Report on the Deliberation Results

February 29, 2024
Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau
Ministry of Health, Labour and Welfare

Brand Name	Fasenra Subcutaneous Injection 30 mg Syringe
	Fasenra Subcutaneous Injection 10 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	April 26, 2023

Results of Deliberation

At its meeting held on February 22, 2024, the Second Committee on New Drugs concluded that the 30 mg formulation of the product under partial change application and the 10 mg formulation of the product under new drug application may be approved and that these results should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The 10 mg formulation of the product is classified as a biological product, and the drug product is classified as a powerful drug. The reexamination period for the 30 mg and 10 mg formulations of the product is 4 years.

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

February 6, 2024
Pharmaceuticals and Medical Devices Agency

The following are the results of review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	(a) Fasenra Subcutaneous Injection 30 mg Syringe (b) Fasenra Subcutaneous Injection 10 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	April 26, 2023
Dosage Form/Strength	(a) Injection: Each syringe (1 mL) contains 30 mg of benralizumab (genetical recombination). (b) Injection: Each syringe (0.5 mL) contains 10 mg of benralizumab (genetical recombination).
Application Classification	(a) Prescription drug, (6) Drug with a new dosage (b) Prescription drug, (6) Drug with a new dosage and (8) Drug in an additional dosage form (during the reexamination period)
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of bronchial asthma in children aged ≥6 years (only for patients with intractable bronchial asthma uncontrolled on conventional therapy), and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication at the dosage and administration shown below, under the following condition. The safety, etc. of the product in the clinical setting should be further investigated by post-marketing surveillance.

Indication

Bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)

(No changes)

Dosage and Administration

(a) The usual dosage for adults, children aged ≥12 years, and children aged ≥6 and <12 years (weighing ≥35 kg) is 30 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(b) The usual dosage for children aged ≥6 and <12 years (weighing <35 kg) is 10 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(Underline denotes additions.)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Attachment

Review Report (1)

January 11, 2024

The following is an outline of the data submitted by the applicant and the content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	(a) Fasenra Subcutaneous Injection 30 mg Syringe (b) Fasenra Subcutaneous Injection 10 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	April 26, 2023
Dosage Form/Strength	(a) Injection: Each syringe (1 mL) contains 30 mg of benralizumab (genetical recombination). (b) Injection: Each syringe (0.5 mL) contains 10 mg of benralizumab (genetical recombination).

Proposed Indication

Bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)

(No changes)

Proposed Dosage and Administration

(a) The usual dosage for adults, children aged ≥12 years, and children aged ≥6 and <12 years (weighing ≥35 kg) is 30 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(b) The usual dosage for children aged ≥6 and <12 years (weighing <35 kg) is 10 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Benralizumab (genetical recombination) (hereinafter also referred to as "benralizumab"), the active ingredient of "Fasenra Subcutaneous Injection 30 mg Syringe and Fasenra Subcutaneous Injection 10 mg Syringe," is a humanized immunoglobulin G1 (IgG1) monoclonal antibody that specifically binds to the α subunit of the human interleukin-5 receptor (IL-5Rα). Benralizumab was discovered by Kyowa Hakko Kirin Co., Ltd. (currently known as Kyowa Kirin Co., Ltd.), and is developed by Kyowa Hakko Kirin Co., Ltd., BioWa, Inc. (the US), MedImmune, LLC (the US), and the applicant (AstraZeneca K.K.). In Japan, benralizumab was approved for the treatment of "bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)" in January 2018.

Bronchial asthma is a chronic inflammatory disease of the respiratory tract, characterized by clinical symptoms such as wheezing, dyspnea, chest tightness, and coughing due to variable airway obstructions (the Asthma Prevention and Management Guidelines [hereinafter referred to as "JGL"] 2021 or the Japanese Pediatric Guidelines for the Treatment and Management of Asthma [hereinafter referred to as "JPGL"] 2023).

The standard drug therapy for pediatric patients with bronchial asthma is inhaled corticosteroid (ICS) treatment, as with bronchial asthma in adults and adolescents. The guideline also recommends the use of add-on therapy with long-acting β-2 agonists (LABA), leukotriene receptor antagonists (LTRA), or theophylline according to the severity. If the disease cannot be controlled with these treatments, the use of biologics such as anti-IgE antibodies and anti-interleukin-5 (IL-5) therapies, as well as systemic corticosteroids should be considered (JPGL 2023). However, treatment options for children with severe asthma who have a history of exacerbations despite therapy with ICS in combination with an additional controller medication are limited.

In Japan, the clinical development of benralizumab for the treatment of severe asthma in children was initiated in November 2019. An application for partial change approval to add the dosage and administration of the 30 mg syringe formulation for severe asthma in children and an application for approval of the dosage form of the 10 mg syringe formulation have recently been filed based on the data from multiregional clinical studies involving Japanese participants.

The 30 mg syringe formulation has been approved for the treatment of severe asthma in adults in >80 foreign countries or regions, including Europe and the US, as of December 2023. In 3 of these countries or regions, including the US, the 30 mg syringe formulation has been approved as a drug for the treatment of severe asthma in adults and children aged ≥12 years. As of December 2023, the dosage and administration of benralizumab for the treatment of severe asthma in children aged ≥6 and <12 years have not been approved in any countries or regions.

2. Quality and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, data relating to quality have been submitted for Fasenra Subcutaneous Injection 10 mg Syringe, for which application was also submitted for approval as a drug in an additional dosage form used for pediatric patients aged ≥6 and <12 years and weighing <35 kg. This report

only contains information on the additional dosage. The review by PMDA identified no major problems with the product as a drug in an additional dosage form.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, no additional study results have been submitted because the "data on non-clinical pharmacology studies" have already been evaluated for the initial approval.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Although this is an application for an additional dosage, no additional study results have been submitted because the "data on non-clinical pharmacokinetic studies" have already been evaluated for the initial approval.

5. Toxicity and Outline of the Review Conducted by PMDA

On the basis of the following toxicity study results, which were submitted in support of the initial application for the treatment of severe asthma in adults, the applicant explained that the study results can ensure the safety of benralizumab in pediatric patients with severe asthma aged ≥6 years.

- An abnormal finding related to the use of benralizumab, namely, decreased eosinophils, was observed in a repeated-dose toxicity study in which benralizumab was subcutaneously or intravenously administered to cynomolgus monkeys for up to 9 months. This finding was not considered as toxicity evidence because it was a change related to the pharmacology of benralizumab (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 25, 2017). Although similar changes were observed in clinical studies of benralizumab in children, there were no adverse events related to decreased eosinophils, such as parasitic infections [see Section 7.R.3].
- In an enhanced pre- and post-natal reproductive and developmental study in pregnant cynomolgus monkeys that evaluated the growth of offspring up to 6.5 months post-natal, which covers the development of humans aged ≥6 years, no toxicological findings were observed (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 25, 2017).

PMDA accepted the applicant's explanation.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

Serum benralizumab concentrations were measured by electrochemiluminescence assay (lower limit of quantitation [LLOQ], 3.86 ng/mL). Serum anti-drug antibodies (ADA) were measured by electrochemiluminescence assay (limit of detection [LOD], 12.5-50 ng/mL). Serum neutralizing antibodies were measured by ligand binding neutralizing antibody assay (LOD, 22.5-37.5 ng/mL).

