Report on the Deliberation Results

March 3, 2016

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

[Brand Name]	Nucala for S.C. Injection 100 mg
[Non-proprietary Name]	Mepolizumab (Genetical Recombination) (JAN*)
[Applicant]	GlaxoSmithKline K.K.
[Date of Application]	May 22, 2015
[Results of Deliberation]	In the meeting held on February 26, 2016, 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 re-examination period is 8 years. Both the drug product and its drug substance are classified as powerful drugs. The product is classified as a biological product.
[Condition of Approval]	The applicant is required to develop and appropriately implement a risk management plan.

**Japanese Accepted Name (modified INN)*

Review Report

February 17, 2016
Pharmaceuticals and Medical Devices Agency

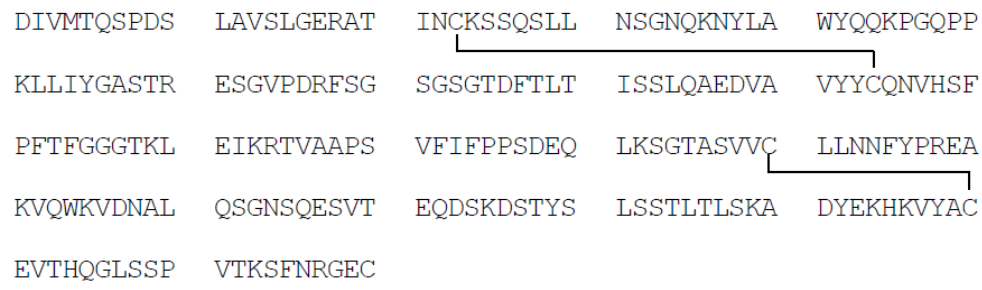
The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand Name]	Nucala for S.C. Injection 100 mg
[Non-proprietary Name]	Mepolizumab (Genetical Recombination)
[Applicant]	GlaxoSmithKline K.K.
[Date of Application]	May 22, 2015
[Dosage form/Strength]	Lyophilized powder in a vial to be reconstituted prior to injection[1]: Each vial contains 144 mg of Mepolizumab (Genetical Recombination).
[Application Classification]	Prescription drug (1) Drug with a new active ingredient
[Definition]	Mepolizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-5 monoclonal antibody and framework regions and constant regions derived from human IgG1. Mepolizumab is produced in Chinese hamster ovary cells. Mepolizumab is a glycoprotein (molecular weight: ca.149,000) composed of 2 H-chains (γ1-chains) consisting of 449 amino acid residues each and 2 L-chains (κ-chains) consisting of 220 amino acid residues each.

[1] The preparation is designed to allow drawing 1 mL of the injectable solution containing 100 mg of Mepolizumab (Genetical Recombination) when it is reconstituted with 1.2 mL of water for injection (JP) prior to injection. Thus, each vial is overfilled with Mepolizumab (Genetical Recombination) to ensure the labeled dose.

[Chemical Structure] Amino acid sequences

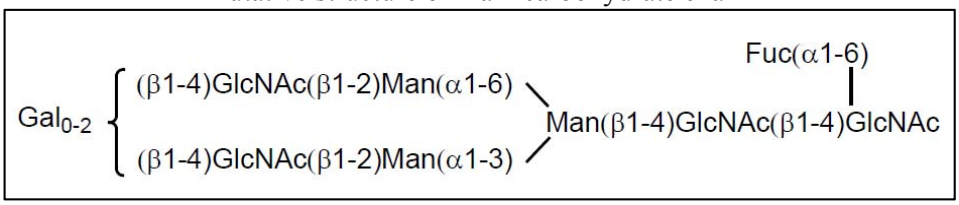
L chain



H chain

Pyroglutamate formation (partial): Q1 in H chain
Glycosylation site: N299 in H chain
Partial processing: K449 in H chain
Interchain disulfide bonds: C220 in L chain - C222 in H chain, C228 in H chain - C228 in H chain, C231 in H chain - C231 in H chain
Intrachain disulfide bonds: shown in solid lines

Putative structure of main carbohydrate chain



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose

Molecular formula:
L chain: $C_{1052}H_{1636}N_{284}O_{343}S_6$
H chain: $C_{2186}H_{3406}N_{582}O_{671}S_{17}$
Molecular weight: 146,126.74 (protein portion of 4 chains)

[Items Warranting Special Mention]
None

[Reviewing Office] Office of New Drug IV

Review Results

February 17, 2016

[Brand Name]	Nucala for S.C. Injection 100 mg
[Non-proprietary Name]	Mepolizumab (Genetical Recombination)
[Applicant]	GlaxoSmithKline K.K.
[Date of Application]	May 22, 2015

[Results of Review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in the treatment of patients with bronchial asthma whose symptoms cannot be controlled by conventional treatment has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrences of serious infections etc., in long-term treatment should be further investigated via post-marketing surveillance.

As a result of its regulatory review, PMDA has concluded that the product may be approved for the indication and dosage and administration as shown below, with the following condition.

[Indication]	Bronchial asthma (only for patients with refractory asthma whose symptoms cannot be controlled by conventional treatment)
[Dosage and Administration]	The usual dosage for adults and adolescents (aged ≥12 years) is 100 mg of Mepolizumab (Genetical Recombination) injected subcutaneously once every 4 weeks.
[Condition of Approval]	The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

January 6, 2016

I. Product Submitted for Registration

[Brand name]	Nucala for S.C. Injection 100 mg
[Non-proprietary name]	Mepolizumab (Genetical Recombination)
[Applicant]	GlaxoSmithKline K.K.
[Date of application]	May 22, 2015
[Dosage form/Strength]	Lyophilized powder in a vial to be reconstituted prior to injection[2]: Each vial contains 144 mg of Mepolizumab (Genetical Recombination).
[Proposed indication]	Bronchial asthma (severe eosinophilic asthma with exacerbation despite conventional treatment)
[Proposed dosage and administration]	The usual dosage for adults and adolescents (aged ≥12 years) is 100 mg of Mepolizumab (Genetical Recombination) injected subcutaneously once every 4 weeks.

II. Summary of the Submitted Data and Outline of the Review by Pharmaceuticals and Medical Devices Agency

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below.

1. Origin or history of discovery, use in foreign countries, and other information

Mepolizumab (Genetical Recombination) (hereinafter referred to as mepolizumab), the active ingredient of "Nucala for S.C. Injection 100 mg," is a humanized anti-human interleukin-5 (IL-5) monoclonal antibody of human immunoglobulin G1 (IgG1) subclass discovered by SmithKline Beecham Limited (currently GlaxoSmithKline).

Bronchial asthma is a respiratory disease characterized by chronic inflammation of the airway, enhanced airway hyperreactivity, reversible airway obstruction, etc. Persistent airway inflammation induces functional disturbance of the airway accompanied by histological changes in the airway structure, resulting in an irreversible airflow limitation. In recent years, bronchial asthma is treated principally by drug therapy with inhaled corticosteroid (ICS) and, depending on the severity, in combination with a long-acting β_2 agonist, a leukotriene receptor antagonist, theophylline, a long-acting anticholinergic agent, an oral corticosteroid, an anti-IgE antibody, etc. (*Asthma Prevention and Management Guideline 2015, JAPAN*; *Global Initiative for Asthma 2014*). However, only a limited number of treatment options are available for patients with severe bronchial asthma with exacerbation and thus potentially-affects prognosis despite the combination therapy with ICS and the above long-term control medications.

It is reported that, in the pathology of bronchial asthma, IL-5 produced by T helper type 2 (Th2) cells plays an important role in the pathogenesis of airway inflammation, mediated by growth and activation of eosinophils (Cohn L et al. *Annu Rev Immunol.* 2004;22:789-815, Wardlaw A J et al. *Br Med Bull*. 2000;56:985-1003, Rothenberg ME. *N Engl J Med*. 1998;338:1592-1600). Mepolizumab binds with high affinity to human IL-5 and inhibits its binding to α subunit of IL-5 receptor complex expressed on the eosinophil surface, thereby neutralizing the biological activity of IL-5. On the basis of these findings, mepolizumab was developed as a therapeutic agent for bronchial asthma.

In foreign countries, Nucala was approved in the US and Europe in November and December, respectively, in 2015 with an indication related to bronchial asthma.

[2] The preparation is designed to allow drawing 1 mL of the injectable solution containing 100 mg Mepolizumab (Genetical Recombination) when it is reconstituted with 1.2 mL of water for injection (JP) prior to injection. Thus, each vial is overfilled to ensure the labeled dose.

In Japan, a clinical development of Nucala for bronchial asthma was initiated in [redacted], [redacted] months before the completion of the foreign phase II/III study (Study MEA112997), and a marketing application has now been filed based on the results of global clinical studies conducted in Japan and other countries/regions.

In this review report, the dose of Nucala is expressed as mepolizumab equivalent.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substances

2.A.(1).1) Preparation and control of cell substrate

Hybridoma cell lines were prepared by fusion of mouse myeloma cells with splenic cells of mice immunized with human IL-5, and the most appropriate clone was selected from the hybridoma cell lines. The gene sequences encoding the variable regions were identified from cDNAs prepared from this clone. Using these sequences, gene fragments encoding humanized variable regions of the heavy and light chains were prepared by substituting amino acid residues based on the human framework homologous to these sequences. To these humanized variable regions were incorporated gene fragments encoding the constant regions of the heavy and light chains of human immunoglobulin G1 (IgG1) to prepare gene expression constructs encoding heavy and light chains. [redacted].

[redacted].

[redacted]. As a result, neither viral nor non-viral adventitious agents were detected within the range of the tests performed.

Master cell bank (MCB) and working cell bank (WCB) are stored in the gas phase of liquid nitrogen. No new MCB is planned to be generated, whereas new WCB will be as appropriate.

2.A.(1).2) Manufacturing process

[redacted].

A quality risk management approach was used in the development of the manufacturing process, and the following critical quality attributes (CQAs) were identified. Based on the process characterization and identification of critical process parameters, etc., the strategy for quality control was constructed.

- Identified CQAs: [redacted]

[redacted]

[redacted].

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

2.A.(1).3) Safety evaluation of adventitious agents

[redacted]. Both raw materials were confirmed to comply with the Standards for Biological Ingredients.

Purity tests were performed on the MCB, WCB, and cells at the limit of *in vitro* cell age (CAL) [see "2.A.(1).1) Preparation and control of cell substrate"]. Unprocessed bulk manufactured at commercial scale was subjected before harvest to a mycoplasma testing, adventitious virus testing, and bioburden testing. The results showed that the bulk was not contaminated by viral or non-viral adventitious agents within the range of tests performed. The mycoplasma testing, adventitious virus testing, and bioburden testing on unprocessed bulk are selected as in-process control tests.

A viral clearance study was performed with model viruses for the purification processes. The results showed that the purification processes have a sufficient viral clearance capacity, as shown in Table 1.

Table 1. Results of viral clearance study

Manufacturing process	Virus clearance factor (log_{10})			
	Xenotropic murine leukemia virus	Porcine parvovirus	Reovirus type 3	Pseudorabies virus
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pH [redacted] treatment	[redacted]	Not performed	Not performed	> [redacted]
[redacted]	> [redacted]	[redacted]	> [redacted]	[redacted]
[redacted]	> [redacted]	Not performed	Not performed	> [redacted]
Virus filtration	> [redacted]	> [redacted]	> [redacted]	> [redacted]
Overall reduction factor	>24.58	>8.95	>13.58	>24.47

2.A.(1).4) Manufacturing process development (comparability)

The main manufacturing process changes made during the drug substance development process are shown below (each manufacturing process is referred to as Process A, B, C, or D [the proposed manufacturing process]). Comparability of the drug substance before and after each change were confirmed. The formulations used in clinical studies were produced from the drug substances prepared mainly by Process C or D. When the manufacturing process was changed from C to D, a clinical study was conducted to compare their pharmacodynamics, immunogenicity, and safety, in addition to the evaluation of the comparability of their quality attributes.

- From Process A to B: [redacted]
- From Process B to C: [redacted]
- From Process C to D: [redacted]

2.A.(1).5) Characterization

(a) Structure

- The primary structure was analyzed by liquid chromatography-tandem mass spectrometry (LC-MS/MS) after reduced tryptic digestion.

- The higher order structure was analyzed by free sulfhydryl analysis, reduced and non-reduced Lys-C digested peptide mapping, far- and near-ultraviolet circular dichroism (CD) spectroscopy, Fourier transform infrared spectroscopy (FTIR), and differential scanning calorimetry (DSC).

- Glycosylation sites, carbohydrate structures, and nonglycosylated form were confirmed by peptide-N-glycosidase F (PNGase F)-treatment followed by liquid chromatography, PNGase F-treatment followed by capillary gel electrophoresis (CGE), reducing CGE, reducing and non-reducing electrospray ionization quadrupole time-of-flight mass spectrometry (ESI-QTOF-MS), and acid-treatment followed by reversed-phase liquid chromatography (RP-HPLC).

(b) Physicochemical properties

- The molecular weight was determined by reducing and non-reducing ESI-QTOF-MS.

- Charge variants were identified by capillary isoelectric focusing (cIEF) and cation exchange chromatography (CEX).

- [redacted].

- Extinction coefficient was determined.

(c) Biological properties

- Binding activity to IL-5 and to neonatal Fc receptor was confirmed by surface plasmon resonance (SPR) spectroscopy.

- The binding rate to, dissociation rate constant, dissociation equilibrium constant, and affinity constant to IL-5 were determined by kinetic analysis using SPR spectroscopy. The results confirmed that mepolizumab had a high affinity for IL-5.

- [redacted].

(d) Product-related substances/product-related impurities

On the basis of above analyses (a) to (c), aggregates, fragments, and charge variants were specified as product-related substances. [redacted]. No specifications have been set for product-related substances.

(e) Process-related impurities

[redacted]. It was confirmed that all process-related impurities were sufficiently removed during the manufacturing process.

2.A.(1).6 Control of drug substance

[redacted].

2.A.(1).7 Stability of drug substance

Main stability studies on the drug substance were conducted as shown in Table 2.

Table 2. Outline of the main stability studies on the drug substance

	Number of batches	Manufacturing process	Storage conditions	Storage period	Storage configuration
Long-term testing	7	Process C	[redacted] ± 10°C	[redacted] months	[redacted]
	5	Process D		[redacted] months [a)]	
	5		[redacted] ± 5°C	[redacted] months [a)]	
Accelerated testing	11		[redacted] ± 3°C	[redacted] months	
Stress testing	10		[redacted] ± 2°C/[redacted] ± 5% RH	[redacted] months	
Freezing-thawing cycle testing	2		Freezing and thawing at [redacted]°C and [redacted]°C, respectively ([redacted] cycles)		
	1		Freezing and thawing at [redacted]°C and [redacted]°C, respectively ([redacted] cycles), followed by storage for [redacted] months at [redacted]°C		
Photostability testing	3		Overall illumination of ≥1.2 million lux·h, integrated near ultraviolet energy of ≥200 W·h/m^2		

a) The stability study is ongoing for [redacted] months.

The long-term testing did not show any clear changes in the quality attributes throughout the test period.

[redacted].

[redacted].

The freezing-thawing cycle testing did not detect any clear change in the quality attributes.

[redacted].

[redacted].

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product and formulation development

The drug product is a lyophilized powder in a vial (10 mL) to be reconstituted prior to injection and contains 144 mg of the drug substance. The drug product contains, as excipients, sucrose, sodium phosphate dibasic heptahydrate, polysorbate 80, and hydrochloric acid. The drug product is designed to allow drawing 1 mL of the injectable solution containing 100 mg mepolizumab when it is reconstituted with 1.2 mL of water for injection (JP) prior to injection. Thus, each vial is overfilled with mepolizumab to ensure the labeled dose. The primary packaging is a glass vial and a bromobutyl rubber stopper, and the secondary packaging is a paper box.

2.A.(2).2) Manufacturing process

The manufacturing process of the drug product is comprised of thawing of the drug substance, pooling and mixing of the drug substance, sterile filtration, filling and partial stoppering, lyophilizing, clamping, examination and storage, labeling, packaging, storage, and testing process.

The manufacturing process has been validated at commercial scale.

2.A.(2).3) Manufacturing process development

The following changes were made during the development of the drug product: Change in the mepolizumab content in the drug product, improvements of the manufacturing process such as lyophilization cycle, and change of the manufacturing site. When the manufacturing process was changed, comparability of quality attributes was evaluated, and the results demonstrated the comparability of the drug product before and after the change.

2.A.(2).4) Control of drug product

The proposed specifications for the drug product include content, description, identification (SPR, cIEF), osmotic pressure, pH, purity (SEC, CGE [reducing], cIEF), water content, bacterial endotoxin,

reconstitution time, uniformity of dosage units, foreign insoluble matter, insoluble particulate matter, sterility, and assay (protein content, potency [SPR], titer [IL-5-neutralizing activity]).

2.A.(2).5) Stability of drug product

Main stability studies of the drug product were conducted as shown in Table 3.

Table 3. Outline of main stability studies of the drug product

	Number of batches	Storage conditions	Storage period	Storage configuration
Long-term testing	3	5 ± 3°C in the inverted position	24 months [a)]	Glass vial with rubber stopper
Accelerated testing	3	[redacted] ± 2°C and [redacted] ± 5% RH in the inverted position	[redacted] months [a)]	
Stress testing	1	[redacted] ± 2°C, [redacted] ± 5% RH	[redacted] months	
Freezing-thawing cycle testing	1	Freezing and thawing at [redacted] °C and [redacted] °C, respectively ([redacted] cycles), followed by storage for [redacted] months at [redacted] ± 2°C and [redacted] ± 5% RH [a)]		
Photostability testing	1	Overall illumination of ≥1.8 million lux·h		Glass vial with rubber stopper (unpackaged or aluminum-packaged)

a) The stability study is ongoing for [redacted] months.

The long-term testing did not show any clear changes in the quality attributes throughout the test period.

[redacted].

[redacted].

[redacted].

[redacted].

On the basis of the above stability study results, a shelf life of 24 months has been proposed for the drug product when stored at 2°C to 8°C avoiding freezing in a bromobutyl rubber-stoppered glass vial and protected from light.

2.A.(3) Reference materials

The primary reference material and the working reference material are prepared from the drug substance and stored at [redacted] °C. The stability of these reference materials is checked every [redacted] months. [redacted].

2.B Outline of the review by PMDA

Based on the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is controlled in an appropriate manner.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The results from the following primary pharmacodynamic studies of mepolizumab were submitted: Studies on the binding affinity for IL-5, studies on the inhibitory effect on the ligand binding to IL-5 receptor, studies on the inhibitory effect on the bioactivity of IL-5, *in vitro* studies on cross-reactivity in

various animal species, and *in vivo* studies on the effect on eosinophil count in blood and in bronchoalveolar lavage fluid (BALF). Also, the results from the following safety pharmacology studies of mepolizumab were submitted: Studies on the central nervous system, cardiovascular system, and respiratory system in cynomolgus monkeys. No secondary pharmacodynamic studies or pharmacodynamic drug interaction studies were conducted.

In this section, pharmacological parameters are expressed in mean values unless otherwise specified.

3.(i).A.(1) Primary pharmacodynamics (4.2.1.1)

3.(i).A.(1).1) Binding affinity to human IL-5 (SB-240563/RSD-100LD3/1, SH2009/00010/00)

The binding affinity between mepolizumab and human IL-5 was investigated by SPR spectroscopy. A sensor chip coated with human IL-5 was attached to an SPR biosensor, and mepolizumab solution was injected into the flow channel. As a result, the dissociation constant (K_d) between mepolizumab and human IL-5 was estimated to be 106 pmol/L. When a sensor chip with mepolizumab immobilized via anti-human IgG antibody was attached to the surface plasmon resonance biosensor, and human IL-5 solution was injected into the flow channel, K_d between human IL-5 and mepolizumab was 110 to 258 pmol/L.

Calorimetric change associated with the binding of mepolizumab to human IL-5 was measured by isothermal titration calorimetry. Thus, when mepolizumab was titrated with human IL-5, the equivalent point was reached at the molar ratio of approximately 1:1, from which K_d between mepolizumab and human IL-5 was estimated to be ≤130 pmol/L.

3.(i).A.(1).2) Effect on the binding of human IL-5 to its receptor (SB-240563/RSD-100LD3/1)

In Drosophila melanogaster cells expressing human IL-5 receptor α chain, the effect of mepolizumab on the binding of ^{125}I-labeled human IL-5 to human IL-5 receptor α chain was investigated. Mepolizumab inhibited the binding of human IL-5 to human IL-5 receptor α chain in a concentration-dependent manner with 50% inhibitory concentration (IC_{50}) of 940 pmol/L.

3.(i).A.(1).3) Effect on human myeloid erythroleukemia cell growth induced by human IL-5 (SB-240563/RSD-100LD3/1)

In a human myeloid erythroleukemia cell line TF-1.28, the effect of mepolizumab on human IL-5 (35 pmol/L)-induced cell growth was investigated, as measured by ^{3}H-labeled thymidine incorporation. Mepolizumab inhibited TF-1.28 cell growth induced by human IL-5 in a concentration-dependent manner with IC_{50} of 73 pmol/L.

3.(i).A.(1).4) Effect on mouse B cell growth induced by human IL-5 (SB-240563/RSD-100LD3/1)

In a mouse B precursor cell line LyH7.B13, the effect of mepolizumab on cell growth induced by human IL-5 (7 pmol/L) was investigated, as measured by ^{3}H-labeled thymidine incorporation. Mepolizumab inhibited human IL-5-induced LyH7.B13 cell growth in a concentration-dependent manner with IC_{50} of 31 pmol/L.

3.(i).A.(1).5) Effects on mouse and monkey IL-5

(a) Effect on mouse IL-5-induced cell growth (CH2005/00951/00, SB-240563/RSD-100LD3/1)

The effect of mepolizumab on LyH7.B13 cell growth induced by mouse IL-5 (7 pmol/L) was investigated, as measured by ^{3}H-labeled thymidine incorporation. Mouse IL-5-induced LyH7.B13 cell growth was not inhibited even in the presence of as much as 1 μmol/L of mepolizumab.

The effect of mepolizumab on TF-1.28 cell growth induced by mouse IL-5 (0.05 ng/mL)[3] was investigated, as measured by ^{3}H-labeled thymidine incorporation. Mouse IL-5-induced TF-1.28 cell growth was not inhibited even in the presence of as much as 10 nmol/L of mepolizumab.

[3] Corresponds to approximately 2 pmol/L, assuming the molecular weight of the disulfide-bond homodimer of mouse IL-5 is 26.2 kDa.

(b) Effect on cell growth induced by cynomolgus monkey IL-5 (CH2008/00044/00, Hart TK et al. *J Allergy Clin Immunol.* 2001;108:250-257)

The effect of mepolizumab on TF-1.28 and LyH7.B13 cell growth induced by human and cynomolgus monkey IL-5 (concentration unknown) was investigated, as measured by ^{3}H-labeled thymidine incorporation. Mepolizumab inhibited both human and cynomolgus monkey IL-5-induced TF-1.28 and LyH7.B13 cell growth in a concentration-dependent manner, with IC_{50} being 75 and 83 pmol/L, respectively, for human IL-5 and 84 and 79 pmol/L, respectively, for cynomolgus monkey IL-5.

3.(i).A.(1).6) Effect on eosinophil differentiation and eosinophil count

(a) Effect on eosinophil differentiation of myelomonocytic cells induced by human and cynomolgus monkey IL-5 (CH2008/00044/00, Hart TK et al. *J Allergy Clin Immunol.* 2001;108:250-257)

In human and cynomolgus monkey myelomonocytic cells, the effect of mepolizumab on eosinophil differentiation induced by human or cynomolgus monkey IL-5 (concentration unknown) was investigated, as measured by eosinophil peroxidase activity. Mepolizumab inhibited IL-5-induced eosinophil differentiation of human and cynomolgus monkey myelomonocytic cells in a concentration-dependent manner, with IC_{50} being 70 and 83 pmol/L, respectively, for human and cynomolgus monkey IL-5 in human myelomonocytic cells and 104 and 116 pmol/L, respectively, in cynomolgus monkey myelomonocytic cells.

(b) Effect on blood eosinophil count in rabbits (SB-240563/RSD-100XMR/1)

A single intravenous administration of mepolizumab (125 mg/kg) caused no change in blood eosinophil count in rabbits. Mepolizumab (250 mg/kg) was administered intravenously in a single dose to rabbits, and then human IL-2 (22 μg/kg) subcutaneously 1, 3, and 5 days later. As a result, mepolizumab did not affect human IL-2-induced increase in eosinophil count.

(c) Effect on blood eosinophil count in monkey (SB-240563/RSD-100LKP/2, SB-240563/RSD-100ZHH/1, SB-240563/RSD-100X0L/2)

To cynomolgus monkeys, mepolizumab (1 mg/kg) was administered intravenously and then subcutaneously approximately 3 months later, and plasma mepolizumab concentration and blood eosinophil count were measured during the treatment period. Based on the time-course data, an indirect response model was developed. The plasma mepolizumab concentration required to decrease blood eosinophil count by 50% was estimated to be 1.43 ± 0.21 μg/mL (mean ± standard deviation [SD]).

Mepolizumab (125 mg/body, approximately 60 mg/kg) was administered subcutaneously twice, 14days apart, to cynomolgus monkeys and blood eosinophil count was measured. Blood eosinophil count decreased by 52% to 88% on Days 8, 14, 22, and 28 compared with the baseline level, while other hematological parameters did not show any changes associated with mepolizumab administration.

Mepolizumab was administered 7 times, 4 weeks apart, intravenously (10 mg/kg, 100 mg/kg) or subcutaneously (10 mg/kg) to cynomolgus monkeys, and blood eosinophil count was measured. Blood eosinophil count on Day 29 to Day 169 decreased by 75% to 100% (10 mg/kg intravenous administration), 85% to 97% (100 mg/kg intravenous administration), and 56% to 94% (10 mg/kg subcutaneous administration) compared with the baseline level, in the respective groups.

(d) Effect on IL-2-induced increase in eosinophil count (SB-240563/RSD-100KN9/1)

It is reported that, in humans, IL-2 administration induces IL-5, resulting in an increase in eosinophil count (MacDonald D et al. *Br J Haematol*. 1990;76:168-173). Mepolizumab (0.05-50 mg/kg) was administered intravenously twice, 28 days apart, to cynomolgus monkeys. Starting from the next day of the second administration, human IL-2 (22 μg/kg) was administered to the animals subcutaneously 6 times, 2 days apart, and blood eosinophils were counted. Mepolizumab inhibited human IL-2-induced increase in blood eosinophil count in a dose-dependent manner, showing a ≥87% decrease in the ≥0.5 mg/kg groups on Day 41. Other hematologic parameters did not show any changes associated with mepolizumab administration.

3.(i).A.(1).7) Effect on a monkey model of allergic asthma (SB-240563/RSD-1013L8/1)

In cynomolgus monkey models of allergic asthma,[4] the effect of a single intravenous administration of mepolizumab (10 mg/kg) on eosinophil count was investigated. At baseline, change in eosinophil count in BALF before and after inhalation of Ascaris antigen was from 0.2×10^3 to 1.9×10^3 cells/μL in the vehicle group (20 mmol/L sodium phosphate solution containing 6.2% sucrose and 0.2% Tween-80) and from 0.2×10^3 to 1.2×10^3 cells/μL in the mepolizumab group, showing a tendency of increase in both groups. Eosinophil count in BALF after Ascaris antigen inhalation at 24 hours, 3 weeks, and 6 weeks after test substance administration was 2.9×10^3, 2.8×10^3, and 2.1×10^3 cells/μL, respectively, in the vehicle group and 1.2×10^3, 0.2×10^3, and 0.4×10^3 cells/μL in the mepolizumab group. In contrast, mepolizumab had no effect on immediate bronchoconstrictor response associated with Ascaris antigen inhalation. The applicant interpreted the results as follows: eosinophil-induced airway inflammation is considered to be associated with delayed-onset of bronchoconstrictor response, whereas immediate bronchoconstrictor response in antigen-sensitized animals is induced by inflammatory mediators released by mast cells etc., after antigen stimulation (Morita H. *The Journal of the Japanese Society of Internal Medicine*. 1996;85:174-177).

