Report on the Deliberation Results

June 1, 2021

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau

Ministry of Health, Labour and Welfare

Brand Name	Twymeeg Tablets 500 mg
Non-proprietary Name	Imeglimin Hydrochloride (JAN*)
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	July 30, 2020

Results of Deliberation

In its meeting held on May 26, 2021, 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 not classified as a biological product or a specified biological product, and the re-examination period is 8 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

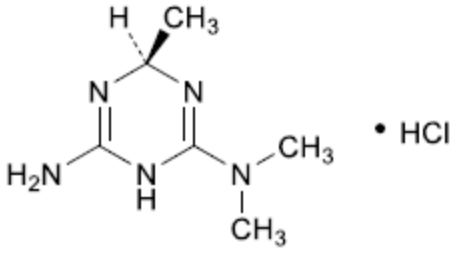
Review Report

April 28, 2021
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	Twymeeg Tablets 500 mg
Non-proprietary Name	Imeglimin Hydrochloride
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	July 30, 2020
Dosage Form/Strength	Film-coated tablets, each containing 500 mg of Imeglimin Hydrochloride
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_6H_{13}N_5 \cdot HCl$
Molecular weight: 191.66
Chemical name: (6*R*)-N^2,N^2,6-Trimethyl-3,6-dihydro-1,3,5-triazine-2,4-diamine monohydrochloride

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 type 2 diabetes mellitus, 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 conditions.

Indication	Type 2 diabetes mellitus
Dosage and Administration	The usual adult dosage is 1000 mg of Imeglimin Hydrochloride administered orally twice daily in the morning and evening.

Approval Condition

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

Attachment

Review Report (1)

March 30, 2021

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	Twymeeg Tablets 500 mg
Non-proprietary Name	Imeglimin Hydrochloride
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	July 30, 2020
Dosage Form/Strength	Film-coated tablets, each containing 500 mg of Imeglimin Hydrochloride
Proposed Indication	Type 2 diabetes mellitus
Proposed Dosage and Administration	The usual adult dosage is 1000 mg of Imeglimin Hydrochloride administered orally twice daily in the morning and evening.

Table of Contents

List of Abbreviations

See Appendix.

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

Twymeeg is a tablet preparation containing imeglimin hydrochloride (hereinafter referred to as "imeglimin"), which was discovered by Merck Serono (Swiss), as its active ingredient.

Type 2 diabetes mellitus is primarily caused by decreased insulin secretion from pancreatic β-cells and increased insulin resistance in organs such as the liver and muscles. Mitochondrial dysfunction is believed to partly contribute to both decreased insulin secretion and increased insulin resistance. Imeglimin is expected to improve mitochondrial functions in the insulin-releasing organ, the pancreas, as well as in insulin target organs such as the liver and muscles, promote insulin secretion while reversing insulin resistance, and consequently decrease blood glucose. Based on their conclusion that the efficacy and safety of imeglimin in the treatment of type 2 diabetes mellitus had been demonstrated, the applicant has recently filed a marketing approval application for imeglimin.

As of March 2021, imeglimin has not been approved in any country or region.

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

2.1 Drug substance

2.1.1 Characterization

The drug substance is a white powder. Its description, solubility, hygroscopicity, melting point, optical rotation, dissociation constant, partition coefficient, and isomers were determined.

The chemical structure of the drug substance was elucidated by an elemental analysis, infrared spectrophotometry (IR), hydrogen and carbon nuclear magnetic resonance spectrometry (^{1}H- and ^{13}C-NMR), mass spectrometry (MS), ultraviolet-visible spectroscopy (UV-VIS), and X-ray crystallography.

2.1.2 Manufacturing process

The drug substance is synthesized using [redacted], [redacted], and [redacted] as the starting materials. The manufacturing method from the starting materials to the intermediate, i.e., Compound A, is identical to that registered in a Master File (MF) (MF Registration Number: [redacted]), and is the same as that for Compound A used in the manufacture of other approved drug products.

For the manufacturing method from Compound A to the drug substance, a quality by design (QbD) approach was used to identify the critical quality attributes (CQAs) listed in Table 1, identify critical process parameters (CPPs) through a quality risk assessment and other measures, and develop the quality control strategy. The [redacted] step and the [redacted] and [redacted] steps are defined as critical steps.

The [redacted] and [redacted] are controlled as critical intermediates.

Table 1. Outline of the quality control strategy for the drug substance

CQA	Quality control methods
[redacted]	Specifications
	Specifications
	Manufacturing method and specifications
	Manufacturing method and specifications
	Manufacturing method and specifications

2.1.3 Control of drug substance

The proposed specifications for the drug substance include content, description, identification (IR, chloride limit test), purity (related substances [high performance liquid chromatography, HPLC], enantiomers [HPLC], residual solvents [gas chromatography, GC]), water, residue on ignition, and assay (HPLC).

2.1.4 Stability of drug substance

Table 2 shows the main stability tests that have been conducted on the drug substance; the test results demonstrated the stability of the drug substance. A photostability test demonstrated that the drug substance is photostable.

Table 2. Stability testing for the drug substance

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot batches	30°C	65%RH	Polyethylene bag (double-layer) + metal drum (with desiccant)	24 months
Accelerated testing	3 pilot batches	40°C	75%RH		6 months

Based on the above, a retest period of 36 months was proposed for the drug substance when stored in a double-layer polyethylene bag and a metal drum (with desiccant) at room temperature, according to the ICH Q1E guidelines. The long-term testing is scheduled be continued for up to 36 months.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is film-coated immediate-release tablets, each containing 500 mg of the drug substance. The drug product contains the following excipients: colloidal silicon dioxide, croscarmellose sodium, hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, titanium oxide, macrogol 4000, and saccharin sodium hydrate.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprising [redacted], tableting, film coating, and packaging/labeling steps. The [redacted] and [redacted] steps are defined as critical process steps in the manufacture of the drug product. Process control parameters and limits are specified in the [redacted] and [redacted] steps.

2.2.3 Control of drug product

The proposed specifications for the drug product consist of content, description, identification (UV-VIS, HPLC), purity (related substances [HPLC]), uniformity of dosage units (mass variation test), dissolution (ultraviolet absorption spectroscopy [UV]), and assay (HPLC).

2.2.4 Stability of drug product

Table 3 shows the stability tests that have been conducted on the drug product; the test results demonstrated the stability of the drug product. A photostability test showed that the drug product is photostable.

Table 3. Stability testing for the drug product

Study	Primary batches	Temperature	Humidity	Storage package	Storage period
Long-term testing	3 pilot batches	25°C	60%RH	Blister pack + aluminum pillow package, or high-density polyethylene bottle (with a polypropylene cap)	18 months
Accelerated testing	3 pilot batches	40°C	75%RH		6 months

Based on the above, a shelf life of 30 months was proposed for the drug product, when stored in a blister pack (polyvinyl chloride film/aluminum foil) and an aluminum pillow (a polyethylene terephthalate/polyethylene/aluminum multi-layer film bag), or in a high-density polyethylene bottle (with a polypropylene cap) at room temperature, according to the ICH Q1E guidelines. The long-term testing is scheduled be continued for up to 36 months.

2.R Outline of the review conducted by PMDA

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

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

The primary pharmacodynamic studies of imeglimin included *in vitro* studies to evaluate its abilities to promote insulin secretion and improve insulin resistance and *in vivo* studies to evaluate its ability to reduce blood glucose in Goto-Kakizaki (GK) rats. The secondary pharmacodynamic studies assessed the binding affinity of imeglimin for various receptors, etc. The safety pharmacology studies assessed the effects of imeglimin on the central nervous, cardiovascular, and respiratory systems, as well as its effects on lactic acidosis. No pharmacodynamic interaction studies were conducted. The results of main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Effects on insulin secretion in pancreatic islets from GK rats (CTD 4.2.1.1.06)

Imeglimin (25, 50, or 100 μmol/L), glucagon-like peptide-1 (GLP-1) (0.1 μmol/L), or the vehicle,[1)] together with glucose (16.7 mmol/L), was added to the pancreatic islets isolated from male GK rats (12 weeks old). Insulin concentrations in the media were determined 20 minutes later by an enzyme-linked immunoassay

[1)] 0.1% Dimethyl sulfoxide

(ELISA). The insulin concentration increased in the imeglimin 50 and 100 μmol/L groups, and the GLP-1 group as compared with the vehicle group.

3.1.1.2 Effects on NAD^+ concentrations in pancreatic islets from GK rats (CTD 4.2.1.1.07)

Imeglimin (100 μmol/L), imeglimin (100 μmol/L) + gallotannin[2] (10 μmol/L), or the vehicle,[1] together with glucose (16.7 mmol/L), was added to the pancreatic islets isolated from male GK rats (10 weeks old). The pancreatic islets were collected 20 minutes later to determine intracellular NAD^+ concentrations by a bioluminescent assay.

The NAD^+ concentration increased in the imeglimin group, but not in the imeglimin + gallotannin group, as compared with the vehicle group.

3.1.1.3 Effects on NAMPT gene expression in pancreatic islets from GK rats (CTD 4.2.1.1.08)

Imeglimin (100 μmol/L), nicotinamide (15 mmol/L), or the vehicle,[1] together with glucose (16.7 mmol/L), was added to the pancreatic islets isolated from male GK rats (13 to 14 weeks old). Nicotinamide phosphoribosyl transferase (NAMPT) gene expression levels in the pancreas were determined 30 minutes later by a reverse transcription quantitative polymerase chain reaction (RT-qPCR) assay. The NAMPT gene expression level increased in the imeglimin and nicotinamide groups as compared with the vehicle group.

3.1.1.4 Effects on the ATP/ADP ratio in pancreatic islets from GK rats (CTD 4.2.1.1.09)

Imeglimin (100 μmol/L), metformin (100 μmol/L), GLP-1 (0.1 μmol/L), or the vehicle,[1] together with glucose (16.7 mmol/L), was added to pancreatic islets isolated from male GK rats (8 to 10 weeks old). The pancreatic islets were collected 10 minutes later to determine ADP and ATP concentrations by a bioluminescent assay. The ratio of ATP to ADP increased in the imeglimin group and tended to increase in the GLP-1 group as compared with the vehicle group, while the metformin group showed a ratio similar to that in the vehicle group.

3.1.1.5 Effects on intracellular calcium concentrations in pancreatic islets from GK rats (CTD 4.2.1.1.10)

Imeglimin (100 μmol/L), GLP-1 (0.1 μmol/L), or the vehicle,[1] together with glucose (16.7 mmol/L), was added to the pancreatic islets isolated from male GK rats (14 weeks old). Intracellular calcium concentrations were determined 10 minutes later using a fluorescent probe.[3] The AUC of intracellular calcium tended to increase in the imeglimin and GLP-1 groups as compared with the vehicle group.

3.1.1.6 Effects on insulin secretion in pancreatic islets from CD38 knockout GK rats (CTD 4.2.1.1.11)

Pancreatic islets were isolated from male GK rats (10 weeks old) and then transfected with CD38 siRNA or control siRNA. At 48 hours after transfection, imeglimin (100 μmol/L), GLP-1 (0.1 μmol/L), or the vehicle,[1] together with glucose (16.7 mmol/L), was added to the pancreatic islets. Insulin concentrations in the media

[2] An inhibitor of nicotinamide mononucleotide adenylyltransferase 1,2,3 (Na/NMNAT-1,2,3), enzymes that synthesize NAD from nicotinamide mononucleotides
[3] FURA-2AM

were determined 20 minutes later by an ELISA. Insulin secretion from the control siRNA-transfected islets increased in both the imeglimin and GLP-1 groups as compared with the vehicle group, whereas insulin secretion from CD38 siRNA-transfected islets increased in the GLP-1 group but not in the imeglimin group, as compared with the vehicle group.

3.1.2 *In vivo* studies

3.1.2.1 8-week treatment study in GK rats (CTD 4.2.1.1.01)

Imeglimin (25, 75, or 150 mg/kg), metformin (25, 75, or 150 mg/kg), or the vehicle[4)] was orally administered to male GK rats (7 to 8 weeks old, 12 to 18/group) twice daily for 8 weeks, and plasma glucose concentrations after 3-hour fasting were determined at Weeks 5 and 8. The plasma glucose concentrations at Weeks 5 and 8 in the imeglimin 150 mg/kg group and those at Week 8 in all the metformin groups decreased as compared with the vehicle group.

3.1.2.2 Oral glucose tolerance test (OGTT) and euglycemic hyperinsulinemic clamp study in STZ-induced diabetic rats (CTD 4.2.1.1.02)

Male Wistar rats (6 weeks old, 10/group) were treated with a single intraperitoneal dose of streptozotocin (STZ) 50 mg/kg. After a 10-day interval, the rats were fasted for 15 hours, and received a single oral dose of imeglimin (150 mg/kg) or vehicle[4)] and a single oral dose of glucose (2 g/kg) 1 hour apart to determine plasma glucose and insulin concentrations. Separately, additional groups of STZ-induced diabetic rats received repeated oral doses of imeglimin (150 mg/kg) or vehicle[4)] twice daily for 2 weeks. The rats were fasted after the last dose and underwent a euglycemic hyperinsulinemic clamp study on the next day after the last dose.

On Day 1 of treatment, plasma glucose and insulin concentrations were determined over time.[5)] The plasma glucose concentrations decreased in the imeglimin group as compared with the vehicle group. The plasma insulin concentrations increased in the imeglimin group at 20 and 60 minutes on Day 1 as compared with the vehicle group.

The results of the euglycemic hyperinsulinemic clamp study indicated that the steady-state glucose infusion rate, when insulin was continuously infused at a constant rate of 0.5 IU/kg/h, increased in the imeglimin group as compared with the vehicle group.

3.1.2.3 OGTT in GK rats (CTD 4.2.1.1.03)

Female GK rats (19 to 20 weeks old, 25/group) were treated with repeated oral doses of imeglimin (200 mg/kg), metformin (200 mg/kg), or vehicle[6)] twice daily for 4 weeks. The rats were fasted for 2 to 3 hours after the last dose, and received a single oral dose of glucose (2 g/kg). Blood samples were collected at 10, 20, 30, 60, 90, and 120 minutes after the glucose load to determine plasma glucose and insulin concentrations.

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4) 0.5% Methylcellulose
5) Predose, and 10, 20, 30, 60, and 120 minutes postdose
6) Distilled water

The plasma glucose concentrations decreased at 20, 30, and 60 minutes after the glucose load in the imeglimin group and at 20 and 30 minutes in the metformin group as compared with the vehicle group. Plasma insulin concentrations in the imeglimin group tended to be high until 30 minutes after the glucose load and tended to be low from 60 minutes onward, whereas insulin concentrations in the metformin group tended to be lower at all timepoints after the glucose load.

3.1.2.4 Hyperglycemic clamp study in Wistar rats (CTD 4.2.1.1.04)

Female Wistar rats (14 to 15 weeks old, 7 to 9/group) were treated with a single oral dose of imeglimin (200 mg/kg), repaglinide (0.1 mg/kg), sitagliptin (3 mg/kg), or the vehicle.[4)] The rats were anesthetized with pentobarbital 15 minutes later, and blood samples were collected at 40 minutes after the time of anesthesia (T0), and 20, 25, and 30 minutes after T0 (Stabilization). Immediately after the blood sampling at 30 minutes from T0, glucose infusion was started targeting a glucose concentration of 9.5 mmol/L. Blood samples were collected at 20, 25, and 30 minutes after the start of glucose infusion (Stage 1). Immediately after the blood sampling at 30 minutes after glucose infusion in Stage 1, the glucose was infused targeting a glucose concentration of 12.5 mmol/L, and blood samples were collected at 20, 25, and 30 minutes after the start of glucose infusion (Stage 2).

Plasma insulin concentrations were determined at each blood sampling timepoint. At T0, plasma insulin concentrations tended to increase in the imeglimin, repaglinide, and sitagliptin groups as compared with the vehicle group. During Stabilization, plasma insulin concentrations tended to decrease in the imeglimin and sitagliptin groups and tended to increase in the repaglinide group as compared with the vehicle group. During Stage 1, plasma insulin concentrations in the imeglimin and sitagliptin groups were similar to those in the vehicle group, but the concentration tended to increase in the repaglinide group as compared with the vehicle group. During Stage 2, plasma insulin concentrations tended to increase in imeglimin, repaglinide, and sitagliptin groups.

3.1.2.5 Hyperglycemic clamp study in N0-STZ-induced diabetic rats (CTD 4.2.1.1.05)

Female Wistar rats (0 weeks old, 9 to 12/group) were treated with STZ (100 mg/kg). After a 15 week interval, the rats received a single oral dose of imeglimin (200 mg/kg), repaglinide (0.1 mg/kg), sitagliptin (3 mg/kg), or vehicle,[4)] and were then anesthetized with pentobarbital 30 minutes later. Blood samples were collected at 40 minutes from the time of anesthesia (T0), and 20, 25, and 30 minutes from T0 (Stabilization). Immediately after the blood sampling at 30 minutes from T0, glucose infusion was started targeting a glucose concentration of 18 mmol/L, and blood samples were collected at 20, 25, and 30 minutes from the start of the infusion (Stage 1). Immediately after the blood sampling at 30 minutes for Stage 1, glucose was infused targeting a glucose concentration of 25 mmol/L, and blood samples were collected at 20, 25, and 30 minutes from the start of the infusion (Stage 2).

Plasma insulin concentrations were determined at each blood sampling timepoint. At T0, plasma insulin concentrations increased in the repaglinide group and tended to increase in the imeglimin and sitagliptin groups as compared with the vehicle group. During Stabilization and Stages 1 and 2, insulin concentrations increased

in the imeglimin group and tended to increase in the repaglinide and sitagliptin groups as compared with the vehicle group.

3.1.2.6 Effects in HFHS-fed mice (CTD 4.2.1.1.14)

Male C57BL/6JO1aHsd mice (5 to 6 weeks old, 10 to 23/group) were fed with a high fat high sucrose (HFHS) diet for 10 weeks. The mice were then treated with oral doses of imeglimin (200 mg/kg) or the vehicle[4)] twice daily, or pioglitazone (20 mg/kg) or a vehicle[4)] once daily, for 6 weeks. Similarly, male C57BL/6JO1aHsd mice (5 to 6 weeks old, 23/group) fed with a standard diet for 10 weeks received oral doses of a vehicle[4)] for 6 weeks.

Blood glucose concentrations were determined once a week in the morning using a glucometer. Blood glucose concentrations decreased in the imeglimin and pioglitazone groups as compared with the vehicle group. Plasma insulin concentrations, determined once a month in the morning, did not differ largely between the imeglimin group and the vehicle group but decreased in the pioglitazone group as compared with the vehicle group.

After the 6-week treatment with imeglimin or the vehicle, DNA or RNA was extracted from the liver and gastrocnemius muscle to determine mitochondrial DNA levels, etc. using an RT-qPCR assay. The mitochondrial DNA level in the liver increased in the imeglimin group as compared with the vehicle group, with no differences in the mRNA or protein level of Pgc1α[7)] in the liver between the groups. The mitochondrial DNA level in the gastrocnemius muscle was similar in the imeglimin group and the vehicle group, but the mRNA level of Pgc1α in the gastrocnemius muscle increased in the imeglimin group as compared with the vehicle group. Oxygen consumption in mitochondria extracted from the quadriceps femoris was investigated. For that purpose, the maximum respiratory volume was measured in the presence of either malate + glutamate or succinate as substrate, after the addition of ADP. In the presence of either substrate, the maximum respiratory volume decreased in the HFHS diet/vehicle group as compared with the standard diet/vehicle group, and tended to increase in the HFHS diet/imeglimin group as compared with the HFHS diet/vehicle group.

Mitochondria were isolated from the liver to determine the protein levels of Complex I and Complex III using Western blotting. In addition, Complex I activity was quantified as the change in absorbance, using decylubiquinone as an electron acceptor and NADH as an electron donor. Complex III activity was quantified as the change in absorbance, using cytochrome c as a substrate. In the HFHS diet/vehicle group, as compared with the standard diet/vehicle group, the Complex III protein level and activity decreased. In contrast, both the protein level and activity of Complex III were restored in the HFHS diet/imeglimin group. Complex I activity did not differ largely between the standard diet/vehicle group and the HFHS diet/vehicle group, whereas it decreased in the HFHS diet/imeglimin group as compared with the HFHS/vehicle group. The Complex I protein level did not differ substantially among the standard diet/vehicle group, the HFHS diet/vehicle group, and the HFHS diet/imeglimin group. Reactive oxygen species (ROS) production was estimated by measuring H_2O_2 release from isolated mitochondria, in the presence of succinate as a substrate. ROS production increased

[7)] Peroxisome proliferator-activated receptor gamma coactivator 1-α, A transcriptional coactivator involved in mitochondrial biosynthesis

in the HFHS diet/vehicle group as compared with the standard diet/vehicle group, whereas it decreased in the HFHS diet/imeglimin group as compared with the HFHS diet/vehicle group.

3.1.3 Other Pharmacodynamics

3.1.3.1 Effects on pancreatic β-cells isolated from ZDF rats (CTD 4.2.1.1.12)

Male Zucker diabetic fatty (ZDF) rats (6 weeks old, 21/group) received oral doses of imeglimin (150 mg/kg) twice daily, sitagliptin (30 mg/kg) once daily, or a vehicle[4)] twice daily for 5 or 8 weeks, and the pancreas was isolated to histologically assess the β-cell mass.

The pancreatic β-cells were stained with a fluoresceinated anti-insulin antibody, and the pancreatic β-cell mass was calculated by quantitating the percentage of the area staining positive for insulin in multiple slices. Pancreatic β-cell mass at Week 5 increased in the imeglimin and sitagliptin groups as compared with the vehicle group. Pancreatic β-cell mass at Week 8 decreased in the sitagliptin group while it tended to increase in the imeglimin group as compared with the vehicle group.

3.1.3.2 Effects on primary human pancreatic islet-derived cells (CTD 4.2.1.1.13)

Primary human pancreatic islet-derived cells were incubated with imeglimin (100 μmol/L) or a vehicle[8)] for 24 hours, and then further incubated in the presence of glucose (30 mmol/L) or fructose (2.5 mmol/L) for 72 hours. Measurements of cell viability by flow cytometry revealed that the percentage of cells undergoing apoptosis in the presence of glucose or fructose decreased in the imeglimin group as compared with the vehicle group.

3.2 Secondary pharmacodynamics (CTD 4.2.1.2)

The inhibitory effects and binding affinity of imeglimin were investigated for 125 enzymes and receptors. The results showed no particular effects of imeglimin on any of the enzymes or receptors.

3.3 Safety pharmacology

The effects of imeglimin on the central nervous system, the cardiovascular system, the respiratory system, and lactic acidosis were evaluated in the safety pharmacology studies presented in Table 4.

[8)] CMRL 1066

Table 4. Summary of safety pharmacology results

Parameter	Test system	Observations/ examinations	Dose of imeglimin	Route of administration	Findings	CTD
Central nervous system	Wister rats (5/sex/group)	Locomotor activity, functional observation battery	0, 150, 500, 1500 mg/kg	Oral	No effects	4.2.1.3.01
Cardiovascular system	HEK293 cells (5 preparations/group)	hERG current	0, 50, 150, 500 μmol/L	*in vitro*	No effects	4.2.1.3.03
	Beagle dogs (3/sex/group)	Heart rate, ECG, and blood pressure	0, 20, 100, 500 mg/kg	Oral	Vomiting in 5 of 6 animals, decreased body weight in 5 of 6 animals, and slightly decreased heart rate in 3 of 6 animals at 500 mg/kg	4.2.1.3.04
Respiratory system	Wistar rats (8 males/group)	Inspiratory time, expiratory time, peak inspiratory and expiratory flows, tidal volume, respiratory rate, relaxation time, respiratory pause, and airway resistance index	0, 150, 500, 1500 mg/kg	Oral	No effects	4.2.1.3.05
Lactic acidosis	Sprague-Dawley rats[a)] (5 to 7 males/group)	Blood lactate concentration, blood glucose concentration, blood H^+, blood HCO_3^- concentration, etc.	0, 25, 50, 75, 100 mg/kg/h	Intravenous infusion	Imeglimin No findings Metformin Deaths in 1 of 5 animals at 50 mg/kg/h, 4 of 7 animals at 75 mg/kg/h, and 5 of 5 animals at 100 mg/kg/h Increased blood lactate concentration at ≥50 mg/kg/h Hypoglycemia at ≥75 mg/kg/h Decreased HCO_3^- concentration and increased H^+ concentration at ≥75 mg/kg/h Fatal lactic acidosis in 5 animals at ≥50 mg/kg/h (1 of 5 animals at 50 mg/kg/h, 2 of 7 animals at 75 mg/kg/h, and 2 of 5 animals at 100 mg/kg/h) Racemate of imeglimin Deaths in 2 of 5 animals at 100 mg/kg/h Enantiomer of imeglimin Hypoglycemia at ≥75 mg/kg/h Deaths in 3 of 6 animals at 75 mg/kg/h	4.2.1.3.06
	Rat liver mitochondria (3 preparations/animal)	mGPDH enzymatic activity	0, 12.5, 25, 50, 75, 100, 175, 250 μmol/L	*in vitro*	Imeglimin No findings Metformin Decreased mGPDH activity at 250 μmol/L	4.2.1.3.07

a) Acute renal failure was induced by repeated subcutaneous doses of gentamicin once daily (250 to 275 mg/kg/day) for 4 days.

3.R Outline of the review conducted by PMDA

3.R.1 Mechanism of action of imeglimin

The applicant's explanation:

Imeglimin is considered to have dual actions, i.e., glucose concentration-dependent insulinotropic effect and insulin resistance improvement.