No study has been conducted to evaluate bioequivalence between the 10 mg syringe formulation and the approved 30 mg syringe formulation.

6.2 Clinical pharmacology

The applicant submitted the results of the multiregional phase III study in pediatric patients with severe asthma aged ≥6 and <15 years (Study D3250C00025 [TATE study]) as evaluation data. Unless otherwise specified, the amount of benralizumab administered is expressed based on the dose of benralizumab.

6.2.1 Multiregional phase III study (CTD 5.3.3.5.1 and 5.3.4.2.1, Study D3250C00025 [TATE study] [November 2019 to September 2022])

Population pharmacokinetic analysis (software: NONMEM version 7.5.0) was performed using data on serum benralizumab concentrations (257 blood samples from 30 subjects) following subcutaneous doses of benralizumab 10 or 30 mg, depending on age and body weight, every 8 weeks (Q8W) (with an additional dose at 4 weeks after the first dose) in Study D3250C00025 (TATE study) in pediatric patients with severe asthma aged ≥6 and <15 years [see Section 7.1]. The pharmacokinetics of benralizumab in pediatric patients with severe asthma was described by the same model as an existing population pharmacokinetic model[1)] established using data from adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years, which were used as prior information, and no new covariates were identified. Table 1 shows the steady-state pharmacokinetic parameters of benralizumab estimated by the final model updated using data following subcutaneous doses of benralizumab 10 or 30 mg Q8W (with an additional dose at 4 weeks after the first dose) in pediatric patients with severe asthma aged ≥6 and <15 years in Study D3250C00025 (TATE study). Table 1 also shows the steady-state pharmacokinetic parameters of benralizumab following subcutaneous doses of benralizumab 30 mg Q8W (with an additional dose at 4 weeks after the first dose) in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years.

Table 2 shows the percent change over time from baseline in blood eosinophil count in Study D3250C00025 (TATE study) in pediatric patients with severe asthma aged ≥6 and <15 years and clinical studies in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years. A reduction in blood eosinophil count from baseline was observed by Week 4 and the reduction was maintained throughout the treatment period in pediatric patients with severe asthma aged ≥6 and <15 years, as with adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years.

ADA was observed in 13.3% (4 of 30) of patients who received the study drug, and all of these patients tested positive for neutralizing antibody.

1) A 2-compartment model with first-order absorption and elimination processes, incorporating the following covariates: body weight and ADA for total clearance (CL), and body weight for V2 and V3 (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017). When establishing the model, the effect of age and age group (adults or adolescents) was investigated. Neither of them were selected as covariates.

Table 1. Steady-state pharmacokinetic parameters of benralizumab estimated using the population pharmacokinetic model)

Population	Dosage regimen (mg Q8W)	N		$AUC_{\tau,ss}$ (μg·day/mL)	$C_{max,ss}$ (μg/mL)	$t_{1/2}$ (day)
Children aged ≥6 and <15 years[b),c)]	10	15		49.2 ± 17.6	2.12 ± 0.51	12.1 ± 4.8
			Japanese (n = 8)	47.7 ± 16.8	2.10 ± 0.46	11.4 ± 4.6
			Non-Japanese (n = 7)	51.0 ± 19.6	2.14 ± 0.60	12.9 ± 5.3
	30	15		107 ± 55	4.30 ± 1.9	15.5 ± 4.4
			Japanese (n = 3)	117 ± 21	4.45 ± 0.90	17.9 ± 0.2
			Non-Japanese (n = 12)	105 ± 61	4.26 ± 2.13	14.9 ± 4.7
Adults and children aged ≥12 years[d)]	30	1,773		56.0 ± 20.5	2.02 ± 0.48	14.6 ± 14.9

Mean ± standard deviation (SD)

a) Pharmacokinetic parameters in adults and children aged ≥12 years were estimated based on an existing population pharmacokinetic model established using data from adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017), and those in children aged ≥6 and <15 years in Study D3250C00025 (TATE study) were estimated based on a population pharmacokinetic model developed by updating the existing model using data from Study D3250C00025 (TATE study).

b) Benralizumab was administered at a dose of 10 mg to children aged ≥6 and <12 years (weighing <35 kg) and at a dose of 30 mg to children aged ≥6 and <12 years (weighing ≥35 kg) and children aged ≥12 and <15 years.

c) Study D3250C00025 (TATE study)

d) Study D3250C00018 (CALIMA study), Study D3250C00017 (SIROCCO study), and Study D3250C00020 (ZONDA study)

Table 2. Percent change (%) over time from baseline in blood eosinophil count following multiple subcutaneous doses of benralizumab

Baseline blood eosinophil count	Population	Study identifier	Dosage regimen (mg Q8W)	Week 4	Week 16	Week 24	Week 48
≥300/μL	Children aged ≥6 and <15 years[a)]	Study D3250C00025 (TATE study)	10	−96.7 ± 2.93 (10)	−96.7 ± 2.85 (10)	−68.7 ± 52.6 (8)	−92.9 ± 11.1 (10)
			30	−93.2 ± 8.02 (9)	−92.6 ± 10.5 (7)	−94.6 ± 5.54 (9)	−95.0 ± 3.98 (9)
	Adults and children aged ≥12 years	Study D3250C00017 (SIROCCO study)	30	−90.6 ± 38.0 (247)	-	−90.8 ± 47.8 (234)	−92.2 ± 32.0 (208)
		Study D3250C00018 (CALIMA study)	30	−96.4 ± 16.3 (280)	-	−90.7 ± 32.6 (259)	-
<300/μL	Children aged ≥6 and <15 years[a)]	Study D3250C00025 (TATE study)	10	−91.0 ± 8.84 (5)	−92.3 ± 7.90 (5)	−90.2 ± 3.26 (4)	−89.5 ± 7.12 (5)
			30	−71.9 ± 40.0 (4)	−88.1 ± 9.87 (4)	−69.6 ± 24.7 (4)	−90.4 ± 6.98 (4)
	Adults and children aged ≥12 years	Study D3250C00017 (SIROCCO study)	30	−89.9 ± 26.4 (114)	-	−79.2 ± 55.4 (114)	−87.1 ± 30.5 (96)
		Study D3250C00018 (CALIMA study)	30	−90.5 ± 63.5 (142)	-	−87.6 ± 45.0 (129)	-

Mean ± SD (N); -, not evaluated.

a) Benralizumab was administered at a dose of 10 mg to children aged ≥6 and <12 years (weighing <35 kg) and at a dose of 30 mg to children aged ≥6 and <12 years (weighing ≥35 kg) and children aged ≥12 and <15 years.

6.R Outline of the review conducted by PMDA

6.R.1 Review from the perspective of clinical pharmacology: Dosage and administration of benralizumab for Japanese pediatric patients with severe asthma aged ≥6 years

The applicant's explanation:

The dosage regimen of benralizumab was set according to age and body weight in the multiregional phase III study, Study D3250C00025 (TATE study), so that the steady-state exposure in pediatric patients with severe asthma aged ≥6 and <15 years would be similar to the exposure in adult patients who received benralizumab at the approved dosage and administration (30 mg Q8W [with an additional dose at 4 weeks after the first dose]) [see Section 7.R.1]. Although the exposure in pediatric patients with severe asthma aged ≥6 and <15 years estimated from the serum benralizumab concentrations measured in this study tended to differ from that

in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years, the trend toward a reduction in blood eosinophil count, which is related to the pharmacology of benralizumab, in patients with severe asthma aged ≥6 and <15 years was generally similar to that in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years [see Section 6.2.1]. Pharmacokinetics in pediatric patients with severe asthma in Study D3250C00025 (TATE study) showed no clear ethnic differences (see Table 1). The percent change from baseline in blood eosinophil count also indicated almost complete depletion of blood eosinophils after Week 4 (Table 2).

