Report on the Deliberation Results

March 8, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Omvoh Intravenous Infusion 300 mg Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes
Non-proprietary Name	Mirikizumab (Genetical Recombination) (JAN*)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 27, 2022

Results of Deliberation

In its meeting held on March 3, 2023, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Approval Conditions

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

**Japanese Accepted Name (modified INN)*

Review Report

February 16, 2023
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a) Omvoh Intravenous Infusion 300 mg (b) Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes
Non-proprietary Name	Mirikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 27, 2022
Dosage Form/Strength	(a) Aqueous injection in a vial: Each vial contains 300 mg of mirikizumab (genetical recombination) (b) Aqueous injection in a syringe: Each syringe contains 100 mg of mirikizumab (genetical recombination)
Application Classification	Prescription drug, (1) Drug(s) with a new active ingredient

Definition

Mirikizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human interleukin-23α (p19) monoclonal antibody, human framework regions and human IgG4 constant regions. In the H-chain, the amino acid residues at positions 223, 229 and 230 are substituted by Pro, Ala and Ala, respectively, and C-terminal Lys is deleted. Mirikizumab is produced in Chinese hamster ovary cells. Mirikizumab is a glycoprotein (molecular weight: ca.147,000) composed of 2 H-chains (γ4-chains) consisting of 441 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

L-chain

DIQMTQSPSS LSASVGDRVT ITCKASDHIL KFLTWYQQKP GKAPKLLIYG
ATSLETGVPS RFSGSGSGTD FTLTISSLQP EDFATYYCQM YWSTPFTFGG
GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV
DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG
LSSPVTKSFN RGEC

H-chain

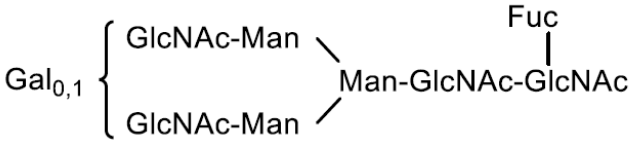
QVQLVQSGAE VKKPGSSVKV SCKASGYKFT RYVMHWVRQA PGQGLEWMGY
INPYNDGTNY NEKFKGRVTI TADKSTSTAY MELSSLRSED TAVYYCARNW
DTGLWGQGTT VTVSSASTKG PSVFPLAPCS RSTSESTAAL GCLVKDYFPE
PVTVSWNSGA LTSGVHTFPA VLQSSGLYSL SSVVTVPSSS LGTKTYTCNV
DHKPSNTKVD KRVESKYGPP CPPCPAPEAA GGPSVFLFPP KPKDTLMISR
TPEVTCVVVD VSQEDPEVQF NWYVDGVEVH NAKTKPREEQ FNSTYRVVSV
LTVLHQDWLN GKEYKCKVSN KGLPSSIEKT ISKAKGQPRE PQVYTLPPSQ
EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP PVLDSDGSFF
LYSRLTVDKS RWQEGNVFSC SVMHEALHNH YTQKSLSLSL G

Intrachain disulfide bonds: Solid lines in the figure

Interchain disulfide bonds: L-chain C214-H-chain C129, H-chain C221-H-chain C221, H-chain C224-H-chain C224

Partial pyroglutamic acid: H-chain Q1, Glycosylation: H-chain N292

Presumed main carbohydrate structure



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

Molecular formula: $C_{6380}H_{9842}N_{1686}O_{2004}S_{48}$ (protein segment, 4 chains)
(H-chain) $C_{2152}H_{3321}N_{573}O_{670}S_{17}$
(L-chain) $C_{1038}H_{1604}N_{270}O_{332}S_{7}$

Molecular weight: ca. 147,000

Items Warranting Special Mention

None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of patients with moderate to severe ulcerative colitis who have an inadequate response to conventional treatment, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indications

(a) Remission induction therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)
(b) Maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

Dosage and Administration

(a) The usual adult dosage is 300 mg of mirikizumab (genetical recombination) intravenously infused every 4 weeks for 3 doses (Weeks 0, 4, and 8). Of note, if the therapeutic response is inadequate at Week 12, the dosage of 300 mg may be administered every 4 weeks for an additional 3 doses (Weeks 12, 16, and 20).
In addition, if patients show a reduced response to maintenance therapy with mirikizumab (genetical recombination) in subcutaneous dosage forms, the dosage of 300 mg may be intravenously infused every 4 weeks for 3 doses.
(b) The usual adult dosage is 200 mg of mirikizumab (genetical recombination) subcutaneously injected every 4 weeks, starting 4 weeks after completion of the induction therapy of mirikizumab (genetical recombination) in intravenous infusion dosage forms.

Approval Condition

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

Attachment

Review Report (1)

December 22, 2022

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

Product Submitted for Approval

Brand Name	(a) Omvoh Intravenous Infusion 300 mg (b) Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes
Non-proprietary Name	Mirikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 27, 2022
Dosage Form/Strength	(a) Aqueous injection in a vial: Each vial contains 300 mg of mirikizumab (genetical recombination) (b) Aqueous injection in a syringe: Each syringe contains 100 mg of mirikizumab (genetical recombination)

Proposed Indications

(a) Remission induction therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

(b) Remission maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

Proposed Dosage and Administration

(a) The usual adult dosage is 300 mg of mirikizumab (genetical recombination) intravenously infused at Weeks 0, 4, and 8 of remission induction therapy. Of note, if the patient does not show an adequate therapeutic response at Week 12, the remission induction therapy may be continued by administering mirikizumab at Weeks 12, 16, and 20.

(b) The usual adult dosage is 200 mg of mirikizumab (genetical recombination) subcutaneously administered, followed by 200 mg every 4 weeks, starting 12 weeks after the start of the intravenous infusion of mirikizumab (genetical recombination) (after completion of the remission induction therapy).

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List of Abbreviations

See Appendix.

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

Ulcerative colitis (UC) is an inflammatory bowel disease that is accompanied by diarrhoea, hematochezia, abdominal pain, and pyrexia during its active phase and is characterized by repeats of remission and relapse. In Japan, UC is designated as a designated intractable disease (Ministry of Health, Labour and Welfare [MHLW] Ministerial Announcement No. 393, Announcement No. 97, dated October 21, 2014). In Japan, treatment for UC (drug therapy, surgical treatment, etc.) is chosen according to the severity. During the active phase, 5-aminosalicylate acid (5-ASA) preparations are widely used for mild to moderate diseases. For patients who have an inadequate response and severe diseases, steroids are used, and for patients resistant to steroids, tacrolimus, biological products, Janus kinase (JAK) inhibitors, etc. are used. In addition, during the remission phase, 5-ASA preparations are mainly used. For steroid-dependent patients, immunomodulatory drugs such as azathioprine are used, and for patients in remission induced by biological products, etc., the same products are used continuously ("Diagnosis Criteria and Treatment Guidelines for Ulcerative Colitis and Crohn's Disease, FY 2021 Revised Edition, dated March 31, 2022" FY 2021 Report "Research on Intractable Inflammatory Bowel Disease" [Hisamatsu group], Research on Policy Planning and Evaluation for Rare and Intractable Diseases, funded by the Health and Labour Sciences Research Grants).

Mirikizumab (genetical recombination) (hereinafter referred to as mirikizumab) is a humanized monoclonal antibody of immunoglobulin G (IgG)4 subclass against the p19 subunit of human interleukin (IL)-23, discovered by Eli Lilly and Company in the US. Mirikizumab has been developed because it is expected to achieve its intended effect in the treatment of UC by neutralizing IL-23, which is involved in mucosal inflammation of UC.

The applicant conducted clinical studies of mirikizumab in patients with moderate to severe UC who had an inadequate response to conventional treatment, thereby demonstrating the efficacy and safety of mirikizumab, and thus submitted the marketing application for mirikizumab.

As of December 2022, mirikizumab has been in an application for approval in the US, EU, etc., and is not approved in any country or region.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

[redacted] of [redacted] immunized with human IL-23 were subjected to flow cytometry to select cells that acted as IL-23 antigen or bound to [redacted], and culture supernatants from [redacted] were then screened to select cells that produced antibodies with the target action based on binding to human IL-23 and non-binding to [redacted]. From the concerned cells, gene fragments coding variable regions of the H-chain and L-chain were isolated and used to generate multiple antibodies, which were then screened for inhibition against binding to the IL-23 receptor. The selected antibody was humanized and optimized. Gene fragments coding variable regions of the H-chain and L-chain of the concerned antibody as well as plasmids coding the constant regions of human IgG4 were integrated to obtain plasmids coding full lengths of the H-chain and L-chain, which were used as a gene expression construct of mirikizumab. The concerned gene expression construct was transfected

into Chinese hamster ovary (CHO) cells, and among the transfected CHO cells, the optimal clone for producing mirikizumab was used to generate the master cell bank (MCB) and working cell bank (WCB).

Characterization and purity tests were performed on MCB, WCB and cells at the limit of *in vitro* cell age (CAL) in accordance with "Viral Safety Evaluation of Biotechnology Products Derived From Cell Lines of Human or Animal Origin" (ICH Q5A [R1] guideline), "Quality of Biotechnological Products: Analysis of the Expression Construct in Cells Used for Production of R-DNA Derived Protein Product" (ICH Q5B guideline), and "Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products" (ICH Q5D guideline). The results demonstrated genetic stability during the manufacturing period, and neither viral nor nonviral adventitious agents were detected in any of the tests performed, except endogenous retrovirus-like particles, which are generally observed in rodent cell lines.

MCB and WCB are stored in the gas phase of liquid nitrogen. The MCB is not planned to be regenerated, but a new WCB is generated as needed.

2.1.2 Manufacturing process

The manufacturing process of the drug substance consists of expansion culture in flasks, seed culture, production culture, initial harvesting, viral inactivation with [redacted], [redacted] chromatography, viral inactivation and clarification with [redacted], [redacted] chromatography, [redacted] filtration, [redacted] filtration, and subdivision, freezing, storage, and testing.

Critical process steps include [redacted], [redacted] with [redacted], [redacted], [redacted] with [redacted], [redacted], and [redacted].

The manufacturing process of the drug substance was validated on a commercial scale.

2.1.3 Safety evaluation of adventitious agents

The manufacturing process of the drug substance does not use biological raw materials other than CHO cells, host cells.

Purity tests have been performed on MCB, WCB, and CAL [see Section 2.1.1]. The unprocessed/unpurified bulk before harvesting on a commercial scale was tested for bioburden, mycoplasma, viruses *in vitro*, and minute virus of mice. Neither viral nor nonviral adventitious agents were detected in any of the tests performed. These tests are in-process control tests on unprocessed/unpurified bulk before harvesting.

In the purification process, a viral clearance study was performed using model viruses. The results showed certain levels of viral clearance capability in the purification process (Table 1).

Table 1. Results of viral clearance study

Manufacturing process	Virus reduction factor (log_{10})			
	Xenotropic murine leukemia virus	Porcine parvovirus	Pseudorabies virus	Reovirus 3
Viral inactivation with [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
Viral inactivation and clarification with [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	≥16.67	5.88	≥8.70	≥6.27

2.1.4 Manufacturing process development

Main changes to the manufacturing process during development of the drug substance are shown below (respective manufacturing processes are referred to as Process A, Process B, Process C, Process D, and Process E, and proposed commercial process). Of note, the phase I study used the formulation prepared from the drug substance manufactured by Process B; the phase II study used the formulation prepared from the drug substance manufactured by Process B or Process C; and the phase III studies used the formulation prepared from the drug substance manufactured by Process D or Process E.

- From Process A to Process B: Introduction of [redacted], changes in the manufacturing scale and [redacted] process
- From Process B to Process C: Change in manufacturing scale
- From Process C to Process D: Introduction of [redacted], changes in [redacted] process, [redacted] process, and formulation
- From Process D to Process E: Changes in manufacturing site, manufacturing scale, [redacted] process, and [redacted]
- From Process E to the proposed commercial process: Change in manufacturing site

The comparability of quality attributes was evaluated for each of the above process changes and comparability of the drug substance before and after each change was confirmed.

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization studies were conducted as shown in Table 2.

Table 2. Parameters evaluated by characterization studies

Primary/higher order structure	Amino acid sequence, N-terminal and C-terminal amino acid sequence, posttranslational modification (pyroglutamate formation, N-linked glycosylation, deamidation, isomerization, oxidation, N-terminal and C-terminal heterogeneity), disulfide bonds, free sulfhydryl group, secondary structure, tertiary structure, quaternary structure, thermostability
Physicochemical properties	Molecular weight/molecular size, charge variants, size variants, IgG subclass analysis, absorptivity
Carbohydrate structure	Glycosylation rate, oligosaccharide profile, carbohydrate structural analysis
Biological properties	IL-23 inhibition, Fcγ receptor (I, IIa, and IIIa) binding affinity, C1q binding affinity, neonatal Fc receptor binding affinity

- Of the biological properties, IL-23 inhibition was assessed based on production of [redacted] from [redacted]-derived [redacted] cell line expressing [redacted] gene through [redacted].

2.1.5.2 Product-related substances/Product-related impurities

On the basis of characterization results in Section 2.1.5.1, the following were identified as product-related substances: Related-substance A ([redacted] and [redacted]), Related-substance B ([redacted]), Related-substance C, Related-substance D, Related-substance E, and Related-substance F. In addition, aggregates, cleavage form, Impurity A, and Impurity B were identified as product-related impurities. Of the product-related impurities, aggregates, cleavage form, and Impurity A are controlled by the specifications for the drug substance and drug product. Of note, an amount of Impurity B has been found to be low throughout the manufacturing results to date, and thus the routine control is considered unnecessary.

2.1.5.3 Process-related impurities

Host cell protein (HCP), host cell deoxyribonucleic acid (DNA), Impurity C, Impurity D, elemental impurity, Impurity E, Impurity F, Impurity G, and Impurity H were identified as process-related impurities. All of the process-related impurities are demonstrated to be adequately removed through the manufacturing process.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include the content, description, identification (high performance liquid chromatography [HPLC], IL-23-binding inhibition cell-based assay, peptide mapping), purity (size exclusion high performance liquid chromatography [SE-HPLC] and capillary electrophoresis-sodium dodecyl sulfate [CE-SDS] [redacted]), charge heterogeneity (capillary isoelectric focusing [cIEF]), bacterial endotoxins, microbial limit, potency (IL-23-binding inhibition cell-based assay), and assay (ultraviolet-visible spectrophotometry [UV/VIS]).

2.1.7 Stability of drug substance

Table 3 shows main stability studies for the drug substance.

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

	Process for the drug substance	Number of batches	Storage condition	Period	Storage form
Long-term	Process E	3	-75 ± 10°C	36 months[a)]	High-density polyethylene container with polypropylene cap
	Process E	3			Polycarbonate container with polypropylene copolymer cap [redacted]
	Proposed commercial process	5		12 months[b)]	
Accelerated	Process E	3	5 ± 3°C	6 months	High-density polyethylene container with polypropylene cap
	Process E	3			Polycarbonate container with polypropylene copolymer cap [redacted]
	Proposed commercial process	3			
Photostability	Process E	1	Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m^2, 15°C		Polycarbonate container

a) The stability study is ongoing for up to [redacted] months.
b) The stability study is ongoing with [redacted] batches for up to [redacted] months and [redacted] batches for [redacted] months.

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

The photostability testing showed that the drug substance was photolabile.

On the basis of the above, a shelf life of 36 months has been proposed for the drug substance when stored in a high-density polyethylene container with polypropylene cap or a polycarbonate container with polypropylene copolymer cap [redacted] at −65°C to −85°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The vial product is an aqueous injection containing 300 mg of mirikizumab per glass vials (15 mL).

The syringe and autoinjector (AI) products are aqueous injection containing 100 mg of mirikizumab per syringes (1 mL). The syringe product is presented as a pre-filled syringe in which a glass syringe with a needle is filled with the drug solution, and the AI product is presented as a pre-filled pen in which a pen injector is attached to the same glass syringe filled with the drug solution. Both drug products are classified as combination products.

All the drug products contain sodium citrate hydrate, anhydrous citric acid, sodium chloride, polysorbate 80, and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process of the vial product consists of preparation of excipient buffer solutions, preparation of the drug solution, sterile filtration, filling/stoppering/closing, labeling/packaging, and testing.

The manufacturing process of the syringe and AI products consists of preparation of excipient buffer solutions, preparation of the drug solution, sterile filtration, filling/closing, assembling, labeling/packaging, and testing.

Critical steps include [redacted] and [redacted] for the vial, syringe, and AI products, [redacted] for the vial product, and [redacted] for the syringe and AI products.

The manufacturing process was validated on a commercial scale.

2.2.3 Manufacturing process development

During development of the drug product, a lyophilized form was changed to the commercial liquid form, and in association with this change, changes were made to [redacted], formulation, [redacted], and [redacted]. The drug product manufactured by the proposed commercial process was used in phase III studies. The comparability of quality attributes was evaluated for the process changes and comparability of the drug product before and after each change was confirmed.

2.2.4 Control of drug product

The proposed specifications for the drug product include the strength, description, identification (HPLC, IL-23-binding inhibition cell-based assay), purity (SE-HPLC and CE-SDS [ ]), charge heterogeneity (cIEF), foreign insoluble matters, insoluble particulate matters, bacterial endotoxins ( ), sterility, potency (IL-23-binding inhibition cell-based assay), and assay (UV/VIS).

2.2.5 Stability of drug product

Table 4 shows main stability studies for the drug product.

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

	Dosage form	Process for drug product[a)]	Number of batches	Storage condition	Period	Storage form
Long-term	Vial	Proposed commercial process	3	5 ± 3°C	24 months[b)]	Vial product: Glass vial with chlorobutyl rubber stopper Syringe product: Glass syringe with a stainless-steel needle and bromobutyl rubber plunger AI product: Syringe product with a pen injector attached
	Syringe		1			
	AI		2			
Accelerated	Vial		3	30°C/75%RH	6 months	
	Syringe		1	30°C/65%RH		
	AI		2			
Photostability[c)]	Vial		1	Overall illumination of ≥1.2 million lux·h, an integrated near ultraviolet energy of ≥200 W·h/m^2, 15°C		

a) The drug substance was manufactured by Process E.
b) The stability study is ongoing for up to months.
c) A photostability testing under a similar condition was conducted using 2 batches of the mg/mL syringe product in which the active ingredient concentration was different from that in the proposed product, and the results were comparable to those obtained from the vial product.

The long-term testing showed a decreasing trend of the monomer and an increasing trend of the aggregates measured by SE-HPLC, a decreasing trend of purity and an increasing trend of the cleavage form by CE-SDS ( ), and a decreasing trend of the main peak and an increasing trend of the variant by cIEF.

In the vial products, the accelerated testing showed a decreasing trend of the monomer measured by SE-HPLC, a decreasing trend of purity by CE-SDS ( ), a decreasing trend of purity and an increasing trend of the cleavage form by CE-SDS ( ), and a decrease of the main peak and an increase of the variant by cIEF. In the syringe and AI products, a decreasing trend of the monomer and an increasing trend of the aggregates measured by SE-HPLC, a decreasing trend of purity by CE-SDS ( ), a decreasing trend of purity and an increasing trend of the cleavage form by CE-SDS ( ), and a decrease of the main peak, an increase of the variant, an increasing trend of , and an increasing trend of by cIEF were observed.

The photostability testing showed that the drug product was photolabile.

On the basis of the above, a shelf life of 24 months has been proposed for the vial product, when stored at 2°C to 8°C in the primary container of a glass vial with a chlorobutyl rubber stopper, protected from light. In addition, a shelf life of 24 months has been proposed for the syringe and AI products, when stored at 2°C to 8°C in the primary container of a glass syringe with a stainless-steel needle and bromobutyl rubber plunger, protected from light.

2.3 Quality by design (QbD)

The quality control strategy has been established based on the following investigations:

- Identification of critical quality attributes (CQAs)

  Of the quality attributes including product-related impurities, process-related impurities, and product attributes, the following CQAs were identified based on the information obtained through the development of mirikizumab, related findings, etc.

  CQA: Potency, aggregates, cleavage form, [redacted], [redacted], host cell DNA, HCP, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], elemental impurity, microbiological safety, adventitious agents (viral safety), insoluble particulate matters, identification (identity), description (appearance), protein content, [redacted] content, pH, osmolality, and dose

- Process characterization

  Processes that might impact CQAs were identified, and in the identified processes, process control parameters that might significantly impact the CQAs and process performance were identified by means of risk assessment, etc. For the chosen parameters, acceptable ranges were confirmed.

- Establishment of control method

  On the basis of the process knowledge including the above process characterization, batch analysis results, stability study results, etc., control methods for the quality attributes of mirikizumab were established with process parameters, in-process control, and the specifications in combination [for control of product-related impurities and process-related impurities, see Sections 2.1.5.2 and 2.1.5.3].

2.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that the quality of the drug substance and the drug product is appropriately controlled.

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

In the primary pharmacodynamics study, binding to and neutralization of IL-23 were investigated. In the safety pharmacology study, effects on the central nervous, cardiovascular, and respiratory systems were investigated.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding of mirikizumab to IL-23 (CTD 4.2.1.1.1)

Binding of mirikizumab to human, cynomolgus monkey, mouse, rat, and rabbit IL-23 as well as human IL-12, IL-27, and IL-35 was investigated by surface plasmon resonance. The dissociation constant (K_D) of mirikizumab to human, cynomolgus monkey, and rabbit IL-23 was 21, 55, and 53,000 pmol/L, respectively. Mirikizumab did not bind to any of mouse and rat IL-23 as well as human IL-12, IL-27, and IL-35.

3.1.1.2 *In vitro* epitope mapping of mirikizumab (CTD 4.2.1.1.2 and 4.2.1.1.3)

The epitope of mirikizumab was investigated by hydrogen-deuterium exchange mass spectrometry and alanine scanning combined with yeast display. Of human IL-23 p19 subunit, 94P, 95S, 97L, 98P, 99D, 123W, 130S, 133P, and 137W were identified as amino acid residues critical to binding of mirikizumab.

3.1.1.3 Effects of mirikizumab on binding of human IL-23 to the receptor (CTD 4.2.1.1.4)

In IL-23 signal transduction, the receptor comprised of 2 subunits, interleukin-23 receptor (IL-23R) and interleukin-12 receptor β-1 (IL-12Rβ1), is involved. Effects of mirikizumab on binding of human IL-23 to the extracellular domain of human IL-23R or human IL-12Rβ1 were investigated by surface plasmon resonance. Mirikizumab inhibited binding of human IL-23 to human IL-23R but did not have any effect on binding of human IL-23 to human IL-12Rβ1.

3.1.1.4 Neutralization of mirikizumab against human and cynomolgus monkey IL-23 (CTD 4.2.1.1.5 and 4.2.1.1.6)

Neutralization of mirikizumab against IL-23 was investigated using an indicator of IL-17 produced in mouse splenocytes in response to stimulation of human IL-23 and human IL-2 or cynomolgus monkey IL-23 and human IL-2. Mirikizumab inhibited human and cynomolgus monkey IL-23 with half maximal inhibitory concentration (IC_{50}) values of 82 and 120 pmol/L, respectively.

Neutralization of mirikizumab against IL-23 was investigated using an indicator of IL-17 produced in human peripheral blood mononuclear cells in response to stimulation of anti-human cluster of differentiation (CD)3 antibody, anti-human CD28 antibody, and human IL-23. Mirikizumab inhibited human IL-23 with the IC_{50} value of 25 ng/mL (equivalent to 177 pmol/L).

3.1.1.5 Effects of mirikizumab on IL-12 signal transduction (CTD 4.2.1.1.7)

Effects of mirikizumab on IL-12 signal transduction were investigated using 2 human T-cell lines (KIT-225 and TALL-104) that expressed IL-23R, IL-12Rβ1, and interleukin-12 receptor β-2 (IL-12Rβ2) and would phosphorylate signal transducer and activator of transcription (STAT)4 in response to stimulation of IL-12. Cell line cultures incubated with mirikizumab in the presence or absence of human IL-23 were stimulated by human IL-12 and then checked for phosphorylated STAT4 protein by western blotting combined with sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE). Mirikizumab did not have any effect on STAT4-mediated IL-12 signal transduction.

3.1.1.6 Binding of mirikizumab to Fc receptor and complement (CTD 4.2.1.1.8)

Binding of mirikizumab to human Fcγ receptor I, IIa, and IIIa (CD64, CD32a, and CD16a, respectively) as well as complement component 1, q subcomponent (C1q) was investigated by *in vitro* binding assay. Binding of mirikizumab to CD64, CD32a, CD16a, and C1q was all comparable to its binding to the negative control antibody (human IgG4 antibody), suggesting that mirikizumab is unlikely to act biologically via the Fc receptor or complement.

3.1.2 *In vivo* studies

3.1.2.1 *In vivo* neutralization of mirikizumab against human IL-23 (CTD 4.2.1.1.9 and 4.2.1.1.10 [Reference data])

Splenocytes from mice repeatedly treated with human IL-23 (10 μg) and mouse IL-2 (3 μg) by intraperitoneal administration produce IL-17 *ex vivo* in response to stimulation of anti-CD3 antibody and anti-CD28 antibody. In this experimental system (4 mice/group), effects of mirikizumab or control antibody (human IgG4 antibody) 1.5 mg intraperitoneally administered were investigated. Mirikizumab inhibited mouse IL-17 production compared with the control antibody *ex vivo*.

A single dose of mirikizumab or control antibody (human IgG4 antibody) 0.54 mg was subcutaneously administered to mice (n = 10/group), and 2 days later human IL-23 (1 μg) was intradermally administered to induce psoriasis-like symptoms. In skin specimens collected 24 hours after intradermal administration of human IL-23, induced messenger ribonucleic acid (mRNA) expressions of IL-17A, IL-17F, and keratin-16 were observed. Mirikizumab inhibited these mRNA expressions compared with the control antibody.

3.1.2.3 Studies using murine surrogate antibody (CTD 4.2.1.1.11 to 4.2.1.1.14 [Reference data])

A surrogate antibody against mouse IL-23 p19 subunit was prepared for mirikizumab because mirikizumab does not bind to rodent IL-23 [see Section 3.1.1.1]. The mouse surrogate antibody bound to mouse IL-23 with K_D of 103 pmol/L and inhibited IL-17 production in mouse splenocytes with the IC_{50} value of 400 pmol/L.

The mouse surrogate antibody or control antibody (mouse IgG1 antibody) at 3 mg/kg was subcutaneously administered to mice (n = 6/group), and 48 hours later topical application of imiquimod 62.5 mg/day was started to induce skin inflammation. The mouse surrogate antibody inhibited induced mRNA expression of IL-17A, IL-17F, and IL-22 in the skin 48 and 96 hours after the start of the topical application of imiquimod compared with the control antibody.

Syngeneic naïve $CD4^+$ T cells were intraperitoneally transplanted to severe combined immunodeficient mice to induce intestinal inflammation. To mice in which survival of the T cells was confirmed 29 days after the transplant (n = 7-8/group), the mouse surrogate antibody at 1, 3, or 10 mg/kg or the control antibody (mouse IgG1 antibody) at 10 mg/kg was subcutaneously administered once weekly for 5 weeks. The mouse surrogate antibody at all doses tended to suppress a decrease in body weight compared with the control antibody, and the histological scores of the colon (combined score for mononuclear cell infiltration, epithelial hyperplasia, and decreased mucin) at the doses of 1 and 3 mg/kg were improved.

3.2 Safety pharmacology

Effects of mirikizumab on the central nervous, cardiovascular, and respiratory systems were evaluated in repeated-dose toxicity studies [see Section 5.2] (Table 5).

Table 5. Outline of safety pharmacology study results

Item	Study system	Evaluation item and method	Dose (mg/kg) (route of administration)	Administration method	Findings	Attached document CTD
Central nervous system Cardiovascular system Respiratory system	Cynomolgus monkey (3 or 5/sex/group)	Body temperature, neurological examination, electrocardiogram, respiratory assessment (depth), respiratory rate	1, 30 (SC) 100 (IV)	Once weekly 4 weeks	No effects	4.2.3.2.1
Cardiovascular system	Cynomolgus monkey (4/sex/group)	Electrocardiogram	10, 100 (SC)	Once weekly 6 months	No effects	4.2.3.2.2
	Cynomolgus monkey (4/sex/group)	Electrocardiogram	100, 300 (IV)	Twice weekly 6 months	No effects	4.2.3.2.3

3.R Outline of the review conducted by PMDA

The applicant's explanation about the pharmacological action of mirikizumab:

In animal models, knockout of IL-23 p19 subunit gene or inhibition of the concerned subunit was suggested to alleviate or prevent intestinal inflammation (*J Clin Invest.* 2006;116:1310-6, *Gastroenterology.* 2007;132:2359-70).

The primary pharmacodynamics studies showed that mirikizumab, IgG4 monoclonal antibody against human IL-23 p19 subunit, binds to and thereby neutralizes human IL-23 [see Section 3.1.1]. In addition, the mouse surrogate antibody has been shown to alleviate the condition in the murine inflammatory bowel disease model [see Section 3.1.2.3].

