

A Phase II, Multicenter, Randomized, Placebo-Controlled Study of Benralizumab, a Humanized Anti-IL-5R Alpha Monoclonal Antibody, in Patients With Eosinophilic Chronic Rhinosinusitis

Tetsuji Takabayashi, MD¹, Daiya Asaka, MD², Yoshitaka Okamoto, MD³, Tetsuo Himi, MD⁴, Shinichi Haruna, MD⁵, Naohiro Yoshida, MD⁶, Kenji Kondo, MD⁷, Mamoru Yoshikawa, MD⁸ , Yasunori Sakuma, MD^{9,10}, Kunihiro Shibata, MD⁹, Motohiko Suzuki, MD¹¹ , Masayoshi Kobayashi, MD¹², Ryo Kawata, MD¹³, Kenzo Tsuzuki, MD¹⁴, Mitsuhiro Okano, MD^{15,16}, Takaya Higaki, MD¹⁶, Sachio Takeno, MD¹⁷ , Satoru Kodama, MD^{18,19}, Syuji Yonekura, MD³, Hiromi Saito, MS²⁰, Akiyo Nozaki, BS²⁰, Nobuyoshi Otori, MD², and Shigeharu Fujieda, MD¹

Abstract

Background: Strong eosinophil infiltration in chronic rhinosinusitis with nasal polyp (CRSwNP) is highly associated with recalcitrance and higher nasal polyp recurrence rate after surgery. The prevalence of eosinophilic CRSwNP (ECRS) is increasing in Asian countries including Japan. Benralizumab is a humanized anti-IL-5R alpha monoclonal antibody that depletes eosinophils by antibody-dependent cell-mediated cytotoxicity.

¹Department of Otorhinolaryngology-Head & Neck Surgery, University of Fukui, Fukui, Japan

²Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo, Japan

³Department of Otorhinolaryngology, Head and Neck Surgery, Chiba University, Chiba, Japan

⁴Department of Otolaryngology, Sapporo Medical University, Hokkaido, Japan

⁵Department of Otorhinolaryngology, Head & Neck Surgery, Dokkyo Medical University, Tochigi, Japan

⁶Department of Otolaryngology, Jichi Medical University Saitama Medical Center, Saitama, Japan

⁷Department of Otolaryngology, University of Tokyo, Tokyo, Japan

⁸Department of Otorhinolaryngology, Toho University Ohashi Medical Center, Tokyo, Japan

⁹Department of Otorhinolaryngology, Yokohama City University Medical Center, Kanagawa, Japan

¹⁰Kagami-Zaitaku Clinic, Kanagawa, Japan

¹¹Departments of Otorhinolaryngology, Nagoya City University, Aichi, Japan

¹²Department of Otorhinolaryngology-Head and Neck Surgery, Mie University Graduate School of Medicine, Mie, Japan

¹³Department of Otolaryngology, Head & Neck Surgery, Osaka Medical College, Osaka, Japan

¹⁴Department of Otolaryngology-Head and Neck Surgery, Hyogo College of Medicine, Hyogo, Japan

¹⁵Department of Otorhinolaryngology, International University of Health and Welfare Mita Hospital, Tokyo, Japan

¹⁶Department of Otolaryngology-Head and Neck Surgery, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

¹⁷Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of Biomedical Sciences, Hiroshima University, Hiroshima, Japan

¹⁸Kodama Jibiinkoka Clinic, Oita, Japan

¹⁹Oita University Faculty of Medicine, Otolaryngology, Head and Neck Surgery, Oita, Japan

²⁰R&D Division, Kyowa Kirin Co., Ltd., Tokyo, Japan

Corresponding Author:

Tetsuji Takabayashi, Department of Otorhinolaryngology-Head & Neck Surgery, University of Fukui, 23-3 Matsuoka-shimoaizuki, Eihei-cho, Yoshida-gun, Fukui 910-1193, Japan.

Email: tetsuji@u-fukui.ac.jp

Objective: To assess the efficacy and safety of benralizumab in patients with ECRS.

Methods: This phase II, randomized, double-blind, placebo-controlled study was conducted in Japan. Patients were randomized 1:2:2 to placebo, a single administration of benralizumab 30 mg, or benralizumab 30 mg every 4 weeks (q4w) for a total of three doses. The primary endpoint was the change in nasal polyp score from baseline at Week 12.

Results: Overall, 56 patients were enrolled (placebo, $n = 11$; benralizumab single dose, $n = 22$; benralizumab q4w, $n = 23$). Although the mean total nasal polyp score began to decrease after the initiation of benralizumab treatment, there were no statistically significant differences in change in nasal polyp score from baseline at Week 12 between benralizumab and placebo (placebo, -0.5 ± 0.8 ; benralizumab single, -0.3 ± 0.8 ; benralizumab q4w, -0.5 ± 1.5). Post-hoc analysis showed that the administration of benralizumab decreased nasal polyp scores ≥ 2 points in 42.2% of ECRS patients and that patients with high blood eosinophil levels had a greater tendency to respond to benralizumab treatment. The safety profile was similar to that in previous studies and no unexpected adverse events were noted.

Conclusion: Although benralizumab did not meet the primary efficacy endpoint, reductions of nasal polyp scores were seen in the benralizumab group compared with the placebo group over the whole study period, especially in patients with high levels of blood eosinophils.

Keywords

benralizumab, eosinophil, interleukin-5, nasal polyp, chronic rhinosinusitis, eosinophilic chronic rhinosinusitis with nasal polyp, phase II clinical trial, randomized, safety, efficacy

Introduction

Chronic rhinosinusitis (CRS) is one of the most common diseases worldwide.¹ CRS is generally classified into two types: CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP).¹ In Asian countries including Japan, CRSwNP is generally recognized as a neutrophilic inflammatory disease. However, a new subtype of CRSwNP, characterized by strong eosinophilic inflammation, has been increasingly observed in Japan.²⁻⁴ This subtype, known as eosinophilic CRSwNP (ECRS), has a lower response to macrolide therapy and a higher tendency to recur after endoscopic sinus surgery.²⁻⁴ ECRS was defined by the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) study and the diagnosis of ECRS is based on one/both sides of the nasal passage, presence of nasal polyps, ethmoid dominant computed tomography (CT) shadow, and the percentage of eosinophils in the peripheral blood (Figure S1).⁵

Interleukin (IL)-5, a key cytokine responsible for the differentiation, proliferation, and activation of eosinophils,^{6,7} binds to the IL-5 receptor (IL-5R) expressed almost exclusively on the surface of eosinophils and basophils.^{6,8} IL-5 is primarily secreted by Th2 cells, mast cells, and eosinophils, which are closely involved in eosinophilic inflammation associated with CRSwNP.⁹ Topical corticosteroid administration was reported to downregulate IL-5 levels and eosinophil numbers in the nasal mucosa of patients with ECRS and eventually reduced nasal polyp size.¹⁰ Furthermore, the number of eosinophils in peripheral blood was positively correlated

with the number of eosinophils in the nasal mucosa.¹¹ Therefore, the downregulation of IL-5 levels and eosinophil numbers in the peripheral blood might ameliorate eosinophilic inflammation in the nasal mucosa, which might reduce nasal polyp size.