The possible mechanism of imeglimin's insulinotropic action is as follows: in the pancreatic islets, imeglimin promotes the gene expression of NAMPT, a rate-limiting enzyme in the salvage pathway that is an NDA synthesis pathway, and increases the intracellular NAD^+ concentration via the salvage pathway (CTD 4.2.1.1.07 and 08). This improves the functions of the mitochondrial electron transport chain and leads to an increase in mitochondrial ATP content. The increased ATP content suppresses K_{ATP} channel activity, and augmented mobilization of extracellular calcium into cells may promote insulin secretion (CTD 4.2.1.1.09 and 10). Furthermore, CD38 knockdown in isolated rat pancreatic islets attenuated the insulinotropic effect of imeglimin (CTD 4.2.1.1.11). cADPR, an NAD^+ metabolite formed by CD38 is known to increase the intracellular Ca^{2+} content in the pancreatic islets and increase glucose-stimulated insulin release from islets (*J*

Biochem. 1995;270:30045-50). This suggests that the intracellular Ca^{2+} content increased by NAD^+ metabolites may be another contributory factor to the insulinotropic effect of imeglimin. In term of its insulin resistance improvement, imeglimin improves liver mitochondrial functions by inhibiting Complex I activity and restoring Complex III activity in liver mitochondria, thereby suppressing ROS production (CTD 4.2.1.1.14; *Diabetes.* 2015;64:2254-64). In a study in which imeglimin was added to hepatocytes isolated from male Wister rats in the presence of cAMP to determine glucose concentrations in the supernatants, imeglimin reduced glucose production in a concentration-dependent manner (*J Diabetes Metab.* 2011;2:DOI:10.4172/2155-6156.1000126). Also in muscles, imeglimin improved insulin resistance by increasing the expression of PgG1α, a transcriptional coactivator involved in mitochondrial biosynthesis, thereby restoring mitochondrial functions in the muscles (CTD 4.2.1.14). Further, imeglimin improves the uptake of glucose by soleus and gastrocnemius muscles in STZ-induced diabetic rats, as well as by H-2Kb muscle cells (*J Diabetes Metab.* 2011;2:DOI:10.4172/2155-6156.1000126).

The *in vivo* studies in which imeglimin was orally administered to non-obese diabetic GK rats, STZ-induced diabetic model rats, and other model animals showed a decrease in blood glucose and a tendency toward increased insulin secretion (CTD 4.2.1.1.01 to 03). In STZ-induced diabetic model rats continuously receiving insulin infusion, imeglimin increased the steady-state glucose infusion rate (CTD 4.2.1.1.02) as compared with the vehicle. The glucose clamp studies in Wistar rats and N0-STZ-induced diabetic model rats showed that imeglimin increased glucose concentration-dependent insulin secretion (CTD 4.2.1.1.04 to 05).

These results indicate that imeglimin has a novel action mechanism that improves mitochondrial functions, thereby promoting glucose concentration-dependent insulin secretion while reducing insulin resistance. Thus imeglimin is expected to have efficacy in the treatment of type 2 diabetes mellitus. As described later, imeglimin's action mechanism is considered different from metformin's, primarily in terms of its competitive inhibition of the liver mitochondrial Complex I, as well as insulin resistance improvement and glucose concentration-dependent insulinotropic action through the restoration of Complex III activity.

The safety pharmacology studies showed no effects of imeglimin on blood pressure or electrocardiographic parameters, despite decreased heart rate, suggesting that imeglimin is unlikely to affect the cardiovascular system significantly (CTD 4.2.1.3.04). In the study on the effects on lactic acidosis in rats, imeglimin caused no deaths or had no clear effect on blood lactate concentrations, unlike metformin that had increased blood lactate concentration and caused deaths in some animals possibly due to lactic acidosis (CTD 4.2.1.3.06). Pyruvic acid formed in glycolysis is used as energy via the mitochondrial electron transport chain. However, when Complex I in the electron transport chain is inhibited by metformin, pyruvic acid is metabolized to lactic acid. Metformin also inhibits mGPDH, which is responsible for the transport to NADH mitochondria formed in the process of the production of pyruvic acid from lactic acid in the cytoplasm. Thus, metformin is considered to cause the lactic acid that is formed from pyruvic acid in glycolysis to be accumulated by suppressing mitochondrial functions and inhibiting mGPDH. In the a study comparing the effects of metformin and imeglimin on Complex I, the V_{max} of Complex I for oxygen consumption was decreased by metformin but was not affected by imeglimin (*Endocrinol Diab Metab.* 2021;00:e00211). This suggests that imeglimin

competitively inhibits Complex I, while metformin may be a noncompetitive inhibitor. In a study investigating oxygen consumption in rat hepatocytes incubated with imeglimin or metformin, metformin reduced both total and rotenone-sensitive oxygen consumption, while imeglimin reduced neither type of consumption (*Endocrinol Diab Metab.* 2021;00:e00211). This suggests that the inhibition of Complex I by imeglimin is independent of oxygen consumption. A comparison of effects on mGPDH activity revealed that mGPDH activity was inhibited by metformin but not by imeglimin (CTD 4.2.1.3.07). Given these, imeglimin is unlikely to induce lactic acidosis in humans.

PMDA's view:

The applicant claims that imeglimin has both glucose concentration-dependent insulinotropic effect and insulin resistance improvement effect. In the *in vitro* studies in the pancreatic islets isolated from GK rats showed increased insulin secretion by the addition of imeglimin, along with increases in NAD^+ concentration, ATP content, and intracellular calcium concentration, etc. However, GK rats are known to show possible increase in cAMP, which is considered to affect insulin secretion (*Diabetes.* 1998;47:498-504), etc. Therefore, the results of the *in vitro* studies need to be interpreted carefully, and it is difficult to judge whether the mechanism observed in GK rats is also true in humans. In the *in vivo* investigation, on the other hand, the glucose clamp studies in GK rats and normal animals, etc. indicated a tendency of insulin secretion to be increased by imeglimin treatment. Imeglimin also increases pancreatic β-cell mass. Given these, imeglimin may have some effect on insulin secretion. In terms of insulin resistance by imeglimin, HFHS diet-fed mice showed restored mitochondrial functions and reduced hepatic glucose production observed in the liver, probably accompanying suppressed Complex I activity and restored Complex III activity. In the skeletal muscles, glucose uptake improved probably through increased expression of PgC1α. In STZ-induced diabetic model rats, imeglimin treatment increased the steady-state glucose infusion rate under continuous insulin infusion. These results suggest that imeglimin can improve insulin resistance. Given these findings, including decreased blood glucose concentrations after the administration of imeglimin in GK rats, STZ-induced diabetic model rats, and other model animals in *in vivo* studies, imeglimin is expected to exhibit efficacy in the treatment of type 2 diabetes mellitus.

Imeglimin has been found to have mechanisms for Complex I activity suppression and Complex III activity restoration in mitochondria. In addition, given its possible effect on insulin secretion, imeglimin may have action mechanisms slightly different from metformin's. While it should be noted that the non-clinical studies showed imeglimin's inhibitory effect on Complex I activity and suppressive effect on glucose production, imeglimin restored Complex III activity, and imeglimin, unlike metformin, had no effect on oxygen consumption, and imeglimin did not affect mGPDH activity. In the safety pharmacology studies, imeglimin did not increase lactate concentration while the equivalent dose level of metformin did. These findings suggest that the risk of lactic acidosis associated with imeglimin treatment may differ from that with metformin. The differences between imeglimin and metformin are discussed further based also on clinical study results, in Sections "7.R.3 Clinical positioning" and "7.R.2 Safety."

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

A single of imeglimin or ^{14}C-imeglimin was administered orally or intravenously to mice, rats, dogs, and monkeys to evaluate the pharmacokinetics of imeglimin. The pharmacokinetics of imeglimin was also evaluated following repeated oral doses based on toxicokinetic data from toxicity studies in mice, rats, and dogs. Plasma concentrations of imeglimin and its enantiomer (*S*-imeglimin) were determined using a liquid chromatography/tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantitation of 10 ng/mL for plasma imeglimin concentrations. In non-clinical studies other than a 26-week repeated-dose study in rats (CTD 4.2.3.2.07), a 52-week repeated-dose study in dogs (CTD 4.2.3.2.10), a 13-week carcinogenicity (preliminary) study in rats (CTD 4.2.3.4.1.01), and an embryo-fetal development study in rats (CTD 4.2.3.5.2.02), plasma imeglimin concentrations were determined without differentiating imeglimin from its enantiomer. Radioactivity levels in biological samples were determined using a liquid scintillation counting method. The results of major non-clinical pharmacokinetic studies are described below.

4.1 Absorption

4.1.1 Single-dose studies (CTD 4.2.2.2.01 to 05)

Table 5 shows the pharmacokinetic parameters of imeglimin following a single intravenous or oral imeglimin or ^{14}C-imeglimin in male and female mice, male rats, female dogs, and female monkeys.

Table 5. Pharmacokinetic parameters of imeglimin following a single intravenous or oral imeglimin or ^{14}C-imeglimin

Animal species	Route of administration	Dose (mg/kg)	Sex	N	C_{max} (μg/mL)	AUC [a)] (μg·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	BA (%)
Mice	Intravenous	5 [b)]	Male	4/timepoint	-	0.791	-	-	-
			Female	4/timepoint	-	1.220	-	-	-
	Oral	5 [b)]	Male	4/timepoint	0.403	0.519	0.5	-	65.6
			Female	4/timepoint	0.253	0.598	0.5	1.22	49.0
Rats	Intravenous	5 [b)]	Male	4/timepoint	-	3.920 (31.3)	-	-	-
	Oral	5 [b)]	Male	4/timepoint	0.362 (16.0)	1.860 (27.7)	1.5 [1, 2]	-	48
Dogs	Intravenous	5 [b)]	Female	3	-	9.630 (8.30)	-	5.76 (8.46)	-
	Oral	5 [b)]	Female	3	1.530 (39.9)	7.400 (27.5)	1 [1, 2]	-	75.8
	Intravenous	5	Female	4	-	8.160 (14)	-	7.52	-
	Oral	5	Female	4	0.904 (33)	5.690 (25)	3.0 [2.0, 4.0]	-	69 (14)
Monkeys	Intravenous	5	Female	3	-	8.320 (38.5)	-	-	-
	Oral	5	Female	3	0.172 (30.8)	2.040 (28.6)	8 [6, 8]	-	26.0 (39.1)

Mean or mean (CV, %) (calculated from the mean values at each timepoint for mice and rats)
Median [range] for t_{max} in rats, dogs, and monkeys; median for t_{max} in mice; -, Not determined
C_{max}, maximum plasma concentration; AUC, area under the drug plasma concentration-time curve; t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; BA, absolute bioavailability
a) $AUC_{0\text{-}6h}$ (AUC from 0 to 6 hours after administration) for mice, $AUC_{0\text{-}24h}$ (AUC from 0 to 24 hours after administration) for rats, and AUC_{last} (AUC from 0 to the last quantifiable time) for dogs and monkeys
b) ^{14}C-imeglimin

4.1.2 Repeated-dose studies (CTD 4.2.3.2.02, 4.2.3.2.07, and 4.2.3.2.10)

Table 6 shows the pharmacokinetic parameters of imeglimin administered orally once daily to male and female mice, rats, and dogs. No isomer conversion of imeglimin was observed in rats or dogs.[9)]

[9)] When repeated oral doses of imeglimin (the content of the enantiomer in the drug substance was [redacted]%) was administered to rats and dogs at 250 mg/kg and 300 mg/kg, respectively, the proportion of the AUC for the enantiomer, among the total for the enantiomer and imeglimin, was [redacted]% in both species.

Table 6. Pharmacokinetic parameters of imeglimin administered as repeated oral doses

Animal species	Dose (mg/kg)	N	Timepoint	C_{max} (μg/mL)		AUC [a] (μg·h/mL)	
				Male	Female	Male	Female
Mice	100	10	Day 1	3.05	4.08	9.51	12.5
			Week 13	2.00	2.31	8.15	10.9
	300	10	Day 1	5.42	5.68	24.8	26.9
			Week 13	4.49	6.55	21.6	30.1
	600	10	Day 1	9.11	5.52	49.3	39.4
			Week 13	9.29	10.7	61.9	79.9
	900	10	Day 1	7.40	15.0	50.9	86.5
			Week 13	10.9	10.5	83.0	77.8
	1200	10	Day 1	12.8	17.6	87.5	107
			Week 13	13.7	19.5	91.6	140
Rats	40	3	Day 1	1.55 (16.6)	1.90 (28.6)	8.08 (22.2)	8.25 (10.7)
			Week 13	1.83 (10.5)	1.63 (37.5)	16.3 (21.7)	8.85 (25.4)
			Week 26	1.68 (9.6)	1.35 (48.4)	11.7 (26.8)	8.87 (36.9)
	100	3	Day 1	2.89 (9.5)	3.59 (12.7)	22.1 (6.8)	20.9 (45.8)
			Week 13	3.25 (8.8)	3.56 (15.4)	29.7 (24.7)	16.2 (63.0)
			Week 26	4.10 (12.3)	3.16 (31.6)	32.9 (3.0)	23.3 (11.0)
	250	3	Day 1	6.04 (4.3)	6.84 (13.9)	47.2 (11.8)	48.3 (21.5)
			Week 13	5.25 (7.0)	8.13 (29.4)	58.8 (7.6)	68.8 (15.0)
			Week 26	6.81 (12.2)	9.49 (20.1)	54.2 (8.0)	65.8 (29.2)
Dogs	30	3	Day 1	5.20 (22.3)	4.13 (27.6)	26.2 (5.4)	22.6 (30.7)
			Week 27	5.87 (11.3)	4.07 (8.7)	35.5 (11.8)	32.3 (24.8)
			Week 52	5.46 (22.5)	3.45 (40.6)	33.0 (16.7)	30.0 (50.3)
	100	3	Day 1	25.7 (16.8)	35.7 (19.4)	94.3 (20.0)	134 (24.9)
			Week 27	19.2 (5.6)	25.6 (38.0)	104 (12.9)	182 (20.9)
			Week 52	22.9 (13.5)	18.0 (80.0)	111 (21.9)	93.4 (69.4)
	300	3	Day 1	89.6 (72.5)	92.0 (4.4)	449 (69.0)	513 (29.8)
			Week 27	59.7 (37.9)	78.9 (25.3)	290 (38.3)	593 (11.8)
			Week 52	50.2 (48.0)	72.5 (9.0)	291 (4.8)	512 (25.4)

Mean or mean (CV, %)

C_{max}, maximum plasma concentration; AUC, area under the drug plasma concentration-time curve

a) $AUC_{0\text{-}24h}$ (AUC from 0 to 24 hours after administration) for mice and dogs, AUC_{last} (AUC from 0 to the last quantifiable time) for rats

4.2 Distribution (CTD 4.2.2.3.01 to 4.2.2.3.04)

A single oral dose of ^{14}C-imeglimin 5 mg/kg was administered to male and female albino rats (1/sex/timepoint) to evaluate the tissue distribution of radioactivity over 24 hours postdose. In male rats, tissue radioactivity peaked at 1 hour postdose in most tissues, except the extraorbital lacrimal gland, intraorbital lacrimal gland, bulbourethral gland,[10] coagulating gland,[10] preputial gland,[10] prostate,[10] lateral nasal gland,[10] pulp, and rectal mucosa.[10] In female rats, the tissue radioactivity levels peaked at 1 hour postdose in most tissues except the extraorbital lacrimal gland,[10] clitoris,[10] lateral nasal gland, and cecum mucosa.[11] In male rats, radioactivity concentrations at 1 hour postdose were higher (1.02- to 6.09-fold) in the following tissues (other than the gastrointestinal tract), in descending order, than in blood: the liver, renal cortex, renal medulla, tongue epithelium, extraorbital lacrimal gland, salivary gland, brown fat, myocardium, thymus, lung, aorta, adrenal medulla, thyroid, intraorbital lacrimal gland, nasal mucosa, uvea, and submandibular lymph nodes. In female rats, radioactivity concentrations at 1 hour postdose were higher (1.04- to 7.02-fold) in the following tissues (other than the gastrointestinal tract), in descending order, than in blood: the renal medulla, lateral nasal gland, renal cortex, liver, salivary gland, brown fat, intraorbital lacrimal gland, tongue epithelium, thyroid, aorta, myocardium, lung, thymus, nasal mucosa, submandibular lymph nodes, uterus, adrenal medulla, pulp, uvea, and spleen. At 24 hours postdose, radioactivity was below the lower limit of quantification in blood, while

[10] A tissue sample at 1 hour postdose could not be taken.

[11] It was likely attributable to exposure to the high-level of radioactivity in the gastrointestinal content.

detectable radioactivity was observed in the lateral nasal gland, preputial gland, extraorbital lacrimal gland, intraorbital lacrimal gland, adrenal medulla, pituitary gland, nasal mucosa, salivary gland, renal medulla, renal cortex, gastric mucosa (the fundus), bulbourethral gland, thyroid, skin, liver, gastric mucosa (other than the fundus), and pancreas in male rats (63 to 2280 ng eq/g); and the lateral nasal gland, clitoris, intraorbital lacrimal gland, colonic mucosa, nasal mucosa, salivary gland, adrenal medulla, and thyroid in female rats (64 to 1770 ng eq/g). However, the tissue radioactivity at 24 hours postdose was lower than that at 1 or 6 hours postdose in most tissues, except for the preputial gland. Tissue radioactivity concentrations following a single intravenous dose of ^{14}C-imeglimin 5 mg/kg in male and female pigmented rats (1/sex/timepoint) were similar to those in albino rats in most tissues, except for the uvea. In albino rats, radioactivity concentrations in the uvea at 1 hour postdose were 1.10- to 1.15-fold the blood radioactivity concentrations, but declined to less than the lower limit of quantification at 24 hours postdose. In pigmented rats, on the other hand, radioactivity concentrations in the uvea were 2.58- to 4.03-fold the blood radioactivity concentrations at 1 hour postdose, and declined to 0.05- to 0.19-fold the blood radioactivity concentrations at 24 hours postdose.[12)] The radioactivity concentrations in pigmented and unpigmented skin in male and female pigmented rats were 1.10- to 1.17-fold and 0.68- to 1.04-fold, respectively. The blood radioactivity concentration at 1 hour postdose as well as both pigmented and unpigmented skin radioactivity concentrations declined to less than the lower limit of quantification at 24 hours postdose.

When a single oral dose of 100 mg/kg ^{14}C-imeglimin was administered to pregnant rats (gestation day 18, 3/timepoint), radioactivity was detected in maternal animals and their fetuses at 1, 6, and 24 hours postdose, with fetal-to-maternal plasma radioactivity concentration ratios of 0.08, 0.30, and 0.70, respectively.

The mean plasma protein binding (ultrafiltration method) of ^{14}C-imeglimin (0.2 to 20 μg/mL) was 3.2% to 9.1% in mice, 3.3% to 8.3% in rats, 4.9% to 5.9% in rabbits, 1.1% to 6.8% in dogs, and 2.1% to 5.8% in monkeys. The mean blood cell-to-plasma radioactivity concentration ratios of ^{14}C-imeglimin (0.2 and 20 μg/mL) were 0.77 and 0.84 in mice, 0.98 and 1.12 in rats, 0.86 and 0.95 in rabbits, 0.31 and 0.22 in dogs, and 1.12 and 1.03 in monkeys [for human data, see Section "6.2.1 Studies using human biomaterials"].

4.3 Metabolism (CTD 4.2.2.2.01 to 03, and 4.2.2.4.02)

The *in vitro* metabolism of ^{14}C-imeglimin was investigated in mouse, rat, rabbit, dog, minipig, and monkey hepatocytes. The mean proportions of unchanged imeglimin after a 24-hour incubation were 88.1% to 90.4% in mice, 72.7% to 90.3% in rats, ≤1.5% in rabbits, 53.1% to 60.1% in dogs, 63.8% to 93.3% in minipigs, and 88.7% to 90.6% in monkeys. A total of 8 metabolites were detected.

Following a single oral dose of ^{14}C-imeglimin 100 mg/kg in male and female mice (4/sex/timepoint), unchanged imeglimin ($AUC_{0\text{-}6h}$) accounted for 95% (males) and 97% (females) of the total plasma radioactivity ($AUC_{0\text{-}6h}$), with 3 metabolites detected in slight amounts. In male and female mice (3/sex), the mean cumulative urinary excretion rates (percent excretion of the administered radioactivity) for 120 hours after a single oral

[12)] The tissue-to-blood radioactivity concentration ratio in the uvea at 24 hours postdose could not be calculated because the blood radioactivity concentration was below the lower limit of quantification.

dose of ^{14}C-imeglimin 100 mg/kg were 64.9% in males and 56.7% in females. The cumulative excretion rates of unchanged imeglimin were 60.7% in males and 52.1% in females. In addition to unchanged imeglimin, 5 major metabolites were found in urine, in both males and females, with cumulative excretion rates of <0.01% to 2.9% in males and <0.01% to 2.8% in females. The mean cumulative fecal excretion rates (percent excretion of the administered radioactivity) by 120 hours postdose were 36.0% in males and 41.7% in females. The cumulative excretion rates of unchanged imeglimin were 35.6% in males and 41.7% in females. In addition to unchanged imeglimin, 2 fecal metabolites were found, with cumulative excretion rates of <0.01% to 0.4% in males and <0.01% in females.

Following a single oral dose of ^{14}C-imeglimin 100 mg/kg in male rats (4/timepoint), unchanged imeglimin ($AUC_{0\text{-}24h}$) accounted for 69% of the total plasma radioactivity ($AUC_{0\text{-}24h}$), and metabolites EMD601811 and EMD647302 ($AUC_{0\text{-}8h}$) accounted for 13% and 3%, respectively, of the total plasma radioactivity, with 2 other metabolites also detected in slight amounts. In 4 male rats, the mean cumulative urinary excretion rate (percent excretion of the administered radioactivity) by 48 hours after a single oral dose of ^{14}C-imeglimin 5 mg/kg was 37.2%. The cumulative excretion rate of unchanged imeglimin was 31.8%. A total of 8 urinary metabolites were found with cumulative excretion rates of <0.01% to 3.4%. The mean cumulative fecal excretion rate (percent excretion of the administered radioactivity) by 48 hours postdose was 51.8%. The cumulative excretion rate of unchanged imeglimin was 50.2%. A total of 4 fecal metabolites were found with cumulative excretion rates of <0.01% to 0.2%.

Following a single oral dose of ^{14}C-imeglimin 100 mg/kg in 3 female dogs, unchanged imeglimin ($AUC_{0\text{-}6h}$) and its metabolite, EMD647302 ($AUC_{0\text{-}6h}$), accounted for 86% and 10% of the total plasma radioactivity ($AUC_{0\text{-}6h}$), respectively, with a slight amount of EMD27355, another metabolite of imeglimin, also detected. The mean urinary excretion rate (percent excretion of the administered radioactivity) by 48 hours postdose was 53.7%, and the cumulative urinary excretion rate of unchanged imeglimin was 43.0%. A total of 3 urinary metabolites were found, with cumulative excretion rates of 1.1% to 7.9%. The mean cumulative fecal excretion rate (percent excretion of the administered radioactivity) by 48 hours postdose was 32.8%, and the cumulative fecal excretion rates of unchanged imeglimin was 32.7%. One fecal metabolite was found with a cumulative excretion rate of 0.1%.

4.4 Excretion (CTD 4.2.2.2.01, 4.2.2.2.03, 4.2.2.4.03, and 4.2.2.5.01)

A single intravenous dose of ^{14}C-imeglimin 5 mg/kg, or a single oral dose of ^{14}C-imeglimin 5 or 100 mg/kg was administered to male and female mice (3/sex/group). The mean cumulative urinary excretion rates (percent excretion of the administered radioactivity) by 120 hours after the intravenous dose were 77.6% in males and 75.2% in females, and those after the oral dose were 48.4% to 54.7% and 56.7% to 62.1%, respectively. The mean cumulative fecal excretion rates after the intravenous dose were 13.0% in males and 14.2% in females, while those after the oral dose were 38.2% to 38.4% and 35.6% to 41.7%, respectively.

A single intravenous or oral dose of ^{14}C-imeglimin 5 mg/kg was administered to male rats (4/group). The mean cumulative urinary excretion rate (percent excretion of the administered radioactivity) by 120 hours after the

intravenous dose was 90.3%, and that after the oral dose was 38.2%. The mean cumulative fecal excretion rate after the intravenous dose was 3.2%, and that after the oral dose was 52.2%.

A single intravenous dose of ^{14}C-imeglimin 5 mg/kg, or a single oral dose of ^{14}C-imeglimin 5 or 100 mg/kg was administered to female dogs (3/group). The mean cumulative urinary excretion rate (percent excretion of the administered radioactivity) by 120 hours after the intravenous dose was 95.2%, while that after the oral dose was 55.1% to 76.6%. The mean cumulative fecal excretion rate after the intravenous dose was 1.0%, while that after the oral dose was 15.6% to 33.0%.

A single oral dose of ^{14}C-imeglimin 5 mg/kg was administered to 4 lactating rats (day 12 postpartum). The milk-to-maternal plasma radioactivity concentration ratios at 1, 2, 4, 8, and 24 hours postdose were 0.62 to 3.06.

4.R Outline of the review conducted by PMDA

4.R.1 Effects of imeglimin on melanin-containing tissues

The results of the distribution study in pigmented rats (CTD 4.2.2.3.01) revealed higher radioactivity concentration in the uvea, a melanin-containing tissue, in pigmented rats than in albino rats. PMDA asked the applicant to explain the safety of imeglimin in human melanin-containing tissues such as eyes and skin.

The applicant's explanation:

Imeglimin has no ultraviolet-visible absorption spectrum in the wavelength range between 290 and 700 nm. The activation of imeglimin by sunlight is thus unlikely to affect eyes or skin. Non-clinical studies, including the 4-, 13-, and 52-week repeated oral dose toxicity studies in dogs,[13)] showed no imeglimin-related histopathological changes in major melanin-containing tissues such as eyes and skin (CTD 4.2.3.2.08 to 10). The safety of imeglimin in melanin-containing tissues such as eyes and skin in humans was evaluated based on the results of clinical studies in Japanese patients (Studies 014 and 018 combined, and Studies 019 and 020). Of the adverse events categorized into the SOC of "eye disorders," those related to the uvea (iris, ciliary body, choroid) or retina were mostly diabetic retinopathy. All reported cases of diabetic retinopathy were associated with diabetes mellitus, arteriosclerosis, etc. or were those for which a causal relationship to the study drug was ruled out. One patient in Study 019 reported an adverse event (leukoderma) categorized into the HLGT of "pigmentation disorders," for which a causal relationship to the study drug was ruled out.

Based on the above, imeglimin is unlikely to pose clinically significant problems with safety in melanin-containing tissues such as eyes and skin.

PMDA accepted the applicant's explanation.

[13)] The highest doses of imeglimin administered in the 4-, 13-, and 52-week repeated oral dose toxicity studies in dogs were 500 mg/kg/day, 500 mg/kg/day, and 300 mg/kg/day, respectively, and the plasma exposure to imeglimin (C_{max} and AUC) in male and female dogs receiving imeglimin 300 mg/kg/day was 27.8- and 11.5-fold, and 40.2- and 20.3-fold, respectively, of the human exposure at the clinical recommended dose (1000 mg, twice daily).