3.(i).A.(1).8) Other pharmacology studies

(a) Effect of anti-human IL-5 antibody, which cross-reacts with mouse IL-5, on blood eosinophil count in mice (SB-240563/RSD-100MZP/2)

Since mepolizumab does not cross-react with mouse IL-5, the effect of rat anti-human IL-5 monoclonal antibody (SB-264091), which cross-reacts with mouse IL-5, on blood eosinophil count in mice was investigated. Vehicle (20 mmol/L sodium phosphate solution containing 150 mmol/L sodium chloride) or SB-264091 (5, 50 mg/kg) was administered intravenously to mice 3 times, one week apart. As a result, blood eosinophil count at 1 to 4 weeks after the initial dose was 0.14×10^3 to 0.36×10^3 cells/μL in the vehicle group and 0.03×10^3 to 0.08×10^3 cells/μL in the mepolizumab group.

3.(i).A.(2) Safety pharmacology (SB-240563/RSD-100KN9/1, SB-240563/RSD-100X0L/2, SB-240563/RSD-100SHZ/1)

In a 2-month repeat-dose toxicity study[5] and a 6-month repeat-dose toxicity study[6] in cynomolgus monkeys, there were no findings related to the central or peripheral nervous system. Electrocardiogram revealed no abnormalities associated with mepolizumab on Day 26 in the 2-month repeat-dose toxicity study and on Day 164 in the 6-month repeat-dose toxicity study. In the 6-month repeat-dose toxicity study, C_{max} and $AUC_{0\text{-}4\ weeks}$ of mepolizumab after the fifth dose were 2432 μg/mL and 808,975 μg·h/mL, respectively, which were approximately 126 and 88 times, respectively, the estimated exposure (C_{max}, 19.3 μg/mL; AUC, 9144 μg·h/mL) after repeated subcutaneous administration of mepolizumab (100 mg) at 4-week intervals to Japanese patients with asthma. In the 6-month repeat-dose toxicity study, plasma mepolizumab concentration 4 days after electrocardiogram measurement was 637 μg/mL, which was approximately 33 times the estimated exposure (C_{max}, 19.3 μg/mL) in Japanese patients with asthma.

Cynomolgus monkeys with a catheter inserted into the femoral artery to monitor blood pressure and heart rate were given intravenous injections, 1 week apart, of vehicle twice and mepolizumab first at 10 mg/kg and then at 100 mg/kg. The following were examined up to 3 hours after each injection: clinical signs, body weight, rectal temperature, arterial pressure, heart rate, respiratory rate, urine excretion parameters (urine volume, osmotic pressure, urine pH, excretion rates of electrolytes and creatinine), serum electrolytes, and serum creatinine concentration. No changes attributable to mepolizumab were observed in any parameters.

3.(i).B Outline of the review by PMDA

The applicant discussed the role of IL-5 in the pathology of bronchial asthma and the mechanism of action of mepolizumab as follows:

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[4] Ascaris antigen was inhaled, and mepolizumab or vehicle was administered 2 weeks later. After 24 hours, 3 weeks, and 6 weeks of the administration of mepolizumab or vehicle, ascaris antigen was inhaled, and BALF and blood samples were collected before and after each antigen inhalation. Animals that showed bronchoconstrictor responses (≥40% increase in pulmonary resistance and ≥40% decrease in dynamic compliance) were used for this study.

[5] Mepolizumab (0.05-50 mg/kg) was administered intravenously twice at a 4-week interval, followed by a 3-month observation.

[6] Mepolizumab (10, 100 mg/kg) was administered subcutaneously or intravenously 7 times, 4 weeks apart, and animals were necropsied at 1 week after the final dose.

IL-5 is a cytokine that is produced in various cells including Th2 cells, eosinophils, mast cells, and basophils, and is involved in the growth, differentiation, survival, and activation of eosinophils. It is reported that IL-5 enhances the release of eosinophils from the bone marrow into the circulating blood and, together with eotaxin, contributes to mobilization of eosinophils from microvessels to the lung (Lopez AF et al. *J Exp Med*. 1988;167:219-224, Wang JM et al. *Eur J Immunol*. 1989;19:701-705, Clutterbuck EJ et al. *Blood.* 1989;73:1504-1512, Collins PD et al. *J Exp Med.* 1995;182:1169-1174, Antoniu SA. *Expert Opin Biol Ther*. 2013;13:257-268, Garcia G et al. *Eur Respir Rev.* 2013;22:251-257). It is considered that eosinophils, upon mobilization to the lung and activation by IL-5, injure the airway epithelium by secreting granular proteins in the airway, resulting in the enhancement of airway hyperreactivity, which in turn induces bronchial asthma and airway constriction. Thus, airway eosinophils are suggested to play an important role in the pathological process of bronchial asthma (Cohn L et al. *Annu Rev Immunol.* 2004;22:789-815). In light of these findings and of the observation that, in *in vivo* studies in which mepolizumab was administered to normal monkeys and to monkey models of allergic asthma, mepolizumab induced continuous decrease in eosinophil count in BALF and in blood, it is expected that mepolizumab, a humanized anti-human IL-5 antibody, is effective for acute exacerbation of bronchial asthma and for asthmatic symptoms through its long-lasting activity to inhibit eosinophilic airway inflammation.

PMDA concluded that the submitted data demonstrate the effect of mepolizumab to inhibit the biological activity of IL-5 and to decrease eosinophil count in an animal model of bronchial asthma, and mepolizumab is thus expected to be effective for immunological allergic reactions induced by eosinophils.

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

The applicant submitted the data on the absorption, distribution, metabolism, excretion, and drug interactions of mepolizumab, namely the data of studies in which mepolizumab was administered subcutaneously and intravenously in cynomolgus monkeys. Plasma mepolizumab concentration was measured by electrochemiluminescence immunoassay (lower limit of quantitation [LLQ], 0.05 μg/mL) or by time resolved fluoroimmunoassay (LLQ, 0.05 μg/mL). Mepolizumab concentration in BALF and anti-mepolizumab antibody (ADA) concentration in serum were measured by electrochemiluminescence immunoassay (LLQ; 0.05 and 0.1 μg/mL, respectively).

Pharmacokinetic parameters are expressed in mean or mean ± SD unless otherwise specified.

3.(ii).A.(1) Absorption

3.(ii).A.(1).1) Single-dose administration (SB240563/RSD-100LKP/2, SB-240563/RSD-100F0G/1)

Mepolizumab was administered subcutaneously or intravenously in a single dose to male and female cynomolgus monkeys. Table 4 shows the pharmacokinetic parameters of mepolizumab. AUC and $t_{1/2}$ were similar between the two dosing regimens. No clear sex difference was observed in the exposure. CL following a single intravenous administration was lower than the hepatic blood flow reported in cynomolgus monkeys (2620 mL/h/kg) and V_{ss} was lower than the total body fluid volume (693 mL/kg) (Davies B et al. *Pharmaceutical Research.* 1993;10:1093-1095), suggesting that most of mepolizumab is present in blood. No ADA was detected following a single intravenous administration of mepolizumab at 3 or 304 mg/kg.

Table 4. Pharmacokinetic parameters following a single-dose administration of mepolizumab to cynomolgus monkeys

Dose	N	Sex	AUC_{inf} (mg·h/mL)	C_{max} (mg/mL)	t_{max} a) (h)	$t_{1/2}$ (day)	CL (mL/h/kg)	V_{ss} (mL/kg)	F (%)
1 mg/kg s.c.	4	Female	7.84 ± 1.78	0.0114 ± 0.0019	84 (48.0-96.0)	14.5 ± 3.8	NA	NA	118 ± 16
1 mg/kg i.v.	4 b)	Female	6.39 ± 1.20	0.0277 ± 0.0013	0.3 (0.1-1.00)	13.1 ± 1.5	0.16 ± 0.018	65.6 ± 5.0	NA
3 mg/kg i.v.	1	Male	15.9	0.094	NA	12.4	0.189	76.0	NA
3 mg/kg i.v.	1	Female	13.2	0.085	NA	9.94	0.227	73.2	NA
304 mg/kg i.v.	1	Male	1359	6.39	NA	11.6	0.224	85.2	NA
304 mg/kg i.v.	1	Female	1450	7.01	NA	11.8	0.210	78.9	NA

NA, not available; AUC, area under the plasma concentration-time curve; C_{max}, maximum plasma concentration; t_{max}, time to maximum plasma concentration; $t_{1/2}$, elimination half-life; CL, total body clearance; V_{ss}, distribution volume at steady state; F, absolute bioavailability; s.c., subcutaneous administration; i.v., intravenous administration
a) Median (range), b) 0.81 mg/kg to 1 animal

3.(ii).A.(1).2) Repeat-dose administration study (toxicokinetics) (SB-240563/RSD-100X0L/2)

Mepolizumab was administered 7 times, 4 weeks apart, subcutaneously (10 mg/kg) or intravenously (10, 100 mg/kg) to male and female cynomolgus monkeys (n = 3/sex/group), and toxicokinetics was investigated. Table 5 shows the pharmacokinetic parameters of mepolizumab. C_{max} and $AUC_{0\text{-}4weeks}$ increased in proportion to dose, and showed no clear sex difference. No ADA was detected in any treatment groups.

Table 5. Pharmacokinetic parameters following repeated subcutaneous or intravenous administration of mepolizumab to cynomolgus monkeys

Dose (mg/kg/4weeks)	Route of administration	N	Time point	Male		Female	
				C_{max} a) (μg/mL)	$AUC_{0\text{-}4week}$ (μg·day/mL)	C_{max} a) (μg/mL)	$AUC_{0\text{-}4week}$ (μg·day/mL)
10	s.c.	3	Day 1	112	44,908	105	43,522
			Week 16	139	63,130	145	57,995
10	i.v.	3	Day 1	179	50,156	157	43,683
			Week 16	264	75,812	221	59,327
100		3	Day 1	2008	605,949	1731	539,203
			Week 16	2670	883,071	2194	734,879

a): Blood concentration at approximately 24 hours after dosing

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Distribution in the lungs (SB-240563/RSD-100X0L/2)

After administration of mepolizumab 7 times, 4 weeks apart, subcutaneously (10 mg/kg) or intravenously (10, 100 mg/kg) to male and female cynomolgus monkeys (n = 3/sex/group), mepolizumab concentration in BALF was measured. Mepolizumab concentration in BALF after 104 days of treatment was 0.068 μg/mL (below the LLQ in 1 male and female each) in the mepolizumab 10 mg/kg subcutaneous dose group, below the LLQ in all animals in the mepolizumab 10 mg/kg intravenous dose group, and 0.30 μg/mL in the mepolizumab 100 mg/kg intravenous dose group. Mepolizumab concentration in BALF was ≤1/500 times the trough level of plasma mepolizumab concentration at the steady state.

3.(ii).A.(2).2) Fetal and placental transfer (CD2003/01020/00)

Mepolizumab (10, 100 mg/kg) was administered intravenously to pregnant cynomolgus monkeys (n = 12/group) on gestation days 20, 50, 80, 110, and 140. Plasma mepolizumab concentration in maternal animals on lactation day 14 and in neonates was 8.6 and 16.9 μg/mL, respectively, in the mepolizumab 10 mg/kg group and 62.8 and 143.0 μg/mL, respectively, in the mepolizumab 100 mg/kg group. In the maternal animal (1 of 24 animals) in which ADA was detected, the exposure to mepolizumab was lower compared with ADA-negative maternal animals. In neonates born to the ADA-positive maternal animal, plasma mepolizumab concentration was below the LLQ while ADA was detected, which suggested that ADA in the maternal animal crossed the placenta.

3.(ii).A.(3) Metabolism (2011N121217_00)
Human-derived hepatocytes were incubated with mepolizumab (0.06 to 600 μg/mL) for 48 hours, revealing no effect of mepolizumab on the mRNA expression level of CYP3A4. Treatment of the cells with rifampicin (10 μmol/L), a compound with CYP3A4-inducing activity, caused an approximately 14-fold increase in mRNA expression level. These results suggested that mepolizumab does not affect the mRNA expression levels of CYP3A4.

3.(ii).A.(4) Excretion
3.(ii).A.(4).1) Excretion in milk (CD2003/01020/00)
Mepolizumab (10, 100 mg/kg) was administered intravenously to pregnant cynomolgus monkeys (n = 12/group) on gestation days 20, 50, 80, 110, and 140. Mepolizumab concentration in milk on lactation day 14 was not detected in the mepolizumab 10 mg/kg group and 0.14 μg/mL in the mepolizumab 100 mg/kg group.

3.(ii).B Outline of the review by PMDA
Based on the submitted data of nonclinical pharmacokinetic studies, PMDA has concluded that the in vivo behavior of mepolizumab has been elucidated to a certain extent.

3.(iii) Summary of toxicology studies
3.(iii).A Summary of the submitted data
The applicant submitted the data of the following toxicology studies of mepolizumab: Single-dose toxicity studies, repeat-dose toxicity studies, reproductive and developmental toxicity studies, local tolerance studies, other toxicity studies (*in vivo* study of the effects on host defense against parasitic infection, human tissue cross-reactivity study), etc. Since mepolizumab does not cross-react with rodent IL-5 [see "3.(i) Summary of pharmacology studies"], toxicity of mepolizumab was studied mainly in cynomolgus monkeys, which cross-react with mepolizumab. However, fertility and embryo-fetal development was studied in mice receiving SB-264091, a homologous antibody of mepolizumab. Unless otherwise specified, 20 mmol/L sodium phosphate solution containing 6.2% sucrose and 0.02% polysorbate 80 was used as vehicle in *in vivo* studies.

3.(iii).A.(1) Single intravenous toxicity study in monkeys (4.2.3.1)
A single intravenous dose of mepolizumab (0 [phosphate-buffered saline], 3, 304 mg/kg) was administered to male and female cynomolgus monkeys. A decrease in eosinophil count was observed in the 304 mg/kg group, whereas no effects were observed on clinical signs, body weight, lymphocyte subsets, or mitogen-stimulated blastogenic response in any of the treatment groups. On the basis of above results, the approximate lethal dose was determined to be >304 mg/kg.

3.(iii).A.(2) Repeat-dose toxicity
A 2-month intravenous and a 6-month intravenous or subcutaneous toxicity studies were conducted in monkeys. Neither study showed death, mepolizumab-related changes in clinical signs, or local irritation. The no observed adverse effect levels (NOAELs) of mepolizumab in the 6-month subcutaneous and intravenous toxicity studies were determined to be 10 and 100 mg/kg, respectively, and at the NOAELs, $AUC_{0\text{-}28days}$ (44.2, 572.5 mg·h/mL) observed were approximately 4.5 and 59 times, respectively, the $AUC_{0\text{-}28days}$ (9.74 mg·h/mL)[7] estimated from the steady state data after multiple subcutaneous doses of mepolizumab (100 mg) were administered to patients with asthma.

3.(iii).A.(2).1) Two-month intermittent intravenous administration study in monkeys (4.2.3.2)
Mepolizumab (0, 0.05, 0.5, 5, 50 mg/kg) was administered intravenously to male and female cynomolgus monkeys on Day 1 and Day 29, and the animals were monitored for the subsequent 3 months. In order to evaluate the pharmacological effect of mepolizumab, Proleukin (22 μg/kg), a recombinant human IL-2 (rhIL-2), was subcutaneously administered, with the purpose of increasing eosinophil count, to the mepolizumab ≥0.05 mg/kg groups every 2 days starting after the second dose of mepolizumab, i.e., from Day 30 to Day 40, 6 times in total. The study included 2 control groups: one

[7] In a clinical study in which multiple subcutaneous doses of mepolizumab (100 mg) were administered to Japanese patients with asthma (5.3.5.1, MEA115588)

(rhIL-2 control group) receiving rhIL-2 only using the same dosing schedule as above; and the other receiving 0 mg/kg mepolizumab and the vehicle for Proleukin.

None of the treatment groups showed death or mepolizumab-related changes in clinical signs, ophthalmologic examination, lymphocyte subset analysis, ADA test, etc. After the initial dose of mepolizumab, the mepolizumab ≥5 mg/kg groups showed decreased eosinophil count. After rhIL-2 administration, the rhIL-2 control group showed a marked increase in eosinophil count, whereas the mepolizumab ≥0.5 mg/kg groups showed suppressed increase in eosinophil count. Eosinophil count in the mepolizumab groups showed a recovery, or tendency of recovery, of eosinophil count on Day 99.

Since the suppressed increase in eosinophil count is the pharmacological effect of the mepolizumab and did not cause any adverse impact, the NOAEL was determined to be 50 mg/kg.

3.(iii).A.(2).2) Six-month repeated subcutaneous and intravenous administration study in monkeys (4.2.3.2)

Mepolizumab was administered subcutaneously (0, 10 mg/kg) or intravenously (0, 10, 100 mg/kg) to male and female cynomolgus monkeys 7 times, 4 weeks apart.

None of the treatment groups showed death or mepolizumab-related changes in clinical signs, ophthalmologic examination, lymphocyte subset analysis, ADA test, etc. The mepolizumab groups showed a decrease in eosinophil count in blood, and in BALF from baseline, but did not show depletion of eosinophil progenitor cells in the bone marrow. Histopathological examination of the injection site showed mild changes such as haemorrhage and inflammation in the mepolizumab groups, but the findings were similar to those in the control group, which suggested that the observed changes were due to the physical effect of administration.

Since the decrease in eosinophil count is the pharmacological effect of the mepolizumab and did not cause any adverse impact, the NOAEL was determined to be 10 mg/kg for subcutaneous administration and 100 mg/kg for intravenous administration.

3.(iii).A.(3) Genotoxicity

Since mepolizumab is a monoclonal antibody preparation, it is considered not to directly act on DNA or other chromosomal components. Therefore, no genotoxicity studies were conducted.

3.(iii).A.(4) Carcinogenicity

Mepolizumab does not have any pharmacological effects on rodents [see "3.(i) Summary of pharmacology studies"], and carcinogenicity studies of SB-264091 are of only limited significance. Therefore, no carcinogenicity studies were conducted in rodents.

The applicant considers that mepolizumab has only a low, if any, carcinogenic risk, for the following reasons.

- The 6-month repeat-dose toxicity study of mepolizumab (4.2.3.2) did not show any findings suggestive of immune suppression except decreased eosinophil count or suggestive of carcinogenicity.
- In a placebo-controlled comparative study of mepolizumab in patients with asthma, the incidence of malignant tumor was similar between the placebo group and the mepolizumab group, and cancer type such as lymphoma suggesting systemic immune suppression was not reported [see "4.(iii).B *Outline of the review by PMDA*"].
- Regarding the effects of IL-5 and eosinophil on tumor growth, it is reported that they are involved in tumor promotion or suppression as shown below, but their roles in tumor growth have not been elucidated.
  - ✓ Among mouse models of methylcholanthrene-induced fibrosarcoma, IL-5 transgenic mice showed a significant decrease in the incidence of tumor and in tumor volume compared with wild-type mice. Eotaxin gene-deficient mice and eotaxin/IL-5-double-deficient mice showed a significant increase in the incidence of tumor and in tumor volume compared with wild-type mice (Simson L et al. *J Immunol*. 2007;178:4222-4229).

- ✓ In a hamster oral cancer model with eosinophil infiltration, anti-IL-5 antibody administration decreased eosinophil count in the tumor tissue and suppressed tumor growth (Wong et al. *Oral Oncol*. 1999;35:496-501).

- In humans or animals, the role of IL-5 and eosinophils in the tumor immune surveillance system remains yet to be elucidated.

3.(iii).A.(5) Reproductive and developmental toxicity

A fertility and embryo-fetal development study of SB-264091 in mice and an extended pre- and postnatal development study of mepolizumab in cynomolgus monkeys were conducted. In the extended pre- and postnatal development study in cynomolgus monkeys, the NOAEL in maternal animals and pups was determined to be 100 mg/kg, and $AUC_{0\text{-}30\ days}$ (254 mg·h/mL) in this study was approximately 26 times the $AUC_{0\text{-}28\ days}$ (9.74 mg·h/mL)[7] estimated from the steady state data after multiple subcutaneous doses of mepolizumab (100 mg) were administered to patients with asthma.

It is reported that IL-5 gene-deficient mice showed prolonged estrous cycle accompanying prolonged estrus, but did not show any adverse impacts on copulation rate, the number of implantation, fertility rate, postnatal development, or maternal function (Robertson SA et al. *J Reprod Fertil.* 2000;120:423-432).

3.(iii).A.(5).1) Study of fertility and embryo-fetal development in mice (4.2.3.5.1)

Vehicle (20 mmol/L sodium phosphate solution containing 150 mmol/L sodium chloride) or SB-264091 (0.5 or 50 mg/kg/day) was administered intravenously to male CD1 mice 5 or 6 times, one week apart, from 5 weeks before mating period until the end of the period, and to female CD1 mice 6 or 7 times, one week apart, from 2 weeks before the mating period until gestation day 14.

Death occurred in 3 of 50 animals in the 50 mg/kg group. There were not sufficient findings to identify the cause of death in these animals. However, in light of the observation that anti-SB-264091 antibody was detected in single dose and 3-time repeat-dose administration studies of SB-264091 in mice, it was considered that the death of 2 animals on the day of SB-264091 administration was caused by anaphylactoid reaction due to anti-SB-264091 antibody production. The cause of death was unknown for the remaining one that died 4 days after the initial dose.

SB-264091 had no effects on sperm count, motile sperm rate, estrus cycle, copulation rate, fertility rate, corpora lutea count, the number of implantation, the number of resorptions, the number of dead fetuses, the number of live fetuses, external appearance, visceral organs, or skeletal test.

On the basis of the above results, the NOAEL was determined to be 50 mg/kg for the fertility and reproductive potential of male and female parent animals and for embryo-fetal development.

3.(iii).A.(5).2) Extended pre- and postnatal development study in monkeys (4.2.3.5.3)

Mepolizumab (0, 10, 100 mg/kg) was administered intravenously to pregnant cynomolgus monkeys 5 times, on gestation days 20, 50, 80, 110, and 140. This study included, in addition to tests usually performed in developmental studies, measurement of drug concentration in milk, ADA, and immunoglobulin in maternal animals and lymphocyte subset analysis and measurement of immunoglobulins in pups. Also, in order to evaluate the effects of mepolizumab on the immune functions, pups were vaccinated with Tripedia (diphtheria and tetanus toxoids and acellular pertussis vaccine adsorbed) at approximately 7 months after birth, and antibody titers against vaccine antigens were measured.

In the maternal animals, decreased eosinophil count was observed in the ≥10 mg/kg group, whereas no effect was observed on the frequency of abortion or stillbirth, gestation period, or delivery. In the pups, no effect was observed on the survival rate, external anomaly, serum immunoglobulin concentration, lymphocyte subset analysis, or antibody production in response to Tripedia vaccine.

On the basis of the above results, the NOAEL was determined to be 100 mg/kg for dams and pups.

3.(iii).A.(6) Local tolerance (4.2.3.6)

Vehicle (80 mmol/L disodium phosphate solution containing 24.8% sucrose and 0.08% polysorbate 80) or mepolizumab (100 mg/mL, the same concentration as the proposed commercial formulation) was administered subcutaneously to the left and right femoral regions of cynomolgus monkeys on Day 1 and Day 15. Slight to mild redness was observed transiently at all injection sites of vehicle or mepolizumab. The injection site reactions reported in clinical studies of mepolizumab were mild to moderate and disappeared within several days. Taking account of these observations, the applicant considers that the local irritation caused by mepolizumab is unlikely to raise any safety concerns in routine clinical use.

3.(iii).A.(7) Other toxicity studies

3.(iii).A.(7).1) Cross-reactivity with human tissues (4.2.3.7.7)

Cross-reactivity of mepolizumab with normal human tissues was investigated. Mepolizumab was bound to granulocytic series in the bone marrow, lymph nodes, reticuloendothelial cells and granulocytes in the splenic red pulp, splenic white pulp, perifollicular lymphocytes and dendrocytes in the tonsil, and inflammatory cells in the prostate gland. These binding patterns were generally consistent with the distribution of IL-5 in human tissues (Andersson J et al. *Immunology*. 1994;83:16-24, Bradding P et al. *J Immunol.* 1993;151:3853-3865, Salvi S et al. *Am J Respir Cell Mol Biol.* 1999;20:984-991).

3.(iii).A.(7).2) *In vivo* study investigating the effect on host defense against parasitic infection (4.2.3.7.2)

After administration of SB-264091, mice were infected with tapeworm *Mesocestoides corti*, and the effect of SB-264091 on host immune response was investigated.

SB-264091 (0.5, 50 mg/kg) was administered 7 times, one week apart, and tetrathyridium of *M. corti* was administered on Day 2, both intraperitoneally, to female C57BL mice ("0.5 mg/kg + infection group," "50 mg/kg + infection group," respectively). The study included the following control groups as well: (i) "The vehicle control group" was given only vehicle (phosphate-buffered saline) intraperitoneally once weekly, 7 times in total; (ii) "the dexamethasone control group" was given, in addition to the regimen for (i), dexamethasone (50 mg/kg) intraperitoneally 2 days before initiation of the study, on Days 1, 5, and 8, and then twice weekly until the study completion; (iii) "the vehicle + infection control group" was given, in addition to the regimen for (i), *M. corti* intraperitoneally on Day 2; and (iv) "the dexamethasone + infection control group" was given, in addition to the regimen for (ii), *M. corti* intraperitoneally on Day 2. On Days 21, 35, and 49, 10 animals in each group were necropsied and subjected to liver and spleen weight measurement, hematological examination (total white blood cell count and eosinophil count), counting of intraperitoneal cells and parasites, and histopathological examination of the liver.

In the vehicle + infection control group, *M. corti* caused increases in body weight, liver weight, spleen weight, total white blood cell count, eosinophil count, and intraperitoneal cell count. The 0.5 mg/kg + infection group and the 50 mg/kg + infection group showed decreases in eosinophil count in blood and peritoneum compared with the vehicle + infection control group, while no clear difference was observed between these two groups in the mortality, body weight, liver weight, spleen weight, total white blood cell count, total intraperitoneal cell count, intraperitoneal parasite count, parasite count per liver tissue section, or extent of encystation and inflammatory cell infiltration. The intraperitoneal parasite count in the 0.5 mg/kg + infection group and in the 50 mg/kg + infection group was similar to that in the vehicle + infection control group on Day 21, and increased to a similar extent on Day 35 and Day 49.

In the vehicle + infection control group, no deaths occurred during the study, whereas in the dexamethasone + infection control group, 18 of 30 animals died before necropsy, showing an impaired immune response to *M. corti*. On Day 21, animals in the dexamethasone + infection control group showed reduced increases in liver weight, spleen weight, total white blood cell count in blood, eosinophil count, and intraperitoneal eosinophil count, as well as increased intraperitoneal parasite count, compared with the vehicle control group with infection.

SB-264091 attenuated the increase in eosinophil count in response to *M. corti* but did not affect the intraperitoneal or intrahepatic parasite count, or the survival of the infected animals.

On the basis of the above results, the applicant explained that SB-264091-induced suppression of increase in eosinophil count does not interfere with the host defense against parasitic infection.

3.(iii).B Outline of the review by PMDA

Based on the submitted data, PMDA has concluded that clinical use of mepolizumab does not pose any specific problems from a toxicological point of view.

4. Clinical data

Mepolizumab concentration in plasma was measured by time-resolved fluoroimmunoassay, electrochemiluminescence immunoassay, or chemiluminescence enzyme immunoassay (LLQ, 50 ng/mL in all assays). Blood eosinophil count was calculated by multiplying the total white blood cell count, measured by a full-automated blood cell counter at the central laboratory, by the proportion of eosinophils.

In the following descriptions, the dose of "Nucala for S.C. Injection 100 mg" and the intravenous formulation is expressed as the dose of mepolizumab and, unless otherwise specified, pharmacokinetic parameters are expressed in mean or mean ± SD.

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

4.(i).A.(1) Bioavailability study (5.3.1.1, Study SB-240563/018 [February 2001 to June 2001])

The bioavailability of mepolizumab was investigated in non-Japanese healthy adult subjects. Table 6 shows the pharmacokinetic parameters observed.