Benralizumab is a humanized, afucosylated, anti-IL-5R alpha monoclonal antibody that is approved for severe eosinophilic asthma in the United States, Europe, and Japan.¹² After the administration of benralizumab, eosinophils are rapidly and almost completely depleted by apoptosis via enhanced antibody-dependent cell-mediated cytotoxicity.¹³ In phase III clinical studies of patients with severe uncontrolled asthma, there was a significant reduction in the annual asthma exacerbation rate and safety was demonstrated after long-term treatment with benralizumab 30 mg compared with placebo.¹³⁻¹⁵ Stratified analysis revealed that benralizumab improved the annual rate of exacerbation and pulmonary function, especially in patients with eosinophilia (blood eosinophil counts ≥ 300 cells/ μ L).^{14,15} Consistent with the “one airway, one disease” concept, these findings suggest that benralizumab may also be effective as a treatment for ECRS.¹⁶ Therefore, the aim of the current study was to evaluate the efficacy and safety of benralizumab in patients with ECRS in Japan.

Methods

Trial Design

This was a phase II, multicenter, randomized, double-blind, placebo-controlled study conducted in Japan from

May 2016 to May 2017 at 16 clinical sites (ClinicalTrials.gov identifier: NCT02772419). Patients were randomized 1:2:2 to receive placebo (placebo administered on Day 1, Week 4, and Week 8), a single administration of benralizumab (hereafter “benralizumab single”) 30 mg/mL solution (benralizumab administered on Day 1 and placebo administered Week 4 and Week 8), or benralizumab 30 mg/mL solution every 4 weeks (q4w; benralizumab administered on Day 1, Week 4, and Week 8) using a dynamic allocation procedure. The severity of ECRS and the presence of complicated asthma were used as stratification factors. This double-blinded trial was where both the physician and patient were blinded to the treatment assignment. The protocol was approved by the institutional review board or ethics committee at each study site, and the study was conducted in accordance with Good Clinical Practice guidelines based on Declaration of Helsinki. Written informed consent was obtained from participants before the start of any procedures. Patient anonymity was preserved using methods approved by the institutional review boards. Details are provided in this article’s Methods section in the online supplemental material.

Patients

The key inclusion criteria were age ≥ 20 and ≤ 75 years at the time of consent, weight ≥ 40 kg at screening, and a total ECRS score of ≥ 11 according to the JESREC scoring system⁵ at enrollment (Figure S1). Patients were also required to have a minimum bilateral nasal polyp score of 3 (maximum score of 8) with a score of ≥ 1 in each nostril at screening and enrollment. The nasal polyp score was measured from 0 to 4 on a 5-grade scale.¹⁷ Details are provided in Table 1 and in this article’s Methods section in the online supplemental material.

Outcome Measures

Patients were followed until the end of treatment at Week 24. The primary endpoint was the change in nasal polyp score from baseline at Week 12. Secondary endpoints included the change in nasal polyp score from baseline to Week 24, CT score of the paranasal sinuses, rhinomanometry, olfactometry (T&T Olfactometer, Daiichi Yakuhin Sangyo Co., Ltd., Tokyo, Japan), Sino-Nasal Outcome Test-22 (SNOT-22) score, symptom severity (visual analog scale [VAS] 0–10 cm), blood eosinophil counts, and pharmacokinetics. CT images of the sinuses evaluated at a CT image Reading Central Review Panel were graded according to the Lund-Mackay system.¹⁸ Safety was assessed using vital signs, symptoms, physical examination, blood analysis, and adverse event reporting.

Statistical Analysis

For efficacy outcomes, the change from baseline in the total right and left nasal polyp score (total nasal polyp score) at Week 12 (95% CI) was summarized for each treatment group. The difference between each treatment group and the placebo group in mean change from baseline in total nasal polyp score at Week 12 (95% CI) was reported. For the exploratory efficacy assessment, change in total nasal polyp score from baseline at Week 12 was compared between the placebo group and each benralizumab group using the Mann-Whitney U-test. Missing data were handled using last observation carried forward imputation. Post-hoc efficacy analyses included the number and percentage of patients with improved total nasal polyp score (≥ 3 and ≥ 2 points improvement categories) at each visit. Details are provided in this article’s Methods section in the online supplemental material.

Results

Study Design and Patients’ Clinical Characteristics

Overall, 56 patients met the inclusion criterion and were randomly assigned to placebo (11 patients), benralizumab single (22 patients), or benralizumab q4w (23 patients) (Figure 1). In total, 52 patients completed the double-blinded period of 24 weeks and 4 patients discontinued the study. One patient in the benralizumab q4w group was discontinued from the study for starting a new treatment because of aggravated ECRS on Day 22. There were no differences in patient clinical characteristics and demographics between the three groups (Table 1). Most patients in each group had a history of asthma and severe ECRS according to the JESREC study criteria (Figure S1). The mean total nasal polyp score at baseline was similar across the three groups (placebo: 5.0 ± 1.6 , benralizumab single: 5.3 ± 1.4 , benralizumab q4w: 5.4 ± 0.9).

