A Phase 2a Study of Benralizumab for Patients with Eosinophilic Asthma in South Korea and Japan

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Key Words

Benralizumab · Eosinophilic asthma · Asthma exacerbation · Anti-interleukin-5 receptor · Eosinophils

Abstract

Background: Airway eosinophils are considered to play an important role in the pathogenesis of asthma. Interleukin-5 is believed to be a key cytokine for the development, proliferation and activation of eosinophils. Benralizumab is an anti-interleukin-5 receptor α monoclonal antibody that depletes blood and airway eosinophils. We conducted a phase 2a study in South Korea and Japan to evaluate the effect of benralizumab in an East Asian population. The primary objective was to evaluate the effect of benralizumab in adults with uncontrolled eosinophilic asthma with 2–6 incidences of exacerbations in the past year using a medium/high dose of inhaled corticosteroids and long-acting β_2 -agonists. **Methods:** This was a multicenter, randomized, double-blind, placebo-controlled study. The subjects ($n = 106$) were randomized into four groups: placebo ($n = 27$) or benralizumab 2 mg ($n = 27$), 20 mg ($n = 26$) and 100 mg ($n = 26$). Benrali-

zumab or placebo were administered subcutaneously on weeks 0 (day 1), 4, 8, 16, 24, 32 and 40. The primary endpoint was the asthma exacerbation rate at week 52. **Results:** The asthma exacerbation rate was reduced by 33, 45 or 36% versus the placebo group when treated with 2, 20 or 100 mg of benralizumab, respectively. The percent mean change in forced expiratory volume at 1 s increased with each of the three doses in subjects treated with benralizumab. **Conclusions:** Benralizumab reduced asthma exacerbation and improved lung function and asthma control in adults with uncontrolled eosinophilic asthma.

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Introduction

Asthma is a problem worldwide, with an estimated 300 million affected individuals [1–3]. Inhaled corticosteroids (ICS) and long-acting β_2 -agonists (LABA) are widely used to treat asthma; however, there are some cases of persistent asthma that are not adequately controlled by combination therapy with ICS and LABA. For these pa-

tients, an anti-IgE antibody (omalizumab) can be used in combination with oral corticosteroids. In recent years, clinical studies to identify the cytokines, chemokines and receptors involved in asthma have been ongoing for the development of novel therapeutics [4].

It has been shown that the number of eosinophils increases at sites of inflammation in various diseases, including asthma. Proteins that are toxic to tissues, such as major basic protein and eosinophil cationic protein, which are released from eosinophils, exfoliate the mucosa of the epithelium and increase airway hyper-responsiveness, thereby causing airway constriction and chronic airway inflammation [5].

Persistent eosinophilic airway inflammation in asthma is believed to increase the risk of subsequent exacerbation [6–9]. In addition, it is known that interleukin (IL)-5 is indispensable for the development, proliferation and activation of eosinophils. Thus, the clinical application of antibodies that target IL-5 and its receptor has been considered in recent years for asthma treatment [10, 11]. Indeed, monoclonal antibodies targeting IL-5, such as mepolizumab and reslizumab, have been shown to reduce blood and sputum eosinophils in patients with moderate-to-severe asthma that is not adequately controlled by ICS and LABA [12–15].

Benralizumab is a humanized, afucosylated IgG1κ monoclonal antibody that targets human IL-5 receptor α [16], which is expressed on eosinophils and basophils [10, 16–18]. In vitro, benralizumab exhibits enhanced antibody-dependent cell-mediated cytotoxicity and induces apoptosis in target cells [16]. Two studies in subjects with atopic or eosinophilic asthma have shown that benralizumab depletes eosinophils in blood [19, 20] and in the airway mucosa and sputum [20].

Recently, a phase 2b study of benralizumab (ClinicalTrials.gov NCT01238861) sponsored by MedImmune demonstrated the efficacy and safety of repeated doses of subcutaneous benralizumab in adults with uncontrolled asthma in European and North and South American countries [21]. We conducted a similarly designed phase 2a study in South Korea and Japan (ClinicalTrials.gov NCT01412736) in asthma patients with suspected eosinophilia to demonstrate the similar efficacy and safety between East Asian and non-Asian populations.