The above results support the proposed dosage and administration of benralizumab determined according to age and body weight for Japanese pediatric patients with severe asthma aged ≥6 and <15 years.

PMDA's view:
The following explanation by the applicant is generally understandable from pharmacokinetic and pharmacodynamic viewpoints: the dosage and administration for Japanese pediatric patients with severe asthma aged ≥6 and <15 years is set as subcutaneous administration of benralizumab 10 or 30 mg, depending on age and body weight, Q8W (with an additional dose at 4 weeks after the first dose). However, the exposure in pediatric patients with severe asthma aged ≥6 and <12 years (weighing ≥ 35 kg) and those aged ≥12 and <15 years who received benralizumab 30 mg Q8W (with an additional dose at 4 weeks after the first dose) tended to be higher than that in adult patients who received benralizumab at the approved dosage and administration. The decision on the appropriateness of the proposed dosage and administration will be made based on efficacy and safety data from Study D3250C00025 (TATE study) [see Section 7.R.5].

6.R.2 ADA

The applicant's explanation about the incidence of ADA in pediatric patients with severe asthma aged ≥6 and <15 years and the impact of ADA on the pharmacokinetics, efficacy, and safety of benralizumab:
In 4 subjects who tested positive for ADAs and neutralizing antibodies in Study D3250C00025 (TATE study), serum benralizumab concentrations tended to be lower and blood eosinophil counts tended to be higher in the ADA-positive subjects than in ADA-negative subjects, as in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years.[2)] Although there are limitations to the evaluation in the limited number of ADA-positive subjects, no clear impact on the efficacy or safety of benralizumab was observed in ADA-positive subjects,[3)] nor were there any clinically meaningful differences in the efficacy or safety of benralizumab between ADA-positive and -negative subjects.

PMDA accepted the applicant's explanation.

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2) In 3 of 4 ADA-positive subjects, ADAs were transiently or persistently detected, at which point the serum benralizumab concentration decreased below the LLOQ and the blood eosinophil count increased to near the baseline level. In 2 subjects who were transiently ADA-positive, the serum benralizumab concentration increased and the blood eosinophil count decreased after ADAs became negative.

3) According to efficacy data, all the 4 subjects who tested positive for ADAs and neutralizing antibodies had a reduced number of asthma exacerbations after receiving benralizumab, compared with that within 12 months before baseline; and 3 of them experienced no asthma exacerbations after receiving benralizumab. According to safety data, no serious events occurred in any of these 4 subjects. Although injection site reaction, which was considered possibly related to the study drug, occurred in 1 subject, the event was mild and resolved, and treatment with benralizumab was continued.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data in the form of the study results data shown in Table 3.

Table 3. Efficacy and safety evaluation data

Phase	Study identifier	Region	Population	Number of enrolled subjects	Outline of dosage regimen	Main endpoints
III	D3250C00025 (TATE)	Multi-regional	Patients with severe asthma accompanied by eosinophilic airway inflammation aged ≥6 and <15 years	30	Benralizumab 10 or 30 mg, depending on age and body weight, Q8W (with an additional dose at 4 weeks after the first dose), s.c.	Pharmacokinetics/ pharmacodynamics Efficacy Safety

7.1 Multiregional phase III study (CTD 5.3.4.2.1, Study D3250C00025 [TATE study] [November 2019 to September 2022])

An open-label, uncontrolled study was conducted in Japan and the US to evaluate the pharmacokinetics/pharmacodynamics, efficacy, and safety of benralizumab in pediatric patients with severe asthma (See Table 4; age, ≥6 and <12 years in the US and ≥6 and <15 years in Japan) whose blood eosinophil count was ≥150/μL at screening and who had asthma exacerbation despite treatment with medium- or high-dose ICS and LABA or other controller medications (target sample size, 30 subjects).

Table 4. Key inclusion/exclusion criteria

Key inclusion criteria
1. Patients weighing ≥15 kg.
2. Patients diagnosed with severe asthma according to the definition in the asthma guidelines available in each country, for ≥12 months prior to screening.
3. Patients who had ≥2 asthma exacerbations requiring systemic corticosteroid treatment or hospitalization despite ICS treatment within 12 months prior to screening or who required continuous maintenance treatment with OCS for asthma control for ≥3 months within 12 months prior to screening.
4. Patients with blood eosinophil count ≥150/μL at screening.
5. Patients who received regular treatment with high-dose ICS (equivalent to ≥250 μg/day of fluticasone propionate) within 12 months prior to screening (patients who used medium-dose ICS according to the guidelines available in each country were also considered to meet this criterion).
6. Patients who used at least 1 additional controller medication (e.g., LABA, LTRA, long-acting anticholinergic agent, or theophylline) other than ICS for ≥3 months prior to screening.
7. Patients with pre-bronchodilator forced expiratory volume in 1 second (FEV_1) ≤110% of the predicted normal value or FEV_1/forced vital capacity (FVC) ≤0.8 at screening or at the start of treatment with benralizumab.

Key exclusion criteria
1. Patients with clinically significant lung disease other than bronchial asthma.
2. Patients who were previously diagnosed with lung or systemic disease, other than bronchial asthma, that was associated with increased blood eosinophil count.
3. Patients with a history of anaphylaxis to biologics.
4. Patients who used immunosuppressants within 3 months prior to screening.
5. Patients who used other biologics (e.g., omalizumab, mepolizumab) within 4 months or 5 half-lives, whichever is longer, prior to screening.

Subjects subcutaneously received benralizumab 10 or 30 mg, depending on age and body weight, Q8W (with an additional dose at 4 weeks after the first dose), as shown in Table 5.

Table 5. Dose of benralizumab by age and body weight

Age	Body weight	Dose
≥6 and <12 years	<35 kg	10 mg
≥6 and <12 years	≥35 kg	30 mg
≥12 and <15 years	-	30 mg

All of 30 subjects (15 treated at 10 mg and 15 treated at 30 mg) who had received ≥1 dose of benralizumab were included in the pharmacokinetic, pharmacodynamic, efficacy, and safety analysis sets.

The study was discontinued in 3.3% (1 of 30) of subjects (1 subject treated at 30 mg), and the reason for the study discontinuation was consent withdrawal.

The Japanese subpopulation consisted of 11 subjects (8 treated at 10 mg and 3 treated at 30 mg), and the study was discontinued in 1 subject treated at 30 mg due to consent withdrawal.

Efficacy endpoints included asthma exacerbation and Interviewer-administered Asthma Control Questionnaire (ACQ-IA) score [for the definition, see Section 10].

Asthma exacerbation occurred in 53.3% (16 of 30) of subjects (47 episodes) (7 of 15 subjects treated at 10 mg [28 episodes] and 9 of 15 subjects treated at 30 mg [19 episodes]). The proportion of patients with a decrease of ≥0.5 point from baseline in ACQ-IA score at Week 48 was 59.3% (16 of 27 subjects) (42.9% [6 of 14] of subjects treated at 10 mg and 76.9% [10 of 13] of subjects treated at 30 mg).