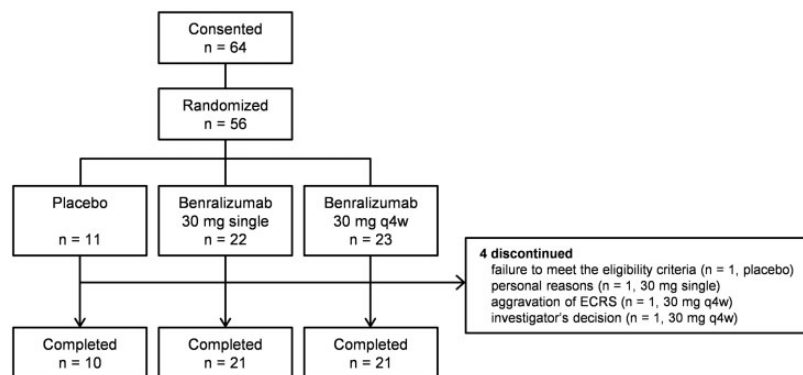
Efficacy

The change from baseline in total nasal polyp score over time in each treatment group is shown in Figure 2. The change in total nasal polyp score from baseline at week 12 at the primary endpoint was -0.5 ± 0.8 (mean $\pm$ SD) in the placebo group, -0.3 ± 0.8 in the benralizumab single group, and -0.5 ± 1.5 in the benralizumab q4w group. The mean difference in change from baseline relative to the placebo group was 0.3 (95% confidence interval [CI]: -0.3 – 0.9) for the benralizumab single group and 0.0 (-1.0 – 1.0) for the benralizumab q4w group. There was no statistically significant difference between either of the benralizumab groups compared with placebo ($p = 0.418$ for benralizumab single,

Table 1. Patient Demographic and Baseline Clinical Characteristics.

Parameter (Unit)	Placebo N = 11	Benralizumab	
		30 mg Single N = 22	30 mg Q4W N = 23
Sex, n (%)			
Female	4 (36.4)	11 (50.0)	11 (47.8)
Male	7 (63.6)	11 (50.0)	12 (52.2)
Age (years), mean $\pm$ SD	53.3 $\pm$ 14.8	54 $\pm$ 10.8	53 $\pm$ 12.3
Height (cm), mean $\pm$ SD	164.22 $\pm$ 9.67	164.55 $\pm$ 7.86	161.63 $\pm$ 8.04
Weight (kg), mean $\pm$ SD	65.31 $\pm$ 12.49	61.73 $\pm$ 11.29	59.64 $\pm$ 10.95
BMI (kg/m ²), mean $\pm$ SD	24.09 $\pm$ 3.3	22.67 $\pm$ 3.13	22.73 $\pm$ 3.12
Medical history (on-going at screening), n (%)			
Asthma	10 (90.9)	18 (81.8)	19 (82.6)
NSAIDs intolerance	5 (45.5)	6 (27.3)	6 (26.1)
Surgical history of the primary disease, n (%)	8 (72.7)	13 (59.1)	15 (65.2)
JESREC score, mean $\pm$ SD	14.6 $\pm$ 2.5	15.5 $\pm$ 2	15.2 $\pm$ 1.6
ECRS severity, n (%)			
Mild	1 (9.1)	1 (4.5)	1 (4.3)
Moderate	2 (18.2)	5 (22.7)	5 (21.7)
Severe	8 (72.7)	16 (72.7)	17 (73.9)
Eosinophils of peripheral blood (%), n (%)			
>2 to $\leq$ 5	3 (27.3)	3 (13.6)	2 (8.7)
>5 to $\leq$ 10	4 (36.4)	8 (36.4)	14 (60.9)
>10	4 (36.4)	11 (50.0)	7 (30.4)
Blood eosinophil count (/uL), mean $\pm$ SD	567.3 $\pm$ 320.4	775.5 $\pm$ 623.4	621.3 $\pm$ 432.3
Blood basophil count (/uL), mean $\pm$ SD	26.1 $\pm$ 24.5	24.6 $\pm$ 18.3	31.2 $\pm$ 23.6
Total nasal polyp score, mean $\pm$ SD	5.0 $\pm$ 1.6	5.3 $\pm$ 1.4	5.4 $\pm$ 0.9
$\geq$ 3 to $\leq$ 4	4 (36.4)	5 (22.7)	3 (13.0)
$\geq$ 5 to $\leq$ 8	7 (63.6)	17 (77.3)	20 (87.0)
VAS, mean $\pm$ SD			
Nasal obstruction (cm)	4.82 $\pm$ 3.22	5.04 $\pm$ 3.14	4.14 $\pm$ 2.93
Rhinorrhea (cm)	5.42 $\pm$ 3.20	4.92 $\pm$ 3.15	4.32 $\pm$ 2.89
Post nasal drip (cm)	3.45 $\pm$ 3.36	4.07 $\pm$ 2.87	3.19 $\pm$ 3.02
Loss of smell (cm)	8.96 $\pm$ 2.78	8.91 $\pm$ 2.27	7.32 $\pm$ 3.67
Headache (cm)	1.23 $\pm$ 1.93	1.77 $\pm$ 2.54	1.56 $\pm$ 2.15
Daily life interference (cm)	4.18 $\pm$ 2.87	3.86 $\pm$ 3.53	4.69 $\pm$ 3.45
Total CT score, mean $\pm$ SD	16.9 $\pm$ 4.2	18.0 $\pm$ 4.2	15.8 $\pm$ 3.8
Total score for SNOT-22, mean $\pm$ SD	30.5 $\pm$ 15.8	34.5 $\pm$ 20.3	31.7 $\pm$ 18.8

q4w, every 4 weeks; SD, standard deviation; BMI, body mass index; NSAID, nonsteroidal anti-inflammatory drug; ECRS, eosinophilic chronic rhinosinusitis; CRSwNP, chronic rhinosinusitis with nasal polyps; VAS, visual analog scale; SNOT-22, Sino-Nasal Outcome Test-22. Data are presented as n (%), unless otherwise noted.