Methods

Study Design

This phase 2a, randomized, double-blind, placebo-controlled, dose-ranging, multicenter study was conducted at 32 sites in South

Korea and Japan between August 2011 and July 2013. The protocol was approved by the institutional review board at each study site. All subjects provided written informed consent before participating in the study, which was conducted in accordance with the principles of the Declaration of Helsinki.

Subjects

Eosinophilic asthma was defined as ELEN index positivity with $\geq 2\%$ sputum eosinophils or FeNO ≥ 50 ppb. The ELEN index was developed as a surrogate marker for sputum eosinophils levels $\geq 2\%$ [21]. Sputum was collected at clinical sites following local procedures and processed using a modified method by Pizzichini et al. [22]. Adults aged 20–75 years with asthma treated with medium- to high-dose ICS/LABA combination therapy [1] for at least 1 year were enrolled in the study. Participants had a documented history of 2–6 exacerbations requiring treatment with systemic corticosteroids (additional treatment with >15 mg/day prednisone, or other medications at a similar dose, for at least 3 consecutive days) in the past year. Eligible subjects had a morning prebronchodilator forced expiratory volume in 1 s (FEV₁) of $\geq 40\%$ but $<90\%$ predicted, and an Asthma Control Questionnaire (ACQ-6) score ≥ 1.5 [23–25] on at least two occasions during screening. Subjects also had to demonstrate postbronchodilator FEV₁ reversibility $\geq 12\%$ and ≥ 200 ml, or a positive response to methacholine challenge (PC₂₀ ≤ 8 mg/ml) [26]. Subjects with a history of cigarette smoking ≥ 10 pack years or who were current smokers were excluded.

Randomization and Masking

Subjects were classified during screening as being ELEN index positive, having $\geq 2\%$ sputum eosinophils or FeNO ≥ 50 ppb. The ELEN index was developed as a surrogate marker for sputum eosinophils levels $\geq 2\%$ [21]. A complete blood count was measured locally in whole blood treated with the anticoagulant ethylenediaminetetraacetic acid using a hematology analyzer. These data were used to calculate the ELEN index for each subject. The results of the ELEN index for each subject were transferred to a central, interactive, web-response system to ensure randomization into the appropriate stratum.

In the present study, all subjects were dichotomized according to a blood eosinophil cut-off point of ≥ 300 cells/ μ l in a prespecified subgroup analysis. This approach is consistent with the analyses of data collected during a randomized clinical phase 2b study with benralizumab (ClinicalTrials.gov NCT01238861).

Study Interventions

Subjects were stratified by country (South Korea/Japan) and baseline ICS dose (medium/high). Eosinophilic subjects were randomized using a central, interactive web-response system, to receive a placebo or 2, 20 or 100 mg of benralizumab (1:1:1:1). The study medication was administered by subcutaneous injection every 4 weeks for the first three doses [weeks 0 (day 1), 4 and 8], and then every 8 weeks (weeks 16, 24, 32 and 40) in a blinded fashion. Subjects maintained the same dose of ICS/LABA from the start of the screening period until week 52.

Assessments

Asthma exacerbations were defined as an increase in asthma symptoms that required treatment with systemic steroids for at least 3 days [27]. Other assessments included lung function, asthma control as assessed by ACQ-6 [23, 24], FeNO measurements

Fig. 1. Flow diagram of the study subjects.

and peripheral blood eosinophil counts. FeNO was measured using Niox Mino (Aerocrine AB, Solna, Sweden). Spirometry was performed using the equipment on site. Peak expiratory flow (PEF) was measured using a Personal Best Peak Flow Meter (Philips, N.J., USA). Safety and tolerability were monitored by recording any adverse events. Efficacy assessments were made until week 52, after which the subjects were followed for at least 16 additional weeks to monitor safety.

Outcomes

The primary endpoint was the annual exacerbation rate, where annual asthma exacerbation rate was defined as the number of asthma exacerbations from week 0 (day 1) to week 52. Exploratory endpoints included blood eosinophil counts.

Statistical Analysis

This study was not designed to demonstrate statistical significance owing to the limitations of the sample size. The sample size ($n = 100$) was determined considering the study feasibility in South Korea and Japan. Therefore, no formal statistical test was performed to assess the difference between the placebo and the active-dose groups.

The full analysis set (FAS) included all randomized subjects who received any dose of investigational product. The primary analyses for efficacy endpoints were conducted in the FAS population. In addition, exploratory efficacy analyses were conducted in the subjects with baseline blood eosinophil counts ≥ 300 cells/ μL .