On the basis of the above results, mirikizumab is expected to be effective in the treatment of UC.

In view of the submitted study results on the primary pharmacodynamics, PMDA considers that mirikizumab is expected to be effective in the treatment of UC. In addition, mirikizumab is considered unlikely to affect the central nervous, cardiovascular, and respiratory systems in view of the submitted study results on the safety pharmacology.

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

The pharmacokinetics of mirikizumab intravenously or subcutaneously administered to monkeys was investigated. Serum concentrations of mirikizumab were determined by enzyme-linked immunosorbent assay (ELISA), and the lower limit of quantification was 200 ng/mL. Amounts of anti-drug antibody (ADA) were determined by an affinity capture and elution (ACE) method.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.2)

Table 6 shows pharmacokinetic parameters of serum mirikizumab in male monkeys after administration of a single intravenous or subcutaneous dose of mirikizumab.

Table 6. Pharmacokinetic parameters of serum mirikizumab in monkeys after single administration

Route of administration	Dose of mirikizumab (mg/kg)	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}inf}$ (μg·h/mL)	$t_{1/2}$ (day)[a)]	Bioavailability (%)[b)]
IV	5	3	150 ± 3	—	6,520 ± 1,366	5 ± 0.6	—
SC	5	3	28 ± 3	20 ± 7	2,776 ± 193	3 ± 0.7	43 ± 3

Mean ± standard deviation (SD); —, Not applicable

a) Calculated from data up to 672 hours post-dose.

b) ($AUC_{0\text{-}inf}$ after subcutaneous administration of mirikizumab/subcutaneous dose) / ($AUC_{0\text{-}inf}$ after intravenous administration of mirikizumab/intravenous dose) × 100

4.1.2 Repeated-dose studies

4.1.2.1 Repeated subcutaneous dose study (CTD 4.2.3.2.2)

The toxicokinetics of mirikizumab was investigated in male and female monkeys after administration of repeated subcutaneous dose of mirikizumab once weekly for 6 months in a toxicity study. Table 7 shows pharmacokinetic parameters of serum mirikizumab. C_{max} and $AUC_{0\text{-}168h}$ values mostly increased with an increasing dose of mirikizumab without clear sex differences. Repeated doses were unlikely to cause definite accumulation. In this study, amounts of ADA have not been determined.

Table 7. Pharmacokinetic parameters of serum mirikizumab in monkeys after repeated subcutaneous administration

Dose of mirikizumab (mg/kg)	Sex	n	Sampling point (Day)	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}168h}$ (μg·h/mL)	$t_{1/2}$ (h)[a)]
10	Male	4	1	36 ± 12	16.0 ± 9.2	2,420 ± 733	34.6 ± 7.0
		2	176	23[b)]	24.0[b)]	1,580[b)]	30.6[c)]
	Female	4	1	39 ± 9	16.0 ± 9.2	2,310 ± 632	30.8 ± 7.2
		4	176	44 ± 10	16.0 ± 9.2	2,990 ± 744	32.7 ± 4.2
100	Male	4	1	329 ± 96	24.0 ± 0.0	21,900 ± 1,300	45.3 ± 12.1
		4	176	417 ± 252	36.0 ± 24.0	25,000 ± 11,500	31.5 ± 10.6
	Female	4	1	288 ± 103	20.0 ± 8.0	16,300 ± 6,590	32.6 ± 5.3
		3	176	287 ± 216	24.0 ± 0.0	17,900 ± 15,200	31.6[b)]

Mean ± SD

a) Calculated from data up to 168 hours post-dose.

b) Mean in 2 animals

c) Individual value in 1 animal

4.1.2.2 Repeated intravenous dose study (CTD 4.2.3.2.3)

The toxicokinetics of mirikizumab was investigated in male and female monkeys after administration of repeated intravenous dose of mirikizumab twice weekly for 6 months in a toxicity study. Table 8 shows pharmacokinetic parameters of serum mirikizumab. C_{max} and $AUC_{0\text{-}96h}$ values mostly increased with an increasing dose of mirikizumab without clear sex differences. Repeated doses were unlikely to cause definite accumulation. Of 16 animals tested, 7 animals were positive for ADA.

Table 8. Pharmacokinetic parameters of serum mirikizumab in monkeys after repeated intravenous administration

Dose of mirikizumab (mg/kg)	Sex	n	Sampling point (Day)	C_{max} (μg/mL)	$AUC_{0\text{-}96h}$ (μg·h/mL)	$t_{1/2}$ (h)[a)]
100	Male	4	1	2,810 ± 515	55,000 ± 4,500	14.9 ± 2.0
		4	176	2,400 ± 563	60,600 ± 4,330	18.9 ± 2.8
	Female	4	1	2,990 ± 491	48,900 ± 7,930	15.8 ± 3.5
		4	176	2,110 ± 406	49,400 ± 21,100	15.2 ± 7.3
300	Male	4	1	6,610 ± 1,450	139,000 ± 9,610	13.0 ± 1.5
		4	176	7,580 ± 585	198,000 ± 12,900	16.6 ± 4.0
	Female	4	1	6,470 ± 843	126,000 ± 21,500	12.2 ± 0.5
		4	176	8,510 ± 2,460	175,000 ± 24,300	15.0 ± 2.2

Mean ± SD
a) Calculated from data up to 96 hours post-dose.

4.2 Distribution

In view of the following points, no non-clinical pharmacokinetic studies for distribution of mirikizumab were conducted.

- Mirikizumab is a humanized IgG4 monoclonal antibody, and its non-antigen-specific distribution was considered similar to that of endogenous IgG4.
- A tissue cross-reactivity study [see Section 5.7.1] showed that mirikizumab did not bind to normal monkey or human tissues, and administered mirikizumab was considered to bind to soluble IL-23 specifically.
- In light of the distribution volume of mirikizumab in humans [see Section 6.2.4], it was considered unlikely to be distributed in tissues.

Placental transfer of mirikizumab has not been studied, but mirikizumab was detected in monkey offspring in a reproductive and developmental toxicity study [see Section 5.5], suggesting that mirikizumab would be transferred into the placenta.

4.3 Metabolism and excretion

Mirikizumab is a humanized IgG4 monoclonal antibody and considered to be degraded into peptides and amino acids and then eliminated after intravenously or subcutaneously administered. No non-clinical pharmacokinetic studies for the metabolism and excretion were conducted.

Excretion of mirikizumab into milk has not been studied, but IgG antibody is transferred into human milk (*J Hum Lact.* 2005;21:439-43), and thus mirikizumab, an IgG antibody, may be excreted into milk.

4.R Outline of the review conducted by PMDA

PMDA has considered that the non-clinical pharmacokinetics of mirikizumab raise no particular problems.

5. Toxicity and Outline of the Review Conducted by PMDA

Toxicity studies conducted for mirikizumab include repeated-dose toxicity, reproductive and developmental toxicity, and other toxicity studies (tissue cross-reactivity study). Unless otherwise specified, a solution containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.02% polysorbate 80 (pH 6.0) was used as vehicle.

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted. Acute toxicity of mirikizumab was evaluated using results after the first dose in 6-month repeated-dose toxicity studies in monkeys (Table 9).

Table 9. Outline of results after the first dose in repeated-dose toxicity studies

Test system	Route of administration	Dose (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	SC	0, 10, 100	No special findings	>100	4.2.3.2.2
Male and female cynomolgus monkeys	IV	0,[a)] 100, 300	No special findings	>300	4.2.3.2.3

a) Solution containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.03% polysorbate 80 (pH 5.5)

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies in monkeys were conducted for up to 6 months (Table 10). Although a hemolytic change attributable to mirikizumab was observed, the concerned finding is a change via an immune reaction that sporadically occurs with biopharmaceuticals (*Toxicol Pathol.* 2013;41:280-302) and is considered to be poorly extrapolated to humans.

In the 6-month repeated intravenous dose study in monkeys, no observed adverse effect level (NOAEL) was determined to be 100 mg/kg (twice weekly). $AUC_{0\text{-}96h}$ of mirikizumab at the NOAEL was 55,000 μg·h/mL, which was approximately 30 and 100 times the dosing-interval corrected[1)] AUC after induction dosing and maintenance dosing in patients with UC, respectively. In the induction period, mirikizumab 300 mg, clinical dose, was intravenously administered once every 4 weeks (Q4W), and AUC was 538 μg·day/mL.[2)] In the maintenance period, mirikizumab 200 mg, clinical dose, was subcutaneously administered Q4W, and AUC was 160 μg·day/mL.[2)]

1) Exposure ratios were calculated using quotients of AUC divided by the dosing interval (96 hours in monkeys and 28 days in humans).
2) $AUC_{tau,\ ss}$ estimated from the population pharmacokinetic analysis [see Section 6.2.4]

Table 10. Outline of repeated-dose toxicity study results

Test system	Route of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached document CTD
Male and female cynomolgus monkeys	SC	4 weeks (once weekly) + 8-week washout	0, 1, 30	≥1: Perivascular eosinophil and mononuclear cell infiltration in subcutaneous tissue of the injection site	30[a)]	4.2.3.2.1
	IV		100	No special findings	100	
Male and female cynomolgus monkeys	SC	6 months (once weekly)	0, 10, 100	≥10: Perivascular eosinophil and mononuclear cell infiltration in subcutaneous tissue of the injection site	100[b)]	4.2.3.2.2
Male and female cynomolgus monkeys	IV	6 months (twice weekly)	0,[c)] 100, 300	300: Low erythrocyte count, hemoglobin value, and hematocrit value (female); increased reticulocyte count (female); mild hemagglutination and morphological changes (anisocytosis, microcyte, polychromatic cells) (female); high blood glucose (male) and cholesterol value; high bilirubin value (female); high spleen weight (female); slightly increased erythroid cell count in the bone marrow (female); extramedullary hematopoiesis in the inguinal lymph node (female); erythrophagocytosis and hemosiderosis in the spleen; and hemosiderin pigmentation in Kupffer cells in the liver (female)	100	4.2.3.2.3

a) The perivascular eosinophil and mononuclear cell infiltration in subcutaneous tissue of the injection site is considered to have little toxicological significance because its severity was not dependent on the dose and was slight. No groups for reversibility evaluation of the concerned finding were included.
b) The perivascular eosinophil and mononuclear cell infiltration in subcutaneous tissue of the injection site is considered to have little toxicological significance because its severity was slight to mild.
c) Solution containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.03% polysorbate 80 (pH 5.5)

5.3 Genotoxicity

Mirikizumab is a monoclonal antibody that does not pass through the nuclear membrane or directly interact with intracellular DNA or other chromosomes, and thus no genotoxicity study was conducted.

5.4 Carcinogenicity

Carcinogenicity study in rodents has not been conducted because mirikizumab does not bind to mouse or rat IL-23.

The applicant's explanation that IL-23-inhibiting effect of mirikizumab is unlikely to pose a carcinogenetic risk, in view of the following points:

- IL-23 p19-deficient mice are known to show the decreased incidence of chemically induced tumorigenesis (*Nature.* 2006;442:461-5). IL-23 is suggested to promote tumor growth and progression by activating local inflammation within the tumor microenvironment, suppressing the immune surveillance system, elevating expression of angiogenic growth factors, and enhancing tumor infiltration and metastasis. IL-23-inhibiting effect of mirikizumab is therefore expected to act toward the reduced carcinogenetic risk.
- Mirikizumab does not bind to cytokines other than IL-23 or cross-react with non-target tissues [see Sections 3.1.1.1 and 5.7.1], and the repeated-dose toxicity studies in monkeys did not present any finding suggestive of off-target effect of mirikizumab.

- The repeated-dose toxicity studies of mirikizumab in monkeys did not present any finding suggestive of enhanced cell growth or any effect on the immune system.
- Clinical study results of mirikizumab and the other IL-23 inhibitors (tildrakizumab [genetical recombination], risankizumab [genetical recombination], guselkumab [genetical recombination], and ustekinumab [genetical recombination]) showed that the incidence of malignant tumor was not higher in patients treated with mirikizumab than in those treated with the drugs in the same class.

5.5 Reproductive and developmental toxicity

An enhanced pre- and postnatal developmental toxicity, including maternal function study in cynomolgus monkeys was conducted (Table 11). Neither embryos nor fetuses were affected, and the NOAEL for embryo-fetal development was 300 mg/kg (twice weekly). $AUC_{0\text{-}96h}$ of mirikizumab at the NOAEL was 127,000 μg·h/mL, which was approximately 69 and 232 times the dosing-interval corrected[1)] AUC after induction dosing and maintenance dosing in patients with UC, respectively. In the induction period, mirikizumab 300 mg, clinical dose, was intravenously administered Q4W, and AUC was 538 μg·day/mL.[2)] In the maintenance period, mirikizumab 200 mg, clinical dose, was subcutaneously administered Q4W, and AUC was 160 μg·day/mL.[2)]

The applicant's explanation:
In view of the above results, placental transfer of mirikizumab [see Section 4.2], and excretion into milk [see Section 4.3], the following statements will be provided to raise caution: Mirikizumab should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the potential risks associated with treatment; and the continuation or discontinuation of breastfeeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding.

Table 11. Outline of reproductive and developmental toxicity study results

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg)	Main findings	NOAEL (mg/kg)	Attached document CTD
Effect on pre- and postnatal development, including maternal function	Female cynomolgus monkey	IV	Maternal animal: Gestation Day 21 to delivery (twice weekly)	0,[a)] 300	Maternal animal: No special findings F1 offspring: No special findings	Maternal animal (general toxicity) : 300 Development of F1 offspring : 300	4.2.3.5.3.1

a) Solution containing 10 mmol/L sodium citrate, 150 mmol/L sodium chloride, and 0.03% polysorbate 80 (pH 5.5)

5.6 Local tolerance

In a part of the repeated-dose toxicity study in cynomolgus monkeys, local tolerance to mirikizumab subcutaneously and intravenously administered was evaluated. Mirikizumab is considered to cause no local irritation when subcutaneously or intravenously administered.

5.7 Other toxicity studies

5.7.1 Tissue cross-reactivity study

A tissue cross-reactivity study was conducted using normal tissue panels of humans and cynomolgus monkeys. No specifically stained images were found in tissues of humans or cynomolgus monkeys (CTD 4.2.3.7.7.1).

5.R Outline of the review conducted by PMDA

On the basis of the submitted data, PMDA has concluded that no particular concerns are raised for clinical use of mirikizumab from a toxicological viewpoint. In addition, the applicant's explanation about their plan to include the following statements in the package insert of mirikizumab to raise caution [see Section 5.5] has no particular problems: Mirikizumab should be used in pregnant women or in women who may possibly be pregnant only if the expected therapeutic benefits outweigh the potential risks associated with treatment; and the continuation or discontinuation of breastfeeding should be considered while taking account of the expected therapeutic benefits and the benefits of maternal feeding.

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

6.1 Summary of biopharmaceutic studies and associated analytical methods

In global phase III studies (Studies I6T-MC-AMAN [Study AMAN], I6T-MC-AMBG [Study AMBG], and I6T-MC-AMAP [Study AMAP]), the vial product (300 mg/15 mL, intravenous), syringe product (100 mg/mL, subcutaneous), and AI product (100 mg/mL, subcutaneous), all of which were in a liquid form as with the proposed products, were used. In a foreign phase I study (Study I6T-JE-AMAD [Study AMAD]) and a global phase II study (Study I6T-MC-AMAC [Study AMAC]), a 75 mg vial (intravenous and subcutaneous) in a lyophilized form of mirikizumab was used.

Serum concentrations of mirikizumab in humans were determined by ELISA, and the lower limit of quantification was 100 ng/mL. Amounts of ADA and the neutralizing antibodies were determined by up-front acid treatment (UFAT) ACE bridging assay, which used UFAT and ACE in combination.

6.2 Clinical pharmacology

6.2.1 Phase I study in healthy adults (CTD 5.3.3.1.1, Study I6T-JE-AMAD, November 2015 to [redacted] 2018)

A placebo-controlled, randomized, double-blind study was conducted at a single study site outside Japan to investigate the pharmacokinetics and safety of mirikizumab in Japanese and non-Japanese healthy adults (target sample size, 60 subjects) after a single intravenous or subcutaneous administration.

For intravenous administration, a single dose of placebo or mirikizumab 60, 200, 600, 1,200, or 2,400 mg was administered. For subcutaneous administration, a single dose of placebo or mirikizumab 200 mg was administered.

All of 51 subjects who received the study drug (10 in the placebo intravenous [IV] group, 2 in the placebo subcutaneous [SC] group, 6 in the mirikizumab 60 mg IV group, 6 in the 200 mg IV group, 9 in the 600 mg IV group, 6 in the 1,200 mg IV group, 6 in the 2,400 mg IV group, 6 in the 200 mg SC

group) were included in the safety analysis. In addition, 38 subjects deemed to be evaluable for pharmacokinetics were included in the pharmacokinetic analysis.

Table 12 shows pharmacokinetic parameters of mirikizumab after a single intravenous or subcutaneous administration of mirikizumab. C_{max} and $AUC_{0\text{-}inf}$ of mirikizumab increased proportionally with the dose administered. The bioavailability of mirikizumab subcutaneously administered was 40%.

Table 12. Pharmacokinetic parameters of mirikizumab after a single-dose administration (pharmacokinetic analysis population)

	Route of administration	Dose of mirikizumab (mg)	n	C_{max} (μg/mL)	t_{max}[a] (h)	$t_{1/2}$ (day)	$AUC_{0\text{-}inf}$ (μg•day/mL)	CL (mL/day)
Overall population	IV	60	6	23.1 (9)	1.3 (0.5-6.0)	10.4 (27)	148 (29)	404 (29)
		200	6	78.8 (13)	0.6 (0.5-2.0)	10.0 (17)	539 (12)	371 (12)
		600	8	250 (16)	0.5 (0.5-2.1)	11.2 (17)	1,970 (24)	305 (24)
		1,200	6	454 (11)	1.8 (1.5-2.1)	11.0 (15)	2,900 (14)	414 (14)
		2,400	6	985 (20)	2.0 (1.5-2.0)	10.6 (16)	5,990 (12)	401 (12)
	SC	200	6	11.8 (39)	72.0 (72.0-168.0)	10.8 (13)	210 (29)	951 (29)[b]
Japanese population	IV	60	3	23.1 (14)	2.1 (0.5-6.0)	11.0 (36)	147 (32)	409 (32)
		200	3	79.3 (15)	0.7 (0.5-2.0)	9.0 (9)	542 (13)	369 (13)
		600	5	248 (16)	0.5 (0.5-2.0)	11.1 (20)	2,070 (14)	290 (14)
		1,200	3	475 (3)	1.5 (1.5-1.5)	11.9 (11)	3,080 (6)	389 (6)
		2,400	3	996 (19)	2.0 (1.5-2.0)	10.9 (12)	6,060 (13)	396 (13)
	SC	200	3	11.3 (62)	72.0 (72.0-168.0)	10.2 (8)	217 (47)	922 (47)[b]

Geometric mean (coefficient of variation [CV], %)
a) Median (Minimum – Maximum)
b) CL/F

ADA was detected in 33.3% (13 of 39) of subjects who received mirikizumab, 55.0% (11 of 20) of Japanese subjects, and 10.5% (2 of 19) of non-Japanese subjects.

In the safety analysis population, adverse events occurred in 5 of 10 subjects in the placebo IV group, 2 of 2 in the placebo SC group, 3 of 6 in the mirikizumab 60 mg IV group, 2 of 6 in the 200 mg IV group, 1 of 9 in the 600 mg IV group, 1 of 6 in the 2,400 mg IV group, and 1 of 6 in the 200 mg SC group. There were no adverse drug reactions, deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2.2 Global phase III induction period study (CTD 5.3.5.1.2, Study I6T-MC-AMAN, June 2018 to January 2021)

Serum mirikizumab concentrations in patients with UC who intravenously received mirikizumab were determined.

Placebo or mirikizumab 300 mg was intravenously administered at Weeks 0, 4, and 8. For an outline of the study and results on the efficacy and safety, see Section 7.2.1.

For the pharmacokinetics, C_{trough} at Weeks 4, 8, and 12 are as shown in Table 13, and the repeated doses did not cause definite accumulation.

Table 13. C_{trough} (μg/mL) after intravenous administration of mirikizumab during the induction period

Dose of mirikizumab	Week	4	8	12
300 mg	n	930	891	836
	C_{trough}	2.30 (148)	2.69 (132)	3.08 (128)

Geometric mean (CV, %)

6.2.3 Global phase III maintenance period study (CTD 5.3.5.1.3, Study I6T-MC-AMBG, October 2018 to November 2021)

Serum mirikizumab concentrations in patients with UC who received mirikizumab were determined.

Patients who had received mirikizumab and met the criteria for clinical improvement in Study AMAN subcutaneously received placebo or mirikizumab 200 mg Q4W in Study AMBG.[3)] While, patients who had failed to meet the criteria for clinical improvement in Study AMAN intravenously received mirikizumab 300 mg for continued induction at Weeks 0, 4, and 8 in Study AMBG, and patients who later achieved meeting the criteria for clinical improvement switched the treatment to subcutaneous administration of mirikizumab 200 mg Q4W. For an outline of the study and results on the efficacy and safety, see Section 7.2.2.

For the pharmacokinetics, C_{trough} at Weeks 0, 4, 12, 24, and 40 are as shown in Table 14, and the repeated doses were unlikely to cause definite accumulation.

Table 14. C_{trough} (μg/mL) after subcutaneous or intravenous administration of mirikizumab[a)]

Route of administration	Dose of mirikizumab	Week[b)]	0	4	12	24	40
SC	200 mg	n	354	352	333	530	464
		C_{trough}	3.7 (110)	1.9 (101)	2.0 (99.7)	2.0 (102)	2.1 (103)
IV	300 mg	n	284	432	327	—	—
		C_{trough}	2.1 (141)	2.2 (136)	2.6 (127)	—	—

Geometric mean (CV, %); —, Not measured

a) This table does not include data on patients who experienced a reduced response to subcutaneous administration of mirikizumab and resumed the induction therapy with intravenous administration of mirikizumab.

b) Number of weeks counted from the start of treatment (Week 0) in Study AMBG

6.2.4 Population pharmacokinetic analysis (CTD 5.3.3.5.1)

A population pharmacokinetic analysis was performed on the pharmacokinetic data of mirikizumab (1,129 patients, 7,578 sampling points) obtained in global phase III studies in patients with UC (Studies AMAN and AMBG [see Sections 7.2.1 and 7.2.2]). For the analysis, a population pharmacokinetic model was constructed from the pharmacokinetic data of mirikizumab (233 patients, 4,103 sampling points) obtained in the phase II study (Study AMAC [see Section 7.1.1]) and then updated with the data from the phase III studies, and the updated model was used (software, NONMEM Version 7.4.2).

The pharmacokinetics of mirikizumab in patients with UC was described as a 2-compartment model with first-order absorption. An analysis on potential covariates[4)] identified covariates of body weight and albumin for CL of mirikizumab, body weight for the distribution volume, and body mass index (BMI) for the bioavailability. The pharmacokinetic parameters of mirikizumab in patients with UC were

3) Patients who had received placebo and achieved clinical improvement in Study AMAN received placebo.

4) The potential covariates analyzed were age, sex, race, body weight, BMI, prior treatment with biological products, history of smoking, creatinine clearance, serum albumin value, C-reactive protein (CRP) value, bilirubin value, fecal calprotectin value, duration of UC, subcutaneous injection site, baseline Modified Mayo score, baseline defecation frequency subscore, baseline rectal bleeding subscore, baseline endoscopic subscore, use of concomitant therapy (corticosteroids, immunosuppressive drugs, and 5-ASA), and ADA.

estimated to be 0.0229 L/h for CL, 3.10 L for distribution volumes of the central compartments, 1.65 L for distribution volumes of the peripheral compartments, 4.83 L for the total distribution volume at steady state, and 9.33 days for $t_{1/2}$.

6.2.5 Exposure-response analysis (CTD 5.3.5.1.1)

An exposure-response relationship was examined using data on the efficacy and serum mirikizumab concentrations obtained in Study AMAC in patients with UC.

For an exposure-response relationship during the induction period, Figure 1 shows a relationship of serum mirikizumab concentrations to results on the efficacy endpoint (modified Mayo score) at Week 12 in Study AMAC in patients with UC, suggesting that intravenous administration of mirikizumab ≥300 mg Q4W would mostly level off the modified Mayo score, regardless of the prior treatment with biological products.

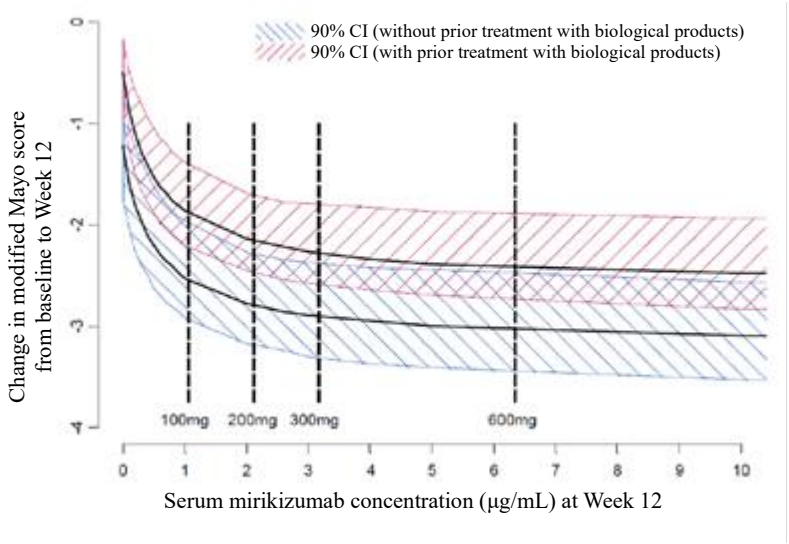


Figure 1. Exposure-response relationship for the efficacy of mirikizumab at Week 12 in patients with UC

6.R Outline of the review conducted by PMDA

6.R.1 Differences in pharmacokinetics of mirikizumab between Japanese and non-Japanese patients with UC

The applicant's explanation about differences in pharmacokinetics of mirikizumab between Japanese and non-Japanese patients with UC:

Table 15 shows estimated pharmacokinetic parameters of mirikizumab based on the population pharmacokinetic analysis [see Section 6.2.4]. When patients with UC subcutaneously received mirikizumab 200 mg Q4W or intravenously received mirikizumab 300 mg Q4W, the exposure in the Japanese patients tended to be slightly higher than that in the non-Japanese patients. The concerned difference was potentially attributable to a difference in physique between Japanese and non-Japanese patients (mean body weight, 64.1 kg for Japanese patients, 73.6 kg for non-Japanese patients), but the difference in exposure attributable to differences in body weight and BMI was considered negligible compared with inter-individual variability (coefficient of variation [CV%] of AUC; 34% for intravenous administration, 58% for subcutaneous administration). The analysis on potential covariates excluded the ethnic difference from the pharmacokinetic covariates [see Section 6.2.4].

As described above, the difference in exposure between Japanese and non-Japanese patients with UC is considered to have no remarkable effect clinically.

Table 15. (Estimated) pharmacokinetic parameters after subcutaneous or intravenous administration of mirikizumab

Race	Route of administration	Dose of mirikizumab	n	$C_{max, ss}$ (μg/mL)	t_{max}[a)] (day)	$AUC_{tau, ss}$ (μg·day/mL)	C_{trough} (μg/mL)
Japanese	SC	200 mg	121	12.4 (36)	5.2 (4.1-5.9)	205 (43)	2.5 (70)
	IV	300 mg	121	110 (14)	—	664 (31)	4.2 (95)
Non-Japanese	SC	200 mg	1,008	10.1 (42)	5.0 (3.3-6.4)	158 (49)	1.7 (81)
	IV	300 mg	1,008	98.9 (19)	—	529 (33)	2.6 (115)

Geometric mean (CV, %); —, Not applicable
a) Median (Minimum – Maximum)

PMDA accepted the applicant's explanation.

6.R.2 Immunogenicity

The applicant's explanation about incidence of ADA and an effect of ADA on pharmacokinetics of mirikizumab:

In the phase III studies in patients with UC (extending over 52 weeks from Study AMAN through Study AMBG), mirikizumab was administered as proposed (the induction period comprised of 3 intravenous doses of 300 mg Q4W followed by the maintenance period comprised of subcutaneous doses of 200 mg Q4W, starting at Week 12), an analysis was performed in a population of patients available for ADA test (UC Treatment Regimen Pooled Analysis Population). Table 16 shows incidences of ADA, suggesting that the incidence of ADA was higher in the Japanese population than in the overall population.

