Report on the Deliberation Results

December 5, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Fasenra Subcutaneous Injection 30 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination) (JAN*)
Applicant	AstraZeneca K.K.
Date of Application	February 22, 2017

Results of Deliberation

In its meeting held on November 24, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Condition of Approval

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

**Japanese Accepted Name (modified INN)*

Review Report

November 15, 2017
Pharmaceuticals and Medical Devices Agency

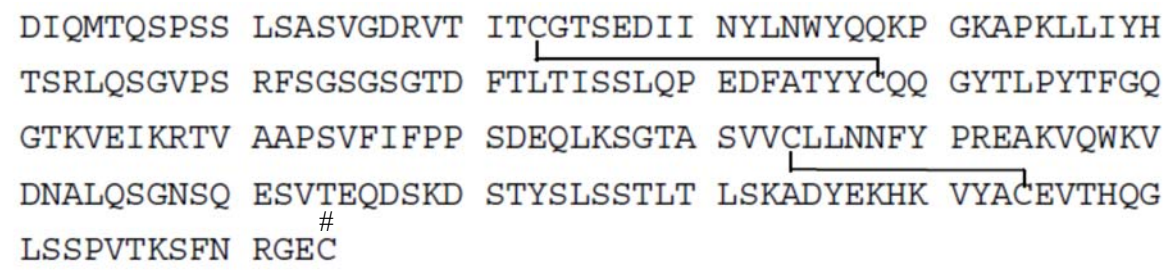
The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Fasenra Subcutaneous Injection 30 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	February 22, 2017
Dosage Form/Strength	Injection: Each syringe contains 30 mg of Benralizumab (Genetical Recombination).
Application Classification	Prescription drug (1) Drug with a new active ingredient
Definition	Benralizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-5 receptor α subunit monoclonal antibody and framework regions and constant regions derived from human IgG1. Benralizumab is produced in glycoprotein 6-α-L-fucosyltransferase-deficient Chinese hamster ovary cells. Benralizumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 451 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

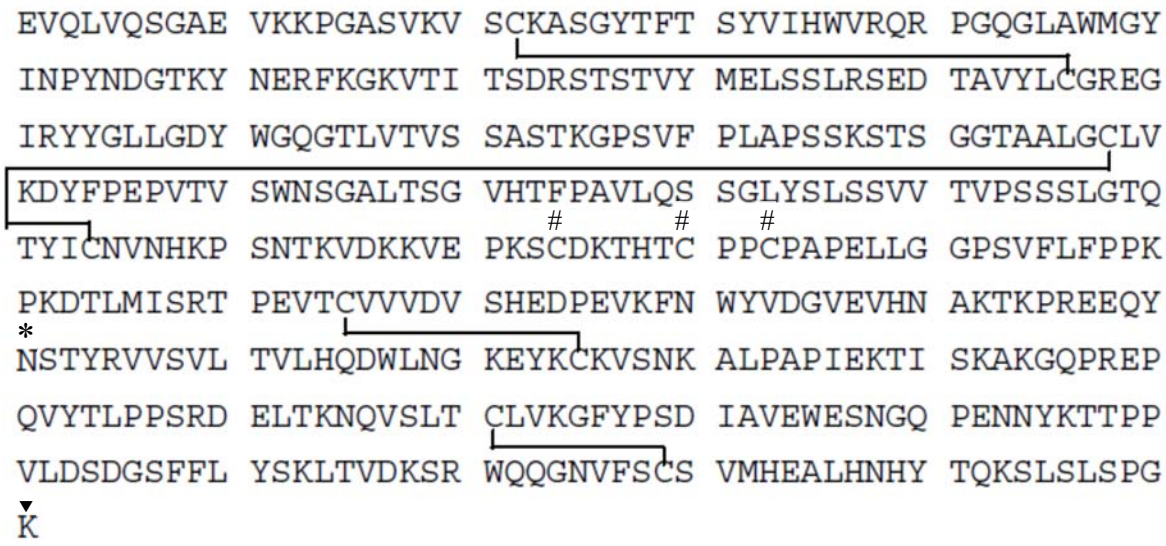
Structure

Amino acid sequence:

Light chain

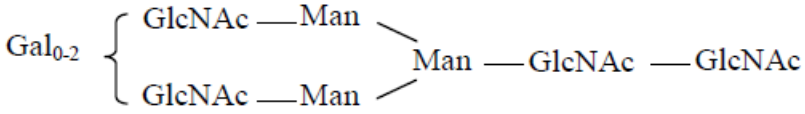


Heavy chain



Glycosylation (*):	H-chain N301
Partial processing (▼):	H-chain K451
Intra-chain disulfide bond (solid line):	L-chain C23-C88, C134-C194 H-chain C22-C96, C148-C204, C265-C325, C371-C429
Inter-chain disulfide bond (#):	L-chain C214 - H-chain C224, H-chain C230 - H-chain C230, H-chain C233 - H-chain C233

Estimated structure of main glycan



Gal: Galactose, GlcNAc: *N*-acetylglucosamine, Man: Mannose

Molecular formula: (Benralizumab) $C_{6492}H_{10060}N_{1724}O_{2028}S_{42}$ (protein moiety, L-chain × 2 + H-chain × 2)
(L-chain × 1) $C_{1035}H_{1603}N_{275}O_{338}S_{6}$
(H-chain × 1) $C_{2211}H_{3431}N_{587}O_{676}S_{15}$

Molecular weight: 146,054.40 (protein moiety, L-chain × 2 + H-chain × 2)

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 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 and dosage and administration shown below, with the following condition. The long-term safety of the product in clinical settings, including the occurrence of serious infection, should be further investigated in a post-marketing surveillance, etc., and resultant findings should be communicated to healthcare professionals and patients.

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

Dosage and Administration
The usual adult dosage 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.

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

Attachment

Review Report (1)

October 20, 2017

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

Product Submitted for Approval

Brand Name	Alrispo Subcutaneous Injection 30 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	February 22, 2017
Dosage Form/Strength	Injection: Each syringe contains 30 mg of Benralizumab (Genetical Recombination).
Proposed Indication	Bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)

Proposed Dosage and Administration

The usual adult dosage 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.

Table of Contents

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 "Alrispo Subcutaneous Injection 30 mg Syringe," is a humanized anti-human interleukin-5 receptor α subunit (IL-5Rα) monoclonal antibody of immunoglobulin G1 (IgG1) subclass discovered by Kyowa Hakko Kirin Co., Ltd. (formerly known as Kyowa Hakko Kogyo Co., Ltd.) and developed by Kyowa Hakko Kirin Co., Ltd., BioWa, Inc. (the US), MedImmune, LLC (the US), and the applicant (AstraZeneca K.K.).

Bronchial asthma is a chronic inflammation disease of the respiratory tract, characterized by variable airway obstructions (wheezing, dyspnea) and coughing (the Asthma Prevention and Management Guideline 2015 [hereinafter referred to as "JGL" or Japanese guideline]). In Japan, an estimated 1.177 million people have bronchial asthma (Summary of Patient Survey, 2014, issued by the Health Statistics Office, Vital, Health and Social Statistics Division, Ministry of Health, Labour and Welfare). Guidelines published in and outside of Japan recommend inhaled corticosteroid (ICS) therapy for the treatment of bronchial asthma as standard therapy. The guidelines also advise the use of add-on therapy with long-acting β-2 agonists (LABA), long acting muskarinic antagonists (LAMA), leukotriene receptor antagonists, or extended-release theophylline preparations according to the severity. The use of anti-Ig E antibodies, anti-interleukin-5 (IL-5) antibodies, and oral corticosteroids (OCS) is recommended for patients who have inadequately responded to these therapies (the Asthma Prevention and Management Guideline 2015 and the Global Initiative for Asthma 2016).

Increased blood eosinophil counts in patients with asthma are related to increased severity, asthma exacerbation, decreased pulmonary function, and death (*Eur Respir Rev.* 2013;22:251-7, *J Asthma Allergy.* 2016;9:1-12, etc.), while IL-5 is a cytokine known to regulate differentiation, proliferation, and activation of eosinophils (*J Exp Med.* 1995;182:1169-74, *Mol Med.* 1996;2:334-48, etc.). Benralizumab binds to IL-5Rα, which is a subunit of IL-5 receptor (IL-5R), and thereby induces antibody-dependent cellular cytotoxicity (ADCC)-mediated apoptosis of IL-5R-expressed eosinophils. Being expected to suppress inflammation associated with increased eosinophil counts, benralizumab has been therefore developed as a drug to treat bronchial asthma.

In foreign countries, the clinical development of benralizumab for the treatment of bronchial asthma was initiated in November 2006. As of October 2017, benralizumab is under review in the US and Europe.

In Japan, the clinical development of benralizumab for the treatment of bronchial asthma was initiated in [redacted] 20[redacted] when a foreign phase II clinical study was ongoing. A marketing application has recently been filed, based on the data from multi-regional clinical studies involving Japanese participants.

The brand name was changed during review [redacted] overseas. In Japan, it was also changed to "Fasenra Subcutaneous Injection 30 mg Syringe" after submission of the application.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrates

A hybridoma cell line was prepared by fusing [redacted] cells to [redacted] cells that had been immunized with [redacted]. Optimization such as humanization based on nucleic acid sequences obtained from the hybridoma cell line has conducted to determine variable regions in the light and heavy chains of anti-human IL-5Rα monoclonal antibody that strongly inhibits binding of [redacted] to [redacted]. The gene expression construct was assembled by inserting [redacted]. The gene expression construct was transfected into [redacted] knockout Chinese hamster ovary (CHO) cells. A clone suitable for production of benralizumab was chosen from the resultant cell line and then used to prepare the master cell bank (MCB) and working cell bank (WCB).

In accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines, the MCB, WCB and cells at the limit of *in vitro* cell age used for production (CAL) were subjected to characterization and purity tests. Results confirmed genetic stability during manufacturing. The tests performed did not detect viruses or non-viral adventitious agents except endogenous retrovirus-like particles that are commonly found in rodent cells.

The MCB and WCB are stored in [redacted]. Although regeneration of MCB is not planned, WCB is to be generated where necessary.

2.1.2 Manufacturing process

Manufacturing process of the drug substance consists of [redacted], main culture, harvest, [redacted] viral inactivation, [redacted] viral removal, [redacted], filling, and [redacted] as well as testing and storage.

Identified critical steps are [redacted].

The manufacturing process of the drug substance has been validated at a commercial production scale.

2.1.3 Safety evaluation of adventitious agents

The manufacturing process of the drug substance involves no biological materials other than the CHO cell lines that are host cells. Although trypsin derived from porcine pancreas is used in manufacture of [redacted] contained in medium for preparation of the WCB, the raw material conforms to the Standard for Biological Ingredients.

The MCB, WCB, and CAL were subjected to purity tests [see Section 2.1.1]. In addition, pre-harvest, unprocessed bulks manufactured at a commercial production scale were subjected to tests for bioburden,

mycoplasma, and *in vitro* adventitious viruses, and transmission electron microscopy. These tests did not detect contamination with viruses or non-viral adventitious agents. Furthermore, in-process control tests specified for pre-harvest, unprocessed bulks include tests for bioburden, mycoplasma, and *in vitro* adventitious viruses.

In the purification process, a viral clearance study was performed using model viruses. The results demonstrated that the purification process showed the certain level of viral-clearance performance (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Pseudorabies virus	Reovirus type 3	Mouse minute virus
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus inactivation	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Virus filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall reduction factor	>15.54[b)]	>19.78[b)]	>8.25[b)]	10.29

[redacted]

b)

[redacted] Overall reduction factor [redacted]

2.1.4 Manufacturing process development (comparability)

Main changes made to the manufacturing process in the drug substance development stage are described below (relevant manufacturing processes are referred to as Processes 1, 1b, and 2, and the proposed process). Clinical studies mainly used the formulations manufactured using the drug substance manufactured by Process 2 and the proposed manufacturing process.

- Process 1 → Process 1b: Addition of [redacted] step and [redacted] step
- Process 1b → Process 2: Changes in [redacted], [redacted], and [redacted] ([redacted] and [redacted], [redacted], etc.)
- Process 2 → the proposed manufacturing process: Changes in [redacted], [redacted], and [redacted] steps ([redacted] and [redacted], [redacted], etc.)

When a change was made to the manufacturing process, the comparability of quality attributes was assessed to confirm that the pre- and post-change drug substance batches were comparable.

The manufacturing process was developed using a quality by design (QbD) approach [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization analyses performed are shown in Table 2.

Table 2. Characterization items

Test items	
Primary/higher order structures	Amino acid sequence, [redacted], disulfide bond, [redacted], secondary structure, tertiary structure, carbohydrate-deficient form
Physicochemical properties	Molecular weight, [redacted]
Carbohydrate structure	[redacted]
Biological properties	IL-5Rα binding activity
	FcγR binding activity ([redacted]), C1q binding activity, FcRn binding activity
	ADCC activity, CDC activity

Tests for biological properties by surface plasmon resonance have confirmed that benralizumab has binding affinity for its antigen (IL-5Rα), Fc gamma receptor (FcγR) ([redacted]), complement component 1, q subcomponent (C1q), and neonatal Fc receptor (FcRn). Tests using [redacted] and [redacted]-expressed [redacted] cell line as effector cells and [redacted] cell line as target cells has confirmed that benralizumab induces ADCC activity in a concentration-dependent manner. Tests using human serum containing complement and human eosinophils as target cells has confirmed that benralizumab does not exhibit complement-dependent cytotoxicity (CDC) activity [see Section 3.1.3]. In addition, the neutralizing activity of benralizumab against IL-5/IL-5Rα has been confirmed by a pharmacology study which evaluated the inhibition of IL-5-dependent cell proliferation [see Section 3.1.2].

2.1.5.2 Product-related substances/Product-related impurities

Based on characterization analysis results shown in Section 2.1.5.1, [redacted], [redacted], [redacted], and [redacted] were identified as product-related substances. In addition, [redacted], Substance A ([redacted]), Substance B, Substance C, Substance D ([redacted]), [redacted], and [redacted] were identified as product-related impurities. Substance A, Substance B, Substance C, and Substance D are controlled by specifications for both drug substance and drug product. [redacted], and [redacted] are controlled in the course of manufacturing process.

2.1.5.3 Process-related impurities

Host cell protein, host cell DNA, [redacted], and [redacted] were identified as process-related impurities. All of the process-related impurities have been confirmed to be adequately removed in the manufacturing process. In addition, Substance E is controlled by the specifications for the drug substance.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, description, identification ([redacted]), pH, purity (sodium dodecyl sulfate [SDS] gel electrophoresis [non-reduced, reduced]

and [redacted]), capillary isoelectric focusing (cIEF), Substance E, bacterial endotoxins, microbial limits, biological activity (ADCC activity), and assay (ultraviolet-visible spectrophotometry).

2.1.7 Stability of drug substance

The main stability studies of the drug substance are shown in Table 3.

Table 3. Summary of main stability studies of the drug substance

Study	Number of batches[a)]	Storage condition	Studied period	Storage form
Long-term	5	−40 ± [redacted]°C	24 months[b)]	[redacted]
Accelerated	5	5 ± [redacted]°C	3 months	
Stress	5	25 ± [redacted]°C/60 ± [redacted]% RH	1 month	

a) Drug substance manufactured through the proposed manufacturing process
b) The study lasted [redacted] months for 2 batches. The stability study is ongoing and will continue for [redacted] months.

Both long-term testing and accelerated testing showed no clear changes in quality attributes throughout the testing period.

The stress testing showed a decreasing trend in [redacted] and an increasing trend in [redacted], and a decreasing trend in [redacted] and an increasing trend in [redacted].

Based on the above, a shelf life of 24 months has been proposed for the drug substance when stored at [redacted]°C to [redacted]°C in [redacted].

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is supplied as each syringe containing 30 mg of benralizumab (genetical recombination) in 1.0 mL of an aqueous solution for injection. The drug product contains the following excipients: L-histidine, L-histidine hydrochloride hydrate, trehalose hydrate, polysorbate 20, and water for injection. The drug product is a combination product in which a needle safety guard is attached to a prefilled syringe with a needle to prevent needle-stick injury after its use.

2.2.2 Manufacturing process

Manufacturing process of the drug product consists of [redacted]; [redacted]; [redacted]; [redacted]; aseptic filtration; [redacted]; and assembly, labeling, packaging, storage, and testing steps. Identified critical steps are [redacted], [redacted], and [redacted].

The manufacturing process of the drug product has been validated at a commercial production scale.

2.2.3 Manufacturing process development

Main changes made to the manufacturing process in the drug product development stage are as follows (relevant manufacturing processes are referred to as Processes 1, 1b, and 2, and the proposed manufacturing process). Clinical studies mainly used the formulations manufactured by Process 2 and the proposed manufacturing process.

- Process 1 → Process 1b: Changes in [redacted], [redacted], [redacted], and [redacted]
- Process 1b → Process 2: Changes in [redacted] (from [redacted] to [redacted]), [redacted], and [redacted]
- Process 2 → the proposed manufacturing process: Changes in [redacted], [redacted] (from [redacted] to [redacted]), [redacted], and [redacted]

When a change was made to the manufacturing process, the comparability of quality attributes was assessed to confirm that the pre- and post-change drug product batches were comparable.

The manufacturing process was developed using a QbD approach [see Section 2.3].

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, description, identification ([redacted]), osmolar ratio, pH, purity (SDS gel electrophoresis [non-reduced, reduced] and [redacted]), cIEF, withdrawable volume, foreign insoluble matters, insoluble particulate matters, sterility, bacterial endotoxins, [redacted], functional test for prefilled syringes, biological activity (ADCC), and assay (ultraviolet-visible spectrophotometry).

2.2.5 Stability of drug product

The major stability studies of the drug product are shown in Table 4.

Table 4. Summary of main stability studies of the drug product

Study	Number of batches[a)]	Storage condition	Studied period	Storage form
Long-term	3	5 ± 3°C	24 months[b)]	Glass syringe with butyl bromide rubber stopper[c)]
Accelerated	6	25 ± [redacted]°C/60 ± [redacted]% RH	6 months	
Stress	6	40 ± [redacted]°C/75 ± [redacted]% RH	3 months	
Photostability	1	Overall illumination of ≥1.2 million lx·hr (cool white fluorescent lamp), an integrated near ultraviolet energy of approximately ≥200 W·h/m^2 (near-ultraviolet fluorescent lamp)		

a) Drug product batches manufactured through the proposed manufacturing process using the drug substance batch manufactured through the proposed manufacturing process.
b) The study lasted [redacted] months for 2 batches.
c) The photostability testing was conducted in a storage form in which the glass syringe with butyl bromide rubber stopper was packaged in a paper box as the secondary package.

The long-term testing showed no clear changes in quality attributes throughout the testing period.

The accelerated testing showed an increasing trend in [redacted], a decreasing trend in [redacted], and an increasing trend in [redacted] in addition to changes observed in the long-term testing.

The stress testing showed a decrease in [redacted] and an increase in [redacted], a decreasing trend in [redacted] and an increasing trend in [redacted], a decreasing trend in [redacted], an increasing trend in [redacted] and an increase in [redacted], a decrease in [redacted], and an increase in [redacted] and a decreasing trend in [redacted].

The photostability testing showed that the drug product in a paper box, the secondary package, was photostable.

Based on the above results, a shelf life of 24 months has been proposed for the drug product in a glass syringe with butyl bromide rubber stopper, when stored at 2°C to 8°C in a paper box protected from light.

2.3 QbD

A QbD approach was applied to development of the drug substance and drug product. The quality control strategy has been developed based on the following investigations.

- Identification of critical quality attributes (CQAs)
  For the quality attributes of benralizumab including product-related substances, product-related impurities, and process-related impurities [see Sections 2.1.5.2 to 2.1.5.3], the following CQAs were identified based on the information obtained through the development, relevant general knowledge, etc.
  CQA: [redacted], Substance B, Substance C, [redacted], Substance D ([redacted] and [redacted]), [redacted], host cell protein, host cell DNA, [redacted], osmolarity, withdrawable volume, [redacted], bioburden, sterility, bacterial endotoxins, viral safety, [redacted], and biological activity

- Process characterization
  Process parameters were classified by risk assessment based on impact on the CQAs, and each process was characterized.

- Development of controls
  Failure mode effects analysis has confirmed that the quality attributes of benralizumab are adequately controlled by combination of process parameter control, in-process control, and specifications, which were established based on the above process characterization, etc. [for control of product-related and process-related impurities, see Sections 2.1.5.2 to 2.1.5.3].

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is adequately controlled.

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

The applicant submitted the results from primary pharmacodynamic studies of benralizumab, namely *in vitro* studies on binding to IL-5Rα, effects on IL-5 signal transduction, and effects on human eosinophils and basophils as well as *in vivo* studies on effects on eosinophils in peripheral blood and eosinophil lineage-committed progenitors in bone marrow from cynomolgus monkeys and effects on the monkey asthma model. No secondary pharmacodynamics or pharmacodynamic drug interaction studies have

been conducted. Although no safety pharmacology studies were conducted, effects on the central nervous, cardiovascular, and respiratory systems were investigated in repeated-dose toxicity studies in cynomolgus monkeys. Unless otherwise specified, pharmacological parameters are expressed in mean values.

3.1 Primary pharmacodynamics

3.1.1 Binding to IL-5Rα (CTD 4.2.1.1-2, 4.2.1.1-3 to 4.2.1.1-4 [Reference data], 4.2.1.1-5)

Binding of benralizumab to human IL-5Rα was investigated by enzyme-linked immunosorbent assay (ELISA). Benralizumab bound to human IL-5Rα in a concentration dependent manner. Binding of benralizumab to human or cynomolgus monkey IL-5Rα was investigated by surface plasmon resonance. Their dissociation constant (K_D) values were 0.016 and 0.042 nmol/L, respectively. Binding of benralizumab to human or mouse IL-5Rα was investigated by flow cytometry. Benralizumab bound to human IL-5Rα but not to mouse IL-5Rα.

Binding of biotinylated benralizumab to IL-5Rα expressed on eosinophils from human peripheral blood was investigated by flow cytometry. Biotinylated benralizumab bound to IL-5Rα expressed on eosinophils.

3.1.2 Effects on IL-5-mediated signal transduction (CTD 4.2.1.1-7)

Human IL-5Rα-expressed mouse pro-B cell line was prepared to investigate the effects of benralizumab on IL-5-induced cell proliferation. Benralizumab inhibited the proliferation of the cells induced by IL-5 (2 ng/mL) in a concentration-dependent manner.

3.1.3 Effects on human eosinophils and basophils (CTD 4.2.1.1-8 to 4.2.1.1-9, 4.2.1.1-10 [Reference data])

ADCC activity of benralizumab on human eosinophils was investigated in a study using autologous peripheral blood mononuclear cells as effector cells. Apoptosis-induced cells accounted for 3.5% to 8.9% (measured value) of the target cell population in the presence of the negative control (anti-dinitrophenyl [DNP] antibody, 1 μg/mL), while such cells accounted for 13.0% to 26.2%, 13.8% to 28.0%, and 15.2% to 33.7% in the presence of benralizumab at 0.01, 0.1, and 1 μg/mL, respectively. In addition, ADCC activity of benralizumab on human eosinophils and basophils was investigated in a similar study using autologous natural killer cells as effector cells. Their 50% effective serum concentrations (EC_{50}) were 0.9 and 0.5 pmol/L, respectively (*J Allergy Clin Immunol.* 2010;125:1344-53).