A total of 100 subjects were to be randomized into four groups in this study, with 25 subjects per treatment group. Assuming that 10% of the enrolled subjects would withdraw from the study, 22 subjects per group allowed for the evaluation of efficacy. The primary object was to evaluate the efficacy of benralizumab (2, 20 and

100 mg) compared with placebo using the annual asthma exacerbation rate. We assumed that approximately 50% of subjects received high-dose ICS and experienced an estimated annual exacerbation rate at baseline of 1.95 exacerbations per year, and that 50% of the subjects received medium-dose ICS with an annual exacerbation rate at baseline of 1.56 exacerbations per year. Furthermore, we assumed that the annual exacerbation rate of subjects treated with 100 mg of benralizumab, regardless of the baseline ICS use, would be reduced by 40% compared with the placebo. Based on these assumptions, a sample size of 22 subjects/group achieved a 40% or greater difference between the group treated with 100 mg of benralizumab and the placebo group with 48.1% probability in 1,000 simulated trials, and achieved a difference of 25% or more with 81.3% probability.

The annual asthma exacerbation rate was defined as the number of asthma exacerbations observed up to week 52. If a subject discontinued treatment before week 52, the annual asthma exacerbation rate for this subject was calculated according to the following formula: observed number of asthma exacerbations/observed days $\times 364$.

For the primary analysis, the annual asthma exacerbation rate was summarized by each treatment group. For the exploratory analysis, the asthma exacerbation rate was analyzed to compare benralizumab (2, 20 and 100 mg) with placebo by negative binomial regression using the baseline ICS dose status (medium vs. high dose) as a covariate. The different follow-up times were adjusted by offset options. No multiplicity adjustment was applied for multiple doses and subgroup analyses.

Secondary efficacy endpoints were summarized by each treatment group. No imputation was applied for missing data.

Table 1. Demographic and other baseline characteristics (FAS population)

Characteristics	Placebo (n = 26)	2 mg benralizumab (n = 26)	20 mg benralizumab (n = 25)	100 mg benralizumab (n = 26)
Gender				
Male	9 (34.6)	13 (50.0)	6 (24.0)	10 (38.5)
Female	17 (65.4)	13 (50.0)	19 (76.0)	16 (61.5)
Age				
Mean $\pm$ SD, years	50.8 $\pm$ 11.8	53.2 $\pm$ 11.3	55.6 $\pm$ 8.9	51.4 $\pm$ 13.8
<65 years	22 (84.6)	21 (80.8)	22 (88.0)	21 (80.8)
$\geq$ 65 years	4 (15.4)	5 (19.2)	3 (12.0)	5 (19.2)
Country				
Japan	11 (42.3)	11 (42.3)	11 (44.0)	11 (42.3)
South Korea	15 (57.7)	15 (57.7)	14 (56.0)	15 (57.7)
Height, cm	160.2 $\pm$ 8.9	161.6 $\pm$ 9.3	156.4 $\pm$ 8.2	161.2 $\pm$ 8.9
Weight, kg	62.6 $\pm$ 12.4	65.1 $\pm$ 15.6	61.9 $\pm$ 14.7	63.6 $\pm$ 10.3
ICS dose ¹				
High	16 (61.5)	16 (61.5)	15 (60.0)	16 (61.5)
Medium	10 (38.5)	10 (38.5)	10 (40.0)	10 (38.5)
Asthma onset				
Childhood ²	7 (26.9)	5 (19.2)	1 (4.0)	5 (19.2)
Later	19 (73.1)	21 (80.8)	24 (96.0)	21 (80.8)
Asthma exacerbation history ³ , counts/year	2.6 $\pm$ 1.0	2.9 $\pm$ 1.1	2.6 $\pm$ 1.1	2.7 $\pm$ 0.9
Blood eosinophil count at week -3				
Mean $\pm$ SD, / μ l	586.5 $\pm$ 443.4	742.7 $\pm$ 972.1	583.2 $\pm$ 412.6	815.4 $\pm$ 1,075.6
$\geq$ 300/ μ l	21 (80.8)	20 (76.9)	19 (76.0)	21 (80.8)
<300/ μ l	5 (19.2)	6 (23.1)	6 (24.0)	5 (19.2)
FeNO, ppb	57.9 $\pm$ 43.2	50.4 $\pm$ 27.7	44.4 $\pm$ 24.2	41.4 $\pm$ 19.9
Mean ACQ-6	1.6 $\pm$ 0.6	1.8 $\pm$ 0.6	1.9 $\pm$ 0.7	1.9 $\pm$ 0.8
FEV ₁ , % ^{4, 5, 6}	68.8 $\pm$ 16.3	65.3 $\pm$ 14.1	70.6 $\pm$ 13.2	67.5 $\pm$ 15.8
FEV ₁ /FVC, % ^{4, 6, 7}	65.2 $\pm$ 13.7	66.3 $\pm$ 12.0	68.6 $\pm$ 10.8	67.8 $\pm$ 9.3