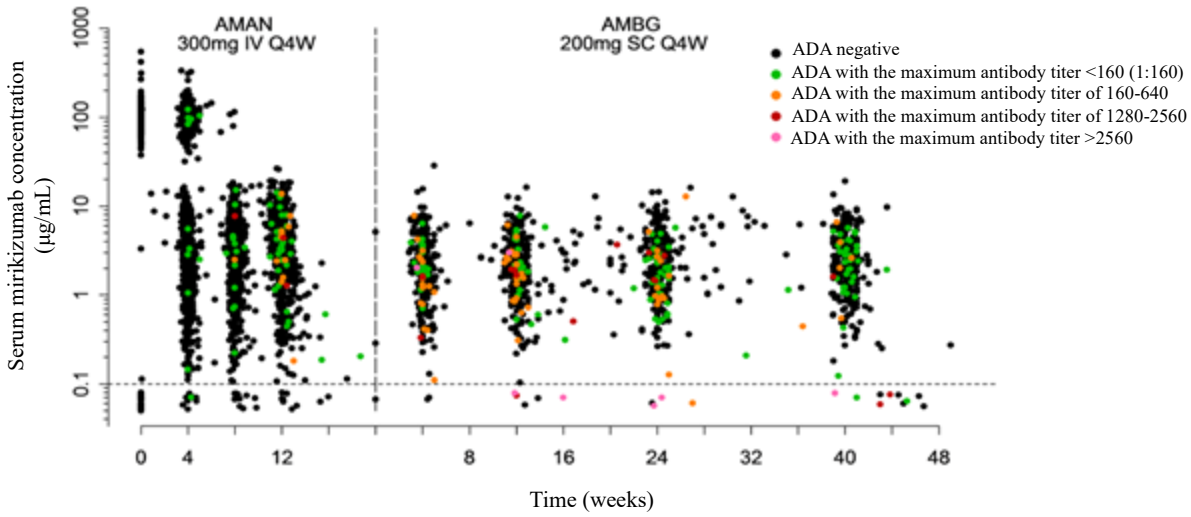
Table 16. Incidence of ADA

	Overall population[a)] (n = 378)	Japanese population (n = 47)
ADA positive	88 (23.3)	25 (53.2)
ADA positive and neutralizing antibody positive	82 (21.7)	23 (48.9)
ADA positive and neutralizing antibody negative	6 (1.6)	2 (4.3)
ADA negative	290 (76.7)	22 (46.8)

Number of patients (%)
a) Excluding Chinese patients in whom ADA was measured by a different method.

Figure 2 shows changes in serum mirikizumab concentration by ADA titer. Serum mirikizumab concentrations in most patients positive for ADA were similar to those in patients negative for ADA, but serum mirikizumab concentrations in a part of patients positive for ADA with the maximum antibody titer ≥160 (1:160) tended to decrease. In addition, based on the profiles of changes in serum mirikizumab concentration and ADA to Week 52 (covering the induction and maintenance periods), of 32 patients positive for ADA with the maximum antibody titer ≥160 (1:160), 10 patients were determined to present serum mirikizumab concentrations decreased by ADA.[5)]

[5)] Patients who met all of the following conditions were determined to present serum mirikizumab concentrations decreased by ADA: (a) ADA with the maximum antibody titer ≥160 (1:160); (b) the mirikizumab concentration was decreased below the cut-off value (0.511 μg/mL) during the maintenance period (the cut-off value was specified from 5 percentile of C_{trough} at Weeks 4, 12, 24, and 40 in patients negative for ADA who subcutaneously received mirikizumab 200 mg Q4W in Study AMBG); and (c) serum mirikizumab concentrations changed after development of ADA.



A horizontal broken line denotes the lower limit of quantification (100 ng/mL).

Figure 2. Relationship between serum mirikizumab concentrations and maximum antibody titers after administration of mirikizumab

The population pharmacokinetic analysis [see Section 6.2.4], on the other hand, excluded the ADA from the pharmacokinetic covariates. In addition, no difference was observed in the estimated CL value of mirikizumab between patients positive for ADA and patients negative or among groups by ADA titer.

A decreasing trend of exposure to mirikizumab associated with development of ADA was limited to a part of patients with high ADA titer in both Japanese and overall populations, and an effect of immunogenicity on exposure in patients with UC is therefore considered to be very limited.

PMDA's view:
Although a decreasing trend of exposure was observed in some patients with high ADA titer, the number of the applicable patients was limited, and the currently available data are considered insufficient to deliver conclusion on the effect of ADA on pharmacokinetics of mirikizumab. Effects of ADA on the efficacy and safety of mirikizumab are discussed in Section 7.R.3.

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

The applicant submitted efficacy and safety evaluation data, in the form of results from 1 global phase II study and 3 global phase III studies including Japanese patients with UC (Table 17).

Table 17. Outline of efficacy and safety evaluation data

Region	Phase	Study	Study population	Group, numbers of patients	Dosage regimen	Primary efficacy endpoint
Global	II	AMAC	Patients with moderate to severe UC	Induction period (double-blind) Placebo: 63 (8 Japanese patients) Mirikizumab 50 mg IV: 63 (5 Japanese patients) Mirikizumab 200 mg IV: 62 (13 Japanese patients) Mirikizumab 600 mg IV: 61 (5 Japanese patients)	3 IV doses of placebo or mirikizumab 50, 200, or 600 mg Q4W[a)]	Proportion of patients in clinical remission at Week 12 of the induction period
				Open-label extended induction period Patients who failed to meet the criteria for clinical improvement at Week 12 of the induction period Mirikizumab 600 mg IV: 32 (3 Japanese patients) Mirikizumab 1,000 mg IV: 96 (18 Japanese patients)	3 IV doses of mirikizumab 600 or 1,000 mg Q4W[b)]	—
				Maintenance period (double-blind) Patients who met the criteria for clinical improvement at Week 12 of the induction period Placebo: 13 (no Japanese patient) Mirikizumab SC Q4W: 47 (4 Japanese patients) Mirikizumab SC Q12W: 46 (6 Japanese patients)	SC doses of placebo or mirikizumab 200 mg Q4W or mirikizumab 200 mg Q12W	—
				Open-label maintenance period Patients who met the criteria for clinical improvement at Week 12 of the open-label extended induction period: 68 (9 Japanese patients)	SC doses of mirikizumab 200 mg Q4W	—
	III	AMAN	Patients with moderate to severe UC	Induction period (double-blind) Placebo: 322 (35 Japanese patients) Mirikizumab IV: 959 (102 Japanese patients)	3 IV doses of placebo or mirikizumab 300 mg Q4W	Proportion of patients in clinical remission at Week 12 of the induction period
	III	AMBG	Patients who completed Study AMAN	Maintenance period (double-blind) Mirikizumab induction responder population (patients who met the criteria for clinical improvement in the mirikizumab IV group in Study AMAN) Placebo: 179 (25 Japanese patients) Mirikizumab SC: 365 (47 Japanese patients)	SC doses of placebo or mirikizumab 200 mg Q4W[c)]	Proportion of patients in clinical remission at Week 40 of the maintenance period
				Placebo induction responder population (patients who met the criteria for clinical improvement in the placebo group in Study AMAN) : 124 (8 Japanese patients)	SC doses of placebo Q4W[c)]	—
				Open-label extended induction period Patients who failed to meet the criteria for clinical improvement at Week 12 of the induction period in Study AMAN: 405 (43 Japanese patients)	3 IV doses of mirikizumab 300 mg Q4W	—
				Open-label maintenance period Patients who met the criteria for clinical improvement at Week 12 of the open-label extended induction period: 230 (22 Japanese patients)	SC doses of mirikizumab 200 mg Q4W	—
	III	AMAP[d)]	Patients who completed Studies AMAC and AMBG	Patients transferred from Study AMAC: 141 Patients transferred from Study AMBG: 751 Patients transferred from Study AMAN: 7[e)]	SC doses of mirikizumab 200 mg Q4W	—

AMAC, I6T-MC-AMAC; AMAN, I6T-MC-AMAN; AMBG, I6T-MC-AMBG; AMAP, I6T-MC-AMAP

a) For the second and third doses in the mirikizumab 50 mg IV and mirikizumab 200 mg IV groups, the dose was increased when the estimated trough concentration was below the threshold.

b) At the start of the study, administration of mirikizumab 600 mg was planned, but the safety data at doses up to 1,200 mg were obtained in Study AMAD [see Section 6.2.1], and the study protocol was revised (dated October 4, 2016) to implement administration of mirikizumab 1,000 mg thereafter.

c) After experiencing a reduced response where applicable, the patient entered the open-label re-induction period and was allowed to intravenously receive 3 doses of mirikizumab 300 mg Q4W.

d) For this application, only the safety data in the overall population were submitted.

e) As exceptional cases, patients in Poland and Turkey who could not enter Study AMBG because of an error of the electronic clinical outcome assessment (eCOA) in Study AMAN were also enrolled.

Table 18 shows the Mayo scoring system used for the efficacy evaluation in the clinical studies included in the submitted data, and Table 19 shows the response criteria used for the primary efficacy endpoint.

Table 18. Mayo scoring system

• Mayo score: Sum of the following 4 subscores (0-12) • Modified Mayo score: Mayo score excluding physician's global assessment score (0-9)	
Stool frequency	0: Normal numbers of stools for subject 1: 1-2 stools more than normal 2: 3-4 stools more than normal 3: ≥5 stools more than normal
Rectal bleeding	The daily bleeding score represents the most severe bleeding of the day. 0: No blood seen 1: Streaks of blood with stool less than half of the time 2: Obvious blood with stool most of the time 3: Blood alone passes
Findings on endoscopy	0: Normal or inactive disease 1: Mild disease (erythema, decreased vascular pattern) 2: Moderate disease (marked erythema, absent vascular pattern, friability, erosions) 3: Severe disease (spontaneous bleeding, ulceration)
Physician's global assessment	0: Normal 1: Mild disease 2: Moderate disease 3: Severe disease

Table 19. Primary efficacy endpoint and response criteria[a)]

Clinical remission	Stool frequency subscore ≤1 with a ≥1-point decrease from induction baseline, rectal bleeding subscore = 0, and endoscopic subscore ≤1
Symptomatic remission	Stool frequency subscore ≤1 with a ≥1-point decrease from induction baseline, rectal bleeding subscore = 0
Steroid-free remission	Clinical remission at Week 40, and symptomatic remission at Week 28 of the maintenance period, and no corticosteroid use for ≥12 weeks prior to Week 40 of the maintenance period
Clinical improvement	Study AMAC A decrease in the modified Mayo score of ≥2 points and ≥35% decrease from baseline, and a decrease of ≥1 point in the rectal bleeding subscore from baseline or a rectal bleeding subscore of ≤1 Studies AMAN and AMBG A decrease in the modified Mayo score of ≥2 points and ≥30% decrease from baseline, and a decrease of ≥1 point in the rectal bleeding subscore from baseline or a rectal bleeding score of ≤1
Endoscopic improvement	Endoscopic subscore ≤1
Symptomatic improvement	≥30% decrease from baseline in the composite clinical endpoint of the sum of stool frequency and rectal bleeding subscores
Reduced response	Study AMBG only ≥2-point increase from Study AMBG baseline in the combined stool frequency + rectal bleeding subscores AND combined stool frequency + rectal bleeding score of ≥4, on 2 consecutive visits (≥7 days apart), with confirmation of negative *Clostridium difficile* testing, and confirmed by endoscopic subscore of ≥2

a) Endoscopic subscore given based on central reading

7.1 Phase II study

7.1.1 Global phase II study (CTD 5.3.5.1.1, Study I6T-MC-AMAC, [redacted] 20[redacted] to May 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 85 study sites (17 study sites in Japan) in 14 countries including Japan to investigate the efficacy and safety of mirikizumab in patients with moderate to severe UC (Table 20 and Table 21) (target sample size, 240 patients [60 per group][6,7)]).

6) Assuming that the proportion of patients in clinical remission at Week 12 was 30% in each of the mirikizumab groups and 7.5% in the placebo group, the sample size of 240 patients (assigned to the mirikizumab and placebo groups in a 1:1:1:1 ratio) would give a statistical power of 89% to comparisons of each of the mirikizumab groups with the placebo group performed by chi-square test at a two-sided significance level of 5%.

7) In each group, approximately one third of the patients (ca. 20 per group) received no prior treatment with biological products, and approximately two thirds (ca. 40 per group) received prior treatment with biological products.

Table 20. Main inclusion criteria

Patients meeting all of the following criteria [for the Mayo score, see Table 18]: ○ Men or women aged ≥18 and ≤75 years ○ Mayo score of 6-12 with an endoscopic subscore of 2-3 (based on central reading) ○ Meeting either of the following conditions: • Patients who are naïve to biological products (anti-TNFα antibody, anti-integrin antibody, etc.) and (a) had an inadequate response or intolerance to oral or intravenous steroids, or had history of steroid dependence, or (b) had an inadequate response or intolerance to either 6-MP or AZA • Patients who are non-naïve to biological products (anti-TNFα antibody, anti-integrin antibody, etc.) with or without history of an inadequate response or intolerance to such treatment ○ Meeting the following conditions: • A dose of an oral 5-ASA preparation or oral steroid, if used, remains constant for ≥2 weeks before screening endoscopy • A dose of 6-MP or AZA, if used, remains constant for ≥8 weeks before the first dose of the study drug ○ Other drugs have been discontinued, as described below, when the first dose of the study drug is given • At least 8 weeks have passed since anti-TNFα antibody was discontinued. • At least 12 weeks have passed since anti-integrin antibody was discontinued. • At least 8 weeks have passed since other experimental biological product for UC therapy was discontinued.

Table 21. Main exclusion criteria

○ Patients with a diagnosis of Crohn's disease ○ Patients with the lesion localized to the rectum only ○ Patients with a diagnosis of toxic megacolon ○ Patients who have a history of surgery or are scheduled to undergo surgery for treatment of UC ○ Patients who have a history of total colectomy or subtotal colectomy, ileostomy, or colostomy ○ Patients who have symptomatic and irreversible intestinal stenosis ○ Patients who received prior treatment with a cyclosporine, thalidomide, steroid enema or suppository or a 5-ASA topical preparation within 30 days before screening endoscopy ○ Patients who underwent prior apheresis within 2 weeks before screening endoscopy ○ Patients who received prior treatment with biological products targeting IL-23 (ustekinumab, etc.)

Figure 3 and Figure 4 outline the study. The study started with a 12-week induction period. The following dosing periods were specified: a 92-week maintenance period to patients who met the criteria for clinical improvement during the induction period, and an extension treatment period to patients who did not meet the criteria for clinical improvement during the induction period (12-week open-label extended induction period and 80-week open-label maintenance period).

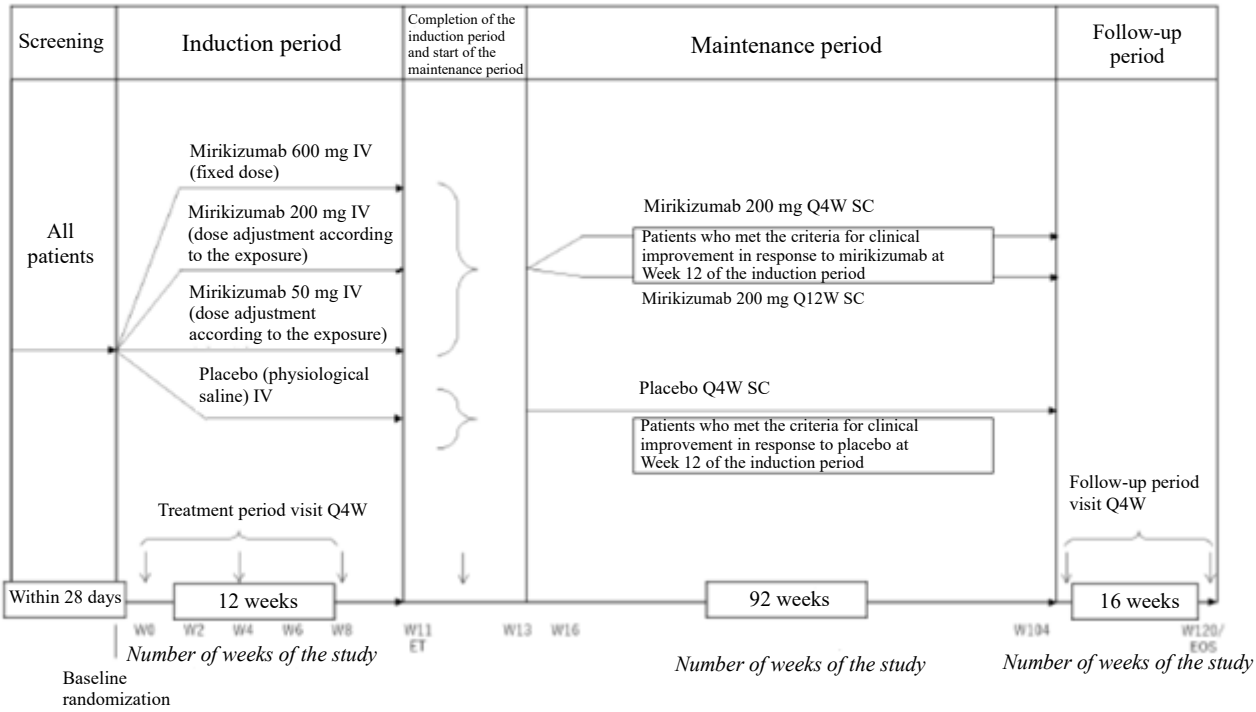


Figure 3. Outline of Study AMAC (induction period and maintenance period)

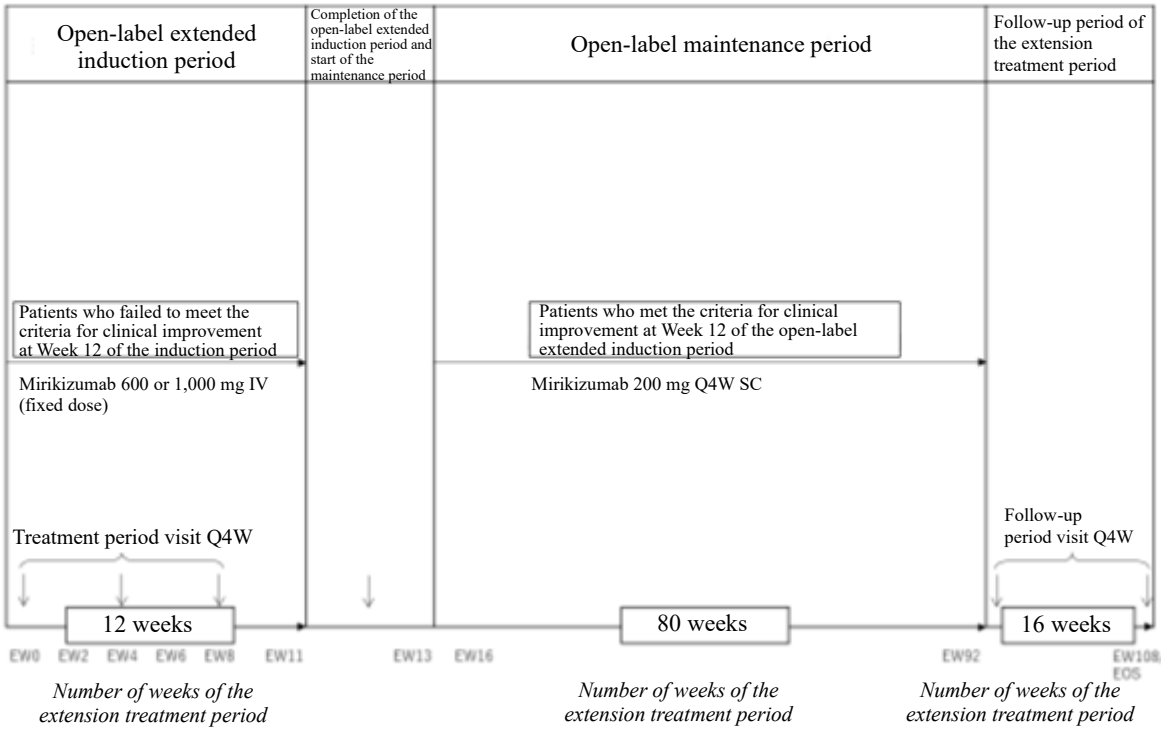


Figure 4. Outline of Study AMAC (extension treatment period)

During the induction period, patients intravenously received 3 doses of placebo or mirikizumab 50, 200, or 600 mg Q4W (Weeks 0, 4, and 8).[8)] Patients who met the criteria for clinical improvement at Week 12 of the induction period entered the maintenance period. During the maintenance period, patients who

8) For the second and third doses in the mirikizumab 50 mg IV and mirikizumab 200 mg IV groups, the dose was increased when the estimated trough concentration was below the threshold specified. In the mirikizumab 50 mg IV and 200 mg IV groups, the mean dose per session was 100 and 250 mg, respectively.

had received mirikizumab during the induction period were randomized to subcutaneously receive mirikizumab 200 mg Q4W or once every 12 weeks (Q12W). Patients who had received placebo during the induction period subcutaneously received placebo Q4W. Patients who had not met the criteria for clinical improvement at Week 12 of the induction period entered the extension treatment period, which consisted of the open-label extended induction period and open-label maintenance period. During the open-label extended induction period, patients intravenously received 3 doses of mirikizumab 600 or 1,000 mg Q4W[9)]. Patients who had met the criteria for clinical improvement at Week 12 of the open-label extended induction period subcutaneously received mirikizumab 200 mg Q4W during the open-label maintenance period.

For the induction period, 249 patients (63 in the placebo group [8 Japanese], 63 in the mirikizumab 50 mg IV group [5 Japanese], 62 in the 200 mg IV group [13 Japanese], 61 in the 600 mg IV group [5 Japanese]) were randomized. All of the 249 patients were included in the intention-to-treat (ITT) population and primary efficacy population. Of the 249 patients, 248 patients were included in the safety analysis population. The remaining 1 patient in the mirikizumab 600 mg IV group (non-Japanese) was excluded because the patient did not receive the study drug.

During the induction period, 10 patients (3 in the placebo group, 2 in the mirikizumab 50 mg IV group, 2 in the 200 mg IV group, 3 in the 600 mg IV group) discontinued the treatment because of "adverse events" in 7 patients (3 in the placebo group, 2 in the mirikizumab 200 mg IV group, 2 in the 600 mg IV group), "consent withdrawal" in 2 patients (1 in the mirikizumab 50 mg IV group, 1 in the 600 mg IV group), and "protocol deviation" in 1 patient (1 in the mirikizumab 50 mg IV group). None of the Japanese patients discontinued the treatment.

In the maintenance period, 106 patients (13 in the placebo group, 27 in the mirikizumab 50 mg IV group [2 Japanese], 37 in the 200 mg IV group [5 Japanese], 29 in the 600 mg IV group [3 Japanese]) who had met the criteria for clinical improvement at Week 12 of the induction period were enrolled. All of the 106 patients received the study drug (13 in the placebo group, 47 in the mirikizumab SC Q4W group [4 Japanese], 46 in the SC Q12W group [6 Japanese]) were included in the efficacy and safety analysis populations for the maintenance period.

During the maintenance period,[10)] 19 patients (6 in the placebo group, 6 in the mirikizumab SC Q4W group, 7 in the Q12W group) discontinued the treatment because of "consent withdrawal" in 10 patients (4 in the placebo group, 2 in the mirikizumab SC Q4W group, 4 in the SC Q12W group), "lack of efficacy" in 3 patients (2 in the placebo group, 1 in the mirikizumab SC Q4W group), "adverse events" in 2 patients (2 in the mirikizumab SC Q12W group), "other reasons" in 2 patients (1 in the mirikizumab SC Q4W group, 1 in the SC Q12W group), "lost to follow-up" in 1 patient (1 in the mirikizumab SC Q4W group), and "investigator's decision" in 1 patient (1 in the mirikizumab SC Q4W group). None of the Japanese patients discontinued the treatment.[10)]

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9) At the start of the study, mirikizumab 600 mg was planned to be administered, but the safety data at doses up to 1,200 mg were obtained in Study AMAD [see Section 6.2.1], and the study protocol was revised (dated October 4, 2016) to implement administration of mirikizumab 1,000 mg thereafter.

10) Discontinuation other than transfer to Study AMAP.

Of 132 patients (47 in the placebo group [8 Japanese], 34 in the mirikizumab 50 mg IV group [3 Japanese], 23 in the 200 mg IV group [8 Japanese], 28 in the 600 mg IV group [2 Japanese]) who had not met the criteria for clinical improvement at Week 12 of the induction period, 128 patients who wished to participate in the extension treatment period were enrolled in the open-label extended induction period. All of the 128 patients received the study drug (32 in the mirikizumab 600 mg IV group [3 Japanese], 96 in the 1,000 mg IV group [18 Japanese])[9] were included in the efficacy and safety analysis populations for the extension treatment period.

During the open-label extended induction period, 14 patients (2 in the mirikizumab 600 mg IV group, 12 in the 1,000 mg IV group) discontinued the treatment because of "consent withdrawal" in 5 patients (2 in the 600 mg IV group, 3 in the 1,000 mg IV group), "adverse events" in 4 patients (4 in the 1,000 mg IV group), "lack of efficacy" in 3 patients (3 in the 1,000 mg IV group), "investigator's decision" in 1 patient (1 in the 1,000 mg IV group), and "other reasons" in 1 patient (1 in the 1,000 mg IV group). Of the Japanese patients, 4 patients (4 in the mirikizumab 1,000 mg IV group) discontinued the treatment because of "lack of efficacy" in 2 patients, "adverse events" in 1 patient, and "investigator's decision" in 1 patient.

In the open-label maintenance period, 68 patients (18 in the mirikizumab 600 mg IV group [2 Japanese], 50 in the 1,000 mg IV group [7 Japanese]) who had met the criteria for clinical improvement at Week 12 of the open-label extended induction period were enrolled. All of the 68 patients received the study drug and were included in the efficacy and safety analysis populations for the open-label maintenance period.

During the open-label maintenance period, 11 patients[10] discontinued because of "lack of efficacy" in 4 patients, "consent withdrawal" in 4 patients, "adverse events" in 2 patients, and "other reasons" in 1 patient. Of the Japanese patients, 1 patient[10] discontinued the treatment because of "adverse events."

Table 22 shows results on the "proportion of patients in clinical remission at Week 12 of the induction period," the primary efficacy endpoint. A comparison between mirikizumab 600 mg IV and placebo, planned as the initial test, did not indicate a statistically significant difference ($P = 0.142$, two-sided significance level of 5%, logistic regression model using the dose group, prior treatment with biological products, and region as explanatory variables). No further comparison of placebo with mirikizumab 200 mg IV or comparison test of placebo with mirikizumab 50 mg IV was performed.

Table 22. Proportion of patients in clinical remission at Week 12 of the induction period (ITT population for the induction period, non-responder imputation [NRI])

	Placebo (n = 63)	Mirikizumab IV		
		50 mg (n = 63)	200 mg (n = 62)	600 mg (n = 61)
Proportion of patients in clinical remission, % (n)	4.8 (3)	15.9 (10)	22.6 (14)	11.5 (7)
Difference between groups (placebo and unadjusted) [95% CI]	—	11.1 [0.7, 21.6]	17.8 [6.2, 29.5]	6.7 [-2.9, 16.3]
Odds ratio to placebo [95% CI][a)]	—	3.61 [0.92, 14.17]	7.22 [1.88, 27.65]	2.93 [0.70, 12.27]
P value[a) b)]	—			0.142

a) Logistic regression model using the dose group, prior treatment with biological products, and region as explanatory variables
b) Tests were planned to be performed by comparisons of placebo with mirikizumab 600 mg, 200 mg, and 50 mg at a two-sided significance level of 5% in this order according to the closed testing procedure to control the probability of Type I errors at 5%.

For the safety during the induction period, adverse events occurred in 54.0% (34 of 63) of patients in the placebo group, 57.1% (36 of 63) of patients in the mirikizumab 50 mg IV group, 51.6% (32 of 62) of patients in the 200 mg IV group, and 53.3% (32 of 60) of patients in the 600 mg IV group, and adverse drug reactions occurred in 15.9% (10 of 63) of patients in the placebo group, 19.0% (12 of 63) of patients in the mirikizumab 50 mg IV group, 11.3% (7 of 62) of patients in the 200 mg IV group, and 20.0% (12 of 60) of patients in the 600 mg IV group. In the Japanese population, adverse events occurred in 5 of 8 patients in the placebo group, 4 of 5 patients in the mirikizumab 50 mg IV group, 9 of 13 patients in the 200 mg IV group, and 3 of 5 patients in the 600 mg IV group, and adverse drug reactions occurred in 1 of 8 patients in the placebo group and 1 of 13 patients in the mirikizumab 200 mg IV group. Table 23 and Table 24 show adverse events and adverse drug reactions, respectively, reported by ≥2% of patients in any group in the overall population.