In the study on ADCC activity using autologous peripheral blood mononuclear cell as effector cells, degranulation of human eosinophils in association with benralizumab was also investigated by comparing eosinophil cationic protein (ECP) and eosinophil-derived neurotoxin (EDN) levels in the culture supernatant to their maximum release levels in the control culture supernatant in which eosinophils were lysed with surfactants. The ECP level (measured value) was undetectable to 1.4% for the negative control (anti-DNP antibody, 1 μg/mL) and 2.5% to 12.4% for the positive control (A23187, 1 μmol/L), while the ECP level for benralizumab at 0.01, 0.1, and 1 μg/mL were 0.0% to 2.3%, 0.2% to 1.3%, and 0.5 to 2.1%, respectively. The EDN level (measured value) was 1.1% to 24.4% for the

negative control (anti-DNP antibody, 1 μg/mL) and 54.5% to 141.1% for the positive control (phorbol 12-myristate 13-acetate, 1 ng/mL), while the EDN level for benralizumab at 0.01, 0.1, and 1 μg/mL were 13.5% to 44.8%, 14.1% to 34.6%, and 15.5% to 36.5%, respectively.

CDC activity of benralizumab on human eosinophils in a normal human serum medium was investigated. Benralizumab (0.01 to 10 μg/mL) did not induce CDC activity.

3.1.4 Effects on eosinophils in peripheral blood and eosinophil lineage-committed progenitors in bone marrow in cynomolgus monkeys (CTD 4.2.3.2-1)

A 9-week repeated-dose toxicity study in cynomolgus monkeys [see Section 5.2.1] was conducted to investigate effects of benralizumab on eosinophils. Benralizumab (0.1, 1, 10, or 30 mg/kg) was intravenously administered to cynomolgus monkeys at an interval of 3 weeks for 9 weeks. Decreases in eosinophils in peripheral blood and eosinophil lineage-committed progenitors in bone marrow were observed.

3.1.5 Effects in monkey asthma model (CTD 4.2.1.1-13 [Reference data])

An animal model was generated as follows: Cynomolgus monkeys sensitized with dinitrophenyl (DNP)-*Ascaris suum* extract underwent inhalation of methacholine to develop airway hyperreactivity. A study using the animal model was conducted to investigate effects of anti-IL-5Rα antibody on the airway hyperreactivity to methacholine. This antibody was expressed in a different cell line from that of benralizumab but had comparable IL-5Rα binding activity and ADCC activity. The anti-IL-5Rα antibody (1 mg/kg) administered intravenously to the animals tended to inhibit airway hyperreactivity to inhaled methacholine after antigen challenge.

3.2 Safety pharmacology (CTD 4.2.3.2-1 to 4.2.3.2-3)

Safety pharmacology endpoints were investigated in 9-week and 9-month repeated-dose toxicity studies in cynomolgus monkeys [see Sections 5.2.1 and 5.2.2]. Benralizumab was intravenously administered at 0.1, 1, 10, or 30 mg/kg to cynomolgus monkeys every 3 weeks for 9 weeks, or benralizumab was administered at 10 or 25 mg/kg intravenously or at 30 mg subcutaneously every 2 weeks for 39 weeks. No changes related to benralizumab were observed in behavior or clinical signs, electrocardiogram, blood pressure, respiratory rate, or blood gases.

3.R Outline of the review conducted by PMDA

PMDA has concluded from the submitted data that benralizumab is shown to decrease eosinophils by binding to IL-5Rα, and thus benralizumab is expected to be effective against bronchial asthma.

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

The applicant submitted data on the absorption and distribution of benralizumab, namely results from intravenous and subcutaneous administration studies in cynomolgus monkeys. Plasma benralizumab concentrations (lower limit of quantitation [LLOQ], 0.02-0.11 μg/mL), serum benralizumab concentrations (LLOQ, 0.066 μg/mL), plasma anti-drug antibody (ADA) (limit of detection, approximately 0.3 μg/mL), and serum ADA (detection sensitivity, approximately 2.8 ng/mL) were measured by ELISA. Benralizumab, which is a monoclonal antibody, is considered to be degraded into

peptides or amino acids for reuse or excretion. No studies were conducted to investigate the metabolism or excretion of benralizumab. Unless otherwise specified, pharmacokinetic parameters are expressed using the mean ± standard deviation (SD).

4.1 Absorption

4.1.1 Single-dose administration (toxicokinetics) (CTD 4.2.3.1-1)

Table 5 shows the pharmacokinetic parameters of benralizumab following a single subcutaneous dose of benralizumab at 30 mg/kg in male cynomolgus monkeys. No animals developed ADAs.

Table 5. Pharmacokinetic parameters following a single subcutaneous dose of benralizumab at 30 mg/kg (male cynomolgus monkeys)

C_{max} (μg/mL)	AUC_{0-t} (μg·day/mL)	$t_{1/2}$ (day)	t_{max} (day)	CL/F (mL/kg/day)
213 ± 20.8	2750 ± 108	9.7 ± 2.9	3.0 [1.5, 3.0]	8.4 ± 1.0

Mean ± SD (t_{max}; median [min, max]), N = 3

4.1.2 Repeated-dose administration (toxicokinetics) (CTD 4.2.3.2-1, 4.2.3.2-3)

A 9-week repeated intravenous dose toxicity study [see Section 5.2.1] and a 9-month repeated intravenous and subcutaneous dose toxicity study [see Section.5.2.2] were conducted to investigate toxicokinetics in cynomolgus monkeys which received benralizumab every 3 weeks (9-week repeated intravenous dose toxicity study) or every 2 weeks (9-month repeated intravenous and subcutaneous dose toxicity study). Table 6 shows the pharmacokinetic parameters of benralizumab. In addition, ADA was detected in 1 each of animals which received intravenous benralizumab at 0.1 mg/kg or 30 mg/kg every 3 weeks (1 male and 1 female) and in 1 each of animals which received intravenous benralizumab at 10 mg/kg or 25 mg/kg every 2 weeks (1 male and 1 female). Development of ADA resulted in a trend toward a decrease in exposure to benralizumab.

Table 6. Pharmacokinetic parameters following repeated doses of benralizumab (cynomolgus monkeys)

Study period Route of administration (regimen)	Dose	Time point	Sex	N	C_{max} (μg/mL)	$AUC_{0\text{-}14day}$ (μg·day/mL)	$t_{1/2}$ (day)	t_{max} (day)	CL or CL/F (mL/kg/day)
9 weeks Intravenous (Q3W)	0.1 mg/kg	1st dose	Male and female	4[a)]	3.28 ± 0.780	23.0 ± 5.43[e)]	7.83 ± 0.633	0.003 [0.003, 0.021]	4.6 ± 1.0
		3rd dose	Male and female	4[a)]	3.10 ± 0.500	27.9 ± 7.76[b)f)]	10.8 ± 4.75[b)]	0.003 [0.003, 0.333]	3.8 ± 1.0[b)]
	1 mg/kg	1st dose	Male and female	6[a)]	32.7 ± 5.43	242 ± 44.9[e)e)]	11.3 ± 1.51[c)]	0.003 [0.003, 0.003]	4.3 ± 0.7[c)]
		3rd dose	Male and female	6[a)]	38.8 ± 3.97	234 ± 44.4[f)]	12.8 ± 1.40[c)]	0.003 [0.003, 0.021]	4.3 ± 0.7
	10 mg/kg	1st dose	Male and female	4[a)]	290 ± 8.16	3090 ± 1450[b)e)]	20.4 ± 18.7[b)]	0.003 [0.003, 0.021]	3.6 ± 1.4[b)]
		3rd dose	Male and female	4[a)]	380 ± 40.8	2450 ± 281[f)]	12.1 ± 3.69[b)]	0.003 [0.003, 0.333]	4.1 ± 0.5
	30 mg/kg	1st dose	Male and female	10[a)]	802 ± 44.7	6750 ± 1190[c)]	10.6 ± 4.89	0.003 [0.003, 0.021]	4.6 ± 0.7
		3rd dose	Male and female	10[a)]	934 ± 86.4	5760 ± 1760[f)]	18.6 ± 9.83[d)]	0.021 [0.003, 0.021]	6.5 ± 5.3
9 months Intravenous (Q2W)	10 mg/kg	1st dose	Male	5	270 ± 40.3	1520 ± 131	15.5 ± 3.32	0.02 [0.02, 0.5]	3.3 ± 0.5
			Female	6	268 ± 46.2	1360 ± 119	12.2 ± 4.57	0.02 [0.02, 0.02]	4.5 ± 0.9
		19th dose	Male	5	317 ± 91.4	2660 ± 835	19.1 ± 5.11	0.5 [0.5, 1.0]	
			Female	6	262 ± 60.5	2040 ± 466	12.0 ± 2.81	0.5 [0.5, 1.0]	
	25 mg/kg	1st dose	Male	5	597 ± 167	3180 ± 522	13.2 ± 1.86	0.02 [0.02, 0.02]	4.6 ± 0.5
			Female	5	656 ± 19.5	3350 ± 376	11.4 ± 2.52	0.02 [0.02, 0.02]	4.6 ± 0.7
		19th dose	Male	5	924 ± 120	6910 ± 1130	10.2 ± 2.49	0.5 [0.5, 0.5]	
			Female	5	743 ± 97.0	5290 ± 414	10.4 ± 3.03	0.5 [0.5, 1.0]	
9 months Subcutaneous (Q2W)	30 mg/kg	1st dose	Male	6	165 ± 49.7	1820 ± 534	15.2 ± 5.16[c)]	3.5 [2.0, 10.0]	7.3 ± 1.9[c)]
			Female	6	270 ± 72.6	2550 ± 568	11.9 ± 2.81	3.0 [2.0, 3.0]	6.7 ± 1.2
		19th dose	Male	6	472 ± 192	4850 ± 1810	17.7 ± 10.7	1.5 [0.5, 5.0]	
			Female	6	341 ± 42.8	3380 ± 472	9.67 ± 2.72	2.0 [2.0, 5.0]	

Mean ± SD (t_{max}; median [min, max])
a) Total number of males and females, b) n = 3, c) n = 5, d) n = 9, e) AUC_{inf}, f) $AUC_{0\text{-}21day}$

4.2 Distribution (CTD 4.2.3.5.3-1)

An enhanced pre- and post-natal development study was conducted to investigate toxicokinetics in pregnant cynomolgus monkeys [see Section 5.5.2] which intravenously received benralizumab at 10 or 30 mg/kg every 2 weeks from gestation day 20 to 22 through 1 month postpartum. Serum benralizumab concentrations in maternal animals and offspring are as shown in Table 7. Serum exposure to benralizumab in offspring increased depending on the maternal exposure. ADA was detected in 1 maternal animal at 10 mg/kg and in 2 maternal animals at 30 mg/kg, but not in offspring.

Table 7. Serum benralizumab concentrations in maternal animals and offspring

	10 mg/kg (μg/mL)		30 mg/kg (μg/mL)	
	Maternal animal	Offspring	Maternal animal	Offspring
Gestation day 20 to 22[a)]	222 ± 39.9 (14)		763 ± 124 (19)	
Gestation day 133[b)]	273 ± 45.4 (13)		957 ± 972 (17)	
Postpartum/lactation day 7	56.3 ± 29.7 (11)	37.3 ± 14.2 (10)	164 ± 102 (13)	109 ± 35.4 (12)
Postpartum/lactation day 28	64.1 ± 23.2 (11)	14.5 ± 5.72 (9)	195 ± 84.9 (12)	53.4 ± 29.1 (11)
Postpartum/lactation day 91	7.20 ± 4.30 (11)	0.749 ± 0.938 (7)	20.3 ± 14.2 (12)	2.10 ± 1.59 (10)

Mean ± SD (N), a) After the first dose, b) After the ninth dose

4.R Outline of the review conducted by PMDA

PMDA has concluded from the submitted non-clinical pharmacokinetic study results that the behavior of benralizumab in the body can be elucidated to a certain extent. Because blood benralizumab concentrations decreased in animals with ADA, clinical effects of ADA should be assessed with consideration of clinical study data [see Section 6.R.2].

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity studies of benralizumab conducted include single-dose toxicity, repeated-dose toxicity, reproductive and developmental toxicity, local tolerance, and other toxicity studies (tissue cross-reactivity study). Benralizumab does not bind to mouse IL-5Rα but binds to cynomolgus monkey IL-5Rα [see Section 3.1.1]. Toxicity studies of benralizumab were conducted in cynomolgus monkeys. Although development of ADA in some animals resulted in a decrease in exposure to benralizumab [see Section 4.1.2], only in a small number of animals developed ADAs. Exposure to benralizumab during the dosing period in any study was considered to be sufficient for toxicity evaluation.

5.1 Single-dose toxicity (CTD 4.2.3.1-1)

Male cynomolgus monkeys received a single subcutaneous dose of benralizumab[1)] at 30 mg/kg. No changes related to benralizumab were observed. Based on the above, the approximate lethal dose was determined to be >30 mg/kg.

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies conducted include 9-week and 9-month intravenous dose toxicity in cynomolgus monkeys as well as 9-month subcutaneous dose toxicity studies in cynomolgus monkeys. The no observed adverse effect level (NOAEL) was determined to be 30 mg/kg in the toxicity study in which benralizumab was administered every 2 weeks for 9 months through a subcutaneous route, the proposed clinical administration route. The estimated $AUC_{0\text{-}56day}$[2)] (16,440 μg·day/mL) at the NOAEL was 238-fold the AUC_{τ}[3)] (69.1 μg·day/mL) in Japanese patients with asthma who subcutaneously received benralizumab at the clinical dose. The changes are not considered to be resulting from the toxicity, because decreases in eosinophils in peripheral blood and bone marrow are changes related to benralizumab and, that is, they are attributable to the pharmacological action of benralizumab [see Section 3.1.3].

5.2.1 Nine-week repeated intravenous dose toxicity study (CTD 4.2.3.2-1)

Males and female cynomolgus monkeys received 4 intravenous doses of benralizumab at 0 (vehicle[4)]), 0.1, 1, 10, or 30 mg/kg every 3 weeks. After the last dose, some of the monkeys in the 0 and 30 mg/kg groups were subjected to the 18-day recovery period. This study included bone marrow smear examination and lymphocyte subset analysis of peripheral blood by flow cytometry.

No deaths occurred. Findings at ≥0.1 mg/kg included decreased eosinophil counts in peripheral blood as well as decreases in eosinophils in sternal and femoral bone marrows, which were not reversible. Decreased neutrophil count in peripheral blood was observed in 2 of 10 animals in the 30 mg/kg group, but this finding was determined to have little toxicological significance, because (i) it was transient and reversible and (ii) the bone marrow smear examination showed no effects on neutrophilic bone marrow cells. Based on the above, the NOAEL was determined to be 30 mg/kg.

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1) The vehicle used was a solution of 10 mmol/L histidine, 300 mmol/L glycine, 0.02% polysorbate 20 at pH 6.0.
2) Value obtained by multiplying $AUC_{0\text{-}14day}$ (males and females pooled) calculated following the 19th dose by 4.
3) Steady-state AUC_{τ}, estimated by the population pharmacokinetic analysis based on the exposure in Japanese patients who have subcutaneously received benralizumab at 30 mg every 8 weeks [see Section 6.2.3].
4) 10 mmol/L citrate buffer solution, 150 mmol/L sodium chloride, 0.02% polysorbate80at pH 6.0

5.2.2 Nine-month repeated intravenous and subcutaneous dose toxicity study (CTD 4.2.3.2-3)

Males and female cynomolgus monkeys received 20 intravenous (IV) doses of benralizumab at 0 (vehicle[5)]), 10, or 25 mg/kg every 2 weeks or 20 subcutaneous (SC) doses at 0 (vehicle[5)]) or 30 mg/kg every 2 weeks. After the last dose, some of the monkeys in all the dose groups were subjected to the 12-week recovery period. This study included male and female hormone analysis and lymphocyte subset analysis. No deaths related to benralizumab occurred.

In the benralizumab groups, decreased eosinophil counts in peripheral blood and bone marrow were observed, but this change was reversible in some of the animals. Findings observed in 1 animal in the 25 mg/kg IV group were petechia and ecchymosis in the hypogastric region, decrease in platelets, and low erythroid parameters, but these changes were found to be reversible following discontinuation of the dose on Day 57. These changes were not considered to be related to benralizumab, because (i) they were transient; (ii) histopathological examination on the skin yielded no abnormal findings; and (iii) the administration resumed after their recovery did not result in similar findings.

Based on the above, the NOAEL was determined to be 25 mg/kg for intravenous administration and 30 mg/kg for subcutaneous administration.

5.3 Genotoxicity

Benralizumab is an antibody-based drug product and is then unlikely to act directly on DNA or other chromosomal components. Thus, no genotoxicity studies have been conducted.

5.4 Carcinogenicity

No carcinogenicity studies using rodent homologous antibodies have been conducted for the following reasons:

- Benralizumab does not bind to mouse IL-5Rα [see Section 3.1.1].
- Human FcγRIIIa and its counterpart, mouse FcγRIV, differ in expressing cells and isotype of binding antibody. It is difficult to generate an alternative model using homologous antibody that exhibits comparable ADCC activity (*Clin Cancer Res.* 2004;10:6248-55).
- In mice, IL-5Rα is expressed not only on eosinophils and basophils but also on B-1 cells (*Adv Immunol.* 2009;101:191-236). IL-5Rα expressing cell types differ among animal species.

Although IL-5 signal and eosinophils were potentially involved in tumorigenesis and tumor growth (*Histol Histopathol.* 1997;12:807-12, *J Cell Sci.* 1998;111:815-23, *Cell Signal.* 2013;25:2025-38, etc.), no consistent conclusion has been reached. Benralizumab, on the other hand, is unlikely to raise carcinogenicity concerns, because in the 9-month repeated intravenous and subcutaneous dose toxicity study, no proliferative or precancerous lesions suggestive of tumorigenesis were observed even in animals with decreased eosinophils [see Section 5.2.2]. The incidence of malignancies did not increase in clinical studies [see Section 7.R.3.3].

[5)] 20 mmol/L histidine, 9% trehalose, 0.004% polysorbate 20 at pH 6.0

5.5 Reproductive and developmental toxicity

A study for effects on pre- and post-natal development, including maternal function was conducted in cynomolgus monkeys. The NOAEL was determined to be 30 mg/kg for maternal animals and offspring. The estimated $AUC_{0\text{-}56day}$[6)] (19,040 μg·day/mL) was 276-fold the AUC_{τ}[3)] (69.1 μg·day/mL) in Japanese patients with asthma who subcutaneously received benralizumab at the clinical dose. In cynomolgus monkeys, benralizumab was found to cross the placenta [see Section 4.2].

5.5.1 Fertility and early embryonic development to implantation

No studies for fertility and early embryonic development to implantation have been conducted for benralizumab. In the 9-month repeated intravenous and subcutaneous dose toxicity study in cynomolgus monkeys [see Section 5.2.2], effects of benralizumab on fertility were evaluated by organ weight measurement and histopathological examination of the male and female reproductive organs, testis volume, sperm examination as well as menstrual cycle. No findings related to benralizumab were obtained in the above evaluation. Benralizumab, therefore, was considered unlikely to affect male and female fertility.

5.5.2 Enhanced pre- and post-natal development study in cynomolgus monkeys (ePPND study) (CTD 4.2.3.5.3-1)

Pregnant cynomolgus monkeys received up to 14 intravenous doses of benralizumab at 0 (vehicle[7)]), 10, or 30 mg/kg every 2 weeks from gestation day 20 to 22 through 1 month postpartum. This study evaluated lymphocyte subset in peripheral blood and immunoglobulins concentration. The offspring were subjected to immunological evaluation for T-cell-dependent antibody responses to keyhole-limpet hemocyanin.

Findings in maternal animals in the 10 and 30 mg/kg groups included decreased eosinophil count in peripheral blood and an increased fetal loss rate on gestation day 100 or later. The increased fetal loss rate fell within the historical range of the laboratory. The change therefore was not considered to be related to benralizumab. In the offspring, decreased eosinophil counts in peripheral blood were observed in the 10 and 30 mg/kg group, but the count was returned to the same level as that in the control group until postnatal day 180. No toxicity attributable to benralizumab was observed. Based on the above, the NOAEL was determined to be 30 mg/kg for maternal animals and offspring.

5.6 Local tolerance

5.6.1 Local tolerance study in rabbits following a single subcutaneous dose (CTD 4.2.3.6-1)

Benralizumab (0 [vehicle[8]], 50 mg/mL[9)]) or physiological saline was subcutaneously administered in a volume of 1 mL to 3 sites on the back of New Zealand White rabbits. Neither macroscopic nor histopathological changes related to benralizumab were observed on the injection sites. Thus, benralizumab was considered to cause no local irritations.

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6) Value obtained by multiplying $AUC_{0\text{-}14day}$ calculated following the ninth dose by 4.
7) 20 mmol/L histidine, 9% trehalose, 0.004% polysorbate 20 at pH 6.0
8) 20 mmol/L histidine, 9% trehalose, 0.02% polysorbate 20 at pH 6.0
9) The vehicle used was a solution of 20 mmol/L histidine, 9% trehalose, 0.004% polysorbate 20at pH 6.0.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study (CTD 4.2.3.7.7-1 to 4.2.3.7.7-2)

Studies were conducted to investigate the cross reactivity of benralizumab against normal tissues from humans and cynomolgus monkeys. In the cynomolgus monkey tissues, plasma protein (soluble IL-5R), mononuclear cells in the spleen, skeletal muscle cells, and cardiomyocytes as well as eosinophil lineage-committed progenitors in bone marrow were stained. In the human tissues, plasma protein (soluble IL-5R), mononuclear cells in the spleen, and skeletal muscle cells were stained. Findings for the staining in the spleen, skeletal muscles, and myocardium were considered to have little toxicological significance, for the following reasons: (i) No changes were observed in these tissues in the 9-month repeated intravenous and subcutaneous dose toxicity study in cynomolgus monkeys [see Section 5.2.2]; and (ii) the staining occurred mainly in the cytoplasm, but benralizumab is unlikely to be distributed to the cytoplasm in the body due to the nature of the antibody. Moreover, the applicant explained that staining in peripheral blood and bone marrow eosinophils were not confirmed in human tissues since endogenous myeloperoxidase was stained.

5.R Outline of the review conducted by PMDA

PMDA has concluded that the submitted data have no particular problems with clinical use of benralizumab from a toxicological viewpoint.

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 or plasma benralizumab concentrations were measured by electrochemiluminescence assay (LLOQ, 3.86-30 ng/mL) or ELISA (LLOQ, 10 ng/mL). ADA was measured by ELISA or electrochemiluminescence assay (detection sensitivity, 6-50 ng/mL). Neutralizing antibody was measured by ligand binding neutralizing antibody assay (detection sensitivity, 22.5-41.7 ng/mL) or by bioassay for ADCC activity on IL-5R-expressed mouse T lymphocytes (detection sensitivity, 1.02-1.10 μg/mL). Unless otherwise specified, the amount of benralizumab administered is expressed based on the dose of benralizumab, and pharmacokinetic parameters are expressed using the mean ± SD.

6.2 Clinical pharmacology

The applicant submitted the following evaluation data: The results from Japanese studies (Studies 4563-001 [CTD 5.3.3.1-1] and 4563-002 [CTD 5.3.3.1-2]) and foreign study (Study MI-CP158 [CTD 5.3.3.2-1]) as well as population pharmacokinetic analysis and exposure-response analysis (CTD 5.3.3.5-1 to 5.3.3.5-2).