5. Toxicity and Outline of the Review Conducted by PMDA

The submitted toxicity data on imeglimin included the results from single dose toxicity studies, repeated dose toxicity studies, genotoxicity studies, carcinogenicity studies, reproductive and developmental toxicity studies, local tolerance studies, and other toxicity studies (antigenicity studies, safety studies of impurities). Unless otherwise specified, 0.25% hydroxypropylmethylcellulose solution was used as the vehicle.

5.1 Single-dose toxicity

Single dose toxicity studies were conducted in mice and rats (Table 7). The approximate lethal doses for orally administered imeglimin were 4000 mg/kg in mice, and >5000 mg/kg (males) and 3000 mg/kg (females) in rats. The approximate lethal doses of intravenously administered imeglimin were 150 mg/kg (males) and 100 mg/kg (females) in mice, and 150 mg/kg in rats.

Table 7. Single dose toxicity studies

Test system	Route of administration	Dose[a)] (mg/kg)	Main findings	Approximate lethal dose (mg/kg)	Submitted data CTD
Male and female mice (Crl:NMRI BR)	Oral	2000, 3000, 4000	Deaths: 4000 (2 of 3 males, 3 of 3 females); dilation of the stomach and jejunum 2000 and 3000: Decreased body weight gain on Day 2 ≥3000: Ataxia 4000: Prone position and dyspnea	4000	4.2.3.1.01
Male and female mice (Crl:NMRI BR)	Intravenous	50 (females), 100, 150, 200 (males)	Deaths: 100 (1 of 3 females), 150 (1 of 3 males, 2 of 3 females), and 200 (3 of 3 males) ≥50: Prone position (females), dyspnea (females), and ataxia (females) ≥100: Prone position (males), dyspnea (males), and ataxia (males) 150: tonic-clonic convulsion (males)	150 (males) 100 (females)	4.2.3.1.02
Male and female rats (Wistar)	Oral	2000 (females), 3000, 4000, 5000 (males)	Deaths: 3000 (1 of 3 females) and 4000 (2 of 3 females); dilation of the stomach and jejunum ≥3000: Ataxia, prone position (females), and dyspnea (females) 4000: Blood-like material around the nose (males) ≥4000: Dyspnea (males) 5000: Salivation	>5000 (males) 3000 (females)	4.2.3.1.03
Male and female rats (Wistar)	Intravenous	100, 150, 200	Deaths: 150 (1 of 3 males, 1 of 3 females) and 200 (3 of 3 males, 3 of 3 females) 100: Tremors (females) 100 and 150: Ataxia ≥100: Dyspnea ≥150: Supine/prone position or lateral position, tonic-clonic convulsion	150	4.2.3.1.04

a) The vehicle was water for injection.

5.2 Repeated-dose toxicity

Repeated oral dose toxicity studies of imeglimin were conducted in mice (up to 13-weeks), rats (up to 26-weeks), and dogs (up to 52-weeks) (Table 8). The primary target organs of toxicity were the stomach, adrenal glands, thyroid gland, and mesenteric lymph nodes.

When imeglimin was administered to rats once daily for 26 weeks, the C_{max} (6810 ng/mL in males, 9490 ng/mL in females) and $AUC_{0\text{-}24h}$ values (54,200 ng·h/mL in males, 65,800 ng·h/mL in females) at the no observed adverse effect level (NOAEL, 250 mg/kg/day) were approximately 3.8- and 5.3-fold, and 2.2- and 2.6-fold,

respectively of the human exposure at the clinical maximum dose (1000 mg twice daily).[14)] When imeglimin was administered to dogs once daily for 52 weeks, the C_{max} (50,200 ng/mL in males, 72,500 ng/mL in females) and $AUC_{0\text{-}24h}$ values (291,000 ng·h/mL in males, 512,000 ng·h/mL in females) at the NOAEL (300 mg/kg/day) were approximately 27.8- and 40.2-fold, and 11.5- and 20.3-fold of the human exposure at the clinical maximum dose.[14)]

[14)] The exposure (C_{max}, 1804.4 ng/mL; AUC, 25,250 ng·h/mL [geometric means]) observed in healthy adults who received multiple doses of imeglimin 1000 mg twice daily for 7 days

Table 8. Repeated dose toxicity studies

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Submitted data CTD
Male and female mice (B6C3F1)	Oral	2 weeks (once daily)	0, 200, 600, 1800	Deaths: 1800 (1 of 16 males); ulcer and thymic atrophy 600: Decreased spleen weight (males) ≥600: Increased body weight (females), increased plasma lactate (males), and focal neutrophilic infiltration in the gastric fundus submucosa (females) 1800: Diarrhea, recess in the flank, soft feces (males), decreased motor activity (males), increased body weight gain (females), increased plasma lactate (females), increased liver weight, increased spleen weight (males), hepatocellular hypertrophy with clear cytoplasm, diffuse neutrophilic infiltration in the gastric fundus submucosa (males), and orthokeratotic hyperkeratosis of the forestomach	600 [a)]	4.2.3.2.01
Male and female mice (B6C3F1)	Oral	13 weeks (once daily)	0, 100, 300, 600, 900, 1200	Deaths[b)]: 900 (1 of 25 females) and 1200 (2 of 25 males and 2 of 25 females) 1200: Increased blood ALP (males), increased blood total bilirubin (females), adrenal cortical cell hypertrophy (males), and mucosal hyperplasia/hyperkeratosis of the forestomach (males)	600	4.2.3.2.02
Male and female rats (Wistar)	Oral	4 weeks (once daily)	0, 150, 500, 1500	150: Decreased blood calcium (males), increased blood ALT/AST (males), hyperplasia of the adrenal fasciculata (males), and activation of thyroid follicles (females) ≥150: Salivation (females), removing bedding material (females), decreased blood chloride, and macrophage hyperplasia in the paracortex and histiocytosis in the sinus of mesenteric lymph nodes ≥500: Salivation (males), removing bedding material (males), decreased blood sodium (males), increased blood ALT (females), decreased blood urea nitrogen, increased liver weight (males), submucosal edema with neutrophilic infiltration in the fundus of the glandular stomach (males), and activation of thyroid follicles 1500: Decreased body weight (males), decreased body weight gain, decreased food consumption, increased blood inorganic phosphorus and calcium (males), decreased blood total protein/ALP (males), decreased blood sodium (females), increased blood AST (females), increased blood lactic acid/triglycerides, increased watery content in the small intestine, increased weights of liver, adrenal, spleen, and kidneys (females), submucosal edema in the distal glandular stomach (males), submucosal edema with neutrophilic infiltration in the glandular stomach (females), and hyperplasia of the adrenal fasciculata	150 [c)]	4.2.3.2.05
Male and female rats (Wistar)	Oral	13 weeks (once daily)	0, 30, 100, 300	30 and 100: Increased blood glucose (males) ≥30: Increased blood lactic acid (males) ≥100: Salivation, removing bedding material, macrophage hyperplasia in the paracortex of mesenteric lymph nodes (males), activation of thyroid follicles (females), and enlarged adrenal fasciculata (females) 300: Increased blood lactic acid (females), increased blood ALT, and macrophage hyperplasia in the paracortex of mesenteric lymph nodes (females)	100 [d)]	4.2.3.2.06
Male and female rats (Wistar)	Oral	26 weeks (once daily) + 8-week washout	0, 40, 100, 250	40: Increased blood sodium and potassium (males), and increased blood lactic acid (females) ≥40: Increased blood calcium (males), increased blood glucose (females), and macrophage hyperplasia in the paracortex of mesenteric lymph nodes 100: Increased food consumption (females) ≥100: Salivation, removing bedding material, and increased blood ALT (males) 250: Increased body weight gain (females) and increased kidney weight (females) The findings were reversible.	250 [e)]	4.2.3.2.07
Male and female dogs (Beagle)	Oral	2 weeks[f)] (once daily)	500→1000→1500	Deaths: 1500 (1 of 1 female); ataxia, tremors, increased blood sodium and decreased blood potassium, mucosal congestion in the small intestine, kidneys, liver, lungs, and stomach, and lymphoid follicle depletion in mesenteric lymph nodes, mandibular lymph nodes, and the spleen ≥500: Vomiting ≥1000: Salivation, decreased motor activity, photophobia, and diarrhea 1500: Low body temperature, prone position (males), decreased body weight, decreased heart rate (females), increased blood chloride (males), and glycogen depletion in the liver		4.2.3.2.03

Table 8. Repeated dose toxicity studies (continued)

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Submitted data CTD
Male and female dogs (Beagle)	Oral	First treatment period: 5 days (once daily) Second treatment period: 5 days (once daily)[g)]	First treatment period: 0, 600, 800, 1000 Second treatment period: 0, 1000	First treatment period: Deaths[g)]: 600 (1 of 3 females), 800 (1 of 3 females), and 1000 (1 of 3 females); lateral position, decreased blood glucose, increased blood lactic acid, glycogen depletion in the liver, and vacuolation of cerebrocortical glial cells and hippocampal neuropil 600: Decreased body weight (males) ≥600: Diarrhea, soft feces, vomiting, salivation, and photophobia 800: Decreased motor activity (females) ≥800: Decreased body weight (females) and decreased food consumption (females) 1000: Decreased motor activity (males) Second treatment period: 1000: Diarrhea, soft feces, vomiting, salivation, photophobia, decreased motor activity, lateral position, abnormal gait, tremors, decreased body weight, decreased food consumption (females), transient low body temperature (males), decreased platelet count (males), decreased blood glucose,[h)] increased blood lactic acid,[g)] increased blood ALT and AST (females), and glycogen depletion in the liver		4.2.3.2.04
Male and female dogs (Beagle)	Oral	4 weeks (once daily)	0, 20, 100, 500	≥100: Vomiting, diarrhea, soft feces, and salivation 500: Miosis, photophobia, protrusion of the nictitating membrane, decreased body weight, decreased food consumption, decreased blood chloride (females), and increased liver weight (males)	100 [i)]	4.2.3.2.08
Male and female dogs (Beagle)	Oral	13 weeks (once daily)	0, 20, 100, 500	≥100: Soft feces, liquid feces, mucoid feces, behavioral depression, decreased body weight gain (females), and decreased food consumption (females) 500: Salivation, vomiting, protrusion of the nictitating membrane, decreased body weight gain (males), decreased food consumption (males), and decreased heart rate	100 [j)]	4.2.3.2.09
Male and female dogs (Beagle)	Oral	52 weeks (once daily) + 8-week washout	0, 30, 100, 300	≥30: Decreased food consumption (females) ≥100: Vomiting, salivation, soft feces, diarrhea (may be accompanied by mucoid feces), and decreased food consumption (males) 300: Behavioral depression (females), photophobia, protrusion of the nictitating membrane, decreased body weight, and increased blood sodium and chloride The findings were reversible.	300 [k)]	4.2.3.2.10

a) All findings reported in the 600 mg/kg/day group were considered to be of little toxicological significance, because the increased body weight and the increased plasma lactate level were minimal, the increased spleen weight was accompanied by no histopathological changes, and the inflammatory changes in the stomach were minimal and also observed in the control group.

b) Deaths also occurred in the 1800 mg/kg group of the 2-week repeated dose toxicity study in mice. Although the causes of deaths remain undetermined, a causal relationship between these deaths and the study drug could not be ruled out.

c) All findings reported in the 150 mg/kg/day group were considered to be of little toxicological significance, because the salivation and removing bedding material were transient, the findings in mesenteric lymph nodes were likely attributable to excessive exposure to imeglimin, the adrenal fasciculata hyperplasia was a mild change observed in only 1 animal, and the findings in the thyroid gland were likely to be adaptive changes associated with the induction of hepatic drug-metabolizing enzymes.

d) All findings reported in the 100 mg/kg/day group were considered to be of little toxicological significance, because the salivation and removing bedding material were transient, the findings in mesenteric lymph nodes were likely attributable to excessive exposure to imeglimin, and the findings in the thyroid gland and the adrenal gland were likely associated with metabolic activation.

e) All findings reported in the study were minimal and improving, and therefore considered to be of little toxicological significance.

f) Imeglimin was administered at 500 mg/kg/day on Day 1, 1000 mg/kg/day on Days 2 to 7, and 1500 mg/kg/day on Days 8 to 14.

g) Initially, the vehicle or imeglimin was planned to be administered once daily for 4 weeks (the first treatment period). However, some animals were dead or sacrificed moribund in the early phase of treatment. Therefore, treatment from Day 6 onward was discontinued, and the study plan was changed so that the causes of deaths that occurred in the first treatment period could be investigated in the subsequent phase of the study (the second treatment period). In the first treatment period, a histopathological examination was performed only on animals which were dead or sacrificed moribund. Based on the results from the second treatment period, the causes of deaths that had occurred in the first treatment period were determined as hypoglycemia associated with the excessive pharmacological effects of imeglimin.

h) Resolved after a 50% glucose solution and physiological saline were intravenously administered

i) Vomiting, diarrhea, soft feces, and salivation observed in the 100 mg/kg/day group were minimal and sporadic, and therefore considered to be of little toxicological significance.

j) The fecal alterations (soft feces, liquid feces, and mucoid feces) observed in the 100 mg/kg/day group were infrequent and sporadic, were not accompanied by any secondary effects, and had a low tendency to result in behavioral depression. Therefore, the findings were considered to be of little toxicological significance.

k) All findings reported in the study were transient and resolved promptly after the discontinuation of imeglimin, and were therefore considered to be of little toxicological significance.

5.3 Genotoxicity

The genotoxicity studies of imeglimin consisted of 2 *in vitro* studies: a bacterial reverse mutation assay and a mouse lymphoma TK assay, and 1 *in vivo* study: a rat bone marrow micronucleus assay (Table 9). Imeglimin tested negative in all these studies, suggesting that imeglimin is unlikely to be genotoxic in the body.

Table 9. Genotoxicity studies

Type of study		Test system	Metabolic activation (treatment)	Concentration (μg/plate or μg/mL) or dose (mg/kg/day)	Test result	Submitted data CTD
in vitro	Bacterial reverse mutation study	Salmonella typhimurium: TA98, TA100, TA102, TA1535, and TA1537 Escherichia coli:WP2*uvrA*	S9-	0 [a)], 5, 15.8, 50, 158, 500, 1580, 5000	Negative	4.2.3.3.1.01
			S9+			
	Mouse lymphoma TK assay	L5178Y/TK$^{+/-}$ mouse lymphoma cells	S9- (3 hours)	0 [a)], 50, 158, 500, 1580, 2810, 5000	Negative	4.2.3.3.1.02
			S9+ (3 hours)	0 [a)], 158, 500, 1580, 5000		
			S9- (24 hours)	0 [a)], 50, 158, 500, 1580, 2810		
in vivo	Rodent micronucleus assay	Male rats (Wistar) Bone marrow		0, 200, 633, 2000 (single oral dose)	Negative	4.2.3.3.2.01

a) Water

5.4 Carcinogenicity

The carcinogenicity studies of imeglimin consisted of a 104-week repeated oral dose carcinogenicity study in rats and a 26-week repeated oral dose carcinogenicity study in Tg-rasH2 mice. The results revealed increased frequency of hemangioma in mesenteric lymph nodes in male rats (Table 10).

Table 10. Carcinogenicity studies

Test system	Route of administration	Treatment duration	Major lesions		Sex	Dose (mg/kg/day)					Non-carcinogenic dose (mg/kg/day)	Submitted data CTD
						0 [a]	0 [b]	125	250	500		
					N	57/sex	57/sex	57/sex	57/sex	66/sex		
Male and female rats (Wistar)	Oral	104 weeks (once daily)	Neoplastic lesions	Mesenteric lymph nodes: hemangiosarcoma	Male	0	0	0	0	0	500	4.2.3.4.1.02
					Female	0	0	0	0	0		
				Whole body: hemangiosarcoma	Male	0	2	0	0	0		
					Female	0	1	0	1	1		
				Mesenteric lymph nodes: hemangioma	Male	10	3	8	11	18		
					Female	0	0	1	3	2		
				Whole body: hemangioma	Male	1	1	3	1	2		
					Female	1	0	0	1	0		
			Non-neoplastic lesions	Mesenteric lymph nodes: angiomatous hyperplasia	Male	2	5	5	10	14		
					Female	2	2	3	4	7		
				Mesenteric lymph nodes: sinusoidal red blood cells	Male	15	9	15	21	24		
					Female	13	12	9	18	22		
			Other non-neoplastic lesions		Salivation, decreased body weight and body weight gain, increased ALT, red or black discoloration/increased frequency of red or black masses in mesenteric lymph nodes, and hypertrophy of the cecum mucosa							

Test system	Route of administration	Treatment duration	Major lesions		Sex	Dose (mg/kg/day)				Non-carcinogenic dose (mg/kg/day)	Submitted data CTD
						0 [b]	500	1000	1500		
					N	25/sex	25/sex	25/sex	25/sex		
Male and female mice (CB6F1-Tg-rasH2)	Oral	26 weeks (once daily)	Neoplastic lesions	Hemolymphoreticular system: malignant lymphoma	Male	0	0	0	0	1500	4.2.3.4.2.02
					Female	0	0	0	1		
				Whole body: hemangiosarcoma	Male	1	2	2	1		
					Female	2	0	0	3		
				Whole body: hemangioma	Male	2	0	0	0		
					Female	0	0	0	0		
				Lung: bronchoalveolar adenoma or cancer	Male	1	0	1	0		
					Female	0	1	1	0		
				Squamous stomach: squamous cell papilloma or papillary carcinoma	Male	0	1	0	0		
					Female	0	0	0	0		
			Other non-neoplastic lesions		Gallbladder dilation, small uterus, increased liver weight, decreased ovary weight, glycogen storage in the liver, epithelial hyperplasia of the larynx, hyperkeratosis and epithelial hyperplasia of the squamous stomach, diffuse hyperplasia of the cecum, decreased frequency of the absence of corpora lutea in the ovaries, decreased frequencies of uterus atrophy/glandular dilation, increased frequency of mucinous degeneration of the vagina, and decreased estrus					

a) Negative control (water)
b) Vehicle control (0.25% hydroxypropylmethylcellulose)

5.5 Reproductive and developmental toxicity

The reproductive and development toxicity studies of imeglimin consisted of a fertility and early embryonic development study in rats, embryo-fetal development studies in rats and rabbits, and a study for effects on pre- and postnatal development, including maternal function, in rats (Table 11). The embryo fetal development study in rabbits revealed fatality and growth retardation observed in embryos/fetuses at the doses that was associated with decreased maternal body weight. In the embryo-fetal development studies in rats and rabbits, the C_{max} and $AUC_{0\text{-}24}$ values at the NOAEL (500 mg/kg in rats, 100 mg/kg in rabbits) were 12,800 ng/mL (rats) and 858 ng/mL (rabbits), and 106,000 ng·h/mL (rats) and 5960 ng·h/mL (rabbits), respectively, which were approximately 7.1- and 0.5-fold, and 4.2- and 0.2-fold of the human exposure at the clinical maximum dose.[14)]

Based on these results and the suggested transfer of imeglimin from pregnant rats to fetuses [see Section "4.2 Distribution"], the applicant explained that imeglimin should not be administered to pregnant women or women who may be pregnant.

Table 11. Reproductive and development toxicity studies

Type of study	Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	Submitted data CTD
Fertility and early embryonic development study	Male rats (Wistar)	Oral	10 weeks prior to mating and throughout the mating period (6 weeks), and until the day before necropsy (once daily)	0, 100, 300, 1000	Parent animals: ≥300: Salivation and removing bedding material 1000: Decreased body weight and decreased body weight gain	Parent animals (general toxicity) : 100 Parent animals (fertility) : 1000	4.2.3.5.1.01
	Female rats (Wistar)		2 weeks prior to mating to gestation day 7 (once daily)	0, 150, 500, 1500	Parent animals: ≥150: Salivation, removing bedding material, and increased water consumption 1500: Decreased body weight gain with decreased food consumption	Parent animals (general toxicity) : 150 [a)] Parent animals (fertility) : 1500	4.2.3.5.1.02
Embryo-fetal development study	Female rats (Wistar)	Oral	Gestation days 6 to 17 (once daily)	0, 150, 500, 1500	Maternal animals: ≥150: Salivation and removing bedding material 1500: Decreased body weight gain with decreased food consumption, decreased body weight, and increased water consumption Fetuses: ≥150: Decreased body weight and incomplete ossification of the hyoid bone	Parent animals (general toxicity) : 500 [a)] Embryo-fetal development : <150	4.2.3.5.2.01
	Female rats (Wistar)	Oral	Gestation days 6 to 17 (once daily)	0, 20, 100, 500	Maternal animals: ≥100: Salivation and removing bedding material 500: Decreased body weight gain with decreased food consumption Fetuses: No noteworthy findings	Parent animals (general toxicity) : 100 [a)] Embryo-fetal development : 500	4.2.3.5.2.02
	Female rabbits (New Zealand White)	Oral	Gestation day 7 to 19 (once daily)	0, 100, 200, 300 [c)]	Maternal animals: Deaths[b)]: 200 (1 of 22 animals) and 300 (18 of 20 animals) ≥200: Abortion, decreased body weight with decreased food consumption, and decreased body weight gain Fetuses: 200: Total resorption of the litter, a tendency toward increased postimplantation loss with a tendency toward a decreased number of live fetuses, decreased body weight (males), and a tendency toward decreased mean body weight	Parent animals (general toxicity) : 100 Embryo-fetal development : 100	4.2.3.5.2.03
Study of effects on pre- and postnatal development, including maternal function	Female rats (Wistar)	Oral	Maternal rats: Gestation day 6 to lactation day 21 (once daily)	0, 250, 500, 1000	Maternal animals: ≥250: Salivation F1 generation: No noteworthy findings	Maternal animals (general toxicity) : 1000 [a)] Development of F1 pups : 1000	4.2.3.5.3.03

a) The salivation and removing bedding material were attributable to the irritant properties of imeglimin; the finding were therefore considered to be of little toxicological significance.

b) One animal in the 200 mg/kg/day group, which had a marked decrease in body weight due to poor food consumption, was sacrificed moribund on gestation day 14. A total of 2 animals in the 300 mg/kg/day group miscarried on gestation day 21 or 22, and a marked decrease in body weight with decreased food consumption was observed in other animals in the same group. All remaining animals in the 300 mg/kg/day group were thus sacrificed moribund by gestation day 29.

c) In the 300 mg/kg/day group, no external/visceral or skeletal examination for fetuses was conducted, because all animals miscarried or were sacrificed moribund.

5.6 Local tolerance

The local tolerance of imeglimin was evaluated in a primary skin irritation study and a primary eye irritation study in rabbits. The results showed that imeglimin has no potential to induce skin or eye irritation (Table 12).

Table 12. Local tolerance studies

Test system	Test method	Main findings	CTD
Female rabbits (New Zealand White)	Imeglimin 0.5 g mixed with water for injection was spread on an adhesive patch and attached to the normal dorsal skin for 4 hours, and skin reactions were observed at 1, 24, 48, and 72 hours after the removal of the patch.	No deaths or changes in clinical observations or body weight that were attributable to imeglimin were found. No skin findings were observed.	4.2.3.6.01
Female rabbits (New Zealand White)	Imeglimin 0.1 g was applied to the conjunctival sac of the left eye, and eye reactions were observed at 1, 24, 48, and 72 hours after application.	No deaths or changes in clinical observations or body weight that were attributable to imeglimin were found. Mild conjunctival redness and chemosis were observed until Day 3 in all of the animals. One animal showed mild eye discharge and a swollen nictitating membrane, which resolved on Day 4.	4.2.3.6.02

5.7 Other toxicity studies

5.7.1 Antigenicity

The antigenicity of imeglimin was evaluated in a local lymph node assay (LLNA) in mice (Table 13). The results showed that imeglimin is not a skin sensitizer.

Table 13. Antigenicity study

Test system	Test method	Main findings	CTD
Female mice (CBA/CaOlaHsd)	Imeglimin[a)] at concentrations of 7.5, 15.0, and 27.3% (25 µL) was repeatedly applied to the dorsal skin of both pinnae for 3 days. At 5 days after the first application, ^{3}H-methylthymidine was intravenously administered and radioactivity in the auricular lymph nodes was measured.	No deaths or changes in pinnae, clinical observations, body weight, or skin that were related to imeglimin were observed. The stimulation index for radioactivity in the lymph nodes was from 1.13 to 1.82.	4.2.3.7.1.01

a) The vehicle was a 10% dimethyl sulfoxide solution.

5.7.2 Safety studies of impurities

A 4-week repeated dose toxicity study in rats was conducted on the enantiomer of imeglimin and Impurity A, an impurity found in the drug substance and in the drug product of imeglimin (Table 14).

The major target organs of toxicity were the adrenal glands (the enantiomer) and the stomach (Impurity A). In view of the NOAEL obtained in the study (500 mg/kg/day for the enantiomer, 50 mg/kg/day for Impurity A), no particular safety concerns were noted regarding the safety of the impurities in association with the clinical use of imeglimin.

The genotoxicity of the enantiomer was evaluated in 2 *in vitro* studies: a bacterial reverse mutation assay (CTD 4.2.3.7.6.02) and a mouse lymphoma TK assay (CTD 4.2.3.7.6.03), and 1 *in vivo* study: a rat bone marrow micronucleus assay (CTD 4.2.3.7.6.04). The enantiomer of imeglimin tested negative in all studies, suggesting that the enantiomer is non-genotoxic. The genotoxicity of Impurity A was evaluated in a bacterial reverse mutation assay (CTD 4.2.3.7.5.03), a mouse lymphoma TK assay (CTD 4.2.3.7.5.04), and a rat bone marrow micronucleus assay (CTD 4.2.3.7.5.05). In the mouse lymphoma TK assay, Impurity A appeared to be mutagenic at the doses at which cell proliferation was inhibited. However, Impurity A tested negative in the bacterial reverse mutation assay, and did not induce a significant increase in micronucleated polychromatic

erythrocytes in the rat bone marrow micronucleus assay. These results indicated that Impurity A is non-genotoxic.

