n = 148) compared to week 56 (n = 181) due to COVID-19 disruptions. Blood eosinophil counts approached baseline levels at week 80. No new safety concerns arose during the extended follow-up period.

DISCUSSION

Persistent symptoms despite standard-of-care therapy[3] and high rates of postsurgical recurrence[5,6] underscore the need for additional treatment options for patients with CRSwNP. In the OSTRO study, which enrolled a nonhomogeneous population of patients with severe, uncontrolled CRSwNP, addition of benralizumab to standard-of-care treatment reduced NPS as well as the severity of patient-reported nasal blockage compared with placebo. Improvements with benralizumab at the primary assessment time point (week 40) were maintained through the end of treatment (week 56). Among the key secondary end points, data were suggestive of positive benralizumab treatment effects on patient-reported DSS. Benralizumab was well tolerated, with a safety profile consistent with clinical data for the approved indication of severe asthma.

Benralizumab exerts its therapeutic effects primarily via eosinophil depletion; it also causes basophil depletion and blockade of IL-5 signaling.[19] In patients with CRSwNP, tissue eosinophilia is associated with greater disease severity, impaired sense of smell, refractory disease, and poor outcomes, including NP recurrence and use of SCS after surgery for NP.[12-15] Peripheral eosinophil counts are also linked to outcomes in CRSwNP, with higher counts predicting increased risk for refractory and recurrent disease.[14] However, the precise etiologic role for and degree of involvement of eosinophils in CRSwNP remains to be determined. The value of targeting eosinophils

TABLE III. Safety summary, safety analysis set

Characteristic	Benralizumab 30 mg (n = 207), no. (%)	Placebo (n = 203), no. (%)
Patients with ≥1 AE	160 (77.3)	160 (78.8)
Serious AEs	23 (11.1)	17 (8.4)
AEs with an outcome of death	0	0
Treatment discontinuation due to an AE	8 (3.9)	6 (3.0)
AE severity		
Mild	64 (30.9)	69 (34.0)
Moderate	70 (33.8)	75 (36.9)
Severe	26 (12.6)	16 (7.9)
Common AEs*		
Nasopharyngitis	36 (17.4)	41 (20.2)
Asthma	19 (9.2)	29 (14.3)
Headache	7 (3.4)	15 (7.4)
Viral upper respiratory tract infection	5 (2.4)	14 (6.9)

*Reported by ≥5% of patients in either treatment group.

was challenged in 2019 by a small study in which treatment with dexpramipexole, whose depletive effects on eosinophil counts vary by patient, did not result in NP size reduction.[28] Interpretation of these results, however, is limited by the lack of a placebo control group, the small sample size, and the proportion of patients who had a limited eosinophil response. In contrast, in the placebo-controlled, phase 3 study of mepolizumab, whose mechanism also involves targeting eosinophils, total endoscopic NPS was significantly reduced from baseline in patients who received mepolizumab versus placebo, thus supporting an eosinophil-targeted strategy for CRSwNP.[29]

Results from OSTRO suggest that CRSwNP is a heterogeneous disease that includes subsets of patients for whom eosinophils may be a more significant contributor to disease pathogenesis as well as patients for whom other inflammatory mediators or alternative pathways are driving the formation and persistence of NPs. This finding highlights the incomplete understanding of the role of eosinophils in the pathogenesis of CRSwNP and reveals an avenue for future research. The OSTRO population had an *a priori* high likelihood of eosinophil-driven etiology by virtue of the requirement for prior surgery for NP and/or use of SCS.[11,30] Among enrolled patients, there was also a considerable proportion with comorbid asthma (67.8%) and the mean baseline blood eosinophil count was high (~450 cells/μL)—additional clinical factors associated with eosinophilic CRSwNP. Within this cohort of patients, subgroup analyses trended toward greater NPS and NBS treatment effects in patients with factors such as comorbid asthma, a history of 2 prior NP surgeries, female sex, lower BMI, and higher baseline blood eosinophil count. From among these parameters, greater treatment response in women may be explained by the greater prevalence of women in the comorbid asthma subgroup relative to the overall study population. Notably, although treatment response was greater in patients with a history of 2 prior NP surgeries compared to those who had 1 or no prior NP surgeries, the trend toward increasing treatment response with number of prior surgeries did not continue for patients with more than 2 prior surgeries. Moreover, when categorized as a binary measure (presence vs absence of NP surgery history), no statistically significant difference in treatment effect was observed. Whereas factors such as comorbid asthma and prior surgery are recognized as influential in CRSwNP,[11,30] the identification of BMI as a potential modifier of phenotype in CRSwNP is a new concept. Because obesity can modulate systemic inflammation and is associated with a more severe asthma phenotype,[31,32] the influence of BMI on treatment response in CRSwNP is an intriguing area for further study.

A greater benralizumab treatment response in patients with comorbid asthma or higher baseline blood eosinophil counts is consistent with the mechanism of benralizumab (eosinophil depletion) and the associations of these factors with an eosinophilic CRSwNP endotype. Peripheral eosinophil count is associated with tissue eosinophilia in CRSwNP and has been proposed as a surrogate marker thereof.[33] Reductions in NPS with benralizumab have previously been linked to baseline blood eosinophil count in patients with CRSwNP,[23,34] and eosinophils in sinonasal mucosa and peripheral blood are elevated to a greater degree in patients with CRS and asthma than in patients with CRS alone.[35-37] In OSTRO, patients with comorbid asthma had higher mean baseline blood eosinophil counts than patients without the disease (Table E1). Preliminary evidence suggests that treatment response may be enhanced in patients with both comorbid asthma and elevated eosinophils; in a case series of patients with severe asthma and comorbid CRSwNP, benralizumab reduced NPS to a greater extent in patients with higher versus lower baseline eosinophil counts.[20] Given the frequent occurrence of asthma and CRSwNP,[30] determining whether asthma influences treatment response has considerable clinical relevance.