6.2.1 Healthy adults (Japanese phase I study; CTD 5.3.3.1-1, Study 4563-001 [[redacted] and CTD 5.3.3.1-2, Study 4563-002 [[redacted])

Japanese healthy adults received a single intravenous dose of benralizumab at 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg or a single subcutaneous dose of benralizumab at 25, 100, or 200 mg. Pharmacokinetic parameters are as shown in Table 8. In Study 4653-001, 2 subjects were found ADA positive.

Table 8. Pharmacokinetic parameters following a single dose (Japanese healthy adults)

Route of administration	Dose	C_{max} (μg/mL)	AUC_{0-t} (μg·day/mL)	MRT (day)	CL (mL/day/kg) or CL/F (mL/day)	V_{ss} (mL/kg) or V_Z/F (mL)	$t_{1/2}$ (day)	t_{max} (day)
IV	0.03 mg/kg	0.5 ± 0.1	3.3 ± 1.0	13.4 ± 2.7	7.8 ± 1.8	102 ± 17.0	10.2 ± 1.9	
	0.1 mg/kg	2.2 ± 0.4	22.0 ± 7.5[a)]	18.3 ± 4.0[a)]	4.4 ± 1.6[a)]	76.3 ± 9.8[a)]	14.4 ± 3.4[a)]	
	0.3 mg/kg	5.8 ± 0.5	68.3 ± 8.6	20.2 ± 2.2	4.4 ± 0.6	86.8 ± 6.5	16.7 ± 2.1	
	1.0 mg/kg	17.5 ± 1.9	216 ± 28.8	23.6 ± 4.7	4.5 ± 0.7	104 ± 7.2	18.7 ± 3.4	
	3.0 mg/kg	59.7 ± 3.6	671 ± 95.9	21.6 ± 2.9	4.4 ± 0.7	93.8 ± 8.8	17.6 ± 1.6	
SC	25 mg	2.0 ± 0.3	59.1 ± 9.8	24.2 ± 4.5	418 ± 73.6	9228 ± 1300	15.6 ± 3.0	7.0 [4.0, 7.0]
	100 mg	7.2 ± 2.4	203 ± 68.8	25.3 ± 3.7	529 ± 206	12,931 ± 4709	17.4 ± 3.0	5.0 [4.0, 7.0]
	200 mg	15.0 ± 5.4	408 ± 131	23.0 ± 3.2	524 ± 180	11,780 ± 4695	15.6 ± 2.6	4.0 [4.0, 7.0]

Mean ± SD; t_{max}, median [min, max]; n = 6, a) n = 5

6.2.2 Patients with asthma

6.2.2.1 Foreign phase I study (CTD 5.3.3.2-1, Study MI-CP158 [November 2006 to September 2008])

Non-Japanese patients with asthma received a single intravenous dose of benralizumab at 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg. Pharmacokinetic parameters are shown in Table 9. In this study, 7 patients were found ADA positive.

Table 9. Pharmacokinetic parameters following a single intravenous dose (non-Japanese patients with asthma)

Dose (mg/kg)	N	C_{max} (μg/mL)	AUC_{0-t} (μg·day/mL)	$t_{1/2}$ (day)	CL (mL/day/kg)	V_{ss} (mL/kg)
0.03	6	1.0 ± 0.3	3.7 ± 1.5	7.3 ± 2.0	6.7 ± 2.6	65.1 ± 27.5
0.1	6	3.5 ± 1.2	18.4 ± 4.3	12.8 ± 4.1	4.0 ± 1.0	67.5 ± 28.4
0.3	6	7.6 ± 1.5	71.7 ± 11.9	18.6 ± 4.2	3.9 ± 0.7	92.7 ± 12.4
1.0	9	23.1 ± 8.6	172 ± 39.8	11.7 ± 4.3	3.6 ± 2.8	51.5 ± 45.1
3.0	6	82.2 ± 18.4	767 ± 106	15.6 ± 2.8	3.9 ± 0.6	70.8 ± 18.2

Mean ± SD

Table 10 shows changes in blood eosinophil counts over time following a single intravenous dose of benralizumab at 0.0003, 0.003, 0.03, 0.1, 0.3, 1.0, or 3.0 mg/kg. Decreased blood eosinophil counts were found on Day 1, and the decreased count persisted in patients treated with benralizumab at ≥0.1 mg/kg until Day 84.

Table 10. Changes in blood eosinophil counts (/μL) over time in Study MI-CP158

Time point	Dose (mg/kg)						
	0.0003[a)]	0.003	0.03	0.1	0.3	1.0[b)]	3.0
Baseline	224 ± 100	233 ± 0.179	235 ± 96	310 ± 204	297 ± 209	381 ± 177	155 ± 130
Day 1	20 ± 17	8 ± 8	10 ± 6	2 ± 4	8 ± 8	9 ± 6	5 ± 8
Day 2	40 ± 26	5 ± 8	7 ± 5	5 ± 5	8 ± 4	4 ± 5	2 ± 4
Day 7	160 ± 75	72 ± 121	0	5 ± 5	5 ± 5	3 ± 5	0
Day 14	154 ± 45	52 ± 63	3 ± 5	2 ± 4	2 ± 4	1 ± 3	0
Day 28	184 ± 85	163 ± 257	2 ± 4	3 ± 5	0	4 ± 5	0
Day 84	180 ± 92[c)]	235 ± 134	-	0[d)]	2 ± 4[e)]	29 ± 77[f)]	0

Mean ± SD, n = 6, a) n = 5, b) n = 9, c) n = 3, d) n = 1, e) n = 5, f) n = 8

6.2.2.2 Multi-regional phase III study (CTD 5.3.5.1-4, Study D3250C00018 [CALIMA study] [August 2013 to March 2016])

In the multi-regional study in patients with asthma [see Section 7.2.1], benralizumab at 30 mg was subcutaneously administered once every 4 weeks (Q4W) or every 8 weeks (Q8W) for 56 weeks. Serum benralizumab concentrations in these patients are shown in Table 11.

Table 11. Serum benralizumab concentrations following multiple subcutaneous doses (safety analysis set, μg/mL)

Time point	30 mg Q8W	30 mg Q4W
Week 8	1.13 ± 0.54 (394)	1.13 ± 0.58 (411)
Week 16	0.41 ± 0.33 (377)	1.32 ± 0.72 (387)
Week 48	0.33 ± 0.27 (337)	1.30 ± 0.72 (353)

Mean ± SD (N)

6.2.3 Population pharmacokinetic analysis (CTD 5.3.3.5-1)

A population pharmacokinetic analysis (NONMEM Version 7.3) was performed using data on serum or plasma benralizumab concentrations from Japanese and foreign clinical studies in patients with asthma (Studies MI-CP158, MI-CP166, MI-CP-186, MI-CP197, MI-CP220, SIROCCO, CALIMA, ZONDA, and D3250C00032) (14,938 concentration data from 2317 patients).

Using a 2-compartment model with the first-order absorption process as the basic model, possible covariates were considered.[10)] The following covariates were selected: Body weight and ADA for total clearance (CL) and body weight for V2 and V3.

Population pharmacokinetic parameters [90% confidence interval (CI)] of benralizumab estimated from the final model were as follows: CL, 0.29 [0.28, 0.30] L/day; V2, 3.1 [3.0, 3.3] L; V3, 2.5 [2.3, 2.7] L; Ka, 3.5 [3.2, 4.0] day; and absolute bioavailability, 59%. Table 12 shows pharmacokinetic parameters at steady state in Japanese or non-Japanese patients with asthma who received benralizumab at 30 mg Q8W, estimated from the final model.

Table 12. Pharmacokinetic parameters at steady state after administration of benralizumab 30 mg Q8W, estimated from the final model (CALIMA study, estimated values)

	C_{max} (μg/mL)	C_{trough} (μg/mL)	AUC_{τ} (μg·day/mL)	CL (L/day)	V_{ss} (L)	k_a (day^{-1})
Japanese	2.35 ± 0.46	0.37 ± 0.23	69.1 ± 19.4	0.275 ± 0.073	5.30 ± 0.81	0.192 ± 0.078
Non-Japanese	2.08 ± 0.44	0.31 ± 0.22	59.1 ± 17.9	0.325 ± 0.090	6.29 ± 1.41	0.201 ± 0.087

Mean ± SD

6.2.4 Exposure-response analysis (CTD 5.3.3.5-2)

An exposure-response relationship was investigated using measured values for the efficacy endpoint (asthma exacerbation rate) and serum benralizumab trough concentration from Japanese and foreign clinical studies in patients with asthma (CALIMA and SIROCCO studies). Table 13 shows the annual asthma exacerbation rate divided into quartiles of serum benralizumab trough concentration.

10) The following covariates were considered: Body weight, sex, age, age group (adults or adolescents), race, smoking habit, hepatic function markers (alkaline phosphatase [ALP], alanine transaminase [ALT], aspartate aminotransferase [AST], total bilirubin [TBL]), creatinine clearance, albumin, ADA, and concomitant medications (montelukast, paracetamol, proton pump inhibitors, macrolide antibiotics, theophylline/aminophylline).

Table 13. Asthma exacerbation rate divided into quartiles of serum benralizumab concentration (CALIMA and SIROCCO studies)

	Serum benralizumab trough concentration range (μg/mL)	Asthma exacerbation rate
Q8W	<0.140	0.69 [0.54, 0.89] (178)
	≥0.140 and <0.256	0.60 [0.46, 0.77] (181)
	≥0.256 and <0.442	0.63 [0.48, 0.81] (175)
	≥0.442	0.54 [0.42, 0.70] (180)
Q4W	<0.797	0.63 [0.49, 0.81] (190)
	≥0.797 and <1.22	0.71 [0.56, 0.90] (185)
	≥1.22 and <1.69	0.57 [0.45, 0.74] (187)
	≥1.69	0.58 [0.45, 0.74] (185)

[95% CI] (N)

In addition, the E_{max} model on asthma exacerbation rate was established using serum benralizumab trough concentrations in the SIROCCO and CALIMA studies, estimated by the population pharmacokinetic analysis. The 90% effective serum concentration (EC_{90}) was estimated to be 0.927 μg/mL.

6.R Outline of the review conducted by PMDA

6.R.1 Ethnic differences in pharmacokinetics and pharmacodynamics of benralizumab

The applicant's explanation about the impact of ethnic factors on the pharmacokinetics of benralizumab and changes in blood eosinophil counts:

Figure 1 shows changes in serum benralizumab concentrations in the benralizumab 30 mg Q8W group and Q4W group in the Japanese and overall populations in the CALIMA study. There were no clear differences in serum benralizumab concentrations in either group between the Japanese and overall populations. The steady-state benralizumab exposure for the benralizumab 30 mg Q8W group, estimated by the population pharmacokinetic analysis, tended to be higher in the Japanese population than in the overall population [see Section 6.2.3], but this difference in exposure were considered attributable to differences in body weight (Japanese Q8W group, 65.2 kg; Japanese Q4W group, 61.5 kg; overall Q8W group, 79.4 kg; overall Q4W group, 78.2 kg). In addition, no clear differences were observed in the effect of benralizumab on blood eosinophil counts between the Japanese and overall populations (Figure 2). Based on the above, data on pharmacokinetics and changes in blood eosinophil counts suggested no ethnic differences that may affect the efficacy or safety of benralizumab.

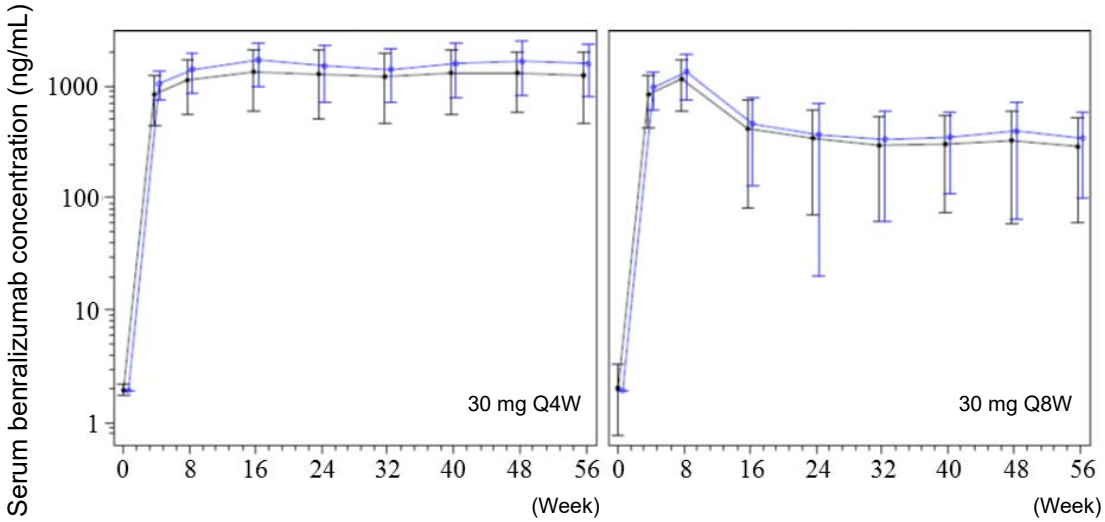

Figure 1. Changes in serum benralizumab concentrations over time in the CALIMA study (black, overall population; blue, Japanese population)

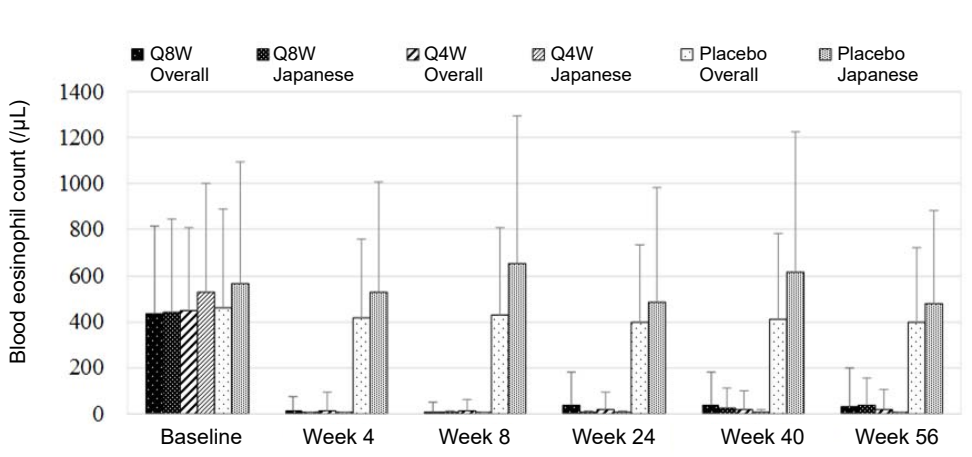

Figure 2. Changes in blood eosinophil counts over time in overall and Japanese populations (CALIMA study, FAS)

PMDA's view:

No clear differences were observed in serum benralizumab concentrations or blood eosinophil counts between the overall and Japanese populations. From pharmacokinetic and pharmacodynamic viewpoints, there are no major problems with the applicant's development strategy in which data from multi-regional studies including Japanese patients with asthma are used to support the efficacy and safety of benralizumab.

6.R.2 ADA

The applicant's explanation about the incidence of ADA and the impact of ADA on pharmacokinetics, efficacy, and safety of benralizumab:

In multi-regional phase III studies in patients with asthma (SIROCCO and CALIMA studies), ADA at ≥1 sampling point during the study period was observed in 14.8% of patients (58 of 393 patients in the SIROCCO study) and 15.0% of patients (64 of 427 patients in the CALIMA study) in the Q8W group

and 11.7% of patients (47 of 402 patients in the SIROCCO study) and 14.4% of patients (63 of 438 patients in the CALIMA study) in the Q4W group. Serum benralizumab concentrations in ADA positive patients tended to be lower than those in ADA negative patients (Figure 3).

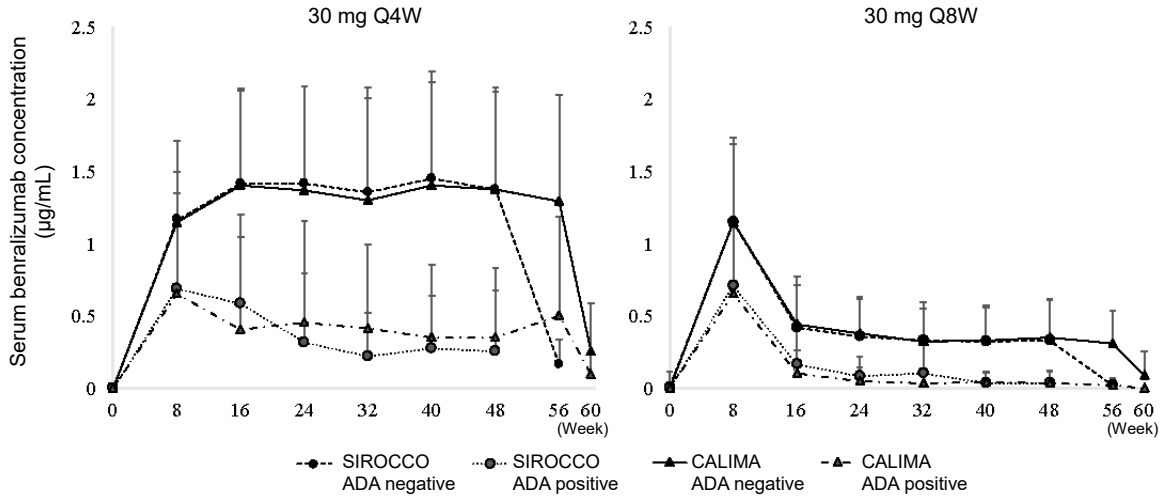

Figure 3. Serum benralizumab concentrations in patients with positive and negative for ADA (SIROCCO and CALIMA studies)

Table 14 and Table 15 show annual asthma exacerbation rates in patients with positive and negative for ADA in the benralizumab 30 mg Q8W and Q4W groups in the SIROCCO and CALIMA studies. No clear effects of ADA on the efficacy of benralizumab were observed.

Table 14. Annual asthma exacerbation rate in patients with positive and negative for ADA (SIROCCO and CALIMA studies)

Group	ADA negative	ADA positive				
		Overall	High antibody titer[a)]	Consistently ADA-positive[b)]	Neutralizing antibody positive	Consistently ADA-positive and neutralizing antibody positive
Q8W	0.71 (698)	0.71 (122)	0.44 (48)	0.62 (81)	0.77 (98)	0.62 (76)
Q4W	0.81 (730)	0.58 (110)	0.53 (51)	0.55 (67)	0.50 (75)	0.47 (60)

(N)

a) Maximum antibody titer at or above the median; b) Tested positive twice or more at the assessment after baseline (duration between the first and last sampling points with the positive result ≥16 weeks) or tested positive at the final assessment

Table 15. Annual asthma exacerbation rate by number of ADA-positive results (SIROCCO and CALIMA studies)

Group	ADA negative	ADA positive					
		Overall	Number of ADA-positive results[a)]				
			≥2	≥3	≥4	≥5	≥6
Q8W	0.71 [0.65, 0.77] (698)	0.71 [0.57, 0.87] (122)	0.57 [0.42, 0.78] (70)	0.59 [0.44, 0.81] (67)	0.63 [0.45, 0.87] (57)	0.63 [0.44, 0.92] (44)	0.65 [0.38, 1.09] (21)
Q4W	0.81 [0.74, 0.87] (730)	0.58 [0.45, 0.74] (110)	0.57 [0.41, 0.80] (58)	0.58 [0.42, 0.81] (57)	0.61 [0.42, 0.87] (48)	0.54 [0.34, 0.84] (34)	0.57 [0.32, 1.01] (20)

[95% CI] (N)

a) Duration between the first and last sampling points with the positive result ≥16 weeks

Table 16 shows all adverse events and hypersensitivity-related events in patients who tested positive or negative for ADA in the SIROCCO and CALIMA studies. There was no clear impact of ADA on the safety.

Table 16. Adverse events in patients who tested positive or negative for ADA (SIROCCO and CALIMA studies)

Group	Q8W		Q4W	
ADA	Negative	Positive	Negative	Positive
N	698	122	730	110
All adverse events	510 (73.1)	93 (76.2)	536 (73.4)	85 (77.3)
Hypersensitivity[a)]	20 (2.9)	5 (4.1)	22 (3.0)	4 (3.6)

N (%), a) Events coded to Standardised MedDRA Query "Hypersensitivity"

As described above, the data suggest no clear impact of ADA on the efficacy and safety of benralizumab.

PMDA's view:
Currently available information does not suggest clinical problems associated with the development of ADA. However, attention should be continuously paid to the impact of ADA on patients who have a significantly decreased response during treatment or who had hypersensitivity reaction.

6.R.3 Dosage regimen in phase III studies

The applicant's explanation about rationale for selecting the dosage regimen in the phase III studies of benralizumab:
Based on results from phase I and phase II studies (Studies MI-CP158, MI-CP166, MI-CP186, and MI-CP197), the threshold concentration of benralizumab necessary to maintain the decreased blood eosinophil counts was estimated to be 10 to 126 ng/mL. The study was designed based on the simulation of benralizumab concentration in lung tissue in the Q8W regimen (Figure 4) and on the assumption that the threshold concentration of benralizumab necessary in lung tissue would be comparable to that in blood. To investigate a dose-response relationship in terms of clinical effect of benralizumab, Study MI-CP220 evaluated the regimens of benralizumab 2, 20, and 100 mg Q8W with the focus on the regimen of 20 mg Q8W (including additional dose at 4 weeks after the first dose).

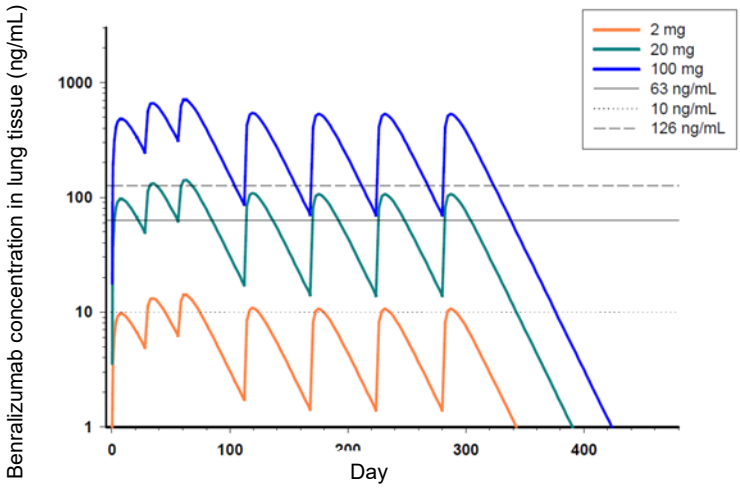

Figure 4. Simulation of benralizumab concentrations in lung tissue

In Study MI-CP220, patients subcutaneously received benralizumab at 2, 20, or 100 mg at Weeks 0, 4, and 8, followed by once every 8 weeks thereafter. In patients with blood eosinophil counts ≥300/μL, multiple endpoints for asthma control such as the annual asthma exacerbation rate and Asthma Control Questionnaire (ACQ) score were improved at the doses of 20 and 100 mg. In addition, the 90% effective dose of benralizumab (ED_{90}) was estimated to be appropriately 30 mg Q8W (including additional dose at 4 weeks after the first dose) according to the dose-response model (E_{max} model) simulating the asthma exacerbation rate based on results from Study MI-CP220. Therefore, a regimen of 30 mg Q8W was selected for multi-regional phase III studies. The simulation suggested that the trough concentration was below the EC_{90} for forced expiratory volume in 1 second (FEV_1) or ACQ in some of the patients receiving the regimen. Given that serum benralizumab concentration is possibly decreased due to ADA, a regimen of 30 mg Q4W that would lead to higher exposure than the above was additionally investigated in the multi-regional phase III studies.