Table 14. Repeated dose toxicity studies of impurities

Test system	Route of administration	Treatment duration	Dose (mg/kg/day)	Main findings	NOAEL (mg/kg/day)	CTD
Male and female rats (Wistar)	Oral	4 weeks (once daily)	Enantiomer 0, 150, 500, 1500	150: Increased blood potassium, total protein, albumin, AST, and ALP (males), decreased blood inorganic phosphorus (females), and increased blood sodium and lactate ≥150: Salivation, removing bedding material, breath sounds (males), increased body weight gain (females), increased blood triglyceride (females), increased blood ALT, and activation of thyroid follicles 500: Increased blood inorganic phosphorus (males), decreased blood chloride and creatinine (males), and increased blood calcium (females) ≥500: Breath sounds (females) and soft feces/unformed feces (females) 1500: Soft feces/unformed feces (males), decreased body weight and decreased body weight gain (males), decreased food consumption (males), increased blood potassium and ALP (males), decreased blood cholesterol (females), increased blood albumin-to-globulin ratio, AST, and lactate, increased liver weight (females), adrenal fasciculata degeneration with single-cell necrosis (males), and adrenal fasciculata hyperplasia (females)	500	4.2.3.7.6.01
Male and female rats (Wistar)	Oral	4 weeks (once daily)	Impurity A 0, 50, 150, 450 [a)]	Deaths: 450 (2 of 13 males, 2 of 13 females) 50: Increased white blood cell and lymphocyte counts (males), and increased blood urea nitrogen (males) 50 and 150: Decreased eosinophil and monocyte counts ≥50: Decreased body weight gain (females), increased blood cholesterol, lactate, and albumin-to-globulin ratio (males), increased blood inorganic phosphorus (females), and increased deposition of golden-brown pigment in the spleen (males) 150: Decreased neutrophil count (males), increased blood albumin (males), decreased blood creatinine and total bilirubin (females), and increased blood ALT ≥150: Salivation, removing bedding material (males), decreased body weight gain (males), decreased food consumption, and erosion/ulceration, transmural inflammation, and submucosal edema/cell infiltration and serositis in the stomach 450: Soft feces/unformed feces (males), removing bedding material, dyspnea, eye discharge, and nasal discharge (females), decreased motor activity, distended abdomen, low body temperature, skin discoloration, incomplete eyelid opening, prone position, recess in the flank, decreased body weight (males), increased reticulocyte, neutrophil, and monocyte counts (males), decreased white blood cell and lymphocyte counts (males), decreased red blood cell count and decreased hematocrit level, decreased blood calcium and urea nitrogen (males), increased blood ALP (males), decreased blood total bilirubin, decreased testis weight, soft and small testis, degeneration of the seminiferous tubules/cellular debris, and decreased sperm count in the ductus epididymis, decreased secretion in the submandibular gland (males), decreased cell count in the femoral and sternal bone marrow (males), absence of estrous cycle and mucus secretion of the vaginal epithelium (females), and extramedullary haemopoiesis of the spleen (males)	50	4.2.3.7.5.02

a) Two male and 2 female rats in the 450 mg/kg group were dead or euthanized moribund. Taking into account the deteriorated conditions of these rats, treatment from Day 15 onward was discontinued and the surviving animals in the group were bred until the scheduled necropsy day.

5.R Outline of the review conducted by PMDA

5.R.1 Vascular proliferative lesions in mesenteric lymph nodes observed in the carcinogenicity study

In the carcinogenicity study in rats, the incidence of hemangioma in mesenteric lymph nodes was higher in the imeglimin groups than in the vehicle control group. PMDA asked the applicant to explain the relationship between this finding and imeglimin treatment.

The applicant's explanation:

The hemangioma in mesenteric lymph nodes observed in the carcinogenicity study of imeglimin in rats were

diagnosed according to the latest version of the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND), which were different from the background data at the testing laboratory of the study. The incidence of hemangioma in mesenteric lymph nodes in the rat carcinogenicity study of imeglimin was thus compared with a report on historical control data on hemangioma in wild-type Wistar rats from the US National Toxicology Program (NTP),[15] etc. The incidence of spontaneous hemangioma in the rat carcinogenicity study of imeglimin tended to be high as compared with the historical incidence of hemangioma in wild-type Wistar rats, although whose specific diagnostic criteria were unknown. In the rat carcinogenicity study of imeglimin, the incidence of hemangioma in mesenteric lymph nodes did not statistically differ between any imeglimin-treated groups or the vehicle control group.[16] These indicated no relationship between imeglimin treatment and the hemangioma in mesenteric lymph nodes observed in the rat carcinogenicity study.

PMDA also asked the applicant to explain the mechanism of how the vascular proliferative lesions (angiomatous hyperplasia and hemangioma) develop in mesenteric lymph nodes as observed in the rat carcinogenicity study of imeglimin, as well as its relevance to humans and the relationship between the vascular proliferative lesions and hemangiosarcoma:

The applicant's explanation:
The following findings are indicative of the possibility that macrophage hyperplasia in the paracortex and histiocytosis in the sinus of mesenteric lymph nodes caused the proliferative changes in rat vascular endothelial cells.

- Macrophage hyperplasia in the paracortex and histiocytosis in the sinus of lymph nodes are known as changes in response to the phagocytosis of an overdosed test substance by macrophages in lymphatic vessels (*Toxicol Pathol.* 2006;34:425-54). In the repeated dose toxicity study of imeglimin in rats, such changes were observed in mesenteric lymph nodes. This suggests the possibility that similar changes could also have occurred since the early phase of treatment in the rat carcinogenicity study of imeglimin, and activated macrophages could have been persistently present in mesenteric lymph nodes.
- In rodents, macrophage activation stimulates the proliferation of vascular endothelial cells through the release of angiogenic growth factors and cytokines (*Toxicol Sci.* 2009;111:4-18)
- Angiomatous hyperplasia of mesenteric lymph nodes, an age-related lesion in rodents, is attributable mainly to the blockage of distal lymphatic vessels (*Toxicol Pathol.* 2019;47:665-783). In the rat carcinogenicity study of imeglimin, macrophage hyperplasia in the paracortex and histiocytosis in the sinus of mesenteric lymph nodes could have blocked the lymph flow since the early phase of treatment, thereby promoting the occurrence of the age-related change in rats.

The following facts indicate the possibility that the small intestine wall of rats could have been more heavily exposed to imeglimin than that of other animal species used in the toxicity studies of imeglimin, resulting in a local overexposure.

[15] https://ntp.niehs.nih.gov/data/controls/
[16] Water

- The daily doses of imeglimin were calculated based on the mean body weight at the end of treatment for the lowest dose at which macrophage hyperplasia accompanied by an increased incidence of angiomatous hyperplasia in mesenteric lymph nodes was observed in the rat carcinogenicity study (250 mg/kg/day), and the highest doses in the Tg-rasH2 mouse carcinogenicity study and the dog 52-week repeated dose toxicity study at which such findings were not observed (1500 mg/kg/day and 300 mg/kg/day, respectively). Subsequently, in light of species differences in the surface area of the small intestinal wall (*J Pharm Sci.* 2015;104:2747-76, *Lab Anim.* 2010;44:176-83, etc.), which is the absorption site of orally administered imeglimin, the daily doses per unit area of the small intestinal wall were calculated. The daily doses of imeglimin at which macrophage hyperplasia accompanied by angiomatous hyperplasia was observed in rats were approximately 5.8- and 5.9-fold the daily doses at which such findings were not observed in mice and dogs, respectively (Table 15).

Table 15. Imeglimin exposure per unit area of the small intestinal wall in the rat, mouse, and dog toxicity studies, and humans receiving the clinical dose

	Rats	Mice	Dogs	Humans (clinical dose)
Body weight-based daily dose (mg/kg/day)	250	1500	300	
Mean body weight	623 g (Week 104)	26.2 g (Week 26)	10.5 kg (Week 52)	
Daily dose (mg/day)	155.8	39.3	3150	2000
Unit area of the small intestinal wall (m^2)	1	1.46	120	200
Daily dose per unit area of the small intestinal wall (mg/m^2)	155.8	26.9	26.3	10.0

- Macrophage hyperplasia was not observed in either the dog or mouse toxicity study of imeglimin. In the Tg-rasH2 mouse carcinogenicity study, neither macrophage hyperplasia nor angiomatous hyperplasia was observed in mesenteric lymph nodes.

Similarly, the clinical dose and the lowest dose in the rat carcinogenicity study, at which macrophage hyperplasia was observed in mesenteric lymph nodes with increased incidence of angiomatous hyperplasia, were converted to daily doses per unit area of the small intestinal wall for comparisons (Table 15). The results indicated that the clinical dose of imeglimin is unlikely to lead to overdose in humans as that observed in the rat carcinogenicity study. Further, imeglimin is non-genotoxic. No similar findings were reported in the repeated dose toxicity studies in other animal species or the carcinogenicity study in Tg-rasH2 mice. Hemangioma rarely occurs in human lymph nodes, and no cases of hemangioma in human mesenteric lymph nodes have been reported. Given these and the characteristics of hemangiomas in human lymph nodes differing from those of rodents' (*Toxicol Sci.* 2009;111:4-18), imeglimin is unlikely to cause vascular proliferative lesions in humans.

The relationship between the vascular proliferative lesions observed in the imeglimin rat carcinogenicity study and hemangiosarcoma was analyzed by summarizing the incidences of hemangiosarcoma in organs/tissues over the whole body in the Tg-rasH2 mouse carcinogenicity study. The results indicated no increases in the incidences of hemangiosarcoma related to imeglimin treatment. Similarly, the incidences of hemangiosarcoma

in organs/tissues over the whole body in the rat carcinogenicity study were analyzed, and the results showed no increases in the incidences of hemangiosarcoma related to imeglimin treatment, with no hemangiosarcoma in mesenteric lymph nodes reported in the study. These study results suggested that there is no relationship between the vascular proliferative lesions and hemangiosarcoma.

PMDA's view:

In terms of the changes observed in rat mesenteric lymph nodes in the imeglimin carcinogenicity study, the development of angiomatous hyperplasia is clearly related to imeglimin treatment because of its incidence increased in a dose-dependent manner. There are diverse conclusions on hemangioma; a report indicates that angiomatous hyperplasia be a possible precursor (*J Toxicol Pathol.* 2016;29:S1-S47) to neoplasia such as hemangioma and hemangiosarcoma, while the other points out that it is unlikely (*Toxicol Pathol.* 2019;47:665-783). Thus, none of the available data provide clear evidence for a relationship between imeglimin treatment and the increased incidence of hemangioma. Even so, the possibility cannot be ruled out that imeglimin treatment might have induced hemangioma, in light of the development of angiomatous hyperplasia observed after imeglimin treatment. Meanwhile, changes in the mesenteric lymph nodes which occurred in response to overexposure, including paracortical macrophage hyperplasia and sinus histiocytosis, were observed in the rat repeated dose toxicity study, and these changes are known to induce vascular proliferative lesions in mesenteric lymph nodes through the release of angiogenic growth factors and cytokines and lymph flow changes. These suggest that the vascular proliferative lesions in mesenteric lymph nodes observed in the rat carcinogenicity study can be assumed to have resulted from paracortical macrophage hyperplasia and sinus histiocytosis in the mesenteric lymph nodes, which were caused by overexposure to imeglimin. Further, in view of the daily dose per unit area of the small intestinal wall in the rat carcinogenicity study and in humans, the local overexposure to imeglimin is unlikely to occur in humans receiving the clinical dose, and the vascular proliferative lesions were not observed in the repeated dose toxicity studies in animal species other than rats or the Tg-rasH2 mouse carcinogenicity study, or in tissues other than mesenteric lymph nodes in the rat carcinogenicity study. Taking into account of these observations, the vascular proliferative lesions in the mesenteric lymph nodes observed in the rat carcinogenicity study are less relevant to humans.

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

During the development process, imeglimin was made available in liquid, capsule, and tablets with different formulations (Tablets A, B, and C, and the proposed formulation). Table 16 presents the drug products used in main clinical studies. The study IDs (except for DD401101, DD401102, RVT-1501-1002, EML017008-002, and EML017008-005) with the prefix of "PXL008-"are indicated without it, e.g., Study PXL008-001 is indicated as Study 001.

Table 16. Drug products used in key clinical studies

Drug product	Development phase (Study No.)	
	Japanese studies	Foreign studies
Tablets A	-	Phase I studies (003, 011) Phase II studies (004, 006, 009)
Tablets B	Phase II study (014)	Phase I studies (016, 022)
Tablets C	Phase I studies (DD401101, DD401102) Phase III studies (018, 019, 020)	Phase I studies (022, 023, 024, RVT-1501-1002)

-, Not applicable

Concentrations of imeglimin and its enantiomer in human biomaterials were determined using the LC-MS/MS method; the lower limit of quantitation was 10 ng/mL for plasma imeglimin concentrations, [redacted] ng/mL for enantiomer concentrations, and 10 μg/mL for urinary imeglimin concentrations. In the clinical studies other than the foreign mass balance study (Study EML017008-002), the combined plasma concentrations of imeglimin and its enantiomer were measured as a plasma imeglimin concentration. Radioactivity in biomaterials and samples from the human mass balance studies was measured using the liquid scintillation counting method.

The applicant submitted biopharmaceutic evaluation data in the form of results from a Japanese food effect study (Study DD401101) and a foreign bioequivalence study (Study 022[17]). The proposed formulation was demonstrated to be equivalent to Tablet C, based on the results of a dissolution study conducted in accordance with Attachment 3 of "Partial Revision of Guidelines for Bioequivalence Studies of Generic Products, etc." (PSEHB/PED Notification No. 0319-1 issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare dated March 19, 2020). Tablet C was demonstrated to be equivalent to Tablet B via bioequivalence testing (Study 022). The results of the main study are summarized below.

6.1.1 Food effect study (CTD 5.3.1.1.01, Study DD401101, [redacted] to [redacted] 20[redacted])

A randomized, open-label, 2-treatment, 2-period crossover study was conducted in Japanese healthy adult men to evaluate food effects on the pharmacokinetics of imeglimin administered as a single oral dose of Tablet C (target sample size, 12).

In Periods 1 and 2, a single oral dose of Tablet C imeglimin 1000 mg was administered under fasting conditions or 30 minutes after the start of breakfast, with a rest period of ≥5 days between the periods. All 12 treated subjects were included in both the pharmacokinetic and safety analysis sets.

The geometric mean ratios (90% confidence intervals [CIs]) of C_{max} and AUC_{last} following a single oral dose of imeglimin under fed conditions to those under fasting conditions were 0.85 [0.75, 0.95] and 0.93 [0.84, 1.04], respectively.

[17] A 2-treatment, 2-period crossover study in non-Japanese healthy adults to evaluate the safety and pharmacokinetics of imeglimin administered as a single oral dose of Tablets B 1000 mg or Tablets C 1000 mg

The safety analysis revealed no adverse events or clinically relevant changes in the clinical laboratory tests, vital signs, or 12-lead electrocardiography.

6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data in the form of results data from 6 Japanese clinical studies (Studies DD401101, DD401102, 014, 018, 019, and 020) and 6 foreign clinical studies (Studies EML017008-002, 001, 011, 016, 023, and 024), as well as the results of a population pharmacokinetic (PPK) analysis based on data from 9 Japanese or foreign clinical studies (Studies DD401102, RVT-1501-1002, EML017008-003,[18)] EML017008-004,[19)] and EML017008-005, 008,[20)] 011, 014, and 018). The applicant also submitted the results of 7 foreign clinical studies (Studies EML017008-001, EML017008-003, EML017008-004, EML017008-005, and RVT-1501-1002, 003, and 008) as reference data. In addition, result data from studies using human biomaterials were submitted. The results of main studies are described below.

6.2.1 Studies using human biomaterials (CTD 4.2.2.3.03 to 04, 4.2.2.4.01 to 02, and 5.3.2.2.01 to 5.3.2.2.11)

The mean plasma protein binding (equilibrium dialysis method) of ^{14}C-imeglimin (0.2 to 20 μg/mL) in humans was 1.20% to 6.4%. The mean blood cell-to-plasma concentration ratio was 0.42 to 0.53.

^{14}C-Imeglimin (1, 10, or 100 μmol/L) was incubated with human liver, lung, kidney, and small intestinal microsomes or S9, to investigate the metabolism of imeglimin. After a 60-minute incubation, no metabolites were detected. ^{14}C-Imeglimin (10 and 100 μmol/L) was incubated with human hepatocytes. The mean proportion of unchanged imeglimin after a 24-hour incubation was 90.0% to 94.3%, with 6 metabolites detected.

The membrane permeability of imeglimin (3000 μmol/L) was evaluated in human colon cancer-derived Caco-2 cells. The apparent permeability coefficient value in the apical to basolateral direction (A → B) of imeglimin was 1.62×10^{-6} cm/second, while that in the basolateral to apical direction (B → A) was 1.24×10^{-6} cm/second, and the apparent permeability coefficient ratio (B → A/A → B) was 0.76. The apparent permeability coefficient ratios (B → A/A → B) of digoxin (a substrate for P-glycoprotein [P-gp], 5 μmol/L) and estrone-3-sulfate (a substrate for breast cancer resistance protein [BCRP], 0.2 μmol/L), as positive controls, were 17.6 and 5.3, respectively. In the presence of PSC833 (10 μmol/L), a P-gp inhibitor, the apparent permeability coefficient ratios (B → A/A → B) of imeglimin and digoxin were 0.95 and 0.82, respectively. In the presence of novobiocin (30 μmol/L), a BCRR inhibitor, the apparent permeability coefficient ratios (B → A/A → B) of imeglimin and estrone-3-sulfate were 0.63 and 0.57, respectively.

[18)] A study in non-Japanese patients with type 2 diabetes mellitus to evaluate the safety, efficacy, and pharmacokinetics of imeglimin (capsules) administered orally at a dose of 1000 mg twice daily or 2000 mg once daily, or metformin 850 mg twice daily for 4 weeks
[19)] A study in non-Japanese patients with type 2 diabetes mellitus to evaluate the safety, efficacy, and pharmacokinetics of imeglimin 500 or 1500 mg, metformin 850 mg, or placebo administered orally twice daily for 8 weeks
[20)] A study in non-Japanese patients with type 2 diabetes mellitus to evaluate the safety, efficacy, and pharmacokinetics of imeglimin 500, 1000, 1500, or 2000 mg, or placebo administered orally twice daily for 24 weeks

In HEK293 cells expressing organic cation transporter (OCT) 1 or OCT2, the uptake of imeglimin was investigated at concentrations of 10 to 3000 μmol/L and 1 to 1500 μmol/L, respectively. The results showed that imeglimin was taken up into the cells via OCT1 and OCT2, with K_m values of 1130 and 41.1 μmol/L, respectively. The uptake of imeglimin (100 μL/L) was investigated in cells expressing MATE1, MATE2-K, OAT1, or OAT3. The uptake ratios (expressing cells/non-expressing cells) of imeglimin were 3.45 to 6.21, 7.78 to 10.50, 0.62 to 1.24, and 0.85 to 1.06, respectively. In the presence of pyrimethamine (1 μmol/L), an MATE1 and MATE2-K inhibitor, the uptake of imeglimin (100 μmol/L) was evaluated in cells expressing MATE1 or MATE2-K. The ratios of the uptake of imeglimin in MATE1-expressing cells to that in non-MATE1-expressing cells were 5.09 in the absence of pyrimethamine and 1.19 in the presence of pyrimethamine, while the ratios of the uptake of imeglimin in MATE2-K-expressing cells to that in non-MATE2-K-expressing cells were 10.18 in the absence of pyrimethamine and 1.89 in the presence of pyrimethamine.

The potential of imeglimin[21)] to inhibit the enzymatic activity of cytochrome P450 (CYP) isoforms (CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4/5) was investigated using human liver microsomes. The results revealed no direct or dose-dependent inhibitory effects of imeglimin on these CYP isoforms.

The potential of imeglimin (20, 60, or 120 μmol/L) to induce the enzymatic activity of CYP isoforms was investigated using human hepatocytes. Imeglimin neither induced the enzymatic activity of CYP1A2, CYP2B6, CYP2C9, CYP2C19, or CYP3A4/5 nor increased the mRNA expression of the CYP isoforms.

The potential of imeglimin to inhibit P-gp was evaluated in Caco-2 cells and P-gp-expressing cells (0.1 to 1000 μmol/L for Caco-2 cells, 1000 to 3000 μmol/L for P-gp-expressing cells). The IC_{50} values were 1000 and >3000 μmol/L, respectively. The potential of imeglimin (300 to 3000 μmol/L) to inhibit BCRP was evaluated in BCRP-expressing membrane vesicles. The IC_{50} value was >3000 μmol/L.

The potential for imeglimin to inhibit OCT1 was evaluated at concentrations of 10 to 1000 μmol/L in OCT1-expressing cells. The K_i value was 154 μmol/L. The potential of imeglimin[22)] to inhibit OCT2, MATE1, MATE2-K, OAT1, OAT3, OATP1B1, and OATP1B3 was evaluated in cells expressing each transporter. The IC_{50} values were 146 μmol/L for OCT2, 19.24 μmol/L for MATE1, and >1000 μmol/L for other transporters.

6.2.2 Studies in healthy adults

6.2.2.1 Phase I study in healthy adults (CTD 5.3.3.1.02: Study 011, January to October 2015)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese and non-Japanese healthy adults to evaluate the safety and pharmacokinetics of single- or multiple-dose oral imeglimin (target sample size: Part A, 24 [Japanese]; Part B, ≤64 [Japanese for Part B1, Japanese and non-Japanese for Part B2]).

[21)] The tested concentrations of imeglimin were 0.1 to 1000 μmol/L for CYP1A2, CYP2C8, CYP2C9, CYP2C19, and CYP2D6, 0.1 to 100 μmol/L for CYP2A6 and CYP2E1, 200 to 1000 μmol/L for CYP2B6, and 0.1 to 6000 μmol/L for CYP3A4/5.
[22)] The tested concentrations of imeglimin were 5 to 1000 μmol/L for OCT2, 1.37 to 1000 μmol/L for MATE1, and 100 to 1000 μmol/L for MATE2-K, OAT1, OAT3, OATP1B1, and OATP1B3.

In Part A, subjects received a single oral dose of imeglimin 500, 1000, or 2000 mg, or placebo on Days 1 and 10, and multiple oral doses of imeglimin 500, 1000, or 2000 mg, or placebo twice daily on Days 4 to 9, under fasting conditions. In Part B1, subjects followed the same regimens as in Part A except that the dose of imeglimin was fixed at 1500 mg and the first dose on Day 4 was administered after a high-fat meal. In Part B2, subjects received a single oral dose of imeglimin 4000, 6000, or 8000 mg, or placebo under fasting conditions.

All 64 treated subjects (24 in Part A and 40 in Part B) were included in the safety analysis set, and 48 subjects who received imeglimin in Part A or Part B were included in the pharmacokinetic analysis set.

Table 17 shows the pharmacokinetic parameters of imeglimin administered as a single oral dose or multiple oral doses under fasting conditions in Japanese healthy adults. Table 18 shows the pharmacokinetic parameters of single-dose oral imeglimin administered under fasting conditions in Japanese and non-Japanese healthy adults. The geometric least-squares mean ratios of the C_{max} and $AUC_{0\text{-}12h}$ (fed/fasting) [90% CI] of imeglimin administered at 1500 mg were 0.95 [0.88, 1.04] and 1.05 [0.92, 1.20], respectively.

Table 17. Pharmacokinetic parameters of imeglimin administered as a single oral dose or multiple oral doses (Part A)

Dose (mg)	Timepoint	N	C_{max} (ng/mL)	AUC (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
500	Day 1	6	1006.6 (23.1)	5867.2 (26.4)	3.0 [3.0, 4.0]	4.5 (101.4)	75.4 (31.6)	484.5 (71.3)
	Day 10	6	994.2 (28.5)	6288.4 (34.3)	2.5 [1.5, 4.0]	10.1 (80.4)	79.5 (34.3)	848.2 (67.2)
1000	Day 1	6	1393.2 (40.3)	8514.8 (35.7)	2.5 [1.5, 3.0]	12.0 (113.0)	89.4 (25.8)	1552.0 (138.1)
	Day 10	6	1804.4 (18.2)	12624.5 (12.5)	2.5 [2.0, 4.0]	13.6 (42.6)	79.2 (12.5)	1042.6 (38.8)
1500	Day 1	6	2217.5 (25.0)	13373.9 (27.7)	3.0 [1.5, 4.0]	11.5 (163.3)	87.4 (24.9)	1455.6 (168.3)
	Day 10	6	2336.0 (16.7)	16007.2 (15.5)	2.5 [2.0, 4.0]	10.7 (83.1)	93.7 (15.5)	986.8 (55.5)
2000	Day 1	6	1787.9 (26.3)	10986.5 (24.3)	2.5 [1.5, 3.0]	11.2 (82.3)	140.4 (23.1)	2267.2 (95.8)
	Day 10	6	2266.7 (32.3)	16671.8 (24.4)	2.5 [1.5, 4.0]	12.1 (38.6)	120.0 (24.4)	1439.0 (38.0)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; AUC, area under the drug plasma concentration-time curve from 0 to 12 hours postdose (Day 1), or area under the drug plasma concentration-time curve over a dosing interval (Day 10); t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

Table 18. Pharmacokinetic parameters of single-dose oral imeglimin (Part B2)

Dose (mg)	Race	N	C_{max} (ng/mL)	$AUC_{0\text{-}12\ h}$ (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (L/h)	V_z/F (L)
4000	Japanese	6	4193.6 (20.2)	22611.6 (15.0)	1.5 [1.0, 4.0]	6.4 (59.9)	137.4 (10.8)	1271.2 (67.7)
6000		6	4040.0 (29.2)	24037.6 (20.0)	2.3 [1.0, 4.0]	11.5 (61.5)	166.8 (28.7)	2759.5 (49.9)
6000	Non-Japanese	6	3450.8 (21.3)	21073.2 (25.0)	1.5 [1.0, 3.0]	11.4 (77.4)	200.0 (18.9)	3274.2 (73.3)
8000		6	4086.2 (35.4)	25746.1 (21.8)	2.0 [1.5, 4.0]	9.0 (57.4)	214.3 (20.1)	2791.7 (51.3)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; $AUC_{0\text{-}12h}$, area under the drug plasma concentration-time curve from 0 to 12 hours postdose
t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

The incidences of adverse events and adverse drug reactions, respectively, throughout Part A and Part B1 were 5 of 8 subjects and 2 of 8 subjects in the placebo group, 2 of 6 subjects and 1 of 6 subjects in the 500 mg group, 2 of 6 subjects and 1 of 6 subjects in the 1000 mg group, 4 of 6 subjects and 2 of 6 subjects in the 1500 mg group, and 2 of 6 subjects and 2 of 6 subjects in the 2000 mg group. The incidences of adverse events and adverse drug reactions, respectively, reported in Japanese subjects in Part B2 were 2 of 4 subjects and 2 of 4 subjects in the placebo group, 0 of 6 subjects and 0 of 6 subjects in the 4000 mg group, and 3 of 6 subjects and 2 of 6 subjects in the 6000 mg group; those in non-Japanese subjects in Part B2 were 1 of 4 subjects and 1 of

4 subjects in the placebo group, 3 of 6 subjects and 3 of 6 subjects in the 6000 mg group, and 6 of 6 subjects and 6 of 6 subjects in the 8000 mg group. No deaths or serious adverse events were reported. No adverse events led to drug discontinuation. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.2.2 Mass balance study (CTD 5.3.3.1.01: Study EML017008-002, [redacted] 20[redacted] to [redacted] 20[redacted])

An open-label study was conducted in non-Japanese healthy adult men to evaluate the pharmacokinetics of single-dose oral ^{14}C-imeglimin (target sample size, 6).