There are limitations that influence the interpretation of results from this study. First, there was a high degree of SCS use in both treatment groups, with greater utilization in the placebo group. Consistent with patient management recommendations,[38] SCS use was permitted as rescue therapy at the investigator's discretion. For the primary and several key secondary end points, data were set to missing from the point of SCS use for NP, with the worst value observed between baseline and time of SCS use replacing the missing value and carried forward through the remainder of the study. This approach is conservative, as its effect on downstream efficacy results may outlast any effect that would result from short-term SCS treatment for patients who infrequently require SCS therapy. Second, decreases in NPS were observed in the placebo group during the early weeks of the study. It is likely that improvement in the placebo group was related to uniformity of and compliance with the background INCS regimen. As the study progressed and more patients in the placebo group received SCS or underwent surgery and were, therefore, subject to imputation with the worst observation carried forward or worst possible value, NPS in the placebo group reverted to baseline. Last, although the predefined subgroup findings present intriguing avenues for further exploration, the study was not designed or powered to detect differences in treatment effects within subgroups.

In conclusion, this study supports the hypothesis that adding benralizumab to standard-of-care therapy to primarily target eosinophils, and to a lesser extent basophils and IL-5 signaling, is beneficial in CRSwNP. Benralizumab significantly reduced NPS and nasal blockage compared with placebo. Enhanced treatment effects in subgroups including patients with comorbid asthma and/or higher baseline blood eosinophil counts highlight the varying degree to which eosinophils are associated with ongoing disease manifestations in CRSwNP, even among patients with features traditionally associated with eosinophilic disease.

This finding warrants further study. Moreover, exploration of parameters that influence treatment response will assist in identifying patients who may derive the greatest clinical benefit from benralizumab.

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Clinical implications: In patients with CRSwNP, benralizumab offers a potential adjunct to standard-of-care therapy to reduce NPS and improve symptoms, including nasal blockage and impaired sense of smell.

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METHODS

Inclusion criteria

Patients were eligible to be included in the study only if all of the following inclusion criteria were met:

1. Capable of giving signed informed consent, which included compliance with the requirements and restrictions, listed in the informed consent form (ICF) and in the clinical study protocol.
2. Provision of signed and dated, written ICF before any mandatory study specific procedures, sampling, and analyses and according to international guidelines and/or applicable European Union guidelines.
3. Provision of signed and dated written genetic informed consent in patients that agreed to participate in the genetic sampling before collection of a sample for genetic analysis.
4. Female or male patients aged 18 to 75 years inclusive, at the time of signing the ICF.
5. Patients with bilateral sinonasal polyposis that, despite treatment with a stable dose of INCS for at least 4 weeks before visit 1 (V1), in addition to a history of treatment with SCS (oral, parenteral) or prior surgery for NPs, had severity consistent with a need for surgery as described by:
   - A minimum total NPS of 5 out of a maximum score of 8 (with a unilateral score of at least 2 for each nostril) at V1, and continuously maintained at V2 to meet the randomization criterion, as determined by the study Imaging Core Lab.
   - Ongoing symptoms for at least 12 weeks before V1.
   - Patient-reported moderate to severe nasal blockage (score 2 or 3) over the 2 weeks before V1 (2-week recall assessment of symptoms, scores 0 [none] to 3 [severe]).
6. SNOT-22 total score ≥30 at enrollment (V1).
7. At least 8 days of evaluable daily diary data in the 14-day period before randomization (baseline biweekly mean score collected from study day −13 to study day 1).
8. At randomization, a biweekly mean NBS of ≥1.5.
9. SNOT-22 total score ≥30 at randomization (V3).
10. At least 70% compliance with INCS during the run-in period based on daily diary.
11. Patients with a minimum weight of 40 kg.
12. Negative serum pregnancy test result at V1 and a negative urine pregnancy test at randomization for female patients of childbearing potential.
13. Women of childbearing potential used an effective form of birth control (confirmed by the investigator), such as total sexual abstinence, a vasectomized sexual partner, or Implanon. Female sterilization was effected by tubal occlusion, any effective intrauterine device/intrauterine system, Depo-Provera injections, oral contraceptive, Evra Patch, or Nuvaring. Women of childbearing potential agreed to use a highly effective method of birth control, as defined above, from enrollment, throughout the study duration and for 16 weeks after the last dose of investigational product.
14. Women not of childbearing potential were defined as women who were either permanently sterilized (hysterectomy, bilateral oophorectomy, or bilateral salpingectomy) or postmenopausal. Women were considered postmenopausal if they had been amenorrheic for 12 months before the planned date of the randomization without alternative medical cause. The following age-specific requirements applied:
   - Women <50 years old were considered postmenopausal if they had been amenorrheic for ≥12 months after cessation of exogenous hormone treatment and if follicle-stimulating hormone levels were in the postmenopausal range.
   - Women ≥50 years old were considered postmenopausal if they had been amenorrheic for ≥12 months after cessation of all exogenous hormone treatment.
15. Male subjects who were sexually active were surgically sterile at least 1 year before V1 or used an adequate method of contraception (condom or condom with spermicide, depending on local regulations) from the first dose of investigational product until 16 weeks after their last dose. Men with a partner (or partners) who was not of childbearing potential were exempt of these requirements.