PMDA accepted the applicant's explanation. PMDA will make the final decision on the dosage and administration of benralizumab based on the efficacy and safety data [see Sections 7.R.2, 7.R.3, and 7.R.6].

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 results from 6 clinical studies as shown in Table 17.

Table 17. List of clinical studies on efficacy and safety

Data category	Region	Study identifier	Phase	Subjects	Number of subjects	Dosage regimen (subcutaneous administration for all the regimens)	Main endpoints
Evaluation	Multi-regional	4563-003	II	Adult patients with asthma uncontrolled despite medium- or high-dose ICS/LABA	(a) 26 (b) 25 (c) 26 (d) 26	(a) Benralizumab 2 mg Q8W[a)] (b) Benralizumab 20 mg Q8W[a)] (c) Benralizumab 100 mg Q8W[a)] (d) Placebo	Efficacy Safety
	Foreign	MI-CP220	II	Adult patients with asthma uncontrolled despite medium- or high-dose ICS/LABA	(a) 81 (b) 81 (c) 222 (d) 222	(a) Benralizumab 2 mg Q8W[a)] (b) Benralizumab 20 mg Q8W[a)] (c) Benralizumab 100 mg Q8W[a)] (d) Placebo	Efficacy Safety
	Multi-regional	D3250C00018 (CALIMA)	III	Adult and pediatric patients with asthma uncontrolled despite medium- or high-dose ICS/LABA	(a) 441 (b) 425 (c) 440	(a) Benralizumab 30 mg Q8W[a)] (b) Benralizumab 30 mg Q4W (c) Placebo	Efficacy Safety
	Foreign	D3250C00017 (SIROCCO)	III	Adult and pediatric patients with asthma uncontrolled despite high-dose ICS/LABA	(a) 398 (b) 399 (c) 407	(a) Benralizumab 30 mg Q8W[a)] (b) Benralizumab 30 mg Q4W (c) Placebo	Efficacy Safety
	Foreign	D3250C00020 (ZONDA)	III	Adult patients with asthma uncontrolled despite high-dose ICS/LABA and OCS	(a) 73 (b) 72 (c) 75	(a) Benralizumab 30 mg Q8W[a)] (b) Benralizumab 30 mg Q4W (c) Placebo	Efficacy Safety
	Multi-regional	D3250C00021 (BORA)	III	Adult or pediatric patients with asthma who completed the CALIMA, SIROCCO, or ZONDA study	2133[b)]	(a) Benralizumab 30 mg Q8W (b) Benralizumab 30 mg Q4W	Efficacy Safety

a) Additional dose at Week 4
b) An interim analysis was performed in Japanese subjects, including 37 subjects in the Q8W group and 36 subjects in the Q4W group.

7.1 Phase II studies

7.1.1 Multi-regional study in patients with asthma (CTD 5.3.5.1-1, Study 4563-003 [August 2011 to October 2013])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in Japan and Korea to evaluate the efficacy and safety of benralizumab in adult patients with asthma (target sample size, 100 subjects [25 per group]). Patients eligible for enrollment in this study were those:

- Who met any of the following criteria for blood or sputum eosinophil counts: (a) patients who were assessed as eosinophil positive by the sponsor based on general hematology test results during the screening period, (b) fractional exhaled nitric oxide (Fe_{NO}) ≥50 ppb, and (c) eosinophils account ≥2% of leukocytes in sputum; and
- Who had exacerbations despite maintenance treatment with medium- or high-dose ICS and LABA.[11)]

[11)] Key inclusion criteria: Patients with asthma aged ≥20 and ≤75 years who meet the following criteria: (a) pre-bronchodilator FEV_1 was 40% to <90% of the predicted value; (b) on treatment at a fixed dose of medium- or high-dose ICS (equivalent to >250 µg/day of fluticasone propionate [FP]) for ≥30 days prior to the screening; (c) asthma exacerbation occurred ≥2 and ≤6 times within 12 months prior to the first dose of the study drug, requiring systemic steroid treatment for ≥3 days, or an increased dose from the maintenance dose for ≥3 days if the patient is on maintenance systemic steroid treatment.

Subjects subcutaneously received benralizumab at 2, 20, or 100 mg or placebo at Weeks 0, 4, and 8 and then every 8 weeks for 52 weeks, in combination with ICS/LABA.[12)]

Of 106 randomized subjects (27 in the 2 mg group, 26 in the 20 mg group, 26 in the 100 mg group, 27 in the placebo group), 103 subjects (26 in the 2 mg group, 25 in the 20 mg group, 26 in the 100 mg group, 26 in the placebo group) who had received at least one dose of the study drug were included in the full analysis set (FAS) and safety analysis set. The FAS was used for the efficacy analysis. The study was discontinued in 15.4% (4 of 26) of subjects in the 2 mg group, 16.0% (4 of 25) of subjects in the 20 mg group, 23.1% (6 of 26) of subjects in the 100 mg group, and 19.2% (5 of 26) of subjects in the placebo group mainly due to consent withdrawal (3.8% [1 of 26] of subjects in the 100 mg group, 7.7% [2 of 26] of subjects in the placebo group).

The FAS included 44 Japanese subjects (11 per group). The study was discontinued in 18.2% (2 of 11) of subjects in the 2 mg group, 18.2% (2 of 11) of subjects in the 20 mg group, 18.2% (2 of 11) of subjects in the 100 mg group, and 9.1% (1 of 11) of subjects in the placebo group mainly due to failure to meet the eligibility criteria (9.1% [1 of 11] of subjects in the 2 mg group, 9.1% [1 of 11] of subjects in the 100 mg group) and adverse events (9.1% [1 of 11] of subjects in the 20 mg group).

Table 18 shows annual asthma exacerbation rates until Week 52, which is the primary efficacy endpoint.

Table 18. Annual asthma exacerbation rate until Week 52 (FAS)

		2 mg	20 mg	100 mg	Placebo
Overall population	Annual asthma exacerbation rate (episodes/patient-year)	2.35 ± 3.23 (26)	1.93 ± 2.62 (25)	2.23 ± 6.06 (26)	3.50 ± 4.58 (26)
	Compared to placebo	0.67	0.55	0.64	
Japanese subpopulation	Annual asthma exacerbation rate (episodes/patient-year)	3.29 ± 3.72 (11)	1.39 ± 2.24 (11)	0.73 ± 1.85 (11)	4.81 ± 5.79 (11)
	Compared to placebo	0.68	0.29	0.15	

Mean ± SD (N)

Adverse events occurred in 96.2% (25 of 26) of subjects in the 2 mg group, 92.0% (23 of 25) of subjects in the 20 mg group, 96.2% (25 of 26) of subjects in the 100 mg group, and 96.2% (25 of 26) of subjects in the placebo group. The major adverse events are shown in Table 19.

No deaths occurred. Serious adverse events occurred in 19.2% (5 of 26) of subjects in the 2 mg group, 16.0% (4 of 25) of subjects in the 20 mg group, 11.5% (3 of 26) of subjects in the 100 mg group, and 19.2% (5 of 26) of subjects in the placebo group. A causal relationship between the study drug and the event in 1 subject in the 2 mg group (asthma) could not be ruled out. Adverse events leading to discontinuation occurred in 4.0% (1 of 25) of subjects in the 20 mg group and 3.8% (1 of 26) of subjects in the 100 mg group. Adverse drug reactions occurred in 42.3% (11 of 26) of subjects in the 2 mg group, 48.0% (12 of 25) of subjects in the 20 mg group, 57.7% (15 of 26) of subjects in the 100 mg group, and 19.2% (5 of 26) of subjects in the placebo group.

[12)] A fixed dose of ICS/LABA was to be administered concomitantly from 3 weeks before the first dose to Week 52.

Table 19. Adverse events reported by ≥3 subjects in any group (safety analysis set)

Event	2 mg (N = 26)	20 mg (N = 25)	100 mg (N = 26)	Placebo (N = 26)
Injection site reaction	4 (15.4)	9 (36.0)	8 (30.8)	0
Upper respiratory tract infection	7 (26.9)	6 (24.0)	8 (30.8)	8 (30.8)
Pyrexia	3 (11.5)	4 (16.0)	7 (26.9)	1 (3.8)
Influenza like illness	4 (15.4)	2 (8.0)	5 (19.2)	1 (3.8)
Arthralgia	0	1 (4.0)	5 (19.2)	1 (3.8)
Headache	1 (3.8)	3 (12.0)	4 (15.4)	0
Stomatitis	3 (11.5)	0	4 (15.4)	0
Nasopharyngitis	10 (38.5)	10 (40.0)	3 (11.5)	13 (50.0)
Rhinitis allergic	3 (11.5)	2 (8.0)	3 (11.5)	2 (7.7)
Eczema	0	2 (8.0)	3 (11.5)	1 (3.8)
Asthma	5 (19.2)	2 (8.0)	2 (7.7)	3 (11.5)
Bronchitis	1 (3.8)	4 (16.0)	2 (7.7)	2 (7.7)
Urticaria	1 (3.8)	6 (24.0)	1 (3.8)	0
Vomiting	3 (11.5)	4 (16.0)	1 (3.8)	0
Insomnia	1 (3.8)	4 (16.0)	1 (3.8)	1 (3.8)
Pharyngitis	4 (15.4)	1 (4.0)	1 (3.8)	2 (7.7)
Chronic sinusitis	3 (11.5)	1 (4.0)	1 (3.8)	3 (11.5)
Injection site erythema	3 (11.5)	4 (16.0)	0	0
Oropharyngeal pain	3 (11.5)	2 (8.0)	0	1 (3.8)
Nausea	3 (11.5)	0	0	0

n (%)

In the Japanese subpopulation, adverse events occurred in 100% (11 of 11) of subjects in the 2 mg group, 90.9% (10 of 11) of subjects in the 20 mg group, 100% (11 of 11) of subjects in the 100 mg group, and 100% (11 of 11) of subjects in the placebo group. The major adverse events are shown in Table 20.

No deaths occurred. Serious adverse events occurred in 9.1% (1 of 11) of subjects in the 2 mg group, 9.1% (1 of 11) of subjects in the 20 mg group, 9.1% (1 of 11) of subjects in the 100 mg group, and 27.3% (3 of 11) of subjects in the placebo group. A causal relationship between the study drug and the event in 1 subject in the 2 mg group (asthma) could not be ruled out. Adverse events leading to discontinuation occurred in 9.1% (1 of 11) of subjects in the 20 mg group. Adverse drug reactions occurred in 72.7% (8 of 11) of subjects in the 2 mg group, 63.6% (7 of 11) of subjects in the 20 mg group, 72.7% (8 of 11) of subjects in the 100 mg group, and 18.2% (2 of 11) of subjects in the placebo group.

Table 20. Adverse events reported by ≥3 subjects in any group (safety analysis set [Japanese subpopulation])

Event	2 mg (N = 11)	20 mg (N = 11)	100 mg (N = 11)	Placebo (N = 11)
Injection site reaction	3 (27.3)	5 (45.5)	4 (36.4)	0
Pyrexia	3 (27.3)	2 (18.2)	4 (36.4)	1 (9.1)
Nasopharyngitis	7 (63.6)	6 (54.5)	3 (27.3)	8 (72.7)
Headache	1 (9.1)	2 (18.2)	3 (27.3)	0
Eczema	0	2 (18.2)	3 (27.3)	0
Stomatitis	3 (27.3)	0	3 (27.3)	0
Arthralgia	0	0	3 (27.3)	1 (9.1)
Bronchitis	1 (9.1)	4 (36.4)	2 (18.2)	2 (18.2)
Injection site erythema	2 (18.2)	3 (27.3)	0	0
Pharyngitis	4 (36.4)	1 (9.1)	0	1 (9.1)
Vomiting	3 (27.3)	1 (9.1)	0	0

n (%)

7.1.2 Foreign study in patients with asthma (CTD 5.3.5.1-2, Study MI-CP220 [December 2010 to August 2013])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in 10 countries, including Russia, Bulgaria, and the US, to evaluate the efficacy and safety of benralizumab in adult patients with asthma uncontrolled despite medium- or high-dose ICS plus LABA[13] (target sample size, 566 subjects; eosinophil positive [EOS+] arm[14], 324 subjects [81 per group]; eosinophil negative [EOS−] arm,[15] 242 subjects [121 per group]).

Subjects subcutaneously received benralizumab at 2, 20, or 100 mg or placebo in the eosinophil positive arm and benralizumab at 100 mg or placebo in the eosinophil negative arm at Weeks 0, 4, and 8 and then every 8 weeks for 52 weeks, in combination with ICS/LABA.[16]

Of 609 randomized subjects (324 in the EOS+ arm [81 in the 2 mg group, 81 in the 20 mg group, 82 in the 100 mg group, 80 in the placebo group]; 285 in the EOS− arm [142 in the 100 mg group, 143 in the placebo group]), 606 subjects (324 in the EOS+ arm [81 in the 2 mg group, 81 in the 20 mg group, 82 in the 100 mg group, 80 in the placebo group]; 282 in the EOS− arm [140 in the 100 mg group, 142 in the placebo group]) who had received at least one dose of the study drug were included in the modified intent-to-treat (mITT) population and safety analysis set. The mITT population was used for efficacy analysis. The study was discontinued in 9.8% (8 of 81) of subjects in the EOS+ 2 mg group, 13.5% (11 of 81) of subjects in the EOS+ 20 mg group, 15.8% (13 of 82) of subjects in the EOS+ 100 mg group, and 13.7% (11 of 80) of subjects in the EOS+ placebo group as well as in 10.7% (15 of 140) of subjects in the EOS− 100 mg group and 9.1% (13 of 142) of subjects in the EOS− placebo group, mainly due to consent withdrawal (7.4% [6 of 81] of subjects in the EOS+ 2 mg group, 4.9% [4 of 81] of subjects in the EOS+ 20 mg group, 9.7% [8 of 82] of subjects in the EOS+ 100 mg group, 7.5% [6 of 80] of subjects in the EOS+ placebo group, 6.4% [9 of 140] of subjects in the EOS− 100 mg group, 7.0% [10 of 142] of subjects in the EOS− placebo group) and lost to follow-up (2.4% [2 of 81] of subjects in the EOS+ 2 mg group, 3.7% [3 of 81] of subjects in the EOS+ 20 mg group, 1.2% [1 of 82] of subjects in the EOS+ 100 mg group, 5.0% [4 of 80] of subjects in the EOS+ placebo group, 1.4% [2 of 140] of subjects in the EOS− 100 mg group, 0.7% [1 of 142] of subjects in the EOS− placebo group).

The EOS+ arm was used for primary efficacy analyses. Table 21 shows the annual asthma exacerbation rate until Week 52.

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[13] Key inclusion criteria: Patients with asthma aged ≥18 and ≤75 years who meet the following criteria: (a) pre-bronchodilator FEV_1 was 40% to <90% of the predicted value; (b) on treatment at a fixed dose of medium- or high-dose of ICS (equivalent to >250 μg/day of FP) for ≥30 days prior to the informed consent; (c) asthma exacerbation occurred ≥2 and ≤6 times within 12 months prior to the informed consent, requiring systemic steroid treatment for ≥3 days, or an increased dose from the maintenance dose for ≥3 days if the patient is on maintenance systemic steroid treatment.

[14] During the screening period, patients were assessed as eosinophil positive based on the score of a proprietary index to predict sputum eosinophil counts (ELEN Index) or Fe_{NO} ≥50 ppb.

[15] Patients were assessed as negative based on the score of the ELEN Index or Fe_{NO} <50 ppb.

[16] A fixed dose of ICS/LABA was to be administered from 3 weeks before the first dose to Week 52.

Table 21. Annual asthma exacerbation rate until Week 52 (mITT population)

	EOS+ arm				EOS− arm	
	2 mg (N = 81)	20 mg (N = 81)	100 mg (N = 82)	Placebo (N = 80)	100 mg (N = 140)	Placebo (N = 142)
Number of asthma exacerbations (episodes)	49	28	27	41	58	74
Overall duration of observation period (patient-year)	75.8	74.7	78.4	71.7	133.6	133.1
Annual asthma exacerbation rate (episodes/patient-year)	0.65	0.37	0.34	0.57	0.43	0.56
Compared to placebo [95% CI][a)]	1.09 [0.61, 1.95]	0.64 [0.34, 1.21]	0.59 [0.32, 1.10]		0.78 [0.49, 1.23]	

a) Poisson regression model with overdispersion adjustment factor using baseline (medium- or high-dose) ICS use status as a covariate

Adverse events[17)] occurred in 69.1% (56 of 81) of subjects in the 2 mg group, 71.6% (58 of 81) of subjects in the 20 mg group, 73.1% (163 of 223) of subjects in the 100 mg group, and 64.7% (143 of 221) of subjects in the placebo group. The major adverse events are shown in Table 22.

No deaths occurred. Serious adverse events occurred in 12.3% (10 of 81) of subjects in the 2 mg group, 7.4% (6 of 81) of subjects in the 20 mg group, 10.8% (24 of 223) of subjects in the 100 mg group, and 10.4% (23 of 221) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 1 subject in the 20 mg group (erythema nodosum), 4 subjects in the 100 mg group (cholecystitis acute, herpes zoster, uterine leiomyoma, polyarteritis nodosa), and 2 subjects in the placebo group (anaphylactic reaction, pneumonia). Adverse events leading to discontinuation occurred in 4.9% (4 of 81) of subjects in the 2 mg group, 2.5% (2 of 81) of subjects in the 20 mg group, 2.7% (6 of 223) of subjects in the 100 mg group, and 1.4% (3 of 221) of subjects in the placebo group. Adverse drug reactions occurred in 21.0% (17 of 81) of subjects in the 2 mg group, 32.1% (26 of 81) of subjects in the 20 mg group, 30.5% (68 of 223) of subjects in the 100 mg group, and 12.7% (28 of 221) of subjects in the placebo group.

Table 22. Adverse events reported by ≥5% of subjects in any group (safety analysis set)

Event	2 mg (N = 81)	20 mg (N = 81)	100 mg (N = 223)	Placebo (N = 221)
Asthma	29 (35.8)	24 (29.6)	72 (32.3)	77 (34.8)
Nasopharyngitis	11 (13.6)	7 (8.6)	26 (11.7)	13 (5.9)
Headache	8 (9.9)	6 (7.4)	22 (9.9)	16 (7.2)
Injection site erythema	2 (2.5)	2 (2.5)	18 (8.1)	0
Upper respiratory tract infection	6 (7.4)	7 (8.6)	16 (7.2)	13 (5.9)
Hypertension	3 (3.7)	0	14 (6.3)	5 (2.3)
Bronchitis	8 (9.9)	6 (7.4)	13 (5.8)	16 (7.2)
Pharyngitis	8 (9.9)	3 (3.7)	13 (5.8)	8 (3.6)
Influenza	3 (3.7)	7 (8.6)	12 (5.4)	14 (6.3)
Rhinitis allergic	3 (3.7)	8 (9.9)	11 (4.9)	7 (3.2)
Arthralgia	4 (4.9)	5 (6.2)	6 (2.7)	2 (0.9)
Back pain	5 (6.2)	2 (2.5)	5 (2.2)	4 (1.8)
Injection site pain	6 (7.4)	4 (4.9)	4 (1.8)	6 (2.7)

n (%)

17) Pooled data from the EOC+ arm and EOC−arm

7.2 Phase III studies

7.2.1 Multi-regional study in patients with asthma (CTD 5.3.5.1-4, Study D3250C00018 [CALIMA study] [August 2013 to March 2016])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in 11 countries, including Japan, Poland, Argentine, and the US, to evaluate the efficacy and safety of benralizumab in pediatric (only in foreign countries) and adult patients with asthma uncontrolled on medium- or high-dose ICS plus LABA[18] (target sample size, 1296 subjects [432 per group]).

Subjects subcutaneously received benralizumab at 30 mg or placebo every 4 or 8 weeks for 56 weeks, in combination with ICS/LABA.[19][20][21]

All of 1306 randomized subjects (441 in the Q8W group, 425 in the Q4W group, 440 in the placebo group) received at least one dose of the study drug. They were included in the FAS and safety analysis set. The FAS was used for efficacy analysis. The study was discontinued in 11.6% (51 of 441) of subjects in the Q8W group, 8.5% (36 of 425) of subjects in the Q4W group, and 8.6% (38 of 440) of subjects in the placebo group mainly due to decision of the subjects (6.1% [27 of 441] of subjects in the Q8W group, 3.5% [15 of 425] of subjects in the Q4W group, 4.3% [19 of 440] of subjects in the placebo group) and lost to follow-up (1.8% [8 of 441] of subjects in the Q8W group, 1.2% [5 of 425] of subjects in the Q4W group, 1.4% [6 of 440] of subjects in the placebo group).

The FAS included 83 Japanese subjects (30 in the Q8W group, 28 in the Q4W group, 25 in the placebo group). In the Japanese subpopulation, the study was discontinued in 10.0% (3 of 30) of subjects in the Q8W group, 14.3% (4 of 28) of subjects in the Q4W group, and 8.0% (2 of 25) of subjects in the placebo group mainly due to decision of the subjects (3.3% [1 of 30] of subjects in the Q8W group, 7.1% [2 of 28] of subjects in the Q4W group, 8.0% [2 of 25] of subjects in the placebo group) and adverse events (7.1% [2 of 28] of subjects in the Q4W group).

Table 23 and Table 24 show annual asthma exacerbation rates until Week 56, the primary efficacy endpoint. The primary efficacy population represented subjects with high-dose ICS and baseline blood eosinophil count ≥300/μL. In the patient population, pairwise comparisons of the Q8W group or Q4W group versus the placebo group presented a statistically significant difference, demonstrating the superiority of benralizumab 30 mg Q8W or Q4W to placebo. Table 25 shows data from the Japanese subpopulation.

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[18] Key inclusion criteria: Patients with asthma aged ≥12 and ≤75 years who met the following criteria: (a) pre-bronchodilator FEV_1 was <80% of the predicted value (<90% for subjects aged 12 to 17 years); (b) on ICS at a dose equivalent to ≥500 μg/day of FP, or ICS/LABA combination product at a medium or high dose, approved as maintenance dose in the country, for ≥3 months prior to the screening; and (c) at least 2asthma exacerbations occurred in 12 months prior to the informed consent.

[19] The dose was required to be consistent throughout a period from the enrollment through run-in period to the end of the study drug treatment period.

[20] In the Q8W group, benralizumab was additionally administered at Week 4 (the Q8W group received a total of 8 doses of benralizumab at Weeks 0 and 4 and from Week 8 to Week 48, while the Q4W group received a total of 14 doses from Week 0 to Week 52).

[21] Subjects aged 12 to 17 years in the EU region were to subcutaneously receive benralizumab at 30 mg or placebo at an interval of 8 weeks (including additional dose at Week 4).

Table 23. Annual asthma exacerbation rate until Week 56
(FAS, patient population with high-dose ICS and baseline blood eosinophil count ≥300/μL)

	Q8W	Q4W	Placebo
N	239	241	248
Number of asthma exacerbations (episodes)	163	163	270
Overall duration of observation period (patient-year)	245.4	254.2	261.2
Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.64	1.03
Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.66 [0.54, 0.82]	0.60 [0.48, 0.74]	0.93 [0.77, 1.12]
Compared to placebo[a] [95% CI], *P* value[a][b]	0.72 [0.54, 0.95] *P* = 0.019	0.64 [0.49, 0.85] *P* = 0.002	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before study participation, and use or non-use of OCS as covariates
b) Two-sided level of significance was 4%. Multiplicity of the test was adjusted by Hochberg' procedure.