Subjects received a single oral dose of ^{14}C-imeglimin 1000 mg. All 6 treated subjects were included in both the safety and pharmacokinetic analysis sets.

The geometric mean plasma C_{max} values of imeglimin and its enantiomer (CV, %) were 1432 (14.2) and [redacted] (12.9) ng/mL, while the geometric mean plasma AUC_{last} values of imeglimin and its enantiomer were 12,223 (16.5) and [redacted] (16.3) ng·h/mL. The geometric mean $t_{1/2}$ values (CV, %) were 13.0 (24.6) and 12.9 (19.1) hours, respectively, while the median t_{max} value [range] was 3.5 [1.5, 4.0] hours for both compounds. In both C_{max} and AUC_{last} values of the sum of imeglimin and enantiomer concentrations, the enantiomer accounted for [redacted]%, suggesting that imeglimin did not isomerize.[23)] The sum of plasma AUC_{last} values of imeglimin and its enantiomer accounted for 84.8% of the plasma AUC_{last} value of radioactivity.

The geometric mean cumulative urinary excretion rate (CV, %) (percent excretion of the administered radioactivity) for 6 days postdose was 43.2 (19.1) %. The cumulative urinary excretion rate of unchanged imeglimin for 6 days postdose was 42.0 (19.3) %.

The geometric mean cumulative fecal excretion rate (CV, %) (percent excretion of the administered radioactivity) for 6 days postdose was 54.8 (15.7) %, with no metabolites detected.

The radioactivity in expired air was below the lower limit of quantitation.

The safety analysis revealed adverse events observed in 4 of 6 subjects and adverse drug reactions in 3 of 6 subjects. No deaths or serious adverse events were reported. No adverse events led to drug discontinuation. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.3 Studies in patients

6.2.3.1 Japanese late phase II monotherapy study (CTD 5.3.5.1.01: Study 014, December 2015 to January 2017)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus to evaluate the dose-response relationship, efficacy, safety, and pharmacokinetics of

[23)] The content of the enantiomer in the drug substance was [redacted]%.

imeglimin administered alone (target sample size, 304 [76 each for the placebo, imeglimin 500, 1000, and 1500 mg groups]) [for the detailed study design, and efficacy and safety results from the study, see Section "7.1 Japanese late phase II monotherapy study"].

Table 19 shows the trough plasma concentrations of oral imeglimin 500, 1000, or 1500 mg administered twice daily.

Table 19. Trough plasma concentrations of oral imeglimin administered twice daily[a)]

Treatment	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Imeglimin 500 mg	307.87 (66.2)	306.98 (61.0)	292.08 (94.8)	341.60 (57.3)	321.38 (72.7)	326.22 (83.4)	339.78 (65.4)
	75	75	72	72	71	70	70
Imeglimin 1000 mg	605.44 (58.7)	648.20 (60.4)	650.35 (56.8)	648.60 (59.6)	634.99 (59.4)	633.12 (52.4)	617.04 (63.9)
	73	72	69	67	67	66	66
Imeglimin 1500 mg	993.20 (65.8)	988.07 (62.6)	928.93 (86.1)	966.13 (71.3)	965.47 (90.5)	985.62 (72.0)	1004.89 (67.1)
	71	70	68	68	67	67	67

Upper row, geometric mean (geometric CV, %), ng/mL; lower row, n
a) Imeglimin concentrations were determined as free base.

6.2.3.2 Japanese phase III monotherapy study (CTD 5.3.5.1.02: Study 018, December 2017 to February 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus to evaluate the efficacy and safety of imeglimin alone (target sample size, 212 [106 each for the placebo and imeglimin 1000 mg groups]) [for the detailed study design, and efficacy and safety results from the study, see Section "7.2 Japanese phase III monotherapy study"].

Table 20 shows the trough plasma concentrations of oral imeglimin 1000 mg administered twice daily.

Table 20. Trough plasma concentrations of oral imeglimin administered twice daily[a)]

Treatment	Week 12	Week 16	Week 20	Week 24
Imeglimin 1000 mg	650.60 (64.321)	533.70 (63.034)	526.76 (54.728)	471.91 (63.384)
	104	103	102	102

Upper row, geometric mean (CV, %), ng/mL; lower row, n
a) Imeglimin concentrations were determined as free base.

6.2.4 Studies on intrinsic factors

6.2.4.1 Pharmacokinetic studies in subjects with renal impairment

6.2.4.1.1 Pharmacokinetic study in subjects with renal impairment (CTD 5.3.3.3.01: Study DD401102, June to October 2018)

An open-label, parallel-group study was conducted in Japanese adults to evaluate the pharmacokinetics and safety of imeglimin by the severity of renal impairment (target sample size, 24). Subjects were classified based on the severity of impairment (estimated glomerular filtration rate [eGFR]:[24)] normal, ≥90 mL/min/1.73 m^2; mild, ≥60 to <90 mL/min/1.73 m^2; moderate, ≥30 to <60 mL/min/1.73 m^2; severe, ≥15 to <30 mL/min/1.73 m^2). Patients requiring dialysis were excluded from the study.

[24)] The severity of renal impairment was categorized according to the following equation based on the serum creatine level at screening: eGFR (mL/min/1.73 m^2) = 194 × the serum creatinine level$^{-1.094}$ × age$^{-0.287}$ × (0.739 [for female subjects])

Subjects with normal renal function, or mild or moderate renal impairment received a single oral dose of imeglimin 1000 mg, while subjects with severe renal impairment received a single oral dose of imeglimin 500 mg.

All 24 treated subjects (6 each with normal renal function, mild renal impairment, moderate renal impairment, and severe renal impairment) were included in both the safety analysis set and the pharmacokinetic analysis set.

Table 21 shows the pharmacokinetic parameters of imeglimin in subjects with normal renal function and in those with renal impairment. The geometric mean ratios [90% CI] of the plasma C_{max} of imeglimin in subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function were 1.42 [1.05, 1.91], 1.52 [1.13, 2.05], and 1.50[1.11, 2.02], respectively. The geometric mean ratios [90% CI] of the plasma AUC_{last} of imeglimin in subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function were 1.49 [1.03, 2.17], 1.81 [1.25, 2.63], and 2.49 [1.71, 3.61], respectively.

Table 21. Pharmacokinetic parameters of imeglimin in subjects with normal renal function and in those with renal impairment

Dose	1000 mg			500 mg
Parameter	Normal renal function (N = 6)	Mild renal impairment (N = 6)	Moderate renal impairment (N = 6)	Severe renal impairment (N = 6)
C_{max} (ng/mL)	1246 (26.2)	1770 (21.1)	1897 (24.8)	1866 (45.7)
AUC_{last} (ng·h/mL)	10020 (28.1)	14950 (43.5)	18160 (33.4)	24920 (48.2)
t_{max} (h)	3.00 [0.50, 3.00]	1.75 [1.00, 6.00]	3.00 [2.00, 6.00]	4.00 [3.00, 6.00]
$t_{1/2}$ (h)	12.65 (101.1)	9.449 (58.9)	18.85 (121.9)	11.68 (63.0)
CL/F (L/h)	95.87 (26.6)	64.65 (42.8)	51.58 (32.4)	19.56 (47.8)
V_z/F (L)	1750 (99.3)	881.3 (80.6)	1403 (114.9)	329.5 (97.1)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; AUC_{last}, area under the drug plasma concentration-time curve from 0 to the last quantifiable time
t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

The safety analysis revealed no adverse events. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.4.1.2 Pharmacokinetic study in patients with moderate or severe renal impairment (CTD 5.3.3.3.03: Study RVT-1501-1002, [redacted] 20[redacted] to [redacted] 20[redacted] [reference data])

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in non-Japanese patients with type 2 diabetes mellitus to evaluate the pharmacokinetics and safety of imeglimin by severity of renal impairment (sample size, 46). The severity of renal impairment was categorized based on eGFR, i.e., chronic kidney disease (CKD) 3b,[25] ≥30 to <45 mL/min/1.73 m^2; CKD 4, ≥15 to <30 mL/min/1.73 m^2. Patients requiring dialysis were excluded from the study.

Patients received imeglimin 500 or 1000 mg, or placebo twice daily for 4 weeks, or imeglimin 1500 mg or placebo once daily for 4 weeks.

[25] The severity of renal impairment was categorized according to the MDRD equation using the serum creatine level at screening: eGFR (mL/min/1.73 m^2) = 175 × the serum creatinine level$^{-1.154}$ × age$^{-0.203}$ × (0.742 [if the patient is female]) × (1.212 [if the patient is an African American])

All 49 treated patients were included in the safety analysis set. Of these, 38 patients receiving imeglimin were included in the pharmacokinetic analysis set.

Table 22 shows the pharmacokinetic parameters of imeglimin on Day 15 in patients with moderate or severe renal impairment.

Table 22. Pharmacokinetic parameters in patients with renal impairment[a)]

Dosage regimen	500 mg twice daily		1000 mg twice daily		1500 mg once daily	
Parameter	CKD 3b (N = 7)	CKD 4 (N = 5)	CKD 3b (N = 6)	CKD 4 (N = 6)	CKD 3b (N = 7)	CKD 4 (N = 5)
C_{max} (ng/mL)	1520.4 (40.7)	1682.1 (29.5)	2682.1 (35.9)	4219.7 (43.2)	2251.2 (22.8)	2654.9 (47.2)
AUC_{last} (ng·h/mL)	12820.0 (40.6)	14937.8 (26.3)	20858.3 (45.9)	35453.9 (46.4)	16011.0 (27.2)	24408.9 (53.8)
t_{max} (h)	3.97 [2.00, 6.00]	4.00 [3.00, 4.03]	2.50 [1.00, 3.00]	2.53 [2.00, 5.85]	3.00 [2.00, 4.00]	3.00 [2.98, 4.05]
CL/F (L/h)	35.98 (38.0)	33.29 (27.2)	46.21 (41.7)	25.03 (42.7)	70.20 (29.8)	40.45 (54.9)
V_z/F (L)	267.47 (15.9)	344.30 (26.4)	417.36 (28.5)	261.26 (79.4)	559.55 (26.7)	604.08 (57.8)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; AUC_{last}, area under the drug plasma concentration-time curve from 0 to the last quantifiable time
t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase
a) Imeglimin concentrations were determined as free base.

The safety analysis revealed adverse events and adverse drug reactions, respectively, observed in 6 of 11 patients and 3 of 11 patients in the placebo group, 3 of 13 patients and 0 of 13 patients in the imeglimin 500 mg group, 8 of 13 patients and 3 of 13 patients in the 1000 mg group, and 7 of 12 patients and 3 of 12 patients in the 1500 mg group. No deaths or serious adverse events were reported. One patient in the imeglimin 1000 mg group discontinued the study treatment due to an adverse event (nausea/vomiting) that was assessed as an adverse drug reaction. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.4.1.3 Foreign pharmacokinetic study in subjects with renal impairment (CTD 5.3.3.3.04: Study EML017008-005, [redacted] 20[redacted] to [redacted] 20[redacted] [reference data])

An open-label, parallel-group study was conducted in non-Japanese adults to evaluate the safety and pharmacokinetics of imeglimin by severity of renal impairment (target sample size, 48). The severity of renal impairment was categorized based on creatinine clearance (CLcr),[26)] i.e., normal, >80; mild, CLcr ≥50 to ≤80; moderate, ≥30 to <50; and severe, <30. Subjects requiring dialysis were excluded from the study.

In Part 1, subjects with normal renal function and those with mild or moderate renal impairment received oral imeglimin (capsules) 1000 mg once daily for 8 weeks. In Part 2, subjects with normal renal function and those with mild or moderate renal impairment received oral imeglimin (capsules) 500 mg twice daily for 7 days, followed by a single oral dose on Day 8. In Part 3, subjects with normal renal function or severe renal impairment received oral imeglimin (capsules) 500 mg twice daily for 7 days, followed by a single oral dose on Day 8.

[26)] Creatinine clearance calculated from the urinary creatinine excretion per 24-hour urine collection

All 51 treated subjects (24 with normal renal function and 27 with renal impairment) were included in the safety analysis set. Of these, except 1 subject with severe renal impairment shown to have an abnormal plasma imeglimin concentration on Day 8,[27] 50 subjects were included in the pharmacokinetic analysis set.

Tables 23 and 24 show the pharmacokinetic parameters of imeglimin in subjects with normal renal function and in those with severe renal impairment. The geometric mean ratios [90% CI] of the plasma C_{max} on Day 8 of imeglimin 1000 mg administered once daily to subjects with mild renal impairment and those with moderate renal impairment to that in subjects with normal renal function were 1.17 [0.97, 1.42] and 1.47 [1.23, 1.77] , respectively. Similarly, the geometric mean ratios [90% CI] of AUC_{τ} on Day 8 were 1.31 [1.04, 1.65] and 1.89 [1.52, 2.35], respectively. The geometric mean ratios [90% CI] of the plasma C_{max} on Day 8 of imeglimin 500 mg administered twice daily to subjects with mild, moderate, and severe renal impairment to that in subjects with normal renal function were 1.28 [1.03, 1.59], 1.95 [1.61, 2.35], and 2.86 [2.08, 3.94], respectively. Similarly, the geometric mean ratios [90% CI] of AUC_{τ} on Day 8 were 1.50 [1.16, 1.94], 2.32 [1.85, 2.92], and 3.56 [2.51, 5.06], respectively.

Table 23. Pharmacokinetic parameters of oral imeglimin 1000 mg administered once daily to subjects with normal renal function and those with renal impairment (Part 1)

	Normal renal function (N = 10)		Mild renal impairment (N = 5)		Moderate renal impairment (N = 6)	
Timepoint	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
C_{max} (ng/mL)	1711 (13.0)	1746 (15.9)	2038 (25.4)	2049 (26.3)	2094 (28.5)	2573 (21.2)
AUC_{τ} (ng·h/mL)	13202 (19.6)	15399 (21.2)	18220 (20.6)	20122 (15.7)	21222 (26.3)	29100 (30.4)
t_{max} (h)	3.75 [2.00, 5.00]	4.00 [3.00, 5.00]	3.00 [2.00, 5.00]	4.00 [3.00, 4.00]	4.00 [3.00, 5.03]	5.00 [4.00, 5.00]
$t_{1/2}$ (h)	4.7 (17.1)	16.4 (70.0)[a]	4.9 (16.9)	15.0 (74.9)	5.9 (19.7)	23.4 (25.9)
CL/F (mL/min)	1214 (20.0)	1082 (21.2)	871 (20.4)	828 (15.7)	725 (26.5)	573 (30.4)
V_z/F (L)	496 (23.2)	1573 (56.5)[a]	370 (26.1)	1073 (58.8)	372 (32.4)	1162 (38.5)

Geometric mean (geometric CV, %), or median [range] for t_{max}

C_{max}, maximum plasma concentration; AUCτ, area under the drug plasma concentration-time curve over a dosing interval, t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

a) n = 8

[27] The subject showed Day 8 t_{max} occurring before the start of the dosing for the day and C_{max} that was low by 92% to 96% as compared with other subjects with severe renal impairment. The data of the subject were treated as outliers and excluded from the pharmacokinetic analysis.

Table 24. Pharmacokinetic parameters of oral imeglimin 500 mg administered twice daily to subjects with normal renal function and in those with renal impairment (Parts 2 and 3)

	Part 2					
	Normal renal function (N = 8)		Mild renal impairment (N = 4)		Moderate renal impairment (N = 6)	
Timepoint	Day 1	Day 8	Day 1	Day 8	Day 1	Day 8
C_{max} (ng/mL)	958 (14.1)	1028 (11.3)	1039 (15.6)	1316 (5.06)	1402 (35.9)	2001 (36.0)
AUC_{τ} (ng·h/mL)	5917 (14.6)	7389 (16.8)	7139 (17.5)	11056 (8.10)	10619 (40.0)	17168 (44.4)
t_{max} (h)	3.25 [2.00, 5.00]	3.50 [3.00, 5.02]	4.00 [3.50, 5.00]	4.00 [4.00, 5.00]	4.00 [3.00, 5.00]	3.50 [2.00, 5.00]
$t_{1/2}$ (h)	3.0 (12.4)	13.2 (78.8)	3.8 (12.5)	26.1 (20.0)	5.4 (38.1)	21.9 (64.6)
CL/F (mL/min)	1273 (16.9)	1128 (16.8)	974 (20.3)	754 (8.10)	555 (61.9)	485 (44.4)
V_z/F (L)	329 (11.0)	1290 (63.0)	318 (15.3)	1704 (23.0)	261 (27.9)	922 (81.8)

	Part 3			
	Normal renal function (N = 6)		Severe renal impairment (N = 5)	
Timepoint	Day 1	Day 8	Day 1	Day 8
C_{max} (ng/mL)	875 (27.2)	998 (29.7)	1677 (21.6)	2857 (29.1)
AUC_{τ} (ng·h/mL)	5765 (30.6)	6974 (31.0)	14392 (25.5)	24833 (34.1)
t_{max} (h)	3.25 [2.00, 5.00]	3.75 [3.00, 5.00]	4.07 [4.00, 5.00]	3.50 [3.50, 5.00]
$t_{1/2}$ (h)	3.3 (12.0)	15.0 (53.2)	7.7 (16.6)	17.6 (61.8)
CL/F (mL/min)	1272 (33.0)	1195 (31.0)	341 (35.8)	336 (34.1)
V_z/F (L)	360 (26.0)	1548 (30.1)	228 (19.0)	511 (102)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; $AUC\tau$, area under the drug plasma concentration-time curve over a dosing interval, t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

The safety analysis revealed adverse events and adverse drug reactions observed in Part 1 in 9 of 10 subjects and 1 of 10 subjects, respectively, in those with normal renal function, 4 of 5 subjects and 2 of 5 subjects, respectively, in those with mild renal impairment, and 3 of 6 subjects and 3 of 6 subjects, respectively, in those with moderate renal impairment; in Parts 2 and 3, 7 of 14 subjects and 3 of 14 subjects, respectively, in those with normal renal function, 3 of 4 subjects and 0 of 4 subjects, respectively, in those with mild renal impairment, 3 of 6 subjects and 2 of 6 subjects, respectively, in those with moderate renal impairment, and 2 of 6 subjects and 0 of 6 subjects, respectively, in those with severe renal impairment. No deaths or serious adverse events were reported. No adverse events led to drug discontinuation. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.4.2 Pharmacokinetic study in subjects with hepatic impairment (CTD 5.3.3.3.02: Study 024, November 2018 to July 2019)

An open-label, parallel-group study was conducted in non-Japanese adults to evaluate the pharmacokinetics and safety of imeglimin in subjects with moderate hepatic impairment (Child-Pugh score of 7 to 9) (target sample size, ≤16).

Subjects received a single oral dose of imeglimin 1000 mg. All 14 treated subjects (7 with normal hepatic function and 7 with moderate hepatic impairment) were included in both the safety analysis set and the pharmacokinetic analysis set.

Table 25 shows the pharmacokinetic parameters of imeglimin in subjects with normal hepatic function and in those with moderate hepatic impairment. The geometric mean ratios [90% CI] of the plasma C_{max} and AUC_{last} of imeglimin in subjects with moderate hepatic impairment to those in subjects with normal hepatic function were 1.29 [1.05, 1.60] and 1.47 [1.19, 1.82], respectively.

Table 25. Pharmacokinetic parameters of imeglimin in subjects with normal hepatic function and in those with moderate hepatic impairment

Parameter	Normal hepatic function (N = 7)	Moderate hepatic impairment (N = 7)
C_{max} (ng/mL)	1300 (11.8)	1680 (35.2)
AUC_{last} (ng·h/mL)	10600 (24.8)	15500 (35.5)
t_{max} (h)	3.00 [0.50, 4.00]	2.00 [1.00, 4.00]
$t_{1/2}$ (h)	8.17 (42.5)	7.23 (35.5)
CL/F (L/h)	91.3 (24.1)	62.8 (34.5)
V_z/F (L)	1080 (44.2)	656 (62.9)

Geometric mean (geometric CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; AUC_{last}, area under the drug plasma concentration-time curve from 0 to the last quantifiable time
t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life; CL/F, apparent total clearance; V_z/F, apparent volume of distribution in the terminal phase

The safety analysis revealed adverse events and adverse drug reactions observed in 1 of 7 subjects and 1 of 7 subjects in those with normal hepatic function, respectively, and 3 of 7 subjects and 3 of 7 subjects, respectively in those with moderate hepatic impairment. No deaths or serious adverse events were reported. No adverse events led to drug discontinuation. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.5 Drug-drug interaction studies (CTD 5.3.3.4.01, Study 001, [redacted] 20[redacted] to [redacted] 20[redacted]; CTD 5.3.3.4.02, Study 003, [redacted] 20[redacted] to [redacted] 20[redacted] [reference data]; CTD 5.3.3.4.03, Study 023, June 2018 to August 2018)

Table 26 shows the results from the drug-drug interaction studies of imeglimin administered orally to healthy adults.

Table 26. Results of drug-drug interaction studies

Study No.	Dose of imeglimin	Concomitant drug and its dose	Plasma analyte	Ratio of the plasma pharmacokinetic parameters (combination therapy/monotherapy)	
				C_{max}	AUC[a)]
001[b)]	1500 mg	Metformin 850 mg	Metformin (N = 15)	0.90 [0.82, 0.97][e)]	0.86 [0.80, 0.92][e)]
003[c)]	1500 mg	Sitagliptin 100 mg	Sitagliptin (N = 16)	1.15 [0.98, 1.35]	1.13 [1.08, 1.19]
023[d)]	1500 mg	Cimetidine 400 mg	Imeglimin (N = 16)	1.34 [1.12, 1.62]	1.27 [1.10, 1.46]

Geometric mean ratios [90% CI] of the plasma pharmacokinetic parameters of imeglimin or the concomitant drug, administered as combination therapy, to those administered as a monotherapy
C_{max}, maximum plasma concentration; AUC, area under the drug plasma concentration-time curve
a) AUC_τ (area under the drug plasma concentration-time curve over a dosing interval) for Studies 001 and 003, or AUC_{last} (area under the drug plasma concentration-time curve from 0 to the last quantifiable time) for Study 023
b) Subjects received multiple oral doses of metformin 850 mg in combination with the placebo for imeglimin (capsules) twice daily on Days 1 to 6, followed by multiple oral doses of metformin 850 mg in combination with imeglimin (capsules) 1500 mg twice daily on Days 7 to 12.
c) Subjects received multiple oral doses of sitagliptin 100 mg once daily (during breakfast) in combination with the placebo for imeglimin twice daily (during breakfast and supper) on Days 1 to 6, followed by multiple oral doses of sitagliptin 100 mg once daily (during breakfast) in combination with imeglimin 1500 mg twice daily (during breakfast and supper) on Days 7 to 12.
d) Subjects received a single oral dose of imeglimin 1500 mg on Day 1, multiple doses of cimetidine 400 mg twice daily on Days 5 to 10, and a single oral dose of imeglimin 1500 mg on Day 8.
e) The data did not include the result from 1 subject who had a t_{max} value of metformin, when treated with imeglimin, of 0 hr, as well as lower plasma drug concentrations and lower urinary excretion of metformin than other subjects.

6.2.6 Pharmacokinetic study

6.2.6.1 Thorough QT/QTc study (CTD 5.3.4.1.01: Study 016, August to December 2016)

A 4-treatment, 4-period crossover study was conducted in non-Japanese healthy adults to evaluate the effects of a single oral dose of imeglimin on the QT/QTc interval (target sample size, 52). The positive control used was a single oral dose of moxifloxacin 400 mg.

Subjects received a single oral dose of imeglimin 2250 mg or 6000 mg, placebo, or moxifloxacin 400 mg in each of the 4 treatment periods. A rest period of ≥7 days was placed between the treatment periods.

All 55 treated subjects were included in the safety analysis set, the pharmacokinetic analysis set, and the electrocardiography analysis population.

Table 27 shows the pharmacokinetic parameters of a single oral dose of imeglimin.

Table 27. Pharmacokinetic parameters of a single oral dose of imeglimin

Dose	N	C_{max} (ng/mL)	AUC_{last} (ng·h/mL)	t_{max} (h)	$t_{1/2}$ (h)
2250 mg	52	2380 (20.5)	17900 (21.1)	2.00 [0.50, 4.05]	4.92 (14.0)
6000 mg	53	6500 (42.2)	36100 (24.2)	1.00 [0.50, 1.52]	5.65 (21.5)

Geometric mean (CV, %), or median [range] for t_{max}
C_{max}, maximum plasma concentration; AUC_{last}, area under the drug plasma concentration-time curve from 0 to the last quantifiable time
t_{max}, time to reach the maximum drug plasma concentration following drug administration; $t_{1/2}$, elimination half life

The electrocardiogram analysis found that the maximum least squares mean differences [90% CI] from placebo in the change from baseline in the QTcF interval after imeglimin dosing (2250 or 6000 mg) occurred at 8 hours postdose at 2250 mg and 6 hours postdose at 6000 mg, which were 4.8 [2.3, 7.2] and 2.9 [0.4, 5.4] milliseconds, respectively, showing the upper limit of 90% CI of <10 milliseconds at both doses. Meanwhile, the maximum least squares mean difference [90% CI] from placebo in the change from baseline in the QTcF interval after moxifloxacin dosing occurred (13.0 [10.6, 15.4] milliseconds) at 2 hours postdose, with the lower limit of 90% CI of >5 milliseconds, indicating that the study had assay sensitivity.

The incidences of adverse events and adverse drug reactions were 17.3% (9 of 52 subjects) and 5.8% (3 of 52 subjects) after placebo dosing, 19.2% (10 of 52 subjects) and 7.7% (4 of 52 subjects) after imeglimin 2250 mg dosing, 52.8% (28 of 53 subjects) and 47.2% (25 of 53 subjects) after imeglimin 6000 mg dosing, and 23.5% (12 of 51 subjects) and 13.7% (7 of 51 subjects) after moxifloxacin dosing. No deaths or serious adverse events were reported. One subject discontinued the study treatment due to an adverse event (rash pruritic) after placebo dosing, which was assessed as an adverse drug reaction. No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

6.2.7 Population pharmacokinetic analysis (CTD 5.3.3.5.01)

A population pharmacokinetic (PPK) analysis (NONMEM, Ver. 7.3.0) was performed based on plasma imeglimin concentration data (8256 timepoints, 867 subjects [493 men and 374 women; 385 Japanese subjects and 482 non-Japanese subjects]) from 9 Japanese or foreign studies (Studies DD401102, RVT-1501-1002, EML017008-003, EML017008-004, EML017008-005, 008, 011, 014, and 018).