Exclusion criteria

1. Patients who underwent any nasal and/or sinus surgery within 3 months before V1.
2. Patients with conditions or concomitant disease that made them nonevaluable for the coprimary efficacy end point, such as:
   - Unilateral antrochoanal polyps.
   - Nasal septal deviation that occluded at least 1 nostril.
   - Acute sinusitis, nasal infection, or upper respiratory infection at screening or in the 2 weeks before screening.
   - Current rhinitis medicamentosa.
   - Allergic fungal rhinosinusitis or allergic fungal sinusitis.
   - Nasal cavity tumors.
3. Clinically important comorbidities that could confound interpretation of clinical efficacy results including but not limited to: active upper or lower respiratory tract infection, cystic fibrosis, primary ciliary dyskinesia, eosinophilic diseases other than asthma (eg, allergic bronchopulmonary aspergillosis/mycosis, eosinophilic granulomatosis with polyangiitis [Churg-Strauss syndrome], hypereosinophilic syndromes), granulomatosis with polyangiitis (Wegener granulomatosis), Young syndrome.
4. Any disorder including but not limited to cardiovascular, gastrointestinal, hepatic, renal, neurologic, musculoskeletal, infectious, endocrine, metabolic, hematologic, psychiatric, or major physical impairment that was not stable in the opinion of the investigator or AstraZeneca and could:
   - Affect the safety of the patient throughout the study.
   - Influence the findings of the studies or their interpretations.
   - Impede the patient's ability to complete the entire duration of study.
5. Patients who experienced an asthma exacerbation requiring systemic (oral and/or parenteral) corticosteroids treatment or hospitalization (>24 hours) for treatment of asthma within 4 weeks before V1.
6. History of anaphylaxis to any biologic therapy or vaccine.
7. Known history of allergy or reaction to any component of the study drug formulation.
8. History of Guillain-Barré syndrome.
9. A helminth parasitic infection diagnosed within 24 weeks before V1 that had not been treated with or failed to respond to standard-of-care therapy.
10. Current malignancy, or history of malignancy, except for:
    - Patients who had basal cell carcinoma, localized squamous cell carcinoma of the skin, or carcinoma-in-situ of the cervix were eligible, provided that the patient's disease was in remission and curative therapy was completed at least 12 months before V1.
    - Patients who had other malignancies were eligible provided that the patient's disease was in remission and curative therapy was completed at least 5 years before V1.

    Note that hormone therapy was allowed. As long as the cancer was in remission for 5 years, the patient was eligible.
11. Any clinically significant abnormal findings in physical examination, vital signs, hematology, clinical chemistry, or urinalysis during screening/run-in period, which in the opinion of the investigator put the patient at risk because of his or her participation in the study, or influenced the results of the study, or the patient's ability to complete the entire duration of the study.
12. Any clinically significant cardiac disease or any electrocardiogram abnormality obtained during the screening/run-in period that put the patient at risk or interfered with study assessments.

13. Positive hepatitis B surface antigen, or hepatitis C virus antibody serology (confirmed by additional testing, such as hepatitis C RNA test, if indicated), or a positive medical history for hepatitis B or C. (Note: Patients with history of hepatitis B vaccination without a history of hepatitis B were allowed to enroll.)
14. History of known immunodeficiency disorder, including a positive HIV test.
15. Infection requiring systemic antibiotics within 14 days before V1.
16. Use of immunosuppressive medication (including but not limited to methotrexate, troleandomycin, cyclosporine, azathioprine, or any experimental anti-inflammatory therapy) within 3 months before V1 and during the study period.
17. Receipt of any marketed or investigational biologic products (monoclonal or polyclonal antibody) within 6 months or 5 half-lives, whichever was longer, before V1 and during the study period. This also applied to patients who previously participated in clinical studies and were treated with monoclonal antibodies (eg, mepolizumab, reslizumab, dupilumab, omalizumab). Note that this restriction did not apply to patients who were confirmed to have only received treatment with placebo.
18. Previous receipt of benralizumab.
19. Receipt of immunoglobulin or blood products within 30 days before V1.
20. Receipt of live attenuated vaccines 30 days before the date of randomization.
21. Receipt of any investigational drug within 30 days or 5 half-lives, whichever was longer, before randomization.
22. Receipt of SCS 4 weeks before V1, or a scheduled SCS treatment during the study period. Note: Sustained release steroids (eg, triamcinolone acetonide [Kenalog]) or depot injections required minimum 6 weeks' washout before V1.
23. Receipt of leukotriene antagonist/modifiers for patients who were not receiving a continuous stable dose for ≥30 days before V1.
24. Concurrent enrollment in another clinical drug interventional trial.
25. Alanine aminotransferase or aspartate aminotransferase level ≥3 times the upper limit of normal confirmed during screening period.
26. Involvement in the planning and/or conduct of the study (applied to both AstraZeneca staff and/or staff at the study site or immediate family members of such individuals).
27. Judgment by the investigator that the patient should not participate in the study if the patient was unlikely to comply with study procedures, restrictions, and requirements.
28. Previous randomization in the present study.
29. Planned major surgical procedures or scheduled NP surgery at the time of the study enrollment and randomization.
30. Initiated or was receiving maintenance therapy with an aspirin desensitization regimen for the management of aspirin-exacerbated respiratory disease at the time of study enrollment or during the run-in period.
31. History of alcohol or drug abuse within 12 months before V1, based on the investigator's assessment.
32. For women only—currently pregnant (or intend to become pregnant), breast-feeding, or lactating.

Randomization

All patients were centrally assigned to randomized study treatment using an Interactive Web Response System/Interactive Voice Response System. Randomization codes were assigned strictly sequentially in each stratum as patients became eligible for randomization. Clinical trial staff involved in the study, the patients, and the investigators involved in the treatment of patients or in their clinical evaluation were not aware of treatment allocation until after the study was completed. The placebo solution was visually matched with benralizumab solution. Both benralizumab and placebo were provided in accessorized prefilled syringes.