Table 6. Pharmacokinetic parameters following subcutaneous, intramuscular, or intravenous administration of mepolizumab (250 mg) to non-Japanese healthy adult subjects

Dose	Site and route of administration	N	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)	t_{max} (day)	$t_{1/2}$ (day)	Bioavailability
250 mg	Abdomen, s.c.	12	1110 ± 372	34.1 ± 12.1	7 (4-14)	17.9 ± 3.3	0.64 [0.55, 0.73]
	Upper arm, s.c.	12	1238 ± 228	34.9 ± 7.3	5 (3-14)	20.4 ± 2.6	0.75 [0.66, 0.82]
	Thigh, s.c.	12	1196 ± 254	38.2 ± 9.1	5 (2-7)	18.5 ± 3.5	0.71 [0.62, 0.82]
	i.m.	12	1395 ± 348	46.9 ± 10.6	4 (3-7)	19.2 ± 4.2	0.81 [0.71, 0.94]
	i.v.	12	1557 ± 250	109 ± 17	0.08 (0.02-0.2)	18.5 ± 2.3	NA

Mean ± SD

t_{max} is expressed in median (range). Bioavailability is expressed in point estimate [90% confidence interval (CI)].

AUC_{inf}, area under plasma drug concentration-time curve; C_{max}, maximum plasma concentration; $t_{1/2}$, elimination half-life; s.c., subcutaneous administration; i.m., intramuscular dosing; i.v., intravenous administration; NA, not applicable

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The applicant submitted data from studies including the following: A clinical pharmacology study in healthy adult subjects (5.3.4.1, Study MEA115705), foreign studies in patients with asthma (5.3.4.2, Study MEA114092; 5.3.5.1, Study MEA112997, etc.), and a global study including Japan (5.3.5.1, Study MEA115588).

4.(ii).A.(1) Study in healthy adult subjects

4.(ii).A.(1).1) Intravenous administration study (5.3.4.1, Study MEA115705 [August 2011 to April 2012])

Pharmacokinetics was investigated in Japanese healthy adult subjects to whom a single intravenous dose of mepolizumab (10, 75, 250, 750 mg) was administered. Table 7 shows pharmacokinetic parameters. AUC_{inf} and C_{max} increased in proportion to dose.

Of all subjects who received the study drug (including placebo), 19% of subjects in the mepolizumab groups (5 of 26 subjects: 3 in the 10 mg group, 1 in the 75 mg group, 1 in the 250 mg group) were positive for anti-mepolizumab antibodies, but no neutralizing antibodies were detected.

Table 7. Pharmacokinetic parameters following a single intravenous administration of mepolizumab to Japanese healthy adult subjects

Dose	N	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)	$t_{1/2}$ (day)	V_{ss} (L)	CL (mL/hr)
10 mg	6	54.6 ± 12.3	2.87 ± 0.27	27.4 ± 10.4	6.52 ± 0.77	7.87 ± 1.68
75 mg	6	493 ± 41.1	26.5 ± 1.8	19.8 ± 2.4	4.40 ± 0.69	6.37 ± 0.55
250 mg	7	1699 ± 172	79.3 ± 11.6	36.1 ± 11.3	5.65 ± 1.35	6.19 ± 0.63
750 mg	7	4496 ± 414	254 ± 28.3	22.7 ± 2.3	4.98 ± 0.54	7.01 ± 0.74

Mean ± SD

4.(ii).A.(2) Study in patients

4.(ii).A.(2).1) Intravenous administration study (5.3.3.2, Study SB-240563/035 [July 1997 to January 1998])

Pharmacokinetics and the effect on blood eosinophil count were investigated in non-Japanese patients with asthma to whom a single intravenous dose of mepolizumab (0.5, 2.5, 10 mg/kg) was administered. Table 8 shows pharmacokinetic parameters. AUC_{inf} and C_{max} increased in proportion to dose. An indirect response model incorporating the suppression rate constant of eosinophil production was established to investigate the relationship between eosinophil count and plasma mepolizumab concentration (observed value). The investigation showed that 50% inhibitory concentration (IC_{50}) of mepolizumab against blood eosinophil count was 0.446 μg/mL (inter-individual variability, 23.3%). No anti-mepolizumab antibodies were detected in any of the subjects.

Table 8. Pharmacokinetic parameters following a single intravenous administration of mepolizumab to non-Japanese patients with asthma

Dose	N	AUC_{inf} (μg·day/mL)	C_{max} (μg/mL)	$t_{1/2}$ (day)	V_{ss} (mL/kg)	CL (mL/hr)
0.5 mg/kg	4	207 ± 34	12.1 ± 2.4	20.9 ± 4.0	68.4 ± 2.5	0.103 ± 0.017
2.5 mg/kg	4	1327 ± 247	79.0 ± 4.3	21.7 ± 2.8	55.4 ± 5.2	0.081 ± 0.015
10 mg/kg	4	4361 ± 168	278 ± 29	20.9 ± 2.6	59.3 ± 3.7	0.096 ± 0.004

Mean ± SD

4.(ii).A.(3) Population pharmacokinetic analysis in patients with asthma

4.(ii).A.(3).1) Study MEA112997 (5.3.5.1, November 2009 to December 2011)

In a clinical study in non-Japanese patients with asthma [see "4.(iii).A.(1).2) Foreign phase II/III study], mepolizumab (75, 250, 750 mg) was administered intravenously at 4-week intervals for 48 weeks. A 2-compartment model with first-order elimination (NONMEM version 6/7)-based population pharmacokinetic (PPK) analysis was performed on the plasma mepolizumab concentration data in this study (1193 time points in 443 patients). In this analysis, the following parameters were evaluated as potential covariates: Body weight, height, age, sex, race, disease condition, baseline blood eosinophil count, baseline free IL-5 and total IL-5 concentrations, and concomitant drugs. As a result, body weight was identified as a significant covariate for clearance (CL) and for the distribution volume of the central compartment (V1). The population parameter values (inter-individual variability [% coefficient of variation (CV)]) in patients estimated by the final model were 0.23 L/day (26%) for CL and 3.2 L (29%) for V1.

Table 9 shows the time course of blood eosinophil count in patients receiving multiple intravenous doses of mepolizumab. Of all patients who received the study drug (including placebo), 1% of patients in the mepolizumab groups (6 of 446 patients: 3 in the 75 mg group, 2 in the 250 mg group, 1 in the 750 mg group) were positive for anti-mepolizumab antibodies, but no neutralizing antibodies were detected.

Table 9. Time course of blood eosinophil count in multiple intravenous doses of mepolizumab to non-Japanese patients with asthma (observed value)

Dose	Baseline	After 4 weeks of treatment	After 24 weeks of treatment	After 48 weeks of treatment	After 56 weeks of treatment
75 mg	250 ± 950 —	60 ± 960 0.23 ± 0.95	50 ± 1040 0.20 ± 1.18	50 ± 960 0.17 ± 1.02	80 ± 1140 0.30 ± 1.02
250 mg	230 ± 1200 —	40 ± 840 0.18 ± 1.20	30 ± 770 0.15 ± 1.32	30 ±750 0.15 ± 1.20	50 ± 880 0.20 ± 1.16
750 mg	250 ± 930 —	30 ± 900 0.13 ± 0.99	30 ± 950 0.13 ± 1.19	30 ± 780 0.10 ± 0.98	30 ± 760 0.13 ± 1.06
Placebo	280 ± 1010 —	230 ± 1140 0.81 ± 0.99	270 ± 1000 0.92 ± 0.98	230 ± 1090 0.73 ± 0.95	250 ± 1110 0.80 ± 1.24

Geometric mean ± geometric SD
Upper row, blood eosinophil count (/μL); lower row, ratio to baseline

4.(ii).A.(3).2) Study MEA114092 (5.3.4.2, February 2011 to March 2012)

Pharmacokinetics of mepolizumab was investigated in a comparative study in non-Japanese patients with asthma[8] (target sample size, 65), to whom mepolizumab was administered 3 times, 4 weeks apart, subcutaneously at a dose of 12.5, 125, or 250 mg (12.5, 125, 250 mg SC groups) or intravenously at a dose of 75 mg (75 mg IV group).

The trough plasma mepolizumab concentration after 4 and 8 weeks of treatment was 1.03 ± 2.04 and 0.96 ± 0.82 μg/mL, respectively, in the 12.5 mg SC group; 6.98 ± 1.82 and 10.1 ± 3.35 μg/mL, respectively, in the 125 mg SC group; 10.9 ± 3.66 and 15.5 ± 4.63 μg/mL, respectively, in the 250 mg SC group, and 3.89 ± 1.57 and 5.49 ± 2.10 μg/mL, respectively, in the 75 mg IV group. Blood eosinophil count tended to decrease relative to baseline from after 3 days of treatment in all groups (Table 10). Of all patients receiving the study drug, approximately 11% of patients (8 of 70 patients: 3 in the 12.5 mg SC group, 2 in the 125 mg SC group, 3 in the 250 mg SC group) were positive for anti-mepolizumab antibodies, but no neutralizing antibodies were detected.

Table 10. Ratio to baseline of blood eosinophil count in multiple doses of mepolizumab in non-Japanese patients with asthma

Time point	12.5 mg SC group	125 mg SC group	250 mg SC group	75 mg IV group
Day 3	0.43 ± 0.35 (21)	0.26 ± 0.32 (15)	0.26 ± 0.27 (22)	0.26 ± 0.30 (10)
Week 4	0.51 ± 0.31 (21)	0.20 ± 0.26 (14)	0.15 ± 0.25 (22)	0.30 ± 0.19 (9)
Week 8	0.36 ± 0.48 (20)	0.16 ± 0.34 (14)	0.11 ± 0.33 (19)	0.17 ± 0.33 (10)
Week 12	0.36 ± 0.42 (20)	0.16 ± 0.35 (14)	0.10 ± 0.29 (21)	0.22 ± 0.33 (11)

Geometric mean ± geometric SD (number of patients)

A PPK analysis (NONMEM version 7) was performed on the plasma mepolizumab concentration data in this study (187 time points in 11 patients receiving intravenous administration, 850 time points in 58 patients receiving subcutaneous administration). Based on the pharmacokinetic parameters and blood eosinophil counts estimated from the PPK analysis, a population pharmacokinetic/pharmacodynamic (PPK-PD) analysis was performed.

For intravenous administration, a 2-comparment model with first-order elimination was chosen as the basic model for analysis, and the following parameters were evaluated as potential covariates: Sex, body weight, age, baseline eosinophil count in blood and sputum, baseline free and total IL-5 concentrations, and baseline inhaled corticosteroid dose. As a result, body weight was identified as a significant covariate for CL and V1. The population parameter values (inter-individual variability [%CV]) in patients estimated by the final model were 0.210 L/day (23.3%) for CL and 3.60 L (17.2%) for V1.

For subcutaneous administration, a 2-compartment model with first-order absorption and elimination processes was chosen as the basic model, and the following parameters were evaluated as potential

[8] Patients who met the following criteria: (a) FEV_1 from 6 a.m. to 1 p.m. was 45% to 90% of the predicted value, (b) being treated with ICS or ICS/LABA at a fixed dose from ≥12 weeks before the first day of the run-in period, (c) blood eosinophil count within 12 months before and at the start of the run-in period and was ≥300/μL (≥200/μL after the first revision of the clinical study protocol).

covariates: Sex, body weight, age, baseline eosinophil count in blood and sputum, baseline free and total IL-5 concentrations, and baseline inhaled corticosteroid dose. As a result, body weight was identified as a covariates for apparent clearance (CL/F) and apparent distribution volume in the central compartment (V2/F). The population parameter values (inter-individual variability [%CV]) in patients estimated by the final model were 0.310 L/day (57.7%) for CL/F and 4.57 L (59.3%) for V2/F.

4.(ii).A.(3).3) Study MEA115588 (5.3.5.1, October 2012 to January 2014)

In a global study in 576 Japanese and non-Japanese patients with asthma [see "4.(iii).A.(1).3) Global phase III study"], mepolizumab was administered subcutaneously at a dose of 100 mg (100 mg SC group), or intravenously at a dose of 75 mg (75 mg IV group), at 4-week intervals for 32 weeks. A PPK analysis (NONMEM version 7) was performed on the plasma mepolizumab concentration data in this study (621 time points in 189 patients in the 100 mg SC group, 605 time points in 188 patients in the 75 mg IV group).

Trough plasma mepolizumab concentration after 4, 16, and 32 weeks of treatment was 4.76 ± 2.61, 8.25 ± 3.91, and 9.17 ± 5.11 μg/mL, respectively, in the 100 mg SC group and 3.72 ± 1.65, 6.85 ± 5.40, and 7.04 ± 3.38 μg/mL, respectively, in the 75 mg IV group, suggesting that the plasma mepolizumab concentration reached the steady state by roughly after 16 weeks of treatment. Blood eosinophil count (geometric mean ± geometric SD) at baseline and after 32 weeks of treatment was 290 ± 1050 and 40 ± 930/μL, respectively, in the 100 mg SC group, 280 ± 990 and 50 ± 940/μL in the 75 mg IV group, and 320 ± 940 and 270 ± 950/μL in the placebo group. Figure 1 shows the time course of ratio to baseline of blood eosinophil count. Of all patients receiving mepolizumab, 4% of patients (16 of 378 patients: 9 in the mepolizumab 100 mg SC group, 7 in the mepolizumab 75 mg IV group) were positive for anti-mepolizumab antibodies, but no neutralizing antibodies were detected.

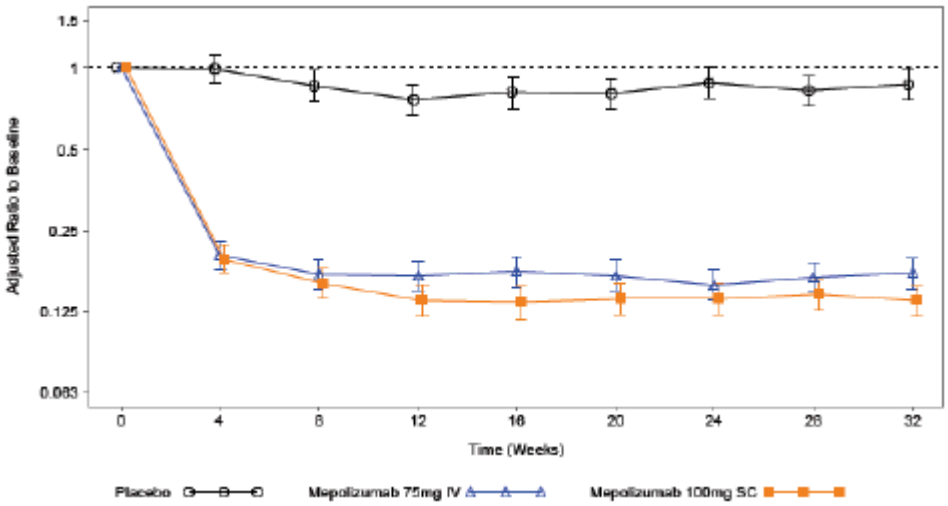

Figure 1. Time course of ratio to baseline of blood eosinophil count (geometric mean with 95% CI)

For intravenous administration, a 2-compartment model with zero-order absorption and first-order elimination, with body weight as a covariate, was chosen as the basic model for analysis, and the following additional parameters were evaluated as potential covariates: Albumin, creatinine clearance, and age. As a result, albumin and creatinine clearance were identified as significant covariates for CL. The population parameter values (inter-individual variability [%CV]) in patients estimated by the final model were 0.220 L/day (21%) for CL and 4.85 L (inter-individual variability not calculated) for V1.

For subcutaneous administration, a 2-comparment model with first-order absorption and elimination, with body weight as a covariate, was chosen as the basic model, and the following parameters were evaluated as potential additional covariates: Albumin, creatinine clearance, and age. As a result, albumin and creatinine clearance were identified as significant covariates for CL/F. The population parameter values (inter-individual variability [%CV]) in patients estimated by the final model were 0.280 L/day (29%) for CL/F and 4.44 L (inter-individual variability not calculated) for V1/F. Table 11 shows the estimated pharmacokinetic parameters in subcutaneous or intravenous administration of mepolizumab.

Table 11. Pharmacokinetic parameters at the steady state in Japanese and non-Japanese patients with asthma receiving multiple doses of mepolizumab (estimated values)

Dose	N	AUC (μg·day/mL)	C_{max} (μg/mL)	T_{max} (h)	CL (mL/h)	CL/F (mL/h)	k (1/h)
100 mg SC	191	343 [327, 360]	16.7 [16.0, 17.4]	94.6 [93.6, 95.6]	—	12.15 [11.57, 12.76]	0.00264 [0.00254, 0.00275]
75 mg IV	190	323 [310, 336]	21.0 [20.3, 21.7]	—	9.67 [9.29, 10.07]	—	0.00186 [0.00181, 0.00192]

Geometric mean [95% CI]; k, elimination constant

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Ethnic difference in the pharmacokinetics and time course of eosinophil count after administration of mepolizumab

The applicant's explanation on the ethnic difference in the pharmacokinetics and in the time course of eosinophil count after mepolizumab administration:

Table 12 shows pharmacokinetic parameters following a single intravenous dose of mepolizumab in Study MEA115705 in Japanese subjects and in Study SB-240563/018 in non-Japanese subjects. No clear difference was observed in pharmacokinetic parameters between Japanese and non-Japanese subjects.

Table 12. Pharmacokinetic parameters following a single intravenous administration of mepolizumab

Study	Dose	C_{max} (μg/mL/mg)	AUC_{inf} (μg·day/mL/mg)
Study MEA115705	10 mg	0.287 ± 0.027	5.463 ± 1.227
	75 mg	0.353 ± 0.024	6.578 ± 0.548
	250 mg	0.317 ± 0.046	6.795 ± 0.689
	750 mg	0.338 ± 0.038	5.994 ± 0.552
Study SB-240563/018	250 mg	0.437 ± 0.069	6.228 ± 1.000

Mean ± SD

In Study MEA115588, trough plasma mepolizumab concentration (observed value) at 4, 16, and 32 weeks after subcutaneous administration of 100 mg was 6.1 ± 2.8 μg/mL (n = 17), 8.5 ± 5.2 μg/mL (n = 17), and 11.1 ± 6.2 μg/mL (n = 15), respectively, in Japanese patients, and 4.6 ± 2.6 μg/mL (n = 170), 8.2 ± 3.8 μg/mL (n = 171), and 9.0 ± 5.0 μg/mL (n = 169), respectively, in non-Japanese patients. C_{max} and AUC (geometric mean [95% confidence interval (CI)]) at the steady state estimated from the population pharmacokinetic analysis of data from Study MEA115588 were 19.3 [16.7, 22.4] μg/mL and 381.0 [312.2, 464.9] μg·day/mL, respectively, in Japanese patients and 16.6 [15.8, 17.4] μg/mL and 342.8 [324.2, 362.4] μg·day/mL, respectively, in non-Japanese patients, showing tendency of slightly higher values in Japanese patients compared with non-Japanese patients. The observed differences were considered to be partly due to a higher proportion of underweight patients in the Japanese population than in the non-Japanese population (mean body weight of subjects; 61.3 kg and 77.7 kg, respectively) resulting in a smaller distribution volume.

Table 13 shows the time course of blood eosinophil count in patients receiving mepolizumab (100 mg) subcutaneously. Baseline blood eosinophil count tended to be higher in Japanese patients, but the difference did not exceed the inter-individual variability. Blood eosinophil count after administration of mepolizumab demonstrated a large inter-individual variability, showing no clear ethnic difference. Taking account of the report that an antibody generally exhibits antagonistic effect when it inhibits 60% to 90% of the target (Grimwood et al. *Pharmacol Ther*. 2009;122:281-301), mepolizumab is expected to exhibit clinical effect associated with the decreased blood eosinophil count in both Japanese and non-Japanese patients.

On the basis of the above data, the applicant considers that there is no clear ethnic difference either in the pharmacokinetics of mepolizumab or in the time course of the blood eosinophil count.

Table 13. Time course of blood eosinophil count in multiple subcutaneous doses of mepolizumab (100 mg)

		Blood eosinophil count (/μL)	Ratio to baseline
Japanese	Baseline	470 ± 1086 (17)	—
	After 16 weeks of treatment	30 ± 1329 (15)	0.06 ± 1.159 (15)
	After 32 weeks of treatment	30 ± 1396 (15)	0.05 ± 1.329 (15)
Non-Japanese	Baseline	280 ± 1038 (175)	—
	After 16 weeks of treatment	40 ± 881 (168)	0.14 ± 1.218 (166)
	After 32 weeks of treatment	40 ± 872 (169)	0.15 ± 1.121 (167)

Geometric mean ± geometric SD (number of patients)

PMDA's view:
Regarding the relationship between the pharmacological effect, as measured by eosinophil count, and clinical effect of mepolizumab, it is practically impossible to evaluate the effect of the ethnic factors on the dose-response relationship from the study results because (i) the study was conducted with only one dose level employed and (ii) blood eosinophil count showed a large inter-individual variability. In both intravenous and subcutaneous administration, the exposure level in Japanese asthma patients tended to exceed that in non-Japanese patients. Therefore, appropriateness of using the data of Study MEA115588 in which Japanese patients participated should be decided based on the comparison of efficacy and safety between the Japanese subpopulation and the entire population in the study.

4.(ii).B.(2) Anti-mepolizumab antibody
The applicant's explanation on the occurrence of anti-mepolizumab antibodies and its relationship with pharmacokinetics and safety:
In Studies MEA112997, MEA115588, and MEA115575, immunogenicity was investigated in 893 of 915 subjects receiving mepolizumab. Of those, 3% (28 of 893) of subjects were positive for anti-mepolizumab antibodies, while 6% (15 of 260) of subjects in the 100 mg SC group. In all studies, the distribution of plasma mepolizumab concentration was similar between antibody-positive and -negative subjects (Figure 2). As an adverse event possibly related to immunogenicity, moderate injection site reaction occurred in 1 anti-mepolizumab antibody-positive subject in Study MEA115575, and this subject discontinued the study because of the adverse event. Injection site reaction occurred in 43 of 1294 antibody-negative subjects, and presence of anti-mepolizumab antibodies did not increase tendency of risks such as injection site reaction. In the anti-mepolizumab antibody-positive subject who had moderate injection site reaction in Study MEA115575, neutralizing antibodies were detected at 2 and 3 months after the final dose.

In Study MEA115588, anti-mepolizumab antibodies were detected in 2 of 17 Japanese subjects receiving subcutaneous administration of mepolizumab. These subjects had adverse events such as muscle stiffness, face oedema/headache/gastroenteritis viral/muscle cramp/pneumonia, but they were mild to moderate and resolved without discontinuation of mepolizumab administration.

On the basis of the above findings, the applicant considers that mepolizumab is unlikely to induce immune response and does not pose any clinical problems associated with the development of anti-mepolizumab antibodies.

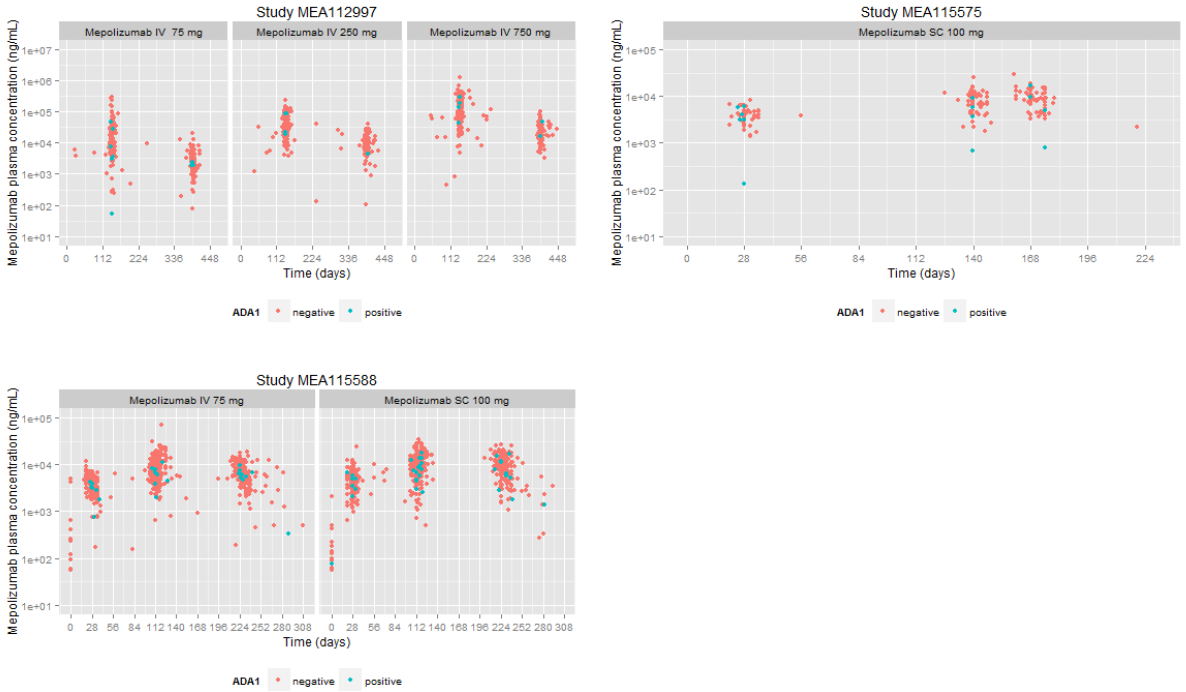

Figure 2. Time course of plasma drug concentration in anti-mepolizumab antibody-positive and -negative subjects in Studies MEA112997, MEA115575, and MEA115588

PMDA's view:
Information available so far does not suggest any clinical problem associated with the development of anti-mepolizumab antibodies. However, if reduced efficacy with long-term use is suggested in many patients after the market launch, a further investigation should be carried out on the relationship between the development of anti-mepolizumab antibodies and efficacy.

4.(ii).B.(3) Dosage and administration of mepolizumab based on a clinical pharmacological point of view

The applicant's justification for the dosage and administration of mepolizumab:
Mepolizumab is considered to exhibit efficacy against the conditions of bronchial asthma with eosinophilic airway inflammation by neutralizing IL-5 bioactivity, a growth and activation factor for eosinophils, thereby decreasing eosinophil count [see "3.(i) Summary of pharmacology studies"]. In Study MEA112997, which was conducted based on the results of the phase II studies of mepolizumab (e.g., Study SB-240563/006) and clinical investigations (Halder P et al. *N Eng J Med.* 2009;360:973-984, Nair P et al. *N Eng J Med.* 2009;360:985-993), efficacy and safety of mepolizumab administered intravenously were evaluated. As a result, superiority of mepolizumab (75, 250, 750 mg) to placebo in the incidence of asthma exacerbation, the primary endpoint, was confirmed, but no dose-response relationship was shown. In Study MEA114092, to investigate the relationship between intravenous or subcutaneous administration and blood eosinophil count thereafter, the applicant planned to evaluate the efficacy and safety of mepolizumab administered subcutaneously. Subcutaneous doses were set at 12.5 mg (predicted 50% inhibitory dose [ID_{50}]), 125 mg, and 250 mg (predicted dose eliciting maximal response) based on the PPK-PD analysis of the data of phase I/II studies in healthy adult subjects, patients with asthma, patients with eosinophilic oesophagitis, and patients with hypereosinophilic syndrome. An intravenous dose of 75 mg was also set. As a result, a non-linear dose-response model was able to be applied to the relationship between the rate of decline in blood eosinophil count at Day 84 and the dose of mepolizumab, and the maximum rate of blood eosinophil count decrease (I_{max}) induced by mepolizumab was estimated to be 89%, and 90% inhibitory dose (ID_{90}) was estimated to be 99 mg SC (Figure 3). Based on these estimations, the subcutaneous dose of mepolizumab was set at 100 mg in Study MEA115588. In the bioavailability study (Study SB-240563/018), the absolute bioavailability in subcutaneous administration was 64% to 75%. In Study MEA112997, the ratio of decline in blood eosinophil count after intravenous administration of mepolizumab (75 mg) at Day 84 relative to baseline was 0.19 ± 1.008 (geometric mean ± geometric SD). From the non-linear dose

response model based on the data of Study MEA114092, it was estimated that a similar extent of decrease [95% CI] in blood eosinophil count (0.14 [0.12, 0.17]) would be achieved by subcutaneous administration of mepolizumab (100 mg). Therefore, the applicant considered that the subcutaneous dose of 100 mg was appropriate to achieve asthma exacerbation-suppressing effect similar to that obtained with the intravenous administration of mepolizumab (75 mg). Study MEA115588 was planned to include the 75 mg intravenous dose group also to evaluate the appropriateness of the above assumption based on the incidence of asthma exacerbation.