Values are n (%) or mean $\pm$ SD unless otherwise indicated.

¹ High ICS dose: budesonide $\geq$ 1,600 or equivalent; medium ICS dose: 800 $\leq$ budesonide < 1,600 or equivalent.

² Childhood defined as age <16 years. ³ Number of exacerbations requiring systemic corticosteroids 12 months prior to the week 3 visit. ⁴ n = 24 in each group. ⁵ FEV₁ (actual)/FEV₁ (predicted) $\times$ 100. ⁶ Data that did not meet ATS/ERS criteria were deleted. ⁷ FEV₁/FVC $\times$ 100.

Results

Subjects

A total of 106 subjects were randomized, of which 103 received treatment and were included in the FAS population (fig. 1). In the eosinophilic-positive cohort, 87/106 (82.1%) subjects were ELEN index positive, 54/106 (50.9%) had FeNO levels $\geq$ 50 ppb and 39/42 (92.9%¹) had sputum eosinophil counts $\geq$ 2%. Across all subjects, 81 had a baseline blood eosinophil count $\geq$ 300 cells/ μ l and 22 subjects had a count <300 cells/ μ l.

The demographic and clinical characteristics were generally similar between treatment groups (table 1).

There was no apparent imbalance in the demographic and other baseline characteristics among all the groups. At baseline, 63 (61.2%) subjects were taking high-dose ICS.

Efficacy

Exacerbation Rate

At week 52, the annual exacerbation rate was reduced by 33, 45 and 36% versus the placebo group when treated with 2, 20 or 100 mg of benralizumab, respectively. In the

¹ The percentage represents the proportion of subjects with a sputum eosinophil count $\geq$ 2% to subjects who received the sputum test.

Table 2. Asthma exacerbation for FAS and subjects with a baseline blood eosinophil count ≥ 300 cells/ μ l

Efficacy endpoint	FAS				Subjects with a baseline blood eosinophil count ≥ 300 cells/ μ l			
	placebo	2 mg benrali-zumab	20 mg benrali-zumab	100 mg benrali-zumab	placebo	2 mg benrali-zumab	20 mg benrali-zumab	100 mg benrali-zumab
Subjects, n	26	26	25	26	21	20	19	21
Annual exacerbation rate, counts/year	3.5	2.4	1.9	2.2	3.9	1.5	1.5	2.4
Rate reduction, %	–	33	45	36	–	61	61	40

subgroup with blood eosinophil counts ≥ 300 cells/ μ l, exacerbation was reduced by 61, 61 and 40% versus the placebo group when treated with 2 g, 20 or 100 mg of benralizumab, respectively (table 2; fig. 2). One subject in the 100-mg group was withdrawn from the study due to asthma exacerbation 12 days after the start of dosing, and the annual exacerbation rate was calculated as 30.3 events per year. This caused the low reduction rate in the annual mean exacerbation rate in the 100-mg dose group. The time course of the cumulative number of exacerbations in each treatment group shows the apparent difference between the placebo and active-dose groups (fig. 3).

Time to First Asthma Exacerbation

The Kaplan-Meier plot of the time to first asthma exacerbation is shown in figure 4. The median time to first asthma exacerbation was prolonged with increasing doses of benralizumab, and was 152 days [95% CI 34 to n.a. (not applicable)] in the placebo group, 204 days (95% CI 106–358) in the 2-mg group, 281 days (95% CI 103.0 to n.a.) in the 20-mg group, and n.a. (95% CI 184.0 to n.a.) in the 100-mg group.