Table 23. Adverse events reported by ≥2% of patients in any group in the overall population (safety analysis population for the induction period)

	Overall population				Japanese population			
	Placebo (n = 63)	Mirikizumab IV			Placebo (n = 8)	Mirikizumab IV		
		50 mg (n = 63)	200 mg (n = 62)	600 mg (n = 60)		50 mg (n = 5)	200 mg (n = 13)	600 mg (n = 5)
All adverse events	54.0 (34)	57.1 (36)	51.6 (32)	53.3 (32)	62.5 (5)	80.0 (4)	69.2 (9)	60.0 (3)
Nasopharyngitis	9.5 (6)	7.9 (5)	4.8 (3)	8.3 (5)	12.5 (1)	40.0 (2)	23.1 (3)	0
Headache	4.8 (3)	4.8 (3)	1.6 (1)	6.7 (4)	0	0	0	0
Gastroenteritis	1.6 (1)	0	4.8 (3)	5.0 (3)	0	0	7.7 (1)	0
Nausea	6.3 (4)	3.2 (2)	3.2 (2)	5.0 (3)	25.0 (2)	20.0 (1)	0	0
Malaise	1.6 (1)	0	4.8 (3)	3.3 (2)	12.5 (1)	0	7.7 (1)	0
Anaemia	4.8 (3)	6.3 (4)	3.2 (2)	3.3 (2)	12.5 (1)	0	7.7 (1)	0
Colitis ulcerative	9.5 (6)	3.2 (2)	3.2 (2)	3.3 (2)	0	0	0	0
Dizziness	1.6 (1)	0	1.6 (1)	3.3 (2)	12.5 (1)	0	7.7 (1)	0
Back pain	0	1.6 (1)	0	3.3 (2)	0	0	0	20.0 (1)
Cough	6.3 (4)	0	0	3.3 (2)	0	0	0	20.0 (1)
Abdominal distension	1.6 (1)	0	0	3.3 (2)	0	0	0	20.0 (1)
Skin infection	0	0	0	3.3 (2)	0	0	0	20.0 (1)
Pruritus	1.6 (1)	1.6 (1)	3.2 (2)	1.7 (1)	0	0	7.7 (1)	0
Fatigue	3.2 (2)	4.8 (3)	1.6 (1)	1.7 (1)	0	0	0	0
Arthralgia	4.8 (3)	3.2 (2)	1.6 (1)	1.7 (1)	0	0	0	0
Iron deficiency anaemia	4.8 (3)	1.6 (1)	0	1.7 (1)	12.5 (1)	0	0	0
Oropharyngeal pain	3.2 (2)	1.6 (1)	0	1.7 (1)	0	0	0	0
Alopecia	3.2 (2)	1.6 (1)	0	1.7 (1)	0	0	0	0
Iron deficiency	0	1.6 (1)	3.2 (2)	0	0	0	0	0
Myalgia	1.6 (1)	0	3.2 (2)	0	0	0	0	0
Weight increased	0	0	3.2 (2)	0	0	0	0	0
γGTP increased	0	4.8 (3)	1.6 (1)	0	0	0	0	0
Upper respiratory tract infection	4.8 (3)	4.8 (3)	0	0	0	0	0	0
ALT increased	0	4.8 (3)	0	0	0	0	0	0
Spinal osteoarthritis	0	3.2 (2)	0	0	0	20.0 (1)	0	0
Clostridium difficile infection	0	3.2 (2)	0	0	0	0	0	0
Haematuria	0	3.2 (2)	0	0	0	0	0	0
Colon dysplasia	3.2 (2)	0	0	0	0	0	0	0

Incidence in % (number of patients with events)
Medical Dictionary for Regulatory Activities Japanese version (MedDRA)/J ver.22.0

Table 24. Adverse drug reactions reported by ≥2% of patients in any group in the overall population (safety analysis population for the induction period)

	Overall population				Japanese population			
	Placebo (n = 63)	Mirikizumab IV			Placebo (n = 8)	Mirikizumab IV		
		50 mg (n = 63)	200 mg (n = 62)	600 mg (n = 60)		50 mg (n = 5)	200 mg (n = 13)	600 mg (n = 5)
All adverse drug reactions	15.9 (10)	19.0 (12)	11.3 (7)	20.0 (12)	12.5 (1)	0	7.7 (1)	0
Headache	1.6 (1)	1.6 (1)	0	5.0 (3)	0	0	0	0
Malaise	0	0	3.2 (2)	3.3 (2)	0	0	7.7 (1)	0
Myalgia	0	0	3.2 (2)	0	0	0	0	0
γGTP increased	0	4.8 (3)	1.6 (1)	0	0	0	0	0
ALT increased	0	3.2 (2)	0	0	0	0	0	0
Alopecia	3.2 (2)	1.6 (1)	0	0	0	0	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.22.0

No deaths occurred during the induction period. During the induction period, serious adverse events occurred in 3.2% (2 of 63) of patients in the placebo group (viral upper respiratory tract infection and

large intestine perforation in 1 patient each), 3.2% (2 of 62) of patients in the mirikizumab 200 mg IV group (colitis ulcerative and gastroenteritis in 1 patient each), and 5.0% (3 of 60) of patients in the 600 mg IV group (squamous cell carcinoma of skin, colitis ulcerative, and gastroenteritis in 1 patient each). Colitis ulcerative in 1 patient in the 200 mg IV group was assessed as a serious adverse drug reaction. In the Japanese population, no serious adverse events occurred during the induction period.

During the induction period, adverse events leading to treatment discontinuation occurred in 4.8% (3 of 63) of patients in the placebo group (colitis ulcerative, colon dysplasia, and psoriatic arthropathy in 1 patient each), 3.2% (2 of 62) of patients in the mirikizumab 200 mg IV group (colitis ulcerative in 2 patients), and 3.3% (2 of 60) of patients in the 600 mg IV group (squamous cell carcinoma of skin and colitis ulcerative in 1 patient each), and colitis ulcerative in 2 patients (1 in the placebo group, 1 in the mirikizumab 200 mg IV group) were assessed as adverse drug reactions. In the Japanese population, no adverse events leading to treatment discontinuation occurred during the induction period.

During the maintenance period, adverse events occurred in 84.6% (11 of 13) of patients in the placebo group, 80.9% (38 of 47) of patients in the mirikizumab SC Q4W group, and 71.7% (33 of 46) of patients in the SC Q12W group, and adverse drug reactions occurred in 30.8% (4 of 13) of patients in the placebo group, 38.3% (18 of 47) of patients in the SC Q4W group, and 15.2% (7 of 46) of patients in the SC Q12W group. In the Japanese population, adverse events occurred in 4 of 4 patients in the mirikizumab SC Q4W group and 5 of 6 patients in the SC Q12W group, and adverse drug reactions occurred in 3 of 4 patients in the SC Q4W group. Table 25 and Table 26 show adverse events and adverse drug reactions, respectively, reported by ≥2 patients in any group in the overall population.

Table 25. Adverse events reported by ≥2 patients in any group in the overall population (safety analysis population for the maintenance period)

	Overall population			Japanese population		
	Placebo (n = 13)	Mirikizumab SC		Placebo (n = 0)	Mirikizumab SC	
		Q4W (n = 47)	Q12W (n = 46)		Q4W (n = 4)	Q12W (n = 6)
All adverse events	84.6 (11)	80.9 (38)	71.7 (33)	—	100 (4)	83.3 (5)
Nasopharyngitis	7.7 (1)	12.8 (6)	17.4 (8)	—	50.0 (2)	50.0 (3)
Tonsillitis	0	0	4.3 (2)	—	0	0
Colitis ulcerative	53.8 (7)	8.5 (4)	15.2 (7)	—	0	0
Influenza	0	6.4 (3)	8.7 (4)	—	50.0 (2)	33.3 (2)
Sinusitis	0	2.1 (1)	8.7 (4)	—	0	0
Upper respiratory tract infection	23.1 (3)	10.6 (5)	6.5 (3)	—	0	0
Headache	7.7 (1)	10.6 (5)	6.5 (3)	—	25.0 (1)	0
Pharyngitis	0	4.3 (2)	6.5 (3)	—	0	16.7 (1)
Back pain	23.1 (3)	2.1 (1)	6.5 (3)	—	0	0
Fatigue	15.4 (2)	2.1 (1)	6.5 (3)	—	0	0
Urinary tract infection	7.7 (1)	2.1 (1)	6.5 (3)	—	0	0
Hypertension	7.7 (1)	8.5 (4)	4.3 (2)	—	0	0
Injection site pain	15.4 (2)	6.4 (3)	4.3 (2)	—	0	0
Injection site erythema	0	4.3 (2)	4.3 (2)	—	0	0
Abdominal pain	7.7 (1)	2.1 (1)	4.3 (2)	—	0	0
Oropharyngeal pain	0	0	4.3 (2)	—	0	0
Arthralgia	0	12.8 (6)	2.2 (1)	—	25.0 (1)	0
Gastroenteritis	0	8.5 (4)	2.2 (1)	—	25.0 (1)	0
Injection site reaction	0	6.4 (3)	0	—	50.0 (2)	0
Diarrhoea	0	6.4 (3)	0	—	25.0 (1)	0
Nausea	15.4 (2)	6.4 (3)	0	—	0	0
Abdominal distension	7.7 (1)	4.3 (2)	0	—	25.0 (1)	0
Cystitis	7.7 (1)	4.3 (2)	0	—	0	0
Cough	0	4.3 (2)	0	—	50.0 (2)	0
Malaise	0	4.3 (2)	0	—	25.0 (1)	0
Oral herpes	0	4.3 (2)	0	—	0	0
Vomiting	0	4.3 (2)	0	—	0	0
Alopecia	0	4.3 (2)	0	—	0	0
Pruritus	0	4.3 (2)	0	—	0	0
ALT increased	0	4.3 (2)	0	—	0	0
γGTP increased	0	4.3 (2)	0	—	0	0
Anxiety	0	4.3 (2)	0	—	0	0
Herpes zoster	15.4 (2)	2.1 (1)	0	—	0	0

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Incidence (number of patients with events)

Table 26. Adverse drug reactions reported by ≥2 patients in any group in the overall population (safety analysis population for the maintenance period)

	Overall population			Japanese population		
	Placebo (n = 13)	Mirikizumab SC		Placebo (n = 0)	Mirikizumab SC	
		Q4W (n = 7)	Q12W (n = 46)		Q4W (n = 4)	Q12W (n = 6)
All adverse drug reactions	30.8 (4)	38.3 (18)	15.2 (7)	—	75.0 (3)	0
Injection site pain	15.4 (2)	6.4 (3)	4.3 (2)	—	0	0
Injection site erythema	0	2.1 (1)	4.3 (2)	—	0	0
Colitis ulcerative	15.4 (2)	0	2.2 (1)	—	0	0
Injection site reaction	0	6.4 (3)	0	—	50.0 (2)	0
Nasopharyngitis	0	4.3 (2)	0	—	25.0 (1)	0
ALT increased	0	4.3 (2)	0	—	0	0
γGTP increased	0	4.3 (2)	0	—	0	0
Upper respiratory tract infection	15.4 (2)	2.1 (1)	0	—	0	0

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Incidence (number of patients with events)

No deaths occurred during the maintenance period. During the maintenance period, serious adverse events occurred in 15.4% (2 of 13) of patients in the placebo group (head injury, appendicitis, and streptococcal bacteraemia in 1 patient each [some patients had multiple events]), 4.3% (2 of 47) in the mirikizumab SC Q4W group (colitis ulcerative and Clostridium difficile infection in 1 patient each), and 2.2% (1 of 46) of patients in the SC Q12W group (colitis ulcerative in 1 patient), and appendicitis and streptococcal bacteraemia in 1 patient in the placebo group were assessed as serious adverse drug reactions. In the Japanese population, no serious adverse events occurred during the maintenance period.

During the maintenance period, adverse events leading to treatment discontinuation occurred in 4.3% (2 of 46) of patients in the mirikizumab SC Q12W group (injection site hypersensitivity and colitis ulcerative in 1 patient each), and injection site hypersensitivity in 1 patient was assessed as an adverse drug reaction. In the Japanese population, no adverse events leading to treatment discontinuation occurred during the maintenance period.

During the extension treatment period, adverse events occurred in 53.1% (17 of 32) of patients in the mirikizumab 600 mg IV group and 46.9% (45 of 96) of patients in the 1,000 mg IV group during the open-label extended induction period, and 73.5% (50 of 68) of patients during the open-label maintenance period, and adverse drug reactions occurred in 12.5% (4 of 32) of patients in the 600 mg IV group and 13.5% (13 of 96) of patients in the 1,000 mg IV group during the open-label extended induction period, and 30.9% (21 of 68) of patients during the open-label maintenance period. In the Japanese population, adverse events occurred in 3 of 3 patients in the mirikizumab 600 mg IV group and 13 of 18 patients in the 1,000 mg IV group during the open-label extended induction period, and 8 of 9 patients during the open-label maintenance period, and adverse drug reactions occurred in 3 of 18 patients in the 1,000 mg IV group during the open-label extended induction period and 2 of 9 patients during the open-label maintenance period. Table 27 and Table 28 show adverse events and adverse drug reactions, respectively, reported by ≥2 patients in any group in the overall population.

Table 27. Adverse events reported by ≥2 patients in any group in the overall population (safety analysis population for the extension treatment period)

	Overall population			Japanese population		
	Open-label extended induction period		Open-label maintenance period (n = 68)	Open-label extended induction period		Open-label maintenance period (n = 9)
	Mirikizumab 600 mg IV (n = 32)	Mirikizumab 1,000 mg IV (n = 96)		Mirikizumab 600 mg IV (n = 3)	Mirikizumab 1,000 mg IV (n = 18)	
All adverse events	53.1 (17)	46.9 (45)	73.5 (50)	100 (3)	72.2 (13)	88.9 (8)
Nasopharyngitis	15.6 (5)	7.3 (7)	20.6 (14)	0	27.8 (5)	55.6 (5)
Influenza	9.4 (3)	0	2.9 (2)	33.3 (1)	0	0
Dry skin	6.3 (2)	1.0 (1)	0	0	0	0
Colitis ulcerative	3.1 (1)	5.2 (5)	10.3 (7)	0	5.6 (1)	0
Upper respiratory tract infection	3.1 (1)	3.1 (3)	8.8 (6)	0	0	0
Iron deficiency anaemia	3.1 (1)	2.1 (2)	1.5 (1)	33.3 (1)	0	0
Flatulence	3.1 (1)	2.1 (2)	1.5 (1)	0	0	0
Gastroenteritis	3.1 (1)	1.0 (1)	4.4 (3)	0	5.6 (1)	0
Sinusitis	3.1 (1)	0	5.9 (4)	0	0	0
Blood CPK increased	3.1 (1)	0	4.4 (3)	0	0	0
Abdominal pain	3.1 (1)	0	2.9 (2)	0	0	0
Arthralgia	0	4.2 (4)	4.4 (3)	0	0	11.1 (1)
Headache	0	4.2 (4)	4.4 (3)	0	0	0
Nausea	0	3.1 (3)	2.9 (2)	0	0	11.1 (1)
Vomiting	0	3.1 (3)	1.5 (1)	0	5.6 (1)	0
Cough	0	2.1 (2)	4.4 (3)	0	0	0
Anaemia	0	2.1 (2)	1.5 (1)	0	5.6 (1)	0
Lymphocyte morphology abnormal	0	2.1 (2)	0	0	11.1 (2)	0
Rectal cancer	0	2.1 (2)	0	0	11.1 (2)	0
Infusion related reaction	0	2.1 (2)	0	0	5.6 (1)	0
Staphylococcal infection	0	2.1 (2)	0	0	0	0
Diarrhoea	0	1.0 (1)	2.9 (2)	0	0	11.1 (1)
Urinary tract infection	0	1.0 (1)	2.9 (2)	0	0	0
Oropharyngeal pain	0	1.0 (1)	2.9 (2)	0	0	0
Back pain	0	0	8.8 (6)	0	0	11.1 (1)
Myalgia	0	0	7.4 (5)	0	0	11.1 (1)
Abdominal pain upper	0	0	5.9 (4)	0	0	0
Vertigo	0	0	4.4 (3)	0	0	22.2 (2)
Large intestine polyp	0	0	4.4 (3)	0	0	11.1 (1)
Eczema	0	0	2.9 (2)	0	0	11.1 (1)
Rectal bleeding	0	0	2.9 (2)	0	0	0
AST increased	0	0	2.9 (2)	0	0	0
γGTP increased	0	0	2.9 (2)	0	0	0
Rash	0	0	2.9 (2)	0	0	0
Influenza like illness	0	0	2.9 (2)	0	0	0
Injection site erythema	0	0	2.9 (2)	0	0	0
Injection site pain	0	0	2.9 (2)	0	0	0
Erectile dysfunction	0	0	2.9 (2)	0	0	0

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Incidence (number of patients with events)

Table 28. Adverse drug reactions reported by ≥2 patients in any group in the overall population (safety analysis population for the extension treatment period)

	Overall population			Japanese population		
	Open-label extended induction period		Open-label maintenance period (n = 68)	Open-label extended induction period		Open-label maintenance period (n = 9)
	Mirikizumab 600 mg IV (n = 32)	Mirikizumab 1,000 mg IV (n = 96)		Mirikizumab 600 mg IV (n = 3)	Mirikizumab 1,000 mg IV (n = 18)	
All adverse drug reactions	12.5 (4)	13.5 (13)	30.9 (21)	0	16.7 (3)	22.2 (2)
Dry skin	6.3 (2)	0	0	0	0	0
Upper respiratory tract infection	0	2.1 (2)	2.9 (2)	0	0	0
Infusion related reaction	0	2.1 (2)	0	0	5.6 (1)	0
Arthralgia	0	2.1 (2)	0	0	0	0
Headache	0	2.1 (2)	0	0	0	0
Nasopharyngitis	0	1.0 (1)	5.9 (4)	0	5.6 (1)	11.1 (1)
Blood CPK increased	0	0	2.9 (2)	0	0	0
Injection site erythema	0	0	2.9 (2)	0	0	0
Injection site pain	0	0	2.9 (2)	0	0	0

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Incidence (number of patients with events)

No deaths occurred during the extension treatment period. For the extension treatment period, serious adverse events occurred in 3.1% (1 of 32) of patients in the mirikizumab 600 mg IV group (breast neoplasm in 1 patient) and 5.2% (5 of 96) of patients in the 1,000 mg IV group (colitis ulcerative, rectal cancer in 2 patients each, platelet count increased and polyarthritis in 1 patient each [some patients had multiple events]) during the open-label extended induction period, and 4.4% (3 of 68) of patients during the open-label maintenance period (transient ischaemic attack, hip fracture, intestinal obstruction, and drug dependence 1 patient each [some patients had multiple events]). A causal relationship to the study drug was denied for all the events. For the extension treatment period in the Japanese population, serious adverse events occurred in 2 of 18 patients in the mirikizumab 1,000 mg IV group (rectal cancer in 2 patients) during the open-label extended induction period.

For the extension treatment period, adverse events leading to treatment discontinuation occurred in 4.2% (4 of 96) of patients in the mirikizumab 1,000 mg IV group (colitis ulcerative in 3 patients and infusion related reaction in 1 patient) during the open-label extended induction period and 2.9% (2 of 68) of patients (colitis ulcerative and myalgia in 1 patient each) during the open-label maintenance period. Infusion related reaction in 1 patient in the 1,000 mg IV group during the open-label extended induction period and colitis ulcerative in 1 patient during the open-label maintenance period were assessed as adverse drug reactions. For the extension treatment period in the Japanese population, adverse events leading to treatment discontinuation occurred in 1 of 18 patients in the mirikizumab 1,000 mg IV group (colitis ulcerative in 1 patient) during the open-label extended induction period and 1 of 9 of patients (myalgia in 1 patient) during the open-label maintenance period, but a causal relationship to the study drug was denied for both events.

7.2 Phase III studies

7.2.1 Global phase III induction period study (CTD 5.3.5.1.2, Study I6T-MC-AMAN, June 2018 to January 2021)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 471 study sites (49 study sites in Japan) in 35 countries or regions including Japan to investigate the efficacy and safety of mirikizumab during the induction period in patients with moderate to severe UC (Table 29 and Table 30) (target sample size, 1160 patients [290 in the placebo group, 870 in the mirikizumab IV group][11,12]).

Table 29. Main inclusion criteria

Patients meeting all of the following criteria [for the modified Mayo score, see Table 18]: ○ Men or women aged ≥18 and ≤80 years ○ Modified Mayo score of 4-9 with an endoscopic subscore of 2-3 (based on central reading) ○ Meeting either of the following conditions: • Conventional-failed patients: Patients who are not non-responders to biological products (anti-TNFα antibody or anti-integrin antibody) and (a) had an inadequate response to, intolerance to, or dependence on oral or intravenous steroids or (b) had an inadequate response or intolerance to either 6-MP or AZA. • Biologic-failed patients: Patients who had an inadequate response or intolerance to anti-TNF-α antibody, anti-integrin antibody, or JAK inhibitor (tofacitinib) ○ Meeting the following conditions: • A dose of an oral 5-ASA preparation or oral steroid, if used, remains constant for ≥2 weeks before screening endoscopy • A dose of 6-MP, AZA, or MTX, if used, remains constant for ≥8 weeks before screening endoscopy

Table 30. Main exclusion criteria

○ Patients with a diagnosis of Crohn's disease ○ Patients with the lesion localized to the rectum only ○ Patients with a diagnosis of toxic megacolon ○ Patients who have a history of extensive colectomy (such as subtotal colectomy) for treatment of UC or are scheduled to undergo such surgery ○ Patients who have intestinal stenosis ○ Patients who received prior treatment with steroid enema or suppository, oral budesonide, or intravenous steroid within 2 weeks before screening endoscopy ○ Patients who received prior treatment with cyclosporine, tacrolimus, mycophenolate mofetil, thalidomide, JAK inhibitors, etc. (excluding AZA, 6-MP, and MTX) within 4 weeks before screening endoscopy ○ Patients who received prior treatment with anti-integrin antibody within 8 weeks before screening endoscopy ○ Patients who underwent prior apheresis within 3 weeks before screening endoscopy ○ Patients who received prior treatment with anti-IL12 p40 antibody or anti-IL-23 p19 antibody (ustekinumab, etc.) ○ Patients who have not respond to≥3 prior treatment with biological products

Figure 5 outlines the study. The study started with a 12-week induction period.

[11] Conventional-failed patients and biologic-failed patients (inadequate responder or intolerant patients) were included approximately in a 1:1 ratio.

[12] Assuming that the proportion of patients in clinical remission at Week 12, the primary endpoint, was 23% in the mirikizumab IV group and 7.8% in the placebo group (30% in the mirikizumab IV group and 12% in the placebo group in a [a] population of conventional-failed patients as well as 16% and 3.5%, respectively, in a [b] population of biologic-failed patients; the study included these populations in a 1:1 ratio), the sample size, when randomized to the placebo and mirikizumab IV groups in a 1:3 ratio, required to ensure a statistical power of >90% in a chi-square test at a two-sided significance level of 0.00125 was calculated to be 1160 in total, including 290 patients in the placebo group and 870 patients in the mirikizumab IV group.

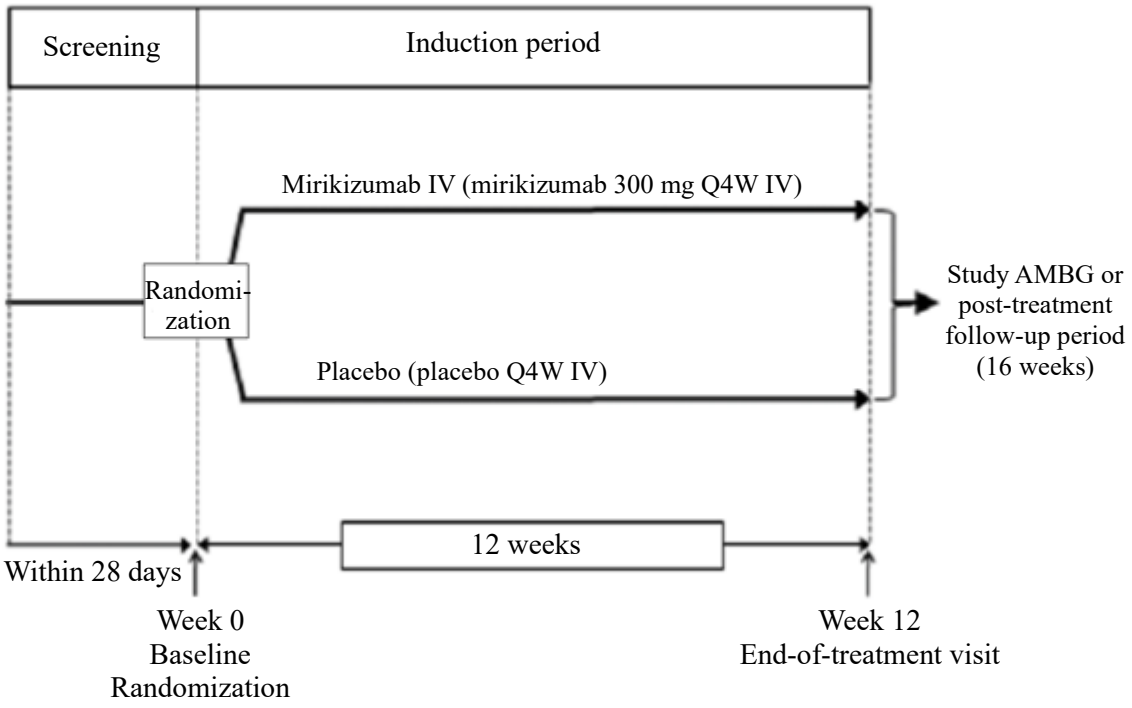

Figure 5. Outline of Study AMAN

Placebo or mirikizumab 300 mg were administered intravenously Q4W (Weeks 0, 4, and 8) at 3 intravenous doses.

After the start of the study, a question presented on the device for patient-reported outcome (PRO) assessment had an error in writing, raising an electronic clinical outcome assessment (eCOA) error due to a failure to obtain correct reports at a part of study sites outside Japan. A total of 118 patients (of these 117 patients received the study drug) affected by the error were excluded from the efficacy analysis population. In association with this, enrollment of an additional 118 patients was planned, and 121 patients were enrolled. In the end, 1281 patients (322 in the placebo group [35 Japanese], 959 in the mirikizumab IV group [102 Japanese]) were randomized and included in the ITT population. Of the 1281 patients, 1279 patients (321 in the placebo group [35 Japanese], 958 in the mirikizumab IV group [102 Japanese]) were included in the safety analysis population. The remaining 2 patients (1 in the placebo group, 1 in the mirikizumab IV group) were excluded because they did not receive the study drug. Of the 1279 patients in the safety analysis population, 1162 patients (294 in the placebo group [35 Japanese], 868 in the mirikizumab IV group [102 Japanese]) were included in the modified Intention-to-Treat (mITT) population and primary efficacy analysis population. The remaining 117 patients were excluded because they were affected by the eCOA error.

A total of 76 patients (37 in the placebo group, 39 in the mirikizumab IV group) discontinued the treatment because of "adverse events" in 38 patients (23 in the placebo group, 15 in the mirikizumab IV group), "consent withdrawal" in 13 patients (8 in the placebo group, 5 in the mirikizumab IV group), "lack of efficacy" in 10 patients (5 in the placebo group, 5 in the mirikizumab IV group), "protocol deviation" in 6 patients (1 in the placebo group, 5 in the mirikizumab IV group), "lost to follow-up" in 3 patients (3 in the mirikizumab IV group), "other reasons" in 3 patients (3 in the mirikizumab IV group), "restriction to study practices due to Coronavirus disease 2019 (COVID-19)" in 2 patients (2 in the

mirikizumab IV group), and "sponsor's termination of contract with the study site" in 1 patient (1 in the mirikizumab IV group). Of the Japanese patients, 12 patients (9 in the placebo group, 3 in the mirikizumab IV group) discontinued the treatment because of "adverse events" in 8 patients (6 in the placebo group, 2 in the mirikizumab IV group) and "lack of efficacy" in 4 patients (3 in the placebo group, 1 in the mirikizumab IV group).

Table 31 shows results on the "proportion of patients in clinical remission at Week 12," the primary efficacy endpoint, demonstrating superiority of mirikizumab IV to placebo (P = 0.00006, two-sided significance level of 0.00125, Cochran-Mantel-Haenszel test). [For the results in the Japanese population, see Section 7.R.2.1.1.]

Table 31. Proportion of patients in clinical remission at Week 12 (mITT population, NRI)

	Placebo (n = 294)	Mirikizumab IV (n = 868)
Proportion of patients in clinical remission, % (n)	13.3 (39)	24.2 (210)
Difference from placebo [99.875% CI][a)]	—	11.1 [3.2, 19.1]
P value[a), b)]	0.00006	

a) Cochran-Mantel-Haenszel test using biologic-failed status, use of steroids at baseline, modified Mayo score at baseline (<7 or ≥7), and region (North America, Europe, or others) as stratification factors.
b) Two-sided significance level of 0.00125

Adverse events occurred in 46.1% (148 of 321) of patients in the placebo group and 44.5% (426 of 958) of patients in the mirikizumab IV group, and adverse drug reactions occurred in 10.9% (35 of 321) of patients in the placebo group and 10.3% (99 of 958) of patients in the mirikizumab IV group. In the Japanese population, adverse events occurred in 54.3% (19 of 35) of patients in the placebo group and 47.1% (48 of 102) of patients in the mirikizumab IV group, and adverse drug reactions occurred in 5.7% (2 of 35) of patients in the placebo group and 9.8% (10 of 102) of patients in the mirikizumab IV group. Table 32 shows adverse events reported by ≥2% of patients in either group in the overall population. There were no adverse drug reactions reported by ≥2% of patients in either group in the overall population. Adverse drug reactions reported by ≥2 patients in either group in the Japanese population were headache (0% [0 of 35] of patients in the placebo group, 2.9% [3 of 102] of patients in the mirikizumab IV group) and pruritus (0% [0 of 35] of patients in the placebo group, 2.0% [2 of 102] of patients in the mirikizumab IV group).