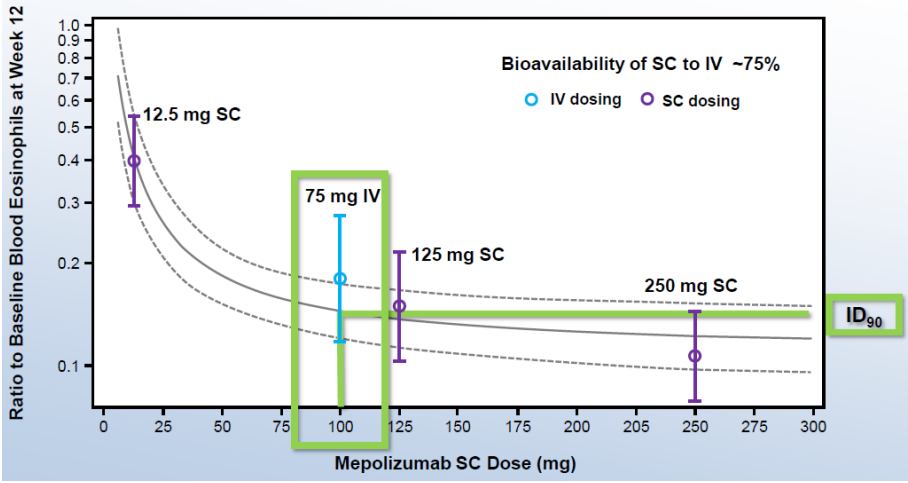

Figure 3. Relationship between the dose of mepolizumab and the rate of decline in blood eosinophil count, estimated from the non-linear dose-response model based on the data of Study MEA114092

(The non-linear dose response model was derived from an indirect response model constructed based on the data of Study SB-240563/035, etc., by adjusting with study results on 12.5 mg SC, 125 mg SC, and 250 mg SC as well as 75 mg IV data in the place of 100 mg SC data, which was assumed appropriate from the absolute bioavailability of 75%).

The applicant's explanation on the relationship between plasma mepolizumab concentration and decreased blood eosinophil count or efficacy:

The relationship between average plasma mepolizumab concentration (C_{av}) and pharmacodynamics or efficacy was investigated based on the results of Studies MEA112997 and MEA115588. As shown in Figure 4, blood eosinophil count at the end of the study tended to decrease slightly with increasing C_{av}, whereas no relationship with C_{av} was observed in the ratio of the incidence of asthma exacerbation relative to the placebo group (Figure 5) or in the change in forced expiratory volume in 1 second (FEV_1) from baseline (Figure 6). In the group receiving 100 mg SC, which is the dose that corresponds to ID_{90} against blood eosinophil count, the estimated C_{av} [95% CI] at the end of the study was 1.22 [1.17, 1.29] µg/mL and the rate of decline in blood eosinophil count relative to the placebo group was 84%.

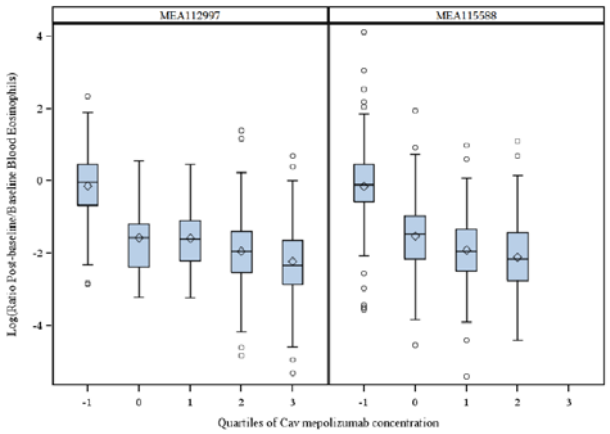

Figure 4. Relationship between plasma mepolizumab concentration and rate of decline in blood eosinophil count from baseline (left, Study MEA112997; right, Study MEA115588)

Mean plasma mepolizumab concentration (estimate): -1, placebo; 0, 4.19-11.27 µg/mL; 1, 11.28-15.68 µg/mL; 2, 15.75-44.54 µg/mL; 3, 44.55-303.60 µg/mL

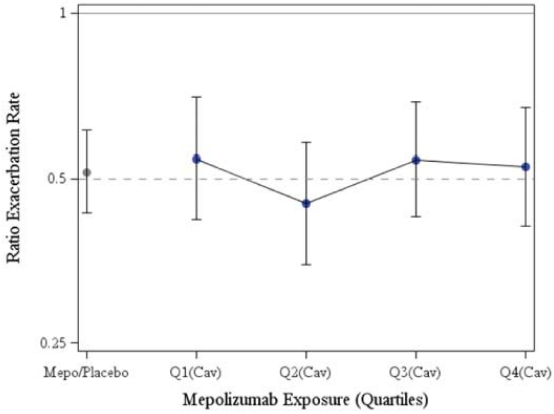

Figure 5. Relationship between plasma mepolizumab concentration and the incidence of asthma exacerbation (pooled data of Studies MEA112997 and MEA115588)

Mean plasma mepolizumab concentration (estimate): Q1, 4.19-11.27 µg/mL; Q2, 11.28-15.68 µg/mL; Q3, 15.75-44.54 µg/mL; Q4, 44.55-303.60 µg/mL

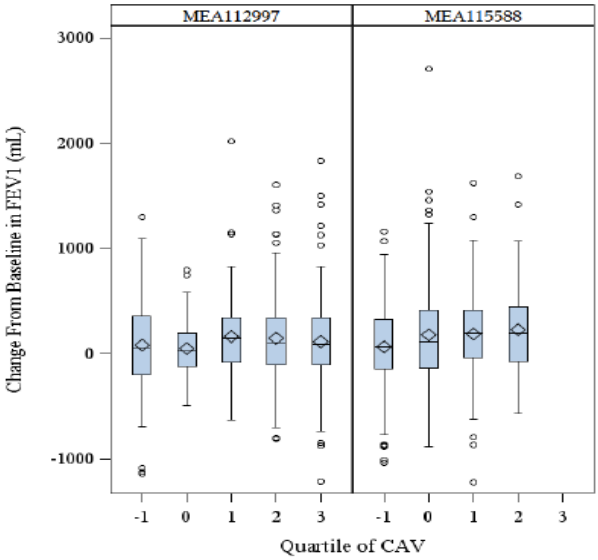

Figure 6. Relationship between plasma mepolizumab concentration and change in FEV_1 from baseline (left, Study MEA112997; right, Study MEA115588)

Mean plasma mepolizumab concentration (estimate): -1, placebo; 0, 4.19-11.27 µg/mL; 1, 11.28-15.68 µg/mL; 2, 15.75-44.54 µg/mL; 3, 44.55-303.60 µg/mL

PMDA's view:

Within the dose range (75-750 mg intravenous administration) of mepolizumab investigated in Study MEA112997, neither dose-response relationship nor exposure-response relationship was observed in the effect to decrease blood eosinophil count or to suppress asthma exacerbation (Table 9, Figures 4 and 5). Nevertheless, it is generally acceptable that Study MEA115588 was conducted using the group receiving 100 mg SC, the dose estimated to be ID_{90} against blood eosinophil count from the non-linear dose-response model and that the study was planned to allow comparison of the rate of asthma exacerbation, etc., with the group receiving 75 mg IV, the minimum effective dose estimated within the range investigated in Study MEA112997. However, taking account of the fact that the submitted data package does not include study data that allow thorough evaluation of the relationship between plasma mepolizumab concentration versus blood eosinophil count after administration of mepolizumab, effect to suppress asthma exacerbation, or other clinical effects, it would have been more desirable if clinical effect at a SC dose of <100 mg had been investigated in order to clarify these relationships and to support the appropriateness of setting the dose based on the effect to decrease blood eosinophil count.

Appropriate dose for subcutaneous administration of mepolizumab will be concluded based on the results of clinical efficacy and safety [see "4.(iii) Summary of clinical efficacy and safety"].

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The applicant submitted efficacy and safety evaluation data, namely the results of the following studies: A foreign phase II study in patients with asthma (Study MEA114092 [5.3.4.2, MEA114092]), a global phase III study involving Japan (Study MEA115588 [5.3.5.1, MEA115588]), foreign phase III studies (Study MEA112997 [5.3.5.1, MEA112997], Study MEA115575 [5.3.5.1, MEA115575]), and a long-term treatment study (Study MEA115661 [5.3.5.2, MEA115661]). The applicant also submitted reference data, namely the results from 14 studies including 2 foreign clinical studies in patients with asthma (Study MEA115666 [5.3.5.2, MEA115666], Study SB-240563/006 [5.3.5.4, SB-240563/006]).

4.(iii).A.(1) Clinical studies in patients with asthma

4.(iii).A.(1).1) Foreign phase II study (5.3.5.4, Study SB-240563/006 [February 1999 to October 1999])

A randomized, placebo-controlled, double-blind, parallel group, comparative study in non-Japanese patients with moderate asthma[9] (target sample size, 378) was conducted to investigate the efficacy and safety of mepolizumab in 5 countries, i.e., the US, the UK, France, Germany, and the Netherlands.

Mepolizumab (250 mg, 750 mg) or placebo was to be administered intravenously 3 times, 4 weeks apart.

All 362 randomized patients (120 in the 250 mg group, 116 in the 750 mg group, 126 in the placebo group) receiving the study drug were included in the intention-to-treat (ITT) population and the safety analysis population, and the ITT population was subjected to efficacy analysis.

Study discontinuation occurred in 8.3% (10 of 120) of patients in the 250 mg group, 3.4% (4 of 116) of patients in the 750 mg group, and 5.6% (7 of 126) of patients in the placebo group. Main reasons for the discontinuation included adverse events (3.3% [4 of 120] of patients in the 250 mg group, 0.9% [1 of 116] of patients in the 750 mg group, 4% [5 of 126] of patients in the placebo group).

Table 14 shows changes in morning peak expiratory flow rate from baseline after 12 weeks of treatment, the primary endpoint. No statistically significant difference was observed in the paired comparison between the placebo group and the 250 or 750 mg group.

Table 14. Change in morning peak flow (L/min) from baseline (ITT population)

	Mepolizumab 250 mg	Mepolizumab 750 mg	Placebo
Baseline	357.0 ± 90.6 (120)	375.7 ± 88.8 (116)	356.1 ± 91.7 (126)
After 12 weeks of treatment	374.6 ± 101.6 (112)	390.2 ± 91.3 (113)	370.8 ± 93.4 (115)
Change	18.1 ± 46.5 (112)	13.4 ± 40.5 (113)	12.5 ± 42.1 (115)
Between-group difference [95% CI] [a)] *P* value[a), b)]	5.69 [-5.56, 16.95] *P* = 0.320	0.85 [-10.37, 12.08] *P* = 0.881	
After 20 weeks of treatment	379.5 ± 102.3 (110)	388.4 ± 92.3 (109)	365.3 ± 96.4 (119)
Change	21.9 ± 50.5 (110)	11.7 ± 45.3 (109)	8.31 ± 51.0 (119)
Between-group difference [95% CI] [a)] *P* value[a), b)]	13.49 [0.71, 26.27] *P* = 0.039	3.42 [-9.39, 16.23] *P* = 0.600	

Mean ± SD (number of patients)

a) Analysis of covariance model with the following explanatory variables: treatment group, region, and interaction between treatment group and region

b) Adjusted for multiplicity by the Bonferroni method

Adverse events occurred in 67.5% (81 of 120) of patients in the 250 mg group, 69.0% (80 of 116) of patients in the 750 mg group, and 76.2% (96 of 126) of patients in the placebo group. Table 15 shows adverse events reported by ≥4% of patients in any group. No deaths occurred.

Serious adverse events occurred in 2.5% (3 of 120) of patients in the 250 mg group, 1.7% (2 of 116) of patients in the 750 mg group, and 3.2% (4 of 126) of patients in the placebo group and the main event

[9] Patients who received a diagnosis of asthma at least 12 months before according to the criteria of the Global Initiative For Asthma/World Health Organization 1995 and met all of the following criteria: (a) FEV_1 before administration of a bronchodilator was ≥50% and <80% of the predicted value, (b) airway reversibility (FEV_1 ≥12%) was observed, and (c) on treatment with a moderate dose of ICS (≤1000 μg/day beclomethasone dipropionate equivalent) for 1 month before the start of the run-in period.

was asthma (1.7% [2 of 116] of patients in the 750 mg group, 0.8% [1 of 126] of patients in the placebo group), but a causal relationship to the study drug was ruled out in all serious adverse events.

Adverse events leading to discontinuation occurred in 3.3% (4 of 120) of patients in the 250 mg group, 0.9% (1 of 116) of patients in the 750 mg group, and 4.0% (5 of 126) of patients in the placebo group.

Adverse events for which a causal relationship to the study drug could not be ruled out (adverse drug reactions) were observed in 3.3% (4 of 120) of patients in the 250 mg group, 3.4% (4 of 116) of patients in the 750 mg group, and 1.6% (2 of 126) of patients in the placebo group.

Table 15. Adverse events reported by ≥4% of patients in any group (safety analysis population)

	Mepolizumab 250 mg (n = 120)	Mepolizumab 750 mg (n = 116)	Placebo (n = 126)
Asthma	25 (21)	20 (17)	30 (24)
Upper respiratory tract infection	23 (19)	23 (20)	22 (18)
Rhinitis	13 (11)	13 (11)	21 (17)
Injury	12 (10)	5 (4)	12 (10)
Headache	9 (8)	16 (14)	15 (12)
Sinusitis	9 (8)	7 (6)	14 (11)
Pharyngitis	7 (6)	5 (4)	12 (10)
Viral infection	6 (5)	5 (4)	6 (5)
Nausea	6 (5)	2 (2)	4 (3)
Diarrhoea	5 (4)	1 (1)	4 (3)
Bronchitis	4 (3)	8 (7)	7 (6)
Myalgia	3 (3)	5 (4)	2 (2)
Back pain	3 (3)	2 (2)	8 (6)
Urinary tract infection	3 (3)	1 (1)	5 (4)
Dyspepsia	2 (2)	0	5 (4)
Conjunctivitis	1 (1)	3 (3)	5 (4)

Number of patients (%)

4.(iii).A.(1).2) Foreign phase II/III study (5.3.5.1, Study MEA112997 [November 2009 to December 2011])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study was conducted to investigate the efficacy and safety of mepolizumab in 13 countries including the US, the UK, France, and Germany. Subjects enrolled in the study were ≥12-year-old non-Japanese patients[10] (target sample size, 604 [151 patients per group]) with severe asthma uncontrolled by long-term control medications such as high dose ICS and long-acting β_2 agonists (LABA) who met at least one of the following criteria related to eosinophil count in blood or sputum: (a) Blood eosinophil count within 12 months before enrollment ≥300/μL, (b) sputum eosinophils (%) within 12 months before enrollment ≥3%, (c) nitric oxide concentration in the expired air within 12 months before enrollment, or at the start of treatment ≥50 ppb, (d) asthma poorly controlled when the maintenance dose of an inhaled corticosteroid (ICS) or an oral corticosteroid (OCS) was reduced by ≤25% within 12 months before enrollment.

Mepolizumab (75 mg, 250 mg, 750 mg) or placebo was administered intravenously at 4-week intervals for 52 weeks.

Of 621 randomized patients, 616 patients (153 in the 75 mg group, 152 in the 250 mg group, 156 in the 750 mg group, 155 in the placebo group) receiving the study drug were included in ITT population and the safety analysis population, and the ITT population was subjected to efficacy analysis.

Study discontinuation occurred in 16% (24 of 153) of patients in the 75 mg group, 14% (21 of 152) of patients in the 250 mg group, 15% (23 of 156) of patients in the 750 mg group, and 18% (28 of 155) of patients in the placebo group. Main reasons for the discontinuation included adverse events (3% [5 of 153] of patients in the 75 mg group, 5% [8 of 152] of patients in the 250 mg group, 6% [9 of 156] of patients in the 750 mg group, 4% [6 of 155] of patients in the placebo group) and consent withdrawal

[10] Patients who received a diagnosis of severe refractory bronchial asthma at least 12 months before according to the criteria of the American Thoracic Society, and met all of the following criteria: (a) FEV_1 before administration of a bronchodilator <80% of the predicted value, (b) continuously treated with a high dose ICS (corresponding to ≥880 μg/day fluticasone propionate [FP]) for the last ≥12 months before enrollment, (c) continuously treated with long-term control medications such as LABA, anti-leukotriene antagonist, and theophylline for the last ≥12 months before enrollment, and (d) ≥2 exacerbations of asthma within 12 months before enrollment, requiring treatment with OCS or systemic corticosteroid.

(5% [8 of 153] of patients in the 75 mg group, 1% [2 of 152] of patients in the 250 mg group, 4% [7 of 156] of patients in the 750 mg group, 7% [11 of 155] of patients in the placebo group).

Table 16 shows the incidence of asthma exacerbation[11] within 52 weeks after treatment initiation, the primary endpoint. Paired comparison between the placebo group versus the 75, 250, and 750 mg groups showed a statistically significant difference, demonstrating the superiority of mepolizumab 75, 250, and 750 mg to placebo.

Table 16. Incidence of asthma exacerbations until after 52 weeks of treatment (frequencies/year, ITT population)

	Mepolizumab 75 mg (n = 153)	Mepolizumab 250 mg (n = 152)	Mepolizumab 750 mg (n = 156)	Placebo (n = 155)
Number of patients with asthma exacerbation (proportion), number of episodes	70 (0.46), 155	85 (0.56), 181	73 (0.47), 152	104 (0.67), 288
Incidence of asthma exacerbation (frequencies/year) [a)]	1.24	1.46	1.15	2.40
Ratio to the placebo group [95% CI] [a)] *P* value [a), b)]	0.52 [0.39, 0.69] *P* < 0.001	0.61 [0.46, 0.81] *P* < 0.001	0.48 [0.36, 0.64] *P* < 0.001	

a) Negative binominal regression model with the following explanatory and offset variables: treatment group, use/non-use of OCS at baseline, region, number of events of asthma exacerbation observed within 12 months before study enrollment (twice, 3 times, ≥4 times), and baseline %FEV_1 as explanatory; and run-in period (logarithmic scale) as offset.

b) If linear contrast test on all dose groups including the placebo group showed a statistically significant difference, paired comparison between each dose group and the placebo group was to be conducted, and 3 paired comparisons were to be adjusted for multiplicity by the Hochberg method. For the secondary endpoints, i.e., (a) change in FEV_1 from baseline before inhaling bronchodilator after 52 weeks of treatment, (b) Asthma Quality of Life Questionnaire (AQLQ) score after 52 weeks of treatment, (c) incidence of asthma exacerbation requiring hospitalization or emergency department visit, (d) Asthma Control Questionnaire (ACQ) score after 52 weeks of treatment, adjustment for multiplicity was made using the Hochberg method for the multiple pairwise comparisons between each dose group and the placebo group that showed a statistically significant difference in the stepdown method with strata defined in the order of the primary endpoint followed by secondary endpoints (a) through (d), and in the endpoints in the upper strata.

Adverse events were observed in 82% (126 of 153) of patients in the 75 mg group, 82% (124 of 152) of patients in the 250 mg group, 78% (122 of 156) of patients in the 750 mg group, and 77% (119 of 155) of patients in the placebo group. Table 17 shows adverse events reported by ≥4% of patients in any group.

[11] Defined as asthma exacerbation requiring administration of systemic corticosteroid for ≥3 days, hospitalization, or emergency department visit. In subjects receiving maintenance therapy with systemic corticosteroid, asthma exacerbation was defined as the condition requiring ≥2 times the maintenance dose for ≥3 days.

Table 17. Adverse events reported by ≥4% of patients in any group (safety analysis population)

	Mepolizumab 75 mg (n = 153)	Mepolizumab 250 mg (n = 152)	Mepolizumab 750 mg (n = 156)	Placebo (n = 155)
Nasopharyngitis	34 (22)	33 (22)	29 (19)	24 (15)
Headache	32 (21)	32 (21)	32 (21)	27 (17)
Bronchitis	17 (11)	13 (9)	13 (8)	15 (10)
Asthma	14 (9)	26 (17)	16 (10)	24 (15)
Back pain	11 (7)	7 (5)	15 (10)	11 (7)
Upper respiratory tract infection	10 (7)	18 (12)	19 (12)	15 (10)
Sinusitis	10 (7)	10 (7)	12 (8)	16 (10)
Cough	8 (5)	11 (7)	9 (6)	11 (7)
Infusion related reaction	8 (5)	12 (8)	19 (12)	10 (6)
Urinary tract infection	8 (5)	8 (5)	1 (0.6)	4 (3)
Pharyngitis	8 (5)	2 (1)	3 (2)	4 (3)
Hypertension	7 (5)	6 (4)	5 (3)	7 (5)
Arthralgia	6 (4)	9 (6)	9 (6)	10 (6)
Fatigue	6 (4)	7 (5)	2 (1)	4 (3)
Rhinitis allergic	6 (4)	6 (4)	6 (4)	2 (1)
Influenza	6 (4)	5 (3)	9 (6)	8 (5)
Lower respiratory tract infection	6 (4)	4 (3)	4 (3)	4 (3)
Ear infection	6 (4)	2 (1)	2 (1)	3 (2)
Dyspnoea	5 (3)	7 (5)	7 (4)	3 (2)
Oedema peripheral	5 (3)	6 (4)	3 (2)	7 (5)
Pain in extremity	5 (3)	4 (3)	8 (5)	5 (3)
Viral infection	5 (3)	3 (2)	6 (4)	3 (2)
Nasal congestion	5 (3)	1 (0.7)	6 (4)	2 (1)
Oropharyngeal pain	4 (3)	12 (8)	6 (4)	7 (5)
Vomiting	4 (3)	7 (5)	3 (2)	2 (1)
Respiratory tract infection	4 (3)	6 (4)	6 (4)	4 (3)
Rhinitis	4 (3)	5 (3)	3 (2)	7 (5)
Dizziness	4 (3)	3 (2)	6 (4)	2 (1)
Chest pain	2 (1)	7 (5)	3 (2)	4 (3)
Diarrhoea	2 (1)	2 (1)	8 (5)	6 (4)
Ligament sprain	1 (0.7)	1 (0.7)	3 (2)	6 (4)

Number of patients (%)

Death occurred in 2 patients in the 250 mg group (asthma, pancreatitis acute/septic shock in 1 patient each) and 1 in the 750 mg group (asphyxia), but a causal relationship to the study drug was ruled out.

Serious adverse events were observed in 13% (20 of 153) of patients in the 75 mg group, 16% (24 of 152) of patients in the 250 mg group, 12% (19 of 156) of patients in the 750 mg group, and 16% (25 of 155) of patients in the placebo group, and the main adverse event was asthma (7% [11 of 153] of patients in the 75 mg group, 11% [16 of 152] of patients in the 250 mg group, 6% [9 of 156] of patients in the 750 mg group, 11% [17 of 155] of patients in the placebo group). Among the serious adverse events observed, a causal relationship to the study drug could not be ruled out in reticulocyte count decreased in 1 patient in the 250 mg group or supraventricular tachycardia in 1 patient in the 750 mg group.

Adverse events leading to discontinuation occurred in 3% (5 of 153) of patients in the 75 mg group, 5% (8 of 152) of patients in the 250 mg group, 6% (9 of 156) of patients in the 750 mg group, and 4% (6 of 155) of patients in the placebo group.

Adverse drug reactions were observed in 18% (28 of 153) of patients in the 75 mg group, 19% (29 of 152) of patients in the 250 mg group, 21% (33 of 156) of patients in the 750 mg group, and 17% (26 of 155) of patients in the placebo group.

4.(iii).A.(1).3) Global phase III study (5.3.5.1, Study MEA115588 [October 2012 to January 2014])

A randomized, placebo-controlled, double-blind, parallel group, comparative study was conducted to investigate the efficacy and safety of mepolizumab in 16 countries including Japan, the US, Korea, and Germany. Subjects enrolled in this study were ≥12-year-old patients[12] (target sample size, 540 [180

[12] Patients who met all of the following criteria: (a) FEV_1 before administration of a bronchodilator <80% of the predicted value (patients ≥18 years of age), FEV_1 before administration of a bronchodilator <90% of the predicted value or FEV_1/FVC <0.8 before administration of a bronchodilator (patients 12-17 years of age), (b) continuously treated with a high dose ICS (corresponding to ≥FP 880 μg/day [≥18 years of age], ≥FP 440μg/day [12-17 years of age] for the last ≥12 months before enrollment, (c) requiring treatment with long-term control medications such as LABA, anti-leukotriene antagonist, and theophylline over 3 months during 12 months before enrollment, and (d) ≥2 exacerbations of asthma within 12 months before enrollment, requiring treatment with OCS or systemic corticosteroid.

patients per group]) with severe asthma uncontrolled by treatment with long-term control medications such as high dose ICS and LABA who met either of the following criteria related to blood eosinophil count: (a) blood eosinophil count within 12 months before enrollment ≥300/μL, or (b) blood eosinophil count at enrollment ≥150/μL.

The patients received subcutaneous or intravenous doses of mepolizumab (100 mg or 75 mg, respectively) or placebo at 4-week intervals for 32 weeks.

Of 580 randomized patients (194 in the 100 mg SC group, 193 in the 75 mg IV group, 193 in the placebo group), 576 patients (194 in the 100 mg SC group, 191 in the 75 mg IV group, 191 in the placebo group) receiving at least 1 dose of the study drug were included in the modified ITT (mITT) population and safety analysis population, and mITT population was subjected to efficacy analysis.

Study discontinuation occurred in 5% (9 of 194) of patients in the 100 mg SC group, 8% (16 of 191) of patients in the 75 mg IV group, and 6% (12 of 191) of patients in the placebo group. Main reasons for the discontinuation included consent withdrawal (2% [4 of 194] of patients in the 100 mg SC group, 5% [9 of 191] of patients in the 75 mg IV group, 3% [5 of 191] of patients in the placebo group).

The mITT population included a Japanese subpopulation consisting of 50 patients (17 in the 100 mg SC group, 17 in the 75 mg IV group, 16 in the placebo group). Among patients in this subpopulation, study was discontinued in 12% (2 of 17) of patients in the 100 mg SC group, 18% (3 of 17) of patients in the 75 mg IV group, and 6% (1 of 16) of patients in the placebo group. The reason for the discontinuation was consent withdrawal in all of them.

Table 18 shows the incidence of asthma exacerbation[11] until after 32 weeks of treatment, the primary endpoint. Paired comparison between the placebo group versus the 100 mg SC group and the 75 mg IV group showed statistically significant difference, demonstrating the superiority of 100 mg SC and 75 mg IV to placebo.

Table 18. Incidence of asthma exacerbation until after 32 weeks of treatment (frequencies/year, mITT population)

	Mepolizumab 100 mg SC (n = 194)	Mepolizumab 75 mg IV (n =191)	Placebo (n = 191)
Number of patients with asthma exacerbation proportion), number of episodes	64 (0.33), 116	70 (0.37), 117	105 (0.55), 216
Incidence of asthma exacerbation (frequencies/year) [a)]	0.83	0.93	1.74
Ratio to the placebo group [95% CI] [a)], *P* value [a), b)]	0.47 [0.35, 0.64] *P* < 0.001	0.53 [0.40, 0.72] *P* < 0.001	

a) Negative binominal regression model with the following explanatory and offset variables: treatment group, use/non-use of OCS at baseline, region, number of events of asthma exacerbation observed within 1 year before study enrollment (twice, 3 times, ≥4 times), and baseline %FEV_1 as explanatory; and run-in period (logarithmic scale) as offset

b) For the primary endpoint, 2 paired comparisons were adjusted for multiplicity by the Hochberg method. For the main secondary endpoints, i.e., (a) incidence of asthma exacerbation requiring hospitalization or emergency department visit, (b) incidence of asthma exacerbation requiring hospitalization, (c) change in FEV_1 from baseline before bronchodilator inhalation after 32 weeks of treatment, and (d) change in St George's Respiratory Questionnaire (SGRQ) score from baseline after 32 weeks of treatment, only if 2 paired comparisons showed statistically significant results in the stepdown method with strata defined in the order of the primary endpoint followed by secondary endpoints (a) through (d) and in the endpoints in the upper strata, paired comparison was performed on endpoints in the lower strata. The Hochberg method was applied only to the primary endpoint, and 2 paired comparisons of main secondary endpoints were not adjusted for multiplicity.