**Figure 1.** Study design. q4w, every 4 weeks; ECRS, eosinophilic chronic rhinosinusitis.

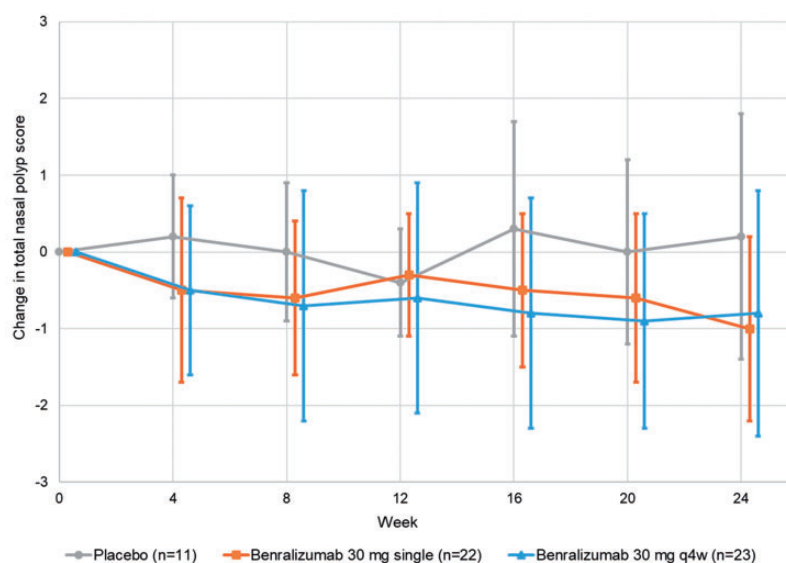


Figure 2. Change from baseline in total nasal polyp score over time (mean $\pm$ SD): Full analysis set. Placebo = patients were administered placebo at Day 1, Week 4, and Week 8; benralizumab 30 mg single = patients were administered benralizumab at Day 1 and placebo Week 4 and Week 8; benralizumab 30 mg q4w = patients were administered benralizumab at Day 1, Week 4, and Week 8. q4w, every 4 weeks.

$p=0.901$ for benralizumab q4w) at the primary endpoint. Although the mean total nasal polyp score began to decrease in both benralizumab groups after the initiation of study treatment, this trend was not observed at the primary endpoint. Thereafter, the nasal polyp score in both benralizumab groups began to decrease again from Week 16 to 24.

Post-hoc analyses showed that the number of patients with ≥ 2 points improvement in total nasal polyp score from baseline during the 24 weeks was 8/23 in the benralizumab q4w group, 11/22 in the benralizumab single group, and 1/11 in the placebo group (Table 2). When a positive response to benralizumab was defined as ≥ 2 points improvement in total nasal polyp from baseline, the response rate of benralizumab was 42.2% (19/45 patients) compared with 9.1% in the placebo group (1/11 patients) ($p=0.0398$, chi-square test). In the placebo group, no patients had an improvement in total nasal polyp score ≥ 3 points. These results suggested that benralizumab treatment decreased the total nasal polyp score in ECRS patients during the 24 weeks from the first administration of benralizumab.

To assess the efficacy of benralizumab treatment in detail, the change in total nasal polyp score from baseline during the 24 weeks from the first administration of benralizumab was stratified by the baseline percentage of peripheral blood eosinophils (Table 2). The response rates to benralizumab were 50.0% of patients with peripheral blood eosinophils $>10\%$ (9/18 patients), 40.9% of patients with 5%–10% peripheral blood eosinophils (9/22 patients), and 20.0% of patients with $<2\%$

peripheral blood eosinophils (1/5 patients). Taken together, these data suggest that ECRS patients with high numbers of blood eosinophils had a greater tendency to respond to benralizumab treatment.

Summary statistics for the change in symptom VAS item scores, CT scores, nasal airway resistance, olfactory test, and SNOT-22 from baseline at Week 12 and Week 24 are shown in Table 3. There were no clinically relevant differences between either of the benralizumab groups and placebo.

Blood Eosinophil Count

Compared with the placebo group, the blood eosinophil count was rapidly and markedly decreased after the initiation of study treatment in both benralizumab groups (Figure 3). The blood eosinophil count remained approximately 0/ μL up to Week 8 in the benralizumab single group and up to Week 12 in the benralizumab q4w group. In addition, compared with placebo, there was a marked decrease in blood basophil count at Week 4 in both benralizumab groups (data not shown).

Safety

Treatment emergent adverse events (TEAEs) were reported in 5/11 patients (45.5%) in the placebo group, 16/22 patients (72.7%) in the benralizumab 30 mg single group, and 13/23 patients (56.5%) in the benralizumab 30 mg q4w group (Table 4). The most common TEAE reported in the benralizumab groups was “nasopharyngitis”, which was reported in three patients

Table 2. Change From Baseline in Total Nasal Polyp Score by Baseline Peripheral Blood Eosinophils.

	Benralizumab q4w (N = 23)				Benralizumab Single (N = 22)				Benralizumab Group (q4w + Single) (N = 45)				Placebo (N = 11)			
	2-5 (N = 2)		5-10 (N = 14)	>10 (N = 7)	2-5 (N = 3)		5-10 (N = 8)	>10 (N = 11)	2-5 (N = 5)		5-10 (N = 22)	>10 (N = 18)	2-5 (N = 3)		5-10 (N = 4)	>10 (N = 4)
	Eosinophil (%)															
Change from baseline in total nasal score	-2	0	2	1	0	0	2	4	0	4	5		1	0	0	
	-3	0	2	1	1	2	2	1	1	4	2		0	0	0	
	-4	0	1	0	0	0	0	1	0	1	1		0	0	0	
	-5	0	0	1	0	0	0	0	0	0	1		0	0	0	
Total		0	5	3	1	4	4	6	1	9	9		1	0	0	

q4w, every 4 weeks.

(27.3%) in the placebo group, nine patients in the benralizumab 30 mg single group (40.9%), and three patients in the benralizumab 30 mg q4w group (13.0%). Most adverse events were mild-to-moderate in severity. No TEAEs leading to death were reported in this study. One patient (4.3%) in the benralizumab 30 mg q4w group reported serious TEAEs of “pneumonia” and “asthma” that required hospitalization. At the time of reporting, both events were recovering/resolving, and neither event was considered related to the investigational product.

Discussion

This is the first placebo-controlled study to evaluate the efficacy and safety of benralizumab in Japanese patients with ECRS. There were no significant differences in the change in total nasal polyp score from baseline at Week 12 at the primary endpoint between patients receiving benralizumab and those receiving placebo (Figure 2). However, reductions of total nasal polyp scores were seen in the benralizumab treatment group compared with placebo during the 24 weeks from the first administration of benralizumab (Table 2). Furthermore, the reduction in total nasal polyp score was higher in patients with high levels of blood eosinophils than in those with low eosinophil levels (Table 2).