In the Japanese subpopulation, asthma exacerbations occurred in 54.5% (6 of 11) of subjects (30 episodes) (4 of 8 subjects treated at 10 mg [25 episodes] and 2 of 3 subjects treated at 30 mg [5 episodes]). The proportion of patients with a decrease of ≥0.5 point from baseline in ACQ-IA score at Week 48 was 60.0% (6 of 10 subjects) (50.0% [4 of 8] of subjects treated at 10 mg and 100.0% [2 of 2] of subjects treated at 30 mg).

Adverse events occurred in 80.0% (24 of 30) of subjects (86.7% [13 of 15] of subjects treated at 10 mg and 73.3% [11 of 15] of subjects treated at 30 mg). Commonly observed adverse events are shown in Table 6.

No deaths or adverse events leading to treatment discontinuation occurred.

Serious adverse events occurred in 16.7% (5 of 30) of subjects (6.7% [1 of 15] of subjects treated at 10 mg [asthma] and 26.7% [4 of 15] of subjects treated at 30 mg [asthma in 3 subjects and asthma/somatic symptom disorder in 1 subject]). A causal relationship to the study drug was ruled out for all events.

Adverse drug reactions occurred in 13.3% (4 of 30) of subjects (20.0% [3 of 15] of subjects treated at 10 mg and 6.7% [1 of 15] of subjects treated at 30 mg).

Table 6. Adverse events reported by ≥2 subjects (safety analysis set)

Event	Subjects treated with benralizumab (N = 30)	Subjects treated at 10 mg (N = 15)	Subjects treated at 30 mg (N = 15)
Nasopharyngitis	6 (20.0)	4 (26.7)	2 (13.3)
Asthma	5 (16.7)	1 (6.7)	4 (26.7)
Pyrexia	4 (13.3)	3 (20.0)	1 (6.7)
Viral upper respiratory tract infection	4 (13.3)	2 (13.3)	2 (13.3)
Constipation	3 (10.0)	2 (13.3)	1 (6.7)
Headache	3 (10.0)	2 (13.3)	1 (6.7)
COVID-19	3 (10.0)	1 (6.7)	2 (13.3)
Urticaria	3 (10.0)	1 (6.7)	2 (13.3)
Cough	3 (10.0)	0	3 (20.0)
Sinusitis	2 (6.7)	2 (13.3)	0
Vomiting	2 (6.7)	2 (13.3)	0
Pain in extremity	2 (6.7)	2 (13.3)	0
Eczema	2 (6.7)	1 (6.7)	1 (6.7)
Allergy to animal	2 (6.7)	1 (6.7)	1 (6.7)
Pharyngitis	2 (6.7)	1 (6.7)	1 (6.7)
Pneumonia	2 (6.7)	0	2 (13.3)
Diarrhoea	2 (6.7)	0	2 (13.3)

n (%)

In the Japanese subpopulation, adverse events occurred in 100% (11 of 11) of subjects. Commonly observed adverse events are shown in Table 7.

No deaths or adverse events leading to discontinuation occurred.

Serious adverse events occurred in 18.2% (2 of 11) of subjects (2 subjects treated at 30 mg [asthma/somatic symptom disorder in 1 subject and asthma in 1 subject]). A causal relationship to the study drug was ruled out for both events.

Adverse drug reactions occurred in 18.2% (2 of 11) of subjects (2 subjects treated at 10 mg).

Table 7. Adverse events reported by ≥2 subjects (safety analysis set, Japanese subpopulation)

Event	Subjects treated with benralizumab (N = 11)	Subjects treated at 10 mg (N = 8)	Subjects treated at 30 mg (N = 3)
Nasopharyngitis	6 (54.5)	4 (50.0)	2 (66.7)
Pyrexia	3 (27.3)	3 (37.5)	0
Constipation	3 (27.3)	2 (25.0)	1 (33.3)
Urticaria	3 (27.3)	1 (12.5)	2 (66.7)
Pharyngitis	2 (18.2)	1 (12.5)	1 (33.3)
Asthma	2 (18.2)	0	2 (66.7)

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of benralizumab for pediatric patients with severe asthma aged ≥6 years:

Bronchial asthma is a chronic inflammatory disease of the respiratory tract, characterized by clinical symptoms such as wheezing, dyspnea, chest tightness, and coughing due to variable airway obstructions. These clinical or pathophysiological characteristics do not substantially differ between children aged ≥6 years and adults

(Global Initiative for Asthma [GINA] 2018, JGL 2018, JPGL 2017). Severe asthma in children is a heterogenous disease with different phenotypes, as with asthma in adults, and eosinophilic airway inflammation is noted in both adult and pediatric patient populations. Eosinophilic airway inflammation is related to the severity of asthma in children as well and represents a characteristic of severe treatment-resistant asthma (*Pediatr Allergy Immunol Pulmonol*. 2018;31:44-55). In adult patients with asthma, increased eosinophil counts are associated with increased severity of symptoms, asthma exacerbation, decreased pulmonary function, and death (*Eur Respir Rev*. 2013;22:251-257, *J Asthma Allergy*. 2016;9:1-12, etc.). In pediatric patients with asthma, increased airway eosinophil counts are also associated with the increased severity of symptoms, severe treatment-resistant asthma, and airway remodeling (*J Allergy Clin Immunol*. 2004;113:94-100, *J Allergy Clin Immunol*. 2012;129:974-982). In view of these findings, the treatment guidelines for bronchial asthma available in and outside Japan are similar, and do not substantially differ between adults and children (GINA 2018, JPGL 2017).

In Study D3250C00018 (CALIMA study) and other studies in Japanese and non-Japanese adult patients with severe asthma (including non-Japanese children aged ≥12 years), there were no clear ethnic differences in the efficacy, safety, pharmacokinetics, or blood eosinophil count-reducing effect of benralizumab (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017). Study D3250C00025 (TATE study) in pediatric patients with severe asthma aged ≥6 years was therefore conducted as a multiregional study. Study D3250C00025 (TATE study) was planned as an open-label, uncontrolled study because the number of pediatric patients with severe asthma accompanied by eosinophilic airway inflammation aged ≥6 years in and outside Japan was extremely limited and it was therefore considered difficult to conduct a confirmatory study enrolling a sufficient number of patients. The efficacy and safety of benralizumab in pediatric patients with severe asthma can be evaluated based on the clinical study results that have already confirmed the efficacy and safety of benralizumab in adult and other patients with severe asthma (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017).

The applicant provided the following explanation about the "patient population" and "dosage regimen" in Study D3250C00025 (TATE study):

- **Patient population**

On the basis of the above-mentioned treatment algorithm for bronchial asthma (JPGL 2017) and the designs of multiregional Study D3250C00018 (CALIMA study) and foreign Study D3250C00017 (SIROCCO study) in adult patients with severe asthma (including non-Japanese children aged ≥12 years), the key inclusion/exclusion criteria shown in Table 4 were established for the patient population of Study D3250C00025 (TATE study).