Table 19 shows the incidence of asthma exacerbation in the Japanese subpopulation.

Table 19. Incidence of asthma exacerbation in Japanese subpopulation (frequencies/year, mITT population)

	Mepolizumab 100 mg SC (n = 17)	Mepolizumab 75 mg IV (n = 17)	Placebo (n = 16)
Incidence of asthma exacerbation (frequencies/year) [a)]	0.88	0.23	2.32
Ratio to the placebo group [95% CI] [a)]	0.38 [0.12, 1.18]	0.10 [0.02, 0.57]	

a) Negative binominal regression model with the following explanatory and offset variables: treatment group, use/non-use of OCS at baseline, number of events of asthma exacerbation observed within 1 year before study enrollment (twice, 3 times, ≥4 times), and baseline %FEV_1 as explanatory; and run-in period (logarithmic scale) as offset

Adverse events were observed in 78% (152 of 194) of patients in the 100 mg SC group, 84% (161 of 191) of patients in the 75 mg IV group, and 83% (158 of 191) of patients in the placebo group. Table 20 shows adverse events reported by ≥4% of patients in any group.

Death occurred in 1 patient in the placebo group (road traffic accident); a causal relationship of the death to the study drug was ruled out.

Serious adverse events were observed in 8% (16 of 194) of patients in the 100 mg SC group, 7% (14 of 191) of patients in the 75 mg IV group, and 14% (27 of 191) of patients in the placebo group. The main serious event was asthma (3% [5 of 194] of patients in the 100 mg SC group, 5% [9 of 191] of patients in the 75 mg IV group, 7% [14 of 191] of patients in the placebo group). Events reported by ≥2 patients in all groups combined were bronchitis (2 patients in the placebo group), herpes zoster (2 patients in the 100 mg SC group), nephrolithiasis (1 patient each in the 100 mg SC and placebo groups), and hypersensitivity (1 patient each in the 100 mg SC and placebo groups). Among the serious adverse events observed, a causal relationship to the study drug could not be ruled out in 1 patient in the 100 mg SC group (herpes zoster) and in 1 patient in the placebo group (epilepsy).

Adverse events leading to discontinuation occurred in 1 patient in the 100 mg SC group (atrial flutter) and in 4 patients in the placebo group (arrhythmia, hypersensitivity, epilepsy, and road traffic accident in 1 patient each).

Adverse drug reactions were observed in 20% (39 of 194) of patients in the 100 mg SC group, 17% (33 of 191) of patients in the 75 mg IV group, and 16% (30 of 191) of patients in the placebo group.

Table 20. Adverse events reported by ≥4% of patients in any group (safety analysis population)

	Mepolizumab 100 mg SC (n = 194)	Mepolizumab 75 mg IV (n = 191)	Placebo (n = 191)
Headache	39 (20)	46 (24)	33 (17)
Nasopharyngitis	33 (17)	45 (24)	46 (24)
Upper respiratory tract infection	24 (12)	22 (12)	27 (14)
Sinusitis	18 (9)	11 (6)	18 (9)
Injection site reaction	17 (9)	5 (3)	6 (3)
Back pain	14 (7)	11 (6)	7 (4)
Asthma	13 (7)	18 (9)	29 (15)
Arthralgia	11 (6)	10 (5)	9 (5)
Bronchitis	9 (5)	14 (7)	18 (9)
Eczema	9 (5)	2 (1)	2 (1)
Pain in extremity	8 (4)	3 (2)	10 (5)
Urinary tract infection	8 (4)	5 (3)	2 (1)
Oropharyngeal pain	7 (4)	12 (6)	15 (8)
Abdominal pain upper	7 (4)	7 (4)	4 (2)
Nasal congestion	7 (4)	5 (3)	1 (0.5)
Gastrooesophageal reflux disease	7 (4)	2 (1)	3 (2)
Dizziness	6 (3)	4 (2)	8 (4)
Gastroenteritis	5 (3)	10 (5)	6 (3)
Cough	5 (3)	8 (4)	9 (5)
Fatigue	5 (3)	8 (4)	9 (5)
Diarrhoea	5 (3)	4 (2)	11 (6)
Nausea	5 (3)	4 (2)	8 (4)
Influenza	4 (2)	10 (5)	6 (3)
Rhinitis	1 (0.5)	7 (4)	4 (2)

Number of patients (%)

In the Japanese subpopulation, adverse events were observed in 71% (12 of 17) of patients in the 100 mg SC group, 82% (14 of 17) of patients in the 75 mg IV group, and 94% (15 of 16) of patients in the placebo group. Table 21 shows adverse events reported by ≥2 patients in any group. No death occurred. Serious adverse events were observed in 24% (4 of 17) of patients in the 100 mg SC group (asthma/influenza, herpes zoster, gallbladder disorder, and asthma in 1 patient each), 6% (1 of 17) of patients in the 75 mg IV group (fractured coccyx), and 25% (4 of 16) of patients in the placebo group (asthma in 4 patients; heat stroke in 1 patient, includes duplicate counting). A causal relationship to the study drug could not be ruled out only in herpes zoster. No adverse events led to discontinuation.

Adverse drug reactions were observed in 12% (2 of 17) of patients in the 100 mg SC group, 6% (1 of 17) of patients in the 75 mg IV group, and 19% (3 of 16) of patients in the placebo group.

Table 21. Adverse events reported by ≥2 patients in any group in Japanese subpopulation (safety analysis population)

	Mepolizumab 100 mg SC (n = 17)	Mepolizumab 75 mg IV (n = 17)	Placebo (n = 16)
Nasopharyngitis	4 (24)	7 (41)	4 (25)
Asthma	2 (12)	5 (29)	9 (56)
Headache	2 (12)	2 (12)	2 (13)
Constipation	2 (12)	1 (6)	0
Diarrhoea	2 (12)	0	2 (13)
Eczema	2 (12)	0	1 (6)
Upper respiratory tract infection	2 (12)	0	0
Migraine	0	0	2 (13)
Bronchitis	0	0	2 (13)
Malaise	0	0	2 (13)
Oropharyngeal pain	0	0	2 (13)

Number of patients (%)

4.(iii).A.(1).4) Foreign phase III study (5.3.5.1, Study MEA115575 [October 2012 to December 2013])

A randomized, placebo-controlled, double-blind, parallel-group, comparative study was conducted to investigate the efficacy and safety of mepolizumab in 10 countries including the US, the UK, France, and Germany. Subjects enrolled in this study were ≥12-year-old non-Japanese patients[13] (target sample size, 120 [60 patients per group]) with severe asthma uncontrolled by treatment with high dose ICS and long-term control medications who met either of the following criteria related to blood eosinophil count: (a) blood eosinophil count within 12 months before enrollment ≥300/μL, and (b) blood eosinophil count at enrollment ≥150/μL.

Mepolizumab (100 mg/dose) or placebo was administered subcutaneously at 4-week intervals for 24 weeks.

The study consisted of 4 phases, as shown below:

(a) OCS dose-optimization phase (for 3-10 weeks): In subjects who met the inclusion criteria, asthma-controlling status was determined based on ACQ-5 score and presence/absence of asthma exacerbation. Optimal OCS dose was determined by decreasing the dose by 5 mg/day every week in patients receiving OCS dose of 20 to 35 mg/day, and by 2.5 mg/day every week in patients receiving OCS dose of 7.5 to 15 mg/day.

(b) Induction phase (Week 0-4 of study drug administration): Patients were randomized to the 100 mg group or the placebo group, and received the optimized OCS dose continuously.

(c) Dose reduction phase (Week 4-20 of study drug administration): Appropriateness of OCS dose reduction was evaluated every 4 weeks, and the dose was reduced in patients who did not meet the criteria.[14] OCS dose was to be reduced by 10 mg/day in patients receiving ≥20 to ≤35 mg/day of OCS, by 5 mg/day in patients receiving ≥10 to <20 mg/day (except for 12.5 mg/day), by 2.5 mg/day in patients receiving ≥5 to <10 mg/day or 12.5 mg/day, and by 1.25 mg/day in patients receiving ≥1.25 to <5 mg/day. In patients for whom the optimal OCS dose was ≥25 mg/day, the dose was to be reduced down to 2.5 mg/day.

[13] Asthma patients who met the following criteria: (a) Continuously treated with systemic corticosteroid (5.0-35 mg/day [prednisolone equivalent]) and high-dose ICS (corresponding to ≥FP 880 μg/day in patients ≥18 years of age and ≥FP 440 μg/day in patients 12-17 years of age) for the last ≥6 months before enrollment, and (b) using additional long-term control medication(s) other than ICS for the last ≥3 months before enrollment or requiring long-term control medications such as LABA, anti-leukotriene antagonist, and theophylline because of worsening of asthma symptoms over 3 months within 12 months before enrollment.

[14] Criteria for not reducing OCS dose: (a) Morning PEF <80% of baseline, (b) mean number of nocturnal awakenings due to asthmatic symptoms increased by ≥50% from baseline, (c) used rescue drug in 2 consecutive days during the previous week ≥4 times more than baseline per day, or used rescue drug ≥12 times a day during the previous week, (d) ACQ-5 score increased by ≥0.5 compared with the score during the evaluation period of the previous month, and (e) occurrence of symptoms of adrenal insufficiency.

(d) Maintenance phase (week 20-24 of study drug administration): OCS dose at week 20 of study drug administration was to be maintained throughout the phase.

All 135 randomized patients (69 in the 100 mg group, 66 in the placebo group) received at least 1 dose of the study drug and were included in the ITT population and the safety analysis population, and the ITT population was subjected to efficacy analysis.

Study was discontinued in 4% (3 of 69) of patients in the mepolizumab 100 mg group and in 6% (4 of 66) of patients in the placebo group. The main reasons for discontinuation were adverse events (3 patients each in the mepolizumab group and placebo group).

Table 22 shows OCS dose reduction rate relative to baseline after 24 weeks of treatment, the primary endpoint. Paired comparison between the 100 mg group and the placebo group showed statistically significant difference, demonstrating the superiority of mepolizumab 100 mg to placebo.

Table 22. OCS dose reduction rate relative to baseline after 24 weeks of treatment (ITT population)

OCS dose reduction rate relative to baseline	Mepolizumab 100 mg (n = 69)	Placebo (n = 66)
90%-100%	16 (23)	7 (11)
75%-<90%	12 (17)	5 (8)
50%-<75%	9 (13)	10 (15)
>0%-<50%	7 (10)	7 (11)
No dose reduction, poorly controlled asthma precluding dose reduction, or treatment discontinuation	25 (36)	37 (56)
Odds ratio relative to the placebo group [95% CI], [a] *P* value[a]	2.39 [1.25, 4.56] *P* = 0.008	

Number of patients (%)

a) Proportional odds model (ordinal multinomial logistic regression model) with the following explanatory variables: treatment group, region, duration of OCS treatment (<5 years or ≥5 years) and OCS dose (optimal dose) at baseline

Adverse events were observed in 83% (57 of 69) of patients in the 100 mg group and in 92% (61 of 66) of patients in the placebo group. Table 23 shows adverse events reported by ≥4% of patients in either group.

Death occurred in 1 patient in the placebo group (gastrointestinal haemorrhage and aspiration); a causal relationship of the death to the study drug was ruled out.

Serious adverse events were observed in 1% (1 of 69) of patients in the 100 mg group (chronic sinusitis/hypokalaemia/fistula) and in 18% (12 of 66) of patients in the placebo group (asthma in 7 patients, pneumonia in 3 patients, etc.). A causal relationship to the study drug was ruled out in all of them.

Adverse events leading to discontinuation were observed in 4% (3 of 69) of patients in the 100 mg group and in 5% (3 of 66) of patients in the placebo group.

Adverse drug reactions were observed in 30% (21 of 69) of patients in the 100 mg group and in 18% (12 of 66) of patients in the placebo group.

Table 23. Adverse events reported by ≥4% of patients in either group (safety analysis population)

	Mepolizumab 100 mg (n = 69)	Placebo (n = 66)
Headache	14 (20)	14 (21)
Nasopharyngitis	10 (14)	10 (15)
Bronchitis	7 (10)	6 (9)
Sinusitis	7 (10)	6 (9)
Fatigue	7 (10)	4 (6)
Arthralgia	5 (7)	4 (6)
Rhinitis	5 (7)	1 (2)
Nausea	4 (6)	6 (9)
Oropharyngeal pain	4 (6)	5 (8)
Injection site reaction	4 (6)	2 (3)
Oedema peripheral	4 (6)	2 (3)
Pain in extremity	4 (6)	1 (2)
Muscle spasms	4 (6)	0
Upper respiratory tract infection	3 (4)	5 (8)
Adrenal insufficiency	3 (4)	4 (6)
Pyrexia	3 (4)	4 (6)
Lower respiratory tract infection	3 (4)	2 (3)
Influenza	3 (4)	1 (2)
Insomnia	3 (4)	1 (2)
Asthma	2 (3)	8 (12)
Dizziness	2 (3)	3 (5)
Pneumonia	2 (3)	3 (5)
Urinary tract infection	2 (3)	3 (5)
Hypersensitivity	1 (1)	3 (5)
Toothache	1 (1)	3 (5)

Number of patients (%)

4.(iii).A.(1).5) Global long-term treatment study (5.3.5.2, Study MEA115661 [May 2013 to March 2015])

An open-label, uncontrolled study was conducted in 19 countries including Japan, the US, France, and Germany to investigate the safety of long-term mepolizumab treatment in patients who had completed Study MEA115588 or MEA115575.

Mepolizumab (100 mg/dose) was administered subcutaneously at 4-week intervals for 52 weeks.

All of 651 treated patients (525 from Study MEA115588; 126 from Study MEA115575) were included in the safety analysis population. Study was discontinued in 10% (66 of 651) of patients; main reasons for the discontinuation included lack of efficacy (3% [19 of 651] of patients), consent withdrawal (2% [14 of 651] of patients), and adverse events (2% [11 of 651] of patients). Adverse events were observed in 86% (558 of 651) of patients. Table 24 shows adverse events reported by ≥4% of patients.

Table 24. Adverse events reported by ≥4% of patients (safety analysis population)

	Entire population (n = 651)	Japanese subpopulation (n = 43)
Nasopharyngitis	196 (30)	28 (65)
Upper respiratory tract infection	101 (16)	2 (5)
Asthma	90 (14)	11 (26)
Headache	88 (14)	2 (5)
Bronchitis	80 (12)	2 (5)
Sinusitis	66 (10)	3 (7)
Back pain	46 (7)	6 (14)
Arthralgia	44 (7)	1 (2)
Oropharyngeal pain	34 (5)	6 (14)
Injection site reaction	29 (4)	1 (2)
Influenza	28 (4)	6 (14)
Nausea	27 (4)	1 (2)
Lower respiratory tract infection	26 (4)	0
Cough	26 (4)	0
Fatigue	24 (4)	1 (2)
Rhinitis	23 (4)	0

Number of patients (%)

No deaths occurred. Serious adverse events were observed in 14% (94 of 651) of patients, and the main event was asthma (6% [38 of 651] of patients). Among the serious adverse events observed, a causal

relationship to the study drug could not be ruled out in 2 patients (abortion spontaneous and type IV hypersensitivity reaction in 1 patient each). Adverse events leading to discontinuation were observed in 2% (12 of 651) of patients and adverse drug reactions in 18% (119 of 651) of patients.

In the Japanese subpopulation, adverse events were observed in 95% (41 of 43) of patients. Serious adverse events were observed in 21% (9 of 43) of patients, and the main event was asthma (16% [7 of 43] of patients), etc. A causal relationship to the study drug was ruled out in all of them. No adverse events led to discontinuation. Adverse drug reactions were observed in 5% (2 of 43) of patients.

The incidence of asthma exacerbation during the period of mepolizumab administration, the other endpoint, was 48% (311 of 651) of patients, and the rate of asthma exacerbation per year [95% CI] was 0.93 [0.83, 1.04].

4.(iii).A.(1).6) Foreign long-term treatment study (5.3.5.2, Study MEA115666 [September 2012 to [redacted] (data cut-off)])

An open-label, uncontrolled study was conducted in 13 countries including the US, the UK, France, and Germany in order to study the efficacy and safety of mepolizumab in long-term use. Subjects enrolled in this study were non-Japanese patients who had received at least 2 doses of the study drug in Study MEA112997 and were confirmed to have been receiving asthma treatment with a long-term control medication over the last 12 weeks before enrollment. The enrolled patients underwent a 10-month washout period after Study MEA112977 and before this study started.

Mepolizumab (100 mg/dose) was administered subcutaneously at 4-week intervals until marketing approval was obtained.

All of 347 treated patients were included in the safety analysis population and in the efficacy analysis population. Study was discontinued in 6% (22 of 347) of patients, and the main reasons for the discontinuation were adverse events (2% [8 of 347] of patients), etc. Adverse events were observed in 85% (295 of 347) of patients. Table 25 shows adverse events reported by ≥4% of patients.

Table 25. Adverse events reported by ≥4% of patients (safety analysis population)

	Mepolizumab 100 mg (n = 347)
Nasopharyngitis	91 (26)
Headache	73 (21)
Upper respiratory tract infection	46 (13)
Asthma	37 (11)
Arthralgia	36 (10)
Back pain	35 (10)
Bronchitis	35 (10)
Sinusitis	30 (9)
Injection site reaction	29 (8)
Rhinitis allergic	19 (5)
Influenza	18 (5)
Oropharyngeal pain	16 (5)
Respiratory tract infection	16 (5)
Pain in extremity	15 (4)
Hypertension	14 (4)
Lower respiratory tract infection	14 (4)
Respiratory tract infection viral	13 (4)

Number of patients (%)

Death occurred in 1 patient (respiratory arrest), for which a causal relationship to the study drug was ruled out. Serious adverse events were observed in 9% (31 of 347) of patients and the main events included asthma (5% [16 of 347] of patients). A causal relationship to the study drug was ruled out in all of them. Adverse events leading to discontinuation were observed in 2% (8 of 347) of patients and adverse drug reactions in 19% (66 of 347) of patients.

4.(iii).B Outline of the review by PMDA

4.(iii).B.(1) Study design

4.(iii).B.(1).1) Patients in clinical studies

The applicant's explanation on the process of the development of mepolizumab:

It is reported that eosinophils play an important role in the onset and progression of bronchial asthma (Reed CE. *Ann Allergy.* 1994;72:376-380, Bousquet J. *New Eng J Med.* 1990;323:1033-1039) and that eosinophil count and IL-5 level in bronchoalveolar lavage fluid collected from patients hospitalized because of asthma exacerbation were higher compared with asymptomatic patients (Sur S. *J Allergy Clin Immunol.* 1995;96:661-668). On the basis of these and other reports, patients with mild to moderate bronchial asthma were investigated in the early stage of clinical studies of mepolizumab, anti-IL-5 antibody. However, clinical development was suspended because the foreign phase II study (Study SB-240563/006) showed that mepolizumab had only a limited effect on the pulmonary function. Subsequently, it was suggested that severe asthma occurs in several expression types including eosinophilic type and neutrophilic type (Wenzel SE et al. *Am J Respir Crit Care Med.* 2004;170:579-582), and that the rate of severe asthma exacerbation is reduced by selecting the treatment method based on the monitoring of eosinophil count in the airway, in addition to conventional treatment selection based on the clinical conditions and evaluation of the pulmonary function (Green RH et al. *Lancet.* 2002;360:1715-1721, Chlumsky J et al. *J Int Med Res.* 2006;34:129-139, Jayaram L et al. *Eur Respir J.* 2006;27:483-494). In addition, it was reported that, in patients with poorly controlled asthma, eosinophil count in sputum tended to be higher compared with patients with well-controlled asthma (Romagnoli M et al. *Eur Respir J.* 2002;20:1370-1377), and that, in a majority of patients with severe asthma who had airway obstruction during the treatment with a combination of high dose ICS and OCS, sputum eosinophils (%) was ≥3% (Ten Brinke A et al. *Am J Respir Crit Care Med.* 2001;164:744-748, The ENFUMOSA study group, *Eur Respir J.* 2003;22:470-477). Inspired by these and other reports, 2 clinical studies (Studies SB-240563/046[15] and CRT110184[16]) were initiated. The results showed that mepolizumab decreased eosinophil count in sputum and blood, reduced the rate of asthma exacerbation, and allowed OCS dose reduction (Haldar P et al. *N Engl J Med.* 2009;360:973-984, Nair P et al. *N Engl J Med.* 2009;360:985-993). On the basis of these findings, the applicant decided to restart the clinical development of mepolizumab targeted at patients with severe asthma who had eosinophilic airway inflammation.

PMDA asked the applicant to explain the appropriateness of using blood eosinophil count as an inclusion criterion for Studies MEA112997, MEA115588, etc.

The applicant's explanation:
The Japanese guideline, *Asthma Prevention and Management Guideline 2015, JAPAN* (JGL Guideline, 2015), states that asthma is a disease caused by chronic airway inflammation, that eosinophilic infiltration is the most characteristic finding, and that diagnosis of eosinophilic inflammation is made if sputum eosinophils are found to be 2% to 3% or more. Global Initiative for Asthma (GINA) 2007 also mentioned the potential usefulness of eosinophil count in sputum as an index for confirming airway inflammation. However, it is not always possible to collect sputum samples, including induced sputum, from all subjects to be tested, Consequently, Study MEA112997 was conducted to investigate an alternative method for diagnosing airway inflammation, in addition to the efficacy and safety of mepolizumab.

It is reported that sputum eosinophils is positively correlated with eosinophil count in blood (Zhang XY et al. *Clin Exp Allergy*. 2014;44:1137-1145, Schleich F et al. *Respir Med.* 2014;108:1723-1732, Wagener AH et al. *Thorax.* 2015;70:115-120). Study MEA112997 was designed by referring to the following reports: patients with blood eosinophil count of ≥230/μL were identified as patients with sputum eosinophils (%) ≥3% in a clinical study in patients with severe asthma in the UK (Greulich T et al. *Eur Respir J.* 2010;36:1005S); the median blood eosinophil count was 300/μL in patients with severe asthma in the British Thoracic Society registry. Thus, patients who met at least one of the following criteria within past 12 months at enrollment (2 weeks before the start of treatment) were enrolled in the study: (a) Blood eosinophil count ≥300/μL, (b) sputum eosinophils (%) ≥3%, (c) nitric oxide in the expired air

[15] A randomized, placebo-controlled, double-blind, parallel-group, comparative study to investigate the efficacy (reduction of the incidence of asthma exacerbation and reduction of OCS dose) and safety of mepolizumab. Mepolizumab (750 mg) or placebo was administered intravenously at weeks 0, 2, 6, 10, 14, and 18 to patients with severe asthma with sputum eosinophils ≥3% and required treatment with OCS and high dose ICS.

[16] A placebo-controlled, randomized, double-blind, parallel-group, comparative study to investigate the efficacy (reduction of the incidence of asthma exacerbation) and safety of mepolizumab when mepolizumab (750 mg) or placebo was administered intravenously at 4-week intervals for 48 weeks to patients with severe asthma with sputum eosinophils ≥3% and showed twice or more asthma exacerbation within the past 12 months even with a high dose ICS treatment.

≥50 ppb, (d) asthma control deteriorated rapidly after ICS or OCS dose was reduced by up to 25%. In Study MEA112997, sputum was collected from 94 of 616 patients in order to investigate the relationship between blood eosinophil count and airway inflammation at enrollment,[17] and blood eosinophils were counted in 76 patients of them. The results showed that blood eosinophil count was ≥150/μL in a majority of patients with sputum eosinophils (%) ≥2%, as shown in Figure 7.

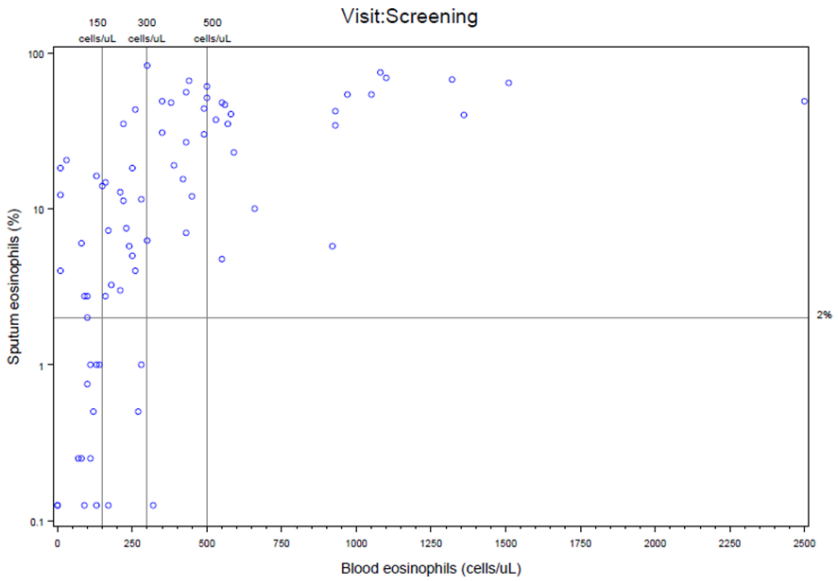

Figure 7. Blood eosinophil count and sputum eosinophils (%) (Study MEA112997)

A modeling analysis[18] of Study MEA112997 data identified blood eosinophil count as an efficacy predictor for mepolizumab and, the incidence of asthma exacerbation[19] was estimated based on the blood eosinophil count at the start of treatment. The results showed that, in patients with blood eosinophil count of 150/μL at the start of treatment, the incidence of asthma exacerbation in the mepolizumab group and the placebo group was 1.16 and 1.65 times per year, respectively, with the ratio [95% CI] being 0.70 [0.53, 0.93], as shown in Figure 8. These results suggested that a clinically significant decrease would be achieved when the cut-off level was set at 150/μL. A subgroup analysis of Study MEA112997 showed that in the subpopulation of patients who had blood eosinophil count of ≤150/μL at the start of treatment but ≥300/μL at some time point during the past 12 months, the incidence of asthma exacerbation in the mepolizumab group and in the placebo group was 1.31 and 1.77 times per year, respectively, with the ratio [95% CI] being 0.74 [0.35, 1.59]. Based on the above results, a confirmatory Study MEA115588 was conducted in patients who met either of the following inclusion criteria related to blood eosinophil count: (a) Blood eosinophil count at enrollment ≥150/μL, and (b) blood eosinophil count within past 12 months ≥300/μL.

[17] Induced sputum samples were collected from patients (target sample size, 30 patients per group) at study centers capable of collection.
[18] A negative binomial distribution model with the following explanatory and offset variables: treatment, use/non-use of OCS at baseline, region, number of events of asthma exacerbation observed within 12 months before enrollment (twice, 3 times, ≥4 times), blood eosinophil count at the start of treatment, and interaction between treatment and blood eosinophil count at the start of treatment as explanatory; and the run-in period (logarithmic scale) as offset.
[19] Defined as conditions requiring systemic corticosteroid administration for ≥3 days, hospitalization, or emergency department visit.

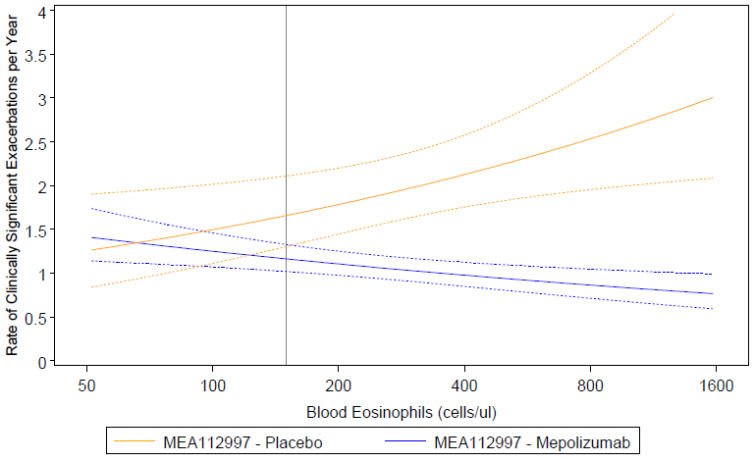

Figure 8. Incidence of asthma exacerbation by blood eosinophil count at the start of treatment (predicted value with 95% CI)

PMDA's view:
It is reported that sputum eosinophil count is high in patients with poorly controlled asthma (Romagnoli M et al. *Eur Respir J.* 2002;20:1370-1377). It is also reported that monitoring sputum eosinophil count is useful in the treatment of asthma exacerbation (Green RH et al. *Lancet.* 2002;360:1715-1721). Taking account of these results together with the pharmacological action of mepolizumab, i.e., eosinophil count reduction through binding to IL-5, the concept of selecting patients to be enrolled in clinical studies based on the eosinophil count is understandable. However, the appropriateness of defining the indication of mepolizumab using the eosinophil count-related criteria employed in clinical studies should be evaluated in a comprehensive manner, taking account of the results of clinical studies, including Study MEA115588 [see "4.(iii).B.(4) Clinical positioning and indication"].