In previous studies of patients with severe uncontrolled eosinophilic asthma,^{13,14} benralizumab treatment rapidly depleted blood and airway eosinophils.¹⁹ Similarly, in this study, benralizumab rapidly depleted blood eosinophils in Japanese patients with ECRS (Figure 3). However, there was no statistically significant difference in the total nasal polyp scores at Week 12 in either of the benralizumab groups compared with placebo. In the placebo group, a high proportion of patients had a history of nasal surgery more than a year before the date of consent and had NSAIDs intolerance, these medical histories might affect the nasal polyp scores. To address this potential limitation, we conducted prespecified subgroup analyses of patients with low and high baseline levels of peripheral eosinophils and showed that the baseline percentage of peripheral blood eosinophils may have influenced the change in total nasal polyp score from baseline at all time points examined. The finding that patients with high blood eosinophils (>10% of peripheral blood) at baseline in the benralizumab groups showed good clinical responses further supports the role of eosinophils in the treatment of ECRS with benralizumab (Table 2). However, only a limited subpopulation showed an improved clinical response, which indicates that ECRS is likely to be characterized by various pathophysiological mechanisms. As mentioned previously, differences in the infiltration of eosinophils into the nasal tissues of patients with nasal

Table 3. Change From Baseline in Secondary Endpoints.

		Week 12				Week 24			
		Benralizumab				Benralizumab			
		Placebo N = 11	30 mg Single N = 22	30 mg Q4W N = 23	Placebo N = 11	30 mg Single N = 22	30 mg Q4W N = 23	Placebo N = 11	30 mg Single N = 22
VA	n	10	22	21	10	21	21	10	21
Nasal obstruction/blockage/ congestion (cm)	Mean ± SD	0.72 ± 2.31	-0.34 ± 2.38	1.06 ± 3.19	1.81 ± 3.14	0.01 ± 2.64	1.21 ± 2.47	1.81 ± 3.14	0.01 ± 2.64
Discolored nasal drainage:anterior (cm)	Mean ± SD	-0.15 ± 3.65	-0.83 ± 2.35	0.33 ± 3.37	0.48 ± 5.02	-0.17 ± 1.86	0.85 ± 2.82	0.48 ± 5.02	-0.17 ± 1.86
Discolored nasal drainage:posterior (cm)	Mean ± SD	0.83 ± 2.82	-1.23 ± 2.8	0.55 ± 3.44	1.57 ± 4.4	-0.49 ± 2.57	0.2 ± 2.59	1.57 ± 4.4	-0.49 ± 2.57
Decreased sense of smell (cm)	Mean ± SD	0.21 ± 3.49	-1.37 ± 3.17	1.46 ± 3.82	0.68 ± 3.07	-1.3 ± 2.55	0.9 ± 4.71	0.68 ± 3.07	-1.3 ± 2.55
Headache (cm)	Mean ± SD	-0.37 ± 0.82	0.74 ± 2.58	-0.41 ± 2.03	0.1 ± 2.29	-0.04 ± 1.8	0.14 ± 2.35	0.1 ± 2.29	-0.04 ± 1.8
Daily life interference (cm)	Mean ± SD	-0.14 ± 3.15	-0.68 ± 3.13	-0.48 ± 3.81	0.09 ± 4.15	0.1 ± 2.63	0 ± 2.51	0.09 ± 4.15	0.1 ± 2.63
Total CT score at Week 12 (LOCF)	n	11	22	22					
Olfactory	Mean ± SD	0.7 ± 2.3	-1.3 ± 2.2	0.7 ± 3.4					
Mean detection threshold	n	9	21	20	9	20	20	9	20
Mean recognition threshold	Mean ± SD	0.13 ± 1.67	0.15 ± 1.14	0.08 ± 1.47	0.64 ± 1.63	-0.35 ± 1.78	-0.24 ± 2.12	0.64 ± 1.63	-0.35 ± 1.78
Bilateral nasal airway resistance	Mean ± SD	0.16 ± 0.44	-0.12 ± 0.63	-0.02 ± 1.22	0.49 ± 1.05	-0.34 ± 1.07	-0.2 ± 1.72	0.49 ± 1.05	-0.34 ± 1.07
Inhalation (Pa/cm ³ /s)	n	8	17	17	6	17	18	6	17
Exhalation (Pa/cm ³ /s)	Mean ± SD	-0.0336 ± 0.0866	0.0111 ± 0.4659	-0.0162 ± 0.2496	0.068 ± 0.1594	-0.0308 ± 0.2933	-0.0183 ± 0.2894	0.068 ± 0.1594	-0.0308 ± 0.2933
SNOT-22	n	8	17	17	6	17	17	6	17
	Mean ± SD	0.1981 ± 0.599	-0.037 ± 0.4058	0.0276 ± 0.3828	0.0217 ± 0.0715	-0.0265 ± 0.3506	0.0788 ± 0.2548	0.0217 ± 0.0715	-0.0265 ± 0.3506
	n	10	22	21	10	21	21	10	21
	Mean ± SD	1.7 ± 11.2	-0.5 ± 17.5	3.1 ± 16.6	9 ± 18.5	-2.4 ± 11.4	2 ± 15.3	9 ± 18.5	-2.4 ± 11.4

qw4, every 4 weeks; VAS, visual analog scale; SD, standard deviation; CT, computed tomography; LOCF, last observation carried forward; SNOT-22, Sino-Nasal Outcome Test-22. Bilateral nasal airway resistance was calculated only for the subjects having right and left scores >0. Bilateral nasal airway resistance = 1/ (1/right side nasal airway resistance + 1/left side nasal airway resistance)

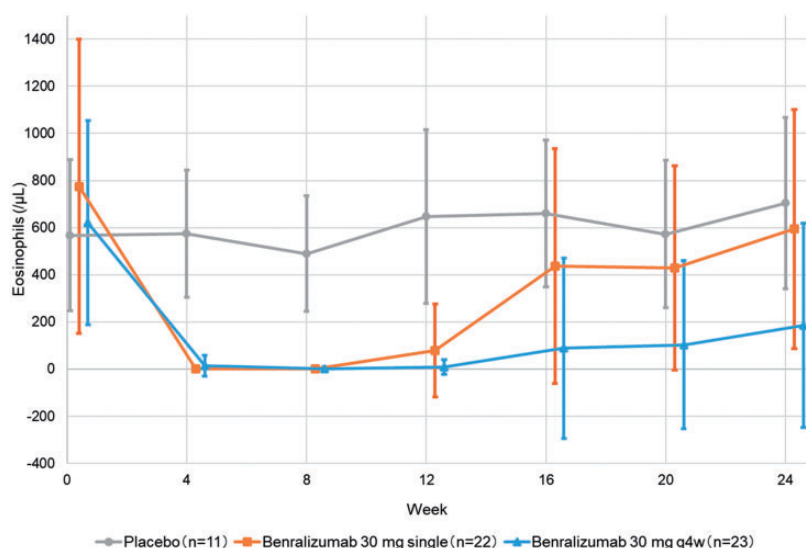


Figure 3. Blood eosinophil count over time (mean $\pm$ SD): Full analysis set. Blood eosinophil count over time (mean $\pm$ SD): Full analysis set. Placebo = patients were administered placebo at Day 1, Week 4, and Week 8; benralizumab 30 mg single = patients were administered benralizumab at Day 1 and placebo at Week 4 and Week 8; benralizumab 30 mg q4w = patients were administered benralizumab at Day 1, Week 4, and Week 8. q4w, every 4 weeks.