Because patients receiving active benralizumab treatment were expected to have lower blood eosinophil counts than patients receiving placebo, all hematology laboratory analyses were conducted by a central laboratory. For any measurements performed after randomization, eosinophil, basophil, and monocyte counts were redacted from any central laboratory reports sent to investigative sites. For laboratory assessments conducted for purposes not related to the clinical trial, each investigational site designated an individual not directly involved in patient management to receive and blind any eosinophil, basophil, or monocyte results before the report was handed over to the site staff involved in the patient's management.

Nasal polyp score

Total NPS represents the sum of the right and left nostril scores, as evaluated by nasal endoscopy. NPs were graded by polyp size, as shown in Table E3.

Statistical analyses

The hierarchical order of analysis for key secondary end points is as follows:

1. Change from baseline in SNOT-22 total score at week 40.
2. Time to the first NP surgery and/or SCS use for NP up to week 56.
3. Time to the first NP surgery up to week 56.
4. Change from baseline in biweekly mean DSS score at week 40.
5. Change from baseline in total NPS at week 56.
6. Change from baseline in biweekly mean NBS at week 56.
7. Change from baseline in SNOT-22 total score at week 56.
8. Change from baseline in biweekly mean DSS score at week 56.
9. Change from baseline in LMS at end of treatment/discontinuation.

Analytic methods. The primary estimand was used for the primary analysis and quantified the difference in outcomes for patients randomized to the benralizumab and placebo arms at the planned time points of the study, regardless of the treatments that patients actually received, where rescue by NP surgery and/or SCS use for NP indicated failure (see Table E4). A composite strategy was used for patients who underwent NP surgery or received SCS for NP. Data collected after use of SCS for NP were set to missing, and the patient's worst observed postbaseline value on or before the time of SCS use for NP was imputed from that point through week 56. Similarly, data collected after NP surgery were set to missing, and the worst possible value was imputed from that point through week 56. For patients who discontinued the study without surgery or SCS use for NP, missing data were imputed using multiple imputation with all patients who did not have surgery or receive SCS for NP.

Coprimary end points. The primary estimand was applied to the coprimary end points using a hybrid method of the worst possible/worst observation carried forward and multiple imputation followed by ANCOVA, with treatment group, baseline scores (baseline total NPS for NPS model and baseline NBS for NBS model), region (United States vs the rest of world), and baseline comorbid asthma status (yes vs no) as covariates. The estimates of the treatment effects at week 40 and week 56 were based on contrasts from this ANCOVA at the respective time points. The analyses used the data collected up to the week 56 visit, regardless of whether patients continued the treatment regimen or not, except for data collected after NP surgery and/or SCS use for NP.

A composite strategy was used for NP surgery and SCS use for NP. If a patient had received SCS therapy for NP before week 56, the data were censored after the time of having the first course of SCS use for NP, and the patient's worst observed value was imputed in their place. For patients rescued by SCS use for NP whose postbaseline values were all missing, or for whom every postbaseline value was after rescue, the baseline was used to impute. If a patient had NP surgery before week 56, the data were censored after the time of the first NP surgery, and the worst possible value was imputed in their place. If there were sufficient evaluable NBS data before rescue in the biweekly period in which rescue occurred, the biweekly mean for that period was based

on the data collected before rescue. Otherwise, the worst possible/worst observation carried forward was imputed for that period as well. For NBS, mean biweekly values were calculated by summing daily entries at 2-week intervals and dividing by the number of nonmissing days if at least 8 days in the interval had evaluable data. If there were fewer than 8 days with evaluable data, then the mean biweekly value was set to missing for that interval.

Analyses included all patients with baseline and at least 1 evaluable postbaseline assessment, and all patients with baseline assessment who were rescued by NP surgery and/or SCS use for NP by week 56.

Key secondary end points. Change from baseline in SNOT-22 total score and change from baseline in DSS were analyzed using a similar ANCOVA analysis as the coprimary end points. For DSS, mean biweekly values were calculated by summing daily entries at 2-week intervals and dividing by the number of nonmissing days, if at least 8 days in the interval had evaluable data. If there were fewer than 8 days with evaluable data, the mean biweekly value was set to missing for that interval.

Change from baseline in LMS score was analyzed using a similar ANCOVA strategy, but with a different intercurrent event strategy. The analyses used the data collected up to the week 56 visit, regardless of whether or not patients continued the study treatment, except for data collected after the NP surgery. Because there was only a single CT scan after baseline that occurred at least 6 months after baseline, the composite (worst observation carried forward) strategy used after SCS use for NP in the primary estimand was not as appropriate as for the main analysis. Instead, the analysis used data collected after SCS use for NP. A composite strategy was used for NP surgery. If a patient had NP surgery before the end-of-treatment/investigational drug's discontinuation CT scan, the data were censored after the time of the first NP surgery, and the worst possible value was imputed in its place.

Other secondary efficacy end points. The NP surgery and the SCS use for NP were summarized up to the week 56 visit for all patients and up to the end of study for those patients in the extended follow-up period. The proportions of patients who underwent NP surgery and/or received SCS for NP were analyzed using the Cochran-Mantel-Haenszel test stratified by region (United States vs the rest of world) and baseline comorbid asthma status (yes vs no). The proportion of patients without each event type through 56 weeks was also estimated by treatment group using the Kaplan-Meier method.

The Cox proportional hazard model described above for the key secondary efficacy variables was used to analyze time to the first SCS use for NP.

The change from baseline in UPSIT score was analyzed using a similar ANCOVA to that used for coprimary end points.

The sinus severity score and change from baseline was summarized using descriptive statistics. The change from baseline in sinus severity score was analyzed using a similar ANCOVA as described for the LMS score.