Lung Function: FEV₁ and Morning PEF

We next assessed the improvement in the predicted FEV₁ from baseline to week 52. The mean percent change in predicted FEV₁ at week 52 was 12.0% in the placebo group, 9.9% with 2 mg of benralizumab, 6.7% with 20 mg of benralizumab and 25.6% with 100 mg of benralizumab (table 3). In the placebo group, the mean percent change in predicted FEV₁ was not significantly improved after the initiation of the study, although it slightly increased at week 52. In the benralizumab group, the mean predicted FEV₁ increased throughout the study period at all doses. In the 2-mg group, the mean percent change in predicted FEV₁ from baseline was 19.6% at week 4 and re-

Fig. 2. Asthma exacerbation rate in the FAS population and subjects with a baseline blood eosinophil count ≥ 300 / μ l. The percent values above the bars indicate the reduction rates compared to the placebo group in each population.

mained around $\geq 15\%$ thereafter. In the 20-mg group, the mean change in predicted FEV₁ at week 16 was 17.1% and remained around 15% thereafter. In the 100-mg group, the mean change in predicted FEV₁ at week 4 was 18.8% and remained around 25% thereafter (fig. 5).

The mean percent change in morning (m)PEF from baseline to week 52 in the placebo, 2-, 20- and 100-mg dose groups was 9.4, 15.2, 15.0 and 16.2%, respectively (table 3). In the placebo group, the mean percent change in mPEF increased over time, but the change remained below 10% throughout the treatment period. In the 20-mg group, the mean percent change in mPEF was around 10% throughout the study period. In the 2- and 100-mg groups, the mean percent change in mPEF remained approximately 15% or more (fig. 6).

Fig. 3. The time course of cumulative exacerbations (FAS).

Fig. 4. Time to first asthma exacerbation (FAS).

Asthma Control Questionnaire

The mean ACQ-6 score decreased more rapidly in the benralizumab groups than in the placebo group. Clinically significant changes in the mean ACQ-6 score, as indicated by a decrease of ≥ 0.5 , were noted from week 8 onward in the 2-mg group and from week 4 onward in the 20- and 100-mg groups (table 3; fig. 7).

Blood Eosinophil Count

In all the benralizumab groups, a marked reduction in peripheral blood eosinophil count was noted after the first dose. The mean peripheral blood eosinophil count

decreased from 563.6–823.8 cells/ μ l at baseline to 1.6–7.1 cells/ μ l at week 1, and further to 0.4 cells/ μ l in each group at week 4, and then remained around 0 cells/ μ l. The cell counts showed some recovery at or after week 16 in the 2-mg group. The blood eosinophil count returned nearly to baseline levels at week 68 in each of the benralizumab groups (fig. 8).

Safety and Tolerability

The safety analysis was conducted in the safety population. The safety population included all subjects who received any dose of investigational product. Treatment-

Fig. 5. Mean percent change in predicted FEV₁ from baseline to week 52 (FAS). Data are presented as the mean $\pm$ SD.

Table 3. Efficacy endpoints

Efficacy endpoint	FAS				Subjects with a blood eosinophil count ≥ 300 cells/ μ l			
	placebo	2 mg benralizumab	20 mg benralizumab	100 mg benralizumab	placebo	2 mg benralizumab	20 mg benralizumab	100 mg benralizumab
Subjects, n	26	26	25	26	21	20	19	21
FEV ₁ , % ¹								
Week 52	12.0 (22.1)	9.9 (15.7)	6.7 (22.8)	25.6 (35.0)	13.5 (22.3)	10.2 (15.5)	9.1 (24.5)	28.1 (36.1)
mPEF, % ²								
Week 52	9.4 (16.5)	15.2 (24.3)	15.0 (28.2)	16.2 (28.8)	9.3 (17.4)	17.2 (25.8)	19.1 (30.3)	13.2 (21.3)
ACQ score								
Week 0	1.6 (0.6)	1.8 (0.6)	1.9 (0.7)	1.9 (0.8)	1.6 (0.5)	1.9 (0.6)	1.9 (0.8)	1.9 (0.9)
Week 52	0.8 (1.0)	0.9 (0.8)	1.0 (0.8)	1.0 (0.9)	1.0 (1.1)	0.9 (0.8)	1.1 (0.8)	1.0 (1.0)
FeNO, ppb								
Week 0	57.9 (43.2)	50.4 (27.7)	44.4 (24.2)	41.4 (19.9)	61.4 (45.9)	54.8 (27.6)	48.9 (24.3)	41.8 (20.5)
Week 52	65.2 (61.0)	57.0 (35.5)	44.8 (21.7)	35.2 (27.3)	70.6 (69.0)	65.1 (33.2)	45.8 (22.9)	38.4 (29.1)

Values in parentheses are SD.