Table 24. Annual asthma exacerbation rate until Week 56 (FAS)

		Baseline blood eosinophil count ≥300/μL			Baseline blood eosinophil count <300/μL		
		Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
High-dose ICS	N	239	241	248	125	116	122
	Number of asthma exacerbations (episodes)	163	163	270	93	102	167
	Overall duration of observation period (patient-year)	245.4	254.2	261.2	122.0	120.7	123.2
	Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.64	1.03	0.76	0.84	1.36
	Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.66 [0.54, 0.82]	0.60 [0.48, 0.74]	0.93 [0.77, 1.12]	0.73 [0.55, 0.95]	0.78 [0.59, 1.02]	1.21 [0.96, 1.52]
	Compared to placebo[a] [95% CI]	0.72 [0.54, 0.95]	0.64 [0.49, 0.85]		0.60 [0.42, 0.86]	0.64 [0.45, 0.92]	
Medium-dose ICS	N	51	47	49			
	Number of asthma exacerbations (episodes)	14	37	29			
	Overall duration of observation period (patient-year)	52.2	46.3	49.4			
	Annual asthma exacerbation rate (episodes/patient-year)	0.27	0.80	0.59			
	Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.27 [0.15, 0.49]	0.73 [0.47, 1.14]	0.57 [0.35, 0.91]			
	Compared to placebo[a] [95% CI]	0.48 [0.22, 1.03]	1.29 [0.67, 2.45]				
ICS dose pooled	N	290	288	297	151	137	143
	Number of asthma exacerbations (episodes)	177	200	299	112	104	184
	Overall duration of observation period (patient-year)	297.6	300.5	310.5	148.4	142.7	145.4
	Annual asthma exacerbation rate (episodes/patient-year)	0.59	0.67	0.96	0.75	0.73	1.27
	Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.59 [0.49, 0.72]	0.63 [0.52, 0.76]	0.87 [0.73, 1.04]	0.71 [0.55, 0.91]	0.64 [0.49, 0.83]	1.13 [0.90, 1.41]
	Compared to placebo[a] [95% CI]	0.68 [0.52, 0.88]	0.72 [0.56, 0.93]		0.63 [0.45, 0.88]	0.56 [0.40, 0.79]	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before study participation, and use or non-use of OCS as covariates

Table 25. Annual asthma exacerbation rate until Week 56 (FAS, Japanese subpopulation)

	Patients with high-dose ICS and baseline blood eosinophil count of ≥300/μL			Overall Japanese subpopulation		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	15	15	16	30	28	25
Number of asthma exacerbations (episodes)	6	13	48	19	38	74
Overall duration of observation period (patient-year)	14.6	15.5	16.7	30.2	28.9	26.5
Annual asthma exacerbation rate (episodes/patient-year)	0.41	0.84	2.87	0.63	1.32	2.80
Annual asthma exacerbation rate[a)] (episodes/patient-year) [95% CI]	0.42 [0.15, 1.18]	0.83 [0.36, 1.89]	2.45 [1.23, 4.89]	0.59 [0.30, 1.14]	0.85 [0.47, 1.54]	2.13 [1.24, 3.64]
Compared to placebo[a)] [95% CI]	0.17 [0.05, 0.60]	0.34 [0.11, 0.99]		0.28 [0.12, 0.65]	0.40 [0.19, 0.85]	

a) Negative binomial regression model using the number of asthma exacerbations in the past 1 year before study participation and use or non-use of OCS as covariates

Adverse events occurred in 74.8% (320 of 428) of subjects in the Q8W group, 73.5% (322 of 438) of subjects in the Q4W group, and 77.7% (342 of 440) of subjects in the placebo group. The major adverse events are shown in Table 26.

Deaths occurred in 2 subjects in the Q8W group (death and colon neoplasm in 1 subject each), 3 subjects in the Q4W group (completed suicide, road traffic accident, and acute myocardial infarction in 1 subject each), and 1 subject in the placebo group (myocardial infarction), but a causal relationship to the study drug was ruled out for any event. Serious adverse events occurred in 9.6% (41 of 428) of subjects in the Q8W group, 10.5% (46 of 438) of subjects in the Q4W group, and 13.9% (61 of 440) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 2 subjects in the Q8W group (asthma, herpes zoster), 1 subject in the Q4W group (urticaria), and 1 subject in the placebo group (non-cardiac chest pain). Adverse events leading to discontinuation occurred in 2.3% (10 of 428) of subjects in the Q8W group, 1.8% (8 of 438) of subjects in the Q4W group, and 1.1% (5 of 440) of subjects in the placebo group. Adverse drug reactions occurred in 12.6% (54 of 428) of subjects in the Q8W group, 11.6% (51 of 438) of subjects in the Q4W group, and 8.2% (36 of 440) of subjects in the placebo group.

Table 26. Adverse events reported by ≥3% of subjects in any group (safety analysis set)

Event	Q8W (N = 428)	Q4W (N = 438)	Placebo (N = 440)
Nasopharyngitis	79 (18.5)	90 (20.5)	92 (20.9)
Asthma	47 (11.0)	61 (13.9)	68 (15.5)
Bronchitis	44 (10.3)	40 (9.1)	52 (11.8)
Headache	34 (7.9)	33 (7.5)	32 (7.3)
Upper respiratory tract infection	36 (8.4)	29 (6.6)	41 (9.3)
Influenza	14 (3.3)	22 (5.0)	24 (5.5)
Sinusitis	20 (4.7)	21 (4.8)	37 (8.4)
Rhinitis allergic	16 (3.7)	20 (4.6)	23 (5.2)
Pyrexia	12 (2.8)	16 (3.7)	6 (1.4)
Back pain	11 (2.6)	16 (3.7)	16 (3.6)
Pharyngitis	10 (2.3)	16 (3.7)	7 (1.6)
Hypertension	18 (4.2)	12 (2.7)	21 (4.8)
Rhinitis	17 (4.0)	12 (2.7)	17 (3.9)
Cough	14 (3.3)	10 (2.3)	8 (1.8)
Arthralgia	14 (3.3)	8 (1.8)	9 (2.0)
Acute sinusitis	5 (1.2)	6 (1.4)	14 (3.2)

n (%)

In the Japanese subpopulation, adverse events occurred in 96.7% (29 of 30) of subjects in the Q8W group, 92.9% (26 of 28) of subjects in the Q4W group, and 100.0% (25 of 25) of subjects in the placebo group. The major adverse events are shown in Table 27.

Death occurred in 1 subject in the Q8W group (death), but a causal relationship between the study drug and the event was ruled out. Serious adverse events occurred in 6.7% (2 of 30) of subjects in the Q8W group, 3.6% (1 of 28) of subjects in the Q4W group, and 4.0% (1 of 25) of subjects in the placebo group. A causal relationship to the study drug was ruled out for any event. Adverse events leading to discontinuation occurred in 6.7% (2 of 30) of subjects in the Q8W group and 10.7% (3 of 28) of subjects in the Q4W group. Adverse drug reactions occurred in 10.0% (3 of 30) of subjects in the Q8W group, 7.1% (2 of 28) of subjects in the Q4W group, and 8.0% (2 of 25) of subjects in the placebo group.

Table 27. Adverse events reported by ≥3 subjects in any group (safety analysis set, Japanese subpopulation)

Event	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)
Nasopharyngitis	13 (43.3)	14 (50.0)	13 (52.0)
Rhinitis allergic	2 (6.7)	4 (14.3)	3 (12.0)
Contusion	1 (3.3)	4 (14.3)	1 (4.0)
Pharyngitis	0	4 (14.3)	1 (4.0)
Eczema	1 (3.3)	3 (10.7)	1 (4.0)
Cystitis	0	3 (10.7)	2 (8.0)
Bronchitis	4 (13.3)	2 (7.1)	4 (16.0)
Asthma	3 (10.0)	2 (7.1)	1 (4.0)
Influenza	1 (3.3)	2 (7.1)	4 (16.0)
Sinusitis	3 (10.0)	1 (3.6)	0
Upper respiratory tract infection	3 (10.0)	1 (3.6)	3 (12.0)
Upper respiratory tract inflammation	3 (10.0)	1 (3.6)	1 (4.0)
Urticaria	4 (13.3)	0	2 (8.0)
Epistaxis	3 (10.0)	0	0
Back pain	0	0	3 (12.0)
Dermatitis atopic	0	0	3 (12.0)

n (%)

7.2.2 Foreign study in patients with asthma (CTD 5.3.5.1-3, Study D3250C00017 [SIROCCO study] [September 2013 to April 2016])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in 17 countries, including the US, Russia, and South Korea, to evaluate the efficacy and safety of benralizumab in pediatric and adult patients with asthma uncontrolled on high-dose ICS plus LABA[22] (target sample size, 1134 subjects [378 per group]).

Subjects subcutaneously received benralizumab at 30 mg or placebo every 4 or 8 weeks for 48 weeks, in combination with ICS/LABA.[23][21][24]

[22] Key inclusion criteria: Patients with asthma aged ≥12 and ≤75 years who met the following criteria: (a) pre-bronchodilator FEV_1 was <80% of the predicted value (<90% for subjects aged 12 to 17 years); (b) on ICS at a dose equivalent to >500 μg/day of FP, or ICS/LABA combination product at the highest dose, approved as maintenance dose in the country (medium dose for subjects aged 12 to 17 years), for ≥3 months prior to the screening; and (c) at least 2 asthma exacerbations occurred in 12 months prior to the informed consent.

[23] A fixed dose was to be administered throughout a period from 3 months prior to the enrollment to the end of the study treatment.

[24] In the Q8W group, benralizumab was additionally administered at Week 4 (the Q8W group received a total of 7 doses of benralizumab at Weeks 0 and 4 and from Week 8 to Week 40, while the Q4W group received a total of 12 doses from Week 0 to Week 44).

Of 1205 randomized subjects (398 in the Q8W group, 400 in the Q4W group, 407 in the placebo group), 1204 subjects (398 in the Q8W group, 399 in the Q4W group, 407 in the placebo group) who had received at least one dose of the study drug were included in the FAS and safety analysis set. The FAS was used for efficacy analysis. The study was discontinued in 10.1% (40 of 398) of subjects in the Q8W group, 11.5% (46 of 399) of subjects in the Q4W group, and 9.8% (40 of 407) of subjects in the placebo group mainly due to decision of the subjects (3.8% [15 of 398] of subjects in the Q8W group, 5.0% [20 of 399] of subjects in the Q4W group, 4.2% [17 of 407] of subjects in the placebo group), lost to follow-up (1.5% [6 of 398] of subjects in the Q8W group, 1.3% [5 of 399] of subjects in the Q4W group, 0.7% [3 of 407] of subjects in the placebo group), and adverse events (1.3% [5 of 398] of subjects in the Q8W group, 1.5% [6 of 399] of subjects in the Q4W group, 0.2% [1 of 407] of subjects in the placebo group).

Table 28 shows annual asthma exacerbation rates until Week 48, the primary efficacy endpoint. The primary efficacy population represented subjects with baseline blood eosinophil count ≥300/μL. In the patient population, pairwise comparisons of the Q8W group or Q4W group versus the placebo group presented a statistically significant difference, demonstrating the superiority of benralizumab 30 mg Q8W or Q4W to placebo.

Table 28. Annual asthma exacerbation rate until Week 48 (FAS)

	Baseline blood eosinophil count ≥300/μL			Baseline blood eosinophil count <300/μL		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	267	275	267	131	124	140
Number of asthma exacerbations (episodes)	156	206	365	122	104	165
Overall duration of observation period (patient-year)	236.1	242.7	238.2	116.0	109.0	125.7
Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.85	1.53	1.05	0.95	1.31
Annual asthma exacerbation rate[a)] (episodes/patient-year) [95% CI]	0.65 [0.53, 0.80]	0.73 [0.60, 0.89]	1.33 [1.12, 1.58]	1.00 [0.78, 1.28]	0.85 [0.65, 1.11]	1.21 [0.96, 1.52]
Compared to placebo[a)] [95% CI], *P* value[a)b)]	0.49 [0.37, 0.64] *P* < 0.001	0.55 [0.42, 0.71] *P* < 0.001		0.83 [0.59, 1.16]	0.70 [0.50, 1.00]	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before study participation, and use or non-use of OCS as covariates
b) Two-sided level of significance was 4%. Multiplicity of the test was adjusted by Hochberg' procedure.

Adverse events occurred in 71.3% (281 of 394) of subjects in the Q8W group, 72.7% (293 of 403) of subjects in the Q4W group, and 76.4% (311 of 407) of subjects in the placebo group. The major adverse events are shown in Table 29.

Deaths occurred in 2 subjects in the Q8W group (sudden death and overdose in 1 subject each), 2 subjects in the Q4W group (cerebral haemorrhage and asthma in 1 subject each), and 2 subjects in the placebo group (pulmonary embolism and death in 1 subject each), but a causal relationship to the study drug was ruled out for any event.

Serious adverse events occurred in 13.7% (54 of 394) of subjects in the Q8W group, 12.7% (51 of 403) of subjects in the Q4W group, and 14.3% (58 of 407) of subjects in the placebo group. A causal relationship to the study drugs could not be ruled out for the events in 3 subjects in the Q4W group (allergic granulomatous angiitis, panic attack, and paraesthesia in 1 subject each) and 1 subject in the placebo group (injection site erythema). Adverse events leading to discontinuation occurred in 2.0% (8

of 394) of subjects in the Q8W group, 2.5% (10 of 403) of subjects in the Q4W group, and 0.7% (3 of 407) of subjects in the placebo group. Adverse drug reactions occurred in 16.2% (64 of 394) of subjects in the Q8W group, 13.6% (55 of 403) of subjects in the Q4W group, and 10.3% (42 of 407) of subjects in the placebo group.

Table 29. Adverse events reported by ≥3% of subjects in any group (safety analysis set)

Event	Q8W (N = 394)	Q4W (N = 403)	Placebo (N = 407)
Asthma	45 (11.4)	60 (14.9)	78 (19.2)
Nasopharyngitis	46 (11.7)	47 (11.7)	47 (11.5)
Upper respiratory tract infection	32 (8.1)	44 (10.9)	36 (8.8)
Headache	37 (9.4)	30 (7.4)	21 (5.2)
Bronchitis	19 (4.8)	24 (6.0)	30 (7.4)
Pharyngitis	23 (5.8)	17 (4.2)	14 (3.4)
Sinusitis	22 (5.6)	17 (4.2)	28 (6.9)
Influenza	19 (4.8)	17 (4.2)	23 (5.7)
Pyrexia	12 (3.0)	16 (4.0)	8 (2.0)
Rhinitis	10 (2.5)	16 (4.0)	15 (3.7)
Cough	13 (3.3)	15 (3.7)	10 (2.5)
Arthralgia	18 (4.6)	11 (2.7)	10 (2.5)
Rhinitis allergic	12 (3.0)	11 (2.7)	8 (2.0)
Back pain	8 (2.0)	11 (2.7)	15 (3.7)
Acute sinusitis	13 (3.3)	10 (2.5)	10 (2.5)
Gastroenteritis	12 (3.0)	9 (2.2)	6 (1.5)
Nausea	12 (3.0)	8 (2.0)	8 (2.0)
Pain in extremity	13 (3.3)	3 (0.7)	5 (1.2)

n (%)

7.2.3 Foreign study in patients with asthma (CTD 5.3.5.1-5, Study D3250C00020 [ZONDA study] [April 2014 to August 2016])

A placebo-controlled, randomized, double-blind, parallel group study was conducted in 12 countries, including Germany, Poland, and Ukraine, to evaluate the efficacy and safety of benralizumab in adult patients with asthma uncontrolled despite high-dose ICS, LABA, and OCS[25] (target sample size, 210 subjects [70 per group]).

Subjects subcutaneously received benralizumab at 30 mg or placebo every 4 or 8 weeks for 28 weeks, in combination with ICS/LABA.[26][27]

This study consisted of the following 4 periods:

(a) OCS optimization phase (Weeks −8 to −2): Asthma control status in subjects who met the inclusion criteria was assessed in accordance with the OCS reduction criteria[28] The OCS dose (≥12.5 mg/day)

[25] Key inclusion criteria: Patients with asthma aged ≥18 and ≤75 years who met the following criteria: (a) pre-bronchodilator FEV_1 was <80% of the predicted value; (b) on ICS at a dose equivalent to >500 μg/day of FP, or ICS/LABA combination product at the highest dose, approved as maintenance dose in the country, for ≥6 months prior to the screening; and (c) on OCS at a dose equivalent to 7.5 to 40 mg/day of prednisone or prednisolone for ≥6 months prior to the screening, and the dose remained unchanged for ≥2 weeks prior to the randomization; (d) at least 1 asthma exacerbation occurred in 12 months prior to the informed consent; and (e) blood eosinophil counts at the time of screening ≥150/μL.

[26] A fixed dose was to be administered throughout a period from the enrollment to the end of the study treatment.

[27] In the Q8W group, benralizumab was additionally administered at Week 4 (the Q8W group received a total of 5 doses of benralizumab at Weeks 0 and 4 and from Week 8 to Week 24, while the Q4W group received a total of 7 doses from Week 0 to Week 24).

[28] The dose of OCS was reduced in subjects who met all the following criteria: (a) pre-bronchodilator FEV_1 was ≥80% of the baseline value; (b) mean morning peak expiratory flow (PEF) over 14 days prior to the visit ≥80% of the baseline value; (c) increase in nocturnal awakenings due to asthma symptoms over 14 days prior to the visit ≤50% of the baseline value; (d) the increased number of use of short-acting β2 agonist (SABA) over 14 days prior to the visit from baseline (or 12 times per day) ≤4; and (e) OCS increase for asthma control was no longer necessary.

was tapered by 5 mg/day every 2 weeks or the OCS dose (≤10 mg/day) was tapered by 2.5 mg/day every 2 weeks to determine the optimized dose of OCS.

(b) Induction phase (from Week 0 to Week 4): Subjects were randomly assigned to the Q8W group, Q4W group, or placebo group at Week 0, and the optimized dose of OCS was continued.

(c) OCS tapering phase (from Week 4 to Week 24): The appropriateness of OCS reduction was assessed in accordance with the OCS reduction criteria every 4 weeks. If applicable, the OCS dose was reduced by 1.25 to 5 mg/day every 4 weeks so as to reach the daily dose of OCS at 0 to 10 mg by Week 24.

(d) Maintenance phase (after Week 24 to Week 28): The dose of OCS at Week 24 was continued.

All of 220 randomized subjects (73 in the Q8W group, 72 in the Q4W group, 75 in the placebo group) received the study drug. They were included in the FAS and safety analysis set. The FAS was used for the efficacy analysis. The study was discontinued in 5.5% (4 of 73) of subjects in the Q8W group, 5.6% (4 of 72) of subjects in the Q4W group, and 4.0% (3 of 75) of subjects in the placebo group mainly due to decision of the subjects (1.4% [1 of 73] of subjects in the Q8W group, 5.6% [4 of 72] of subjects in the Q4W group), death (2.7% [2 of 73] of subjects in the Q8W group), and meeting the discontinuation criteria (1.4% [1 of 73] of subjects in the Q8W group, 1.3% [1 of 75] of subjects in the placebo group).

Table 30 shows percent reduction in the final dose of OCS from baseline while maintaining asthma control, the primary efficacy endpoint. Pairwise comparisons of the Q8W group or Q4W group versus the placebo group presented a statistically significant difference, demonstrating the superiority of benralizumab at 30 mg given at an interval of 8 or 4 weeks to placebo.

Table 30. Percent reduction in the final dose of OCS from baseline at Week 28 (FAS)

	Q8W (N = 73)	Q4W (N = 72)	Placebo (N = 75)
OCS dose at baseline (mg)	14.3 ± 7.8 (10.0)	15.8 ± 8.8 (10.0)	14.2 ± 6.4 (10.0)
OCS dose at Week 28 (mg)	6.4 ± 6.9 (5.0)	8.3 ± 10.8 (5.0)	11.3 ± 8.5 (10.0)
Percent reduction from baseline (%)	57.8 ± 43.6 (75.0)	56.0 ± 46.6 (75.0)	20.5 ± 54.4 (25.0)
Median difference from placebo[a] (%) [95% CI][a], *P* value[b]	37.5 [20.8, 50.0] *P* < 0.001	33.3 [16.7, 50.0] *P* < 0.001	

Mean ± SD (median)
Percent reduction was determined according to the following equation: (Baseline dose − dose at the final assessment) / baseline dose × 100. The estimated dose at the final assessment in the subjects who discontinued the study was defined as a dose one-step higher than that at the time of discontinuation.
a) Hodges-Lehmann procedure
b) Wilcoxon rank-sum test. Two-sided level of significance was 5%. Multiplicity of the test was adjusted by Hochberg' procedure.

Adverse events occurred in 75.3% (55 of 73) of subjects in the Q8W group, 68.1% (49 of 72) of subjects in the Q4W group, and 82.7% (62 of 75) of subjects in the placebo group. The major adverse events are shown in Table 31.

Deaths occurred in 2 subjects in the Q8W group (pneumonia and cardiac failure acute in 1 subject each). A causal relationship between the study drug and pneumonia could not be ruled out. Serious adverse events occurred in 9.6% (7 of 73) of subjects in the Q8W group, 9.7% (7 of 72) of subjects in the Q4W group, and 18.7% (14 of 75) of subjects in the placebo group. A causal relationship to the study drug could not be ruled out for the events in 2 subjects in the Q8W group (pneumonia and presyncope in 1 subject each) and 1 subject in the Q4W group (hypersensitivity). Adverse events leading to

discontinuation occurred in 4.1% (3 of 73) of subjects in the Q8W group and 2.7% (2 of 75) of subjects in the placebo group. Adverse drug reactions occurred in 16.4% (12 of 73) of subjects in the Q8W group, 6.9% (5 of 72) of subjects in the Q4W group, and 13.3% (10 of 75) of subjects in the placebo group.

Table 31. Adverse events reported by ≥3% of subjects in any group (safety analysis set)

Event	Q8W (N = 73)	Q4W (N = 72)	Placebo (N = 75)
Nasopharyngitis	11 (15.1)	11 (15.3)	15 (20.0)
Asthma	2 (2.7)	8 (11.1)	18 (24.0)
Headache	6 (8.2)	5 (6.9)	4 (5.3)
Sinusitis	4 (5.5)	5 (6.9)	8 (10.7)
Bronchitis	7 (9.6)	4 (5.6)	12 (16.0)
Upper respiratory tract infection	5 (6.8)	4 (5.6)	5 (6.7)
Influenza	1 (1.4)	3 (4.2)	5 (6.7)
Rhinitis	6 (8.2)	2 (2.8)	2 (2.7)
Hypertension	3 (4.1)	2 (2.8)	2 (2.7)
Back pain	2 (2.7)	2 (2.8)	4 (5.3)
Cough	1 (1.4)	2 (2.8)	4 (5.3)
Dyspnea	1 (1.4)	2 (2.8)	4 (5.3)
Vertigo	3 (4.1)	1 (1.4)	2 (2.7)
Nausea	0	1 (1.4)	3 (4.0)
Pneumonia	3 (4.1)	0	3 (4.0)
Presyncope	3 (4.1)	0	0
Oral candidiasis	0	0	4 (5.3)
Status asthmaticus	0	0	3 (4.0)

n (%)

7.2.4 Long-term treatment study in patients with asthma (CTD 5.3.5.1-6, Study D3250C00021 [BORA study] [November 2014 to [redacted] 20[redacted], data cut-off (only data from Japanese subjects)])

A randomized, double-blind, parallel group study was conducted in 24 countries, including Japan, to evaluate the long-term safety of benralizumab in patients with asthma who had completed one of the 3 studies, the SIROCCO, CALIMA, and ZONDA studies (target sample size, 1200 subjects [600 in the Q8W group, 600 in the Q4W group]). Although this study is still ongoing under a blinded condition, data cut-off was implemented on [redacted], 20[redacted] when the last enrolled Japanese subject completed the 56-week treatment period, the results of an interim analysis only in Japanese subjects were submitted.