4.(iii).B.(1).2) Evaluation period of Study MEA115588

The applicant's justification for the evaluation period of Study MEA115588:
In Study MEA112997, the effect of mepolizumab to suppress asthma exacerbation was observed after 32 weeks of treatment and lasted for 52 weeks (Figure 9). Decreased blood eosinophil count was observed from after the first dose and lasted for 52 weeks (Figure 10). In Study MEA114092 which investigated the immunogenicity of mepolizumab (12.5 to 250 mg) in multiple subcutaneous administration, the occurrence of anti-mepolizumab antibody was reported by 12% (8 of 69) of subjects. No neutralizing antibody was detected and no enhanced immunogenicity was observed during the follow-up period. These results suggest that the efficacy of mepolizumab is unlikely to be attenuated by the development of anti-mepolizumab antibodies.

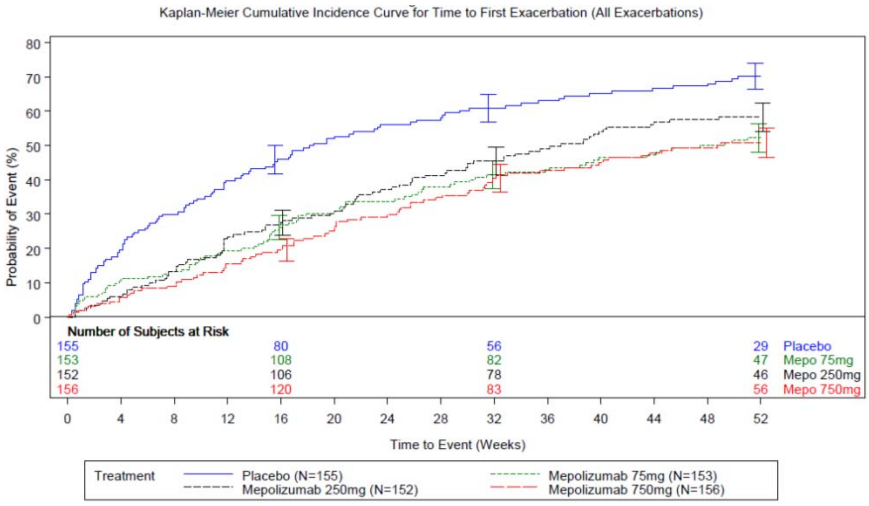

Figure 9. Kaplan-Meier curves with the first asthma exacerbation as the event (Study MEA112997)

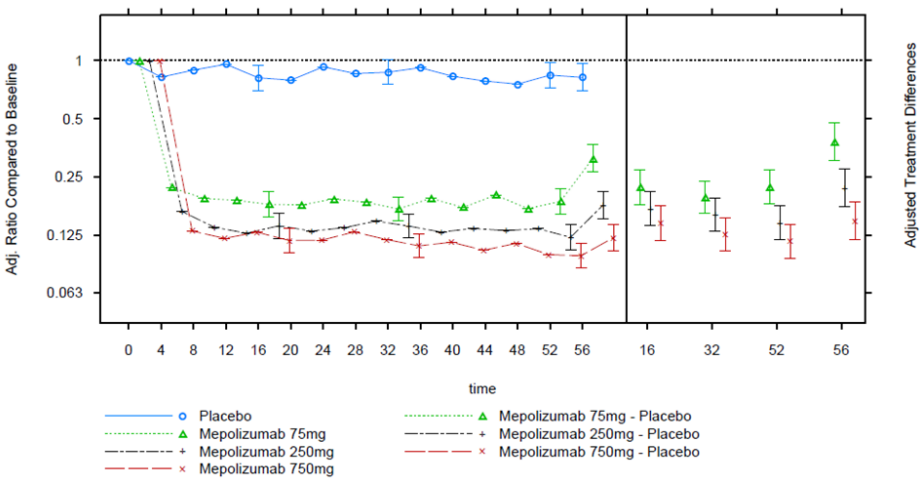

Figure 10. Ratio to baseline of blood eosinophil count (Study MEA112997)

Consequently, the applicant considered that the effect of mepolizumab in reducing asthma exacerbation was able to be evaluated by a 32-week follow-up of patients in Study MEA115588.

PMDA's view:
The primary endpoint in Study MEA115588 was the incidence of asthma exacerbation and, at the start of the study, no data were available on the incidence in subcutaneous administration. Taking account of these, the evaluation period should have been set at 52 weeks.

4.(iii).B.(2) Efficacy

4.(iii).B.(2).1) Effect in reducing asthma exacerbation

The applicant's explanation of the effect of mepolizumab in reducing asthma exacerbation:
The incidence of asthma exacerbation, the primary endpoint in Studies MEA115588 and MEA112997, is shown in Table 26. The data demonstrated the superiority of mepolizumab 100 mg SC or 75 mg IV to placebo. The time to the first asthma exacerbation in these studies is shown in Figures 11 and 9. As is evident in Table 26, the incidence of asthma exacerbation requiring hospitalization or emergency department visit tended to be lower in the mepolizumab group. In Study MEA115575 in patients with asthma poorly controlled by OCS, high dose ICS, and other long-term control medications, the ratio [95% CI] of asthma exacerbation in the 100 mg SC group relative to the placebo group after 24 weeks of treatment was 0.68 [0.47, 0.99]. The effect of mepolizumab in reducing asthma exacerbation was observed even in the concomitant treatment with reduced OCS doses.

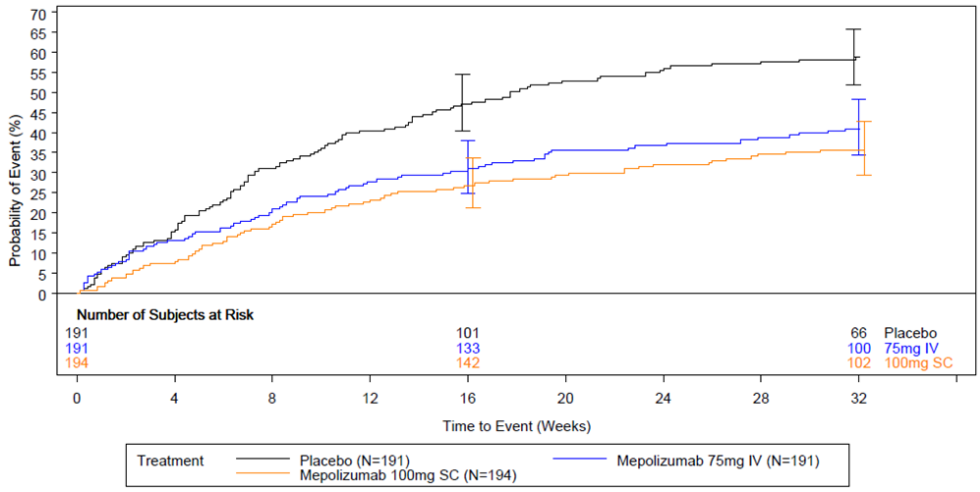

Figure 11. Kaplan-Meier curves with the first asthma exacerbation counted as the event (Study MEA115588)

Table 26. Incidence of asthma exacerbation in Study MEA115588 (mITT population) and Study MEA112997 (ITT population)

	Study MEA115588 [c]			Study MEA112997 [d]	
	100 mg SC (n = 194)	75 mg IV (n = 191)	Placebo (n = 191)	75 mg IV (n = 153)	Placebo (n = 155)
Incidence of asthma exacerbation [a] (frequencies/year) [b]	0.83	0.93	1.74	1.15	2.40
Ratio to the placebo group [95% CI] [b] *P* value [b]	0.47 [0.35, 0.64] *P* < 0.001	0.53 [0.40, 0.72] *P* < 0.001		0.48 [0.36, 0.64] *P* < 0.001	
Incidence of exacerbation requiring hospitalization or emergency department visit (frequencies/year) [b]	0.08	0.14	0.20	0.17	0.43
Ratio to the placebo group [95% CI] [b] Adjusted *P* value [b]	0.39 [0.18, 0.83] *P* = 0.030	0.68 [0.33, 1.41] *P* = 0.299		0.40 [0.19, 0.81] *P* = 0.011	
Incidence of exacerbation requiring hospitalization (frequencies/year) [b]	0.03	0.06	0.10	0.11	0.18
Ratio to the placebo group [95% CI] [b] Adjusted *P* value [b]	0.31 [0.11, 0.91] *P* = 0.299	0.61 [0.23, 1.66] *P* = 0.334		0.61 [0.28, 1.33] *P* = 0.214	

a) Defined as worsening of asthma requiring systemic corticosteroid administration for ≥3 days, hospitalization, or emergency department visit.
b) Negative binominal regression model with the following explanatory and offset variables: treatment group, use/non-use of OCS at baseline, region, number of events of asthma exacerbation observed within 1 year before study enrollment (twice, 3 times, ≥4 times), and baseline %FEV_1 as explanatory; and run-in period (logarithmic scale) as offset
c) For the primary endpoint, 2 paired comparisons were adjusted for multiplicity by the Hochberg method. For the secondary endpoints, i.e., (i) incidence of asthma exacerbation requiring hospitalization or emergency department visit, (ii) incidence of asthma exacerbation requiring hospitalization, (iii) change in FEV_1 from baseline before bronchodilator inhalation after 32 weeks of treatment, and (iv) change in SGRQ score from baseline after 32 weeks of treatment, only if 2 paired comparisons showed statistically significant results in the stepdown method with strata defined in the order of the primary endpoint followed by secondary endpoints (i) through (iv) and in the endpoints in the upper strata, paired comparison was performed on endpoints in the lower strata. The Hochberg method was applied only to the primary endpoint, and 2 paired comparisons on secondary endpoints were not adjusted for multiplicity. Adjusted *P* value is given.
d) For the primary endpoint, if linear contrast test on all dose groups including the placebo group showed a statistically significant difference, paired comparison between each dose group and the placebo group was to be conducted, and 3 paired comparisons were to be adjusted for multiplicity by the Hochberg method. For the secondary endpoints, i.e., (i) change in FEV_1 from baseline before bronchodilator inhalation after 52 weeks of treatment, (ii) change in AQLQ score from baseline after 52 weeks of treatment, (iii) incidence of asthma exacerbation requiring hospitalization or emergency department visit, (iv) change in ACQ score from baseline after 52 weeks of treatment, the Hochberg method was used to adjust for statistical multiplicity for the multiple pairwise comparisons between the placebo group and each dose group that showed a statistically significant difference in the stepdown method with strata defined in the order of the primary endpoint followed by secondary endpoints (i) through (iv), and in the endpoints in the upper strata. Adjusted *P* value is given.

Table 27 shows the comparison of the results in the entire population and the Japanese subpopulation in Studies MEA115588 and MEA115661. The incidence of asthma exacerbation was similar between the Japanese subpopulation and the entire population.

Table 27. Incidence of asthma exacerbation in the entire population and the Japanese subpopulation in Studies MEA115588 and MEA115661

	Study MEA115588			Study MEA115661
	100 mg SC	75 mg IV	Placebo	100 mg SC
Entire population				
Number of patients	194	191	191	651
Incidence (frequencies/year) [a]	0.83	0.93	1.74	0.93
Ratio to the placebo group [95% CI] [a]	0.47 [0.35, 0.64]	0.53 [0.40, 0.72]		
Japanese subpopulation				
Number of patients	17	17	16	43
Incidence (frequencies/year) [a]	0.88	0.23	2.32	1.41
Ratio to the placebo group [95% CI] [a]	0.38 [0.12, 1.18]	0.10 [0.02, 0.57]		

a) Negative binominal regression model with the following explanatory and offset variables: treatment group, use/non-use of OCS at baseline, region, number of events of asthma exacerbation observed within 1 year before study enrollment (twice, 3 times, ≥4 times), and baseline %FEV_1 as explanatory; and run-in period (logarithmic scale) as offset (in the Japanese subpopulation, region was excluded from the explanatory variables)

PMDA asked the applicant to explain whether or not patient characteristics that tended to differ between the entire population and the Japanese subpopulation in Study MEA115588 are likely to affect the efficacy evaluation of mepolizumab.

The applicant's explanation:
Patient characteristics that tended to differ between the entire population and the Japanese subpopulation included the following: Body weight (76.3 kg in the entire population, 61.3 kg in the Japanese subpopulation; hereinafter in this section, data are described in the same order), percentage of patients

aged ≥65 years (14%, 30%), blood eosinophil count at enrollment (360/μL in the placebo group and 320/μL in the mepolizumab IV and SC groups; 470/μL in the placebo group, 600/μL in the mepolizumab IV group, and 450/μL in the mepolizumab SC group [all expressed in median]), mean frequencies of exacerbation within the past 12 months (3.6/year, 4.6/year), and mean daily OCS dose (13.2 mg/day, 4.8 mg/day). A subgroup analysis of these factors was conducted on the incidence of asthma exacerbation. The results did not show any clear difference between subgroups, except the incidence among subgroups classified by blood eosinophil count at enrollment, as shown in Table 28. Thus, the differences in the distribution of these characteristics were unlikely to have affected the efficacy evaluation.

Table 28. Ratio of the incidence of asthma exacerbation to that in the placebo group in subpopulations (Study MEA115588)

Characteristic		Number of patients (100 mg SC group/75 mg IV group/placebo group)	Ratio of the incidence in the 100 mg SC group to the placebo group [95% CI]	Ratio of the incidence in the 75 mg IV group to the placebo group [95% CI]
Age	<65 years	164/167/165	0.51 [0.37, 0.70]	0.61 [0.45, 0.83]
	≥65 years	30/24/26	0.28 [0.12, 0.65]	0.18 [0.06, 0.49]
Body weight	≤60 kg	41/40/33	0.32 [0.14, 0.75]	0.48 [0.20, 1.16]
	>60 kg, ≤75 kg	67/50/65	0.39 [0.23, 0.65]	0.36 [0.20, 0.66]
	>75 kg, ≤90 kg	55/63/54	0.58 [0.34, 1.00]	0.73 [0.44, 1.23]
	>90 kg	31/38/39	0.64 [0.33, 1.21]	0.62 [0.34, 1.13]
Frequencies of exacerbation within the past 12 months	Twice	74/82/90	0.53 [0.30, 0.94]	0.57 [0.33, 0.96]
	3 times	48/47/46	0.30 [0.16, 0.55]	0.56 [0.33, 0.94]
	≥4 times	72/62/55	0.44 [0.29, 0.69]	0.40 [0.25, 0.64]
Mean daily OCS dose	Not used	142/143/147	0.34 [0.23, 0.51]	0.53 [0.37, 0.76]
	<15 mg/day	35/31/30	0.83 [0.49, 1.41]	0.49 [0.27, 0.88]
	≥15 mg/day	17/13/13	0.68 [0.29, 1.63]	0.81 [0.34, 1.97]
Blood eosinophil count at enrollment	<150/μL	35/30/21	0.91 [0.44, 1.90]	0.94 [0.43, 2.07]
	≥150/μL, <300/μL	49/49/59	0.48 [0.27, 0.86]	0.66 [0.37, 1.17]
	≥300/μL, <500/μL	45/50/48	0.48 [0.26, 0.89]	0.60 [0.34, 1.06]
	≥500/μL	61/56/60	0.21 [0.12, 0.36]	0.26 [0.15, 0.45]

Taking account of the following, PMDA has concluded that the efficacy of mepolizumab in patients with severe asthma was demonstrated in Study MEA115588 and that, based on the results of the study, mepolizumab is expected to be effective in Japanese patients with severe asthma.

- Mepolizumab (100 mg SC) was shown to be superior to placebo in reducing the incidence of asthma exacerbation.

- The incidence of asthma exacerbation was shown to be consistent between the entire population and the Japanese subpopulation. In the subgroup analysis by patient characteristics that showed difference in the distribution between the entire population and the Japanese subpopulation, none of those patient characteristics possibly affected the efficacy evaluation of mepolizumab, except blood eosinophil count.

The results of the subgroup analysis of Study MEA115588 suggested a possible effect of blood eosinophil count at the start of treatment on the efficacy of mepolizumab. Appropriateness of selecting patients to be treated on the basis of blood eosinophil count will be discussed in "4.(iii).B.(4) Clinical positioning and indication."

4.(iii).B.(2).2) Effect to improve respiratory function etc.

The applicant's explanation of the effect of mepolizumab to improve respiratory function, etc.:

Table 29 shows the change in FEV_1 from baseline in each treatment group in Studies MEA115588 and MEA112997. In Study MEA115588, the change in FEV_1 from baseline after 32 weeks of treatment was greater in the 100 mg SC and 75 mg IV groups compared with the placebo group. In Study MEA112997, the change in FEV_1 was greater in the 75 mg IV group than in the placebo group after 52 weeks of treatment, whereas the between-group difference after 32 weeks of treatment was only 3 mL, showing a tendency different from that observed in Study MEA115588. The cause of the difference observed between the two studies is unclear. However, given the report that, in patients with severe asthma, there is only a weak correlation between respiratory function and changes in asthma symptoms (such as exacerbation) or level of airway inflammation (Reddel HK et al. *Am J Respir Crit Care Med.* 2009;180:59-99), it is well conceivable that such differences are observed between studies.

Table 29. Change in FEV_1 (mL) from baseline in Studies MEA115588 (mITT population) and MEA112997 (ITT population)

	Study MEA115588[b)]			Study MEA112997[c)]	
	100 mg SC	75 mg IV	Placebo	75 mg IV	Placebo
Baseline	1730 ± 659 (194)	1860 ± 702 (191)	1860 ± 631 (191)	1808 ± 637 (153)	1899 ± 653 (155)
After 32 weeks of treatment	1942 ± 731 (185)	2057 ± 747 (176)	1940 ± 613 (179)	1967 ± 654 (136)	2046 ± 729 (134)
Change	204 ± 398 (185)	187 ± 494 (176)	70 ± 415 (179)	154 ± 425 (136)	152 ± 470 (134)
Difference from the placebo group [95% CI] [a)] Adjusted *P* value [a)]	98 [11, 184] *P* = 0.334	100 [13, 187] *P* = 0.334		3 [-97, 102] -	
After 52 weeks of treatment				1965 ± 654 (129)	1969 ± 730 (127)
Change				133 ± 399 (129)	87 ± 464 (127)
Difference from the placebo group [95% CI] [a)] Adjusted *P* value [a)]				61 [-39, 161] *P* = 0.229	

Mean ± SD (number of patients)

a) Mixed repeated measures model with the following explanatory variables: the baseline value, use/non-use of OCS at baseline, number of events of asthma exacerbation observed within 12 months before the start of the run-in period (twice, 3 times, ≥4 times), treatment group, region, day of administration, interaction between day of administration and the baseline value, and interaction between day of administration and treatment group

b) Same as in Table 26

c) Same as in Table 26

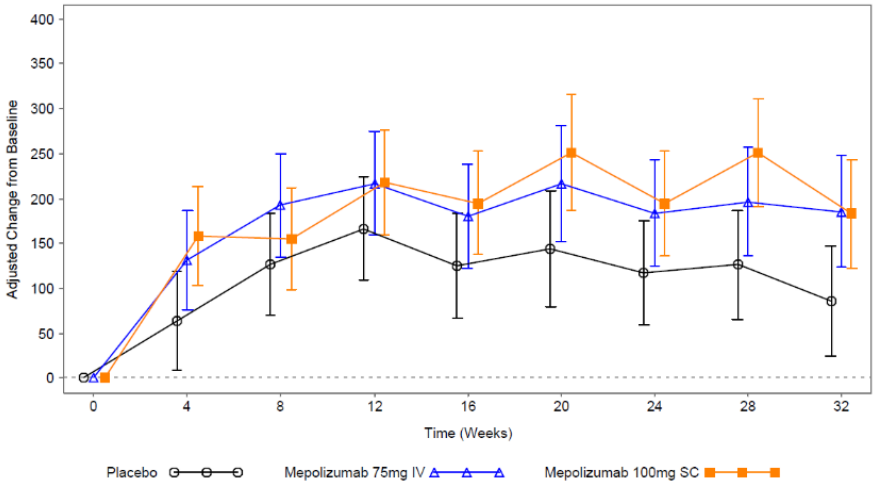

Figure 12. Time course of FEV_1 (mL) from baseline to administration of bronchodilator (Study MEA115588, adjusted mean with 95% CI)

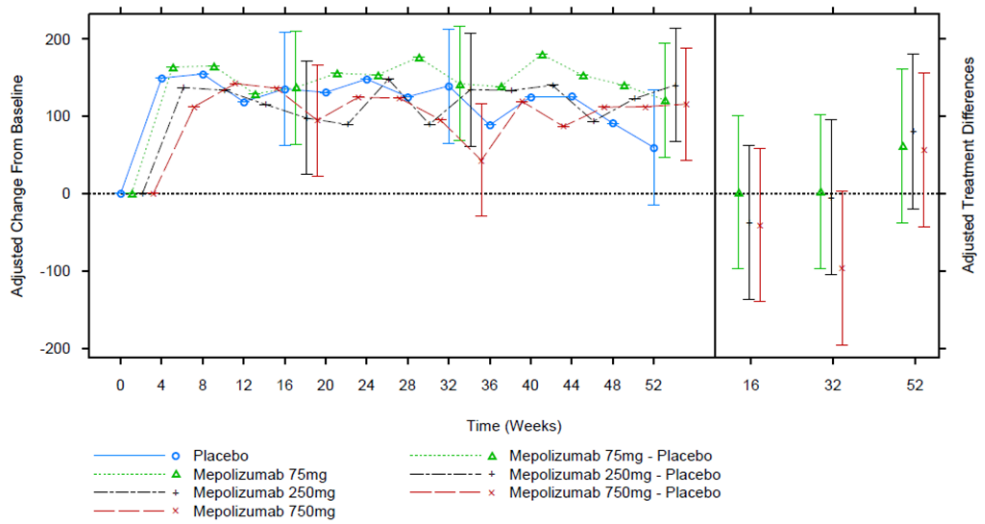

Figure 13. Time course of FEV_1 (mL) from baseline to administration of bronchodilator (Study MEA112997, adjusted mean with 95% CI)

In Study MEA115575 in which the OCS dose-reducing effect was investigated in patients with severe asthma, change in FEV_1 from baseline after 24 weeks of treatment was 121 ± 484 mL in the 100 mg SC group and -21 ± 464 mL in the placebo group, with the difference with the placebo group [95% CI] being 114 [-42, 271] mL. In Study MEA115661, which was conducted as an extended, long-term treatment study of Studies MEA115588 and MEA115575, the change (mean ± SD) in FEV_1 from baseline in patients who had received placebo in the preceding study was evaluated. As a result, it was 115 ± 451 mL after 28 weeks of treatment (n = 229) and 100 ± 448 mL after 52 weeks of treatment (n = 223).

PMDA's view:
In Study MEA115588, the change in FEV_1 from baseline in the 100 mg SC group and in the 75 mg IV group tended to be greater compared with the placebo group, whereas in Study MEA112977, no superiority over the placebo group was observed (Figures 12 and 13). Given these inconsistent data, the effect of mepolizumab on respiratory function is unclear. It is thus currently difficult to position mepolizumab as a drug to be used alone in expectation of rapid improvement of asthma symptoms. It should be cautioned that mepolizumab should be used in combination with long-term control medications such as bronchodilators and ICS and that careful consideration should be given to the reduction of the dose of long-term control medications during the treatment with mepolizumab.

4.(iii).B.(3) Safety
The applicant explained the safety of mepolizumab as described below, on the basis of the following data: (i) the pooled data of placebo-controlled, comparative studies (Studies MEA112997, MEA115588, and MEA115575) in patients with severe asthma (the placebo-controlled severe asthma study [PCSA] population); (ii) the data of extended treatment study in patients with severe asthma (Study MEA115661 [data locked on [redacted]]); (iii) the pooled data of open-label, uncontrolled studies (Studies MEA115661 and MEA115666 [data cut-off [redacted]]) in patients with severe asthma (the open label extension [OLE] population); and (iv) the pooled data of 19 studies[20] including those conducted in patients other than asthma patients (the all-studies population).
Table 30 summarizes adverse events in the PCSA population and in the OLE population, and Table 31 shows adverse events reported by ≥4% of patients either in the 100 mg SC group or in the 75 mg IV group in the PCSA population.

In the PCSA population, death was reported in 5 patients. The causes were asthma[21] and pancreatitis acute/septic shock (1 patient each in the 250 mg IV group), asphyxia[22] (1 patient in the 750 mg IV group), road traffic accident and aspiration/gastrointestinal haemorrhage (1 patient each in the placebo group). Deaths in other patients in the all-studies population include the following: (i) 1 patient (respiratory arrest) in the 100 mg SC group in Study MEA115666; (ii) 1 patient (cardiac arrest) in the 750 mg IV group in Study MHE100185 in patients with hypereosinophilic syndrome; (iii) 4 patients (sudden death, cardiac failure/sepsis/multi-organ failure, pneumonia aspiration/respiratory failure, angioimmunoblastic T-cell lymphoma/cardiopulmonary failure) in the 750 mg IV group in Study MHE100901, the extended study of Study MHE100185; and (iv) 13 patients (cardiac arrest/myocardial infarction, cardiac failure congestive, myocardial infarction, right ventricular failure, bacterial sepsis, neoplasm malignant/respiratory failure, multi-organ failure, disease progression, dyspnoea, infection/multi-organ failure, Klebsiella sepsis, respiratory failure, hepatitis/lactic acidosis/lung infiltration/metabolic acidosis/respiratory failure/sepsis/shock) in the mepolizumab group in Study MHE104317, which was conducted as part of the compassionate-use program involving mainly patients with life-threatening or severe hypereosinophilic syndrome. A causal relationship of the fatal adverse

[20] The following studies in addition to the PCSA and OLE populations: Study SB-240563/006 in patients with moderate asthma, Studies MHE100185, MHE100901, and MHE104317 in patients with hypereosinophilic syndrome, Studies MEE103226 and MEE103219 in patients with eosinophilic oesophagitis and patients with pediatric eosinophilic esophagitis, Study SB-240563/045 in patients with atopic dermatitis, and clinical pharmacology studies in healthy subjects and asthma patients (Studies SB-240563/018, MEA115705, SB-240563/001, SB-240563/035, SB-240563/036, MEA114092, and SB-240563/017).

[21] One patient with asthma (56-year-old woman) had a previous history of admission to the intensive care unit for the treatment of severe asthmatic attack. At 11 hours after the second dose of mepolizumab 250 mg IV, asthmatic attack occurred, resulting in cardiopulmonary failure and death eventually. The investigator identified asthma as the cause of death and ruled out the causal relationship of mepolizumab with death.

[22] One patient with asphyxia (54-year-old man) committed suicide by hanging after 298 days of administration of mepolizumab 750 mg IV (19 days after the last dose).

events to the study drug was ruled out except for angioimmunoblastic T-cell lymphoma in 1 patient in Study MHE100901 and for multi-organ failure in 1 patient in Study MHE104317.