- **Dosage regimen**

Using a population pharmacokinetic model developed from the data of Japanese and foreign clinical studies in adult patients with severe asthma and pediatric patients with severe asthma aged ≥12 years (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017), the ratio of the steady-

state exposure in pediatric patients with asthma following administration of benralizumab 10 or 30 mg, as per body weight, Q8W to adult exposure was predicted (see Table 8). In view of the predicted results, and given the fact that most children aged ≥12 years weigh ≥35 kg in the US[4)] and the approved dosage and administration in the US,[5)] subcutaneous administration of benralizumab 10 or 30 mg, depending on age and body weight, Q8W (with an additional dose at 4 weeks after the first dose) was employed in Study D3250C00025 (TATE study), as shown in Table 5.

Table 8. Steady-state exposure in pediatric patients with asthma following subcutaneous administration of benralizumab 10 or 30 mg, as per body weight, Q8W

Dose	10 mg			30 mg			30 mg
Body weight	<30 kg	<35 kg	<40 kg	≥30 kg	≥35 kg	≥40 kg	Adults
$AUC_{\tau,ss}$ (μg·day/mL)[a)]	47.7	45.3	43.3	100.7	92.0	84.2	56.5
Ratio to adult exposure	0.85	0.81	0.77	1.80	1.64	1.50	—

a) Median predicted by the population pharmacokinetic model

PMDA's view:

The applicant's explanation that it was difficult to conduct a confirmatory study enrolling pediatric patients with severe asthma aged ≥6 years is understandable. Although Study D3250C00025 (TATE study) was an open-label, uncontrolled study, the efficacy and safety of benralizumab in Japanese pediatric patients with severe asthma aged ≥6 years can be evaluated based on the results of Study D3250C00025 (TATE study) conducted with the above-mentioned patient population and dosage and administration, and in reference to the results of multiregional Study D3250C00018 (CALIMA study), foreign Study D3250C00017 (SIROCCO study), and other studies in adult patients with severe asthma (including non-Japanese children aged ≥12 years).

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.2 Efficacy

The applicant's explanation about the efficacy of benralizumab in pediatric patients with severe asthma aged ≥6 years:

- **Prevention of asthma exacerbations and asthma control**

Table 9 and Table 10 show the rate of asthma exacerbations and the proportion of patients with a reduction from baseline in the number of asthma exacerbations, respectively, in Study D3250C00025 (TATE study) in pediatric patients with severe asthma aged ≥6 years. In patients treated with benralizumab, the number of asthma exacerbations tended to decrease from the baseline value. Table 11 shows changes over time in the proportion of patients with improvement in ACQ-IA, Clinical Gloval Impression of Change (CGIC), and Interviewer-administered Patient Global Impression of Change (PGIC-IA) scores, which are endpoints for asthma symptoms and asthma control. Benralizumab tended to improve the ACQ-IA, CGIC, and PGIC-IA scores from baseline.

4) https://www.cdc.gov/growthcharts/cdc_charts.htm (last accessed on: January 11, 2024)
5) Approved dosage and administration for adults and adolescents aged ≥12 years in the US:
Recommended dose is 30 mg every 4 weeks for the first 3 doses, followed by once every 8 weeks thereafter.

The results of endpoints in the Japanese subpopulation showed tendencies toward a reduction in the rate of asthma exacerbations and improvement in asthma control from baseline in the Japanese subpopulation, as in the overall population, although the number of Japanese subjects assessed in the analysis is limited.

Table 9. Rate of asthma exacerbations (Study D3250C00025 [TATE study])

		Overall population (N = 30)	Japanese subpopulation (N =11)
Overall duration of observation period (patient-years)		27.2	9.44
Any asthma exacerbation			
	Number of exacerbations in the past 1 year (baseline)[a)]	3.4 ± 2.8	4.5 ± 4.2
	Proportion of patients with exacerbations during the study period[b)]	53.3 (16/30)	54.5 (6/11)
	Number of exacerbations during the study period (episodes per patient)[a)]	1.6 ± 2.9	2.7 ± 4.5
	Annualized asthma exacerbation rate (episodes per patient-year)	1.73	3.18
Asthma exacerbation requiring hospitalization			
	Number of exacerbations in the past 1 year (baseline)[a)]	0.5 ± 0.8	0.9 ± 0.9
	Proportion of patients with exacerbations during the study period[b)]	16.7 (5/30)	18.2 (2/11)
	Number of exacerbations during the study period (episodes per patient)[a)]	0.2 ± 0.4	0.2 ± 0.4
	Annualized asthma exacerbation rate (episodes per patient-year)	0.18	0.21

a) Mean ± standard deviation (SD)
b) % (n/N)

Table 10. Proportion of patients with a reduction from baseline in the number of asthma exacerbations (Study D3250C00025 [TATE study])

	Overall population	Japanese subpopulation
Proportion of patients with a reduction from baseline in the number of asthma exacerbations	73.3 (22/30)	63.6 (7/11)
Proportion of patients with ≥50% reduction from baseline in the number of asthma exacerbations	53.3 (16/30)	54.5 (6/11)

% (n/N)

Table 11. Changes over time in the proportion of patients with improvement in ACQ-IA, CGIC, and PGIC-IA scores (Study D3250C00025 [TATE study])

	Week 16	Week 24	Week 32	Week 40	Week 48
Proportion of patients with a reduction of ≥0.5 point from baseline in ACQ-IA score					
Overall population	53.6 (15/28)	53.8 (14/26)	65.5 (19/29)	60.7 (17/28)	59.3 (16/27)
Japanese subpopulation	50.0 (5/10)	60.0 (6/10)	50.0 (5/10)	60.0 (6/10)	60.0 (6/10)
Proportion of patients with improvement in CGIC score					
Overall population	86.2 (25/29)	88.5 (23/26)	92.9 (26/28)	-	100 (29/29)
Japanese subpopulation	81.8 (9/11)	80.0 (8/10)	80.0 (8/10)	-	100 (10/10)
Proportion of patients with improvement in PGIC-IA score					
Overall population	89.7 (26/29)	84.6 (22/26)	86.2 (25/29)	-	89.7 (26/29)
Japanese subpopulation	81.8 (9/11)	70.0 (7/10)	80.0 (8/10)	-	80.0 (8/10)

% (n/N)

To indicate an improvement in the respiratory function, Table 12 shows the change from baseline in pre-bronchodilator FEV_1 in Study D3250C00025 (TATE study). The respiratory function tended to slightly improve from baseline at Week 48 in both the overall population and the Japanese subpopulation. The extent of improvement was smaller in the Japanese subpopulation than the overall population, possibly because (1) the number of Japanese subjects assessed was limited and (2) there was only little room for improvement of respiratory function in the Japanese subpopulation (baseline $\%FEV_1$: 89.6 ± 18.2 in the overall population and 94.6 ± 10.6 in the Japanese subpopulation).

Table 12. Change from baseline in pre-bronchodilator FEV_1 (L) (Study D3250C00025 [TATE study])

	Overall population	Japanese subpopulation
Baseline	1.668 ± 0.439 (29)	1.784 ± 0.512 (11)
Week 48	1.817 ± 0.540 (29)	1.758 ± 0.568 (10)
Change from baseline	0.200 ± 0.431 (28)	0.060 ± 0.386 (10)

Mean ± SD (N)

- **Efficacy of benralizumab by subgroup**

Table 13 shows the proportion of patients with a reduction from baseline in the number of asthma exacerbations by dose of ICS maintenance therapy (medium- or high-dose) and by baseline blood eosinophil count (≥150/μL and <300/μL, or ≥300/μL) in Study D3250C00025 (TATE study). Although the results should be interpreted carefully because of the limited number of subjects assessed, there were no clear differences by dose of ICS maintenance therapy or baseline blood eosinophil count.