Table 4. Treatment-Emergent Adverse Events in the Safety Population.

PT	Placebo		Benralizumab			
			30 mg Single		30 mg Q4W	
	N = 11		N = 22		N = 23	
	n	(%)	n	(%)	n	(%)
Pyrexia	2	(18.2)	5	(22.7)	4	(17.4)
Nasopharyngitis	3	(27.3)	9	(40.9)	3	(13.0)
Influenza	1	(9.1)	2	(9.1)	0	
Headache	0		0		2	(8.7)
Asthma	0		0		2	(8.7)
Upper respiratory tract inflammation	0		2	(9.1)	0	
Subjects with any TEAE	5	(45.5)	16	(72.7)	13	(56.5)

PT, preferred term; q4w, every 4 weeks; TEAE, treatment-emergent adverse event. Coding dictionary: MedDRA version 19.1. This table displays TEAEs by preferred term that occurred in 2 or more patients in any benralizumab group.

polyps might be related to ethnicity.²⁰ Using nasal polyp tissue homogenates, a previous study reported that 80% of nasal polyps from patients in Europe expressed IL-5 compared with 20%–60% of nasal polyps from patients in Asia.²⁰ We did not obtain nasal polyp tissues from patients at baseline or after the initiation of study treatment; therefore, we were unable to confirm whether eosinophil counts in patient nasal polyps were high. Biological markers that reflect eosinophilic inflammation in the nasal mucosa might be useful for predicting responses to benralizumab treatment in ECRS patients.

There were no clinically relevant differences in the change in SNOT-22 score from baseline at Week 12 and Week 24 in the benralizumab groups because symptom scores at baseline were low in this study. The SNOT-22 score at baseline was lower than that in the mepolizumab phase II study.²¹ In the mepolizumab study, the total SNOT-22 score at baseline was 49.5 in the placebo group and 51.5 in the mepolizumab group.²¹ In contrast, the total SNOT-22 score at baseline in this study was 30.5 ± 15.8 in the placebo group, 34.5 ± 20.3 in the benralizumab single group, and 31.7 ± 18.8 in the benralizumab q4w group. The VAS symptom scores for

symptom severity were also lower compared with the mepolizumab phase II study.²¹

In this study, patients received investigational product at Day 1, Week 4, and Week 8, and they were continuously observed for 4 months after the final administration of investigational product until the end of treatment at Week 24. Although patients received only one or three doses of benralizumab during the study, more patients showed an improvement in total nasal polyp score of 2 or 3 points from baseline at Week 24 compared with at Week 12. Moreover, there appeared to be a gradual decrease in mean total nasal polyp score from Week 16 onwards to Week 24. There was a decrease in blood eosinophil counts to 0/ μ L within 4 weeks of treatment suggesting a delay in the effect of benralizumab on eosinophils with regard to the nasal polyp score.

However, there were several limitations in this study, the duration of administration was too short and the sample size was too small to investigate this further. The design of future studies should include larger sample sizes, longer treatment durations, and nasal tissue samples so that the potential effects of benralizumab can be evaluated in greater detail.

Consistent with previous studies, benralizumab was relatively safe and well-tolerated.^{13,14} There were no clinically significant TEAEs related to the study drug and the profile of TEAEs in patients with ECRS was similar to the safety and tolerability profile reported previously.

Conclusion

Although benralizumab did not meet the primary efficacy endpoint, reduced nasal polyp scores were seen in the benralizumab groups compared with placebo at all time-points, and especially in patients with high levels of blood eosinophils. Even within ECRS patients, clinical presentation can be heterogeneous and the underlying mechanisms that contribute to disease pathology are not fully understood.^{1,22–24} Therefore, further studies with longer treatment durations and appropriate patient groups are needed to determine whether benralizumab can be a potential treatment for patients with ECRS.

Acknowledgments

We would like to thank the patients, investigators, and site staff who participated in this study. We would also like to thank AstraZeneca for their specific advice on the study. Editing assistance was provided by Serina Stretton, PhD, CMPP, and Jacqueline Atkinson, BA (Hons), of Envision Pharma Group and was funded by Kyowa Kirin Co., Ltd.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or

publication of this article: S. Fujieda received lecture fees in an advisory role from Kyowa Kirin Co., Ltd. H. Saito and A. Nozaki are employees of Kyowa Kirin Co., Ltd. The other authors declare that there is no conflict of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by Kyowa Kirin Co., Ltd.

ORCID iDs

Mamoru Yoshikawa  <https://orcid.org/0000-0002-5908-1752>
Motohiko Suzuki  <https://orcid.org/0000-0002-9555-0341>
Sachio Takeno  <https://orcid.org/0000-0002-9853-2501>

Supplemental Material

Supplemental material for this article is available online

References

1. Fokkens WJ, Lund VJ, Mullol J, et al. European position paper on rhinosinusitis and nasal polyps 2012. *Rhinol Suppl.* 2012;23:3 p preceding table of contents, 1–298.
2. Fujieda S, Imoto Y, Kato Y, et al. Eosinophilic chronic rhinosinusitis. *Allergol Int.* 2019;68:403–412.
3. Haruna S, Nakanishi M, Otori N, Moriyama H. Histopathological features of nasal polyps with asthma association: an immunohistochemical study. *Am J Rhinol.* 2004;18:165–172.
4. Nakayama T, Yoshikawa M, Asaka D, et al. Mucosal eosinophilia and recurrence of nasal polyps – new classification of chronic rhinosinusitis. *Rhinology.* 2011;49:392–396.
5. Tokunaga T, Sakashita M, Haruna T, et al. Novel scoring system and algorithm for classifying chronic rhinosinusitis: the JESREC Study. *Allergy.* 2015;70:995–1003.
6. Takatsu K, Takaki S, Hitoshi Y. Interleukin-5 and its receptor system: implications in the immune system and inflammation. *Adv Immunol.* 1994;57:145–190.
7. Rothenberg ME, Hogan SP. The eosinophil. *Annu Rev Immunol.* 2006;24:147–174.
8. Toba K, Koike T, Shibata A, et al. Novel technique for the direct flow cytometric analysis of human basophils in unseparated blood and bone marrow, and the characterization of phenotype and peroxidase of human basophils. *Cytometry.* 1999;35:249–259.
9. Hamilos DL, Leung DY, Wood R, et al. Evidence for distinct cytokine expression in allergic versus nonallergic chronic sinusitis. *J Allergy Clin Immunol.* 1995;96:537–544.
10. Wang C, Lou H, Wang X, et al. Effect of budesonide transnasal nebulization in patients with eosinophilic chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol.* 2015;135:922–929.
11. Ishitoya J, Sakuma Y, Tsukuda M. Eosinophilic chronic rhinosinusitis in Japan. *Allergol Int.* 2010;59:239–245.
12. Nagase H, Ueki S, Fujieda S. The role of IL-5 and anti-IL-5 treatment in eosinophilic diseases: asthma, eosinophilic