Table 30 summarizes severe adverse events in the PCSA population. The major adverse events were asthma (1.9% [5 of 263] of patients in the 100 mg SC group, 5.8% [20 of 344] of patients in the 75 mg IV group, 9.9% [15 of 152] of patients in the 250 mg IV group, 5.8% [9 of 156] of patients in the 750 mg IV group, 9.2% [38 of 412] of patients in the placebo group) and pneumonia (0.3% [1 of 263] of patients in the 100 mg SC group, 0.3% [1 of 344] of patients in the 75 mg IV group, 0% in the 250 mg IV group, 1.3% [2 of 156] of patients in the 750 mg IV group, 0.7% [3 of 412] of patients in the placebo group). A causal relationship to the study drug was ruled out in these adverse events. In the all-studies population, serious adverse events were observed in 14% (291 of 2022) of patients. Of these, serious adverse events for which a causal relationship to the study drug could not be ruled out were reticulocyte count decreased (250 mg IV group in Study MEA112997), supraventricular tachycardia (750 mg IV group in Study MEA112997), epilepsy (placebo group in Study MEA115588), herpes zoster (1 subject in the 100 mg SC group in Study MEA115588), abortion spontaneous and type IV hypersensitivity reaction (1 subject each in the 100 mg SC group in Study MEA115661), motor neurone disease and optic neuritis/spinal disorder/myelitis transverse, and T-lymphocyte count increased (1 subject each in the 750 mg IV group in Study MHE100901), lymphoma, angioimmunoblastic T-cell lymphoma, pulmonary embolism, lobar pneumonia, multi-organ failure, and hypereosinophilic syndrome (1 subject each in the 750 mg IV group in Study MHE104317).

Table 30. Summary of adverse events in the PCSA and OLE populations (safety analysis population)

	The PCSA population					The OLE population
	100 mg SC (n = 263)	75 mg IV (n = 344)	250 mg IV (n = 152)	750 mg IV (n = 156)	Placebo (n = 412)	100 mg SC (n = 998)
Adverse events	209 (79)	287 (83)	124 (82)	122 (78)	338 (82)	764 (77)
Serious adverse events excluding deaths	17 (6)	34 (10)	23 (15)	18 (12)	63 (15)	83 (8)
Adverse events leading to death	0	0	2 (1)	1 (0.6)	2 (0.5)	1 (0.1)
Adverse events leading to study discontinuation	3 (1)	4 (1)	8 (5)	8 (5)	12 (3)	15 (2)
Adverse drug reactions	60 (23)	61 (18)	29 (19)	33 (21)	67 (16)	151 (15)
Total exposure period (patient-year) [a)]	147	254	142	143	284	643

Number of patients (%)
a) Exposure period = (last day of administration – first day of administration + 29)/365.25

Table 31. Adverse events reported by ≥4% of patients in the 100 mg SC or 75 mg IV group in the PCSA population (safety analysis population)

	100 mg SC (n = 263)	75 mg IV (n = 344)	250 mg IV (n = 152)	750 mg IV (n = 156)	Placebo (n = 412)
Headache	53 (20)	78 (23)	32 (21)	32 (21)	74 (18)
Nasopharyngitis	43 (16)	79 (23)	33 (22)	29 (19)	80 (19)
Upper respiratory tract infection	27 (10)	32 (9)	18 (12)	19 (12)	47 (11)
Sinusitis	25 (10)	21 (6)	10 (7)	12 (8)	40 (10)
Injection site reaction	21 (8)	10 (3)	0	0	13 (3)
Bronchitis	16 (6)	31 (9)	13 (9)	13 (8)	39 (9)
Back pain	16 (6)	22 (6)	7 (5)	15 (10)	20 (5)
Arthralgia	16 (6)	16 (5)	9 (6)	9 (6)	23 (6)
Asthma	15 (6)	32 (9)	26 (17)	16 (10)	61 (15)
Fatigue	12 (5)	14 (4)	7 (5)	2 (1)	17 (4)
Pain in extremity	12 (5)	8 (2)	4 (3)	8 (5)	16 (4)
Oropharyngeal pain	11 (4)	16 (5)	12 (8)	6 (4)	27 (7)
Eczema	11 (4)	5 (2)	4 (3)	3 (2)	2 (0.4)
Urinary tract infection	10 (4)	13 (4)	8 (5)	1 (0.6)	9 (2)
Influenza	7 (3)	16 (5)	5 (3)	9 (6)	15 (4)
Pharyngitis	7 (3)	13 (4)	2 (1)	3 (2)	8 (2)
Gastroenteritis	6 (2)	14 (4)	0	4 (3)	9 (2)
Cough	5 (2)	16 (5)	11 (7)	9 (6)	21 (5)
Hypertension	4 (2)	13 (4)	6 (4)	5 (3)	12 (3)

Number of patients (%)

Table 32 shows the incidence of adverse events in each study period. There was no tendency of increase in the incidence with increasing duration of treatment.

Table 32. Incidence of adverse events by week in the study in the PCSA population and Study MEA115661

	The PCSA population		Study MEA115661				
Weeks in the study (Number of patients, combined mepolizumab group/placebo group)	Week 0-11 (915/412)	Week 12-23 (915/412)	Week 0-11 (414/237)	Week 12-23 (414/237)	Week 24-35 (414/237)	Week 36-47 (414/237)	Week 48 and thereafter (414/237)
Combined mepolizumab group [a)]	570 (62)	482 (53)	242 (58)	232 (56)	219 (53)	190 (46)	77 (19)
Placebo group [a)]	264 (64)	233 (57)	137 (58)	138 (58)	128 (54)	119 (50)	52 (22)

Number of patients (%)
a) For data of Study MEA115661, patients were classified into the combined mepolizumab group or the placebo group according to the treatment group in the preceding study (Study MEA115588 or MEA115575).

The safety of mepolizumab in Japanese was evaluated based on the data obtained from 50 Japanese subjects who participated in Study MEA115588 and were included in the PCSA population, and from 43 Japanese subjects who participated in Study MEA115661 [For the safety in the Japanese subpopulation in each of Studies MEA115588 and MEA115661, see "4.(iii).A.(1).3) Global phase III study (5.3.5.1, Study MEA115588) and 4.(iii).A.(1).5) Global long-term treatment study (5.3.5.2, Study MEA115661)"]. The incidence of adverse events in the Japanese subpopulation was similar to that in the entire population.

PMDA reviewed the following events, taking account of the adverse events in clinical studies, pharmacological actions of mepolizumab, etc.

4.(iii).B.(3).1) Infections (serious infection, opportunistic infection, and parasitic infection)
The applicant's explanation of the incidence of infection etc., after administration of mepolizumab:
IL-5 is a major regulatory factor in the differentiation, function, and survival of eosinophils. By inhibiting IL-5, mepolizumab decreases eosinophil count in blood and tissues and suppresses the activity of eosinophils. Since eosinophils are involved in innate immunity, potential risk of infection caused by mepolizumab was investigated.

Table 33 shows the incidence of infections and infestations (system organ class [SOC]) in the PCSA population[23] and in the OLE population. Death caused by septic shock[24] occurred in 1 patient in the 250 mg IV group, but the incidence of infections and infestations in the mepolizumab groups were generally similar to those in the placebo group. As an infestation-related adverse event, parasitic gastroenteritis was observed in 1 patient in the 100 mg SC group in Study MEA115588, but the adverse event was assessed as non-serious, and mepolizumab administration was continued. Opportunistic infections were observed in 13 patients in the PCSA population (3 in the 100 mg SC group [herpes zoster in 2, gastrointestinal fungal infection in 1], 4 in the 75 mg IV group [herpes zoster in 4], 2 in the 750 mg IV group [ophthalmic herpes zoster, respiratory moniliasis in 1 each], 4 in the placebo group [herpes zoster in 2, blastomycosis, ophthalmic herpes simplex in 1 each]) and in 8 patients in the OLE population (herpes zoster and oesophageal candidiasis in 3 each, aspergillus infection and enteritis infectious in 1 each). As regards tuberculosis, there were no new occurrences or reactivation of latent tuberculosis during the period of study drug administration either in the PCSA or OLE populations.

Table 33. Incidence of infections and infestations (SOC) (safety analysis population)

	The PCSA population				The OLE population
	100 mg SC (n = 263)	75 mg IV (n = 344)	Combined mepolizumab group (n = 915)	Placebo (n = 412)	100 mg SC (n = 998)
All infection-related events	136 (52)	209 (61)	519 (57)	239 (58)	549 (55)
Serious infection-related events excluding deaths	7 (3)	8 (2)	23 (3)	14 (3)	16 (2)
Total exposure period (patient-year)	147	254	687	284	643
Exposure-adjusted incidence [a)]					
All infection-related events	1729.0	1718.8	1603.1	1753.4	1663.9
Serious infection-related events excluding deaths	54.2	31.5	37.8	49.3	26.4

Number of patients (%)
a) Exposure-adjusted incidence (number of patients with events/1000 patient-years) = (number of patients with adverse events/total exposure days [patient-year]) × 1000

[23] Patients with clinically significant respiratory comorbidities, including concomitant infection, were excluded from enrollment.
[24] Septic shock occurred secondary to pancreatitis acute, and its causal relationship to mepolizumab was ruled out.

Thus, the above results of clinical studies do not suggest any risks of infection induced by mepolizumab. Nevertheless, for the safety of patients to be treated with mepolizumab, the applicant plans to provide a caution in the package insert etc., that Helminthic infection should be treated before starting mepolizumab treatment if the patient is infected, and to continuously investigate the risk of infections etc., induced by mepolizumab in the post-marketing surveillance etc.

PMDA's view:
Currently there are no findings suggestive of any clear relationship between mepolizumab and infection. However, taking account of the facts that the effects of suppressing IL-5 and blood eosinophil count on the immune system is unclear and that treatment experience with mepolizumab is limited in clinical studies, risk of serious infection induced by mepolizumab should be continuously investigated in the post-marketing surveillance etc.

4.(iii).B.(3).2) Malignant tumor

The applicant's explanation on the incidence of malignant tumor after administration of mepolizumab:
The 6-month repeat-dose toxicity study did not show any findings suggestive of carcinogenicity of mepolizumab but there are suggestions that IL-5 and eosinophils are involved in the promotion and suppression of tumor growth [see "3.(iii) Summary of toxicology studies"].

In the PCSA population, malignant tumor was observed in 0.3% (1 of 344) of patients in the 75 mg IV group (basal cell carcinoma), 0.7% (1 of 152) of patients in the 250 mg IV group (uterine cancer), and 0.7% (3 of 412) of patients in the placebo group (basosquamous carcinoma, prostate cancer, and squamous cell carcinoma in 1 patient each), showing no tendency of increase in the incidence with increasing exposure to mepolizumab. In the OLE population, malignant tumor was observed in 4 patients (2 in Study MEA115661 [gastric cancer, breast cancer], 2 in Study MEA115666 [prostate cancer, breast cancer], but a causal relationship to mepolizumab was ruled out in all of them. Of 28 events of malignant tumor (25 in the mepolizumab group, 3 in the placebo group) observed in the all-studies population, a causal relationship to mepolizumab could not be ruled out in 3 patients in the mepolizumab group (Table 34). However, no consistent tendency was observed in the number of days from the start of mepolizumab administration to event onset, or in the number of doses administered.

Table 34. Events of malignant tumor for which a causal relationship to mepolizumab could not be ruled out (the all studies population)

Study	Treatment group	Primary disease	Age (sex)	Event	Days to event onset	Doses administered to event onset	Days to even onset from the last dose	Outcome
MHE100185	750 mg IV	Hypereosinophilic syndrome	46 (male)	Angioimmunoblastic T-cell lymphoma	570 days	19	23 days	Death
MHE104317	750 mg IV	Hypereosinophilic syndrome	54 (female)	Angioimmunoblastic T-cell lymphoma	165 days	6	6 days	Improved/ recovering
MHE104317	750 mg IV	Hypereosinophilic syndrome	36 (female)	Lymphoma	221 days	7	11 days	Not improved/ not recovered

PMDA's view:
Currently there is no clear causal relationship between mepolizumab and occurrence of malignant tumor. However, the clinical studies conducted did not involve a sufficient number of patients to evaluate the risk of malignant tumor and, in light of published papers etc., the possibility cannot be ruled out that mepolizumab affects the tumor suppressing mechanism [see "3.(iii) Summary of toxicology studies"]. Information on the risk of malignant tumor induced by mepolizumab, including that in published reports, should be continuously collected after the market launch.

4.(iii).B.(3).3) Cardiovascular, thromboembolic, and ischemic adverse events

The applicant's explanation on the incidence of cardiovascular thromboembolic (CVT) and ischemic adverse events after mepolizumab administration:
Study MEA112997 showed imbalance in the incidence of serious cardiac disorders among treatment groups (2 patients in the 75 mg IV group, 1 patient in the 250 mg IV group, 4 patients in the 750 mg IV group, 1 patient in the placebo group). Therefore, in phase III studies (Studies MEA115588, MEA115575, MEA115661, and MEA115666), an independent data monitoring committee (IDMC) and a Clinical Endpoint Committee (CEC) evaluated cardiovascular safety. As shown in Table 35, the estimated hazard ratio [95% CI] of serious CVT in the mepolizumab group relative to the placebo group

in the PCSA population was 1.25 [0.35, 4.49]. A total of 14 patients experienced serious CVT. Of them, 11 patients had current or a past history of cardiovascular disease or risk factors, excluding 2 patients in the placebo group and 1 patient in the 750 mg IV group. In light of these findings, mepolizumab is unlikely to increase the risk of cardiovascular events.

In the OLE population, atrial fibrillation (0.2% [2 of 998] of patients) was the only serious CVT or ischemic adverse event reported by ≥2 patients, and a causal relationship of fibrillation to mepolizumab was ruled out in both patients.

Table 35. Incidence of serious CVT and ischemic adverse events (safety analysis population)

Group	The PCSA population						The OLE population
Treatment group	100 mg SC (n = 263)	75 mg IV (n = 344)	250 mg IV (n = 152)	750 mg IV (n = 156)	Combined mepolizumab (n = 915)	Placebo (n = 412)	100 mg SC (n = 998)
Serious CVT [a)]	1 (0.4)	4 (1)	2 (1)	4 (3)	11 (1)	3 (0.7)	8 (0.8)
Ischemic adverse events	0	2 (0.6)	2 (1)	2 (1)	6 (0.7)	2 (0.5)	-

Number of patients (%)
a) Events classified as cardiac disorders, nervous system disorders, or vascular disorders (SOC) according to MedDRA Version 16.1

PMDA's view:
Currently there are no data that suggest a clear relationship between mepolizumab and the occurrence of CVT or ischemic adverse events. Information on the risk of CVT and ischemic adverse events induced by mepolizumab, including that available in published reports, should be continuously collected after the market launch.

4.(iii).B.(3).4) Systemic reactions and injection site reactions

The applicant's explanation on the incidence of systemic reactions and injection site reactions after administration of mepolizumab:
Table 36 shows the incidence of systemic reactions and injection site reactions in the PCSA and OLE populations. The incidence of injection site reactions in the 100 mg SC group tended to be higher than that in the placebo (saline) or the 75 mg IV group, but all of them were mild to moderate and none of them serious. Most of the events resolved within several days. No events were identified as anaphylactic reactions for which a causal relationship to the study drug could not be ruled out.

Table 36. Incidence of systemic reactions and injection site reactions (safety analysis population)

	The PCSA population						The OLE population
	100 mg SC (n = 263)	75 mg IV (n =344)	250 mg IV (n = 152)	750 mg IV (n = 156)	Combined mepolizumab (n = 915)	Placebo (n = 412)	100 mg SC (n = 998)
Systemic reactions	7 (3)	12 (4)	15 (10)	20 (13)	54 (6)	20 (5)	17 (2)
Infusion related reaction	0	8 (2)	12 (8)	19 (12)	39 (4)	11 (3)	0
Hypersensitivity	3 (1)	2 (0.6)	1 (0.7)	2 (1)	8 (0.9)	7 (2)	5 (0.5)
Injection related reaction	3 (1)	0	0	0	3 (0.3)	3 (0.7)	7 (0.7)
Type IV hypersensitivity reaction	0	2 (0.6)	2 (1)	0	4 (0.4)	0	4 (0.4)
Administration related reaction	2 (0.8)	1 (0.3)	0	0	3 (0.3)	0	0
Rash	0	0	0	0	0	0	1 (0.1)
Injection site reactions	21 (8)	11 (3)	0	0	32 (3)	14 (3)	54 (5)
Injection site reaction	20 (8)	10 (3)	0	0	30 (3)	13 (3)	52 (5)
Infusion site reaction	0	1 (0.3)	0	0	1 (0.1)	0	0
Injection site erythema	1 (0.4)	0	0	0	1 (0.1)	0	0
Injection site pain	1 (0.4)	0	0	0	1 (0.1)	0	1 (0.1)
Adverse drug reaction	0	0	0	0	0	1 (0.2)	0
Injection site discomfort	0	0	0	0	0	0	2 (0.2)
Injection related reaction	0	0	0	0	0	0	1 (0.1)
Local reaction	0	0	0	0	0	0	1 (0.1)

Number of patients (%)

Most of the injection site reactions were non-serious and were reversible. However, systemic reactions such as hypersensitivity occurred after mepolizumab administration, and injection site reactions tended to occur with a higher incidence in the 100 mg SC group compared with the placebo group. Taking account of these findings, caution will be provided regarding the possible occurrence of hypersensitivity

reactions. Also, systemic reactions and injection site reactions will be included as important identified risks in the risk management plan and as priority investigation items in the post-marketing surveillance. Relevant information will be continuously collected after the market launch.

PMDA's view:
In the 100 mg SC group, the incidence of injection site reaction tended to be high, and systemic reactions such as hypersensitivity were also observed. Therefore, the incidence of hypersensitivity including anaphylaxis as well as injection site reactions should be continuously investigated in the post-marketing surveillance, etc.

4.(iii).B.(3).5) Safety in children

The applicant's explanation on the safety of mepolizumab in children:
In the subpopulation of patients 12 to 17 years of age, no sufficient investigation was performed because of the limited number of patients available for the study. Nevertheless, as shown in Table 37, there were no additional safety concerns compared with subpopulations of different age, and no adverse events led to study discontinuation. In the 12 to 17-year old subpopulation, serious adverse events occurred in 14% (4 of 28) of patients, which were asthma in 3 patients (1 in the 250 mg IV group, 2 in the placebo group) and dyshidrotic eczema in 1 patient (100 mg SC group). A causal relationship to mepolizumab was ruled out in all these events, and the events resolved during the continued treatment with mepolizumab.

Table 37. Incidence of adverse events by age (the PCSA population, safety analysis population)

	100 mg SC (n = 263)	75 mg IV (n = 344)	Combined mepolizumab (n = 915)	Placebo (n = 412)
12-17 years old	n = 9	n = 9	n = 19	n = 9
All adverse events	7 (78)	9 (100)	17 (89)	6 (67)
Headache	2 (22)	2 (22)	4 (21)	1 (11)
Abdominal pain upper	2 (22)	1 (11)	3 (16)	1 (11)
Nasopharyngitis	1 (11)	3 (33)	4 (21)	2 (22)
Upper respiratory tract infection	1 (11)	2 (22)	3 (16)	0
18-64 years old	n = 216	n = 302	n = 814	n = 366
All adverse events	172 (80)	249 (82)	656 (81)	298 (81)
Headache	48 (22)	71 (24)	181 (22)	68 (19)
Nasopharyngitis	33 (15)	64 (21)	155 (19)	66 (18)
Upper respiratory tract infection	20 (9)	29 (10)	85 (10)	38 (10)
Asthma	12 (6)	31 (10)	81 (10)	56 (15)
Bronchitis	13 (6)	29 (10)	66 (8)	35 (10)
≥65 years	n = 38	n = 33	n = 82	n = 37
All adverse events	30 (79)	29 (88)	69 (84)	34 (92)
Nasopharyngitis	9 (24)	12 (36)	25 (30)	14 (38)
Headache	3 (8)	5 (15)	10 (12)	5 (14)
Arthralgia	5 (13)	2 (6)	9 (11)	2 (5)
Upper respiratory tract infection	6 (16)	1 (3)	8 (10)	9 (24)
Asthma	3 (8)	1 (3)	7 (9)	3 (8)

Number of patients (%)

Table 38 shows the incidence of adverse events in long-term mepolizumab treatment. The safety profile in the 12- to 17-year old subpopulation was similar to that in the entire population. There were no additional safety concerns compared with the safety profile in the PCSA population.

Table 38. Adverse events reported by ≥3 patients in 12-17 year old subpopulation (Study MEA115661, safety analysis population)

	100 mg SC	
	12-17 years old (n = 26)	Entire population (n = 651)
All adverse event	21 (81)	558 (86)
Nasopharyngitis	7 (27)	196 (30)
Asthma*	5 (19)	90 (14)
Headache	4 (15)	88 (14)
Sinusitis	5 (19)	66 (10)
Bronchitis	4 (15)	80 (12)
Upper respiratory tract infection	3 (12)	101 (16)
Gastroenteritis	3 (12)	17 (3)
Rhinitis allergic	3 (12)	15 (2)

Number of patients (%)
* Worsening/exacerbation of asthma

In Study MEE103219,[25] a foreign study of mepolizumab in 2 to 17-year-old patients with eosinophilic esophagitis, major adverse events observed were nasopharyngitis, vomiting, cough, diarrhoea, headache, oropharyngeal pain, abdominal pain upper, and pyrexia. No deaths occurred. Serious adverse events were observed in 5 patients (foreign body trauma, asthma/sinusitis, oesophageal injury, eosinophilic oesophagitis, chest discomfort), but all of them resolved and their causal relationship to mepolizumab was ruled out.

Since the safety profile of mepolizumab did not tend to differ between patients aged ≤17 years and the entire population, there are no particular safety concerns in children.

PMDA's view:
The currently available data do not show any obvious difference in the safety profile of mepolizumab or the incidence of adverse events between pediatric patients and the entire population. However, because of the limited number of children investigated in clinical studies, safety of mepolizumab in this patient group should be continuously investigated in the post-marketing surveillance, etc.

Consequently, PMDA considers the safety of mepolizumab as follows:
Given the submitted clinical data, the safety of patients with severe asthma being treated with mepolizumab is controllable. However, mepolizumab is expected to be used for long-term treatment, and the risk of infections etc., caused by the long-term suppression of IL-5 and blood eosinophil count is unclear. Thus, patient conditions should be carefully monitored during treatment with mepolizumab. Safety information obtained from the Japanese subpopulation suggests that there are no adverse events specific to Japanese patients. Nevertheless, treatment experience with mepolizumab in Japanese patients is currently limited, and safety information on long-term mepolizumab treatment should be continuously collected in the post-marketing surveillance etc.

4.(iii).B.(4) Clinical positioning and indication

4.(iii).B.(4).1) Clinical positioning

The applicant's explanation on the clinical positioning of mepolizumab:
Mepolizumab is thought to be used as an additional therapy for patients with asthma that becomes exacerbated even after conventional treatment corresponding to treatment step 4 in JGL Guideline, 2015 (Treatment Step 4). For patients at Treatment Step 4, the Guideline recommends the concomitant use of high dose ICS with multiple drugs among LABA, leukotriene receptor antagonist, extended-release theophylline preparation, or long-acting anticholinergic agent. For patients with persistent symptoms despite this concomitant use of high dose ICS with therapeutic agents, the Guideline recommends the use of anti-IgE antibody and OCS. However, use of anti-IgE antibody is limited to patients who are positive for perennial inhaled antigen and in whom the body weight and blood IgE level are within a certain range, and OCS has to be administered not as continued doses but as intermittent doses for a short-time period, whenever possible. Thus, only limited treatment options are available for the above patients.

[25] A randomized, double-blind, parallel-group, comparative study in 59 pediatric patients with eosinophilic esophagitis (including 27 patients aged 12-17 years) conducted in order to investigate the safety, pharmacokinetics, and reduction of eosinophil count in the esophageal epithelium within the reference range after intravenous administration of mepolizumab (0.55, 2.5, 10 mg/kg) 3 times, 4 weeks apart.

In Studies MEA115588 and MEA112997, the add-on effect of mepolizumab to conventional treatment was investigated in asthma patients with eosinophilic airway inflammation that gets aggravated even under treatment with high dose ICS and other long-term control medications. The results showed that subcutaneous (100 mg) and intravenous (75 mg) administration of mepolizumab both caused a statistically significant decrease in the incidence of asthma exacerbation compared with placebo. In addition, subcutaneous administration of mepolizumab (100 mg) allowed OCS dose reduction in Study MEA115575 in asthma patients with eosinophilic airway inflammation poorly responsive to OCS, high dose ICS, and other long-term control medications.

On the basis of the above study results, the applicant considers it significant to make mepolizumab available as an option for add-on treatment for asthma patients with eosinophilic airway inflammation that becomes aggravated even under treatment with high dose ICS and other long-term control medications.

PMDA's view:
Given the results of clinical studies obtained so far, mepolizumab is qualified as an add-on drug for Treatment Step 4 in asthma patients with eosinophilic airway inflammation. Before starting the treatment with mepolizumab, patients should be selected by carefully evaluating the expected treatment benefit individually, based on the patient characteristics investigated in clinical studies. Mepolizumab should therefore be administered by physicians versed in the treatment of bronchial asthma.

4.(iii).B.(4).2) Intended patients
The applicant's justification for the proposed indication and precautions for indications:
Mepolizumab inhibits signal transduction of IL-5, which regulates the growth, differentiation, and activation of eosinophils in blood and tissues, and thus suppresses production of eosinophils in peripheral blood and tissues. The following have been reported: excess IL-5 production is observed in patients with bronchial asthma (Robinson DS et al. *N Engl J Med.* 1992;326:298-304, Sur S et al. *J Allergy Clin Immunol.* 1995;96:661-668); and airway inflammation mainly caused by eosinophils plays a central role in the onset and progression of bronchial asthma (Cohn L at al. *Annu Rev Immunol.* 2004;22:789-815) [see "4.(iii).B.(1) Study design"]. Studies MEA112997 and MEA115588 were conducted on the basis of these findings, and the results demonstrated the efficacy of mepolizumab in patients with severe asthma who have eosinophilic airway inflammation [see "4.(iii).B.(2) Efficacy"]. Consequently, the proposed indication was set as "Bronchial asthma (severe eosinophilic asthma with exacerbation despite conventional treatment)".

In order to determine the criteria of blood eosinophil count to select eligible patients to be treated with mepolizumab, a modeling analysis similar to that corresponding to Figure 8 was performed, and the ratio of the incidence of asthma exacerbation in Study MEA115588 was predicted (Figure 14). As a result, the ratio [95% CI] of the incidence of asthma exacerbation was 0.61 [0.45, 0.82] in patients with baseline blood eosinophil count of 150/μL, a result similar to that observed in Study MEA112997. Also, as shown in Figures 15 and 16, the effect of mepolizumab in reducing asthma exacerbation tended to be greater in patients who had a higher blood eosinophil count at enrollment (2 weeks before the start of study treatment in Study MEA112997, 1-6 weeks before in Study MEA115588) or at the start of treatment.