Table 13. Proportion of patients with a reduction from baseline in the number of asthma exacerbations by subgroup according to patient characteristics (Study D3250C00025 [TATE study])

Overall population	Dose of ICS maintenance therapy		Baseline blood eosinophil count	
	Medium-dose	High-dose	≥150/μL and <300/μL	≥300/μL
73.3 (22/30)	71.4 (5/7)	77.3 (17/22)	77.8 (7/9)	71.4 (15/21)

% (n/N)

Given that the results of multiregional Study D3250C00018 (CALIMA study) and foreign Study D3250C00017 (SIROCCO study) in adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) have demonstrated the efficacy of benralizumab in patients with asthma uncontrolled with high-dose ICS and LABA, benralizumab can be expected to have efficacy in the treatment of Japanese pediatric patients with severe asthma aged ≥6 years.

PMDA's view:

In Study D3250C00025 (TATE study) in pediatric patients with severe asthma aged ≥6 years, the rate of asthma exacerbations tended to decrease and the endpoints for asthma control tended to improve after treatment with benralizumab, compared with before the start of treatment. The trends in the Japanese subpopulation were consistent with those in the overall population. The analyses of pharmacokinetic and pharmacodynamic data in Study D3250C00025 (TATE study) showed no substantial differences in the trend toward a reduction in blood eosinophil count between children aged ≥6 years and adults [see Section 6.R.1].

The pathogenesis of asthma is generally similar in adults and children. Given that the efficacy of benralizumab in adult patients with severe asthma, including Japanese patients, has been demonstrated in multiregional Study D3250C00018 (CALIMA study) and foreign Study D3250C00017 (SIROCCO study) conducted in adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) (see the Review Report of "Fasenra Subcutaneous Injection 30 mg Syringe" dated November 15, 2017), benralizumab can be expected to have efficacy in the treatment of Japanese pediatric patients with severe asthma aged ≥6 years.

The eligibility of patients for benralizumab treatment is discussed in Section 7.R.4.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.3 Safety

The applicant's explanation about the safety of benralizumab in pediatric patients with severe asthma aged ≥6 years based on the results of Study D3250C00025 (TATE study) and pooled data from Japanese and foreign clinical studies in adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) (pooled phase III adult population):

The safety of benralizumab in Study D3250C00025 (TATE study) is described in Section 7.1. There are no particular safety concerns regardless of the dose.

Table 14 shows a summary of the safety of benralizumab in Study D3250C00025 (TATE study) and the pooled population of phase III studies in adults as well as the incidence of adverse events of special interest identified based on the pharmacological action of benralizumab and disease characteristics.

Although the results should be interpreted carefully because of different designs (open-label or blind) and scales of these studies, there were no significant differences in the incidence of adverse events between pediatric patients with severe asthma aged ≥6 years who received benralizumab (overall population) and adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) who received benralizumab.

There were no significant differences in the incidence of adverse events of special interest, except for infections and hypersensitivity, between pediatric patients with severe asthma aged ≥6 years who received benralizumab (overall population) and adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) who received benralizumab. The incidence of infections and hypersensitivity tended to be high in pediatric patients with severe asthma aged ≥6 years, but all of the reported events were non-serious.

Although the number of Japanese pediatric patients with severe asthma enrolled in Study D3250C00025 (TATE study) was limited, the results of the study suggested no clear differences in the safety profile of benralizumab between the overall population and the Japanese subpopulation.

Table 14. Summary of the safety of benralizumab (safety analysis set)

	Study D3250C00025 (TATE study) (Patients with severe asthma aged ≥6 and <15 years)		Pooled phase III population[a] (Adult patients with severe asthma [including non-Japanese pediatric patients aged ≥12 years])		
	Overall population	Japanese subpopulation	30 mg Q8W[b]	30 mg Q4W	Placebo
N	30	11	822	841	847
Total exposure period (patient-years)	29.4	10.1	799.2	830.2	837.6
Summary of adverse events					
Any adverse event	24 (80.0) 81.7	11 (100) 108.5	605 (73.6) 75.7	621 (73.8) 74.8	661 (78.0) 78.9
Serious adverse events	5 (16.7) 17.0	2 (18.2) 19.7	95 (11.6) 11.9	97 (11.5) 11.7	119 (14.0) 14.2
Adverse events leading to treatment discontinuation	0	0	18 (2.2) 2.3	18 (2.1) 2.2	8 (0.9) 1.0
Adverse drug reactions	4 (13.3) 13.6	2 (18.2) 19.7	118 (14.4) 14.8	106 (12.6) 12.8	78 (9.2) 9.3
Death	0	0	4 (0.5) 0.5	5 (0.6) 0.6	3 (0.4) 0.4
Adverse events of special interest					
Infections	20 (66.7) 68.1	10 (90.9) 98.7	423 (51.5) 52.9	451 (53.6) 54.3	480 (56.7) 57.3
Serious infections	0	0	21 (2.6) 2.6	12 (1.4) 1.5	21 (2.5) 2.5
Parasitic infections	0	0	0	0	1 (0.1) 0.1
Helminth infections	0	0	0	0	0
Malignancies	0	0	1 (0.1) 0.1	3 (0.4) 0.4	1 (0.1) 0.1
Hypersensitivity	6 (20.0) 20.4	4 (36.4) 39.5	89 (10.8) 11.1	95 (11.3) 11.4	97 (11.5) 11.6
Serious hypersensitivity	0	0	4 (0.5) 0.5	4 (0.5) 0.5	3 (0.4) 0.4
Injection site reaction	1 (3.3) 3.4	1 (9.1) 9.9	18 (2.2) 2.3	27 (3.2) 3.3	16 (1.9) 1.9

Top, n (%); Bottom, number of events per 100 patient-years adjusted by the total exposure period

a) Study D3250C00018 (CALIMA study) and Study D3250C00017 (SIROCCO study)

b) With an additional dose at 4 weeks after the first dose.

In some foreign countries or regions, benralizumab has been approved in patients including pediatric patients with severe asthma aged ≥12 years. In addition, no new safety concerns, including the safety of benralizumab in pediatric patients with severe asthma, have been identified in the periodic benefit-risk assessment report (estimated cumulative exposure of 205,204 patient-years for the period from November 14, 2021 to November 13, 2022) or the post-marketing safety data on benralizumab collected in and outside Japan (as of [redacted], 20[redacted]).

In view of the above, the submitted data have so far suggested no clear concerns about the safety of benralizumab in pediatric patients with severe asthma aged ≥6 years, compared with the safety profile of benralizumab in the treatment of adult patients with severe asthma, which is the approved indication.