- granulomatosis with polyangiitis, and eosinophilic chronic rhinosinusitis. *Allergol Int.* 2020;69:178–186.
13. Yanagibashi T, Satoh M, Nagai Y, Koike M, Takatsu K. Allergic diseases: from bench to clinic – contribution of the discovery of interleukin-5. *Cytokine.* 2017;98:59–70.
 14. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2 -agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet.* 2016;388:2115–2127.
 15. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet.* 2016;388:2128–2141.
 16. Grossman J. One airway, one disease. *Chest.* 1997;111:11S–16S.
 17. Meltzer EO, Hamilos DL, Hadley JA, et al. Rhinosinusitis: developing guidance for clinical trials. *J Allergy Clin Immunol.* 2006;118:S17–S61.
 18. Lund VJ, Mackay IS. Staging in rhinosinusitis. *Rhinology.* 1993;31:183–184.
 19. Laviolette M, Gossage DL, Gauvreau G, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol.* 2013;132:1086–1096.
 20. Wang X, Zhang N, Bo M, et al. Diversity of T_H cytokine profiles in patients with chronic rhinosinusitis: a multicenter study in Europe, Asia, and Oceania. *J Allergy Clin Immunol.* 2016;138:1344–1353.
 21. Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol.* 2017;140:1024–1031.
 22. Kato A. Immunopathology of chronic rhinosinusitis. *Allergol Int.* 2015;64:121–130.
 23. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol.* 2016;137:1449–1456.
 24. Takabayashi T, Schleimer RP. Formation of nasal polyps: the roles of innate type 2 inflammation and deposition of fibrin. *J Allergy Clin Immunol.* 2020;145:740–750.

A phase II, multicenter, randomized, placebo-controlled study of benralizumab, a humanized anti-IL-5R alpha monoclonal antibody, in patients with eosinophilic chronic rhinosinusitis

Tetsuji Takabayashi, MD^{1*}, Daiya Asaka, MD², Yoshitaka Okamoto, MD³, Tetsuo Himi, MD⁴, Shinichi Haruna, MD⁵, Naohiro Yoshida, MD⁶, Kenji Kondo, MD⁷, Mamoru Yoshikawa, MD⁸, Yasunori Sakuma, MD^{9,10}, Kunihiro Shibata, MD⁹, Motohiko Suzuki, MD¹¹, Masayoshi Kobayashi, MD¹², Ryo Kawata, MD¹³, Kenzo Tsuzuki, MD¹⁴, Mitsuhiro Okano, MD^{15,16}, Takaya Higaki, MD¹⁶, Sachio Takeno, MD¹⁷, Satoru Kodama, MD^{18,19}, Syuji Yonekura, MD³, Hiromi Saito, PhD²⁰, Akiyo Nozaki, PhD²⁰, Nobuyoshi Otori, MD², Shigeharu Fujieda, MD¹

¹Department of Otorhinolaryngology-Head & Neck Surgery, University of Fukui,
Fukui, Japan

²Department of Otorhinolaryngology, Jikei University School of Medicine, Tokyo,
Japan

³Department of Otorhinolaryngology, Head and Neck Surgery, Chiba University, Chiba,
Japan

⁴Department of Otolaryngology, Sapporo Medical University, Hokkaido, Japan

⁵Department of Otorhinolaryngology, Head & Neck Surgery, Dokkyo Medical University, Tochigi, Japan

⁶Department of Otolaryngology, Jichi Medical University Saitama Medical Center, Saitama, Japan

⁷Department of Otolaryngology, University of Tokyo, Tokyo, Japan

⁸Department of Otorhinolaryngology, Toho University Ohashi Medical Center, Tokyo, Japan

⁹Department of Otorhinolaryngology, Yokohama City Medical Center, Kanagawa, Japan

¹⁰Kagami-zaitaku Clinic, Kanagawa, Japan

¹¹Departments of Otorhinolaryngology, Nagoya City University, Aichi, Japan

¹²Department of Otorhinolaryngology-Head and Neck Surgery, Mie University Graduate School of Medicine, Mie, Japan

¹³Department of Otolaryngology, Head & Neck Surgery, Osaka Medical College, Osaka, Japan

¹⁴Department of Otolaryngology-Head and Neck Surgery, Hyogo College of Medicine, Hyogo, Japan

¹⁵Department of Otorhinolaryngology, International University of Health and Welfare

Mita Hospital, Tokyo, Japan

¹⁶Department of Otolaryngology-Head and Neck Surgery, Okayama University

Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

¹⁷Department of Otorhinolaryngology, Head and Neck Surgery, Graduate School of

Biomedical Sciences, Hiroshima University, Hiroshima, Japan

¹⁸Kodama Jibiinkoka Clinic, Oita, Japan

¹⁹Oita University Faculty of Medicine, Otolaryngology, Head and Neck Surgery

Oita, Japan

²⁰Kyowa Hakko Kirin Co., Ltd., Tokyo, Japan

*Corresponding author. Department of Otorhinolaryngology-Head & Neck Surgery,

University of Fukui, 23-3 Matsuoka-shimoaizuki, Eiheiji-cho, Yoshida-gun, Fukui,

Japan, 910-1193.

E-mail address: tetsuji@u-fukui.ac.jp

Facsimile: +81-776-61-8118.

Telephone: +81-776-61-3111.