Subgroup analyses. To explore uniformity of the overall treatment effect, subgroup analyses were performed for NPS and NBS at weeks 40 and 56 using ANCOVA with patients stratified by standard baseline demographic and clinical parameters (ie, sex, age, geographic region, BMI) and by clinical characteristics with relevance to CRSwNP disease severity, treatment response, and/or association with eosinophilic disease (ie, NP surgery history, prior use of SCS for NP, comorbid disease, atopic status, baseline IgE concentration, and baseline blood eosinophil count). The category designations were as follows: sex (male vs female), age (<65 vs ≥65 years), geographic region (United States vs the rest of world), BMI (≤30 vs >30 kg/m^2; ≤35 vs >35 kg/m^2), prior NP surgery history (yes vs no), number of prior NP surgeries (0, 1, 2, >2), prior SCS use for NP (yes vs no), baseline comorbid asthma status (yes vs no), baseline aspirin-exacerbated respiratory disease status (yes vs no), atopic status (positive vs negative), quartiles of baseline IgE, and quartiles of baseline blood eosinophil count.

Responder analyses. Responder analyses were performed for NPS at weeks 24, 40, and 56. A responder was defined as a patient who experienced a 1-point decrease from baseline in NPS score. The NPS responder analyses used a logistic regression model with covariates of treatment group, baseline total NPS scores, region, and baseline comorbid asthma status. Patients with missing data were counted as non-responders for that time point.

Efficacy estimates

Efficacy estimands are listed in Table E4.

ADA data

For benralizumab-treated patients, ADA prevalence was 16.9% and ADA incidence was 13.7%; ADA prevalence in placebo-treated patients was 4.9%. The prevalence of neutralizing antibodies was 10.0% in the benralizumab group; no placebo patients were neutralizing antibody positive. Blood eosinophil counts at baseline and week 40 by ADA subgroup are listed in Table E5.

The incidence of AEs in treatment-emergent ADA-positive patients was generally similar to that of ADA-negative patients (71.4% vs 78.4%, respectively). Although there was a numerically higher incidence of hypersensitivity AEs observed in treatment-emergent ADA-positive patients in the benralizumab group (7/28, 25.0%) relative to ADA-negative patients in the benralizumab group (11/172, 6.4%), none of the events in treatment-emergent ADA-positive patients was considered causally related to benralizumab by the investigator.

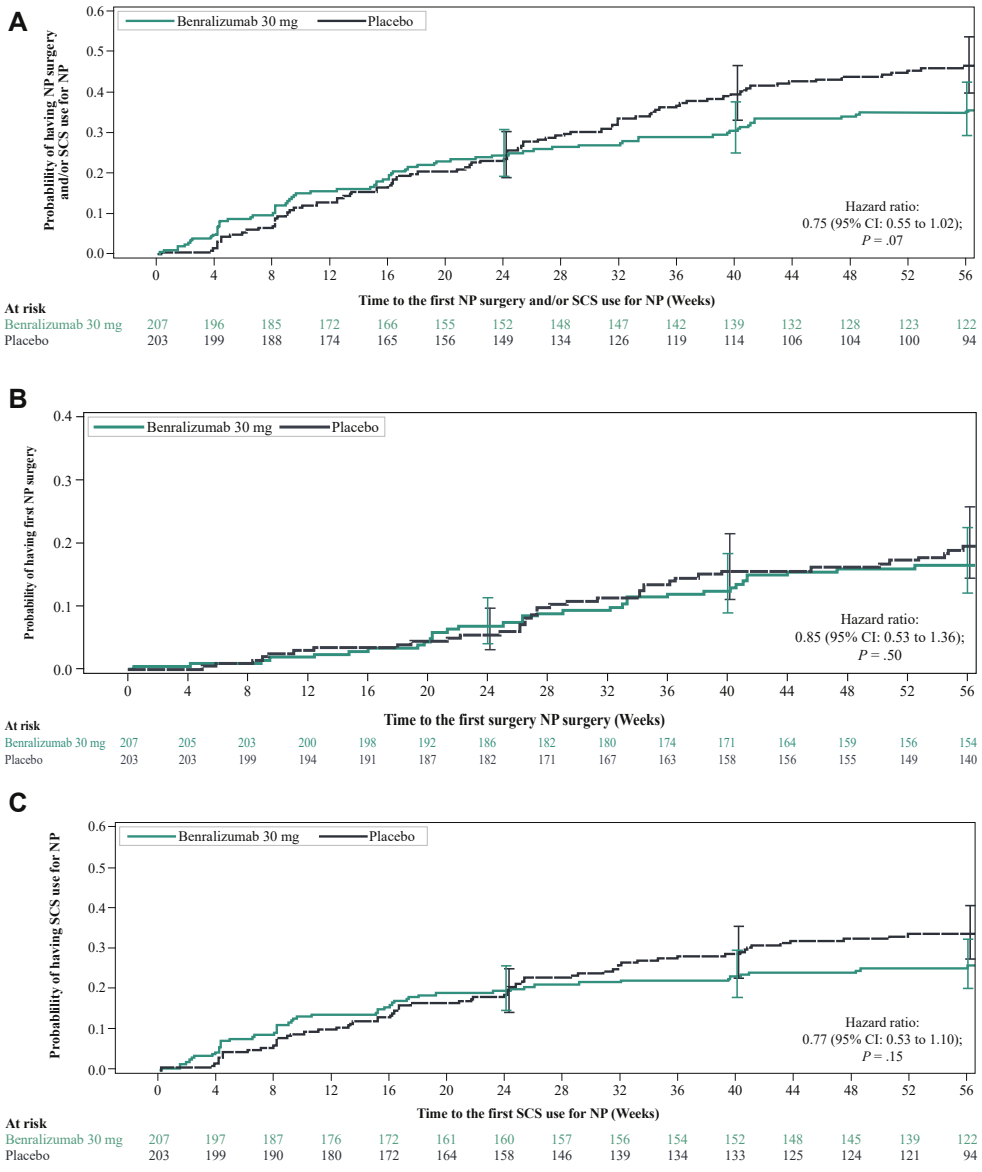
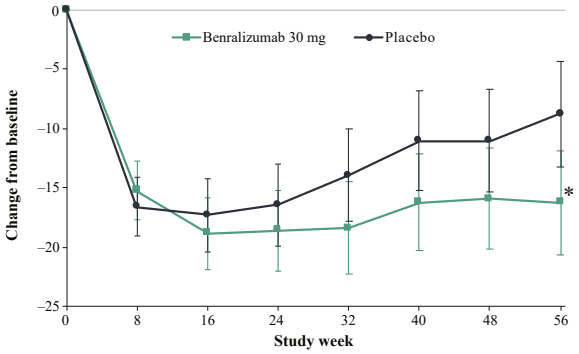
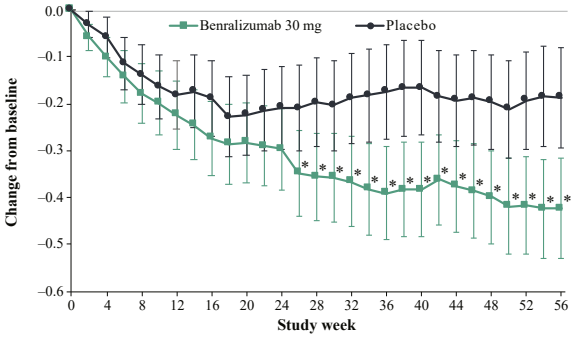