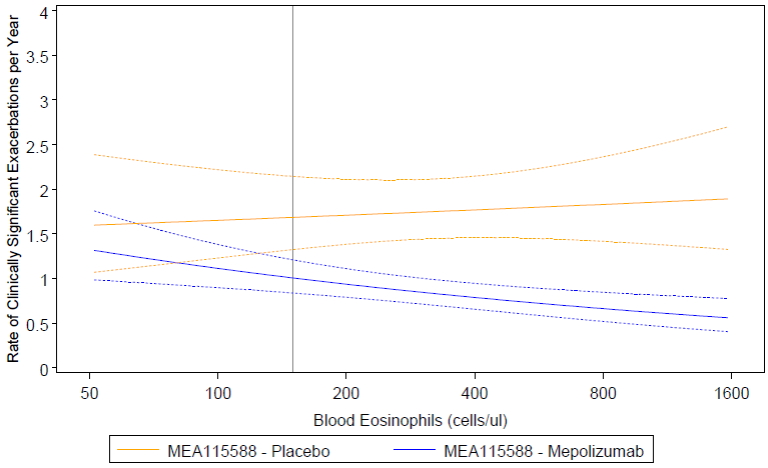

Figure 14. Incidence of asthma exacerbation by blood eosinophil count at the start of treatment (predicted value with 95% CI)

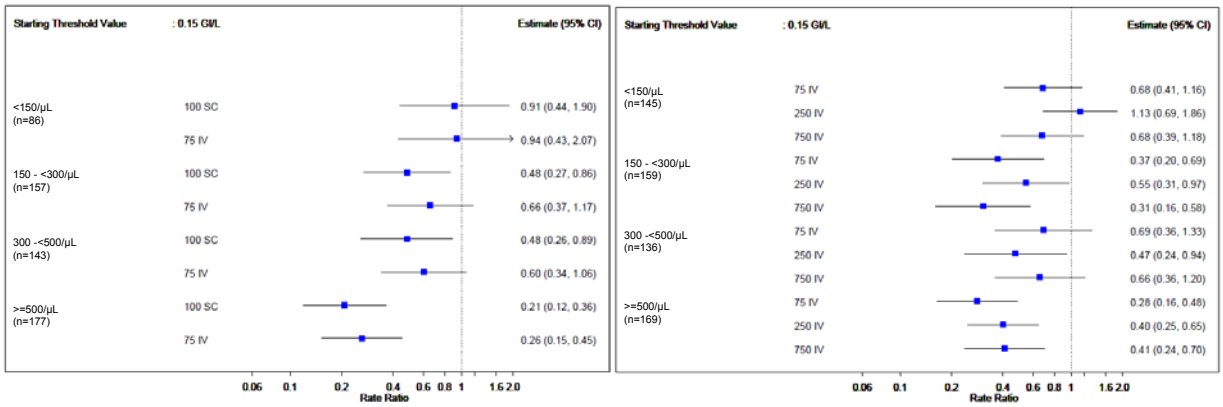

Figure 15. Subpopulation analysis of the ratio of the incidence of asthma exacerbation relative to placebo by blood eosinophil count at enrollment (left, Study MEA115588; right, Study MEA112997)

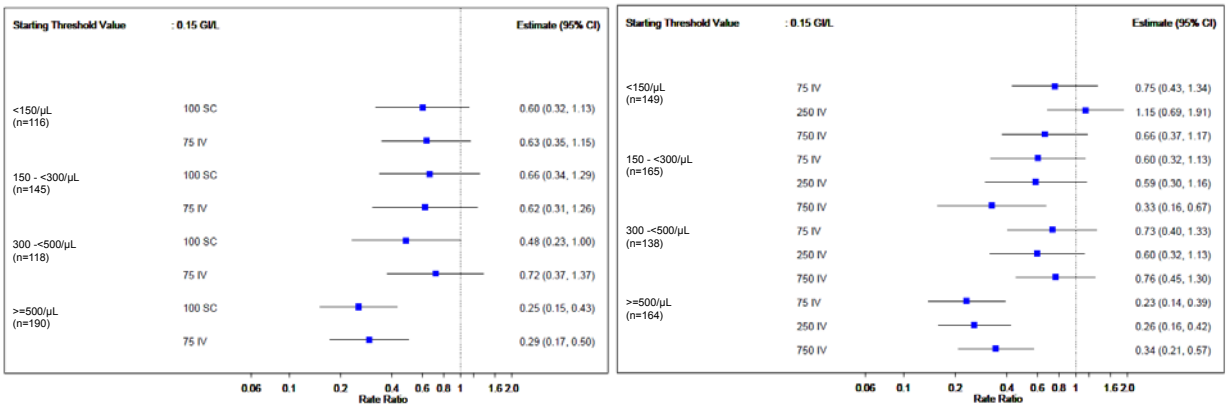

Figure 16. Subpopulation analysis of the ratio of the incidence of asthma exacerbation relative to placebo by blood eosinophil count at the start of treatment (left, Study MEA115588; right, Study MEA112997)

Table 39 shows the results of subgroup analysis on the incidence of asthma exacerbation performed in Studies MEA112997 and MEA115588. The subgroups met one of the following criteria or not: blood eosinophil count ≥300/µL in the past 12 months; and blood eosinophil count ≥150/µL at the start of treatment. In the subgroup that met the criterion "blood eosinophil count ≥300/µL in the past 12 months" only, the ratio [95% CI] of the incidence of asthma exacerbation relative to the placebo group was 0.80

[0.38, 1.68] in Study MEA112997 and 0.67 [0.36, 1.23] in Study MEA115588, showing a tendency of a smaller effect of mepolizumab compared with the subgroup that met both criteria (ratio [95% CI] of the incidence of asthma exacerbation relative to the placebo group was 0.48 [0.38, 0.59] in the pooled data of both studies). Nevertheless, the results are of clinical significance, in light of the fact that the target patients of the clinical studies were those with asthma exacerbation despite the concomitant use of antiasthmatic drugs including high dose ICS. In contrast, in the subgroup that met neither of the criteria, the ratio of the incidence of asthma exacerbation relative to the placebo group was 0.90 [0.49, 1.64] in Study MEA112997, suggesting that mepolizumab is not expected to be effective in this subgroup.

Table 39. Incidence of asthma exacerbation in Studies MEA112997 and MEA115588

Criteria for blood eosinophil count		Study MEA112997		Study MEA115588		Pooled data
≥300/μL in the past 12 months	≥150/μL at the start of treatment	No. of patients (combined mepolizumab groups/ placebo group)	Ratio of the incidence of asthma exacerbation (combined mepolizumab groups/ placebo group) [95% CI]	No. of patients (combined mepolizumab groups/ placebo group)	Ratio of the incidence of asthma exacerbation (combined mepolizumab groups/ placebo group) [95% CI]	Ratio of the incidence of asthma exacerbation (combined mepolizumab groups/ placebo group) [95% CI]
No	No	76/18	0.90 [0.49, 1.64]	12/10	0.54 [0.08, 3.52] a)	0.73 [0.43, 1.22]
Yes	Yes	230/80	0.44 [0.32, 0.61]	262/133	0.48 [0.36, 0.65]	0.48 [0.38, 0.59]
No	Yes	116/41	0.44 [0.28, 0.69]	34/24	0.33 [0.07, 1.49]	0.44 [0.29, 0.67]
Yes	No	39/16	0.80 [0.38, 1.68]	72/22	0.67 [0.36, 1.23]	0.67 [0.42, 1.08]

a) All subjects enrolled in Study MEA115588 had to meet the blood eosinophil count criteria for the past or at enrollment.

Consequently, the applicant considered that the Precautions for Indications section should be set as "(1) Nucala should be used in patients with blood eosinophil count of ≥150/μL at the start of treatment or ≥300/μL in the past 12 months, and (2) Nucala should be used in patients on a combination therapy of high dose inhaled corticosteroid and other long-term control medications."

PMDA asked the applicant to explain whether or not blood eosinophil count shows diurnal and daily variations and to explain the appropriateness of using the blood eosinophil count in selecting patients to be treated with mepolizumab.

The applicant's explanation:
It is suggested that the diurnal variations of blood eosinophil count in patients with asthma are relatively small during the daytime, whereas the count increases during the night-time (Spector SL et al. *J Asthma.* 2012;49:807-810), as is the case observed for healthy adult subjects (Hobbs GE et al. *Can Med Assoc J.* 1954;70:533-536, Sennels HP et al. *Scan J Clin Lab Invest.* 2011;71:532-541). Daily variations in blood eosinophil count in Japanese subjects assigned to the placebo group in Study MEA115588 are shown in Figure 17. In addition, blood eosinophil count at the start of treatment was <150/μL in 15.9% (76 of 477) of subjects for whom the count at enrollment was ≥150/μL (Table 40). Thus, blood eosinophil count showed a certain extent of daily variations. However, the mean blood eosinophil count (measured at multiple time points) throughout the study period was ≥150/μL in 85% (98 of 115) of subjects in Study MEA112997 and 86% (143 of 167) in Study MEA115588, among those with blood eosinophil count at enrollment (at 1 time point) of ≥150/μL (Katz LE et al. *Annals ATS.* 2014;11:531-536). Consequently, the applicant considers it appropriate, in selecting patients to be treated with mepolizumab in clinical settings, to use the criteria for blood eosinophil count specified in Study MEA115588.

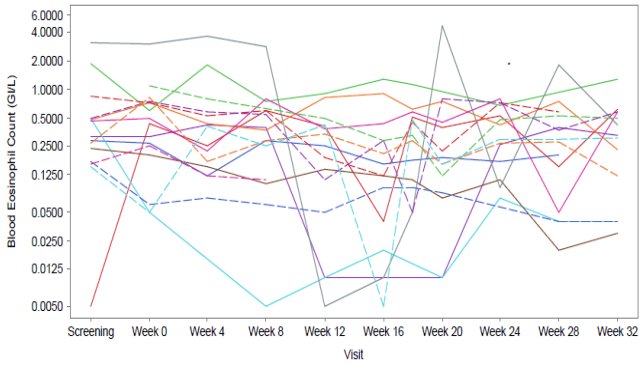

Figure 17. Time course of blood eosinophil count in Japanese subjects assigned to the placebo group in Study MEA115588

Table 40. Number of subjects with blood eosinophil count of ≥150/μL or <150/μL at enrollment or the start of treatment in Study MEA115588

	≥150/μL at enrollment	<150/μL at enrollment	Missing data at enrollment
≥150/μL at the start of study drug treatment	65.5% (377/576)	8.3% (48/576)	0.7% (4/576)
<150/μL at the start of study drug treatment	13.2% (76/576)	6.4% (37/576)	0.3% (2/576)
Missing data at the start of study drug treatment	4.2% (24/576)	0.2% (1/576)	1.2% (7/576)

PMDA's view on the intended population for mepolizumab:
While the efficacy of mepolizumab was not demonstrated in the clinical study (Study SB-240563/006) conducted in patients with moderate asthma with no inclusion criteria for eosinophil count, mepolizumab was shown to be effective in reducing asthma exacerbation in Studies MEA112997 and MEA115588, which were conducted only in patients who met a preset criterion for blood or sputum eosinophil count. In light of the above results, it is understandable to limit the use of mepolizumab to patients with bronchial asthma who have airway inflammation mainly caused by eosinophils. The results shown in Figures 15 and 16 may be interpreted as indicating the tendency that the greater the number of baseline blood eosinophil count, the greater the benefit obtainable from mepolizumab. However, the submitted clinical data contain data only in limited number of patients with low baseline blood eosinophil count. In addition, blood eosinophil count shows diurnal and daily variations. Therefore, it is practically impossible to set a cut-off level of blood eosinophil count to predict/determine the presence or absence of benefits obtainable from mepolizumab. If the cut-off level of blood eosinophil count were determined based only on the currently available evidence, it would be necessary to repeat the test in some patients until they are judged eligible for receiving mepolizumab, possibly causing a delay in the decision to start treatment. Also, should an inappropriate cut-off level be set, patients who can be treated with mepolizumab might lose the opportunity of receiving the treatment. Moreover, among patients with severe persistent asthma meeting Treatment Step 4 of JGL Guideline 2015, patients who have exacerbation even under concomitant treatment with high dose ICS and other long-term control medications (the disease conditions for which mepolizumab is intended to be used) have not only very few treatment options but also a high risk of asthma exacerbation. When asthma exacerbation occurs, symptoms are serious in these patients. It should also be taken into account that the submitted clinical data do not suggest any particular safety problems in patients treated with mepolizumab.

Consequently, PMDA considers that the Indication and Precautions for Indications sections should not invariably exclude patients with blood eosinophil count below a pre-set cut-off level, and that caution should be provided, instead, so that the physicians versed with the clinical data of mepolizumab select patients by considering their blood eosinophil count as reference data, after thoroughly understanding the efficacy and safety of mepolizumab.

4.(iii).B.(4).3) Indication
On the basis of the discussion in "4.(iii).B.(4).2) Intended patients," the fact that the disease concept for eosinophilic asthma is not established, and the descriptions on the indication for drugs in the same class, PMDA has concluded that the indication of Nucala should be "Bronchial asthma (only for patients with

refractory asthma whose symptoms cannot be controlled by conventional treatment) and that Precautions for Indications should include the following.

(Precautions for Indications)
(1) Nucala should be administered as an add-on drug in patients with poorly controlled, refractory asthma who suffer from asthma exacerbation requiring systemic corticosteroid etc., even under concomitant treatment with high dose inhaled corticosteroid and other long-term control medications.

(2) The higher the baseline blood eosinophil count in the patient, the greater the tendency of effect of Nucala in reducing exacerbation frequency of bronchial asthma. Patients to be treated with Nucala should be selected only after thorough understanding of the relationship between the baseline blood eosinophil count and efficacy in patients treated in the clinical studies (see "Clinical Studies").

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

4.(iii).B.(5) Dosage and administration

The applicant's explanation:
Study MEA115588 demonstrated the superiority of mepolizumab 100 mg SC over placebo in the incidence of asthma exacerbation, the primary endpoint. The results in the Japanese subpopulation were consistent with those in the entire population. Mepolizumab 100 mg SC did not pose any particular safety concerns, and there were no clear differences in adverse events observed between the Japanese subpopulation and the entire population. Therefore, it is appropriate to set the dosage and administration of mepolizumab as 100 mg SC. The superiority of mepolizumab 75 mg IV over placebo was also demonstrated, but the subcutaneous administration was selected as the proposed administration route for the convenience of patients and healthcare professionals.

PMDA asked the applicant to explain the appropriateness of setting the mepolizumab dose for adolescents (aged ≥12 years) at 100 mg, the same dose as that for patients aged ≥18 years and to explain the necessity of mepolizumab in pediatric patients.

The applicant's explanation:
Among 25 adolescent patients (12 to 17 years of age) enrolled in Study MEA115588 (7 in the 100 mg SC group, 9 in the 75 mg IV group, 9 in the placebo group), asthma exacerbation occurred in 18.8% (3 of 16) of patients in the 75 mg IV and 100 SC groups combined and in 33.3% (3 of 9) of patients in the placebo group, showing a tendency similar to that observed in the entire population. The safety profile of mepolizumab in adolescent patients (12 to 17 years of age) was similar to that observed in adult patients [see "4.(iii).B.(3) Safety"]. The exposure to mepolizumab at the steady state after subcutaneous administration of mepolizumab 100 mg at 4-week intervals was estimated by population pharmacokinetic analysis of the data obtained in Study MEA115588. In subgroups of ≥18 years and 12 to 17 years of age, C_{max} (median [minimum, maximum]) was 16.0 [7.2, 35.1] and 26.7 [20.4, 29.1] μg/mL, respectively, and AUC was 337 [117, 796] and 571 [428, 671] μg·day/mL, respectively, showing that the estimated exposure in adolescent patients (12 to 17 years of age) was within the range estimated in patients ≥18 years of age. The effect of mepolizumab to decrease blood eosinophil count was not different between the subpopulation of 12 to 17 years of age and the entire population (Table 41).

Thus, there is no clear difference in the efficacy, safety, or pharmacokinetics of mepolizumab between adult patients and adolescent patients (12 to 17 years of age). The applicant therefore considers that it is appropriate to set the dosage and administration of Nucala as 100 mg administered subcutaneously in adolescents as in patients ≥18 years of age.

Table 41. Time course of blood eosinophil count in adolescent (12 to 17-year-old) subpopulation and in the entire population (Study MEA115588)

		Adolescent (12 to 17-year-old) subpopulation			Entire population		
		100 mg SC (n = 7)	75 mg IV (n = 9)	Placebo (n = 9)	100 mg SC (n = 194)	75 mg IV (n = 191)	Placebo (n = 191)
At the start of treatment	Number of patients	7	9	9	192	188	189
	Geometric mean (/μL)	240	280	210	290	280	320
Week 16	Number of patients	6	9	9	183	175	177
	Geometric mean (/μL)	30	50	220	40	50	250
Week 32	Number of patients	7	8	8	184	172	173
	Geometric mean (/μL)	40	40	250	40	50	270

As are the cases with adult patients, some pediatric patients require frequent hospitalization despite the standard treatment and high dose OCS is used to control the symptoms for an extended period, posing problems of adverse drug reactions such as failure to thrive (Fitzpatrick AM et al. *J Allergy Clin Immunol*. 2010;125:851-857, Dolan CM et al. *Ann Allergy Asthma Immunol.* 2004;92:32-39). In 90% of patients given a diagnosis of severe asthma at the age of 7 years, the symptom continued even at the age of 42 years (Phelan PD et al. *J Allergy Clin Immunol.* 2002;109:189-194). Patients who had transient or persistent wheezing before school age have reduced respiratory function at the age of 11 to 16 years when compared with patients without wheezing, and are more prone to develop chronic obstructive pulmonary disease in their adulthood (Morgan WJ et al. *Am J Respir Crit Care Med.* 2005;172:1253-1258). Taking account of these and other reports, the applicant considers that there is a high need for mepolizumab in adolescents with severe asthma as is the case with adult patients, because the symptoms in this patient population are likely to persist even after adolescence.

PMDA's view:
In Study MEA112997, the effect in reducing asthma exacerbation was not different among the 3 intravenous doses investigated, and the minimum effective intravenous dose remains unknown. In Study MEA115588, only 100 mg SC and 75 mg IV were investigated. Therefore, the data submitted for the application are insufficient particularly in clarifying the dose-response relationship of subcutaneous doses and clinical effect. In Japanese patients, no dose-response relationship of mepolizumab was investigated for subcutaneous or intravenous administration. Thus, lower doses should have been investigated in Study MEA115588. Nevertheless, the following findings have been found in the clinical studies: (1) the efficacy of mepolizumab 75 mg in intravenous administration was confirmed in Study MEA115588 which included Japanese patients and in Study MEA112997; (2) in Study MEA115588, the effect of 100 mg SC in reducing asthma exacerbation turned out to be similar to that obtained with 75 mg IV; and (3) no particular safety concerns were raised by mepolizumab treatment. On the basis of these, PMDA considers it appropriate to set the dosage and administration of mepolizumab in Japanese patients with severe asthma as proposed in the following: "The usual dosage for adults and adolescents (aged ≥12 years) is 100 mg Mepolizumab (Genetical Recombination) injected subcutaneously once every 4 weeks." Since only a limited number of adolescents were investigated, further information on the efficacy and safety of mepolizumab in patients of this age group should be collected after market launch.

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

4.(iii).B.(6) Post-marketing investigations

The applicant plans to conduct a post-marketing surveillance with a 1-year observation period on 1000 patients in order to collect information on the safety and efficacy of mepolizumab in routine clinical use, including the occurrences of adverse events such as systemic reactions (e.g., allergic reactions that may occur as adverse drug reactions to mepolizumab), injection site reaction, and infection. The applicant also plans to conduct a randomized, placebo-controlled, double-blind, parallel group, comparative study. In the study, mepolizumab (100 mg) or placebo will be administered subcutaneously at 4-week intervals for 52 weeks to patients with asthma who have been treated with mepolizumab for ≥3 years (target sample size, 300 [150 patients per group]), to investigate the necessity of continued administration. The time to the first occurrence of asthma exacerbation will be used as the primary endpoint in this study.

PMDA's view:

The submitted clinical data do not suggest any particular concerns raised by mepolizumab treatment. However, there are only limited data on long-term mepolizumab treatment, and further information is necessary on the occurrences of serious infections, which are concerns common to immunosuppressive agents. To collect such information, a post-marketing surveillance with long-term treatment should be conducted.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

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

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

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

The assessment is currently ongoing. The results and PMDA's conclusion will be reported in the Review Report (2).

IV. Overall Evaluation

Based on the submitted data, the efficacy of Nucala in the treatment of bronchial asthma has been demonstrated and its safety is acceptable in view of its observed benefits. Nucala provides a new treatment option for bronchial asthma, and thus has clinical significance. Occurrences of serious infection in long-term treatment, safety in pediatric and elderly patients, etc., should be further investigated in the post-marketing surveillance.

This application may be approved if Nucala is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

February 16, 2016

I. Product Submitted for Registration

[Brand name] Nucala for SC Injection 100 mg
[Non-proprietary name] Mepolizumab (Genetical Recombination)
[Name of applicant] GlaxoSmithKline K.K.
[Date of application] May 22, 2015

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, 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) Efficacy and dosage and administration

The conclusion by PMDA on the efficacy and dosage and administration of "Nucala for S.C. Injection 100 mg" as described in the Review Report (1) was supported by the expert advisors.

(2) Indication and Precautions for Indications

As described in the Review Report (1), in light of the results of clinical studies including Studies SB-240563/006, MEA115588, and MEA112997, PMDA considers that (1) mepolizumab is expected to be beneficial in patients with severe asthma who have airway inflammation mainly caused by eosinophils, (2) no data are available which demonstrates that the efficacy of mepolizumab cannot be expected in severe asthma patients with a history of exacerbation, and with their blood eosinophil count being below the cut-off level, and (3) it is thus practically impossible to set a cut-off level of blood eosinophil count based on the submitted data [see "4.(iii).B.(4).2) Intended patients" of the Review Report (1)]. Eosinophilic asthma is not clearly characterized in international clinical practice guidelines such as Global Initiative for Asthma (GINA) 2015 and ERS/ATS. Taking account of the above, PMDA concluded that (1) the package insert should include, in the Clinical Studies section, the inclusion criterion on blood eosinophil count used in Study MEA115588 and the results of analyses on this study's subgroups by blood eosinophil count at enrollment and treatment initiation, and (2) the package insert should provide the information, described below, regarding the patients to be treated with Nucala, also in Indication and Precautions for Indications sections.

[Indication] Bronchial asthma (<u>only for patients with refractory asthma whose symptoms cannot be controlled by</u> ~~severe eosinophilic asthma with exacerbation despite~~ conventional treatment)
(The struck-through part was removed from, and the underlined part was added to the proposed indication.)

Precautions for Indications

(1) Nucala should be administered as an add-on drug in patients with poorly controlled, refractory asthma who suffer from asthma exacerbation requiring systemic corticosteroid etc., even under concomitant treatment with high dose inhaled corticosteroid and other long-term control medications.

(2) The higher the baseline blood eosinophil count in the patient, the greater the tendency of effect of Nucala in reducing exacerbation frequency of bronchial asthma. Patients to be treated with Nucala should be selected only after thorough understanding of the relationship between the baseline blood eosinophil count and efficacy in patients treated in the clinical studies (see "Clinical Studies").

At the Expert Discussion, the above conclusions by PMDA were generally supported by the expert advisors, with the following comments.

- The Japanese Guideline for Asthma Prevention and Management 2015 states that airway inflammation strongly suggestive of asthma is usually eosinophilic. Therefore, if this information in the Guideline is provided in the Precautions for Indications section etc., mepolizumab will be used appropriately without the description "eosinophilic asthma" in the indication as proposed by the applicant.

- "Severe eosinophilic asthma" is an appropriate term to describe the patient population who responded to mepolizumab in the clinical studies. However, a clear definition of the term is difficult because the phenotypes (eosinophilic, neutrophilic, etc.) often overlap with each other.

- Caution should be provided to avoid discrepancy between the patient population in whom the efficacy of mepolizumab was demonstrated in the clinical studies and the patients for whom mepolizumab is indicated.

- Healthcare professionals in clinical settings should be appropriately informed (i) that appropriateness of using mepolizumab should be determined by referring to the patient's blood eosinophil count since mepolizumab is considered to exhibit its clinical efficacy by decreasing eosinophil count, and (ii) the clinical data available suggest that patients with low baseline blood eosinophil count may not be sufficiently responsive to mepolizumab. Healthcare professionals should also be advised to avoid using mepolizumab inappropriately regardless of blood eosinophil count.

- In light of the results of the foreign phase III study (Study MEA115575), mepolizumab is considered to be effective also in severe asthma patients in whom asthma exacerbation is successfully controlled by continued administration of systemic corticosteroid.

Based on the Expert Discussion etc., PMDA instructed the applicant to provide the following cautions in the Indication and Precautions for Indications sections of Nucala. The applicant took appropriate measures and responded that information materials for healthcare professionals will be prepared that assist selection of patients to be treated with Nucala.

[Indication] Bronchial asthma (only for patients with refractory asthma whose symptoms cannot be controlled by conventional treatment)

Precautions for Indications

(1) Nucala should be administered as an add-on drug in patients who suffer from asthma exacerbation requiring systemic corticosteroid etc., even under concomitant treatment with high dose inhaled corticosteroid and other long-term control medications.

(2) The higher the baseline blood eosinophil count in the patient, the greater the tendency of the effect of Nucala in reducing exacerbation frequency of bronchial asthma. Clinical data, albeit limited, suggest the possibility that Nucala may not be sufficiently effective in reducing the exacerbation frequency of bronchial asthma in patients with a low baseline blood eosinophil count. Patients to be treated with Nucala should be selected only after taking into account their blood eosinophil count, and thorough understanding of the mechanism of action of Nucala and the relationship between the baseline blood eosinophil count and efficacy observed in the clinical studies (see "Clinical Studies").

(3) Safety and risk management plan (draft)

The Expert Discussion supported the conclusion by PMDA on the safety of Nucala described in the Review Report (1).

In light of the results of the review in "4.(iii).B.(6) Post-marketing investigations" of the Review Report (1) and of the comments raised by the expert advisors at the Expert Discussion, PMDA has concluded it is appropriate that the draft risk management plan for Nucala should include safety and efficacy evaluations as listed in Table 42 and additional pharmacovigilance activities and risk minimization activities as shown in Table 43.

Table 42. Safety and efficacy specifications in risk management plan (draft)

Safety specifications		
Important identified risks	Important potential risks	Important missing information
None	• Hypersensitivity such as anaphylaxis • Immunogenicity • Infection • Malignant tumor	None
Efficacy specifications		
• Efficacy in routine clinical use • Efficacy duration after discontinuation of long-term treatment		

Table 43. Outline of additional pharmacovigilance activities and risk minimization activities in the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey • Post-marketing clinical study [a)]	• Early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals (for selection of patients to be treated)

a) Efficacy and safety of Nucala after study discontinuation will be evaluated in the patients enrolled in a long-term treatment study of Nucala conducted until the marketing approval.

Based on the above, PMDA instructed the applicant to conduct a post-marketing surveillance to investigate these items.

The applicant explained their plan to conduct a specified drug use-results survey in patients with severe asthma uncontrolled even by conventional treatment (target sample size, 1000; a 1-year observation period), as shown in Table 44, thereby to investigate the safety and efficacy of Nucala in routine clinical use, with hypersensitivity (such as anaphylaxis), infection, and malignant tumor as priority items to be investigated. The applicant also explained that, after the end of the observation period, they will follow up patients for occurrence of malignant tumor until after 3 years of treatment, thereby further investigating the safety of Nucala in long-term treatment.

Table 44. Outline of specified drug use-results survey plan (draft)

Objective	To collect and evaluate information related to long-term safety and efficacy in routine clinical use
Survey method	Central registration system
Patients population	Patients with severe asthma uncontrolled even by conventional treatment
Observation period	1 year (After the end of this observation period, a 2-year follow-up survey will be conducted regardless of whether treatment is discontinued or not)
Target sample size	1000
Priority investigation items	Hypersensitivity such as anaphylaxis Infection Malignant tumor
Main investigation items	Patient characteristics (reason to use Nucala, disease duration, severity, comorbidities, history of smoking, etc.) Previous treatment for bronchial asthma Concomitant drugs/therapies Administration of Nucala Blood tests (blood eosinophil count, serum total IgE concentration) Efficacy evaluation (frequencies of exacerbation, respiratory function test, etc.) Adverse events

PMDA considers that the survey should be conducted promptly and information obtained from the survey should be provided appropriately to healthcare professionals in clinical settings.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted 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 for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the application documents submitted.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted 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 for the data submitted in the new drug application (5.3.5.1, 5.3.5.2). As a result, PMDA concluded that the clinical studies as a whole were conducted in compliance with GCP and that there should be no problem with conducting a regulatory review based on the product application documents submitted. The inspection revealed following findings at some medical institutions although they did not significantly affect the evaluation of the study as a whole. These were notified to the head of the medical institutions for improvement.

(Matters that should be improved)
Medical institutions

- Protocol deviations (blood sampling for unnecessary laboratory tests, noncompliance with the rules for documenting adverse events in electronic case report forms, partially missing laboratory data due to defects in sample collection and shipment)
- The investigator obtained the renewed informed consent from some patients by providing the explanation on the extended study participation using the information material which had not been authorized by the head of the medical institution.

IV. Overall Evaluation

As a result of the above review, PMDA concludes that Nucala may be approved for the indication and dosage and administration as shown below, with the following condition. Since Nucala is a drug with a new active ingredient, the re-examination period is 8 years. The drug substance and the drug product are both classified as powerful drugs, and the drug product is classified as a biological product.

[Indication]	Bronchial asthma (only for patients with refractory asthma whose symptoms cannot be controlled by conventional treatment)
[Dosage and administration]	The usual dosage for adults and adolescents (aged ≥12 years) is 100 mg of Mepolizumab (Genetical Recombination) injected subcutaneously once every 4 weeks.
[Condition for approval]	The applicant is required to develop and appropriately implement a risk management plan.