The subjects included in the PPK analysis had the following baseline characteristics (median [range]): age, 59.0 [20.0, 80.0] years; body weight, 77.0 [35.6, 148] kg; BMI, 27.7 [18.1, 55.3] kg/m^2; and eGFR, 81.4 [14.1, 152] mL/min/1.73 m^2.

The basic model was constructed as a 2-compartment model comprising an administration site compartment involving lag time, dose-dependent relative bioavailability, and first-order absorption and first-order elimination from the central compartment, incorporating eGFR as a covariate for apparent clearance from the central compartment, dosage form and food intake as covariates for lag time and the absorption rate constant, and dosage form as a covariate for relative bioavailability.

A covariate analysis using a stepwise approach was then used to test race (Japanese vs. non-Japanese) as a covariate for lag time, relative bioavailability, and the absorption rate constant, as well as age, race, sex, and body weight as a covariate for apparent clearance from the central compartment (CL/F), apparent clearance between the central and peripheral compartments (Q/F), apparent distribution in the central compartment (V_c/F), and apparent distribution in the peripheral compartment (V_p/F). As a result, the final model incorporated age and body weight as a covariate for CL/F, body weight as a covariate for V_c/F, and age and race as covariates for Q/F.

The AUC ratios, relative to the steady-state $AUC_{24,ss}$ value estimated for a patient population with median characteristic data (age, 63 years; body weight, 69.1 kg; eGFR, 72.8 mL/min/1.73 m^2) in a Japanese phase III monotherapy study (Study 018) who received multiple oral doses of imeglimin 1000 mg twice daily, were estimated when age, body weight, and eGFR were varied. The resulting estimation revealed that the $AUC_{24,ss}$ values in patients aged 40 and 80 years would be 0.86- and 1.08-fold, respectively, of the $AUC_{24,ss}$ value in patients aged 63 years; the $AUC_{24,ss}$ values in patients weighing 40 and 100 kg would be 1.27- and 0.87-fold of the $AUC_{24,ss}$ value in patients weighing 69.1 kg; and, the $AUC_{24,ss}$ values in patients with eGFRs of 15 and 100 mL/min/1.73 m^2 would be 2.49- and 0.78-fold of the $AUC_{24,ss}$ value in patients with an eGFR of 72.8 mL/min/1.73 m^2.

6.R Outline of the review conducted by PMDA

6.R.1 Food effects

The applicant's explanation:

Based on the plasma imeglimin concentration data collected over 12 hours postdose in the food effects studies (Studies DD401101, 011, and EML017008-001[28)]), the steady-state C_{max} and AUC_{τ} following multiple doses of imeglimin under fasting and fed conditions were estimated (Table 28). The estimated C_{max} value increased under fasting conditions as compared with that under fed conditions in Study DD401101. However, the percent increase was 18%. Further, the percent increases in C_{max} and AUC_{τ} were ≤10% in the other studies. Thus, the estimated exposure to multiple doses of imeglimin administered under fasting conditions is unlikely to differ substantially from that under fed conditions.

[28)] A study conducted in non-Japanese healthy adults to evaluate the safety and pharmacokinetics of a single oral dose of imeglimin capsules (100, 250, 500, 1000, 2000, 3000, or 4000 mg) or placebos, and those of oral imeglimin capsules (250, 500, 1000, 1500, or 2000 mg), metformin 850 mg, or placebo administered twice daily for 7 days (except for Day 7, on which the study drug was administered once in the morning). Patients in the imeglimin 1000 mg multiple doses group took a high-fat meal before the administration of study drug on Day 4, to evaluate food effects on the pharmacokinetics of imeglimin.

Table 28. Estimated steady-state C_{max} and AUC_{τ} of imeglimin administered as multiple oral doses under fasting and fed conditions

Study No.	DD401101		011		EML017008-001	
Dose	1000 mg		1500 mg		1000 mg	
Parameter	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)	C_{max} (ng/mL)	AUC_{τ} (ng·h/mL)
Fasting	1858 (28.8)	12020 (31.4)	2419 (24.1)	15010 (28.1)	1385 (21.9)	8606 (28.4)
Fed	1570 (27.9)	11230 (29.1)	2313 (18.6)	16090 (10.3)	1366 (19.6)	9469 (30.9)
Ratio (fasting/fed)	1.18	1.07	1.05	0.93	1.01	0.91

Geometric mean (geometric CV, %)

C_{max}, maximum plasma concentration; AUC_{τ}, area under the drug plasma concentration-time curve over a dosing interval

PMDA accepted the applicant's explanation. In light of the fact that the Japanese phase II and III studies (Studies 014, 018, 019, and 020) recommended postprandial dosing, the necessity of meal instructions in the dosage regimen is discussed in Section "7.R.5 Dosage and Administration."

6.R.2 Patients with renal impairment

The applicant's explanation:

Results from the clinical pharmacology studies in subjects with renal impairment (Studies DD401102, RVT-1501-1002, and EML017008-005) indicated increased exposure to imeglimin with increasing severity of renal impairment. In view of the results of the mass balance study (Study EML017008-002), which showed that orally administered imeglimin was mostly excreted unchanged in urine or feces, absorbed imeglimin is presumed to be poorly metabolized in the intestines or the liver and eliminated unchanged primarily via renal excretion. In response to these results, the necessity of adjusting the dosage regimen for imeglimin according to the severity of renal impairment was examined. Based on the results from the Japanese phase II and III studies (Studies 014, 018, 019, and 020), in principle, the 1000-mg twice daily regimen was considered the appropriate dosage regimen of imeglimin [see Section "7.R.5 Dosage and Administration"]. Accordingly, based on the exposure levels in the patient population that has common patient characteristics[29] to those in the Japanese phase II and III studies, the exposure ($AUC_{24,ss}$) to imeglimin in patients with different severities of renal impairment was analyzed, in comparison with the exposure estimated in the reference group receiving imeglimin 1000 mg twice daily using a PPK model. Table 29 shows the ratios of steady-state exposure, relative to that in the reference group,[30] in patients with type 2 diabetes mellitus and renal impairment who received multiple oral doses of imeglimin 500, 1000, or 1500 mg twice daily.

[29] The proportions of patients with CKD 1, CKD 2, and CKD 3, in patients treated with imeglimin in the Japanese phase II and III studies (Studies 014 and 018) were 14.4%, 72.5%, and 13.1% respectively in Study 014, and 9.7%, 74.8%, and 15.5% respectively in Study 018.

[30] The reference group was defined as a population consisting of 1000 patients randomly sampled from the combined patient population of the Japanese phase II monotherapy study (Study 014) and the Japanese phase III monotherapy study (Study 018). The mean eGFR (range) in the reference group was 74.32 (47.20 to 137.6) mL/min/1.73 m^2, which reflected the characteristics of the whole patient population of these studies.

Table 29. Estimated ratios of the $AUC_{24,ss}$ of imeglimin administered orally twice daily by severity of renal impairment

Dosage regimen	Reference[a)]	CKD 2[b)]	CKD 3a[c)]	CKD 3b[d)]	CKD 4[e)]
500 mg twice daily	0.56 [0.27, 1.1]	-	0.74 [0.39, 1.4]	0.95 [0.51, 1.7]	1.2 [0.66, 2.5]
1000 mg twice daily	1.0 [0.48, 2.0]	1.0 [0.55, 1.9]	1.3 [0.71, 2.6]	1.7 [0.85, 3.4]	2.2 [1.2, 4.4]
1500 mg twice daily	1.4 [0.64, 2.9]	-	-	-	-

Median [2.5th percentile, 97.5th percentile]; $AUC_{24,ss}$, area under the drug plasma concentration-time curve at steady state over a 24-hour interval

a) The mean eGFR (range) in the reference group was 74.32 (47.20 to 137.6) mL/min/1.73 m^2.

b) CKD 2: A population consisting of 1000 patients with stage 2 CKD (60≤ eGFR <90), randomly sampled from the combined patient population of the Japanese phase II monotherapy study (Study 014) and the Japanese phase III monotherapy study (Study 018)

c) CKD 3a: A population consisting of patients in the reference group, in which only the eGFR data were replaced with the eGFR range for stage 3a CKD (45≤ eGFR <60)

d) CKD 3b: A population consisting of patients in the reference group, in which only the eGFR data were replaced with the eGFR range for stage 3b CKD (30≤ eGFR <45)

e) CKD 4: A population consisting of patients in the reference group, in which only the eGFR data were replaced with the eGFR range for stage 4 CKD (15≤ eGFR <30)

Patients with CKD 2 or 3a receiving oral imeglimin 1000 mg twice daily were found to have exposure comparable to that in the reference group, indicating no necessity of dose adjustment for these patients. The $AUC_{24,ss}$ value estimated in patients with CKD 3b or 4 receiving oral imeglimin 1000 mg twice daily tended to be higher than that in the reference group, with $AUC_{24,ss}$ ratios relative to the reference group of 1.7 in patients with CKD 3b and 2.2 in patients with CKD 4. In contrast, the $AUC_{24,ss}$ values in patients with CKD 3b or 4 receiving oral imeglimin 500 mg twice daily were presumed to be comparable to that in the reference group, with $AUC_{24,ss}$ ratios relative to the reference group of 0.95 in patients with CKD 3b and 1.2 in those with CKD 4. Thus, the dosage of imeglimin should be reduced to 500 mg twice daily in patients with CKD 3b or 4.

No clinical studies of imeglimin in patients with CKD 5 (eGFR <15 mL/min/1.73 m^2) have been conducted in Japan or overseas. However, the eGFR values in the clinical studies in European and American patients were recalculated uniformly using the CKD-EPI creatinine equation, and a total of 4 patients (2 in Study RVT-1501-1002 and 2 in Study EML017008-005) categorized as having CKD 5 were found to have been enrolled. The mean eGFR (range) in these 4 patients was 14.2 (14.1, 14.5) mL/min/1.73 m^2. The mean body weight (range) in these 4 patients, 92.7 (83.7, 104) kg, was considerably different from that in the reference group, 68.8 (35.6, 124.0) kg. Accordingly, the $AUC_{24,ss}$ of oral imeglimin 500 mg administered once daily to patients with CKD 5 was estimated using a PPK model, after their body weights were adjusted to those in the reference group, and a model-based analysis estimated that the $AUC_{24,ss}$ of oral imeglimin 500 mg administered once daily to patients with CKD 5 would be 0.93-fold the $AUC_{24,ss}$ of oral imeglimin 1000 mg administered twice daily in the reference group. These results indicated that the dosage of imeglimin should be reduced to 500 mg once daily in Japanese patients with both type 2 diabetes mellitus and CKD 5. No clinical studies of imeglimin have been conducted in patients receiving dialysis.

PMDA's view:

Because absorbed imeglimin is considered to be mostly eliminated unchanged via renal excretion and the exposure to imeglimin has been shown to increase with increasing severity of renal impairment, the necessity of adjusting the dosage of imeglimin according to the severity of renal impairment was examined. Based on the PPK model-based estimation performed by the applicant, etc., a level of exposure to imeglimin comparable to that observed in the Japanese phase II and III studies is expected to be achieved by 1000-mg twice daily oral dosing in patients with type 2 diabetes mellitus and CKD 2 or 3a, and by 500-mg twice daily oral dosing in patients with type 2 diabetes mellitus and CKD 3b or 4.

Meanwhile, the applicant also explained, based on the estimated exposure obtained using the PPK-model analysis, that imeglimin should be administered to patients with CKD 5 at 500 mg once daily. However, imeglimin is eliminated primarily via renal excretion, and no data are available from patients with an eGFR of ≤14 mL/min/1.73 m^2 who were treated with imeglimin for type 2 diabetes mellitus. There is a limitation in the PPK model-based estimation of exposure in this patient population. The exposure in patients with type 2 diabetes mellitus and an eGFR of ≤14 mL/min/1.73 m^2 may exceed the estimated exposure presented in Table 29.

The appropriateness of dose adjustment for patients with renal impairment and the necessity of cautionary advice through the package insert will be determined based on the safety results from the clinical studies and the above review [see Section "7.R.6.1 Patients with renal impairment"].

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 data from 1 Japanese phase II study (Study 014), 2 foreign phase II studies (Studies 006 and 009), and 3 Japanese phase III studies (Studies 018, 019, and 020) (Table 30). The applicant also submitted the results of 4 foreign phase II studies as reference data.

Table 30. Efficacy and safety evaluation data

Data category	Geographical location	Study identifier	Phase	Study population	No. of patients treated	Dosage regimen	Main endpoints
Evaluation data	Japan	014	II	Patients with type 2 diabetes mellitus	299	Placebo or imeglimin (500, 1000, 1500 mg) orally administered twice daily	Efficacy Safety
	Japan	018	III	Patients with type 2 diabetes mellitus	213	Placebo or imeglimin 1000 mg orally administered twice daily	Efficacy Safety
	Japan	019	III	Patients with type 2 diabetes mellitus	714	Imeglimin 1000 mg orally administered twice daily	Safety Efficacy
	Japan	020	III	Patients with type 2 diabetes mellitus	215	Placebo or imeglimin 1000 mg orally administered twice daily (Double-blind phase, 16 weeks; open-label phase, 36 weeks)	Efficacy Safety
	Foreign	006	II	Patients with type 2 diabetes mellitus	33	Placebo or imeglimin 1500 mg orally administered twice daily	Efficacy Safety
	Foreign	009	II	Patients with type 2 diabetes mellitus	59	Placebo or imeglimin 1500 mg orally administered twice daily	Efficacy Safety

A summaries of the main clinical studies are presented below. HbA1c values are expressed as national glycohemoglobin standardization program (NGSP) values.

7.1 Japanese late phase II monotherapy study (CTD 5.3.5.1.01: Study 014, December 2015 to January 2017)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus who had not been treated for the disease or had inadequate glycemic control with an oral hypoglycemic agent, to evaluate the dose-response relationship, efficacy, and safety of imeglimin alone (target sample size, 304[31)] [76 each in the placebo group, the imeglimin 500 mg group, the 1000 mg group, and

[31)] With an anticipated between-group difference in the change in HbA1c of 0.5% and a standard deviation for each group of 1.0%, the study would require 304 patients to provide 80% statistical power at a 2-sided significance level of 5%, allowing for approximately 15% drop-out.

the 1500 mg group]) [for pharmacokinetic results, see Section "6.2.3.1 Japanese late phase II monotherapy study"].

The main inclusion criteria included patients with type 2 diabetes mellitus aged ≥20 to ≤75 years, no prior treatment for type 2 diabetes mellitus or ongoing monotherapy with an oral hypoglycemic agent for 12 weeks prior to screening, HbA1c of ≥7.0% to <10.0% at screening and the pre-randomization visit, and eGFR of ≥50 mL/min/1.73 m^2 at screening and ≥45 mL/min/1.73 m^2 at the pre-randomization visit.

The study consisted of the screening phase (1 to 3 weeks), the single-blind, placebo run-in phase (6 or 10 weeks[32)]), the double-blind phase (24 weeks), and the follow-up phase (1 week).

Patients received multiple oral doses of imeglimin 500, 1000, or 1500 mg, or placebo twice daily.

All 299 randomized patients (75 in the placebo group, 75 in the imeglimin 500 mg group, 74 in the 1000 mg group, and 75 in the 1500 mg group) were included in the safety analysis set. Of these, 296 who received ≥1 dose of the study drug and had HbA1c data at baseline and ≥1 post-baseline timepoints (75 in the placebo group, 75 in the 500 mg group, 73 in the 1000 mg group, and 73 in the 1500 mg group) were included in the full analysis set (FAS). The FAS population was the primary efficacy analysis set. A total of 32 patients (11 in the placebo group, 5 in the 500 mg group, 8 in the 1000 mg group, and 8 in the 1500 mg group) discontinued the study. The reasons for discontinuation were adverse events in 8 patients (1 in the placebo group, 2 in the 1000 mg group, and 5 in the 1500 mg group), the use of prohibited concomitant medications in 1 patient (the placebo group), poor glycemic control in 7 patients (6 in the placebo group and 1 in the 1000 mg group), HbA1c of ≥10% at consecutive visits in 5 patients (2 in the placebo group, 2 in the 500 mg group, and 1 in the 1000 mg group), consent withdrawal in 9 patients (1 in the placebo group, 3 in the 500 mg group, 2 in the 1000 mg group, and 3 in the 1500 mg group), and protocol deviation in 2 patients (2 in the 1000 mg group).

Table 31 presents the efficacy results based on the change in HbA1c from baseline to Week 24, which was the primary endpoint. The results demonstrated the superiority of imeglimin over placebo at all doses.

[32)] Patients who were on monotherapy with an existing hypoglycemic agent at the time of screening discontinued the monotherapy at screening, and were randomized after 6 weeks (10 weeks for monotherapy with a thiazolidinedione [TZD]). Patients who had no prior treatment for type 2 diabetes mellitus were randomized 6 weeks after screening.

Table 31. Changes in HbA1c from baseline to Week 24 (Study 014, FAS)

Treatment	Baseline	Week 24	Change from baseline[a)]	Difference from placebo[a)]	*P*-value[b)]
Placebo	7.89 ± 0.68 (n = 75)	8.03 ± 0.93 (n = 65)	0.43 ± 0.09	-	-
Imeglimin 500 mg	7.94 ± 0.68 (n = 75)	7.77 ± 0.89 (n = 70)	-0.09 ± 0.09	-0.52 [-0.77, -0.27]	<0.0001
Imeglimin 1000 mg	7.85 ± 0.65 (n = 73)	7.27 ± 0.76 (n = 66)	-0.51 ± 0.09	-0.94 [-1.19, -0.68]	<0.0001
Imeglimin 1500 mg	7.91 ± 0.62 (n = 73)	7.35 ± 0.79 (n = 67)	-0.57 ± 0.09	-1.00 [-1.26, -0.75]	<0.0001

%; Mean ± standard deviation, least squares mean ± standard error for the change from baseline, or least square mean [95% CI] for the difference from placebo; -, not applicable

a) Mixed model with repeated measures (MMRM) including treatment, timepoint, type of prior treatment, and treatment-by-timepoint interaction as fixed effects, and the baseline HbA1c as a covariate, and assuming an unstructured covariance matrix

b) 2-sided significance level of 5%, adjusted for multiplicity by a closed testing procedure starting from the highest dose

Table 32 presents the results of the main secondary endpoints (changes from baseline to Week 24).

Table 32. Results of main secondary endpoints (Study 014, FAS)

	Placebo (N = 75)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 73)	Imeglimin 1500 mg (N = 73)
Fasting blood glucose (mg/dL)[a)]	16.6 ± 3.33	8.0 ± 3.29	-8.0 ± 3.34	-8.0 ± 3.39
Proportion of patients who achieved HbA1c of <7.0% (%)[b)]	5.3 (4 of 75 patients)	13.3 (10 of 75 patients)	35.6 (26 of 73 patients)	28.8 (21 of 73 patients)

Least squares mean ± standard error

a) MMRM including treatment, timepoint, HbA1c at randomization (<8.0% vs. ≥8.0%), type of prior treatment, and treatment-by-timepoint interaction as fixed effects, and the baseline value as a covariate, and assuming an unstructured covariance matrix

b) Proportion of patients who achieved HbA1c of <7.0% = number of patients who achieved an HbA1c <7.0%/total number of patients. Patients who had no HbA1c data at Week 24 were counted as patients who failed to achieve an HbA1c of <7%.

Table 33 shows the incidences of adverse events reported with an incidence of ≥5% in any treatment group and the incidences of those assessed as adverse drug reactions.

Table 33. Incidences of adverse events reported with a ≥5% incidence in any treatment group and those assessed as adverse drug reactions (Study 014, safety analysis set)

Events	Placebo (N = 75)		Imeglimin 500 mg (N = 75)		Imeglimin 1000 mg (N = 74)		Imeglimin 1500 mg (N = 75)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	68.0 (51)	8.0 (6)	68.0 (51)	5.3 (4)	62.2 (46)	5.4 (4)	73.3 (55)	24.0 (18)
Nasopharyngitis	14.7 (11)	0 (0)	26.7 (20)	0 (0)	20.3 (15)	0 (0)	24.0 (18)	0 (0)
Diarrhoea	0 (0)	0 (0)	4.0 (3)	0 (0)	5.4 (4)	1.4 (1)	8.0 (6)	4.0 (3)
Abdominal discomfort	0 (0)	0 (0)	1.3 (1)	0 (0)	2.7 (2)	0 (0)	9.3 (7)	5.3 (4)
Hypoglycaemia	1.3 (1)	1.3 (1)	6.7 (5)	1.3 (1)	2.7 (2)	1.4 (1)	5.3 (4)	5.3 (4)
Nausea	1.3 (1)	1.3 (1)	1.3 (1)	0 (0)	1.4 (1)	1.4 (1)	6.7 (5)	5.3 (4)
Hyperglycaemia	12.0 (9)	1.3 (1)	4.0 (3)	1.3 (1)	1.4 (1)	0 (0)	1.3 (1)	0 (0)
Back pain	0 (0)	0 (0)	5.3 (4)	0 (0)	1.4 (1)	0 (0)	1.3 (1)	0 (0)
Vomiting	5.3 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	5.3 (4)	2.7 (2)
Culture urine positive	1.3 (1)	0 (0)	1.3 (1)	0 (0)	0 (0)	0 (0)	5.3 (4)	1.3 (1)

Incidence, % (n); MedDRA (ver. 19.0)

One death was reported in the 1500 mg group (pancreatic carcinoma metastatic), for which a causal relationship to the study drug was ruled out. Serious adverse events were reported in 1 patient in the placebo group (meniscus injury) and 4 patients in the 1000 mg group (bradycardia, solid pseudopapillary tumour of the pancreas, prostate cancer, and clavicle fracture in 1 patient each); a causal relationship to the study drug was ruled out for all these events. Adverse events led to drug discontinuation in 8 patients in the placebo group (hyperglycaemia in 7 patients and rash in 1 patient), 2 patients in the 500 mg group (hyperglycaemia in 2 patients), 3 patients in the 1000 mg group (prostate cancer, vertigo positional, and hyperglycaemia in 1 patient each), and 5 patients in the 1500 mg group (vomiting in 2 patients, and stomatitis, feeling abnormal, and

pancreatic carcinoma metastatic in 1 patient each). Of these adverse events, those reported in 1 patient in the placebo group (hyperglycaemia), 1 patient in the 500 mg group (hyperglycaemia), and 4 patients in the 1500 mg group (vomiting in 2 patients, and stomatitis and feeling abnormal in 1 patient each) were assessed as adverse drug reactions.

Hypoglycemia was reported with incidences of 1.3% (1 of 75 patients) in the placebo group, 6.7% (5 of 75 patients) in the 500 mg group, 2.7% (2 of 74 patients) in the 1000 mg group, and 5.3% (4 of 75 patients) in the 1500 mg group. None of these cases were severe.[33)]

No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.2 Japanese phase III monotherapy study (CTD 5.3.5.1.02: Study 018, December 2017 to February 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus who had inadequate glycemic control with diet and exercise therapies alone or in combination with monotherapy with an existing oral hypoglycemic agent to evaluate the efficacy and safety of imeglimin alone (target sample size, 212[34)] [106 each in the placebo group and the imeglimin 1000 mg group]) [for pharmacokinetic results from the study, see Section "6.2.3.2 Japanese phase III monotherapy study"].

The main inclusion criteria included patients with type 2 diabetes mellitus aged ≥20 years, ongoing diet and exercise therapies alone or in combination with monotherapy with a stable dose of an oral hypoglycemic agent for 12 weeks prior to screening, HbA1c of ≥7.0% to <10.0%[35)] at screening and the pre-randomization visit, and eGFR of ≥50 mL/min/1.73 m^2 at screening and ≥45 mL/min/1.73 m^2 at the pre-randomization visit.

The study consisted of the screening phase (2 or 9 weeks[36)]), the single-blind placebo run-in phase (4 weeks), the double-blind phase (24 weeks), and the follow-up phase (1 week).

Patients received multiple oral doses of imeglimin 1000 mg or placebo twice daily.

All 213 randomized patients (107 in the placebo group and 106 in the 1000 mg group) were included in the safety analysis set. Of these, 212 patients who received ≥1 dose of the study drug and had HbA1c data at baseline and ≥1 post-baseline timepoints (106 in the placebo group and 106 in the 1000 mg group) were included in the FAS. The FAS population was the primary efficacy analysis set. A total of 19 patients (11 in

[33)] Hypoglycemia requiring third-party assistance for the intake of carbohydrate or glucagon, or other resuscitative actions

[34)] With an anticipated between-group difference in the change in HbA1c of 0.5% and a standard deviation for each group of 1.0%, the study would require 85 patients for each group to provide 90% statistical power at a 1-sided significance level of 2.5%. Allowing for approximately 20% drop-out, a sample size of 106 per group was set.

[35)] Patients who had received an existing oral hypoglycemic agent at a stable dose for ≥12 weeks prior to screening were required to have an HbA1c of ≥7.0% to ≤9.0% at screening.

[36)] If the patient was treated with diet and exercise therapies alone, the screening phase was 2 weeks. If the patient was on monotherapy with an existing oral hypoglycemic agent at the time of screening, the screening phase was 9 weeks, including a 1-week screening period and an 8-week washout period that followed the discontinuation of the oral hypoglycemic agent.

the placebo group and 8 in the 1000 mg group) discontinued the study. The reasons for discontinuation were adverse events in 5 patients (1 in the placebo group and 4 in the 1000 mg group), the use of prohibited concomitant medications in 1 patient (in the 1000 mg group), poor glycemic control in 5 patients (all in the placebo group), and consent withdrawal in 8 patients (5 in the placebo group and 3 in the 1000 mg group).

Table 34 presents the efficacy results based on the change in HbA1c from baseline to Week 24, which was the primary endpoint. The results demonstrated the superiority of imeglimin 1000 mg over placebo.