FIG E1. Time to event analyses, Kaplan-Meier cumulative incidence curves. **A,** Time to first NP surgery and/or SCS use for NPs. **B,** Time to first NP surgery. **C,** Time to first SCS use for NPs.



Benralizumab	205	200	199	198	198	193	190	190
Placebo	199	198	195	193	198	190	183	184

FIG E2. Change from baseline in SNOT-22 total score during the main study period. Data are least-squares means ± 95% CIs for the full analysis set. SNOT-22 total score range, 0-110. *P < .05 for the comparison of benralizumab and placebo.



Benralizumab	207	200	200	196	192	191	186	179
Placebo	203	195	194	191	186	181	184	175

FIG E3. Change from baseline in biweekly mean DSS score during the main study period. Data are least-squares means ± 95% CIs for the full analysis set. DSS range, 0-3. *P < .05 for the comparison of benralizumab and placebo.

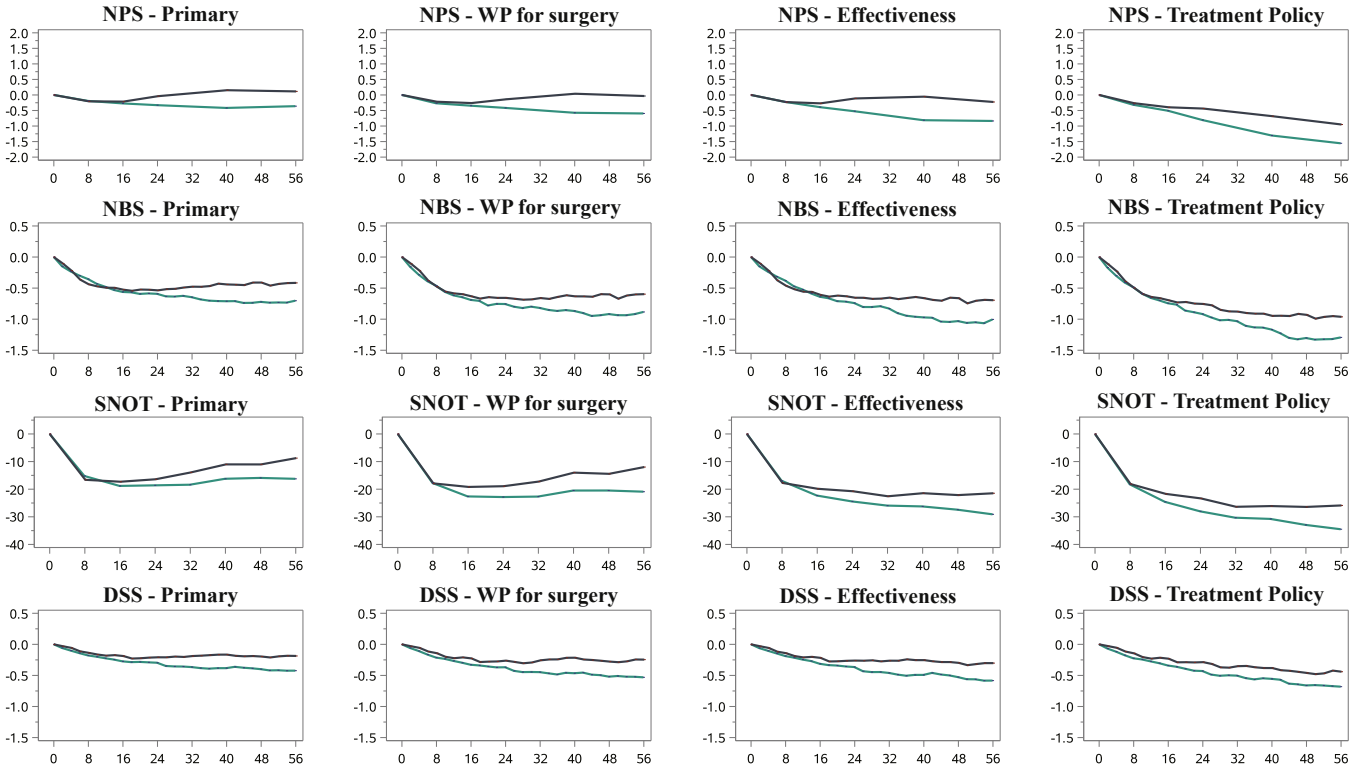


FIG E4. Change from baseline in total NPS, biweekly mean NBS, SNOT-22 total score, and biweekly DSS score by time point using various estimand methods. Table E4 provides descriptions of the analyses. Data are least-squares means. Baseline is defined as the last valid value on or before the date of randomization. The *x-axis* shows time in weeks; *y-axis,* change from baseline. *Green lines* represent benralizumab 30 mg; *gray lines,* placebo. *WP,* Worst possible.