PMDA's view:

The submitted data have so far suggested no clear concerns about the safety of benralizumab in pediatric patients with severe asthma aged ≥6 years, compared with the safety profile of benralizumab for the approved indication (the treatment of adult patients with severe asthma), and the safety of benralizumab in pediatric patients with severe asthma aged ≥6 years is acceptable. Therefore, the same safety measures as those taken for benralizumab used for the approved indication i.e., severe asthma in adults (e.g., ensuring that benralizumab

is administered by physicians with expertise in the treatment of the disease for which the drug is indicated), should also be implemented continuously, as well as close monitoring of patients for known adverse drug reactions. However, since the number of Japanese pediatric patients with severe asthma assessed in Study D3250C00025 (TATE study) is very limited, the applicant should continuously collect information on the safety of benralizumab in Japanese pediatric patients with severe asthma through post-marketing surveillance or by other means and should provide the obtained information to healthcare professionals as appropriate.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about the clinical positioning of benralizumab:

JPGL 2023 recommends the use of either medium-dose ICS/LABA or high-dose ICS as standard therapy in Step 4 for pediatric patients with severe asthma aged ≥6 years, and also advises physicians to consider the use of add-on leukotriene receptor antagonists (LTRA) or theophylline. If the disease cannot be controlled with these treatments, the guideline recommends considering the use of biologics, high-dose ICS/LABA, a higher dose of ICS, or systemic corticosteroids. However, the use of corticosteroids may cause systemic adverse drug reactions and growth disorder; therefore, the guideline states that high-dose ICS should not be used in children aimlessly over a long period of time, but should be administered under the supervision of physicians with expertise in the treatment of asthma in children while assessing adverse drug reactions related to adrenal function, etc.

Although the results of Study D3250C00025 (TATE study) which was an open-label, uncontrolled study should be interpreted carefully, the efficacy of benralizumab was demonstrated, regardless of the dose (medium or high) of ICS maintenance therapy [see Section 7.R.2], in pediatric patients with intractable severe asthma uncontrolled with conventional therapy and its safety is considered acceptable in such patients [see Section 7.R.3]. In view of the above, benralizumab should be used as an add-on therapy in pediatric patients with severe asthma who have exacerbations despite conventional therapy corresponding to Step 4 treatment (medium- or high-dose ICS in combination with an additional controller medication).

PMDA's view:

Multiregional Study D3250C00018 (CALIMA study) and foreign Study D3250C00017 (SIROCCO study) in adult patients with severe asthma (including non-Japanese pediatric patients aged ≥12 years) demonstrated the efficacy of benralizumab in the treatment of patients with asthma uncontrolled with high-dose ICS and LABA. Benralizumab is positioned as an add-on therapy to high-dose ICS+LABA and other medications in the treatment of asthma in adults. Given that the present application is based on a development plan in reference to the above-mentioned clinical study results [see Section 7.R.1] and in view of the results of Study D3250C00025 (TATE study) and the current treatment algorithm for asthma in children, the clinical positioning of benralizumab for the treatment of asthma in children is the same as that in adults, i.e., an add-on option for pediatric patients with severe asthma uncontrolled with combination therapies such as high-dose ICS+LABA in Step 4 recommended in the guideline.

Before the start of treatment with benralizumab in pediatric patients with severe asthma, physicians should appropriately determine the eligibility of patients for the treatment after carefully assessing the expected benefits and risks of benralizumab in individual pediatric patients, as in adult patients. Benralizumab should be administered by physicians with expertise in the treatment of bronchial asthma. In addition, physicians with a thorough understanding of the mechanism of action of benralizumab and the relationship between baseline blood eosinophil count and the efficacy of benralizumab should determine the eligibility of patients for the treatment, taking the patient's blood eosinophil count into consideration. To this end, the applicant should continue to advise physicians to do so. In principle, benralizumab should be used in combination with controller medications such as ICS, and the dose reduction of controller medications during treatment with benralizumab should be carefully determined.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.5 Dosage and administration

PMDA's view:

On the basis of the data submitted and the reviews in Sections 6.R.1, 7.R.1, 7.R.2, and 7.R.3, and given that the efficacy of benralizumab in pediatric patients with severe asthma aged ≥6 years was demonstrated with the dosage regimen used in Study D3250C00025 (TATE study) and that its safety is acceptable, the proposed dosage and administration of benralizumab for pediatric patients with severe asthma aged ≥6 years can be accepted as it is.

Proposed dosage and administration: The usual dosage for children aged ≥12 years and children aged ≥6 and <12 years (weighing ≥35 kg) is 30 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

The usual dosage for children aged ≥6 and <12 years (weighing <35 kg) is 10 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

The above PMDA's conclusion will be discussed at the Expert Discussion.

7.R.6 Post-marketing investigations and safety measures

The applicant's explanation:

There are currently no new particular concerns about the safety profile of benralizumab in pediatric patients with severe asthma aged ≥6 years, compared with that for the approved indication (severe asthma in adults). However, since the number of subjects assessed is limited, the applicant will conduct post-marketing

surveillance to confirm the safety, etc. of benralizumab in the clinical setting and continue the current safety measures for adult patients with severe asthma.

PMDA's view:
As discussed in Section 7.R.3, there are currently no new concerns about the safety profile of benralizumab, compared with that for the approved indication (severe asthma in adults). The safety of benralizumab in pediatric patients with severe asthma aged ≥6 years is acceptable. However, since the number of Japanese pediatric patients with severe asthma assessed in clinical studies is very limited, the applicant should continue to investigate the safety, etc. of benralizumab through post-marketing surveillance.

Prior to the use of benralizumab in pediatric patients with severe asthma, the same safety measures as those taken for benralizumab used for the approved indication (severe asthma in adults) should be taken (e.g., ensuring that benralizumab is administered by physicians with expertise in the treatment of the disease for which the drug is indicated).

The above PMDA's conclusion and additional safety measures will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and the Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The data for partial change application and new drug application were subjected to document-based inspection and data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The data for partial change application and new drug application (CTD 5.3.4.2.1) were subjected to on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that benralizumab has efficacy in the treatment of severe asthma in children aged ≥6 years, and that benralizumab has acceptable safety in view of its benefits. Benralizumab is clinically meaningful because it offers a new treatment option for pediatric patients with severe asthma aged ≥6 years. The safety, etc. of benralizumab in Japanese pediatric patients with severe asthma in the clinical setting should be further investigated through post-marketing surveillance.

PMDA has concluded that benralizumab may be approved if the comments of the Expert Discussion do not indicate any particular problems with benralizumab.

10. Others

Efficacy endpoints in clinical studies of benralizumab are defined as shown below.

Item	Definition
Asthma exacerbation	Worsening of asthma meeting at least one of the following conditions: [1] Use of systemic corticosteroids (or a temporary increase in the dose of oral corticosteroids) [2] Emergency room or urgent outpatient care that requires systemic corticosteroids [3] Hospitalization due to asthma
ACQ-IA score	Asthma control questionnaire consisting of questions on asthma symptoms (5 items; nocturnal awakenings, morning symptoms, activity limitation, shortness of breath, and wheezing) and reliever use (1 item), each of which is scored on a 7-point scale from 0 (completely controlled) to 6 (severely uncontrolled).
CGIC and PGIC-IA scores	Improvement rating assessed by the investigator (CGIC score) or the patient (PGIC-IA score), compared with the health condition at study initiation, which is scored on a 7-point scale of 1 (Very much improved), 2 (Much improved), 3 (Minimally improved), 4 (No change), 5 (Minimally worse), 6 (Much worse), and 7 (Very much worse).

Events listed in Section 7.R.3 are defined as shown below.