¹ Mean percent change in predicted FEV₁: (% predicted FEV₁ at week 52 – % predicted FEV₁ at week 0)/% predicted FEV₁ at week 0 $\times$ 100 (%). ² Mean percent change in mPEF: (mPEF at week 52 – mPEF at week 0)/mPEF at week 0 $\times$ 100 (%).

emergent adverse events were reported by more than 90% of the subjects in all cohorts (placebo, 96%; 2 mg, 96%; 20 mg, 92%; 100 mg, 96%). Adverse events that occurred in 5% or more of subjects in the combined benralizumab group, regardless of causality, are shown in table 4. The adverse events that occurred in 30% or more of the subjects in the benralizumab group were nasopharyngitis, injection site reaction and upper respiratory tract infection. Nasopharyngitis and upper respiratory tract infection also occurred in over 30% of the subjects in the placebo group. Two subjects receiving benralizumab were discontinued due to

bronchitis/overwork and injection-site reaction. Most of the adverse events were mild to moderate in severity.

Serious adverse events occurred in 5 out of 26 subjects in the placebo group (19%), 5 out of 26 subjects in the 2-mg benralizumab group (19%), 4 out of 25 subjects in the 20-mg group (16%) and 3 out of 26 subjects in the 100-mg group (12%). Asthma was the most common serious adverse event, reported by 2 subjects (8%) in the placebo group, 4 subjects (15%) in the 2-mg benralizumab group, 1 subject (4%) in the 20-mg group and 2 subjects (8%) in the 100-mg group. There were no deaths.

Fig. 6. Mean percent change in mPEF from baseline to week 52 (FAS). Data are presented as the mean $\pm$ SD.

Fig. 7. The mean ACQ-6 score from baseline to week 52 (FAS).

Fig. 8. The mean blood eosinophil counts (FAS). Data are presented as the mean $\pm$ SD.

Table 4. Treatment-emergent adverse events (safety population)

	Placebo (n = 26)		2 mg benralizumab (n = 26)		20 mg benralizumab (n = 25)		100 mg benralizumab (n = 26)	
	n	%	n	%	n	%	n	%
Subjects with any adverse events	25	96.2	25	96.2	23	92.0	25	96.2
Nasopharyngitis	13	50.0	10	38.5	10	40.0	3	11.5
Injection site reaction	0		4	15.4	9	36.0	8	30.8
Upper respiratory tract infection	8	30.8	7	26.9	6	24.0	8	30.8
Pyrexia	1	3.8	3	11.5	4	16.0	7	26.9
Influenza-like illness	1	3.8	4	15.4	2	8.0	5	19.2
Asthma	3	11.5	5	19.2	2	8.0	2	7.7
Vomiting	0		3	11.5	4	16.0	1	3.8
Headache	0		1	3.8	3	12.0	4	15.4
Allergic rhinitis	2	7.7	3	11.5	2	8.0	3	11.5
Urticaria	0		1	3.8	6	24.0	1	3.8
Stomatitis	0		3	11.5	0		4	15.4
Injection site erythema	0		3	11.5	4	16.0	0	
Bronchitis	2	7.7	1	3.8	4	16.0	2	7.7
Pharyngitis	2	7.7	4	15.4	1	4.0	1	3.8
Arthralgia	1	3.8	0		1	4.0	5	19.2
Insomnia	1	3.8	1	3.8	4	16.0	1	3.8
Chronic sinusitis	3	11.5	3	11.5	1	4.0	1	3.8
Acute sinusitis	2	7.7	1	3.8	2	8.0	2	7.7
Otitis media	1	3.8	1	3.8	2	8.0	2	7.7
Oropharyngeal pain	1	3.8	3	11.5	2	8.0	0	
Eczema	1	3.8	0		2	8.0	3	11.5
Constipation	0		1	3.8	2	8.0	1	3.8
Diarrhea	0		2	7.7	0		2	7.7
Large intestinal polyp	0		1	3.8	1	4.0	2	7.7
Fatigue	2	7.7	1	3.8	1	4.0	2	7.7
Feeling hot	0		0		2	8.0	2	7.7
Myalgia	1	3.8	1	3.8	2	8.0	1	3.8
Back pain	0		1	3.8	1	4.0	2	7.7
Rhinitis perennial	0		2	7.7	0		2	7.7
Hypertension	0		2	7.7	1	4.0	1	3.8

The table displays treatment-emergent adverse events by preferred term that occurred in 5% or more subjects in the combined benralizumab group.