TABLE E1. Study disruptions due to COVID-19

Parameter	Benralizumab 30 mg (n = 207)	Placebo (n = 203)	Total (n = 410)
Patients randomized before the pandemic, no. (%)*	207 (100.0)	203 (100.0)	410 (100.0)
Patients ongoing during COVID-19 pandemic, no. (%)*	124 (59.9)	122 (60.1)	246 (60.0)
Patients with ≥1 COVID-19 disruption/important protocol deviation, no. (%)	130 (62.8)	134 (66.0)	264 (64.4)
Total duration of observed follow-up (years)	263.4	254.2	517.6
Total duration of follow-up during COVID-19 pandemic (years)*	25.8	24.3	50.1
Follow-up relative to overall follow-up (%)	9.8	9.6	9.7
Total duration of observed COVID-19 disruptions (years)†	9.1	8.9	18.0
Observed disruption relative to overall follow-up (%)	3.5	3.5	3.5
Study week of first observed disruption, no. (%)	99 (47.8)	95 (46.8)	194 (47.3)
Weeks 0 to 40	0	1 (0.5)	1 (0.2)
Weeks 41 to 56	28 (13.5)	30 (14.8)	58 (14.1)
Weeks 57 to 80	71 (34.3)	64 (31.5)	135 (32.9)
Patients missing ≥1 dose of study drug due to COVID-19, no. (%)	7 (3.4)	12 (5.9)	19 (4.6)
Patients with 1 missed dose	7 (3.4)	12 (5.9)	19 (4.6)
Patients missing ≥2 consecutive doses of study drug due to COVID-19, no. (%)	0	0	0
Patients with changed scheduled study assessment due to COVID-19, no. (%)	99 (47.8)	95 (46.8)	194 (47.3)
Patients who missed ≥1 study visit	3 (1.4)	3 (1.5)	6 (1.5)
Changed format of ≥1 scheduled visit	98 (47.3)	95 (46.8)	193 (47.1)
On-site visit, partial	46 (22.2)	44 (21.7)	90 (22.0)
Remote visit	52 (25.1)	55 (27.1)	107 (26.1)
Phone	51 (24.6)	53 (26.1)	104 (25.4)
Video	1 (0.5)	3 (1.5)	4 (1.0)
Other	1 (0.5)	1 (0.5)	2 (0.5)
Scheduled visits missed or changed, no. (%)			
1 visit	75 (36.2)	66 (32.5)	141 (34.4)
2 visits	20 (9.7)	27 (13.3)	47 (11.5)
3 visits	4 (1.9)	2 (1.0)	6 (1.5)
Patients with any COVID-19 disruption to other medications, no. (%)	3 (1.4)	2 (1.0)	5 (1.2)
Rescue	0	0	0
Maintenance medications for disease under study	3 (1.4)	2 (1.0)	5 (1.2)
SCS	0	0	0
Other	0	0	0

*Any date before March 11, 2020, was considered before the pandemic. Any date on or after this time was considered during the pandemic.
†Total durations of observed disruptions were calculated on the basis of visit dates where any COVID-19 disruption was observed. The end date of a disruption was the next available visit where no disruption was observed or a patient's final study visit, whichever was earlier.

TABLE E2. Demographics and baseline characteristics, comorbid asthma set

Parameter	Patients with comorbid asthma		Patients without comorbid asthma	
	Benralizumab 30 mg (n = 142)*	Placebo (n = 136)*	Benralizumab 30 mg (n = 65)†	Placebo (n = 67)†
Age (years), mean ± SD	51.1 ± 12.4	50.2 ± 14.0	47.8 ± 12.2	50.4 ± 13.9
Male sex, no. (%)	84 (59.2)	70 (51.5)	58 (89.2)	51 (76.1)
Race, no. (%)				
White	136 (95.8)	127 (93.4)	61 (93.8)	63 (94.0)
Black	2 (1.4)	4 (2.9)	2 (3.1)	4 (6.0)
Asian	2 (1.4)	1 (0.7)	1 (1.5)	0
Other	2 (1.4)	4 (2.9)	1 (1.5)	0
BMI (kg/m^2), mean ± SD	27.3 ± 5.3	28.3 ± 5.8	27.3 ± 4.8	28.9 ± 7.4
BMI category, no. (%)				
Normal (≤25 kg/m^2)	55 (38.7)	41 (30.1)	18 (27.7)	18 (26.9)
Overweight (>25 to ≤30 kg/m^2)	54 (38.0)	48 (35.3)	33 (50.8)	29 (43.3)
Obese (>30 to ≤35 kg/m^2)	23 (16.2)	33 (24.3)	6 (9.2)	12 (17.9)
Morbidly obese (>35 kg/m^2)	10 (7.0)	14 (10.3)	8 (12.3)	8 (11.9)
Anosmia, no. (%)‡	109 (86.5)	110 (89.4)	38 (73.1)	42 (73.7)
AERD, no. (%)	60 (42.3)	53 (39.0)	2 (3.1)	6 (9.0)
Prior NP surgery, no. (%)	112 (78.9)	110 (89.4)	39 (60.0)	39 (58.2)
No. of surgeries, median (range)	2 (1, 40)	2 (1, 15)	2 (1, 10)	2 (1, 5)
Years since surgery, mean ± SD	7.46 ± 6.72	7.11 ± 5.47	5.42 ± 5.38	6.50 ± 5.48
History of SCS use for NP, no. (%)	109 (76.8)	93 (68.4)	52 (80.0)	53 (79.1)
No. of courses in past 12 months, median (range)	1 (0, 10)	1 (0, 7)	1 (0, 3)	1 (0, 6)
Baseline IgE (IU/mL), mean ± SD	249 ± 399	243 ± 530	137 ± 136	270 ± 591
Baseline blood eosinophil count (cells/μL)				
Mean ± SD	495.4 ± 406.2	465.6 ± 251.0	343.8 ± 217.2	405.7 ± 229.4
Median (range)	415.0 (60, 3670)	420.0 (80, 1710)	280 (40, 1110)	360 (110, 1300)
Atopic by Phadiatop, no. (%)	78 (56.9)	75 (56.4)	33 (53.2)	27 (45.0)
Region, no. (%)				
United States	27 (19.0)	27 (19.9)	12 (18.5)	12 (17.9)
Rest of world	115 (81.0)	109 (80.1)	53 (81.5)	55 (82.1)