Table 32. Adverse events reported by ≥2% of patients in either group in the overall population (safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
All adverse events	46.1 (148)	44.5 (426)	54.3 (19)	47.1 (48)
Nasopharyngitis	3.1 (10)	4.1 (39)	5.7 (2)	9.8 (10)
Anaemia	5.9 (19)	3.3 (32)	5.7 (2)	1.0 (1)
Headache	2.8 (9)	3.3 (32)	0	4.9 (5)
Colitis ulcerative	7.5 (24)	1.8 (17)	14.3 (5)	3.9 (4)
Iron deficiency anaemia	2.2 (7)	1.0 (10)	2.9 (1)	2.0 (2)
Abdominal pain	2.2 (7)	0.7 (7)	5.7 (2)	0
Arthralgia	1.2 (4)	2.1 (20)	0	2.0 (2)

Incidence in % (number of patients with events)
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No deaths occurred. Serious adverse events occurred in 5.3% (17 of 321) of patients in the placebo group and 2.8% (27 of 958) of patients in the mirikizumab IV group, and serious adverse drug reactions occurred in 1.6% (5 of 321) of patients in the placebo group and 0.3% (3 of 958) of patients in the mirikizumab IV group (Table 33). In the Japanese population, serious adverse events occurred in 8.6% (3 of 35) of patients in the placebo group (colitis ulcerative, sinusitis, and deep vein thrombosis in 1 patient each) and 2.9% (3 of 102) of patients in the mirikizumab IV group (colitis ulcerative in 2 patients and pneumonia in 1 patient), and sinusitis in 1 patient in the placebo group and colitis ulcerative in 1 patient in the mirikizumab IV group were assessed as serious adverse drug reactions.

Table 33. Serious adverse events (safety analysis population)

Group	Serious adverse events
Placebo	Colitis ulcerative[a)] in 10 patients, anaemia, sinusitis,[a)] acute sinusitis, penile vein thrombosis,[a)] deep vein thrombosis, acute myocardial infarction, malnutrition, and renal colic in 1 patient each (some patients had multiple events)
Mirikizumab IV	Colitis ulcerative[a)] in 8 patients, pneumonia in 2 patients, cytomegalovirus colitis, Klebsiella infection,[a)] intestinal sepsis, viral infection, gastroenteritis viral, lower gastrointestinal haemorrhage, anaemia, deep vein thrombosis,[a)] adenocarcinoma of colon, ovarian enlargement, uterine leiomyoma, arteriosclerosis, hypertension, diabetes mellitus, type 2 diabetes mellitus, ankylosing spondylitis, spinal compression fracture, spinal fracture, and vertigo in 1 patient each (some patients had multiple events)

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a) Events assessed as adverse drug reactions (colitis ulcerative in 3 patients in the placebo group and in 2 patients in the mirikizumab IV group and the other events in 1 patient each)

Adverse events leading to treatment discontinuation occurred in 7.2% (23 of 321) of patients in the placebo group (colitis ulcerative in 19 patients, sinusitis, acute myocardial infarction, conjunctivitis allergic, and arthritis in 1 patient each) and 1.6% (15 of 958) of patients in the mirikizumab IV group (colitis ulcerative in 5 patients, infusion related hypersensitivity reaction in 3 patients, lymphopenia in 2 patients, pyoderma gangrenosum, skin ulcer, intestinal sepsis, spinal fracture, and deep vein thrombosis in 1 patient each), and adverse drug reactions leading to treatment discontinuation occurred in 1.6% (5 of 321) of patients in the placebo group (colitis ulcerative in 3 patients, sinusitis and conjunctivitis allergic in 1 patient each) and 0.6% (6 of 958) of patients in the mirikizumab IV group (infusion related hypersensitivity reaction in 3 patients, colitis ulcerative, skin ulcer, and deep vein thrombosis in 1 patient each). In the Japanese population, adverse events leading to treatment discontinuation occurred in 17.1% (6 of 35) of patients in the placebo group (colitis ulcerative in 4 patients, sinusitis and arthritis in 1 patient each) and 2.0% (2 of 102) of patients in the mirikizumab IV group (colitis ulcerative in 2 patients), and sinusitis in 1 patient in the placebo group and colitis ulcerative in 1 patient in the mirikizumab IV group were assessed as adverse drug reactions.

7.2.2 Global phase III maintenance period study (CTD 5.3.5.1.3, Study I6T-MC-AMBG, October 2018 to November 2021)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted at 368 study sites (48 study sites in Japan) in 34 countries or regions including Japan to investigate the efficacy and safety of mirikizumab during the maintenance period in patients with UC (Table 34) who had completed Study AMAN (target sample size, 1044 patients [470 responders to induction therapy with mirikizumab

(mirikizumab induction responder population); 157 in the placebo group, 313 in the mirikizumab SC group][13]).

Table 34. Main inclusion and exclusion criteria

Main inclusion criteria • Patients meeting all of the following criteria: ○ Patients who received at least 1 study drug administration in Study AMAN and completed the study ○ Patients with all the items in the modified Mayo score, required at the completion of Study AMAN, assessed Main exclusion criteria • Patients in whom colonic epithelial dysplasia was found at the baseline endoscopy for this study (Week 12 of Study AMAN) or gastrointestinal carcinoma was diagnosed during Study AMAN

Figure 6 outlines the study. Patients who had met the criteria for clinical improvement at Week 12 of Study AMAN entered the maintenance period of Study AMBG. Patients who had not met the criteria for clinical improvement at Week 12 of Study AMAN entered the open-label extended induction period of Study AMBG.

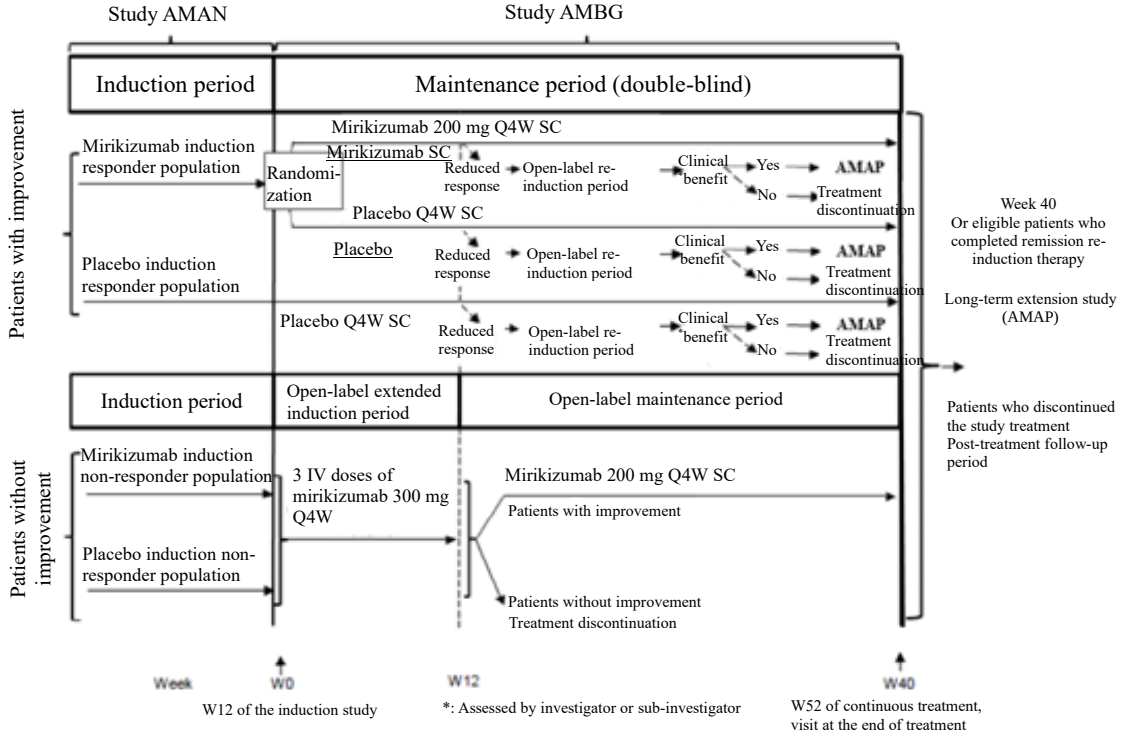

Figure 6. Outline of Study AMBG

Patients who had met the criteria for clinical improvement at Week 12 of the induction period with mirikizumab in Study AMAN (mirikizumab induction responder population) subcutaneously received placebo or mirikizumab 200 mg Q4W in a blinded manner during the maintenance period. Patients who had met the criteria for clinical improvement at Week 12 of the induction period with placebo in Study AMAN (placebo induction responder population) subcutaneously received placebo Q4W in a blinded

[13] Assuming that the proportion of patients in clinical remission at Week 40 was 47% in the mirikizumab SC group and 27% in the placebo group, the sample size of 470 patients in the mirikizumab induction responder population (assigned to the mirikizumab SC and placebo groups in a 2:1 ratio) would give a statistical power of 95% to chi-square test at a two-sided significance level of 5%. To secure the mirikizumab induction responder population of 470 patients, the number of patients required to be enrolled in Study AMBG was calculated to be 1044 on the assumption that of patients with UC who completed Study AMAN, 60% were responders during the induction period and 75% were in the mirikizumab group in Study AMAN.

manner during the maintenance period. Patients who had not met the criteria for clinical improvement at Week 12 of the induction period with mirikizumab or placebo in Study AMAN (mirikizumab induction non-responder population and placebo induction non-responder population, respectively) intravenously received 3 doses of mirikizumab 300 mg Q4W during the open-label extended induction period. Patients who had met the criteria for clinical improvement at Week 12 of the open-label extended induction period entered the open-label maintenance period and subcutaneously received mirikizumab 200 mg Q4W. Of note, patients who had met the criteria for reduced response (Table 19) were allowed to enter the open-label re-induction period and intravenously receive 3 doses of mirikizumab 300 mg Q4W in an open-label manner.

In the mirikizumab induction responder population, 581 patients (192 in the placebo group [25 Japanese], 389 in the mirikizumab SC group [47 Japanese]) were randomized, and all patients received the study drug and were included in the ITT population and safety analysis population. Of the 581 patients in the ITT population, 544 patients (179 in the placebo group [25 Japanese], 365 in the mirikizumab SC group [47 Japanese]) were included in the mITT population and primary efficacy analysis population. The remaining 37 patients were excluded because they were affected by the eCOA error [see Section 7.2.1].

In the mirikizumab induction responder population, 115 patients[10)] (73 in the placebo group, 42 in the mirikizumab SC group) discontinued the treatment during the maintenance period because of "reduced response (transferred to the open-label re-induction period)" in 61 patients (42 in the placebo group, 19 in the mirikizumab SC group), "adverse events" in 22 patients (16 in the placebo group, 6 in the mirikizumab SC group), "consent withdrawal" in 15 patients (7 in the placebo group, 8 in the mirikizumab SC group), "lack of efficacy" in 14 patients (8 in the placebo group, 6 in the mirikizumab SC group), "lost to follow-up" in 1 patient (1 in the mirikizumab SC group), "investigator's decision" in 1 patient (1 in the mirikizumab SC group), and "protocol deviation" in 1 patient (1 in the mirikizumab SC group). Of the Japanese patients, 12 patients[10)] (8 in the placebo group, 4 in the mirikizumab SC group) discontinued the treatment during the maintenance period because of "reduced response (transferred to the open-label re-induction period)" in 5 patients (4 in the placebo group, 1 in the mirikizumab SC group), "adverse events" in 5 patients (3 in the placebo group, 2 in the mirikizumab SC group), and "consent withdrawal" in 2 patients (1 in the placebo group, 1 in the mirikizumab SC group).

In the placebo induction responder population, all of 135 patients (8 Japanese) enrolled received the study drug and were included in the ITT population and safety analysis population.

In the placebo induction responder population, 45 patients[10)] discontinued the treatment during the maintenance period because of "reduced response (transferred to the open-label re-induction period)" in 29 patients, "lack of efficacy" in 7 patients, "consent withdrawal" in 6 patients, "adverse events" in 1 patient, "pregnancy" in 1 patient, and "protocol deviation" in 1 patient. Of the Japanese patients, 1 patient[10)] discontinued the treatment during the maintenance period because of "reduced response (transferred to the open-label re-induction period)."

In the mirikizumab and placebo induction non-responder populations, all of 461 patients enrolled in the open-label extended induction period (313 in the mirikizumab induction non-responder population [25 Japanese], 148 in the placebo induction non-responder population [18 Japanese]) received the study drug and were included in the ITT population and safety analysis population.

During the open-label extended induction period, 190 patients (142 in the mirikizumab induction non-responder population, 48 in the placebo induction non-responder population) discontinued the treatment because of "lack of efficacy" in 162 patients (122 in the mirikizumab induction non-responder population, 40 in the placebo induction non-responder population), "adverse events" in 11 patients (10 in the mirikizumab induction non-responder population, 1 in the placebo induction non-responder population), "consent withdrawal" in 6 patients (5 in the mirikizumab induction non-responder population, 1 in the placebo induction non-responder population), "protocol deviation" in 5 patients (3 in the mirikizumab induction non-responder population, 2 in the placebo induction non-responder population), "restriction to study practices due to COVID-19" in 4 patients (1 in the mirikizumab induction non-responder population, 3 in the placebo induction non-responder population), "investigator's decision" in 1 patient (mirikizumab induction non-responder population), and "other reasons" in 1 patient (placebo induction non-responder population). Of the Japanese patients, 21 patients (14 in the mirikizumab induction non-responder population, 7 in the placebo induction non-responder population) discontinued the treatment because of "lack of efficacy" in 19 patients (13 in the mirikizumab induction non-responder population, 6 in the placebo induction non-responder population), "adverse events" in 1 patient (mirikizumab induction non-responder population), and "restriction to study practices due to COVID-19" in 1 patient (placebo induction non-responder population).

In the open-label maintenance period, 271 patients (171 in the mirikizumab induction non-responder population [11 Japanese], 100 in the placebo induction non-responder population [11 Japanese]) who had met the criteria for clinical improvement at Week 12 of the open-label extended induction period were enrolled, and all patients received the study drug and were included in the ITT population and safety analysis population.

During the open-label maintenance period, 15 patients[10)] (10 in the mirikizumab induction non-responder population, 5 in the placebo induction non-responder population) discontinued the treatment because of "lack of efficacy" in 9 patients (4 in the mirikizumab induction non-responder population, 5 in the placebo induction non-responder population), "adverse events" in 4 patients (4 in the mirikizumab induction non-responder population), "restriction to study practices due to COVID-19" in 1 patient (mirikizumab induction non-responder population), and "protocol deviation" in 1 patient (mirikizumab induction non-responder population). Of the Japanese patients, 3 patients (2 in the mirikizumab induction non-responder population, 1 in the placebo induction non-responder population) discontinued the treatment because of "adverse events" in 1 patient (mirikizumab induction non-responder population), "restriction to study practices due to COVID-19" in 1 patient (mirikizumab induction non-responder population), and "lack of efficacy" in 1 patient (placebo induction non-responder population).

Table 35 shows results on the "proportion of patients in clinical remission at Week 40 of the maintenance period," the primary efficacy endpoint, demonstrating superiority of mirikizumab SC to placebo ($P <$

0.001, two-sided significance level of 0.05, Cochran-Mantel-Haenszel test). [For the results in the Japanese population, see Section 7.R.2.2.1.]

Table 35. Proportion of patients in clinical remission at Week 40 (mirikizumab induction responder population, mITT population, NRI)

	Placebo (n = 179)	Mirikizumab SC (n = 365)
Proportion of patients in clinical remission, % (n)	25.1 (45)	49.9 (182)
Difference from placebo [95% CI][a)]	—	23.2 [15.2, 31.2]
P value[a), b)]	<0.001	

a) Cochran-Mantel-Haenszel test using biologic-failed status, use of steroids at the baseline of Study AMAN, region (North America, Europe, or others), and clinical remission at Week 12 of Study AMAN as stratification factors
b) Two-sided significance level of 0.05

For the safety during the maintenance period, adverse events occurred in 68.8% (132 of 192) of patients in the placebo group and 64.5% (251 of 389) of patients in the mirikizumab SC group in the mirikizumab induction responder population, and adverse drug reactions occurred in 16.7% (32 of 192) of patients in the placebo group and 16.7% (65 of 389) of patients in the mirikizumab SC group. In the Japanese population, adverse events occurred in the 88.0% (22 of 25) of patients in the placebo group and 89.4% (42 of 47) of patients in the mirikizumab SC group, and adverse drug reactions occurred in 12.0% (3 of 25) of patients in the placebo group and 21.3% (10 of 47) of patients in the mirikizumab SC group.

In the placebo induction responder population, adverse events occurred in 60.7% (82 of 135) of patients and adverse drug reactions in 14.8% (20 of 135) of patients. In the Japanese population, adverse events occurred in 50.0% (4 of 8) of patients and adverse drug reactions in 12.5% (1 of 8) of patients.

Table 36 and Table 37 show adverse events and adverse drug reactions, respectively, reported by ≥2% of patients in any group in the overall population.

Table 36. Adverse events reported by ≥2% of patients in any group in the overall population (maintenance period, safety analysis population)

	Overall population			Japanese population		
	Placebo induction responder (n = 135)	Mirikizumab induction responder		Placebo induction responder (n = 8)	Mirikizumab induction responder	
		Placebo (n = 192)	Mirikizumab SC (n = 389)		Placebo (n = 25)	Mirikizumab SC (n = 47)
All adverse events	60.7 (82)	68.8 (132)	64.5 (251)	50.0 (4)	88.0 (22)	89.4 (42)
Colitis ulcerative	13.3 (18)	20.8 (40)	6.7 (26)	12.5 (1)	24.0 (6)	8.5 (4)
Nasopharyngitis	6.7 (9)	5.7 (11)	7.2 (28)	25.0 (2)	20.0 (5)	21.3 (10)
Anaemia	5.9 (8)	4.7 (9)	2.1 (8)	12.5 (1)	0	0
Pyrexia	4.4 (6)	2.6 (5)	3.3 (13)	0	0	2.1 (1)
Blood CPK increased	3.7 (5)	2.6 (5)	2.6 (10)	0	4.0 (1)	2.1 (1)
COVID-19	3.7 (5)	2.1 (4)	2.1 (8)	0	0	0
Headache	3.7 (5)	1.0 (2)	4.1 (16)	0	0	4.3 (2)
Arthralgia	3.0 (4)	4.2 (8)	6.7 (26)	0	0	6.4 (3)
Back pain	3.0 (4)	2.1 (4)	1.8 (7)	0	0	2.1 (1)
Abdominal pain	2.2 (3)	2.1 (4)	2.8 (11)	0	0	0
Neutropenia	2.2 (3)	1.0 (2)	0.3 (1)	0	0	0
Diarrhoea	2.2 (3)	0.5 (1)	2.6 (10)	12.5 (1)	0	0
Hyperglycaemia	2.2 (3)	0.5 (1)	1.0 (4)	0	0	2.1 (1)
Hypertriglyceridaemia	2.2 (3)	0	0.5 (2)	0	0	0
Injection site pain	1.5 (2)	3.1 (6)	4.4 (17)	0	0	6.4 (3)
Upper respiratory tract infection	1.5 (2)	2.6 (5)	1.8 (7)	0	4.0 (1)	0
Nausea	1.5 (2)	2.6 (5)	1.0 (4)	0	4.0 (1)	0
Pruritus	1.5 (2)	2.1 (4)	1.0 (4)	0	0	0
Rash	1.5 (2)	0	3.6 (14)	0	0	2.1 (1)
Fatigue	0.7 (1)	2.1 (4)	2.6 (10)	0	0	0
Sinusitis	0.7 (1)	2.1 (4)	0.8 (3)	0	4.0 (1)	2.1 (1)
Injection site reaction	0.7 (1)	0.5 (1)	2.6 (10)	0	0	2.1 (1)
Hypertension	0.7 (1)	0.5 (1)	2.3 (9)	0	0	4.3 (2)
Injection site erythema	0.7 (1)	1.0 (2)	2.1 (8)	0	4.0 (1)	0
Arthritis	0.7 (1)	2.1 (4)	0.5 (2)	0	0	0
Gastrooesophageal reflux disease	0	0.5 (1)	2.6 (10)	0	0	2.1 (1)

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Incidence (number of patients with events)

Table 37. Adverse drug reactions reported by ≥2% of patients in any group in the overall population (maintenance period, safety analysis population)

	Overall population			Japanese population		
	Placebo induction responder (n = 135)	Mirikizumab induction responder		Placebo induction responder (n = 8)	Mirikizumab induction responder	
		Placebo (n = 192)	Mirikizumab SC (n = 389)		Placebo (n = 25)	Mirikizumab SC (n = 47)
All adverse drug reactions	14.8 (20)	16.7 (32)	16.7 (65)	12.5 (1)	12.0 (3)	21.3 (10)
Colitis ulcerative	2.2 (3)	2.6 (5)	0	0	0	0
Injection site pain	1.5 (2)	3.1 (6)	4.1 (16)	0	0	6.4 (3)
Injection site reaction	0.7 (1)	0.5 (1)	2.6 (10)	0	0	2.1 (1)
Injection site erythema	0.7 (1)	1.0 (2)	2.1 (8)	0	4.0 (1)	0

MedDRA/J ver. 24.1
Incidence (number of patients with events)

During the maintenance period, death occurred in 1 patient (COVID-19)[14)] in the placebo group in the mirikizumab induction responder population.

During the maintenance period, serious adverse events occurred in 7.8% (15 of 192) of patients in the placebo group and 3.3% (13 of 389) of patients in the mirikizumab SC group in the mirikizumab induction responder population, and of these, the events in 4 patients in the placebo group were assessed as serious adverse drug reactions. In the placebo induction responder population, serious adverse events occurred in 5.2% (7 of 135) of patients, and of these, the event in 1 patient was assessed as a serious adverse drug reaction (Table 38). In the Japanese population, serious adverse events occurred in 8.0% (2 of 25) of patients in the placebo group (colitis ulcerative in 2 patients and autoimmune thyroiditis in 1 patient [some patients had multiple events]) and 4.3% (2 of 47) of patients in the mirikizumab SC group (inguinal hernia and gastric cancer in 1 patient each) in the mirikizumab induction responder population, and autoimmune thyroiditis in 1 patient in the placebo group was assessed as a serious adverse drug reaction.

Table 38. Serious adverse events (maintenance period, safety analysis population)

Group	Serious adverse events
Placebo induction responder population	Colitis ulcerative,[a)] Cytomegalovirus colitis, brain contusion, patella fracture, road traffic accident, deep vein thrombosis, pneumonia, gastroenteritis, and sacral pain in 1 patient each (some patients had multiple events)
Placebo group in the mirikizumab induction responder population	Colitis ulcerative in 6 patients, rectal haemorrhage, rectal polyp, anaphylactic reaction,[a)] autoimmune thyroiditis,[a)] presyncope,[a)] subcutaneous abscess,[a)] large intestine infection, asthma, COVID-19, ischaemic stroke, and hypoglycaemia in 1 patient each (some patients had multiple events)
Mirikizumab SC group in the mirikizumab induction responder population	Lipoma, rectocele, COVID-19 pneumonia, gastroenteritis, spinal compression fracture, migraine, diverticulitis, blood glucose increased, inguinal hernia, gastric cancer, hypokalaemia, retinal detachment, retinopexy, back pain, and depression suicidal in 1 patient each (some patients had multiple events)

MedDRA/J ver. 24.1
a) Events considered as adverse drug reactions

During the maintenance period, adverse events leading to treatment discontinuation occurred in 8.3% (16 of 192) of patients in the placebo group (colitis ulcerative in 11 patients, anaphylactic reaction, COVID-19, arthralgia, presyncope, and hypotension in 1 patient each) and 1.5% (6 of 389) of patients in the mirikizumab SC group (colitis ulcerative in 2 patients, injection site hypersensitivity, oedema peripheral, autoimmune hepatitis, and gastric cancer in 1 patient each) in the mirikizumab induction responder population, and anaphylactic reaction, arthralgia, presyncope, and hypotension in 1 patient each in the placebo group and oedema peripheral in 1 patient in the mirikizumab SC group were assessed as adverse drug reactions. During the maintenance period, an adverse event leading to treatment discontinuation occurred in 0.7% (1 of 135) of patients in the placebo induction responder population (ulcerative colitis in 1 patient), and the concerned event was assessed as an adverse drug reaction. In the Japanese population, adverse events leading to treatment discontinuation occurred in 12.0% (3 of 25) of patients in the placebo group (colitis ulcerative in 3 patients) and 4.3% (2 of 47) of patients in the

[14)] 5[redacted]-year old non-Japanese man. On Day 184 of the placebo treatment in Study AMBG (on Day 282 from the first dose of mirikizumab in Study AMAN and Day 220 from the last dose of mirikizumab), COVID-19 occurred, and it was turned into the severe disease on Day 190, resulting in hospitalization. On Day 198, the patient additionally experienced ischaemic stroke and was admitted to an intensive care unit. On Day 199, the patient was discharged from the intensive care unit and returned to the infectious disease ward to continue the treatment for COVID-19. On Day 211 (on Day 309 from the first dose of mirikizumab in Study AMAN and Day 247 from the last dose of mirikizumab), the patient experienced cardiogenic shock and died. For a causal relationship to the study drug, COVID-19 was considered to be “unrelated” by the investigator.

mirikizumab SC group (injection site hypersensitivity, and gastric cancer in 1 patient each) in the mirikizumab induction responder population, but a causal relationship to the study drug was denied for all the events.

For the safety during the open-label extended induction period, adverse events occurred in 29.1% (43 of 148) of patients and adverse drug reactions in 5.4% (8 of 148) of patients in the placebo induction non-responder population, and adverse events occurred in 38.3% (120 of 313) of patients and adverse drug reactions in 7.3% (23 of 313) of patients in the mirikizumab induction non-responder population. For the safety in the Japanese population, adverse events occurred in 33.3% (6 of 18) of patients and adverse drug reactions in 11.1% (2 of 18) of patients in the placebo induction non-responder population, and adverse events and adverse drug reactions occurred in 44.0% (11 of 25) and 12.0% (3 of 25), respectively, in the mirikizumab induction non-responder population. Table 39 shows adverse events reported by ≥2% of patients in either population in the overall population. There were neither adverse drug reactions reported by ≥2% of patients in either population in the overall population nor adverse drug reactions reported by ≥2 patients in either population in the Japanese population.

Table 39. Adverse events reported by ≥2% of patients in either population in the overall population (open-label extended induction period, safety analysis population)

	Overall population		Japanese population	
	Placebo induction non-responder (n = 148)	Mirikizumab induction non-responder (n = 313)	Placebo induction non-responder (n = 18)	Mirikizumab induction non-responder (n = 25)
All adverse events	29.1 (43)	38.3 (120)	33.3 (6)	44.0 (11)
Nasopharyngitis	4.7 (7)	2.6 (8)	11.1 (2)	12.0 (3)
Headache	2.0 (3)	1.6 (5)	0	4.0 (1)
Colitis ulcerative	1.4 (2)	2.6 (8)	5.6 (1)	0
Arthralgia	0.7 (1)	4.5 (14)	0	4.0 (1)

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Incidence (number of patients with events)

During the open-label extended induction period, no deaths occurred. During the open-label extended induction period, serious adverse events occurred in 2.7% (4 of 148) of patients in the placebo induction non-responder population, and of these, event in 1 patient was assessed as a serious adverse drug reaction. In the mirikizumab induction non-responder population, serious adverse events occurred in 5.4% (17 of 313) of patients, and of these, events in 3 patients were assessed as serious adverse drug reactions (Table 40). In the Japanese population, serious adverse events occurred in 5.6% (1 of 18) of patients in the placebo induction non-responder population (colitis ulcerative in 1 patient) and 4.0% (1 of 25) of patients in the mirikizumab induction non-responder population (rectal cancer in 1 patient), and rectal cancer in 1 patient was assessed as a serious adverse drug reaction.