Discussion

In this phase 2a study in patients with eosinophilic asthma in South Korea and Japan, we could show the dose-response of the time course of cumulative exacerbations, time to first asthma exacerbation and blood eosinophil counts. Benralizumab showed a reduction in the asthma exacerbation rate compared to placebo and a trend toward an improved FEV₁ and mPEF at doses of 20 and 100 mg. The blood eosinophil count was depleted at all doses during the treatment period and had almost recovered at approximately 28 weeks after the final admin-

istration of the study medication. However, the asthma exacerbation rate, FEV₁, mPEF and ACQ-6 did not show any apparent dose-response effects. The safety profile was shown to be acceptable between 2 and 100 mg of benralizumab every 4 weeks for the first 3 doses and then every 8 weeks for 4 additional doses.

In the phase 2b study (ClinicalTrials.gov NCT 01238861) sponsored by MedImmune, the rate of reduction in annual exacerbation rates in subjects receiving 2, 20 and 100 mg of benralizumab was -7, 57 and 43%, respectively, in subjects with baseline blood eosinophil levels ≥ 300 cells/ μ l. Changes in FEV₁ from baseline were

between 0.16 and 0.2 liters in all active doses. These results demonstrated the efficacy and safety of repeated doses of subcutaneous benralizumab in adults with uncontrolled asthma in Europe and North and South America with baseline blood eosinophils levels ≥ 300 cells/ μ l [21]. Therefore, we conducted subgroup analyses for the efficacy endpoints in the present phase 2a study using subjects with baseline blood eosinophils ≥ 300 cells/ μ l. In the subgroup analysis, the annual exacerbation rate was reduced by 61, 61 and 40% versus the placebo group for treatment with 2, 20 or 100 mg of benralizumab, respectively. These results from our phase 2a study replicate the results from the phase 2b study by MedImmune in the 20- and 100-mg dose groups, suggesting that benralizumab is effective not only in European and American populations, but also in East Asian populations, such as Korean and Japanese. Based on these findings, we are now conducting two larger phase 3 studies in South Korea and Japan (ClinicalTrials.gov NCT01914757 and NCT01928771) as part of the global asthma phase 3 program for benralizumab.

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ringer Ingelheim, GlaxoSmithKline, Novartis, Astellas and Torii pharma. Y.T. reports personal fees outside the submitted work from Kyowa Hakko Kirin Co. Ltd., Teijin Pharma, Ono Pharma and Kyorin Pharma. N.I. and T.N. are full-time employees of Kyowa Hakko Kirin Co. Ltd.

Appendix

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References

- 1 Global Initiative for Asthma (GINA): Global Strategy for Asthma Management and Prevention, updated 2012. <http://www.ginasthma.org>.
- 2 Reddel H, Ware S, Marks G, Salome C, Jenkins C, Woolcock A: Differences between asthma exacerbations and poor asthma control. *Lancet* 1999;353:364–369.
- 3 Masoli M, Fabian D, Holts S, Beasley R; Global Initiative for Asthma (GINA) Program: The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004;59:469–478.
- 4 Hamby N, Nair P: Monoclonal antibodies for the treatment of refractory asthma. *Curr Opin Pulm Med* 2014;20:87–94.
- 5 Japanese Society of Allergology: Asthma Prevention and Management Guideline 2012 (in Japanese). Tokyo, Kyowa Kikaku, 2012.
- 6 Di Franco A, Bartoli ML, Carnevali S, Cianchetti S, Bacci E, Dente FL, Giannini D, Taccola M, Vagaggini B, Paggiaro PL: Analysis of sputum cell counts during spontaneous moderate exacerbations of asthma in comparison to the stable phase. *J Asthma* 2003;40:155–162.
- 7 Scott KA, Wardlaw AJ: Eosinophilic airway disorders. *Semin Respir Crit Care Med* 2006;27:128–133.
- 8 Zhang JY, Wenzel SE: Tissue and BAL based biomarkers in asthma. *Immunol Allergy Clin North Am* 2007;27:623–632.
- 9 Holgate ST: Mechanism of asthma and implications for its prevention and treatment: a personal journey. *Allergy Asthma Immunol Res* 2013;5:343–349.
- 10 Molino NA, Gossage D, Kolbeck R, Parker JM, Geba GP: Molecular and clinical rationale for therapeutic targeting of interleukin-5 and its receptor. *Clin Exp Allergy* 2012;42:712–737.
- 11 Uhm TG, Kim BS, Chung IY: Eosinophil development, regulation of eosinophil-specific genes, and role of eosinophil in the pathogenesis of asthma. *Allergy Asthma Immunol Res* 2012;4:68–79.