Subjects who had been assigned to the benralizumab group in the preceding study received benralizumab in combination with ICS/LABA at the same dosage regimen as done previously, and subjects who had been assigned to the placebo group received subcutaneous benralizumab at 30 mg every 4 or 8 weeks for 56 weeks (108 weeks for non-Japanese subjects aged 12 to 17 years) in combination with ICS/LABA.[29)]

A total of 73 subjects (37 in the Q8W group, 36 in the Q4W group) received the study drug and were included in the FAS and safety analysis set. The breakdown of the subjects is as follows: 50 subjects who had received benralizumab in the CALIMA study (26 in the Q8W group, 24 in the Q4W group) and 23 subjects who had received placebo in the CALIMA study before being randomized in this study (11 in the Q8W group, 12 in the Q4W group). The study was discontinued in 5.4% (2 of 37) of subjects

[29)] In the Q8W group, benralizumab was additionally administered at Week 4. All the subjects aged 12 to 17 years in the EU region were assigned to the Q8W group.

in the Q8W group and 8.3% (3 of 36) of subjects in the Q4W group due to decision of the subjects (2.7% [1 of 37] of subjects in the Q8W group) and others (2.7% [1 of 37] of subjects in the Q8W group, 8.3% [3 of 36] of subjects in the Q4W group).

Adverse events occurred in 94.6% (35 of 37) of subjects in the Q8W group and 97.2% (35 of 36) of subjects in the Q4W group. The major adverse events are shown in Table 32.

No deaths occurred. Serious adverse events occurred in 8.1% (3 of 37) of subjects in the Q8W group and 11.1% (4 of 36) of subjects in the Q4W group. A causal relationship to the study drug was ruled out for any event. No adverse events leading to discontinuation occurred. Adverse drug reactions occurred in 5.4% (2 of 37) of subjects in the Q8W group and 8.3% (3 of 36) of subjects in the Q4W group.

Table 32. Adverse events reported by ≥3 subjects in any group (safety analysis set, Japanese subpopulation)

Event	Q8W (N = 37)	Q4W (N = 36)
Viral upper respiratory tract infection	17 (45.9)	20 (55.6)
Rhinitis allergic	4 (10.8)	7 (19.4)
Pharyngitis	2 (5.4)	5 (13.9)
Herpes zoster	1 (2.7)	5 (13.9)
Influenza	2 (5.4)	4 (11.1)
Asthma	4 (10.8)	3 (8.3)
Bronchitis	3 (8.1)	3 (8.3)
Gastroenteritis	1 (2.7)	3 (8.3)
Pyrexia	0	3 (8.3)
Hypertension	0	3 (8.3)
Conjunctivitis allergic	3 (8.1)	2 (5.6)
Upper respiratory tract infection	3 (8.1)	1 (2.8)

n (%)

In this study (2133 subjects), deaths occurred in 9 subjects (cardiac arrest and death in 2 subjects each; multi-organ failure, fall, asthma, ischaemic stroke, and cystitis in 1 subject each) as of the time of data cut-off in [redacted] 20[redacted]. A causal relationship between the study drug and multi-organ failure could not be ruled out.

7.R Outline of the review conducted by PMDA

7.R.1 Development plan

The applicant's explanation about the development plan of benralizumab:

In Japan, patients with bronchial asthma are treated in accordance with the JGL consisting of diagnostic criteria and treatment algorithm that follow the Global Initiative for Asthma (GINA) 2016, a clinical practice guideline available in Europe and the US. In addition, there are no differences in pharmacokinetics of benralizumab between Japanese and non-Japanese patients that may affect the efficacy and safety [see Section 6.R.1]. Therefore, it was possible to evaluate the efficacy and safety of benralizumab in Japanese patients with asthma based on clinical data package from multi-regional phase III studies involving Japan.

- Patient population, primary efficacy population

The applicant decided to proceed with clinical development of benralizumab by targeting patients with severe asthma uncontrolled despite combination therapy with high-dose ICS and LABA, as

recommended in Step 4 in the JGL, and to collect information on patients receiving medium-dose ICS (CALIMA study) and about OCS reduction (ZONDA study) from the clinical studies.

Results from the foreign phase II study (Study MI-CP220) (Table 33) indicated that patients with higher baseline blood eosinophil count tended to have higher response to benralizumab. More specifically, patients with baseline blood eosinophil count ≥300/μL tended to have higher response to benralizumab than those with baseline blood eosinophil count <300/μL. In the multi-regional phase III studies (CALIMA and SIROCCO studies), the primary efficacy population was defined as the patient population with baseline blood eosinophil count ≥300/μL. Because this reference blood eosinophil count of 300/μL was defined based on the results of exploratory investigation, the multi-regional phase III studies also included patients with baseline blood eosinophil count <300/μL to accommodate evaluation of the efficacy of benralizumab irrespective of blood eosinophil counts.

Table 33. Annual asthma exacerbation rate by blood eosinophil count (Study MI-CP220, mITT population)

		2 mg	20 mg	100 mg	Placebo
Baseline blood eosinophil count <200/μL	N	6	3	70	83
	Annual asthma exacerbation rate (episodes/patient-year)	0.22	0	0.51	0.66
	Compared to placebo	-	-	0.77	
Baseline blood eosinophil count ≥200/μL	N	75	78	151	139
	Annual asthma exacerbation rate (episodes/patient-year)	0.67	0.39	0.35	0.50
	Compared to placebo	1.30	0.76	0.70	
Baseline blood eosinophil count <300/μL	N	16	11	124	139
	Annual asthma exacerbation rate (episodes/patient-year)	0.21	0.82	0.42	0.49
	Compared to placebo	0.43	1.70	0.84	
Baseline blood eosinophil count ≥300/μL	N	65	70	97	83
	Annual asthma exacerbation rate (episodes/patient-year)	0.75	0.30	0.38	0.68
	Compared to placebo	1.07	0.43	0.57	
Baseline blood eosinophil count <400/μL	N	31	28	163	170
	Annual asthma exacerbation rate (episodes/patient-year)	0.52	0.47	0.47	0.50
	Compared to placebo	1.06	0.95	0.93	
Baseline blood eosinophil count ≥400/μL	N	50	53	58	52
	Annual asthma exacerbation rate (episodes/patient-year)	0.72	0.33	0.23	0.78
	Compared to placebo	0.94	0.43	0.30	

PMDA's view:

PMDA accepted the above explanation. It is possible to evaluate the efficacy and safety of benralizumab in patients with bronchial asthma based on the submitted clinical data package with the focus on results from the multi-regional phase III study (CALIMA study) involving Japanese patients. In addition, the therapeutic confirmatory study is acceptable because it was designed to select the annual asthma exacerbation rate as the primary endpoint and to include patients with severe bronchial asthma uncontrolled despite high- or medium-dose ICS and LABA. PMDA intends to assess how baseline blood eosinophil count affect the efficacy evaluation of benralizumab, based on data from phase III studies including the CALIMA study.

7.R.2 Efficacy

7.R.2.1 Efficacy of benralizumab

The applicant's explanation about suppressive effects of benralizumab on asthma exacerbation:
The results from phase III studies (CALIMA and SIROCCO studies) demonstrated the superiority of both benralizumab 30 mg Q8W and Q4W regimens to placebo [see Table 34]in terms of the primary endpoint of the annual asthma exacerbation rate [for the definition, see Section 10] in patients with asthma with eosinophil counts ≥300/μL on high-dose ICS. Data from the Japanese subpopulation in the CALIMA study showed a similar trend to those from the overall population.

Figure 5 presents the time to first asthma exacerbation in the two studies. The time to first asthma exacerbation tended to be prolonged in the benralizumab group than in the placebo group in both studies. Table 35 shows details of asthma exacerbation by event. The annual asthma exacerbation rate tended to be lower in the benralizumab group than in the placebo group for any event in the SIROCCO study and for the event requiring OCS in the CALIMA study.

Table 34. Annual asthma exacerbation rate in phase III studies (FAS, patient population with high-dose ICS and baseline blood eosinophil count ≥300/μL)

	CALIMA study						SIROCCO study		
	Overall			Japanese subpopulation			Overall		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	239	241	248	15	15	16	267	275	267
Number of asthma exacerbations (episodes)	163	163	270	6	13	48	156	206	365
Overall duration of observation period (patient-year)	245.4	254.2	261.2	14.6	15.5	16.7	236.1	242.7	238.2
Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.64	1.03	0.41	0.84	2.87	0.66	0.85	1.53
Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.66 [0.54, 0.82]	0.60 [0.48, 0.74]	0.93 [0.77, 1.12]	0.42 [0.15, 1.18]	0.83 [0.36, 1.89]	2.45 [1.23, 4.89]	0.65 [0.53, 0.80]	0.73 [0.60, 0.89]	1.33 [1.12, 1.58]
Compared to placebo[a] [95% CI], *P* value[a][b]	0.72 [0.54, 0.95] *P* = 0.019	0.64 [0.49, 0.85] *P* = 0.002		0.17 [0.05, 0.60]	0.34 [0.11, 0.99]		0.49 [0.37, 0.64] *P* < 0.001	0.55 [0.42, 0.71] *P* < 0.001	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before this study participation, and use or non-use of OCS as covariates
b) Two-sided level of significance was 4%. Multiplicity of the test was adjusted by Hochberg' procedure.

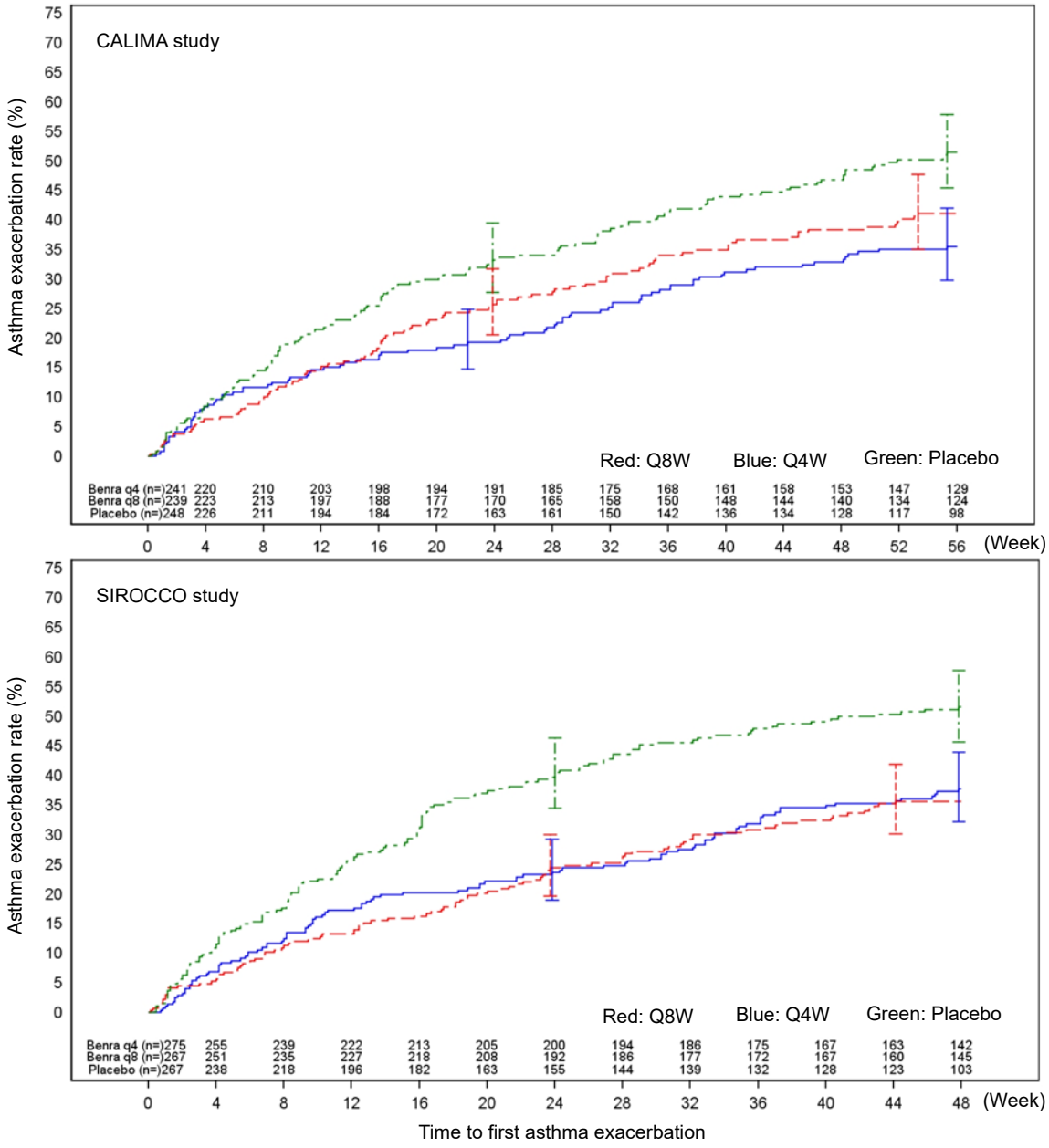

Figure 5. Kaplan-Meier plot on the first asthma exacerbation
(FAS, patient population with high-dose ICS and baseline blood eosinophil count ≥300/μL)

Table 35. Annual asthma exacerbation rate in phase III studies
(FAS, patient population with high-dose ICS and baseline blood eosinophil count ≥300/μL)

			CALIMA study			SIROCCO study		
			Q8W (N = 239)	Q4W (N = 241)	Placebo (N = 248)	Q8W (N = 267)	Q4W (N = 275)	Placebo (N = 267)
Overall duration of observation period (patient-year)			245.4	254.2	261.2	236.1	242.7	238.2
All asthma exacerbations		Number of asthma exacerbations (episodes)	163	163	270	156	206	365
		Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.64	1.03	0.66	0.85	1.53
		Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.66 [0.54, 0.82]	0.60 [0.48, 0.74]	0.93 [0.77, 1.12]	0.65 [0.53, 0.80]	0.73 [0.60, 0.89]	1.33 [1.12, 1.58]
		Compared to placebo[a] [95% CI] *P* value[a][b]	0.72 [0.54, 0.95] *P* = 0.019	0.64 [0.49, 0.85] *P* = 0.002		0.49 [0.37, 0.64] *P* < 0.001	0.55 [0.42, 0.71] *P* < 0.001	
Event	Systemic corticosteroid	Number of asthma exacerbations (episodes)	133	136	236	134	169	313
		Annual asthma exacerbation rate (episodes/patient-year)	0.54	0.54	0.90	0.57	0.70	1.31
		Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.58 [0.46, 0.73]	0.54 [0.43, 0.67]	0.88 [0.72, 1.06]	0.59 [0.47, 0.75]	0.68 [0.55, 0.85]	1.29 [1.06, 1.56]
		Compared to placebo[a] [95% CI]	0.66 [0.49, 0.89]	0.61 [0.46, 0.82]		0.46 [0.34, 0.62]	0.53 [0.40, 0.71]	
	Emergency room or urgent outpatient care visit	Number of asthma exacerbations (episodes)	11	11	11	6	18	25
		Annual asthma exacerbation rate (episodes/patient-year)	0.04	0.04	0.04	0.03	0.07	0.10
		Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.06 [0.03, 0.12]	0.04 [0.02, 0.08]	0.04 [0.02, 0.08]	0.03 [0.01, 0.08]	0.08 [0.04, 0.14]	0.13 [0.07, 0.24]
		Compared to placebo[a] [95% CI]	1.38 [0.49, 3.88]	0.95 [0.35, 2.61]		0.23 [0.09, 0.62]	0.59 [0.29, 1.20]	
	Hospitalization	Number of asthma exacerbations (episodes)	18	12	15	14	17	26
		Annual asthma exacerbation rate (episodes/patient-year)	0.07	0.05	0.06	0.06	0.07	0.11
		Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.07 [0.04, 0.13]	0.05 [0.03, 0.10]	0.05 [0.03, 0.09]	0.07 [0.03, 0.14]	0.09 [0.04, 0.18]	0.14 [0.07, 0.27]
		Compared to placebo[a] [95% CI]	1.48 [0.65, 3.37]	1.02 [0.42, 2.49]		0.48 [0.22, 1.03]	0.62 [0.31, 1.27]	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before this study participation, and use or non-use of OCS as covariates
b) Two-sided level of significance was 4%. Multiplicity of the test was adjusted by Hochberg' procedure.

Changes from baseline in pre-bronchodilator FEV_1 at the end of treatment (Table 36) in the CALIMA and SIROCCO studies (Week 56 in the CALIMA study, Week 48 in the SIROCCO study) tended to be higher in the benralizumab group than in the placebo group. Data from the Japanese subpopulation in the CALIMA study showed a similar trend to those from the overall population.

Table 36. Pre-bronchodilator FEV_1 (L) in phase III studies (FAS, patient population with high-dose ICS and baseline blood eosinophil count ≥300/μL)

	CALIMA study						SIROCCO study		
	Overall			Japanese subgroup			Q8W	Q4W	Placebo
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo			
Baseline	1.758 ± 0.622 (239)	1.750 ± 0.570 (239)	1.815 ± 0.648 (245)	1.721 ± 0.506 (15)	1.466 ± 0.488 (15)	1.616 ± 0.652 (16)	1.660 ± 0.574 (266)	1.673 ± 0.577 (273)	1.654 ± 0.580 (262)
End of treatment	2.077 ± 0.786 (211)	2.058 ± 0.689 (218)	1.997 ± 0.800 (223)	2.142 ± 0.522 (13)	2.065 ± 0.562 (13)	1.761 ± 0.636 (15)	2.075 ± 0.736 (236)	2.006 ± 0.703 (237)	1.919 ± 0.748 (236)
Change from baseline	0.332 ± 0.518 (211)	0.340 ± 0.469 (216)	0.206 ± 0.471 (221)	0.400 ± 0.419 (13)	0.605 ± 0.441 (13)	0.163 ± 0.451 (15)	0.398 ± 0.546 (235)	0.353 ± 0.503 (236)	0.237 ± 0.508 (233)
Difference from placebo[a)] [95% CI]	0.116 [0.028, 0.204]	0.125 [0.037, 0.213]		0.198 [−0.118, 0.514]	0.334 [0.020, 0.647]		0.159 [0.068, 0.249]	0.106 [0.016, 0.196]	

Mean ± SD (N)

a) Repeated measures analysis model using baseline value, region, use or non-use of OCS, time point, and interaction of the dose group with time point as covariates

The primary endpoint of the ZONDA study was percent reduction in final OCS dose compared with baseline (defined as 100%) while maintaining asthma control. The study demonstrated the superiority of both benralizumab 30 mg Q8W and Q4W regimens to placebo in terms of the primary endpoint (Table 30). In addition, the percentage of patients who achieved OCS reduction at Week 28 tended to be higher in the benralizumab group than in the placebo group [see Table 37].

Table 37. Results by percent OCS reduction at Week 28, ZONDA study (FAS)

	Q8W (N = 73)	Q4W (N = 72)	Placebo (N = 75)
Reduction (>0%)	58 (79.5)	55 (76.4)	40 (53.3)
≥90% reduction[a)]	27 (37.0)	24 (33.3)	9 (12.0)
≥75% reduction	37 (50.7)	38 (52.8)	15 (20.0)
≥50% reduction	48 (65.8)	48 (66.7)	28 (37.3)
No change or increase	15 (20.5)	17 (23.6)	35 (46.7)

n (%)

a) Only subjects with baseline OCS dose ≤12.5 mg were allowed to have 100% reduction.

In the CALIMA and SIROCCO studies, some of the subjects were not randomized in accordance with the ICS dose definition specified in the protocol.

The applicant's explanation about this matter and its impact on the efficacy:

In the protocols for these studies, high-dose ICS was defined as a dose equivalent to fluticasone propionate dry powder >500 μg per day. The protocols, however, specified that stratification by ICS dose might be performed at the discretion of the investigator because of differences in approved dose, type, and dosage form of steroids among participating countries. As a consequence, some of the patients were included in a different ICS stratum from that initially specified.

Actual ICS doses in subjects included in these studies underwent scrutiny, and an additional analysis was performed as defined in the protocol. The results of the analysis showed that both the annual asthma exacerbation rate (Table 38) and pre-bronchodilator FEV_1 at the end of treatment (Table 39) were comparable to those of the primary analysis.

Table 38. Additional analysis of annual asthma exacerbation rate in phase III studies (FAS, patient population with high-dose ICS redefined and baseline blood eosinophil count ≥300/μL)

	CALIMA study			SIROCCO study		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	227	223	229	252	256	252
Number of asthma exacerbations (episodes)	153	158	249	140	192	349
Overall duration of observation period (patient-year)	235.4	236.3	242.0	223.2	227.2	225.3
Annual asthma exacerbation rate (episodes/patient-year)	0.65	0.67	1.03	0.63	0.85	1.55
Annual asthma exacerbation rate[a)] (episodes/patient-year) [95% CI]	0.66 [0.53, 0.81]	0.61 [0.49, 0.75]	0.91 [0.75, 1.10]	0.60 [0.48, 0.75]	0.73 [0.59, 0.89]	1.32 [1.10, 1.57]
Compared to placebo[a)] [95% CI]	0.72 [0.54, 0.96]	0.67 [0.50, 0.89]		0.46 [0.34, 0.61]	0.55 [0.42, 0.72]	

a) Negative binomial regression model using the number of asthma exacerbations in the past 1 year before study participation and use or non-use of OCS as covariates

Table 39. Additional analysis of pre-bronchodilator FEV_1 (L) in phase III studies (FAS, patient population with high-dose ICS redefined and baseline blood eosinophil count ≥300/μL)

	CALIMA study			SIROCCO study		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
Change from baseline[a)]	0.347 (203)	0.335 (202)	0.229 (205)	0.398 (223)	0.343 (220)	0.251 (221)
Difference from placebo[a)] [95% CI]	0.118 [0.027, 0.210]	0.106 [0.014, 0.198]		0.147 [0.054, 0.240]	0.093 [0.000, 0.185]	

Estimate from the model (N)

a) Repeated measures analysis model using baseline value, region, use or non-use of OCS, time point, and interaction of the dose group with time point as covariates

Based on the above, the applicant considers that the efficacy of benralizumab in patients with severe asthma has been demonstrated by the data submitted.

PMDA's view:

The phase III studies (CALIMA, SIROCCO, and ZONDA studies) demonstrated the superiority of both benralizumab 30 mg Q8W and Q4W regimens to placebo in patients with asthma uncontrolled despite high-dose ICS and LABA in terms of the annual asthma exacerbation rate and percent reduction in OCS dose. In addition, respiratory function parameters tended to improve in the benralizumab group compared with the placebo group. The data supported the efficacy of benralizumab in this patient population. Furthermore, the efficacy data in the Japanese subgroup were consistent to those in the overall population in the CALIMA study; accordingly, the data supported the efficacy of benralizumab in Japanese patients with bronchial asthma. In the studies, some of the patients were included in a different ICS stratum from that initially specified. This matter is a significant problem that compromise the integrity of clinical study data, although it was found to have no considerable impact on the efficacy evaluation of benralizumab. The applicant should have ensured strict adherence to the specified definition.