Table 34. Changes in HbA1c from baseline to Week 24 (Study 018, FAS)

Treatment	Baseline	Week 24	Change from baseline[a)]	Difference from placebo[a)]	*P*-value[b)]
Placebo	7.93 ± 0.68 (n = 106)	7.86 ± 0.79 (n = 96)	0.15 ± 0.07	-	-
Imeglimin 1000 mg	7.99 ± 0.76 (n = 106)	7.25 ± 0.74 (n = 98)	-0.72 ± 0.07	-0.87 [-1.04, -0.69]	<0.0001

%; Mean ± standard deviation, least squares mean ± standard error for the change from baseline, or least square mean [95% CI] for the difference from placebo; -, not applicable

a) Mixed model with repeated measures (MMRM) including treatment, timepoint, type of prior treatment, and treatment-by-timepoint interaction as fixed effects, and the baseline HbA1c as a covariate, and assuming an unstructured covariance matrix

b) 2-sided significance level of 5%

Table 35 presents the results of the main secondary endpoints (changes from baseline to Week 24).

Table 35. Results of main secondary endpoints (Study 018, FAS)

	Placebo (N = 106)	Imeglimin 1000 mg (N = 106)
Fasting blood glucose (mg/dL)[a)]	12.88 ± 2.84	-5.65 ± 2.80
Proportion of patients who achieved HbA1c of <7.0% (%)[b)]	7.5 (8 of 106 patients)	35.8 (38 of 106 patients)

Least squares mean ± standard error

a) MMRM including treatment, timepoint, HbA1c at randomization (<8.0% vs. ≥8.0%), type of prior treatment, and treatment-by-timepoint interaction as fixed effects, and the baseline value as a covariate, and assuming an unstructured covariance matrix

b) Proportion of patients who achieved an HbA1c of <7.0% = number of patients who achieved an HbA1c <7.0%/total number of patients. Patients who had no HbA1c data at Week 24 were counted as patients who failed to achieve an HbA1c of <7.0%.

Table 36 shows the incidences of adverse events and adverse drug reactions reported with a ≥2% incidence in either treatment group.

Table 36. Incidences of adverse events reported with a ≥2% incidence in either treatment group and those assessed as adverse drug reactions (Study 018, safety analysis set)

Events	Placebo (N = 107)		Imeglimin 1000 mg (N = 106)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	44.9 (48)	6.5 (7)	44.3 (47)	4.7 (5)
Nasopharyngitis	8.4 (9)	0 (0)	17.0 (18)	0 (0)
Pharyngitis	1.9 (2)	0 (0)	2.8 (3)	0 (0)
Muscle spasms	0.9 (1)	0 (0)	2.8 (3)	0 (0)
Hypoglycaemia	0.9 (1)	0.9 (1)	2.8 (3)	1.9 (2)
Dyslipidaemia	2.8 (3)	0 (0)	1.9 (2)	0 (0)
Hyperglycaemia	6.5 (7)	1.9 (2)	0 (0)	0 (0)
Dizziness	2.8 (3)	0 (0)	0 (0)	0 (0)

Incidence, % (n); MedDRA (ver. 20.1)

No deaths were reported. Serious adverse events were observed in 1 patient in the placebo group (lower limb fracture), 4 patients in the imeglimin 1000 mg group (femur fracture/radius fracture, spondylitic myelopathy, ileus, and bladder cancer in 1 patient each). A causal relationship to the study drug was ruled out in all events.

Adverse events led to drug discontinuation in 6 patients in the placebo group (hyperglycaemia in 6 patients) and 3 patients in the imeglimin 1000 mg group (spondylitic myelopathy, diarrhoea/vomiting, and bladder cancer in 1 patient each). The hyperglycaemia in 2 patients in the placebo group and the diarrhoea and vomiting in the imeglimin 1000 mg group were assessed as adverse drug reactions.

Hypoglycemia was reported with incidences of 0.9% (1 of 107 patients) in the placebo group and 2.8% (3 of 106 patients) in the imeglimin 1000 mg group. None of these were severe cases.[33)]

No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.3 Japanese phase III long-term monotherapy and combination therapy study (CTD 5.3.5.2.01: Study 019, January 2018 to October 2019)

An open-label study was conducted in Japanese patients with type 2 diabetes mellitus who had inadequate glycemic control by diet and exercise therapies alone or in combination with an oral hypoglycemic agent to evaluate the efficacy and safety of imeglimin alone or in combination therapies (target sample size, 691 [125 each in the imeglimin monotherapy group and the imeglimin + sulfonylurea [SU] group, and 63 each in the imeglimin + glinide group, the imeglimin + biguanides [BG] group, the imeglimin + α-glucosidase inhibitor [α-GI] group, the imeglimin + TZD group, the imeglimin + dipeptidyl peptidase-4 [DPP-4] inhibitor group, the imeglimin + sodium glucose cotransporter 2 [SGLT-2] inhibitor group, and the imeglimin + glucagon-like peptide-1 [GLP-1] receptor agonist group]).

The main inclusion criteria for the imeglimin monotherapy group included patients with type 2 diabetes mellitus aged ≥20 years, ongoing diet and exercise therapies alone for 12 weeks prior to screening, HbA1c of ≥7.0% to <10.0% at screening, and an eGFR of ≥50 mL/min/1.73 m^2 at screening. The main inclusion criteria for the combination therapy groups included patients with type 2 diabetes mellitus aged ≥20 years, ongoing diet and exercise therapies in combination with monotherapy with a stable dose of hypoglycemic agent (SU, glinide, BG, α-GI, TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist) for 12 weeks prior to screening, HbA1c of ≥7.5% to <10.5% and eGFR of ≥60 mL/min/1.73 m^2 at screening.

The study consisted of the screening phase (2 weeks), the single-blind, placebo run-in phase (2 weeks), the open-label phase (52 weeks), and the follow-up phase (1 week).

Imeglimin was administered orally at 1000 mg twice daily. The concomitant hypoglycemic agent was administered according to the dosage regimen previously being used.

All 714 patients who entered in the open-label phase (134 in the imeglimin monotherapy group, 127 in the imeglimin + SU group, 64 in the imeglimin + glinide group, 64 in the imeglimin + BG group, 64 in the imeglimin + α-GI group, 65 in the imeglimin + TZD group, 63 in the imeglimin + DPP-4 inhibitor group, 63 in the imeglimin + SGLT2 inhibitor group, and 70 in the imeglimin + GLP-1 receptor agonist group) were

included in the safety analysis set. A total of 82 patients (10 in the imeglimin monotherapy group, 17 in the imeglimin + SU group, 6 in the imeglimin + glinide group, 11 in the imeglimin + BG group, 4 in the imeglimin + α-GI group, 4 in the imeglimin + TZD group, 8 in the imeglimin + DPP-4 inhibitor group, 3 in the imeglimin + SGLT2 inhibitor group, and 19 in the imeglimin + GLP-1 receptor agonist group) discontinued the study treatment. The reasons for discontinuation were adverse events in 31 patients (3 in the imeglimin monotherapy group, 3 in the imeglimin + SU group, 1 in the imeglimin + glinide group, 7 in the imeglimin + BG group, 1 in the imeglimin + α-GI group, 3 in the imeglimin + TZD group, 4 in the imeglimin + DPP-4 inhibitor group, and 9 in the imeglimin + GLP-1 receptor agonist group), use of prohibited concomitant medications in 2 patients (1 in the imeglimin + BG group and 1 in the imeglimin + GLP-1 receptor agonist group), poor glycemic control in 18 patients (1 in the imeglimin monotherapy group, 7 in the imeglimin + SU group, 1 in the imeglimin + α-GI group, 1 in the imeglimin + TZD group, 1 in the imeglimin + DPP-4 inhibitor group, 1 in the imeglimin + SGLT2 inhibitor group, and 6 in the imeglimin + GLP-1 receptor agonist group), consent withdrawal in 30 patients (6 in the imeglimin monotherapy group, 7 in the imeglimin + SU group, 4 in the imeglimin + glinide group, 3 in the imeglimin + BG group, 2 in the imeglimin + α-GI group, 3 in the imeglimin + DPP-4 inhibitor group, 2 in the imeglimin + SGLT2 inhibitor group, and 3 in the imeglimin + GLP-1 receptor agonist group), and lost to follow-up in 1 patient (in the imeglimin + glinide group).

Table 37 presents the results of main efficacy endpoints (changes from baseline to Week 52) in the imeglimin monotherapy group and the combination therapy groups.

Table 37. Results of main efficacy endpoints (changes from baseline to Week 52; Study 019, safety analysis set)

Treatment	HbA1c (%)		Fasting blood glucose (mg/dL)		Proportion of patients who achieved HbA1c of <7.0% (%)[b)]
	Baseline	Change[a)]	Baseline	Change[a)]	
Imeglimin monotherapy (N = 134)	7.83 ± 0.73	-0.46 ± 0.07	163.10 ± 25.63	-11.18 ± 2.36	38.8 (52 of 134 patients)
Imeglimin + SU (N = 127)	8.63 ± 0.90	-0.56 ± 0.08	185.11 ± 37.73	-15.01 ± 2.67	13.4 (17 of 127 patients)
Imeglimin + glinide (N = 64)	8.48 ± 0.84	-0.70 ± 0.13	179.70 ± 33.60	-16.06 ± 4.31	25.0 (16 of 64 patients)
Imeglimin + BG (N = 64)	8.16 ± 0.61	-0.67 ± 0.09	174.80 ± 30.81	-24.44 ± 3.40	23.4 (15 of 64 patients)
Imeglimin + α-GI (N = 64)	8.37 ± 0.77	-0.85 ± 0.09	173.78 ± 31.44	-19.47 ± 3.26	23.4 (15 of 64 patients)
Imeglimin + TZD (N = 65)	8.72 ± 0.94	-0.88 ± 0.11	171.49 ± 32.28	-17.74 ± 3.56	18.5 (12 of 65 patients)
Imeglimin + DPP-4 inhibitor (N = 63)	8.23 ± 0.75	-0.92 ± 0.11	180.02 ± 32.99	-23.45 ± 4.57	33.3 (21 of 63 patients)
Imeglimin + SGLT2 inhibitor (N = 63)	8.50 ± 0.75	-0.57 ± 0.07	165.51 ± 27.84	-12.31 ± 2.62	7.9 (5 of 63 patients)
Imeglimin + GLP-1 (N = 70)	8.66 ± 0.85	-0.12 ± 0.13	190.94 ± 39.72	-16.94 ± 4.63	7.1 (5 of 70 patients)

Mean ± standard deviation, or least squares mean ± standard error for the change from baseline
GLP-1, GLP-1 receptor agonist
a) MMRM including timepoint as a fixed effect, and baseline value and baseline value-by-timepoint interaction as covariates, and assuming an unstructured covariance matrix
b) Proportion of patients who achieved HbA1c of <7.0% = number of patients who achieved HbA1c <7.0%/total number of patients. Patients who had no HbA1c data at Week 52 were counted as patients who failed to achieve HbA1c of <7.0%.

Figures 1 and 2 show the changes in HbA1c from baseline to Week 52 in the imeglimin monotherapy group and the combination therapy groups.

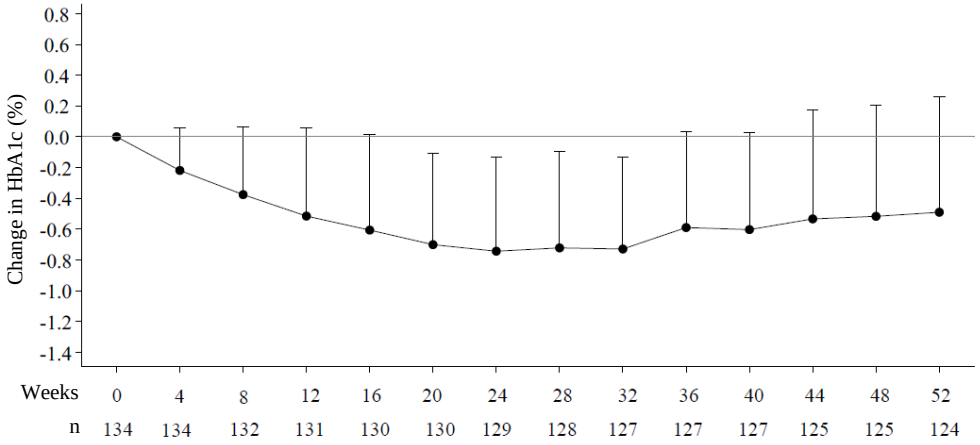

Figure 1. Changes in HbA1c from baseline to Week 52 (imeglimin monotherapy)
(Study 019, mean + standard deviation)

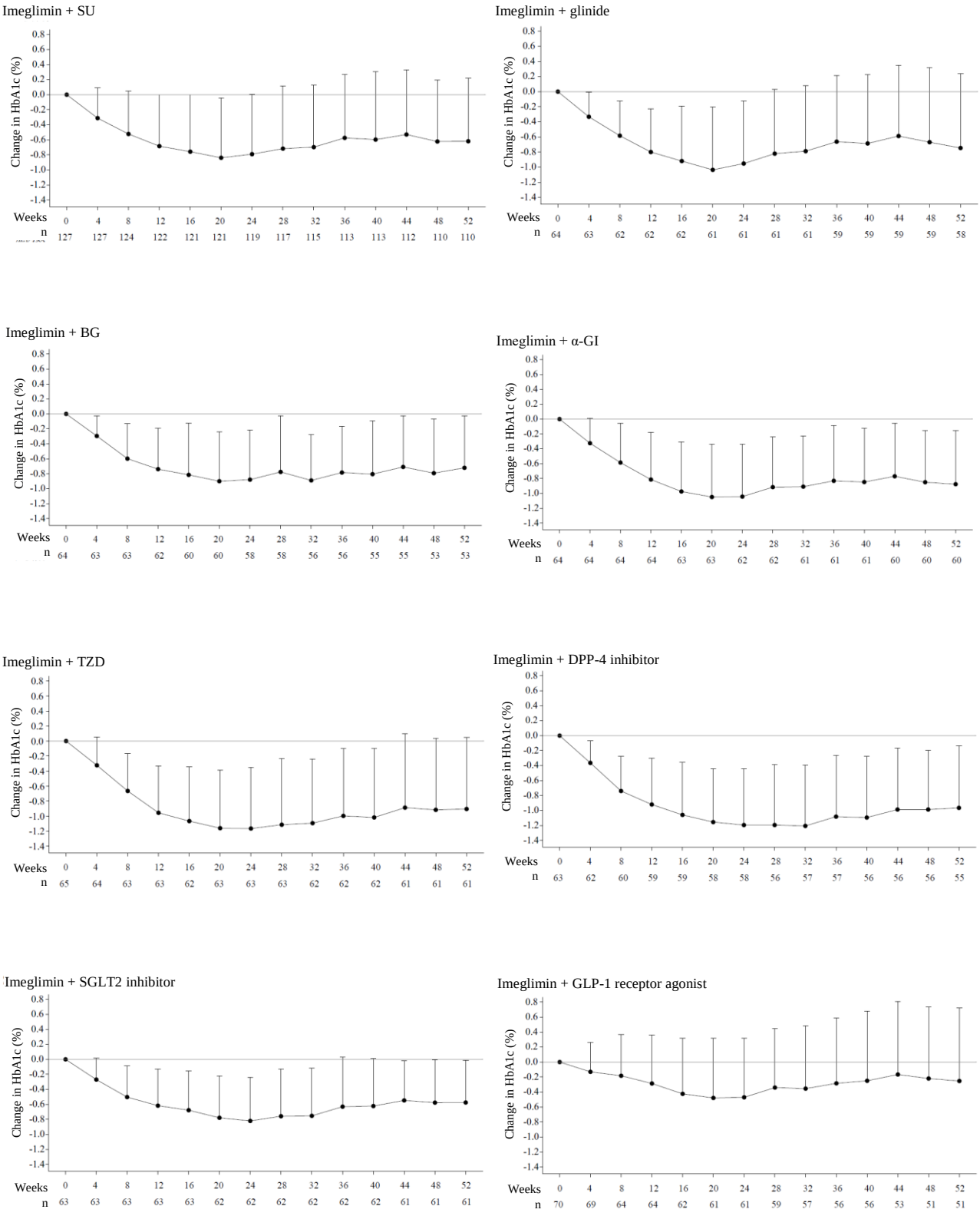

Figure 2. Changes in HbA1c from baseline to Week 52 (combination therapies) (Study 019, mean + standard deviation)

Table 38 shows the incidences of adverse events reported with a ≥5% incidence in any treatment group, and the incidences of those assessed as adverse drug reactions.

Table 38. Incidences of adverse events reported with a ≥5% incidence in any treatment group and those assessed as adverse drug reactions (Study 019, safety analysis set)

Events	Imeglimin monotherapy (N = 134)		Imeglimin + SU (N = 127)		Imeglimin + glinide (N = 64)		Imeglimin + BG (N = 64)		Imeglimin + α-GI (N = 64)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	73.1 (98)	9.7 (13)	80.3 (102)	21.3 (27)	84.4 (54)	15.6 (10)	75.0 (48)	37.5 (24)	51.6 (33)	9.4 (6)
Nasopharyngitis	29.9 (40)	0 (0)	30.7 (39)	0 (0)	42.2 (27)	0 (0)	25.0 (16)	0 (0)	7.8 (5)	0 (0)
Nausea	6.7 (9)	3.0 (4)	0.8 (1)	0 (0)	0 (0)	0 (0)	12.5 (8)	10.9 (7)	1.6 (1)	0 (0)
Pharyngitis	6.0 (8)	0 (0)	3.9 (5)	0 (0)	6.3 (4)	0 (0)	0 (0)	0 (0)	3.1 (2)	0 (0)
Constipation	3.7 (5)	2.2 (3)	6.3 (8)	3.1 (4)	3.1 (2)	0 (0)	1.6 (1)	0 (0)	3.1 (2)	3.1 (2)
Hypoglycaemia	3.7 (5)	1.5 (2)	16.5 (21)	11.8 (15)	14.1 (9)	6.3 (4)	9.4 (6)	7.8 (5)	3.1 (2)	3.1 (2)
Back pain	3.7 (5)	0 (0)	7.9 (10)	0 (0)	4.7 (3)	0 (0)	1.6 (1)	0 (0)	3.1 (2)	0 (0)
Hyperglycaemia	3.7 (5)	0 (0)	5.5 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	0 (0)
Diarrhoea	3.0 (4)	0.7 (1)	2.4 (3)	0.8 (1)	6.3 (4)	4.7 (3)	17.2 (11)	15.6 (10)	0 (0)	0 (0)
Influenza	3.0 (4)	0 (0)	7.1 (9)	0 (0)	3.1 (2)	0 (0)	7.8 (5)	0 (0)	1.6 (1)	0 (0)
Gastrooesophageal reflux disease	2.2 (3)	0 (0)	7.1 (9)	0.8 (1)	1.6 (1)	0 (0)	3.1 (2)	1.6 (1)	0 (0)	0 (0)
Eczema	1.5 (2)	0 (0)	3.1 (4)	0 (0)	4.7 (3)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Bronchitis	0.7 (1)	0 (0)	0.8 (1)	0 (0)	6.3 (4)	0 (0)	3.1 (2)	0 (0)	0 (0)	0 (0)
Vomiting	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	6.3 (4)	4.7 (3)	0 (0)	0 (0)
Spinal osteoarthritis	0.7 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	0 (0)
Intervertebral disc protrusion	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	1.6 (1)	0 (0)	0 (0)	1.6 (1)	0 (0)
Hypertension	0 (0)	0 (0)	5.5 (7)	0 (0)	3.1 (2)	0 (0)	1.6 (1)	0 (0)	4.7 (3)	0 (0)

Events	Imeglimin + TZD (N = 65)		Imeglimin + DPP-4 inhibitor (N = 63)		Imeglimin + SGLT2 inhibitor (N = 63)		Imeglimin + GLP-1 receptor agonist (N = 70)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	76.9 (50)	9.2 (6)	79.4 (50)	22.2 (14)	76.2 (48)	11.1 (7)	80.0 (56)	11.4 (8)
Nasopharyngitis	27.7 (18)	0 (0)	30.2 (19)	0 (0)	31.7 (20)	0 (0)	28.6 (20)	0 (0)
Nausea	1.5 (1)	1.5 (1)	7.9 (5)	6.3 (4)	6.3 (4)	3.2 (2)	4.3 (3)	4.3 (3)
Pharyngitis	4.6 (3)	0 (0)	4.8 (3)	0 (0)	7.9 (5)	0 (0)	1.4 (1)	0 (0)
Constipation	1.5 (1)	0 (0)	7.9 (5)	1.6 (1)	3.2 (2)	1.6 (1)	1.4 (1)	0 (0)
Hypoglycaemia	3.1 (2)	0 (0)	7.9 (5)	3.2 (2)	6.3 (4)	3.2 (2)	2.9 (2)	0 (0)
Back pain	6.2 (4)	0 (0)	1.6 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	1.5 (1)	0 (0)	3.2 (2)	1.6 (1)	1.6 (1)	0 (0)	11.4 (8)	0 (0)
Diarrhoea	3.1 (2)	3.1 (2)	3.2 (2)	0 (0)	3.2 (2)	0 (0)	4.3 (3)	0 (0)
Influenza	4.6 (3)	0 (0)	1.6 (1)	0 (0)	3.2 (2)	0 (0)	1.4 (1)	0 (0)
Gastrooesophageal reflux disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.4 (1)	0 (0)
Eczema	1.5 (1)	0 (0)	7.9 (5)	0 (0)	3.2 (2)	0 (0)	5.7 (4)	0 (0)
Bronchitis	6.2 (4)	0 (0)	0 (0)	0 (0)	3.2 (2)	0 (0)	0 (0)	0 (0)
Vomiting	3.1 (2)	3.1 (2)	3.2 (2)	1.6 (1)	1.6 (1)	0 (0)	2.9 (2)	2.9 (2)
Spinal osteoarthritis	0 (0)	0 (0)	6.3 (4)	0 (0)	1.6 (1)	0 (0)	1.4 (1)	0 (0)
Intervertebral disc protrusion	0 (0)	0 (0)	6.3 (4)	0 (0)	0 (0)	0 (0)	1.4 (1)	0 (0)
Hypertension	4.6 (3)	0 (0)	1.6 (1)	0 (0)	1.6 (1)	0 (0)	2.9 (2)	0 (0)

Incidence, % (n); MedDRA (ver. 20.1)

A death was reported in the imeglimin monotherapy group (subarachnoid haemorrhage), for which a causal relationship to the study drug was ruled out. Serious adverse events were reported in 4 patients in the imeglimin monotherapy group (appendicitis, subarachnoid haemorrhage, post procedural haemorrhage, and atrial fibrillation in 1 patient each), 11 patients in the imeglimin + SU group (clavicle fracture, colon cancer stage I, rectal cancer, angina unstable, acute myocardial infarction, contusion, subdural haematoma, pneumothorax traumatic, uterine leiomyoma, lower gastrointestinal haemorrhage, and synovitis in 1 patient each), 1 patient in the imeglimin + glinide group (testis cancer), 4 patients in the imeglimin + BG group (myocardial infarction, cholangiocarcinoma, appendicitis, and large intestine polyp in 1 patient each), 4 patients in the imeglimin + α-GI group (cholecystitis/drug-induced liver injury, ovarian cyst, angina unstable, and heat illness in 1 patient each), 4 patients in the imeglimin + TZD group (enterovesical fistula, craniocerebral injury, inflammation, and

pneumonia bacterial in 1 patient each), 3 patients in the imeglimin + DPP-4 inhibitor group (multiple fractures, large intestine polyp, and endometrial cancer stage III in 1 patient each), 4 patients in the imeglimin + SGLT2 inhibitor group (cardiac failure/pneumonia, lacunar infarction, large intestine polyp, and spinal fracture in 1 patient each), and 5 patients in the imeglimin + GLP-1 receptor agonist group (lumbar spinal stenosis, invasive ductal breast carcinoma, dermoid cyst, coronary artery stenosis, and cerebral infarction/coronary artery stenosis in 1 patient each); a causal relationship to the study drug was ruled out for all of the events. Adverse events led to drug discontinuation in 3 patients in the imeglimin monotherapy group (hyperglycaemia in 3 patients), 9 patients in the imeglimin + SU group (hyperglycaemia in 7 patients, and colon cancer stage I and rectal cancer in 1 patient each), 1 patient in the imeglimin + glinide group (testis cancer), 7 patients in the imeglimin + BG group (decreased appetite, abdominal pain upper, diarrhoea, nausea, cholangiocarcinoma, platelet count decreased, and vomiting in 1 patient each), 2 patients in the imeglimin + α-GI group (gastritis and hyperglycaemia in 1 patient each), 4 patients in the imeglimin + TZD group (enterovesical fistula, hyperglycaemia, vomiting, and nausea in 1 patient each), 5 patients in the imeglimin + DPP-4 inhibitor group (erectile dysfunction, decreased appetite, nausea, multiple fractures, and hyperglycaemia in 1 patient each), 1 patient in the imeglimin + SGLT2 inhibitor group (hyperglycaemia), and 15 patients in the imeglimin + GLP-1 receptor agonist group (hyperglycaemia in 8 patients, and abdominal pain upper, cholelithiasis, nausea, dyspepsia, diabetic neuropathy, invasive ductal breast carcinoma, and decreased appetite in 1 patient each). Of these adverse events, those reported in 6 patients in the imeglimin + BG group (nausea, abdominal pain upper, vomiting, diarrhoea, decreased appetite, and platelet count decreased in 1 patient each), 1 patient in the imeglimin + α-GI group (gastritis), 2 patients in the imeglimin + TZD group (nausea and vomiting in 1 patient each), 4 patients in the imeglimin + DPP-4 inhibitor group (nausea, decreased appetite, hyperglycaemia, and erectile dysfunction in 1 patient each), and 4 patients in the imeglimin + GLP-1 receptor agonist group (nausea, abdominal pain upper, dyspepsia, and decreased appetite in 1 patient each) were assessed as adverse drug reactions.

The incidences of hypoglycemia were 3.7% (5 of 134 patients) in the imeglimin monotherapy group, 16.5% (21 of 127 patients) in the imeglimin + SU group, 14.1% (9 of 64 patients) in the imeglimin + glinide group, 9.4% (6 of 64 patients) in the imeglimin + BG group, 3.1% (2 of 64 patients) in the imeglimin + α-GI group, 3.1% (2 of 65 patients) in the imeglimin + TZD group, 7.9% (5 of 63 patients) in the imeglimin + DPP-4 inhibitor group, 6.3% (4 of 63 patients) in the imeglimin + SGLT2 inhibitor group, and 2.9% (2 of 70 patients) in the imeglimin + GLP-1 receptor agonist group, with no cases assessed as being severe.[33)]
No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.4 Japanese phase III imeglimin + insulin combination therapy study (CTD 5.3.5.1.03: Study 020, February 2018 to September 2019)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted in Japanese patients with type 2 diabetes mellitus who had inadequate glycemic control by insulin therapy alone or in combination with

an oral hypoglycemic agent to evaluate the efficacy and safety of imeglimin administered in combination with an insulin product (target sample size, 212[37] [106 each in the placebo group and the imeglimin group]).