Materials and Methods

Trial design

This was a phase II, multicenter, randomized, double-blind, placebo-controlled study conducted in Japan from May 2016 to May 2017 at 16 clinical sites (ClinicalTrials.gov identifier: NCT02772419). The study consisted of a screening period up to 4 weeks (from informed consent to randomization), a double-blinded treatment period from Day 1 to Week 24, and a follow-up period. Patients received either benralizumab 30 mg/mL solution or placebo by subcutaneous injection (investigational product). Patients who fulfilled all of the eligibility criteria (eligible patients) were randomized 1:2:2 to receive placebo (placebo administered on Day 1, Week 4, and Week 8), benralizumab single (benralizumab administered on Day 1 and placebo administered Week 4 and Week 8) or benralizumab every 4 weeks (q4w; benralizumab administered on Day 1, Week 4, and Week 8), using a dynamic allocation procedure. The severity of ECRS and the presence of complicated asthma were used as stratification factors. Randomization was performed at the Case Enrollment Center. The protocol was approved by the institutional review board at each study site and the study was conducted in accordance with Good Clinical Practice guidelines based on the Declaration of Helsinki. Written informed consent was obtained from participants before the start of any

procedures. Patient anonymity was preserved using methods approved by the institutional review boards.

Patients

The key inclusion criteria were age ≥ 20 and ≤ 75 years at the time of consent, weight ≥ 40 kg at screening, and a total ECRS score of ≥ 11 according to the JESREC scoring system⁵ at enrollment. Patients were also required to have a minimum bilateral nasal polyp score of 3 (maximum score of 8), with a score of ≥ 1 in each nostril at screening and at enrollment. The nasal polyp score was measured from 0 to 4 on a 5-grade scale.¹⁷ The key exclusion criteria were any concomitant disease that was considered to affect nasal polyp scores (e.g., severe deflected septum and allergic fungal sinusitis); any nasal surgery (including polypectomy) within 1 year before the date of consent; patients unsuitable for proper evaluation of nasal polyp scores because of nasal surgery or any other reason, as judged by the investigator; unable to evaluate the safety of the investigational product correctly; and a Sino-Nasal Outcome Test-22 (SNOT-22) score < 7 at enrollment. Use of systemic corticosteroid (including oral) and corticosteroid nasal drops (excluding spray) were prohibited 4 weeks before enrollment up to the end of the double-blinded period. Restricted medications included corticosteroid nasal drops (spray),

anti-allergic agents (leukotriene receptor antagonists, Th2 cytokine inhibitors, thromboxane A₂ receptor antagonists, thromboxane A₂ synthesis inhibitors), and macrolide antibiotics. Patients were required not to initiate the use of restricted medications or to change the dosing regimens of existing restricted medications.

Outcome measures

Patients were followed until the end of treatment at Week 24 (double-blinded treatment period). The primary endpoint was the change in nasal polyp score from baseline at Week 12. Secondary endpoints included the change in nasal polyp score from baseline to Week 24, CT score of the paranasal sinuses, rhinomanometry, olfactometry (T&T Olfactometer, Daiichi Yakuhin Sangyo Co., Ltd., Tokyo, Japan), SNOT-22 score, symptom severity (visual analog scale [VAS] 0–10 cm), blood eosinophil counts, and pharmacokinetics. CT images of the sinuses were graded according to the Lund-Mackay system.¹⁸ Safety was assessed using vital signs, symptoms, physical examination, blood analysis, and adverse event reporting.

Statistical analysis

Because this study is the first to assess benralizumab in patients with ECRS, the effect size is unknown. Thus, on the basis of what was feasible, the sample size was set at 50 eligible patients for enrollment (20 in the benralizumab 30 mg q4w group, 20 in the benralizumab 30 mg single group, and 10 in the placebo group). The full analysis set (FAS), in whom efficacy was evaluated, consisted of all patients who were assigned to receive the investigational product at enrollment, received the investigational product at least once, and had efficacy data after administration of the investigational product. The safety analysis set, in whom safety was evaluated, consisted of all patients who were assigned to receive the investigational product and received investigational product at least once. For efficacy outcomes, the change in the total right and left nasal polyp score (total nasal polyp score) from baseline at Week 12 (95% confidence interval [CI]) was summarized for each treatment group. The difference between each treatment group and the placebo group in mean change from baseline in total nasal polyp score at Week 12 (95% CI) was reported. For the exploratory efficacy assessment, the change in total nasal polyp score from baseline at Week 12 was compared between the placebo group and each benralizumab group (30 mg q4w or 30 mg single) using the Mann-Whitney *U*-test. Chi-square tests were used to evaluate statistically significant differences between benralizumab treatments. Multiplicity adjustments were not considered. Missing data

were handled using last observation carried forward imputation. For exploratory outcomes, the change in total nasal polyp score from baseline at Week 12 was compared between the placebo group and each benralizumab group (30 mg q4w or 30 mg single) using the Mann-Whitney *U*-test. Multiplicity adjustments were not considered. Post-hoc efficacy analyses included the number and percentage of patients (FAS) with improved total nasal polyp score (≥ 3 and ≥ 2 points improvement categories) at each visit. Each percentage was calculated according to the number of patients assessed at the visit. CT scores were evaluated by a CT image Reading Central Review Panel. For safety outcomes, a treatment-emergent adverse event (TEAE) was defined as any adverse event that occurred or worsened after the administration of the investigational product. TEAEs were summarized by MedDRA version 19.1 Preferred Terms. SAS Drug Development 4.5 (SAS 9.4, SAS Institute Inc.) was used for statistical analyses.

Figure legends

Figure S1

JESREC score criteria for the diagnosis of ECRS and Diagnostic algorithm for ECRS severity

JESREC score criteria for the diagnosis of ECRS (*left panel*). Diagnostic algorithm for

ECRS severity. Patients with CRS were classified into four groups by JESREC score, blood eosinophilia, ethmoid dominant shadow in CT, and comorbidity (bronchial asthma, aspirin/NSAIDs intolerance). The moderate/severe ECRS groups showed type 2 dominant inflammation and the non-ECRS/mild ECRS groups showed type 1/type 3 mixed inflammation (*right panel*).

JESREC score criteria

Factor	Score
Side affected	
both side	3
one side	0
With nasal polyps	2
Without nasal polyps	0
CT changes; ethmoid/maxillary ≥ 1	2
Peripheral blood eosinophils (%)	
$>2\%$ and $\leq 5\%$	4
$>5\%$ and $\leq 10\%$	8
$>10\%$	10
Diagnosis	JESREC score
ECRS	≥ 11 points
Non-ECRS	≤ 10 points

Diagnosis algorithm