- 12 Castro M, Mathur S, Hargreave F, Boulet LP, Xie F, Young J, Wilkins HJ, Henkel T, Nair P; Res-5-0010 Study Group: Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med* 2011;184:1125–1132.
- 13 Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, Marshall RP, Bradling P, Green RH, Wardlaw AJ, Pavord ID: Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973–984.
- 14 Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, Hargreave FE, O'Byrne PM: Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985–993.
- 15 Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, Ortega H, Chanez P: Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651–659.
- 16 Kolbeck R, Kozhich A, Koike M, Peng L, Andersson CK, Damschroder MM, Reed JL, Woods R, Dall'acqua WW, Stephens GL, Erjefelt JS, Bjermer L, Humbles AA, Gossage D, Wu H, Kiener PA, Spitalny GL, Mackay CR, Molfino NA, Coyle AJ: MEDI-563, a humanized anti-IL-5 receptor alpha mAb with enhanced antibody-dependent cell-mediated cytotoxicity function. *J Allergy Clin Immunol* 2010;125:1344–1353.e2.
- 17 Takatsu K, Dickason RR, Huston DP: Interleukin 5; in Bondy C, LeRoith C (eds): *Growth Factors and Cytokines in Health and Disease. Cytokines, Part A*. Amsterdam, Elsevier, 1997.
- 18 Toba K, Koike T, Shibata A, Hashimoto S, Takahashi M, Masuko M, Azegami T, Takahashi H, Aizawa Y: Novel technique for the direct flow cytofluorometric 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.
- 19 Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck R, Coyle AJ, Koike M, Spitalny GL, Kiener PA, Geba GP, Molfino NA: Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol* 2010;125:1237–1244.e2.
- 20 Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, Busse WW, Wenzel S, Wu Y, Datta V, Kolbeck R, Molfino NA: Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013;132:1086–1096.e5.
- 21 Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, Gossage DL, Ward CK, Wu Y, Wang B, Khatry DB, van der Merwe R, Kolbeck R, Molfino NA, Raible DG: Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014;2:879–890.
- 22 Pizzichini E, Pizzichini MM, Efthimiadis A, Hargreave FE, Dolovich J: Measurement of inflammatory indices in induced sputum: effects of selection of sputum to minimize salivary contamination. *Eur Respir J* 1996;9:1174–1180.
- 23 Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR: Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–907.
- 24 Juniper EF, Svensson K, Mörk AC, Ståhl E: Measurement properties and interpretation of three shortened versions of the asthma control questionnaire. *Respir Med* 2005;99:553–558.
- 25 Juniper EF, Bousquet J, Abetz L, Bateman ED; GOAL Committee: Identifying 'well-controlled' and 'not well-controlled' asthma using the Asthma Control Questionnaire. *Respir Med* 2006;100:616–621.
- 26 Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ: Guidelines for methacholine and exercise challenge testing – 1999. *Am J Respir Crit Care Med* 2000;161:309–329.
- 27 Reddel HK, Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, Chanez P, Enright PL, Gibson PG, de Jongste JC, Kerstjens HA, Lazarus SC, Levy ML, O'Byrne PM, Partridge MR, Pavord ID, Sears MR, Sterk PJ, Stolf SW, Sullivan SD, Szeffler SJ, Thomas MD, Wenzel SE; American Thoracic Society/European Respiratory Society Task Force on Asthma Control and Exacerbations: An official American Thoracic Society/European Respiratory Society statement: asthma control and exacerbations: standardizing endpoints for clinical asthma trials and clinical practice. *Am J Respir Crit Care Med* 2009;180:59–99.