Table 40. Serious adverse events (open-label extended induction period, safety analysis population)

Group	Serious adverse events
Placebo induction non-responder population	Colitis ulcerative in 2 patients, tonsillitis, and pneumonia[a)] in 1 patient each
Mirikizumab induction non-responder population	Colitis ulcerative in 4 patients, colitis, Campylobacter gastroenteritis, Bacillus infection, Escherichia infection, Klebsiella infection, appendicitis,[a)] sepsis, pneumoperitoneum, ileus, large intestine perforation, colectomy total, intervertebral disc protrusion, immune thrombocytopenia,[a)] adenocarcinoma of colon, rectal cancer,[a)] pruritus, nephrolithiasis, ureterolithiasis, peptic ulcer, maculopathy, pneumonia in 1 patient each (some patients had multiple events)

MedDRA/J ver. 24.1
a) Events considered as adverse drug reactions

During the open-label extended induction period, adverse events leading to treatment discontinuation occurred in 0.7% (1 of 148) of patients in the placebo induction non-responder population (colitis ulcerative in 1 patient) and 3.2% (10 of 313) of patients in the mirikizumab induction non-responder population (colitis ulcerative in 4 patients, colitis, immune thrombocytopenia, hypersensitivity, hepatic enzyme increased, adenocarcinoma of colon, and colectomy total in 1 patient each), and immune thrombocytopenia, hypersensitivity, hepatic enzyme increased in 1 patient each in the mirikizumab induction non-responder population were assessed as adverse drug reactions. In the Japanese population, an adverse event leading to treatment discontinuation occurred in 1 patient in the mirikizumab induction non-responder population (hypersensitivity), and the concerned event was assessed as an adverse drug reaction.

For the safety during the open-label extended maintenance period, adverse events occurred in 56.0% (56 of 100) of patients and adverse drug reactions in 12.0% (12 of 100) of patients in the placebo induction non-responder population, and adverse events occurred in 57.9% (99 of 171) of patients and adverse drug reactions in 13.5% (23 of 171) of patients in the mirikizumab induction non-responder population. For the safety in the Japanese population, adverse events occurred in 54.5% (6 of 11) of patients in the placebo induction non-responder population (no adverse drug reactions occurred), and adverse events occurred in 81.8% (9 of 11) of patients and adverse drug reactions in 18.2% (2 of 11) of patients in the mirikizumab induction non-responder population.

Table 41 and Table 42 show adverse events and adverse drug reactions, respectively, reported by ≥2% of patients in either population in the overall population.

Table 41. Adverse events reported by ≥2% of patients in either population in the overall population (open-label extended maintenance period, safety analysis population)

	Overall population		Japanese population	
	Placebo induction non-responder (n = 100)	Mirikizumab induction non-responder (n = 171)	Placebo induction non-responder (n = 11)	Mirikizumab induction non-responder (n = 11)
All adverse events	56.0 (56)	57.9 (99)	54.5 (6)	81.8 (9)
Arthralgia	6.0 (6)	7.6 (13)	0	9.1 (1)
Headache	6.0 (6)	4.1 (7)	9.1 (1)	18.2 (2)
Nasopharyngitis	5.0 (5)	5.3 (9)	0	18.2 (2)
Upper respiratory tract infection	4.0 (4)	2.9 (5)	0	0
Injection site reaction	3.0 (3)	1.8 (3)	0	9.1 (1)
Pyrexia	3.0 (3)	1.8 (3)	9.1 (1)	0
Haemorrhoids	3.0 (3)	1.8 (3)	0	0
Hypertension	3.0 (3)	0	0	0
Vaccination complication	3.0 (3)	0	0	0
Diarrhoea	2.0 (2)	3.5 (6)	0	0
COVID-19	2.0 (2)	2.3 (4)	0	0
Clostridium difficile infection	2.0 (2)	0.6 (1)	0	0
Abdominal pain	2.0 (2)	0.6 (1)	0	0
Oropharyngeal pain	2.0 (2)	0	0	0
Dyspepsia	2.0 (2)	0	0	0
Oedema peripheral	2.0 (2)	0	0	0
Muscle strain	2.0 (2)	0	0	0
Colitis ulcerative	1.0 (1)	6.4 (11)	0	18.2 (2)
Anaemia	1.0 (1)	4.7 (8)	0	18.2 (2)
Injection site pain	1.0 (1)	3.5 (6)	0	0
Gastrooesophageal reflux disease	1.0 (1)	2.3 (4)	0	9.1 (1)

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Incidence (number of patients with events)

Table 42. Adverse drug reactions reported by ≥2% of patients in either population in the overall population (open-label extended maintenance period, safety analysis population)

	Overall population		Japanese population	
	Placebo induction non-responder (n = 100)	Mirikizumab induction non-responder (n = 171)	Placebo induction non-responder (n = 11)	Mirikizumab induction non-responder (n = 11)
All adverse drug reactions	12.0 (12)	13.5 (23)	0	18.2 (2)
Injection site reaction	3.0 (3)	1.8 (3)	0	9.1 (1)
Injection site pain	1.0 (1)	3.5 (6)	0	0

MedDRA/J ver. 24.1
Incidence (number of patients with events)

During the open-label extended maintenance period, no deaths occurred. During the open-label extended maintenance period, serious adverse events occurred in 2.0% (2 of 100) of patients in the placebo induction non-responder population (colitis and influenza in 1 patient each) and 3.5% (6 of 171) of patients in the mirikizumab induction non-responder population (colitis ulcerative in 2 patients, sepsis, cellulitis, acute coronary syndrome, Kaposi's sarcoma, and tooth extraction in 1 patient each [some patients had multiple events]), and colitis ulcerative and acute coronary syndrome in 1 patient each in the mirikizumab induction non-responder population were assessed as serious adverse drug reactions. In the Japanese population, serious adverse events occurred in 8.0% (2 of 25) of patients in the mirikizumab induction non-responder population (colitis ulcerative, sepsis, and tooth extraction in 1 patient each [some patients had multiple events]), but a causal relationship to the study drug was denied for all the events.

During the open-label extended maintenance period, adverse events leading to treatment discontinuation occurred in 2.3% (4 of 171) of patients in the mirikizumab induction non-responder population (colitis ulcerative in 3 patients, Kaposi's sarcoma in 1 patient), and colitis ulcerative in 1 patient was assessed as an adverse drug reaction. In the Japanese population, an adverse event leading to treatment discontinuation occurred in 1 patient in the mirikizumab induction non-responder population (colitis ulcerative), but a causal relationship to the study drug was denied for the event.

A total of 90 patients met the criteria for reduced response (Table 20) during the maintenance period and then entered the open-label re-induction period (received re-induction therapy) (29 in the placebo induction responder population [1 Japanese], 42 in the placebo group in the mirikizumab induction responder population [4 Japanese], 19 in the mirikizumab SC group in the mirikizumab induction responder population [1 Japanese]), and they were included in the ITT population and safety analysis population for the open-label re-induction period.

For the safety during the open-label re-induction period, adverse events occurred in 41.1% (37 of 90) of patients and adverse drug reactions in 8.9% (8 of 90) of patients. In the Japanese population, adverse events occurred in 3 of 6 patients and an adverse drug reaction in 1 of 6 patients. Adverse events reported by ≥2 patients in the overall population were anaemia, headache (5 patients each), arthralgia (4 patients), Clostridium difficile infection, sinusitis, leukopenia, chest pain, and dizziness (2 patients each). There were no adverse drug reactions reported by ≥2 patients in the overall population, or adverse events or adverse drug reactions reported by ≥2 patients in the Japanese population.

During the open-label re-induction period, no deaths occurred. During the open-label re-induction period, serious adverse events occurred in 3.3% (3 of 90) of patients (colitis ulcerative, pneumonia, arthralgia, and neurologic somatic symptom disorder in 1 patient each [some patients had multiple events]), and all events were assessed as serious adverse drug reactions. In the Japanese population, a serious adverse event was neurologic somatic symptom disorder in 1 patient and assessed as a serious adverse drug reaction.

During the open-label re-induction period, adverse events leading to treatment discontinuation occurred in 2.2% (2 of 90) of patients (colitis ulcerative and pneumonia in 1 patient each), and both events were assessed as adverse drug reactions. In the Japanese population, no adverse events leading to treatment discontinuation occurred.

7.3 Long-term extension study (CTD 5.3.5.2.1, Study I6T-MC-AMAP, since [redacted] 20[redacted] [ongoing as of [redacted] 20[redacted]], data cut-off on [redacted] [redacted], 20[redacted])

An open-label, long-term extension study was conducted at 351 study sites (51 study sites in Japan) in 36 countries or regions including Japan, in the following patients (target sample size, 800-960 patients): Patients who had completed the 40-week maintenance period or open-label maintenance period in Study AMAC; patients who had completed 40-week maintenance period or 28-week open-label maintenance period in Study AMBG; and patients who had entered the open-label re-induction period during the maintenance period of Study AMBG and were considered to have gained clinical benefits. Of note,

patients who could not enter Study AMBG because of the eCOA error in Study AMAN [see Section 7.2.1] were also enrolled in this study.

Mirikizumab 200 mg was subcutaneously administered Q4W.

All of 899 patients enrolled in this study (141 from Study AMAC, 751 from Study AMBG, 7 from Study AMAN) received the study drug and were included in the safety analysis population.

The applicant submitted only the safety data in the overall population as of the data cut-off ([redacted], 20[redacted]) in this application.

A total of 81 patients discontinued the treatment because of "lack of efficacy" in 25 patients, "consent withdrawal" in 22 patients, "adverse events" in 17 patients, "investigator's decision" in 7 patients, "lost to follow-up" in 6 patients, "other reasons" in 3 patients, and "death" in 1 patient.

Adverse events occurred in 59.1% (531 of 899) of patients and adverse drug reactions in 10.8% (97 of 899) of patients. Table 43 shows adverse events reported by ≥2% of patients in the overall population. An adverse drug reaction reported by ≥2% of patients in the overall population was injection site pain (2.2%, 20 of 899 patients).

Table 43. Adverse events reported by ≥2% of patients in the overall population (safety analysis population)

	Overall population (n = 899)
All adverse events	59.1 (531)
Colitis ulcerative	10.6 (95)
Nasopharyngitis	6.6 (59)
COVID-19	6.0 (54)
Headache	5.0 (45)
Arthralgia	3.7 (33)
Pyrexia	3.2 (29)
Injection site pain	2.3 (21)
Upper respiratory tract infection	2.1 (19)
Hypertension	2.1 (19)
Back pain	2.0 (18)

Incidence in % (number of patients with events)
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Death occurred in 1 patient (COVID-19 pneumonia).[15)] Serious adverse events occurred in 4.4% (40 of 899) of patients, and of these, cerebellar stroke and cerebellar syndrome in 1 patient were assessed as serious adverse drug reactions (Table 44).

15) 6[redacted]-year old non-Japanese man. The patient was assigned to the mirikizumab IV group in Study AMAN and completed the induction period, then was enrolled in the mirikizumab induction non-responder population in Study AMBG and completed the maintenance period, and entered Study AMAP. On Day 433 from the first dose of mirikizumab in Study AMAN (on Day 2 from the last dose of mirikizumab), the patient experienced COVID-19 pneumonia, and on Day 436, he was hospitalized with a subjective symptom of dyspnea. Although medications for COVID-19 were performed, his condition worsened with decreased oxygen saturation etc., and bradycardia occurred, resulting in death, on Day 457 (Day 26 from the last dose of mirikizumab). For a causal relationship to the study drug, COVID-19 pneumonia was determined as "unrelated" by the investigator.

Table 44. Serious adverse events (safety analysis population)

Events
Uterine leiomyoma, appendicitis in 3 patients each, colitis ulcerative, angina unstable, osteoarthritis in 2 patients each, cerebellar stroke,[a)] cerebellar syndrome,[a)] tonsillitis, post procedural haemorrhage, adenocarcinoma of colon, meniscus injury, stag horn calculus, pilonidal cyst, abdominal pain, intracranial aneurysm, prostate cancer, cerebrovascular insufficiency, transient ischaemic attack, contusion, rib fracture, road traffic accident, cubital tunnel syndrome, postoperative wound infection, syphilis, intestinal haemorrhage, upper limb fracture, malignant melanoma, COVID-19 pneumonia, COVID-19, humerus fracture, joint dislocation, lacunar infarction, cerebral infarction, acetabulum fracture, facial bones fracture, ilium fracture, pelvic fracture, cholecystitis acute, loose body in joint, synovitis, inguinal hernia, atrial fibrillation, cardiac failure acute, cardiogenic shock, arthralgia, loss of consciousness, retinal detachment, vestibular disorder, endometriosis, large intestine infection, rash, dyspnoea, throat tightness in 1 patient each (some patients had multiple events)

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a) Events considered as adverse drug reactions

Adverse events leading to treatment discontinuation occurred in 2.4% (22 of 899) of patients (colitis ulcerative in 14 patients, adenocarcinoma of colon, COVID-19 pneumonia, dermatitis, drug hypersensitivity, extranodal marginal zone B-cell lymphoma [MALT type], hepatic enzyme increased, malignant melanoma, and scleritis in 1 patient each), and adverse drug reactions leading to treatment discontinuation occurred in 0.7% (6 of 899) of patients (colitis ulcerative in 3 patients, dermatitis, drug hypersensitivity, extranodal marginal zone B-cell lymphoma [MALT type] in 1 patient each).

7.R Outline of the review conducted by PMDA

7.R.1 Enrollment of Japanese patients in the global studies in patients with UC

The evaluation data on the efficacy and safety submitted for this application were comprised of results from a phase II study (Study AMAC) and phase III studies (Studies AMAN, AMBG, and AMAP), all of which were conducted as global studies.

The applicant's explanation about differences in endogenous and exogenous ethnic factors between Japan and the major participant countries, Europe and North America:
For the endogenous ethnic factors, the phase I study (Study AMAD) demonstrated that a single intravenous dose of mirikizumab 600 mg, the highest dose planned in a global phase II study (Study AMAC), was tolerated by Japanese patients and pharmacokinetics did not clearly differ between Japanese and non-Japanese patients [see Section 6.2.1]. On the basis of the above results, Japanese patients were enrolled in the global phase II study (Study AMAC) and global phase III studies (Studies AMAN, AMBG, and AMAP). The population pharmacokinetic analysis using pharmacokinetic data from the global phase III studies (Studies AMAN and AMBG) [see Section 6.2.4] revealed no clinically relevant differences in pharmacokinetics between Japanese and non-Japanese patients with UC [see Section 6.R.1].

For exogenous ethnic factors, a therapeutic system of UC in Japan is similar to those in Europe and North America. The modified Mayo score, used as an indicator of the efficacy evaluation, is established by excluding physician's global assessment from the Mayo score, which is widely used for UC assessment in and outside Japan. It is comprised of stool frequency, rectal bleeding, and endoscopic subscores and represents activity of UC. The applicant therefore considers it acceptable to evaluate the efficacy of mirikizumab using this score.

As described above, the enrollment of Japanese patients in the global studies has no problems.

PMDA considers that the enrollment of Japanese patients in the global studies has no problems and the efficacy and safety of mirikizumab in Japanese patients with UC may be evaluated based on results from Studies AMAN, AMBG, and AMAP, global phase III studies.

7.R.2 Efficacy

According to the review in Sections 7.R.2.1 and 7.R.2.2, PMDA considered that mirikizumab has been demonstrated to induce and maintain remission in patients with moderate to severe UC who had an inadequate response to conventional treatment.

7.R.2.1 Induction period

7.R.2.1.1 Results on the primary endpoint

The applicant's explanation about results on the primary endpoint in Study AMAN, a global phase III induction period study:

Results on the proportion of patients in clinical remission at Week 12, the primary endpoint in Study AMAN, demonstrated superiority of mirikizumab IV to placebo in the overall population (Table 31). As shown in Table 45, results on the primary endpoint in the Japanese population had a similar trend to those in the overall population.

As described above, mirikizumab is demonstrated to be effective in patients with moderate to severe UC during the induction period.

Table 45. Results on the primary endpoint (Study AMAN, mITT population, NRI)

	Overall population		Japanese population	
	Placebo (n = 294)	Mirikizumab IV (n = 868)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Proportion of patients in clinical remission at Week 12, % (n)	13.3 (39)	24.2 (210)	2.9 (1)	32.4 (33)
Difference from placebo [99.875% CI][a)]	11.1 [3.2, 19.1]		30.0 [11.5, 48.5]	

a) Cochran-Mantel-Haenszel test using biologic-failed status, use of steroids at baseline, modified Mayo score at baseline (<7 or ≥7), and region (North America, Europe, or others) as stratification factors.

7.R.2.1.2 Result on the main secondary endpoints

The applicant's explanation about the main secondary endpoints in Study AMAN:

As shown in Table 46, results on all of the main secondary endpoints tended to be higher in the mirikizumab IV group than in the placebo group in Study AMAN, and the Japanese population also showed a similar trend to that in the overall population.

Table 46. Results on the main secondary endpoints (Study AMAN, mITT population, NRI)

	Overall population		Japanese population	
	Placebo (n = 294)	Mirikizumab IV (n = 868)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Proportion of patients with clinical improvement at Week 12, % (n)	42.2 (124)	63.5 (551)	22.9 (8)	71.6 (73)
Difference from placebo [99.875% CI]	21.4 [10.8, 32.0]		45.0 [15.9, 74.1]	
Proportion of patients with endoscopic improvement at Week 12, % (n)	21.1 (62)	36.3 (315)	8.6 (3)	41.2 (42)
Difference from placebo [99.875% CI]	15.4 [6.3, 24.5]		31.6 [9.4, 53.8]	

7.R.2.1.3 Efficacy by patient characteristic

The applicant's explanation about the efficacy by patient characteristic in Study AMAN:

Table 47 shows results on the proportion of patients in clinical remission at Week 12 by main patient characteristic in Study AMAN. Although it should be noted that some subgroups have a limited sample size, the results tended to be higher in the mirikizumab IV group than in the placebo group in all the subgroups.

Table 47. Proportion of patients in clinical remission at Week 12 by main patient characteristic (Study AMAN, mITT population, NRI)

		Placebo (n = 294)	Mirikizumab IV (n = 868)
Age	<40 years	15.5 (23/148)	27.7 (109/393)
	≥40 years	11.0 (16/146)	21.3 (101/475)
Sex	Male	12.1 (20/165)	19.8 (105/530)
	Female	14.7 (19/129)	31.1 (105/338)
Baseline BMI (kg/m^2)[a)]	≥18.5 and <25	12.8 (19/149)	27.7 (125/451)
	≥25 and <30	11.8 (9/76)	19.5 (46/236)
	≥30 and <40	15.4 (6/39)	19.3 (22/114)
Prior non-response to biological products or JAK inhibitors	Yes	8.5 (10/118)	15.3 (55/361)
	None	16.5 (29/176)	30.6 (155/507)
Baseline corticosteroid use	Yes	16.8 (19/113)	20.2 (71/351)
	None	11.0 (20/181)	26.9 (139/517)
Baseline immunomodulatory drug use	Yes	15.9 (11/69)	19.0 (40/211)
	None	12.4 (28/225)	25.9 (170/657)
Duration of disease	<1 year	12.1 (4/33)	30.6 (26/85)
	≥1 year and <3 years	16.7 (13/78)	25.6 (54/211)
	≥3 years and <7 years	13.2 (10/76)	24.7 (58/235)
	≥7 years	11.2 (12/107)	21.4 (72/337)
Baseline disease location	Left-sided colitis	12.8 (24/188)	26.7 (145/544)
	Pancolitis	14.6 (15/103)	19.5 (62/318)

a) Patients with BMI <18.5 kg/m^2 and ≥40 kg/m^2 were excluded from the tabulation due to limited sample size.

PMDA's view on the efficacy of mirikizumab during the induction period, based on the review in Sections 7.R.2.1.1 to 7.R.2.1.3:

Results on the proportion of patients in clinical remission at Week 12, the primary endpoint in Study AMAN, demonstrated superiority of mirikizumab IV to placebo. In the Japanese population, the proportion of patients in clinical remission was also higher in the mirikizumab IV group than in the placebo group, and the result was consistent with that as observed in the overall population, although it should be noted that the sample size is limited (Table 45). In addition, results on the main secondary endpoints and by patient characteristic showed no trends that raised particular problems (Table 46 and Table 47).

As shown above, mirikizumab has been demonstrated to induce remission in patients with moderate to severe UC who had an inadequate response to conventional treatment, and the efficacy can be expected in the Japanese population as well.

7.R.2.2 Maintenance period

7.R.2.2.1 Primary endpoint

The applicant's explanation about results on the primary endpoint in Study AMBG, a global phase III maintenance period study:

Results on the proportion of patients in clinical remission at Week 40 of the maintenance period, the primary endpoint in Study AMBG, demonstrated superiority of mirikizumab SC to placebo in the overall population (Table 35). As shown in Table 48, results on the primary endpoint in the Japanese population had a similar trend to those in the overall population.

As described above, mirikizumab is demonstrated to be effective in patients with moderate to severe UC during the maintenance period.

Table 48. Results on the primary endpoint
(Study AMBG, mirikizumab induction responder population, mITT population, NRI)

	Overall population		Japanese population	
	Placebo (n = 179)	Mirikizumab SC (n = 365)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Proportion of patients in clinical remission at Week 40 of the maintenance period, % (n)	25.1 (45)	49.9 (182)	28.0 (7)	48.9 (23)
Difference from placebo [95% CI][a)]	23.2 [15.2, 31.2]		16.2 [-6.8, 39.2]	

a) Cochran-Mantel-Haenszel test using biologic-failed status, use of steroids at baseline of Study AMAN, region (North America, Europe, or others), and clinical remission at Week 12 of Study AMAN as stratification factors

7.R.2.2.2 Result on the main secondary endpoints

The applicant's explanation about the main secondary endpoints in Study AMBG:

As shown in Table 49, results on the main secondary endpoints tended to be higher in the mirikizumab SC group than in the placebo group in Study AMBG, and the Japanese population also showed a similar trend to that in the overall population.

Table 49. Results on the main secondary endpoints
(Study AMBG, mirikizumab induction responder population, mITT population, NRI)

	Overall population		Japanese population	
	Placebo (n = 179)	Mirikizumab SC (n = 365)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Proportion of patients in clinical remission at Week 40 of the maintenance period in those in clinical remission at Week 12 of the induction period, % (maintenance responders/induction responders)	36.9 (24/65)	63.6 (91/143)	45.5 (5/11)	59.1 (13/22)
Difference from placebo [95% CI]	24.8 [10.4, 39.2]		8.9 [-28.1, 46.0]	
Proportion of patients with endoscopic improvement at Week 40 of the maintenance period, % (n)	29.1 (52)	58.6 (214)	28.0 (7)	57.4 (27)
Difference from placebo [95% CI]	28.5 [20.2, 36.8]		27.0 [4.0, 49.9]	
Proportion of patients in steroid-free remission at Week 40 of the maintenance period, % (n)	21.8 (39)	44.9 (164)	28.0 (7)	44.7 (21)
Difference from placebo [95% CI]	21.3 [13.5, 29.1]		13.0 [-10.4, 36.4]	

7.R.2.2.3 Efficacy by patient characteristic

The applicant's explanation about the efficacy by patient characteristic in Study AMBG:

Table 50 shows results on the proportion of patients in clinical remission at Week 40 of the maintenance period by main patient characteristic during the maintenance period. Although it should be noted that some subgroups have a limited sample size, the results tended to be higher in the mirikizumab SC group than in the placebo group in all the subgroups.

Table 50. Proportion of patients in clinical remission at Week 40 of the maintenance period by main patient characteristic (Study AMBG, mirikizumab induction responder population, mITT population, NRI)

		Placebo (n = 179)	Mirikizumab SC (n = 365)
Age	<40 years	24.7 (23/93)	51.3 (81/158)
	≥40 years	25.6 (22/86)	48.8 (101/207)
Sex	Male	24.0 (25/104)	50.9 (109/214)
	Female	26.7 (20/75)	48.3 (73/151)
Baseline BMI (kg/m^2)[a)]	≥18.5 and <25	26.8 (26/97)	51.0 (100/196)
	≥25 and <30	17.4 (8/46)	46.4 (45/97)
	≥30 and <40	34.6 (9/26)	51.3 (20/39)
Prior non-response to biological products or JAK inhibitors	Yes	15.6 (10/64)	46.1 (59/128)
	None	30.4 (35/115)	51.9 (123/237)
Baseline corticosteroid use	Yes	17.6 (12/68)	45.2 (61/135)
	None	29.7 (33/111)	52.6 (121/230)
Baseline immunomodulatory drug use	Yes	28.2 (11/39)	50.0 (39/78)
	None	24.3 (34/140)	49.8 (143/287)
Duration of disease	<1 year	23.5 (4/17)	52.4 (22/42)
	≥1 year and <3 years	25.0 (9/36)	50.5 (50/99)
	≥3 years and <7 years	20.3 (12/59)	56.8 (54/95)
	≥7 years	29.9 (20/67)	43.4 (56/129)
Baseline disease location	Left-sided colitis	31.1 (37/119)	52.1 (122/234)
	Pancolitis	13.6 (8/59)	46.1 (59/128)

a) Patients with BMI <18.5 kg/m^2 and ≥40 kg/m^2 were excluded from the tabulation due to limited sample size.

PMDA's view on the efficacy of mirikizumab during the maintenance period, based on the review in Sections 7.R.2.2.1 to 7.R.2.2.3:

Results on the proportion of patients in clinical remission at Week 40 of the maintenance period, the primary endpoint in Study AMBG, demonstrated superiority of mirikizumab SC to placebo. In the Japanese population, the proportion of patients in clinical remission was also higher in the mirikizumab SC group than in the placebo group, and the result was consistent with that as observed in the overall population, although it should be noted that the sample size is limited (Table 48). In addition, results on the main secondary endpoints and by patient characteristic showed no trends that raised particular problems (Table 49 and Table 50).

As shown above, mirikizumab has been demonstrated to maintain remission in patients with moderate to severe UC who had an inadequate response to conventional treatment but therapeutically responded to the induction therapy with mirikizumab, and the efficacy can be expected in the Japanese population as well.

7.R.3 Safety

For the safety evaluation of mirikizumab, PMDA compared the mirikizumab group with the placebo group during each of the induction period (including the open-label extended induction period and re-

induction period) and maintenance period in the global phase III studies in patients with UC (Studies AMAN and AMBG). In some investigations, data from the global phase II study (Study AMAC) and long-term extension study (Study AMAP) were additionally included.

As a result of the review in Sections 7.R.3.1 to 7.R.3.3, PMDA considers that mirikizumab has acceptable safety, provided that it is used by physicians with adequate knowledge about mirikizumab and knowledge about and experience in the treatment of UC. Of note, because the number of Japanese patients evaluated in the clinical studies is limited, the applicant is required to continue collecting information through post-marketing surveillance etc. and evaluate the safety.

7.R.3.1 Incidences of adverse events

Incidences of adverse events in the global phase III studies (Studies AMAN and AMBG) are summarized as shown below.

7.R.3.1.1 Induction period

Table 51 shows outline of incidences of adverse events in Study AMAN, presenting no clinically relevant differences between the mirikizumab IV and placebo groups. The Japanese population presented no problematic trend in comparison with the overall population.

Table 51. Outline of adverse events and adverse drug reactions during the induction period (Study AMAN, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
All adverse events	46.1 (148)	44.5 (426)	54.3 (19)	47.1 (48)
All adverse drug reactions	10.9 (35)	10.3 (99)	5.7 (2)	9.8 (10)
Deaths	0	0	0	0
Serious adverse events	5.3 (17)	2.8 (27)	8.6 (3)	2.9 (3)
Serious adverse drug reactions	1.6 (5)	0.3 (3)	2.9 (1)	1.0 (1)
Adverse events leading to treatment discontinuation	7.2 (23)	1.6 (15)	17.1 (6)	2.0 (2)

Incidence in % (number of patients with events)

Table 52 shows outline of incidences of adverse events in patients who had received mirikizumab but not met the criteria for clinical improvement at Week 12 in Study AMAN and then entered the open-label extended induction period in Study AMBG and in patients who had received mirikizumab during the maintenance period in Study AMBG, met the criteria for reduced response, and then entered the open-label re-induction period. Incidences of adverse events during the open-label extended induction period (mirikizumab induction non-responder population) and open-label re-induction period (mirikizumab SC group in the mirikizumab induction responder population) in Study AMBG showed no problematic trend in comparison with those in the mirikizumab IV group in Study AMAN.

Table 52. Outline of adverse events and adverse drug reactions during the open-label extended induction period and open-label re-induction period (Study AMBG, safety analysis population)

	Open-label extended induction period (mirikizumab induction non-responder population)		Open-label re-induction period (mirikizumab SC group in the mirikizumab induction responder population)		Reference: Mirikizumab IV group in Study AMAN
	Overall population (n = 313)	Japanese population (n = 25)	Overall population (n = 19)	Japanese population (n = 1)	Overall population (n = 958)
All adverse events	38.3 (120)	44.0 (11)	31.6 (6)	0	44.5 (426)
All adverse drug reactions	7.3 (23)	12.0 (3)	5.3 (1)	0	10.3 (99)
Deaths	0	0	0	0	0
Serious adverse events	5.4 (17)	4.0 (1)	0	0	2.8 (27)
Serious adverse drug reactions	1.0 (3)	4.0 (1)	0	0	0.3 (3)
Adverse events leading to treatment discontinuation	3.2 (10)	4.0 (1)	0	0	1.6 (15)

Incidence in % (number of patients with events)

PMDA confirmed that incidences of adverse events in the mirikizumab IV group during the induction period showed no clinically relevant trend in comparison with those in the placebo group and that the Japanese population presented no problematic trend in comparison with the overall population. In addition, incidences of adverse events in patients who entered the open-label extended induction or re-induction period in both overall and Japanese populations showed no clinically relevant trend in comparison with those in the mirikizumab IV group during the induction period.