7.R.2.2 Blood eosinophil counts and efficacy

The applicant's explanation about the efficacy in patients with blood eosinophil counts <300/μL:

Table 40 shows the annual asthma exacerbation rate in subjects on high-dose ICS in the phase III studies (CALIMA and SIROCCO studies) by baseline blood eosinophil count. The annual asthma exacerbation rate tended to be decreased even in the subgroup of patients with blood eosinophil counts <300/μL.

Table 40. Annual asthma exacerbation rate in phase III studies by baseline blood eosinophil count (FAS, subjects on high-dose ICS, until Week 56 in the CALIMA study and until Week 48 in the SIROCCO study)

	CALIMA study						SIROCCO study					
	Blood eosinophil counts ≥300/μL			Blood eosinophil counts <300/μL			Blood eosinophil counts ≥300/μL			Blood eosinophil counts <300/μL		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	239	241	248	125	116	122	267	275	267	131	124	140
Number of asthma exacerbations (episodes)	163	163	270	93	102	167	156	206	365	122	104	165
Overall duration of observation period (patient-year)	245.4	254.2	261.2	122.0	120.7	123.2	236.1	242.7	238.2	116.0	109.0	125.7
Annual asthma exacerbation rate (episodes/patient-year)	0.66	0.64	1.03	0.76	0.84	1.36	0.66	0.85	1.53	1.05	0.95	1.31
Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.66 [0.54, 0.82]	0.60 [0.48, 0.74]	0.93 [0.77, 1.12]	0.73 [0.55, 0.95]	0.78 [0.59, 1.02]	1.21 [0.96, 1.52]	0.65 [0.53, 0.80]	0.73 [0.60, 0.89]	1.33 [1.12, 1.58]	1.00 [0.78, 1.28]	0.85 [0.65, 1.11]	1.21 [0.96, 1.52]
Compared to placebo[a] [95% CI] *P* value[a][b]	0.72 [0.54, 0.95] *P* = 0.019	0.64 [0.49, 0.85] *P* = 0.002		0.60 [0.42, 0.86]	0.64 [0.45, 0.92]		0.49 [0.37, 0.64] *P* < 0.001	0.55 [0.42, 0.71] *P* < 0.001		0.83 [0.59, 1.16]	0.70 [0.50, 1.00]	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before this study participation, and use or non-use of OCS as covariates

b) Two-sided level of significance was 4%. Multiplicity of the test was adjusted by Hochberg' procedure.

Figure 6 shows a locally weighted scatter plot smooth (LOESS) plot based on the scatter plot of the annual asthma exacerbation rate against the baseline blood eosinophil count in the high-dose ICS subset in the pooled data from the CALIMA and SIROCCO studies.

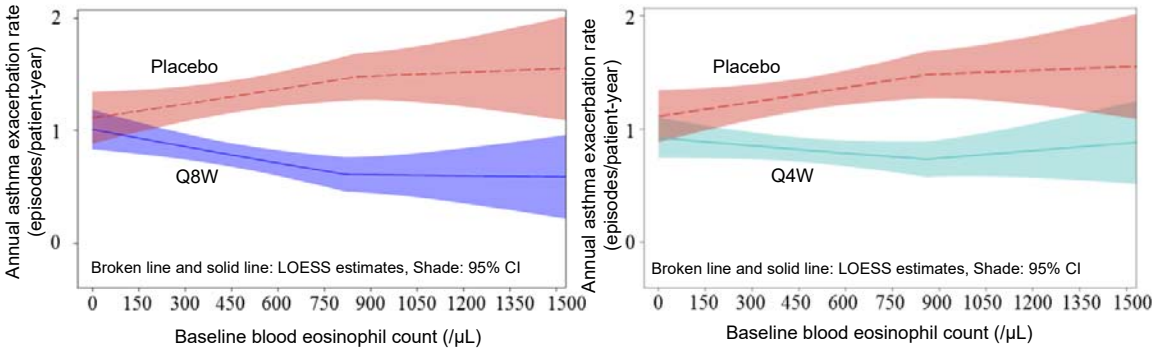

Figure 6. Relationship of asthma exacerbation rate with blood eosinophil count (FAS, high-dose ICS subset)

PMDA's view:

Benralizumab is expected to reduce asthma exacerbation also in patients with baseline blood eosinophil count <300/μL. However, the data suggested that benralizumab have a smaller reducing effect on asthma exacerbation in patients with lower blood eosinophil counts. Therefore, the following caution statement should be provided: The eligibility of patients for treatment with benralizumab should be determined considering their baseline blood eosinophil count [see Section 7.R.5].

7.R.3 Safety

The applicant explained the safety of benralizumab, based on pooled data from CALIMA and SIROCCO studies (pooled phase III population), data from Japanese subjects in the CALIMA study (placebo-controlled Japanese population), and pooled data from Japanese subjects in the CALIMA and BORA studies (pooled Japanese population). The applicant's explanation is as follows:

Table 41 summarizes data on the safety of benralizumab in the pooled phase III population, placebo-controlled Japanese population, and pooled Japanese population.

Table 41. Summary of the safety of benralizumab in patients with asthma

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Total exposure period (patient-year)	764.5	794.9	795.6	30.0	27.9	26.1	68.5	65.4
Death	3 (0.4)	4 (0.5)	2 (0.2)	1 (3.3)	0	0	1 (2.4)	0
Adverse events	601 (73.1)	615 (73.1)	653 (77.1)	29 (96.7)	26 (92.9)	25 (100.0)	40 (97.6)	38 (95.0)
Serious adverse events	92 (11.2)	92 (10.9)	115 (13.6)	2 (6.7)	1 (3.6)	1 (4.0)	5 (12.2)	5 (12.5)
Adverse events leading to discontinuation	18 (2.2)	17 (2.0)	7 (0.8)	2 (6.7)	3 (10.7)	0	2 (4.9)	3 (7.5)
Adverse drug reactions	118 (14.4)	106 (12.6)	78 (9.2)	3 (10.0)	2 (7.1)	2 (8.0)	5 (12.2)	5 (12.5)

n (%)

Table 42 shows major adverse events in pooled phase III population, and Table 43 shows major adverse events in the placebo-controlled Japanese population and pooled Japanese population. No clear differences were observed in the type or incidence of adverse events among these populations.

Table 42. Adverse events reported by ≥3% of subjects in any group (pooled phase III population)

Event	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)
Nasopharyngitis	125 (15.2)	137 (16.3)	139 (16.4)
Asthma	92 (11.2)	121 (14.4)	146 (17.2)
Upper respiratory tract infection	68 (8.3)	73 (8.7)	77 (9.1)
Bronchitis	63 (7.7)	64 (7.6)	82 (9.7)
Headache	71 (8.6)	63 (7.5)	53 (6.3)
Influenza	33 (4.0)	39 (4.6)	47 (5.5)
Sinusitis	42 (5.1)	38 (4.5)	65 (7.7)
Pharyngitis	33 (4.0)	33 (3.9)	21 (2.5)
Pyrexia	24 (2.9)	32 (3.8)	14 (1.7)
Rhinitis allergic	28 (3.4)	31 (3.7)	31 (3.7)
Rhinitis	27 (3.3)	28 (3.3)	32 (3.8)
Back pain	19 (2.3)	27 (3.2)	31 (3.7)
Cough	27 (3.3)	25 (3.0)	18 (2.1)
Hypertension	28 (3.4)	23 (2.7)	33 (3.9)
Arthralgia	32 (3.9)	19 (2.3)	19 (2.2)

n (%)

Table 43. Major adverse events in the placebo-controlled and pooled Japanese populations

Placebo-controlled Japanese population (reported by ≥3 subjects in any group)				Pooled Japanese population (reported by ≥5% of subjects in either group)		
Event	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Event	Q8W (N = 41)	Q4W (N = 40)
Nasopharyngitis	13 (43.3)	14 (50.0)	13 (52.0)	Nasopharyngitis[a)]	23 (56.1)	26 (65.0)
Rhinitis allergic	2 (6.7)	4 (14.3)	3 (12.0)	Rhinitis allergic	6 (14.6)	10 (25.0)
Contusion	1 (3.3)	4 (14.3)	1 (4.0)	Pharyngitis	2 (4.9)	8 (20.0)
Pharyngitis	0	4 (14.3)	1 (4.0)	Herpes zoster	1 (2.4)	6 (15.0)
Eczema	1 (3.3)	3 (10.7)	1 (4.0)	Bronchitis	6 (14.6)	5 (12.5)
Cystitis	0	3 (10.7)	2 (8.0)	Influenza	3 (7.3)	5 (12.5)
Bronchitis	4 (13.3)	2 (7.1)	4 (16.0)	Contusion	3 (7.3)	5 (12.5)
Asthma	3 (10.0)	2 (7.1)	1 (4.0)	Asthma	6 (14.6)	4 (10.0)
Influenza	1 (3.3)	2 (7.1)	4 (16.0)	Eczema	2 (4.9)	4 (10.0)
Sinusitis	3 (10.0)	1 (3.6)	0	Pyrexia	2 (4.9)	4 (10.0)
Upper respiratory tract infection	3 (10.0)	1 (3.6)	3 (12.0)	Hypertension	0	4 (10.0)
Upper respiratory tract inflammation	3 (10.0)	1 (3.6)	1 (4.0)	Conjunctivitis allergic	4 (9.8)	3 (7.5)
Urticaria	4 (13.3)	0	2 (8.0)	Pneumonia bacterial	2 (4.9)	3 (7.5)
Epistaxis	3 (10.0)	0	0	Cystitis	1 (2.4)	3 (7.5)
Back pain	0	0	3 (12.0)	Diarrhoea	1 (2.4)	3 (7.5)
Dermatitis atopic	0	0	3 (12.0)	Gastroenteritis	1 (2.4)	3 (7.5)
				Cataract	0	3 (7.5)
				Seasonal allergy	0	3 (7.5)
				Upper respiratory tract infection	4 (9.8)	2 (5.0)
				Upper respiratory tract inflammation	3 (7.3)	2 (5.0)
				Sinusitis	4 (9.8)	1 (2.5)
				Urticaria	4 (9.8)	1 (2.5)
				Epistaxis	3 (7.3)	0
				Tonsillitis	3 (7.3)	0

n (%)

a) Including an event reported as viral upper respiratory tract infection in the BORA study

Deaths occurred in 9 subjects in the pooled phase III population (overdose, death, and colon neoplasm in 1 subject each in the Q8W group; cerebral haemorrhage, asthma, completed suicide, and road traffic accident in 1 subject each in the Q4W group; pulmonary embolism and death in 1 subject each in the placebo group). Of these, only 1 subject in the Q8W group (death) was Japanese. In addition, deaths occurred in 3 subjects (sudden death in the Q8W group, acute myocardial infarction in the Q4W group, myocardial infarction in the placebo group) during the follow-up period, but a causal relationship to the study drug was ruled out for any death.

Serious adverse events occurred in 11.9% (299 of 2510) of subjects in the pooled phase III population (11.2% [92 of 822] of subjects in the Q8W group, 10.9% [92 of 841] of subjects in the Q4W group, and 13.6% [115 of 847] of subjects in the placebo group). The events reported by >2 subjects in any group were asthma (5.1% [42 of 822] of subjects in the Q8W group, 5.1% [43 of 841] of subjects in the Q4W group, 6.4% [54 of 847] of subjects in the placebo group), pneumonia (0.2% [2 of 822] of subjects in the Q8W group, 0.2% [2 of 841] of subjects in the Q4W group, 0.7% [6 of 847] of subjects in the placebo group), pneumonia bacterial (0.1% [1 of 822] of subjects in the Q8W group, 0.2% [2 of 841] of subjects in the Q4W group, 0.4% [3 of 847] of subjects in the placebo group), osteoarthritis (0.1% [1 of 822] of subjects in the Q8W group, 0.2% [2 of 841] of subjects in the Q4W group, 0.4% [3 of 847] of subjects in the placebo group), hypertension (0.4% [3 of 822] of subjects in the Q8W group, 0% in the Q4W group, 0.1% [1 of 847] of subjects in the placebo group), and nephrolithiasis (0% in the Q8W group, 5.1% [43 of 841] of subjects in the Q4W group, 6.4% [54 of 847] of subjects in the placebo group). No clear differences were observed among the groups. In the pooled Japanese population, serious adverse

events occurred in 12.2% (5 of 41) of subjects in the Q8W group (death, appendicitis, ligament rupture, patella fracture, and large intestine benign neoplasm in 1 subject each) and 12.5% (5 of 40) of subjects in the Q4W group (multiple fractures, endocrine test abnormal, gallbladder cancer, asthma, and middle lobe syndrome in 1 subject each), but a causal relationship to the study drug was ruled out for any event. During the follow-up period, serious adverse events occurred in 2 subjects (asthma and interstitial lung disease in 1 subject each in the Q4W group) in the pooled Japanese population. A causal relationship to the study drug could not be ruled out for interstitial lung disease.

PMDA reviewed the following events in consideration of pharmacological actions of benralizumab and incidences of adverse events in clinical studies.

7.R.3.1 Infections

The applicant's explanation about incidence of infections related to benralizumab:

Table 44 shows the incidence of infections in clinical studies. The incidence of infections was similar among the treatment groups in the pooled phase III population and placebo-controlled Japanese population. Serious infection reported by ≥2 subjects in any group were pneumonia, pneumonia bacterial, influenza, appendicitis, and urinary tract infection bacterial. In the placebo-controlled Japanese population, serious infection occurred in 1 subject in the Q8W group (appendicitis) and 1 subject in the placebo group (pneumonia bacterial). Although both events were severe in severity, a causal relationship to the study drug was ruled out for both. Herpes zoster was non-serious, except for that in 1 subject in the Q8W group in the pooled phase III population. No serious herpes zoster occurred in either the placebo-controlled or pooled Japanese population.

Table 44. Incidences of adverse events related to infections

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Infections and infestations (System Organ Class)								
Adverse events	412 (50.1)	445 (52.9)	466 (55.0)	24 (80.0)	19 (67.9)	20 (80.0)	33 (80.5)	34 (85.0)
Serious adverse events	18 (2.2)	12 (1.4)	19 (2.2)	1 (3.3)	0	1 (4.0)	1 (2.4)	0
Herpes zoster (preferred term)	5 (0.6)	2 (0.2)	6 (0.7)	0	1 (3.6)	0	1 (2.4)	6 (15.0)
Major serious adverse events (preferred term) classified into Infections and infestations (System Organ Class)								
Pneumonia	2 (0.2)	2 (0.2)	6 (0.7)	0	0	0	0	0
Pneumonia bacterial	1 (0.1)	2 (0.2)	3 (0.4)	0	0	1 (4.0)	0	0
Influenza	2 (0.2)	2 (0.2)	1 (0.1)	0	0	0	0	0
Appendicitis	2 (0.2)	0	0	1 (3.3)	0	0	1 (2.4)	0
Urinary tract infection bacterial	0	0	2 (0.2)	0	0	0	0	0

n (%)

Patients with chronic hepatitis B, patients at a risk of reactivation of hepatitis B virus, and patients with chronic hepatitis C were excluded from clinical studies, and thus effects of benralizumab on reactivation of hepatitis B or C virus remain unclear. No events coded to reactivation of hepatitis B or C virus occurred in the pooled phase III population. In addition, no events coded to reactivation of tuberculosis occurred either.

Based on the above, data from clinical studies of benralizumab do not suggest an increased incidence of infections related to benralizumab. However, published literature report that the incidence of infections was elevated in patients with asthma (*J Allergy Clin Immunol.* 2008;122:719-23, *Allergy Asthma Proc.*

2009;30:540-5, etc.). In consideration of the reports, the applicant will continue investigating a risk of infections through a post-marketing surveillance.

PMDA's view:
Currently available data suggest no clear relationship of benralizumab with infections, but a risk of infections related to benralizumab should be further investigated through a post-marketing surveillance, because (i) serious infection events occurred in benralizumab-treated subjects in clinical studies; (ii) whether the pharmacological actions of benralizumab (suppression of IL-5 signal transduction and reduction of eosinophil counts) would affect the immune system remains unclear; and (iii) experience with use of benralizumab in clinical studies is limited.

7.R.3.2 Infection parasitic

The applicant's explanation about the incidence of infection parasitic related to benralizumab:
Decreased eosinophil counts after the use of benralizumab may compromise a natural ability to eliminate parasites, because anti-IL-5 antibody increased survival of *Trichinella spiralis* in mice with eosinophil counts decreased (*Parasite Immunol.* 2000;22:487-92); and infection is commonly associated with a marked increase in eosinophil counts.

Although no infection parasitic was reported in any of the pooled phase III population, placebo-controlled Japanese population, and pooled Japanese population, benralizumab may potentially induce susceptibility to infection parasitic or worsening of infection parasitic due to its mechanism of action. For these reasons, the package insert will advise that patients already infected with parasites should undergo treatment of infection parasitic before receiving benralizumab. In addition, the applicant will continue investigating a risk of infection parasitic through a post-marketing surveillance.

PMDA's view:
Currently available clinical study data suggest no clear relationship of benralizumab with infection parasitic, but benralizumab may potentially compromise the natural ability to eliminate parasites by reducing eosinophil counts because of its mechanism of action. The package insert should advise that patients already infected with parasites should undergo treatment of infection parasitic before receiving benralizumab. Futher, the incidence of infection parasitic should be further investigated through a post-marketing surveillance.

7.R.3.3 Malignancies

The applicant's explanation about the incidence of malignancies related to benralizumab:
Eosinophils are possibly involved in tumor growth, because (i) eosinophilic infiltration was observed in solid cancers, more specifically, epithelial tumors (*Clin Cancer Res.* 1996;2:1867-71); and (ii) increased eosinophil counts were reported as a favorable prognostic factor for some types of solid tumors (*J Pathol.* 1999;189:487-95, *ASCO Annual Meeting Proceedings.* 2011;29:1583).

Table 45 shows the incidence of malignancies in clinical studies. The incidence of malignancies was similar among the treatment groups in the pooled phase III population. Malignancies except for non-melanoma skin cancer (NMSC) occurred in 6 subjects in the pooled phase III population (1 subject in

the Q8W group [colon neoplasm], 3 subjects in the Q4W group [ovarian epithelial cancer, gallbladder cancer, and gastric cancer in 1 subject each], 2 subjects in the placebo group [breast cancer and prostate cancer in 1 subject each]). Of these, 1 subject in the Q4W group (gallbladder cancer) was Japanese. A causal relationship to the study drug was ruled out for any event.

Table 45. Adverse events related to malignancies

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Malignancies	2 (0.2) 0.25	3 (0.4) 0.36	2 (0.2) 0.24	0	1 (3.6) 3.44	0	0	1 (2.5) 1.39
NMSC	1 (0.1) 0.13	0	0	0	0	0	0	0
Malignancy[a)] (except for NMSC)	1 (0.1) 0.13	3 (0.4) 0.36	2 (0.2) 0.24	0	1 (3.6) 3.44	0	0	1 (2.5) 1.39
Solid cancer (except for NMSC)	1 (0.1) 0.13	3 (0.4) 0.36	2 (0.2) 0.24	0	1 (3.6) 3.44	0	0	1 (2.5) 1.39
Hematologic malignancy	0	0	0	0	0	0	0	0

Top, n (%); Bottom, number of events per 100 patient-years adjusted by the total exposure period
a) Events identified by Standardised MedDRA Query "Malignancies"

In view of the incidence of malignancies related to drugs in the same class (the incidence rate of malignancies for omalizumab [genetical recombination] was 0.414/100 patient-years in the omalizumab group and 0.445/100 patient-years in the placebo group in a clinical study and 1.60/100 patient-years in the omalizumab group and 1.91/100 patient-years in the control group in a post-marketing observational study; and the incidence of malignancies for mepolizumab [genetical recombination] was 0.3%-0.7% in the mepolizumab group and 0.7% in the placebo group in a clinical study), no marked increase in the risk of malignancies has been observed in patients receiving benralizumab.

PMDA's view:
Currently available data suggest no clear relationship of benralizumab with malignancies, but the incidence of malignancies should be further investigated through a post-marketing surveillance, because (i) the number of subjects included in the clinical studies is not large enough for evaluation of the risk of malignancies; and (ii) benralizumab may potentially increase the risk of malignancies due to its pharmacological action.

7.R.3.4 Cardiovascular events

Although there is no evidence suggesting that cardiovascular events are directly related to the pharmacological action of benralizumab, the events may result in a serious outcome. The applicant investigated the incidence of cardiovascular events related to benralizumab.

The applicant's explanation about the incidence of cardiovascular events:
Table 46 shows the incidence of cardiovascular events as determined by the safety endpoint adjudication committee established by the sponsor. The incidence of cardiovascular events was similar among the treatment groups in the pooled phase III population. A causal relationship to the study drug was ruled out for any of the events. In the placebo-controlled Japanese population, death in 1 subject in the Q8W group was adjudicated to be attributable to the cardiovascular system.

Table 46. Incidences of cardiovascular events

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Cardiovascular events[a)]	4 (0.5)	3 (0.4)	4 (0.5)	1 (3.3)	0	0	1 (2.4)	0
Cardiovascular death	2 (0.2)	1 (0.1)	1 (0.1)	1 (3.3)	0	0	1 (2.4)	0
Myocardial infarction	1 (0.1)	2 (0.2)	2 (0.2)	0	0	0	0	0
Hospitalisation due to angina unstable	1 (0.1)	0	0	0	0	0	0	0
Stroke	0	0	1 (0.1)	0	0	0	0	0

n (%)

a) Events coded to the Standardised MedDRA Queries "Myocardial infarction," "Ischaemic cerebrovascular conditions," and "Haemorrhagic cerebrovascular conditions"

PMDA's view:

Although data show no clear relationship of benralizumab with cardiovascular events, post-marketing information about cardiovascular events related to benralizumab should continue to be collected through published literature and by other means.

7.R.3.5 Hypersensitivity

The applicant's explanation about the incidence of hypersensitivity including anaphylaxis during treatment with benralizumab:

Table 47 shows the incidence of adverse events related to hypersensitivity. The incidence of such events was similar among the treatment groups in the pooled phase III population. Serious adverse events related to hypersensitivity occurred in 3 subjects in the Q8W group (drug hypersensitivity, urticaria papular, and anaphylactic reaction in 1 subject each), 3 subjects in the Q4W group (urticaria, urticaria papular, and allergic granulomatous angiitis in 1 subject each), and 2 subjects in the placebo group (drug hypersensitivity and erythema nodosum in 1 subject each) in the pooled phase III population. A causal relationship to the study drug could not be ruled out for urticaria or allergic granulomatous angiitis. The events of drug hypersensitivity were found related to allergy to metamizole (Q8W group) and diclofenac (placebo group), and the event of anaphylactic reaction was found related to food/peanut allergy. In the placebo-controlled or pooled Japanese population, no serious adverse events related to hypersensitivity occurred.