AERD, Aspirin-exacerbated respiratory disease.

*Baseline data were available in the benralizumab and placebo groups for, respectively, 126 and 123 patients (anosmia), 141 and 136 patients (IgE), 142 and 135 patients (eosinophil count), and 137 and 133 patients (atopic status).

†Baseline data were available in the benralizumab and placebo groups for, respectively, 52 and 57 patients (anosmia), 63 and 65 patients (IgE), 64 and 67 patients (eosinophil count), and 62 and 60 patients (atopic status).

‡Anosmia was defined as an UPSIT score of ≤18.

TABLE E3. Grading of nasal polyps

Polyp score	Polyp size
0	No polyps.
1	Small polyps in the middle meatus not reaching below the inferior border of the middle turbinate.
2	Polyps reaching below the lower border of the middle turbinate.
3	Large polyps reaching the lower border of the inferior turbinate or large polyps of score 2 with additional large polyps medial to the middle turbinate.
4	Large polyps causing complete or near-complete obstruction of the inferior nasal cavity (ie, touching the floor of the nose).

NPS total scores range from 0 to 8.

TABLE E4. Efficacy estimands

				Intercurrent event strategy				
				Primary analysis	Sensitivity analysis			
					Primary estimand (Alternate imputation)			
Analysis set	End point	Population-level summary	Intercurrent event	Primary estimand	NP surgery only	DRMI	Effectiveness estimand	Treatment policy estimand
FAS*	CFB in NPS, NBS, SNOT-22, DSS	LSMD from CFB ANCOVA after hybrid WP/WOCF, MI. Week 40 is the primary time point	NP surgery	Worst possible	Worst possible	Worst possible	MMRM excluding data after intercurrent event	MMRM without imputation where all data as observed through week 56 are included regardless of intercurrent event
			SCS_NP	WOCF	Treatment policy§	WOCF		
			Treatment discontinuation	Treatment policy§	Treatment policy§	Treatment policy‖		
CT analysis subset of FAS†	CFB in LMS	LSMD from CFB ANCOVA after WP imputation. EOT/IPD	NP surgery	Worst possible	Worst possible	NA	NA	NA
			SCS_NP	Treatment policy	WOCF	NA		
			Treatment discontinuation	Treatment policy	Treatment policy	NA		
FAS‡	Time to first NP surgery and/or SCS_NP	Hazard ratio from Cox proportional hazards model. Events beyond week 56 were not included	Treatment discontinuation	Treatment policy	NA		NA	NA
	Time to first NP surgery		SCS_NP	Treatment policy (for time to first NP surgery only)	NA		NA	NA

CFB, Change from baseline; *DRMI,* dropout reason-based multiple imputation; *EOT,* end of treatment; *FAS,* full analysis set; *IPD,* investigational product discontinuation; *LSMD,* least-squares mean difference; *MAR,* missing at random; *MI,* multiple imputation; *MMRM,* mixed-effects model for repeated measures; *NA,* not applicable; *SCS_NP*, SCS for NP; *WOCF,* worst observed carried forward; *WP,* worst possible.

*Treatment of CRSwNP with benralizumab versus placebo, regardless of compliance; rescue indicates treatment failure.

†Treatment of CRSwNP with benralizumab versus placebo, regardless of compliance; rescue with NP surgery indicates treatment failure.

‡Treatment of CRSwNP with benralizumab versus placebo, regardless of compliance.

§MI (MAR) for missingness after study discontinuation.

‖MI (DRMI) for missingness after study discontinuation.

TABLE E5. Blood eosinophil counts at baseline and week 40 by ADA subgroup

	ADA positive		Treatment-emergent ADA positive		ADA negative		Neutralizing antibody positive	
Characteristic	**No.**	**BEC**	**No.**	**BEC**	**No.**	**BEC**	**No.**	**BEC**
Benralizumab								
Baseline	35	380 (260, 600)	28	370 (245, 595)	171	370 (240, 540)	20	430 (285, 570)
Week 40	32	40 (20, 160)	26	50 (20, 180)	139	30 (10, 40)	18	125 (30, 360)
Placebo								
Baseline	10	600 (280, 890)	4	835 (480, 1350)	192	400 (270, 550)	0	NA
Week 40	8	475 (310, 685)	3	760 (590, 800)	158	340 (220, 510)	0	NA

Blood eosinophil count (BEC) data are presented as medians (Q1, Q3). *NA,* Not applicable.