7.R.3.1.2 Maintenance period

Table 53 shows outline of incidences of adverse events in Study AMBG, presenting no clinically relevant differences between the mirikizumab SC and placebo groups. The Japanese population presented no problematic trend in comparison with the overall population.

Table 53. Outline of adverse events and adverse drug reactions during the maintenance period (Study AMBG, mirikizumab induction responder population, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 192)	Mirikizumab SC (n = 389)	Placebo (n = 25)	Mirikizumab SC (n = 47)
All adverse events	68.8 (132)	64.5 (251)	88.0 (22)	89.4 (42)
All adverse drug reactions	16.7 (32)	16.7 (65)	12.0 (3)	21.3 (10)
Deaths	0.5 (1)	0	0	0
Serious adverse events	7.8 (15)	3.3 (13)	8.0 (2)	4.3 (2)
Serious adverse drug reactions	2.1 (4)	0	4.0 (1)	0
Adverse events leading to treatment discontinuation	8.3 (16)	1.5 (6)	12.0 (3)	4.3 (2)

Incidence in % (number of patients with events)

PMDA confirmed that incidences of adverse events in the mirikizumab SC group during the maintenance period showed no clinically relevant trend in comparison with those in the placebo group and that the Japanese population presented no problematic trend in comparison with the overall population.

7.R.3.2 Safety by treatment duration

The applicant's explanation about the safety by treatment duration:

Pooled data from 4 studies, including the global phase II study (Study AMAC) and global phase III studies (Studies AMAN, AMBG, and AMAP), were used to evaluate the safety by treatment duration.

Table 54 shows incidences of adverse events by treatment duration from the first dose of mirikizumab. The incidences of adverse events did not increase with increasing treatment duration in either the overall or Japanese population.

Table 54. Incidences of adverse events by treatment duration from the first dose of mirikizumab (pooled population from Studies AMAC, AMAN, AMBG, and AMAP)

	Overall population						Japanese population					
	Weeks 0-13 (n = 1,442)	Weeks 14-26 (n = 1,395)	Weeks 27-39 (n = 1,283)	Weeks 40-52 (n = 1,133)	Week ≥52 (n = 1,004)	Entire period (n = 1,442)	Weeks 0-13 (n = 158)	Weeks 14-26 (n = 153)	Weeks 27-39 (n = 138)	Weeks 40-52 (n = 125)	Week ≥52 (n = 107)	Entire period (n = 158)
All adverse events	42.9 (619)	18.0 (251)	6.6 (85)	5.8 (66)	8.6 (86)	76.8 (1,107)	49.4 (78)	24.8 (38)	8.0 (11)	7.2 (9)	5.6 (6)	89.9 (142)
Deaths	0	0.1 (2)	0	0.1 (1)	0.1 (1)	0.3 (4)	0	0	0	0	0	0
Serious adverse events[a)]	2.9 (42)	2.4 (34)	2.3 (29)	1.1 (13)	3.8 (38)	10.1 (145)	4.4 (7)	2.0 (3)	2.9 (4)	3.2 (4)	2.8 (3)	12.0 (19)
Adverse events leading to treatment discontinuation	1.6 (23)	1.5 (21)	0.8 (10)	1.0 (11)	2.1 (21)	6.0 (86)	1.9 (3)	2.0 (3)	1.4 (2)	2.4 (3)	4.7 (5)	10.1 (16)
Adverse events reported by ≥5% of patients in the overall population during the entire period												
Colitis ulcerative	2.1 (31)	3.1 (43)	3.0 (39)	2.1 (24)	8.3 (83)	15.3 (220)	4.4 (7)	3.9 (6)	2.9 (4)	1.6 (2)	4.7 (5)	15.2 (24)
Nasopharyngitis	4.6 (67)	2.9 (40)	1.7 (22)	1.8 (20)	2.9 (29)	12.3 (178)	12.0 (19)	11.1 (17)	4.3 (6)	3.2 (4)	7.5 (8)	34.2 (54)
Arthralgia	1.9 (28)	3.1 (43)	1.9 (25)	1.0 (11)	2.6 (26)	9.2 (133)	1.9 (3)	2.0 (3)	2.2 (3)	0	1.9 (2)	7.0 (11)
Headache	3.4 (49)	1.5 (21)	1.2 (15)	0.8 (9)	3.6 (36)	9.0 (130)	3.8 (6)	1.3 (2)	0.7 (1)	2.4 (3)	4.7 (5)	10.8 (17)
Anaemia	3.0 (43)	1.2 (17)	0.8 (10)	0.8 (9)	1.0 (10)	6.2 (89)	1.9 (3)	0.7 (1)	1.4 (2)	0.8 (1)	0	4.4 (7)
COVID-19	0.3 (5)	0.9 (12)	0.6 (8)	1.1 (12)	5.0 (50)	6.0 (87)	0	0	0	0	0.9 (1)	0.6 (1)
Upper respiratory tract infection	1.3 (19)	1.2 (17)	0.8 (10)	0.6 (7)	2.0 (20)	5.1 (73)	0.6 (1)	0	0	0.8 (1)	0.9 (1)	1.9 (3)
Pyrexia	1.2 (17)	1.0 (14)	0.5 (7)	0.8 (9)	2.5 (25)	5.0 (72)	1.9 (3)	0.7 (1)	0	1.6 (2)	8.4 (9)	9.5 (15)

Incidence in % (number of patients with events)
MedDRA/J ver.24.1
a) Except deaths

PMDA confirmed that in results of a pooled analysis on data from 4 studies, including the global phase II study (Study AMAC) and global phase III studies (Studies AMAN, AMBG, and AMAP), the incidences of adverse events did not tend to increase with increasing treatment duration in either the overall or Japanese population.

7.R.3.3 Adverse events of special interest

PMDA reviewed the safety results mainly from the global phase III studies (Studies AMAN and AMBG) with special attention to the adverse events of special interest defined by the applicant, adverse events of which the incidence was higher in a mirikizumab group than in the placebo group, and adverse events of special interest defined for other IL-23 inhibitors (ustekinumab, risankizumab, etc.) as with mirikizumab.

7.R.3.3.1 Infections

The applicant's explanation about infections:

Among infections reported,[16] the applicant defined serious infections and opportunistic infections[17] as infections of special interest.

Table 55 shows incidences of infections during the induction period. In both overall and Japanese populations, incidences of serious infections and opportunistic infections were low, and no remarkable differences were observed in incidence of serious infections between the placebo and mirikizumab IV groups, but an infection leading to treatment discontinuation (intestinal sepsis) occurred in 1 patient in the mirikizumab IV group.

Table 55. Summary of incidences of infections of special interest during the induction period (serious infections and opportunistic infections) (Study AMAN, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Infections	14.0 (45)	15.1 (145)	17.1 (6)	17.6 (18)
Serious infections	0.6 (2)	0.7 (7)	2.9 (1)	1.0 (1)
Pneumonia	0	0.2 (2)	0	1.0 (1)
Klebsiella infection	0	0.1 (1)	0	0
Cytomegalovirus colitis	0	0.1 (1)	0	0
Gastroenteritis viral	0	0.1 (1)	0	0
Intestinal sepsis	0	0.1 (1)	0	0
Viral infection	0	0.1 (1)	0	0
Sinusitis	0.3 (1)	0	2.9 (1)	0
Acute sinusitis	0.3 (1)	0	0	0
Opportunistic infections	0.3 (1)	0.5 (5)	0	0
Herpes zoster	0.3 (1)	0.1 (1)	0	0
Cytomegalovirus colitis	0	0.2 (2)	0	0
Oesophageal candidiasis	0	0.1 (1)	0	0
Intestinal tuberculosis	0	0.1 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.0

Table 56 shows incidences of infections during the maintenance period. In both overall and Japanese populations, incidences of serious infections and opportunistic infections were low, and no remarkable differences were observed in incidence of serious infections between the placebo and mirikizumab SC groups. No infections leading to treatment discontinuation, not limited to infections of special interest, occurred.

[16] Identified using a list of preferred terms (PTs) in the MedDRA (MedDRA PT) according to Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and post-marketing surveillance (*Ann Rheum Dis.* 2015;74:2107-16). However, applicability of oral candidiasis and oral fungal infection to the infections of special interest was determined based on the infection site.

[17] Events classified as "Opportunistic infections (narrow)" of MedDRA Standardized MedDRA query (SMQ)

Table 56. Summary of incidences of infections of special interest during the maintenance period (serious infections and opportunistic infections) (Study AMBG, mirikizumab induction responder population, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 192)	Mirikizumab SC (n = 389)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Infections	22.9 (44)	23.9 (93)	44.0 (11)	42.6 (20)
Serious infections	1.6 (3)	0.8 (3)	0	0
COVID-19	0.5 (1)	0	0	0
Large intestine infection	0.5 (1)	0	0	0
Subcutaneous abscess	0.5 (1)	0	0	0
COVID-19 pneumonia	0	0.3 (1)	0	0
Diverticulitis	0	0.3 (1)	0	0
Gastroenteritis	0	0.3 (1)	0	0
Opportunistic infections	0	1.3 (5)	0	2.1 (1)
Herpes zoster	0	1.0 (4)	0	0
Oral candidiasis	0	0.3 (1)	0	2.1 (1)

Incidence in % (number of patients with events)
MedDRA/J ver.24.1

Table 57 shows details of patients with serious adverse drug reactions of infections associated with mirikizumab in any of the clinical studies in the submitted data.

Table 57. List of patients with serious adverse drug reactions of infections associated with mirikizumab

Study	Time of onset	Age	Sex	Race	PT [a]	Severity	Time to onset (days)[b]	Duration (days)	Action on mirikizumab	Outcome
Study AMAN	Induction period	5[redacted]	Female	Non-Japanese	Klebsiella infection	Severe	83	152	Continued	Unresolved
Study AMBG	Open-label extended induction period	2[redacted]	Male	Non-Japanese	Appendicitis	Severe	16	1	Continued	Resolved
	Open-label extended induction period	2[redacted]	Female	Non-Japanese	Pneumonia	Moderate	52	13	Continued	Resolved
	Open-label re-induction period	6[redacted]	Female	Non-Japanese	Pneumonia	Severe	68	103	Discontinuation of treatment	Resolving

a) Study AMAN used MedDRA/J ver.24.0, and Studies AMBG and AMAP used MedDRA/J ver.24.1.
b) The number of days from the first dose of the study drug in the study

PMDA's view:
PMDA confirmed that serious infections and opportunistic infections infrequently occurred in Studies AMAN and AMBG and that there were no clinically relevant differences between each of the mirikizumab groups and the placebo group. The applicant, however, should provide caution about serious infections in the package insert because mirikizumab may increase the risk of infections by inhibiting IL-23, and serious infections for which a causal relationship to mirikizumab could not be ruled out occurred.

7.R.3.3.2 Hypersensitivity reactions

The applicant's explanation about hypersensitivity reactions[18]:
The applicant investigated data on hypersensitivity reactions that occurred on the day of the study treatment and on the following day of the study treatment or thereafter.

[18] Events classified as "Anaphylactic reaction (narrow)," "Hypersensitivity (narrow)," or "Angioedema (narrow)" of MedDRA SMQ

Table 58 shows incidences of hypersensitivity reactions during the induction period. In both overall and Japanese populations, the incidences were low, and no remarkable differences were observed in incidence between the placebo and mirikizumab IV groups. In the mirikizumab IV group, no serious hypersensitivity reactions occurred on the day of the study treatment or on the following day of the study treatment or thereafter, but hypersensitivity reactions leading to treatment discontinuation occurred in 0.3% (3 of 958) of patients (infusion related hypersensitivity reaction in all of 3) on the day of the study treatment.

Table 58. Summary of incidences of hypersensitivity reactions during the induction period (Study AMAN, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Hypersensitivity reactions occurred on the day of the study treatment	0.3 (1)	1.0 (10)	0	1.0 (1)
Infusion related hypersensitivity reaction	0.3 (1)	0.4 (4)	0	0
Infusion related reaction	0	0.3 (3)	0	1.0 (1)
Dermatitis acneiform	0	0.1 (1)	0	0
Eczema	0	0.1 (1)	0	0
Swelling face	0	0.1 (1)	0	0
Hypersensitivity reactions occurred on the following day of the study treatment or thereafter	2.2 (7)	2.5 (24)	2.9 (1)	2.0 (2)
Rash	0.6 (2)	0.5 (5)	0	0
Urticaria	0.3 (1)	0.4 (4)	0	0
Conjunctivitis allergic	0.3 (1)	0.2 (2)	0	1.0 (1)
Eczema	0.3 (1)	0.1 (1)	2.9 (1)	1.0 (1)
Dermatitis contact	0.3 (1)	0.1 (1)	0	0
Rash erythematous	0.3 (1)	0.1 (1)	0	0
Rhinitis allergic	0.3 (1)	0	0	0
Rash pruritic	0	0.3 (3)	0	0
Rash pustular	0	0.2 (2)	0	0
Dermatitis	0	0.1 (1)	0	1.0 (1)
Dermatitis acneiform	0	0.1 (1)	0	0
Drug hypersensitivity	0	0.1 (1)	0	0
Idiopathic urticaria	0	0.1 (1)	0	0
Rash macular	0	0.1 (1)	0	0
Rash maculo-papular	0	0.1 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.0

Table 59 shows incidences of hypersensitivity reactions on the day of the study treatment and on the following day of the study treatment or thereafter during the maintenance period. In both overall and Japanese populations, the incidences were low. In the Japanese population, hypersensitivity reactions did not occur in the placebo group but occurred in the mirikizumab SC group. In the mirikizumab SC group in the overall population, serious hypersensitivity reactions did not occur, but a hypersensitivity reaction leading to treatment discontinuation (injection site hypersensitivity) occurred in 0.3% (1 of 389) of patients on the following day of the study treatment or thereafter.

Table 59. Summary of incidences of hypersensitivity reactions during the maintenance period (Study AMBG, mirikizumab induction responder population, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 192)	Mirikizumab SC (n = 389)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Hypersensitivity reactions occurred on the day of the study treatment	1.0 (2)	1.8 (7)	0	4.3 (2)
Anaphylactic reaction	0.5 (1)	0	0	0
Dermatitis allergic	0.5 (1)	0	0	0
Hypersensitivity	0	0.8 (3)	0	2.1 (1)
Rash	0	0.5 (2)	0	2.1 (1)
Injection site rash	0	0.3 (1)	0	0
Injection site urticaria	0	0.3 (1)	0	0
Hypersensitivity reactions occurred on the following day of the study treatment or thereafter	2.6 (5)	6.9 (27)	0	6.4 (3)
Hypersensitivity	0.5 (1)	0.5 (2)	0	2.1 (1)
Rash pruritic	0.5 (1)	0.3 (1)	0	0
Lip swelling	0.5 (1)	0	0	0
Rash erythematous	0.5 (1)	0	0	0
Rhinitis allergic	0.5 (1)	0	0	0
Rash	0	3.3 (13)	0	0
Dermatitis contact	0	0.5 (2)	0	4.3 (2)
Conjunctivitis allergic	0	0.3 (1)	0	0
Dermatitis	0	0.3 (1)	0	0
Eczema	0	0.3 (1)	0	0
Hand dermatitis	0	0.3 (1)	0	0
Injection site dermatitis	0	0.3 (1)	0	0
Injection site hypersensitivity	0	0.3 (1)	0	2.1 (1)
Injection site urticaria	0	0.3 (1)	0	0
Perioral dermatitis	0	0.3 (1)	0	0
Rash maculo-papular	0	0.3 (1)	0	0
Swelling of eyelid	0	0.3 (1)	0	0
Urticaria	0	0.3 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.1

In the clinical studies of the submitted data, a serious adverse drug reaction of hypersensitivity associated with mirikizumab occurred in 1 patient (immune thrombocytopenia).

PMDA's view:
On the basis of the data on hypersensitivity, PMDA confirmed that neither serious adverse drug reactions of hypersensitivity nor serious anaphylaxis associated with mirikizumab occurred in Study AMAN or AMBG. The applicant, however, should provide caution about serious hypersensitivity in the package insert because events leading to treatment discontinuation such as infusion related hypersensitivity reaction occurred and because serious hypersensitivity are known risk of conventional IL-23 inhibitors (ustekinumab, risankizumab, etc.).

7.R.3.3.3 Infusion site reactions and injection site reactions

The applicant's explanation about infusion site reactions[19)] to an intravenous dose of mirikizumab and injection site reactions[20)] to a subcutaneous dose of mirikizumab:
Table 60 shows incidences of infusion site reactions to intravenous doses during the induction period. In both overall and Japanese populations, the incidences were low, and no remarkable differences were observed in incidence between the placebo and mirikizumab IV groups. In the mirikizumab IV group,

19) Events classified as "Infusion site reactions" of MedDRA high level term (HLT), except ones related to joints
20) Events classified as "Injection site reactions" of MedDRA HLT, except ones related to joints

neither serious infusion site reactions nor infusion site reactions leading to treatment discontinuation occurred.

Table 60. Summary of incidences of infusion site reactions during the induction period (Study AMAN, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Infusion site reactions	0.3 (1)	0.4 (4)	0	1.0 (1)
Infusion site paraesthesia	0.3 (1)	0.1 (1)	0	0
Infusion site erythema	0	0.1 (1)	0	1.0 (1)
Infusion site pain	0	0.1 (1)	0	0
Infusion site pruritus	0	0.1 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.0

Table 61 shows incidences of injection site reactions to subcutaneous doses during the maintenance period. In both overall and Japanese populations, the incidences were low, but they tended to be higher in the mirikizumab SC group than in the placebo group. In the mirikizumab SC group, no serious injection site reactions occurred on the day of the study treatment or on the following day of the study treatment or thereafter, but injection site hypersensitivity leading to treatment discontinuation occurred in 0.3% (1 of 389) of patients on the following day of the study treatment or thereafter. The concerned patient is the same patient who discontinued the treatment in the previous section for hypersensitivity reactions.

Table 61. Summary of incidences of injection site reactions during the maintenance period (Study AMBG, mirikizumab induction responder population, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 192)	Mirikizumab SC (n = 389)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Injection site reactions	4.2 (8)	8.7 (34)	4.0 (1)	10.6 (5)
Injection site pain	3.1 (6)	4.4 (17)	0	6.4 (3)
Injection site erythema	1.0 (2)	2.1 (8)	4.0 (1)	0
Injection site reaction	0.5 (1)	2.6 (10)	0	2.1 (1)
Injection site bruising	0	0.5 (2)	0	0
Injection site pruritus	0	0.5 (2)	0	0
Injection site dermatitis	0	0.3 (1)	0	0
Injection site haematoma	0	0.3 (1)	0	0
Injection site hypersensitivity	0	0.3 (1)	0	2.1 (1)
Injection site oedema	0	0.3 (1)	0	0
Injection site paraesthesia	0	0.3 (1)	0	0
Injection site rash	0	0.3 (1)	0	0
Injection site urticaria	0	0.3 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.1

In the clinical studies of the submitted data, neither infusion site reactions nor injection site reaction, considered as serious adverse drug reaction associated with mirikizumab, occurred.

On the basis of the data on infusion site reactions to intravenous doses of mirikizumab and injection site reactions to subcutaneous doses of mirikizumab, PMDA confirmed that neither infusion site reaction nor injection site reaction, considered as serious adverse drug reactions associated with mirikizumab, occurred in Study AMAN or AMBG.

7.R.3.3.4 Events related to hepatic disorders

The applicant's explanation about events related to hepatic disorders[21]:

Table 62 shows incidences of events related to hepatic disorders during the induction period. In both overall and Japanese populations, the incidences were low, and no remarkable differences were observed in incidence between the placebo and mirikizumab IV groups. In the mirikizumab IV group, neither events related to serious hepatic disorders nor events related to hepatic disorders leading to treatment discontinuation occurred.

Table 62. Summary of incidences of events related to hepatic disorders during the induction period (Study AMAN, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 35)	Mirikizumab IV (n = 102)
Hepatic disorders	1.6 (5)	1.6 (15)	0	1.0 (1)
γGTP increased	0.6 (2)	0.4 (4)	0	0
AST increased	0.3 (1)	0.5 (5)	0	0
ALT increased	0.3 (1)	0.4 (4)	0	0
Hepatic enzyme increased	0.3 (1)	0	0	0
Hepatomegaly	0.3 (1)	0	0	0
Liver function test value abnormal	0.3 (1)	0	0	0
Blood bilirubin increased	0	0.3 (3)	0	0
Hepatic function abnormal	0	0.1 (1)	0	1.0 (1)
Hyperbilirubinaemia	0	0.1 (1)	0	0
Hypertransaminasaemia	0	0.1 (1)	0	0
Liver function test increased	0	0.1 (1)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.0

Table 63 shows incidences of events related to hepatic disorders during the maintenance period. In both overall and Japanese populations, the incidences were low. In the Japanese population, events related to hepatic disorders did not occur in the placebo group but occurred in the mirikizumab SC group. In the mirikizumab SC group, no events related to serious hepatic disorders occurred, but an event leading to treatment discontinuation (autoimmune hepatitis) occurred in 0.3% (1 of 389) of patients.

Table 63. Summary of incidences of events related to hepatic disorders during the maintenance period (Study AMBG, mirikizumab induction responder population, safety analysis population)

	Overall population		Japanese population	
	Placebo (n = 192)	Mirikizumab SC (n = 389)	Placebo (n = 25)	Mirikizumab SC (n = 47)
Hepatic disorders	2.1 (4)	3.1 (12)	0	6.4 (3)
γGTP increased	0.5 (1)	1.0 (4)	0	2.1 (1)
ALT increased	0.5 (1)	1.0 (4)	0	2.1 (1)
Hepatic steatosis	0.5 (1)	0.3 (1)	0	2.1 (1)
Hepatic enzyme increased	0.5 (1)	0.3 (1)	0	0
Liver function test value abnormal	0.5 (1)	0	0	0
AST increased	0	0.8 (3)	0	2.1 (1)
Blood bilirubin increased	0	0.5 (2)	0	2.1 (1)
Autoimmune hepatitis	0	0.3 (1)	0	0
Nonalcoholic fatty liver disease	0	0.3 (1)	0	0
Liver function test increased	0	0.5 (2)	0	0

Incidence in % (number of patients with events)
MedDRA/J ver.24.1

[21] Events classified as "Cholestasis and jaundice of hepatic origin (narrow and broad)," "Hepatitis, non-infectious (narrow and broad)," "Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (narrow and broad)," or "Liver-related coagulation and bleeding disturbances (narrow)" of MedDRA SMQ

In the clinical studies of the submitted data, no events related to hepatic disorders, considered as serious adverse drug reactions associated with mirikizumab, occurred, but an event (hepatic enzyme increased) meeting the Hy's law criteria for laboratory values (defined based on the Guidance for industry. Drug-Induced Liver Injury: premarketing Clinical Evaluation. U.S. Department of Health and Human Services, Food and Drug Administration. July 2009) occurred in 1 patient[22)] during the open-label extended induction period in Study AMBG. The concerned event was assessed as an adverse drug reaction.

PMDA's view:
PMDA confirmed that events related to hepatic disorders infrequently occurred in Studies AMAN and AMBG and that there were no clinically relevant differences between each of the mirikizumab groups and the placebo group. The applicant, however, should include in the package insert a cautionary statement that liver function tests should be performed, because hepatic enzyme increased meeting the Hy's law criteria for laboratory values occurred. In addition, the applicant should pay attention to events related to hepatic disorders in post-marketing settings as well and, if new information becomes available, provide it to healthcare professionals appropriately.

7.R.3.3.5 Malignancies

The applicant's explanation about malignancies[23)]:
Malignancies occurred in 2 patients in the mirikizumab IV group (adenocarcinoma of colon) in Study AMAN, in 1 patient in the placebo group (basal cell carcinoma), and 1 patient in the mirikizumab SC group (gastric cancer) in Study AMBG. In the Japanese population, malignancies occurred in 1 patient in the mirikizumab SC group (gastric cancer) in Study AMBG. The pooled analysis on data from the global phase II study (Study AMAC) and global phase III studies (Studies AMAN, AMBG, and AMAP) (overall safety pooled analysis) revealed that in addition to the above 3 patients in the mirikizumab groups in Studies AMAN and AMBG, 13 patients experienced malignancies (rectal cancer, squamous cell carcinoma of skin in 3 patients each, adenocarcinoma of colon, prostate cancer, carcinoid tumour of the gastrointestinal tract, extranodal marginal zone B-cell lymphoma (MALT type), Kaposi's sarcoma, malignant melanoma, and basal cell carcinoma in 1 patient each).

Table 64 shows incidences of malignancies in the study populations, including the overall safety pooled analysis population (exposure-adjusted number of events per 100 person-years).

22) The patient was transferred from the induction period (mirikizumab IV group) in the Study AMAN to the open-label extended induction period (mirikizumab induction non-responder population) in Study AMBG. On Day 122 from the first dose of mirikizumab for the induction period, "hepatic enzyme increased" occurred, leading to discontinuation of mirikizumab. On Day 150, hepatic dysfunction meeting the Hy's law criteria for laboratory values (aspartate aminotransferase [AST] increased to >3 × upper limit of normal [ULN], alanine aminotransferase [ALT] increased to >3 × ULN, total bilirubin increased to >2 × ULN) occurred, but on Day 178, the AST, ALT, and total bilirubin values all returned to the normal. The maximum AST, ALT, and total bilirubin values were >9.9 (on Day 136 from the first dose of mirikizumab for the induction period), >17.9 (on Day 136), and >2.4 (on Day 150) × ULN, respectively.
23) Events classified as "Malignancies" of MedDRA SMQ

Table 64. Incidences of malignancies in Studies AMAN and AMBG and overall safety pooled analysis population
(exposure-adjusted number of events per 100 person-years)

	Study AMAN		Study AMBG		Overall safety pooled analysis population
	Placebo (n = 321)	Mirikizumab IV (n = 958)	Placebo (n = 192)	Mirikizumab SC (n = 389)	All patients treated with mirikizumab (n = 1,442)
Total exposure period (person-years)	72.1	221.8	119.3	286	2,250.9
Malignancies	0	0.9	0.8	0.3	0.7
Adenocarcinoma of colon	0	0.9	0	0	0.1
Rectal cancer	0	0	0	0	0.1
Prostate cancer	0	0	0	0	0.1
Gastric cancer	0	0	0	0.3	0.04
Carcinoid tumour of the gastrointestinal tract	0	0	0	0	0.04
Extranodal marginal zone B-cell lymphoma (MALT type)	0	0	0	0	0.04
Kaposi's sarcoma	0	0	0	0	0.04
Malignant melanoma	0	0	0	0	0.04
Squamous cell carcinoma of skin	0	0	0	0	0.1
Basal cell carcinoma	0	0	0.8	0	0.04

PMDA's view:
To date, PMDA has confirmed that mirikizumab does not tend to increase a risk of malignancies in patients with UC. The applicant, however, should provide caution about malignancies in the package insert in view of the approved IL-23 inhibitors (ustekinumab, risankizumab, etc.), of which the package inserts raise caution about malignancies. In addition, the applicant should pay attention to malignancies in post-marketing settings as well and, if new information becomes available, provide it to healthcare professionals appropriately.

7.R.3.3.6 Cardiovascular disorders

The applicant' explanation about cardiovascular disorders[24]:
During the induction period, cardiovascular disorders occurred in 2 patients in the placebo group (atrial fibrillation and acute myocardial infarction in 1 patient each) and 1 patient in the mirikizumab IV group (hypertension) in Study AMAN. In the Japanese population, no cardiovascular disorders occurred. A serious cardiovascular disorder occurred in 1 patient in the mirikizumab IV group (hypertension) in Study AMAN. During the maintenance period in Study AMBG, no cardiovascular disorders occurred.

In the clinical studies of the submitted data, a serious adverse drug reaction associated with mirikizumab occurred only in 1 patient (acute coronary syndrome)[25] during the open-label extended maintenance period in Study AMBG.

PMDA's view:
PMDA confirmed that cardiovascular disorders infrequently occurred in Studies AMAN and AMBG and that there were no clinically relevant differences between each of the mirikizumab groups and the

[24] Events applicable to deaths from cardiovascular events, myocardial infarction, hospitalization due to angina unstable, hospitalization due to cardiac failure, hospitalization due to hypertension, serious arrhythmia, resuscitation from sudden death, cardiogenic shock, and coronary revascularisation
[25] 6[redacted]-year old non-Japanese man. Severe acute coronary syndrome occurred on Days 127 and 249 from the first dose of mirikizumab in Study AMBG and resolved 5 and 3 days later, respectively. Mirikizumab was continued for both events.

placebo group. To date, it is difficult to make a definite conclusion on a risk of cardiovascular disorders associated with mirikizumab. The applicant should pay attention to cardiovascular disorders in post-marketing settings as well and, if new information becomes available, provide it to healthcare professionals appropriately.