Item	Definition
Infections	“Infections and infestations” (System Organ Class [SOC])
Serious infections	Serious adverse events coded to “infections and infestations” (SOC)
Parasitic infections	“Ectoparasitic disorders,” “helminthic disorders,” and “protozoal infectious disorders” (High Level Group Terms [HLGT])
Helminth infections	“Helminthic disorders” (HLGT)
Malignancies	“Malignant tumours” (Standardised MedDRA Queries [SMQ])
Hypersensitivity	“Hypersensitivity” (SMQ, narrow)
Serious hypersensitivity	Serious adverse events coded to “hypersensitivity” (SMQ, narrow)
Injection site reaction	“Injection site reaction” (High Level Term [HLT])

Review Report (2)

February 5, 2024

Product Submitted for Approval

Brand Name	(a) Fasenra Subcutaneous Injection 30 mg Syringe
	(b) Fasenra Subcutaneous Injection 10 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	April 26, 2023

List of Abbreviations

See Appendix.

1. Content of the Review

The comments made during the Expert Discussion and the subsequent review conducted by PMDA are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations, etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions, etc. by the Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Development plan, efficacy, clinical positioning, and dosage and administration

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the development plan, efficacy, clinical positioning, and dosage and administration of benralizumab described in the Review Report (1).

In view of the discussions at the Expert Discussion, PMDA has come to the following conclusion concerning the use of benralizumab in pediatric patients with severe asthma aged ≥6 years: benralizumab should be administered as an add-on therapy to pediatric patients who have asthma exacerbations requiring systemic corticosteroid treatment despite therapy with high-dose ICS in combination with an additional controller medication, as in adult patients. PMDA instructed the applicant to modify the precautionary statements in the Precautions for Indications section of the package insert so that the same precautions as those for adults would be taken for children. The applicant responded that the instruction would be addressed appropriately.

1.2 Safety and post-marketing investigations and safety measures

At the Expert Discussion, the expert advisors supported the PMDA's conclusions concerning the safety of benralizumab and post-marketing investigations and safety measures described in the Review Report (1), and raised the following comments:

- Given that the significance of blood eosinophil count for a diagnosis of asthma in children is not clear, benralizumab should be administered by physicians with expertise in the treatment of bronchial asthma

who can appropriately determine the eligibility of patients for benralizumab treatment after properly understanding the patient's condition taking the patient characteristics and laboratory test results (comorbidities such as allergic rhinitis, atopic dermatitis, or urticaria, as well as blood eosinophil count, IgE level, etc.) into consideration.

- The applicant should collect information on the safety of benralizumab in the clinical setting, particularly information on the incidence of parasitic infections that are expected to occur in relation with its mechanism of action, through post-marketing surveillance.

In view of the review in Section "7.R.6 Post-marketing investigations and safety measures" of the Review Report (1) and the discussions at the Expert Discussion, PMDA instructed the applicant again to continue to appropriately implement the same safety measures as those taken for benralizumab used for the approved indication, i.e., severe asthma in adults (e.g., appropriately providing physicians with information on the eligibility of patients for benralizumab treatment as well as advising the physicians to ensure that benralizumab is administered by physicians with expertise in the treatment of bronchial asthma), so that benralizumab will be appropriately used in pediatric patients with severe asthma aged ≥6 years. PMDA has also concluded that the current risk management plan (draft) of the product should include the safety specification shown in Table 15, and that the applicant should conduct the additional pharmacovigilance activities and risk minimization activities shown in Table 16. PMDA instructed the applicant to conduct post-marketing surveillance that can cover these matters.

Table 15. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious hypersensitivity	• Serious infections • Parasitic infections • Malignancies • Immunogenicity	None
Efficacy specification		
None		

(No changes)

Table 16. Summary of additional pharmacovigilance activities, efficacy surveys and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy surveys and studies	Additional risk minimization activities
• Early post-marketing phase vigilance (bronchial asthma in children) • Specified use-results survey (long-term) • Specified use-results survey (bronchial asthma in children)	None	• Provision of information collected through early post-marketing phase vigilance (bronchial asthma in children) • Preparation and provision of materials for healthcare professionals (proper selection of patients eligible for treatment)

(Underline denotes additions.)

The applicant's explanation:

As shown in Table 17, the applicant plans to conduct a specified use-results survey in pediatric patients with severe asthma aged ≥6 years to evaluate the safety and efficacy of benralizumab in the clinical setting.

Table 17. Outline of specified use-results survey (draft)

Objective	To collect and evaluate information on the safety and efficacy of benralizumab in the clinical setting.
Survey method	Central registry
Population	Pediatric patients with severe asthma aged ≥6 and <15 years
Observation period	1 year
Planned sample size	40 patients (for safety analysis)
Main survey items	• Safety specification: Serious hypersensitivity, serious infections, parasitic infections, malignancies • Patient characteristics (age, sex, body weight, disease duration, severity, past history/concurrent diseases, etc.) • Concomitant drugs/therapies • Status of treatment with benralizumab • Adverse events • Efficacy

PMDA has accepted the applicant's responses and considers that obtained information should be provided to healthcare professionals in an appropriate and prompt manner.

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication at the dosage and administration shown below, with the following condition. Since the present application has been submitted for a drug with a new dosage, the reexamination period is 4 years for the dosage and administration proposed in the present application. The 10 mg formulation of the product is classified as a biological product, and the drug product is classified as a powerful drug.

Indication

Bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)

(No changes)

Dosage and Administration

(a) The usual dosage for adults, children aged ≥12 years, and children aged ≥6 and <12 years (weighing ≥35 kg) is 30 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(b) The usual dosage for children aged ≥6 and <12 years (weighing <35 kg) is 10 mg of benralizumab (genetical recombination) administered by subcutaneous injection every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

(No changes from the proposed dosage and administration)

Approval Condition

The applicant is required to develop and appropriately implement a risk management plan.

Appendix

List of Abbreviations

ACQ-IA	Interviewer-administered asthma control questionnaire
ADA	Anti-drug antibody
$AUC_{\tau,ss}$	Area under the time-concentration curve over a dosing interval at steady-state
Benralizumab	Benralizumab (Genetical Recombination)
CGIC	Clinical global impression of change
$C_{max,ss}$	Maximum concentration at steady state
Fasenra	Fasenra Subcutaneous Injection 30 mg Syringe and Fasenra Subcutaneous Injection 10 mg Syringe
FEV_1	Forced expiratory volume in 1 second
$\%FEV_1$	Percentage of FEV_1 to predicted normal value
FVC	Forced vital capacity
GINA	Global initiative for asthma
HLGT	High level group term
HLT	High level term
ICS	Inhaled corticosteroid
Ig	Immunoglobulin
IL-5	Interleukin-5
JGL 2021 (or 2018)	Asthma Prevention and Management Guidelines 2021 (or 2018), edited by the Japanese Society of Allergology
JPGL 2023 (or 2017)	Japanese Pediatric Guidelines for the Treatment and Management of Asthma 2023 (or 2017), edited by the Japanese Society of Pediatric Allergy and Clinical Immunology
LABA	Long-acting β_2 agonist
LTRA	Leukotriene receptor antagonist
OCS	Oral corticosteroid
PGIC-IA	Interviewer-administered patient global impression of change
Q8W	Once every 8 weeks
SMQ	Standardised MedDRA Queries
SOC	System organ class
$t_{1/2}$	Elimination half-life
PMDA	Pharmaceuticals and Medical Devices Agency

* Non-proprietary names of biological products are described without the term “(genetical recombination).”