Table 47. Incidence s of adverse events related to hypersensitivity[a)]

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Hypersensitivity[b)]	24 (2.9)	26 (3.1)	28 (3.3)	4 (13.3)	1 (3.6)	3 (12.0)	4 (9.8)	2 (5.0)
Urticaria	15 (1.8)	16 (1.9)	15 (1.8)	4 (13.3)	0	2 (8.0)	4 (9.8)	1 (2.5)
Drug hypersensitivity	3 (0.4)	2 (0.2)	2 (0.2)	0	0	0	0	0
Swelling face	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	0	0
Face oedema	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Urticaria papular	1 (0.1)	1 (0.1)	0	0	0	0	0	0
Angioedema	0	1 (0.1)	1 (0.1)	0	0	0	0	0
Allergic gastroenteritis	0	1 (0.1)	0	0	1 (3.6)	0	0	1 (2.5)
Allergic granulomatous angiitis	0	1 (0.1)	0	0	0	0	0	0
Allergic pharyngitis	0	1 (0.1)	0	0	0	0	0	0
Palatal oedema	0	1 (0.1)	0	0	0	0	0	0
Reaction to preservatives	0	1 (0.1)	0	0	0	0	0	0
Drug eruption	1 (0.1)	0	1 (0.1)	0	0	0	0	0
Anaphylactic reaction	1 (0.1)	0	0	0	0	0	0	0
Laryngeal oedema	1 (0.1)	0	0	0	0	0	0	0
Lip swelling	1 (0.1)	0	0	0	0	0	0	0

n (%)
a) Events listed in this table are those that occurred in any benralizumab group in the pooled phase III population.
b) Events coded to the Standardised MedDRA Query "Hypersensitivity"

There was no clear trend between development of ADA and hypersensitivity-related adverse events. Of subjects who experienced these events, 1 subject in the Q8W group (urticaria papular) and 2 subjects in the Q4W group (urticaria papular and allergic granulomatous angiitis in 1 subject each) were found to have ADA.

According to the above clinical study results, serious adverse events related to hypersensitivity occurred in subjects receiving benralizumab, although there was no trend toward an increase in the incidence in the benralizumab group as compared with the placebo group. Therefore, the package insert will advise that patients should be carefully monitored during the treatment with benralizumab, and that appropriate measure should be taken if any of the events occurs.

PMDA's review:
Serious hypersensitivity-related adverse events which are possibly related to benralizumab occurred in clinical studies. The relevant precautions should be provided in the package insert and hypersensitivity-related adverse events including anaphylaxis should be further investigated through a post-marketing surveillance.

7.R.3.6 Injection site reaction

The applicant's explanation about the incidences of injection site reaction related to benralizumab:
Table 48 shows the incidence of adverse events related to injection site reaction. In the pooled phase III population, adverse events related to injection site reaction occurred more frequently in the benralizumab group than in the placebo group, but most of the events were non-serious except for the event in 1 non-Japanese subject (injection site erythema) in the placebo group and mild in severity.

Table 48. Incidences of adverse events related to injection site reaction[a)]

	Pooled phase III population			Placebo-controlled Japanese population			Pooled Japanese population	
	Q8W (N = 822)	Q4W (N = 841)	Placebo (N = 847)	Q8W (N = 30)	Q4W (N = 28)	Placebo (N = 25)	Q8W (N = 41)	Q4W (N = 40)
Injection site reaction[b)]	18 (2.2)	27 (3.2)	16 (1.9)	0	1 (3.6)	1 (4.0)	1 (2.4)	1 (2.5)
Injection site erythema	8 (1.0)	8 (1.0)	3 (0.4)	0	0	1 (4.0)	0	0
Injection site pain	7 (0.9)	8 (1.0)	5 (0.6)	0	0	0	0	0
Injection site pruritus	2 (0.2)	4 (0.5)	2 (0.2)	0	0	0	1 (2.4)	0
Injection site reaction	0	3 (0.4)	1 (0.1)	0	1 (3.6)	0	0	1 (2.5)
Injection site induration	0	3 (0.4)	0	0	0	0	0	0

n (%)
a) Events listed in this table are those reported by ≥3 subjects in any benralizumab group in the pooled phase III population.
b) Events coded to the High Level Term "Injection site reactions"

PMDA's view:
There was a trend toward an increase in the incidence of adverse events related to injection site reaction in the benralizumab group as compared with the placebo group in clinical studies. The package insert, therefore, should include precautions for these adverse events. In addition, the applicant should collect the relevant information through a post-marketing surveillance, and should communicate findings to healthcare professionals, as appropriate.

7.R.3.7 Use in the elderly

The applicant's explanation about the incidences of adverse events in the elderly (aged ≥65 years):
Table 49 shows the incidence of adverse events by age in the pooled phase III population. The incidences of adverse events in the Q8W group and placebo group tended to be higher in the elderly subgroup than in the non-elderly subgroup. The incidence of adverse events leading to treatment discontinuation in the Q4W group tended to be lower in the elderly subgroup than in the non-elderly subgroup, but the incidences of such events in the Q8W and placebo groups were similar in the elderly and non-elderly subgroups. The incidence of serious adverse events tended to be higher in the elderly subgroup than in the non-elderly subgroup. Deaths occurred in 8 non-elderly subjects (3 subjects in the Q8W group, 4 subjects in the Q4W group, 1 subject in the placebo group) and in 1 elderly subject (placebo group). An analysis of the incidence of individual events showed that bronchitis was more common in elderly subjects than in non-elderly subjects in the Q8W group.

Although the number of elderly subjects participating in the clinical studies is limited, analyses of the safety profile of benralizumab in the elderly and non-elderly subgroups did not indicate a trend of particular concern.

Table 49. Incidences of adverse events by age (pooled phase III population)

	<65 years			≥65 years		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	731	732	727	91	109	120
Adverse events	526 (72.0)	538 (73.5)	553 (76.1)	75 (82.4)	77 (70.6)	100 (83.3)
Nasopharyngitis	108 (14.8)	122 (16.7)	113 (15.5)	17 (18.7)	15 (13.8)	26 (21.7)
Asthma	81 (11.1)	106 (14.5)	124 (17.1)	11 (12.1)	15 (13.8)	22 (18.3)
Upper respiratory tract infection	65 (8.9)	61 (8.3)	73 (10.0)	3 (3.3)	12 (11.0)	4 (3.3)
Headache	65 (8.9)	56 (7.7)	48 (6.6)	12 (13.2)	9 (8.3)	11 (9.2)
Bronchitis	51 (7.0)	55 (7.5)	71 (9.8)	6 (6.6)	7 (6.4)	5 (4.2)
Serious adverse events	78 (10.7)	77 (10.5)	94 (12.9)	14 (15.4)	15 (13.8)	21 (17.5)
Death	3 (0.4)	4 (0.5)	1 (0.1)	0	0	1 (0.8)
Adverse events leading to treatment discontinuation	16 (2.2)	16 (2.2)	6 (0.8)	2 (2.2)	1 (0.9)	1 (0.8)

n (%)

PMDA's view:

Currently available data do not show any clear concern about the safety profile of benralizumab and the incidence of adverse events in the elderly. The safety profile of benralizumab in the elderly aged ≥65 years, however, should be further investigated through a post-marketing surveillance, because (i) there is a trend toward an increase in the incidence of serious adverse events in the subgroup of subjects aged ≥65 years as compared with the subgroup of subjects aged <65 years; and (ii) the number of subjects aged ≥65 years participating in the clinical studies is limited.

PMDA's view on the safety of benralizumab based on the review in Sections 7.R.3.1 to 7.R.3.7:

The submitted clinical study data do not suggest significant concerns about the safety of benralizumab in patients with severe asthma, and the reported adverse events are manageable. Patients should be carefully monitored during treatment with benralizumab, because (i) serious adverse events including serious hypersensitivity occurred in the clinical studies; and (ii) therapy with benralizumab may be prolonged, and a risk of infections as a consequence of long-term inhibition of IL-5 signaling and of sustained reduction in blood eosinophil counts remains unclear at present. In addition, the applicant should continue collecting information on the long-term safety of benralizumab through a post-marketing surveillance because the current experience with use of benralizumab in Japanese patients is limited, although the safety data from the Japanese subpopulation have not identified any events specific to Japanese patients.

A final decision on the PMDA's conclusion will be made, taking also account of comments raised in the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of benralizumab:

As described in the review in Section 7.R.2, the CALIMA and SIROCCO studies demonstrated that benralizumab reduced annual asthma exacerbation rate in patients with asthma uncontrolled despite high-dose ICS/LABA, and that benralizumab also tended to improve respiratory function. In addition, the ZONDA study showed that benralizumab reduced the dose of OCS in patients with severe asthma treated with high-dose ICS/LABA and OCS. On the other hand, the CALIMA study also evaluated the efficacy of benralizumab in patients with asthma on medium-dose ICS/LABA, but could not demonstrate the consistent efficacy of benralizumab as compared to placebo [see Table 24].

Based on the above, benralizumab is considered to be positioned as an add-on therapy to high-dose ICS and LABA in patients with severe asthma who suffer asthma exacerbation despite receiving the therapy recommended as the Step 4 therapy in the JGL, namely, combination therapy with high-dose ICS plus LABA, leukotriene receptor antagonists, extended-release theophylline preparations and/or long-acting anticholinergics. The Step 4 therapy presented in the Japanese clinical practice guideline recommend the use of IgE antibody or OCS for patients with asthma uncontrolled despite combination therapy with high-dose ICS and additional therapeutic drugs. Benralizumab may be positioned as one of the add-on drugs in the Step 4 therapy as with the above drugs.

PMDA's view:
Based on the available clinical study data, benralizumab may be used as an option for add-on therapy in patients with severe asthma uncontrolled despite combination therapy with high-dose ICS plus LABA in the Step 4 therapy in the JGL. In addition, the eligibility of patients for treatment with benralizumab should be carefully determined considering the expected benefits and risks of the therapy for individual patients based on the characteristics of patients included in the clinical studies. Benralizumab, therefore, should be administered by physicians with expertise for the treatment of bronchial asthma.

7.R.5 Indication

PMDA's review:
As described in the review in Section 7.R.2, the submitted clinical study data have demonstrated the efficacy of benralizumab in patients with asthma uncontrolled despite high-dose ICS/LABA. With consideration of the clinical positioning of benralizumab, which is expected to be used for patients with intractable bronchial asthma uncontrolled on conventional therapy, benralizumab should be indicated for the treatment of "bronchial asthma (only for patients with intractable bronchial asthma uncontrolled on conventional therapy)," and the package insert should advise that benralizumab should be used as an add-on therapy only in patients who suffer from asthma exacerbation despite maintenance combination therapy with high-dose ICS and other drugs. In addition, as reviewed in Section 7.R.2.2, the efficacy of benralizumab can be expected irrespective of blood eosinophil counts, but the submitted data indicated that the efficacy of benralizumab tended to be higher in patients with higher baseline blood eosinophil count. Therefore, the Precautions for Indications section in the package insert should advise that the eligibility of patients for treatment with benralizumab should be determined considering their blood eosinophil counts.

The above PMDA's conclusions about the indication of benralizumab and the Precautions for Indications will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

The applicant's explanation about the proposed dosage and administration:
The multi-regional phase III studies (SIROCCO and CALIMA studies) demonstrated the superior efficacy of both benralizumab 30 mg Q8W and Q4W regimens to placebo in terms of the primary endpoint of annual asthma exacerbation rate. No clear differences in efficacy were observed between

these regimens for any other efficacy endpoint. In addition, the safety profile did not largely differ between these regimens, nor there were any concerns about tolerability.

Based on the above, the applicant has proposed the following dosage and administration of benralizumab: Benralizumab 30 mg is administered every 4 weeks for the first 3 doses (Weeks 0, 4, and 8), followed by once every 8 weeks thereafter.

PMDA has concluded that the proposed dosage and administration (benralizumab 30 mg is administered every 4 weeks for the first 3 doses [Weeks 0, 4, and 8], followed by once every 8 weeks thereafter) is acceptable.

7.R.7 Post-marketing safety measures

The applicant plans to conduct a post-marketing surveillance to confirm the safety and efficacy of benralizumab including long-term safety and efficacy in post-marketing clinical use.

PMDA's view:
As described in the review in Section 7.R.3, the safety of benralizumab is acceptable based on the clinical study data. However, a post-marketing surveillance should be conducted to investigate the long-term safety profile of benralizumab, because (i) serious adverse events (such as serious hypersensitivity) were reported in the clinical studies; and (ii) therapy with benralizumab may be prolonged, and risks of infections and malignancies as a consequence of long-term inhibition of IL-5 signaling remains unclear at present. The post-marketing surveillance should be used to identify the safety profile of benralizumab including unknown adverse events as early as possible and to continue evaluating the safety and efficacy of benralizumab carefully.

In addition, the applicant should inform healthcare professionals such as physicians of relevant information by using materials to ensure that benralizumab is used by physicians with adequate knowledge about benralizumab and expertise for treatment of bronchial asthma and thereby to ensure the proper use of benralizumab.

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

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

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

Currently, the inspection is ongoing. The results and conclusion of PMDA will be presented in the Review Report (2).

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

Currently, the inspection is ongoing. The results and conclusion of PMDA will be presented in the Review Report (2).

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 bronchial asthma, and that benralizumab has acceptable safety in view of its benefits. Benralizumab can offer an option for treatment of bronchial asthma and thus has clinical significance. Safety information included serious hypersensitivity, and serious adverse events such as serious infections and malignancies may occur. The applicant, therefore, should advise treating physicians that patients should be carefully monitored during treatment with benralizumab, and appropriate measures, including interruption of benralizumab, should be taken if any adverse event is observed. The safety and efficacy of benralizumab in clinical settings including long-term efficacy and safety should be further investigated in the post-marketing surveillance.

PMDA has concluded that Fasenra (benralizumab) may be approved if Fasenra is not considered to have any particular problems based on comments from the Expert Discussion.

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: • Use of systemic corticosteroids (or a temporary increase in a maintenance dose of oral corticosteroids) for at least 3 days • An emergency room or urgent outpatient care visit due to worsening of asthma that requires systemic corticosteroids • Hospitalization due to asthma
ACQ-6	Asthma control questionnaire consisting of questions on asthma symptoms (5 items), self-administered rescue bronchodilator use (1 item), and FEV_1 (1 item), which are scored on a 7-point scale from 0 (completely controlled) to 6 (severely uncontrolled). A patient with the mean score of ≤0.75 is assessed as well-controlled, while a patient with the mean score of ≥1.5 is assessed as not well-controlled.
FEV_1 (forced expiratory volume in one second)	Forced expiratory volume in the first one second in a forced vital capacity measurement

Review Report (2)

November 13, 2017

Product Submitted for Approval

Brand Name	Fasenra Subcutaneous Injection 30 mg Syringe
Non-proprietary Name	Benralizumab (Genetical Recombination)
Applicant	AstraZeneca K.K.
Date of Application	February 22, 2017

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (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 Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy and dosage and administration

The expert advisors of the Expert Discussion supported the conclusions of PMDA about the efficacy of benralizumab and the dosage and administration described in the Review Report (1).

1.2 Indications and precautions for indications

The expert advisors of the Expert Discussion supported the conclusions of PMDA about the indications of benralizumab and the Precautions for Indications statement described in the Review Report (1), and raised the following comments:

- Taking into account that the LOESS plot presented in Figure 6 in Section 7.R.2.2 in the Review Report (1) suggests that the effect of benralizumab tended to be reduced in patients with baseline blood eosinophil count <300/μL, clinical data from subgroups analysis by baseline blood eosinophil count should be provided to healthcare professionals to advise them that the eligibility of patients for treatment with benralizumab should be determined considering blood eosinophil counts.

In response to the comments from the Expert Discussion, PMDA instructed the applicant to include the following precautionary statements in the Precautions for Indications section of the package insert. The applicant responded to the instruction appropriately. In addition, the applicant accepted to prepare materials describing data from patient subgroups according to baseline blood eosinophil count as reference information and provide healthcare professionals with the materials to ensure that they can appropriately determine the eligibility of patients for treatment with benralizumab.

Precautions for Indications

(1) Benralizumab should be administered as an add-on therapy only to patients who have a history of asthma exacerbations requiring systemic corticosteroid treatment despite combination therapy with high dose inhaled corticosteroid and additional maintenance treatment.

(2) The effect of benralizumab to reduce bronchial asthma exacerbation rate tended to be greater in patients with higher baseline blood eosinophil count. Although the data are limited, bronchial asthma exacerbation may be controlled inadequately in patients with low baseline blood eosinophil count. 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 observed in clinical studies should determine the eligibility of patients for treatment with benralizumab considering the patient's blood eosinophil count (see the "Clinical Studies" section).

1.3 Safety and risk management plan (draft)

The expert advisors of the Expert Discussion supported the conclusions of PMDA about the safety and post-marketing safety measures described in the Review Report (1).

In view of the results of the review in Section "7.R.7 Post-marketing safety measures" in the Review Report (1) and of the comments raised by the expert advisors of the Expert Discussion, PMDA has concluded that the current risk management plan (draft) for Fasenra (benralizumab) should include the safety and efficacy specifications presented in Table 50, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 51. PMDA instructed the applicant to conduct a post-marketing surveillance that allows these investigations.

Table 50. 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 • Parasite infections • Malignancies • Immunogenicity	• None
Efficacy specification		
• Efficacy in clinical use		

Table 51. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (long-term)	• Provision of data from early post-marketing phase vigilance • Preparation and provision of materials for healthcare professionals (guideline for indication for appropriate patients)

The applicant's explanation:

As shown in Table 52, the applicant plans to conduct a specified use-results survey (target sample size of 600) with 1-year observation period in patients with asthma uncontrolled on conventional therapy to

evaluate the safety and efficacy of benralizumab in clinical settings. This survey will focus on serious infections as the key survey item. In addition, after the end of the observation period, a 2-year follow-up survey with the focus on the incidence of malignancies will be conducted to further investigate the long-term safety of benralizumab.

Table 52. Outline of specified use-results survey (draft)

Objective	To confirm the long-term safety and efficacy of benralizumab in clinical settings
Survey method	Central registry
Population	Patients with bronchial asthma uncontrolled on conventional therapy
Observation period	1 year (after end of the observation period, 2-year follow-up survey)
Planned sample size	600 patients (for safety analysis)
Main survey items	• Key survey item: Serious infections • Patient characteristics (body weight, age, disease duration, severity, concurrent disease/past history, etc.) • Prior treatment • Status of treatment with benralizumab • Laboratory test (white blood cell count, differential white blood count, total serum IgE level) • Concomitant drugs/therapies • Efficacy evaluation (respiratory function test, etc.) • Adverse events

PMDA has accepted these actions and considers that obtained information should be communicated to healthcare professionals in an appropriate and prompt manner.

1.4 Others (development for use in pediatrics)

The applicant's explanation about the efficacy of benralizumab in pediatric patients and future development plan:

Two clinical studies included some non-Japanese pediatric patients with asthma aged ≥12 years,[30)] namely 55 pediatric patients (21 in the Q8W group, 11 in the Q4W group, 23 in the placebo group) in the CALIMA study and 53 pediatric patients (19 in the Q8W group, 11 in the Q4W group, 23 in the placebo group) in the SIROCCO study. Table 53 shows the annual asthma exacerbation rate in the pooled pediatric population of these studies. The annual asthma exacerbation rate in the benralizumab group does not present any improving trend as compared with the placebo group. In light of the limited number of pediatric patients with asthma included in these studies, no clear conclusion about the efficacy of benralizumab in pediatric patients has been reached at present. The development plan of benralizumab for pediatric use will be further investigated.

[30)] In Japan, only patients aged ≥18 years were included in the studies.

Table 53. Efficacy of benralizumab in pediatric patients aged ≥12 and <18 years (pooled data from the CALIMA and SIROCCO studies, FAS)

	Baseline blood eosinophil count ≥300/μL			Overall subgroup of pediatric patients aged ≥12 and <18 years		
	Q8W	Q4W	Placebo	Q8W	Q4W	Placebo
N	24	17	27	40	22	46
Number of asthma exacerbations (episodes)	17	16	8	26	16	18
Overall duration of observation period (patient-year)	21.8	13.8	24.7	37.8	18.9	43.2
Annual asthma exacerbation rate (episodes/patient-year)	0.78	1.16	0.32	0.69	0.85	0.42
Annual asthma exacerbation rate[a] (episodes/patient-year) [95% CI]	0.81 [0.43, 1.53]	1.14 [0.56, 2.32]	0.32 [0.14, 0.71]	0.70 [0.42, 1.18]	0.78 [0.38, 1.62]	0.41 [0.23, 0.73]
Compared to placebo[a] [95% CI]	2.54 [0.91, 7.03]	3.56 [1.23,10.32]		1.70 [0.78, 3.69]	1.89 [0.75, 4.80]	

a) Negative binomial regression model using the region, number of asthma exacerbations in the past 1 year before study participation, and use or non-use of OCS as covariates

PMDA has accepted the applicant's explanation and considers it desirable to continue investigating the development plan of benralizumab in pediatric patients with asthma including Japanese pediatric patients.

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

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

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. On the basis of the inspection and assessment, some of the case report forms in Study D3250C00018 (CTD 5.3.5.1-4) were found to have no signature of the investigator. The above issue was found, but the investigator signed the relevant case report forms to warrant the content. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

The new drug application data (CTD 5.3.5.1-1, CTD 5.3.5.1-4, CTD 5.3.5.1-6) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indication and the dosage and administration as shown below, with the following condition of approval. Since the product contains a new active ingredient, the re-examination period is 8 years. The

product is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

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

Dosage and Administration

The usual adult dosage 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.

Condition of Approval

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

Appendix

List of Abbreviations

ADA	Anti-drug antibody
ADCC	Antibody-dependent cellular cytotoxicity
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under serum (plasma) concentration-time curve
Benralizumab	Benralizumab (Genetical Recombination)
C1q	Complement component 1, q subcomponent
CAL	Cells at the limit of *in vitro* cell age used for production
CDC	Complement-dependent cytotoxicity
[redacted]	[redacted]
CI	Confidence interval
cIEF	Capillary isoelectric focusing
CL, CL/F	Total clearance, apparent clearance
C_{max}	Maximum serum (plasma) concentration
CQA	Critical quality attribute
DNP	Dinitrophenyl
ECP	Eosinophil cationic protein
EC_x	x% effective serum concentration (x = 50, 80, or 90)
EDN	Eosinophil-derived neutrotoxin
ELISA	Enzyme-linked immunosorbent assay
FAS	Full analysis set
Fasenra	Fasenra Subcutaneous Injection 30 mg Syringe
FcRn	Neonatal Fc receptor
FcγR	Fc gamma receptor
Fe_{NO}	Fractional exhaled nitric oxide
FEV_1	Forced expiratory volume in 1 second
FP	Fluticasone propionate
FUT8	Fucosyltransferase 8
ICS	Inhaled corticosteroid
Ig	Immunoglobulin
IL-5	Interleukin-5
IL-5R	Interleukin-5 receptor
IL-5Rα	Interleukin-5 receptor α subunit
JGL	Asthma Prevention and Management Guideline 2015
K_D	Dissociation constant
LABA	Long-acting β_2 agonist
LAMA	Long-acting muscarinic antagonist
MCB	Master cell bank
Mepolizumab	Mepolizumab (Genetical Recombination)
mITT	Modified intent-to-treat
MRT	Mean residence time
[redacted]	[redacted]
NMSC	Non-melanoma skin cancer
OCS	Oral corticosteroid
Omalizumab	Omalizumab (Genetical Recombination)
PEF	Peak expiratory flow
PMDA	Pharmaceuticals and Medical Devices Agency
QbD	Quality by design
QxW	One every x weeks (x = 4 or 8)
RH	Relative humidity
SABA	Short-acting β_2 agonist

SDS	Sodium dodecyl sulfate
[redacted]	[redacted]
$t_{1/2}$	Elimination half-life
TBL	Total bilirubin
t_{max}	Time to maximum serum (plasma) concentration
V_{ss}, V_z/F	Volume of distribution at steady state, apparent volume of distribution in elimination phase
WCB	Working cell bank