7.R.3.3.7 Anti-drug antibody (ADA)

The applicant's explanation about development of ADA in patients with UC receiving mirikizumab and the effects on the safety and efficacy:

In the UC Treatment Regimen Pooled Analysis Population from Studies AMAN and AMBG [see Section 6.R.2], 23.3% (88 of 378) of patients were positive for ADA, and 21.7% (82 of 378) of patients were positive for neutralizing antibody. As shown in Table 65, no remarkable differences were observed in incidence of hypersensitivity, infusion site reaction, or injection site reaction between patients positive and patients negative for ADA, and there were no clear effects of ADA on the safety of mirikizumab.

Table 65. Incidences of adverse events by ADA status (UC Treatment Regimen Pooled Analysis Population)

PT (MedDRA/J ver.24.1)	Positive (n = 88)	Negative (n = 290)
Hypersensitivity (SMQ narrow or broad)	15.9 (14)	15.2 (44)
Hypersensitivity (SMQ narrow)	5.7 (5)	11.0 (32)
Infusion site reactions (HLT)	0	0.3 (1)
Injection site reactions (HLT)	10.2 (9)	8.3 (24)

Incidence in % (number of patients with events)

In the UC Treatment Regimen Pooled Analysis Population, patients evaluable for the efficacy and ADA were included in the UC Treatment Regimen Immunogenicity and Efficacy Analysis Population. In this analysis population, 24.4% (87 of 356) of patients were positive for ADA, and 75.6% (269 of 356) of patients were negative. Table 66 shows the efficacy by ADA titer, suggesting that the efficacy tended to decrease with increasing ADA titer, but the number of patients with high antibody titer was limited.

Table 66. Results on the efficacy at Week 40 of the maintenance period by ADA titer (UC Treatment Regimen Immunogenicity and Efficacy Analysis Population)

	Positive (n = 87)	Negative (n = 269)	1:80		1:160		1:320		1:640		1:1280	
			< (n = 307)	≥ (n = 49)	< (n = 324)	≥ (n = 32)	< (n = 338)	≥ (n = 18)	< (n = 344)	≥ (n = 12)	< (n = 349)	≥ (n = 7)
Proportion of patients in clinical remission, % (n)	57.5 (50)	47.6 (128)	49.5 (152)	53.1 (26)	51.2 (166)	37.5 (12)	51.5 (174)	22.2 (4)	50.6 (174)	33.3 (4)	50.4 (176)	28.6 (2)
Proportion of patients with endoscopic improvement, % (n)	65.5 (57)	56.5 (152)	58.3 (179)	61.2 (30)	59.6 (193)	50.0 (16)	59.5 (201)	44.4 (8)	59.0 (203)	50.0 (6)	59.0 (206)	42.9 (3)
Proportion of patients with clinical improvement, % (n)	82.8 (72)	79.6 (214)	80.5 (247)	79.6 (39)	81.2 (263)	71.9 (23)	81.1 (274)	66.7 (12)	81.1 (279)	58.3 (7)	80.8 (282)	57.1 (4)

Incidence in % (number of patients with events)

PMDA's view:

PMDA confirmed that no remarkable differences were observed in incidence of adverse events between patients positive for and patients negative for ADA. In addition, data on the efficacy by ADA titer

suggested that the efficacy tended to decrease with increasing ADA titer, but to date, ADA is considered unlikely to have substantial effects on the safety and efficacy of mirikizumab because the number of patients with high ADA titer was limited. The applicant, however, should inform healthcare professionals that the efficacy may decrease in patients positive for ADA.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of mirikizumab:

In Japan, patients with UC who have had an inadequate response to conventional treatment such as 5-ASA preparations, steroids, and immunomodulatory drugs receive biological products (anti-tumor necrosis factor [TNF]α antibodies [infliximab, adalimumab, and golimumab], anti-$\alpha_4\beta_7$ integrin antibody [vedolizumab (genetical recombination)], anti-IL-12/23 p40 antibody [ustekinumab]), JAK inhibitors, etc., but to any of these drugs, a certain proportion of the patients do not respond or are intolerant. Needs for drugs with a different mechanism of action remain high.

Mirikizumab is an IL-23 inhibitor targeting p19 subunit of IL-23, a cytokine involved in colonic mucosal inflammation, and acts through a mechanism of action different from those of the conventional drugs for treatment of UC.

The global phase III studies (Studies AMAN, AMBG, and AMAP) in patients with moderate to severe UC who had had an inadequate response to conventional treatment demonstrated that mirikizumab induced and maintained remission [see Section 7.R.2] and had acceptable safety without clinically particular problems [see Section 7.R.3]. Of note, Studies AMAN and AMBG included the key secondary endpoint of bowel urgency, which was not covered by the Mayo score, and the score on the numeric rating scale (NRS)[26] (NRS score) for bowel urgency was improved both at Week 12 of the induction period in Study AMAN and Week 40 of the maintenance period in Study AMBG (Table 67). As shown above, mirikizumab is considered to offer a new therapeutic option for patients with moderate and severe UC who have had an inadequate response to conventional treatment.

Table 67. Results on NRS for bowel urgency in the phase III studies (Studies AMAN and AMBG) (mITT population)

	Study AMAN (at Week 12 of the induction period)		Study AMBG (at Week 40 of the maintenance period)	
	Placebo (n = 294)	Mirikizumab IV (n = 868)	Placebo (n = 179)	Mirikizumab SC (n = 365)
Change in NRS score for bowel urgency from baseline (least square mean ± standard error)	-1.63 ± 0.14	-2.59 ± 0.08	-2.74 ± 0.20	-3.80 ± 0.14
Difference between groups (mirikizumab − placebo) (least square mean [95% CI])	-0.95 [-1.47, -0.44]		-1.06 [-1.51, -0.61]	
Proportion of patients with NRS score for bowel urgency of 0 or 1 (%) (No. of patients with the score achieved/No. of patients assessed)[a]	—	—	25.0% (43/172)	42.9% (144/336)
Difference between groups (mirikizumab − placebo) [95% CI]	—		18.1 [9.8, 26.4]	

a) Proportion of patients with the baseline NRS score ≥3 in Study AMAN

[26] A new numeric rating scale developed by the applicant to measure bowel urgency in patients in the past 24 hours. The 11-point scale ranges from 0 (no bowel urgency) to 10 (worst possible bowel urgency). The 7-day average of electronic diary data entered daily is presented.

In view of the patient populations and results in the global phase III studies (Studies AMAN and AMBG), PMDA considers that mirikizumab can offer a therapeutic option for patients with moderate to severe UC who have had an inadequate response to conventional treatment (steroids, azathioprine, etc.) as with other biological products and JAK inhibitors.

7.R.5 Indications

PMDA's view on the indications of mirikizumab:

The global phase III study (Studies AMAN and AMBG) demonstrated that mirikizumab induced and maintained remission in patients with moderate to severe UC who had had an inadequate response to conventional treatment [see Section 7.R.2], and these studies and the long-term extension study (Study AMAP) showed that mirikizumab had the acceptable safety [see Section 7.R.3].

The indications of mirikizumab IV dosage form should be "remission induction therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)" as proposed for approval. In view of the primary efficacy analysis population in Study AMBG, which included patients with clinical improvement in response to intravenous doses of mirikizumab, the indication of mirikizumab SC dosage forms should be "maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)" by modifying the proposed indication. For conventional treatment, the following cautionary statement should be included in the Precautions Concerning Indications section in view of the inclusion and exclusion criteria in the clinical studies: "Mirikizumab should be indicated only for patients who still have definite clinical symptoms caused by the disease even after appropriate prior treatment with other drugs (steroids, azathioprine, etc.)."

7.R.6 Dosage and administration

7.R.6.1 Induction period

7.R.6.1.1 Dosage regimen for the induction period

The applicant's explanation about the dosage regimen for the induction period:

The induction period in the global phase II study (Study AMAC) consisted of the placebo, mirikizumab 50 mg IV, 200 mg IV, and 600 mg IV groups.[8)] The "proportion of patients in clinical remission at Week 12 of the induction period," the primary endpoint, was lower in the mirikizumab 600 mg IV group than in the 200 mg IV group, and at the doses ≥200 mg, the efficacy did not tend to increase with increasing dose (Table 22). The exposure-response analysis using data on the efficacy and serum mirikizumab concentrations obtained in Study AMAC [see Section 6.2.5] suggested that the efficacy of mirikizumab would level off at the doses ≥300 mg. In view of the above, 3 doses of mirikizumab 300 mg were intravenously administered Q4W in Study AMAN, a global phase III induction period study. Study AMAN demonstrated superiority of mirikizumab IV to placebo [see Section 7.R.2.1.1] and the acceptable safety [see Section 7.R.3].

In Study AMAN, patients who had not met the criteria for clinical improvement after 3 intravenous doses of mirikizumab 300 mg Q4W (at Week 12 of the induction period) entered the open-label extended induction period (mirikizumab induction non-responder population) in Study AMBG and received 3 intravenous doses of mirikizumab 300 mg Q4W (stayed the induction period for 24 weeks in total).

At the end of the open-label extended induction period (at Week 24 of the induction period), 53.7% (146 of 272) and 11.4% (31 of 272) of the patients met the criteria for clinical improvement and clinical remission, respectively. In patients who had not met the criteria for clinical improvement at Week 12 of the induction period, an additional 3 doses Q4W were considered to have a potential induction effect to a certain extent. For the safety, no clinically relevant differences were observed between the mirikizumab IV group in Study AMAN and the open-label extended induction period in Study AMBG [see Section 7.R.3.1.1].

In view of the above results, a dosage regimen comprised of 3 intravenous doses of mirikizumab 300 mg Q4W is proposed for the induction period. For patients who have not adequately responded to the treatment at Week 12, the extension of the induction period to 24 weeks (for an additional 3 intravenous doses of mirikizumab 300 mg Q4W) is also proposed.

PMDA's view:
The dose of mirikizumab 300 mg used in Study AMAN is not adequately justified, because Study AMAC did not use the dose of 300 mg for the induction period; and the efficacy tended to be lower in the mirikizumab 600 mg IV group than in the 200 mg IV group (Table 22). On the basis of the results obtained in Study AMAN, however, PMDA considers it acceptable to administer 3 intravenous doses of mirikizumab 300 mg Q4W during the induction period. In view of results obtained during the open-label extended induction period in Study AMBG, patients who have not adequately responded to the treatment at Week 12 may receive an additional 3 intravenous doses of mirikizumab 300 mg Q4W. The applicant, however, should provide caution concerning patients who have not responded to the treatment with mirikizumab for up to 24 weeks, instructing physicians to discontinue mirikizumab and consider switching to other treatment.

7.R.6.2 Maintenance period

7.R.6.2.1 Dosage regimen for the maintenance period

The applicant's explanation about the dosage regimen for the maintenance period:
In the global phase II study (Study AMAC), the proportion of patients who achieved clinical remission at Week 40 of the maintenance period tended to be higher in the mirikizumab SC Q4W group than in the SC Q12W group (37.0% [17 of 46] of patients in the mirikizumab SC Q12W, 46.8% [22 of 47] of patients in the mirikizumab SC Q4W). In view of this result, mirikizumab 200 mg was subcutaneously administered Q4W in Study AMBG, a global phase III maintenance period study. Study AMBG demonstrated superiority of mirikizumab SC to placebo [see Section 7.R.2.2.1] and the acceptable safety [see Section 7.R.3]. On the basis of the dosage regimen in Study AMBG, a dosage regimen comprised of subcutaneous doses of mirikizumab 200 mg Q4W is proposed for the maintenance period.

In view of results obtained in Study AMBG, PMDA considers it acceptable to subcutaneously administer mirikizumab 200 mg Q4W.

7.R.6.2.2 Re-induction in the case of reduced response

The applicant's explanation about re-induction in the case of a reduced response to mirikizumab during the maintenance period:

In Study AMBG, patients who had met the criteria for a reduced response were allowed to enter the open-label re-induction period and receive 3 intravenous doses of mirikizumab 300 mg Q4W. For the re-induction, patients who were considered to have gained clinical benefits by the investigator were allowed to enter the long-term extension study (Study AMAP) and resume subcutaneous doses of mirikizumab 200 mg Q4W within 4 to 8 weeks after the third intravenous dose for re-induction. Of note, only 1 re-induction session (comprised of 3 intravenous doses Q4W) was allowed, and patients who were not considered to have gained clinical benefits by the investigator discontinued mirikizumab.

In Study AMBG, 5.2% (19 of 365) of patients in the mirikizumab SC group in the mirikizumab induction responder population underwent re-induction. Of these patients, 63.2% (12 of 19) and 36.8% (7 of 19) of patients met the criteria for symptomatic improvement and the criteria for symptomatic remission, respectively, after the re-induction (4 weeks after the third dose), showing the efficacy to a certain extent. For the safety, no clinically relevant differences were observed between the mirikizumab IV group in Study AMAN and the open-label re-induction period in Study AMBG [see Section 7.R.3.1.1].

In view of the above results, a re-induction regimen comprised of 3 intravenous doses of mirikizumab 300 mg Q4W is proposed for patients who have a reduced response to mirikizumab subcutaneously administered for maintenance. Because there are no clinical study results in patients with ≥2 re-induction sessions, the cautionary statement will be included in the Precautions Concerning Dosage and Administration section.

PMDA's view:

In view of the applicant's explanation, PMDA considers it acceptable to administer 3 intravenous doses of mirikizumab 300 mg Q4W for re-induction to patients who have a reduced response to mirikizumab subcutaneously administered for maintenance. The applicant, however, should include the following cautionary statements in the Precautions Concerning Dosage and Administration section: (a) Patients who have not responded to the re-induction therapy should discontinue mirikizumab; (b) patients who have responded to the re-induction therapy should resume subcutaneous administration of mirikizumab 4 weeks after the third intravenous dose for re-induction; and (c) because there are no clinical study results in patients with ≥2 re-induction sessions, for patients who have a reduced response again, physicians should consider switching to other treatment.

7.R.6.3 Concomitant use with existing drugs for treatment of UC

The applicant's explanation about concomitant use of mirikizumab with the existing drugs for treatment of UC:

In the global phase III studies (Studies AMAN, AMBG, and AMAP), the efficacy and safety were not evaluated in patients with UC who received mirikizumab concomitantly with the existing biological products or JAK inhibitors for treatment of UC. At present, mirikizumab should not be concomitantly used with other biological products or JAK inhibitors.

Baseline concomitant use with steroids and immunomodulatory drugs was found in 40.4% (351 of 868) and 24.3% (211 of 868) of patients in the mirikizumab IV group (mITT population) in Study AMAN respectively, and in 37.0% (135 of 365) and 21.4% (78 of 365) of patients in the mirikizumab SC group (mITT population) during the maintenance period in Study AMBG, respectively. For the safety, no clinically relevant differences were observed in incidence of adverse events between patients with and without baseline use of steroids or immunomodulatory drugs. The efficacy tended to be higher in the mirikizumab IV and SC groups than in the placebo group irrespective of baseline use of steroids or immunomodulatory drugs [see Sections 7.R.2.1.3 and 7.R.2.2.3]. On the basis of the above, concomitant use with steroids and immunomodulatory drugs has no particular problem.

PMDA's view:
Mirikizumab has not been administered concomitantly with the existing biological products or JAK inhibitors in the clinical studies in patients with UC; and the concomitant use may enhance the immune suppression, potentially increasing the risk of infections. The following cautionary statement should be included in the Precautions Concerning Dosage and Administration section: Mirikizumab should not be used with existing biological products or JAK inhibitors.

7.R.6.4 Self-injection during the maintenance period

The applicant's explanation about the safety and efficacy in Japanese patients with UC performing self-injection:
In the long-term extension study (Study AMAP), Japanese patients with UC performed 3 self-injection doses using the syringe product or AI product (10 patients for each product). For the efficacy, the rectal bleeding subscore, stool frequency subscore, and the total score of these subscores did not show any increasing trend before or after the 3 self-injection doses using the syringe product or AI product. The self-injection did not affect the efficacy. For the safety, during a period of 3 self-injection doses, adverse events occurred in 4 of 10 patients using the syringe product (pyrexia in 2 patients, malaise, constipation, stitch abscess, insomnia, and hip arthroplasty in 1 patient each [some patients had multiple events]) and 1 of 10 patients using the AI product (headache), and neither serious adverse events nor adverse events leading to treatment discontinuation occurred. Furthermore, no adverse events related to the medical devices occurred.

As described above, the safety of the self-injection using the syringe product or AI product during the maintenance period raised no definite concern, and the efficacy was not affected.

PMDA considers that mirikizumab may be self-injected during the maintenance period, provided that the patient is instructed by a physician and qualified for the self-injection.

7.R.7 Post-marketing investigations

The applicant considers it necessary to evaluate the safety of mirikizumab in long-term use through post-marketing surveillance and thus plans a post-marketing database survey to investigate serious infections (including opportunistic infections), severe hepatic disorders, malignancies, and major cardiovascular events.

PMDA's view:
The policy that investigate the proposed events using the database in the post-marketing surveillance is acceptable, but details of the survey plan should be further discussed.

7.R.8 Development for pediatric population

The applicant has been proceeding with development targeting pediatric patients with moderate to severe UC, and a clinical study in pediatric patients with UC aged ≥2 and <18 years is currently ongoing.

In view of prevalence of UC in the pediatric population, PMDA considers it necessary to proceed with the development of mirikizumab targeting pediatric patients with UC.

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

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

The inspection is currently ongoing. The results and conclusion of PMDA will be reported in the Review Report (2).

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

The inspection is currently ongoing. The results and conclusion of PMDA will be reported in the Review Report (2).

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

On the basis of the data submitted, PMDA has concluded that mirikizumab has efficacy in the treatment of patients with moderate to severe ulcerative colitis who have inadequately responded to conventional treatment, and that mirikizumab has acceptable safety in view of its benefits. Mirikizumab is clinically meaningful because it offers a new treatment option for patients with ulcerative colitis.

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

Review Report (2)

February 15, 2023

Product Submitted for Approval

Brand Name	(a) Omvoh Intravenous Infusion 300 mg (b) Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes
Non-proprietary Name	Mirikizumab (Genetical Recombination)
Applicant	Eli Lilly Japan K.K.
Date of Application	May 27, 2022

List of Abbreviations

See Appendix.

1. Content of the Review

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

1.1 Efficacy and safety

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Sections "7.R.2 Efficacy" and "7.R.3 Safety" of the Review Report (1).

1.2 Indications

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.5 Indications" of the Review Report (1).

PMDA has concluded that the Indications and Precautions Concerning Indications should be specified as shown below.

Indications

Omvoh Intravenous Infusion 300 mg:

Remission induction therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes:
Maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

Precautions Concerning Indications
Omvoh Intravenous Infusion 300 mg, Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes (common):
Mirikizumab should be indicated only for patients who still have definite clinical symptoms caused by the disease even after appropriate prior treatment with other drugs (steroids, azathioprine, etc.).

1.3 Dosage and administration

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.6 Dosage and administration" of the Review Report (1).

PMDA has concluded that the Dosage and Administration and Precautions Concerning Dosage and Administration should be specified as shown below.

Dosage and Administration
Omvoh Intravenous Infusion 300 mg:
The usual adult dosage is 300 mg of mirikizumab (genetical recombination) intravenously infused every 4 weeks for 3 doses (Weeks 0, 4, and 8). Of note, if the therapeutic response is inadequate at Week 12, the dosage of 300 mg may be administered every 4 weeks for an additional 3 doses (Weeks 12, 16, and 20).
In addition, if patients show a reduced response to maintenance therapy with mirikizumab (genetical recombination) in subcutaneous dosage forms, the dosage of 300 mg may be intravenously infused every 4 weeks for 3 doses.

Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes:
The usual adult dosage is 200 mg of mirikizumab (genetical recombination) subcutaneously injected every 4 weeks, starting 4 weeks after completion of the induction therapy of mirikizumab (genetical recombination) in intravenous infusion dosage forms.

Precautions Concerning Dosage and Administration
Omvoh Intravenous Infusion 300 mg:

- If the patient has shown a therapeutic response 4 weeks after the third or sixth dose of mirikizumab, use of mirikizumab (genetical recombination) in a subcutaneous dosage form should be started as maintenance therapy (for dosage regimens for maintenance therapy, see the electronic package insert of mirikizumab [genetical recombination] in subcutaneous dosage forms). If the patient has not shown a therapeutic response within 4 weeks after the sixth dose of mirikizumab, discontinue the use of mirikizumab and consider switching to other treatment.

- If the patient has shown a therapeutic response to 3 doses of mirikizumab after showing a reduced response to maintenance therapy with mirikizumab (genetical recombination) in a subcutaneous dosage form, use of subcutaneous dosage form should be resumed 4 weeks after the third dose. If the patient has not shown a therapeutic response, discontinue the use of mirikizumab and consider switching to other treatment. If the patient shows a reduced response to maintenance therapy in the subcutaneous dosage form again, consider switching to other treatment. There are no clinical studies to evaluate the safety and efficacy of mirikizumab in patients who show a reduced response during the maintenance therapy for the second or subsequent time.
- Mirikizumab should not be used with biological products or JAK inhibitors because the safety and efficacy of such concomitant use have not been established.

Omvoh Subcutaneous Injection 100 mg Autoinjectors, Omvoh Subcutaneous Injection 100 mg Syringes:

- If the patient has shown a therapeutic response to 3 doses of mirikizumab (genetical recombination) in an intravenous infusion dosage form after a reduced response to the maintenance therapy with mirikizumab, use of mirikizumab should be resumed 4 weeks after the third dose (for dosage regimens in the case of a reduced response, see the electronic package insert of mirikizumab [genetical recombination] in intravenous infusion dosage forms). If the patient shows a reduced response to the maintenance therapy with mirikizumab again, consider switching to other treatment. There are no clinical studies to evaluate the safety and efficacy of mirikizumab (genetical recombination) in intravenous infusion dosage forms in patients who show a reduced response during the maintenance therapy for the second or subsequent time.
- To administer mirikizumab (genetical recombination) 200 mg subcutaneously, 2 units of mirikizumab should be used.
- Mirikizumab should not be used with biological products or JAK inhibitors because the safety and efficacy of such concomitant use have not been established.

1.4 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported PMDA's conclusion on issues presented in Section "7.R.7 Post-marketing investigations" of the Review Report (1).

PMDA has concluded that the risk management plan (draft) for mirikizumab should include the safety and efficacy specifications presented in Table 68, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 69.

Of note, details of the post-marketing database survey plan should be further discussed and the concerned survey should be conducted in accordance with an appropriate plan.

Table 68. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Serious infections • Serious hypersensitivity	• Hepatic disorders • Cardiovascular events • Malignancies • Immunogenicity	• None
Efficacy specification		
• None		

Table 69. Summary of additional pharmacovigilance activities and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Post-marketing database survey (serious infections, hepatic disorders, cardiovascular events, malignancies)	• Disseminate data gathered during early post-marketing phase vigilance • Organize and disseminate materials for healthcare professionals • Organize and disseminate materials for patients

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

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

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

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

The new drug application data (CTD 5.3.5.1.2, CTD 5.3.5.1.3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, the clinical studies were conducted in accordance with the GCP overall, and PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. However, the following findings were noted in some of the study sites and the sponsor, although they did not have a significant impact on evaluation of the studies overall. They were notified to the head of the concerned study site and sponsor, respectively, of findings requiring corrective action.

Findings requiring corrective action

5.3.5.1.3

Study site

- Informed consent forms obtained from patients participating in the clinical study did not have the seal or signature of the investigator who explained to the patients with the form.

Sponsor

- The sponsor failed to find through monitoring that informed consent forms obtained from some of the patients participating in the clinical study did not have the signature of the investigator who explained to the patients with the form.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying the indications and the dosage and administration proposed for approval as shown below, with the following approval condition. The product is a drug with a new active ingredient, and the re-examination period is 8 years. It is classified as a biological product. The drug product and its drug substance are both classified as powerful drugs.

Indications

(a) Remission induction therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)
(b) Maintenance therapy for moderate to severe ulcerative colitis (for use only in patients who had an inadequate response to conventional treatment)

Dosage and Administration

(a) The usual adult dosage is 300 mg of mirikizumab (genetical recombination) intravenously infused every 4 weeks for 3 doses (Weeks 0, 4, and 8). Of note, if the therapeutic response is inadequate at Week 12, the dosage of 300 mg may be administered every 4 weeks for an additional 3 doses (Weeks 12, 16, and 20).
In addition, if patients show a reduced response to maintenance therapy with mirikizumab (genetical recombination) in subcutaneous dosage forms, the dosage of 300 mg may be intravenously infused every 4 weeks for 3 doses.
(b) The usual adult dosage is 200 mg of mirikizumab (genetical recombination) subcutaneously injected every 4 weeks, starting 4 weeks after completion of the induction therapy of mirikizumab (genetical recombination) in intravenous infusion dosage forms.

Approval Condition

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

Appendix

List of Abbreviations

5-ASA	5-Aminosalicylate acid
6-MP	6-Mercaptopurine
ACE	Affinity capture and elution
ADA	Anti-drug antibody
Adverse drug reaction	Adverse event for which a causal relationship to the study drug cannot be ruled out
ALT	Alanine aminotransferase
AI	Autoinjector
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
$AUC_{0\text{-inf}}$	AUC up to infinity
AZA	Azathioprine
BMI	Body mass index
C1q	Complement component 1, q subcomponent
CAL	Cells at the limit of in vitro cell age
CD	Cluster of differentiation
cDNA	Complementary DNA
CE-SDS	Capillary electrophoresis-sodium dodecyl sulfate
CHO cells	Chinese hamster ovary cells
cIEF	Capillary isoelectric focusing
CL	Clearance
CL/F	Apparent clearance after administration of the drug
C_{max}	Maximum concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CQA	Critical quality attribute
CRP	C-reactive protein
CTD	Common technical document
C_{trough}	Trough serum concentration
DNA	Deoxyribonucleic acid
eCOA	Electronic clinical outcome assessment
[redacted]	[redacted]
ELISA	Enzyme-linked immunosorbent assay
GCP	Good clinical practice
HCP	Host cell protein
HLT	High level term
HPLC	High performance liquid chromatography
IC_{50}	Half maximal inhibitory concentration
ICH	International Council for Harmonisation of Technical Requirements of Pharmaceuticals for Human Use
ICH Q5A (R1) guideline	"Viral Safety Evaluation of Biotechnology Products Derived from Cell Lines of Human or Animal Origin" (PMSB/ELD Notification No. 329 dated February 22, 2000)
ICH Q5B guideline	Analysis of the Expression Construct in Cell Lines Used for Production of rDNA-derived Protein Products (PMSB/ELD Notification No. 3 dated January 6, 1998)
ICH Q5D guideline	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 dated July 14, 2000)
IgG	Immunoglobulin G
IL	Interleukin

IL-12Rβ1	Interleukin-12 receptor β-1
IL-12Rβ2	Interleukin-12 receptor β-2
IL-23R	Interleukin-23 receptor
ITT	Intention-to-Treat
IV	Intravenous
JAK	Janus kinase
K_D	Dissociation constant
LC-MS	Liquid chromatography - mass spectrometry
MCB	Master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
Mirikizumab	Mirikizumab (Genetical Recombination)
mITT	Modified Intention-to-Treat
mRNA	Messenger RNA
MTX	Methotrexate
NRI	Non-responder imputation
NRS	Numeric rating scale
PMDA	Pharmaceuticals and Medical Devices Agency
PRO	Patient-reported outcome
PT	Preferred term
QbD	Quality by design
Q4W	Once every 4 weeks
Q12W	Once every 12 weeks
Risankizumab	Risankizumab (Genetical Recombination)
RNA	Ribonucleic acid
SC	Subcutaneous
SDS-PAGE	Sodium dodecyl sulfate polyacrylamide gel electrophoresis
SE-HPLC	Size exclusion high performance liquid chromatography
SMQ	Standardized MedDRA query
STAT	Signal transducer and activator of transcription
Study AMAC	Study I6T-MC-AMAC
Study AMAD	Study I6T-JE-AMAD
Study AMAN	Study I6T-MC-AMAN
Study AMAP	Study I6T-MC-AMAP
Study AMBG	Study I6T-MC-AMBG
$t_{1/2}$	Elimination half-life
t_{max}	Time to reach maximum concentration
TNF	Tumor necrosis factor
Tofacitinib	Tofacitinib citrate
UC	Ulcerative colitis
UFAT	Up-front acid treatment
Ustekinumab	Ustekinumab (Genetical Recombination)
UV/VIS	Ultraviolet-visible spectrophotometry
Vedolizumab	Vedolizumab (Genetical Recombination)
WCB	Working cell bank
γGTP	Gamma glutamyl transpeptidase