The main inclusion criteria included patients with type 2 diabetes mellitus aged≥20 years, a 12-week insulin therapy before randomization visit at the daily dose within ±10%, and eGFR of ≥60 mL/min/1.73 m^2 at screening, (a) ongoing insulin therapy (basal insulin or premixed/combination insulin of ≥8 to ≤40 IU/day once or twice daily), HbA1c of ≥7.5% to <11.0% at screening and the pre-randomization visit, or (b) ongoing insulin therapy (basal insulin or premixed/combination insulin of ≥8 to ≤40 IU/day once or twice daily) in combination with monotherapy with a stable dose of an existing oral hypoglycemic agent for 12 weeks prior to screening, HbA1c of ≥7.5% to ≤10.0% at screening and ≥7.5% to <11.0% at the pre-randomization visit.

The study consisted of the screening phase (2 or 9 weeks[38]), the single-blind placebo run-in phase (4 weeks), the double-blind phase (16 weeks), and the open-label phase (36 weeks).

Patients received oral imeglimin 1000 mg or placebo twice daily in the double-blind phase, and oral imeglimin 1000 mg twice daily in the open-label phase. In the double-blind phase, the dosage of the concomitant insulin was required to be within ±10% of the average daily dose of insulin administered during the 7 days prior to randomization. However, a ≥10% decrease in the dosage was allowed for safety reasons. If the daily dose of insulin exceeded the pre-randomization dosage by 10%, the patient was considered in need of rescue therapy, and treatment with the study drug was discontinued. In the open-label phase, dosage adjustment for the concomitant insulin was allowed.[39]

All 215 randomized patients (107 in the placebo group and 108 in the imeglimin mg group) were included in the safety analysis set. Of these, 214 who received ≥1 dose of the study drug and had HbA1c data at baseline and ≥1 post-baseline timepoints (106 in the placebo group and 108 in the imeglimin group) were included in the FAS. The FAS population was the primary efficacy analysis set. In the double-blind phase, 208 patients (101 in the placebo group and 107 in the imeglimin group) completed the study treatment, and 7 patients (6 in the placebo group and 1 patient in the imeglimin group) discontinued the study treatment. The reasons for discontinuation were adverse events in 2 patients (1 in the placebo group and 1 in the imeglimin group), poor glycemic control in 2 patients (both in the placebo group), and consent withdrawal in 3 patients (all in the placebo group). In the open-label phase, 197 patients (94 in the placebo/imeglimin group [consisting of patients who received placebo in the double-blind phase and imeglimin in the open-label phase] and 103 in the imeglimin/imeglimin group [consisting of patients who receive imeglimin both in the double-blind and open-label phases]) completed the study treatment and 11 patients (7 in the placebo/imeglimin group and 4 in the imeglimin/imeglimin group) discontinued the study treatment. The reasons for discontinuation were adverse

[37] With an anticipated between-group difference in the change in HbA1c of 0.5% and a standard deviation for each group of 1.0%, the study would require 85 patients for each group, to provide 90% statistical power at a 1-sided significance level of 2.5%. Allowing for approximately 20% drop-out, a sample size of 106 per group was set.

[38] Patients who were on insulin therapy alone at the time of screening underwent a 2-week screening. Patients who were on insulin therapy in combination with an oral hypoglycemic agent at the time of screening underwent a 9-week screening including a 1-week screening period and a 8-week washout period that followed the discontinuation of the oral hypoglycemic agent.

[39] No dosage adjustment of insulin was performed if SMBG was >70 to ≤100 mg/dL. The dose of insulin was allowed to be decreased by 2 units if SMBG was ≤70 mg/dL; increased by 2 units if SMBG was >100 to ≤140 mg/dL; and increased by 4 units if SMBG was >140 mg/dL.

events in 6 patients (4 in the placebo/imeglimin group and 2 in the imeglimin/imeglimin group), protocol deviations in 1 patient (the placebo/imeglimin group), poor glycemic control in 3 patients (1 in the placebo/imeglimin group and 2 in the imeglimin/imeglimin group), and consent withdrawal in 1 patient (in the placebo/imeglimin group).

Table 39 presents the efficacy results based on the change in HbA1c from baseline to Week 16, which was the primary endpoint. The results demonstrated the superiority of imeglimin over placebo.

Table 39. Changes in HbA1c from baseline to Week 16 (Study 020, FAS)

Treatment	Baseline	Week 16	Change from baseline[a)]	Difference from placebo[a)]	*P*-value[b)]
Placebo	8.82 ± 0.81 (n = 106)	8.72 ± 0.98 (n = 102)	-0.03 ± 0.07	-	-
Imeglimin	8.74 ± 0.72 (n = 108)	8.06 ± 0.97 (n = 107)	-0.63 ± 0.07	-0.60 [-0.80, -0.40]	<0.0001

%; Mean ± standard deviation, least squares mean ± standard error for the change from baseline, or least square mean [95% CI] for the difference from placebo; -, not applicable

a) Mixed model with repeated measures (MMRM) including treatment, timepoint, type of prior treatment, and treatment-by-timepoint interaction as fixed effects, and the baseline HbA1c as a covariate, and assuming an unstructured covariance matrix

b) 2-sided significance level of 5%

Figure 3 presents the changes in HbA1c from baseline to Week 52.

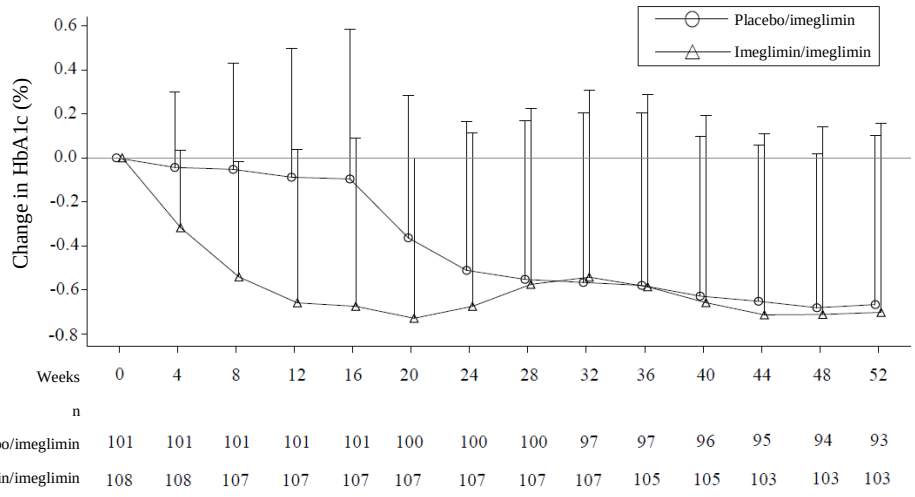

Figure 3. Changes in HbA1c from baseline to Week 52
(Study 020, Long-term Efficacy Population,[40)] mean + standard deviation)

Table 40 shows the results of main secondary endpoints (changes from baseline).

[40)] The "Long-term Efficacy Population" consisted of patients who were assigned to the imeglimin group and received ≥1 dose of the study drug during the double-blind phase or patients who were assigned to the placebo group in the double-blind phase and received ≥1 dose of imeglimin during the open-label phase.

Table 40. Results of main secondary endpoints (Study 020, Long-term Efficacy Population)

		Placebo	Imeglimin
HbA1c (%)	Week 16	-0.10 ± 0.68 (n = 101)	-0.68 ± 0.77 (n = 107)
	Week 52[b)]	-0.67 ± 0.77 (n = 93)	-0.70 ± 0.86 (n = 103)
Fasting blood glucose (mg/dL)	Week 16	0.66 ± 34.21 (n = 101)	-9.24 ± 35.58 (n = 107)
	Week 52[b)]	-3.62 ± 42.09 (n = 93)	-5.49 ± 46.58 (n = 103)
Proportion of patients who achieved HbA1c of <7.0% (%)[a)]	Week 16	1.0 (1 of 101 patients)	7.4 (8 of 108 patients)
	Week 52[b)]	1.0 (1 of 101 patients)	8.3 (9 of 108 patients)

Mean ± standard deviation

a) Proportion of patients who achieved HbA1c of <7.0% = number of patients who achieved HbA1c <7.0%/total number of patients.

b) The start of the double-blind phase in the placebo/imeglimin group and the imeglimin/imeglimin group were regarded as the baseline. Patients who had no HbA1c data at Week 16 or 52 were counted as patients who failed to achieve HbA1c of <7.0%.

Tables 41 and 42 show the incidences of adverse events reported with a ≥2% incidence in either treatment group, and the incidences of those assessed as adverse drug reactions in the double-blind phase (16 weeks) and the entire treatment phase (52 weeks), respectively.

Table 41. Incidences of adverse events reported with a ≥2% incidence in either treatment group and those assessed as adverse drug reactions (Study 020, 16-week double-blind treatment phase, safety analysis set)

Events	Placebo (N = 107)		Imeglimin (N = 108)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	47.7 (51)	12.1 (13)	52.8 (57)	14.8 (16)
Hypoglycaemia	15.9 (17)	6.5 (7)	21.3 (23)	12.0 (13)
Nasopharyngitis	7.5 (8)	0 (0)	14.8 (16)	0 (0)
Bronchitis	0 (0)	0 (0)	2.8 (3)	0 (0)
Constipation	0.9 (1)	0 (0)	2.8 (3)	1.9 (2)
Dizziness	2.8 (3)	1.9 (2)	0.9 (1)	0 (0)
Pyrexia	2.8 (3)	0 (0)	0.9 (1)	0 (0)
Hyperglycaemia	2.8 (3)	0.9 (1)	0 (0)	0 (0)

Incidence, % (n); MedDRA (ver. 20.1)

Table 42. Incidences of adverse events reported with a ≥2% incidence in either treatment group and those assessed as adverse drug reactions (Study 020, entire 52-week treatment phase, safety analysis set)

Events	Placebo/imeglimin[a)] (N = 101)		Imeglimin/imeglimin (N = 108)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	76.2 (77)	15.8 (16)	85.2 (92)	25.9 (28)
Hypoglycaemia	35.6 (36)	15.8 (16)	36.1 (39)	21.3 (23)
Nasopharyngitis	15.8 (16)	0 (0)	33.3 (36)	0 (0)
Back pain	1.0 (1)	0 (0)	5.6 (6)	0 (0)
Constipation	0 (0)	0 (0)	5.6 (6)	2.8 (3)
Influenza	4.0 (4)	0 (0)	4.6 (5)	0 (0)
Hypertension	2.0 (2)	0 (0)	4.6 (5)	0 (0)
Bronchitis	5.0 (5)	0 (0)	3.7 (4)	0 (0)
Muscle spasms	1.0 (1)	0 (0)	3.7 (4)	0 (0)
Seasonal allergy	1.0 (1)	0 (0)	3.7 (4)	0 (0)
Spinal osteoarthritis	0 (0)	0 (0)	3.7 (4)	0 (0)
Headache	3.0 (3)	0 (0)	2.8 (3)	0 (0)
Gastrooesophageal reflux disease	2.0 (2)	0 (0)	2.8 (3)	0 (0)
Nausea	2.0 (2)	0 (0)	2.8 (3)	0.9 (1)
Cystitis	1.0 (1)	0 (0)	2.8 (3)	0.9 (1)
Abdominal discomfort	1.0 (1)	0 (0)	2.8 (3)	0 (0)
Arthralgia	1.0 (1)	0 (0)	2.8 (3)	0 (0)
Contusion	0 (0)	0 (0)	2.8 (3)	0 (0)
Diarrhoea	2.0 (2)	1.0 (1)	1.9 (2)	0.9 (1)
Pyrexia	2.0 (2)	0 (0)	1.9 (2)	0 (0)
Gastroenteritis	4.0 (4)	0 (0)	0.9 (1)	0 (0)
Upper respiratory tract inflammation	3.0 (3)	0 (0)	0.9 (1)	0 (0)
Toothache	2.0 (2)	0 (0)	0.9 (1)	0 (0)

Table 42. Incidences of adverse events reported with a ≥2% incidence in either treatment group and those assessed as adverse drug reactions (Study 020, entire 52-week treatment phase, safety analysis set) (continued)

Events	Placebo/imeglimin[a)] (N = 101)		Imeglimin/imeglimin (N = 108)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
Diabetic retinopathy	2.0 (2)	0 (0)	0.9 (1)	0 (0)
Conjunctivitis	2.0 (2)	0 (0)	0 (0)	0 (0)
Chronic gastritis	2.0 (2)	0 (0)	0 (0)	0 (0)
Sputum increased	2.0 (2)	0 (0)	0 (0)	0 (0)
Papillary thyroid cancer	2.0 (2)	0 (0)	0 (0)	0 (0)

Incidence, % (n); MedDRA (ver. 20.1)
a) Events that developed after the start of treatment with imeglimin

In the double-blind phase, no deaths occurred. In the open-label phase, one death was reported in the placebo/imeglimin group (sudden death), for which a causal relationship to the study drug was ruled out. In the double-blind phase, serious adverse events were reported in 3 patients in the placebo group (dizziness, Guillain-Barre syndrome, and pneumonia in 1 patient each), and 1 patient in the imeglimin group (pulmonary embolism/venous thrombosis limb). Those reported in 2 patients in the placebo group (dizziness and Guillain-Barre syndrome) were assessed as adverse drug reactions. In the open-label phase, serious adverse events were reported in 6 patients in the placebo/imeglimin group (papillary thyroid cancer in 2 patients, and sudden death, hepatic function abnormal, pancreatic carcinoma, and clavicle fracture in 1 patient each) and 6 patients in the imeglimin/imeglimin group (sciatica, retinal detachment, epilepsy, erysipelas, pulmonary embolism/venous thrombosis limb, and coronary artery stenosis in 1 patient each). A causal relationship to the study drug was ruled out for all these events. In the double-blind phase, adverse events led to drug discontinuation in 4 patients in the placebo group (hyperglycaemia in 3 patients and Guillain-Barre syndrome in 1 patient) and 1 patient in the imeglimin group (nausea). Those reported in 2 patients in the placebo group (hyperglycaemia and Guillain-Barre syndrome in 1 patient each) and 1 patient in the imeglimin group (nausea) were assessed as adverse drug reactions. In the open-label phase, adverse events led to drug discontinuation in 3 patients in the placebo/imeglimin group (papillary thyroid cancer in 2 patients and pancreatic carcinoma in 1 patient) and 5 patients in the imeglimin/imeglimin group (hyperglycaemia in 2 patients, and uterine leiomyoma, nausea, and blood glucose abnormal in 1 patient each). The event reported in 1 patient in the imeglimin/imeglimin group (nausea) was assessed as an adverse drug reaction.

The incidences of hypoglycemia in the double-blind phase were 15.9% (17 of 107 patients) in the placebo group and 21.3% (23 of 108 patients) in the imeglimin group, while those in the open-label phase were 35.6% (36 of 101 patients) in the placebo/imeglimin group and 36.1% (39 of 108 patients) in the imeglimin/imeglimin group, with no cases assessed as severe.[33)]

No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.5 Foreign phase II study (CTD 5.3.4.2.01: Study 006, April 2012 to May 2013)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted overseas[41)] to evaluate the efficacy and safety of imeglimin in patients with type 2 diabetes mellitus (target sample size, 30 [15 each in the placebo group and the imeglimin 1500 mg group]).

The main inclusion criteria included patients with type 2 diabetes mellitus aged ≥18 to ≤75 years, having no prior treatment for diabetes mellitus or currently being on a monotherapy with an hypoglycemic agent (metformin, DPP-4 inhibitor, or α-GI), and HbA1c of ≥6.0% to ≤8.0% at screening.

The study consisted of the screening phase (1 to 21 days), the washout phase (14 days), and the treatment phase (7 days).

Patients received oral imeglimin 1500 mg or placebo twice daily.

All 33 randomized patients (15 in the placebo group and 18 in the imeglimin 1500 mg group) were included in the safety analysis set. Of these, 30 patients (15 each in the placebo group and the imeglimin 1500 mg group) who received ≥1 dose of the study drug and underwent a hyperglycemic clamp test were included in the intention-to-treat (ITT) population and used for the primary efficacy analysis. Three patients in the imeglimin 1500 mg group discontinued the study. The reasons for discontinuation were adverse events in 2 patients and consent withdrawal in 1 patient.

Table 43 presents the efficacy results based on insulin secretion in the hyperglycemic clamp test.

Table 43. Insulin secretion in the hyperglycemic clamp test (Study 006, ITT)

	Placebo (N = 15)	Imeglimin 1500 mg (N = 15)
$AUC_{0\text{-}45\ min}$	8227.5 ± 3878.8	14956.8 ± 9978.6
incremental $AUC_{0\text{-}45\ min}$	4522.8 ± 2576.8	9609.9 ± 8604.9
$AUC_{0\text{-}10\ min}$	977.8 ± 512.6	2359.0 ± 2345.5
$AUC_{10\text{-}45\ min}$	7249.7 ± 3399.3	12597.8 ± 7925.6

min·pmol/L; Mean ± standard deviation
$AUC_{0\text{-}45\ min}$: AUC of serum insulin for the 45 minutes after the start of glucose injection
incremental $AUC_{0\text{-}45\ min}$: baseline-corrected AUC of serum insulin during the 45 minutes after the start of glucose injection
$AUC_{0\text{-}10\ min}$: AUC of serum insulin over the 10 minutes after the start of glucose injection (the first-phase of insulin secretion)
$AUC_{10\text{-}45\ min}$: AUC of serum insulin from 10 minutes to 45 minutes after the start of glucose injection (the second-phase of insulin secretion)

The safety analysis revealed the incidences of adverse events and adverse drug reactions of 6.7% (1 of 15 patients) and 0% (0 of 15 patients), respectively, in the placebo group, and 38.9% (7 of 18 patients) and 22.2% (4 of 18 patients), respectively, in the imeglimin 1500 mg group. The adverse drug reactions reported in the imeglimin 1500 mg group were diarrhoea in 2 patients, gastroenteritis/vomiting in 1 patient, and epigastric discomfort in 1 patient. No deaths were reported. A serious adverse event was reported in 1 patient in the imeglimin 1500 mg group (gastroenteritis), for which a causal relationship to the study drug was ruled out. Adverse events led to drug discontinuation in 2 patients in the imeglimin 1500 mg group

41) France

(gastroenteritis/syncope, and atrial fibrillation in 1 patient each). A causal relationship to the study drug was ruled out for both cases.

There were no reports of hypoglycemia.

No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.6 Foreign phase II study (CTD 5.3.4.2.02: Study 009, August 2013 to October 2014)

A placebo-controlled, randomized, double-blind, parallel-group study was conducted overseas[42)] to evaluate the efficacy and safety of imeglimin in patients with type 2 diabetes mellitus (target sample size, 60 [30 each in the placebo group and the imeglimin 1500 mg group]).

The main inclusion criteria included patients with type 2 diabetes mellitus aged ≥18 to ≤75 years, receiving metformin alone at a stable dose of ≥1500 mg/day for ≥12 weeks prior to screening, and HbA1c of 6.8% to 9.0% at screening and 7.2% to 9.5% at the pre-randomization visit.

The study consisted of the screening phase (≤3 weeks), the single-blind placebo-washout phase (4 weeks), the double-blind phase (18 weeks), and the follow-up phase (1 week). Metformin therapy was discontinued during the single-blind placebo-washout phase.

Patients received multiple oral doses of imeglimin 1500 mg or placebo twice daily.

All 59 randomized patients (29 in the placebo group and 30 in the imeglimin 1500 mg group) were included in the safety analysis set. Of these, 57 patients (28 in the placebo group and 29 in the imeglimin 1500 mg group) who received ≥1 dose of the study drug and had primary and main secondary endpoint data at baseline and at ≥1 post-baseline timepoints were included in the ITT population, which was used for the primary efficacy analysis. A total of 16 patients (11 in the placebo group and 5 in the imeglimin 1500 mg group) discontinued the study. The reasons for discontinuation were consent withdrawal in 4 patients (all in the imeglimin 1500 mg group), protocol deviations in 1 patient (in the placebo group), adverse events in 1 patient (in the placebo group), and inadequate response (requiring rescue therapy due to hyperglycaemia-related adverse events) in 10 patients (9 in the placebo group and 1 in the imeglimin 1500 mg group).

Tables 44 and 45 present efficacy results based on change from baseline to Week 18 in the AUC ($AUC_{0\text{-}180min}$) of blood glucose during OGTT, and the change in HbA1c from baseline to Week 18.

[42)] Hungary, Latvia, and Romania

Table 44. Changes from baseline to Week 18 in blood glucose ($AUC_{0\text{-}180min}$) during OGTT (Study 009, ITT population)

Treatment	Baseline	Week 18	Change from baseline[a)]
Placebo	3024.8 ± 552.0 (n = 28)	2748.3 ± 618.0 (n = 27[b)])	-291.0 ± 88.0
Imeglimin 1500 mg	3181.0 ± 679.0 (n = 29)	2380.9 ± 352.7 (n = 29)	-720.7 ± 87.7

mmol/L·min; Mean ± standard deviation, or least squares mean ± standard error for the change from baseline
a) Analysis of covariance, including country and treatment as factors, and baseline AUC as a covariate (last observation carried forward [LOCF])
b) A patient who had no on-treatment AUC data was excluded from the analysis.

Table 45. Changes in HbA1c from baseline to Week 18 (Study 009, ITT)

Treatment	Baseline	Week 18	Change from baseline[a)]
Placebo (N = 28)	8.14 ± 0.61	8.30 ± 1.24	0.17 ± 0.17
Imeglimin 1500 mg (N = 29)	8.12 ± 0.56	7.68 ± 0.73	-0.46 ± 0.17

%, Mean ± standard deviation, or least squares mean ± standard error for the change from baseline
a) Analysis of covariance, including country and treatment as factors, and baseline HbA1c as a covariate (LOCF)

Table 46 shows the incidences of adverse events reported by ≥2 patients in either treatment group and those assessed as adverse drug reactions.

Table 46. Incidences of adverse events reported by ≥2 patients in either treatment group and those assessed as adverse drug reactions (Study 009, safety analysis set)

Events	Placebo (N = 29)		Imeglimin 1500 mg (N = 30)	
	Adverse events	Adverse drug reactions	Adverse events	Adverse drug reactions
All events	58.6 (17)	13.8 (4)	26.7 (8)	3.3 (1)
Hyperglycaemia	41.4 (12)	13.8 (4)	16.7 (5)	3.3 (1)
Left ventricular hypertrophy	0 (0)	0 (0)	6.7 (2)	0 (0)
Diabetic neuropathy	10.3 (3)	0 (0)	0 (0)	0 (0)

Incidence, % (n); MedDRA (ver 17.1)

No deaths were reported. Serious adverse events were reported in 1 patient in the imeglimin 1500 mg group (cerebrovascular accident/hypertension/Meigs' syndrome), for which a causal relationship to the study drug was ruled out. Adverse events led to drug discontinuation in 10 patients in the placebo group (hyperglycaemia in 10 patients) and 1 patient in the imeglimin 1500 mg group (hyperglycaemia). Those reported in 4 patients in the placebo group (hyperglycaemia in 4 patients) and 1 patient in the imeglimin 1500 mg group (hyperglycaemia) were assessed as adverse drug reactions.

There were no reports of hypoglycemia.

No clinically relevant changes in clinical laboratory tests, vital signs, or 12-lead electrocardiography were reported.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy of imeglimin as a monotherapy

The applicant's explanation:

The changes in HbA1c from baseline to Week 24 in the imeglimin groups of the phase II monotherapy study

(Study 014) are shown in Table 31. A significant decrease in HbA1c was seen in all imeglimin-treated groups as compared with the placebo group. The decrease in the 1000 mg group was greater than that in the 500 mg group and comparable to that in the 1500 mg group. In addition, the results of the phase III monotherapy study (Study 018) demonstrated the superiority of imeglimin 1000 mg over placebo in the decrease in HbA1c from baseline to Week 24 as shown in Table 34. Further, the decreased HbA1c was sustained up to Week 52 in the imeglimin monotherapy group of the long-term monotherapy and combination therapy study (Study 019) (Figure 1).

Accordingly, the efficacy of imeglimin 1000 mg alone administered twice daily has been demonstrated.

PMDA's view:
Based on the following study results reviewed, etc., the efficacy of imeglimin monotherapy for type 2 diabetes mellitus has been demonstrated.

- The results from the phase II and III monotherapy studies (Studies 014 and 018, respectively) demonstrated the superiority of imeglimin 1000 mg over placebo in change from baseline in HbA1c to Week 24, which was the primary endpoint in both studies.
- The efficacy of imeglimin was sustained over 52 weeks in the imeglimin monotherapy group of the long-term monotherapy and combination therapy study (Study 019), demonstrating the long-term efficacy of imeglimin monotherapy.

7.R.1.2 Efficacy of imeglimin as part of combination therapies

The applicant's explanation:
The efficacy of imeglimin in combination therapies was evaluated in the study on long-term monotherapy and combination therapy (Study 019). When imeglimin 1000 mg was administered in combination with SU, glinide, BG, α-GI, TZD, DPP-4 inhibitor, SGLT2 inhibitor, or GLP-1 receptor agonist, the decrease in HbA1c was sustained over 52 weeks by all combinations, with no large differences by type of concomitant hypoglycemic agent (Table 37, Figure 2).

The efficacy of imeglimin administered in combination with insulin was evaluated in the imeglimin + insulin combination therapy study (Study 020). The results demonstrated the superiority of imeglimin over placebo in the decrease in HbA1c from baseline to Week 16 (Table 39), and the decreased HbA1c was sustained over 52 weeks of administration (Table 40, Figure 3). Table 47 shows changes in HbA1c during the double-blind phase by type of insulin therapy (basal insulin vs. premixed/combination insulin). The decrease in HbA1c was observed regardless of the type of insulin product.

Table 47. Changes in HbA1c from baseline to Week 16 by type of concomitant insulin therapy (Study 020, FAS)

	Placebo	Imeglimin
Basal insulin	-0.04 ± 0.77 (n = 76)	-0.70 ± 0.83 (n = 73)
Premixed/combination insulin	-0.14 ± 0.47 (n = 29)	-0.63 ± 0.62 (n = 35)

%; Mean ± standard deviation, LOCF

The study results demonstrate the efficacy of imeglimin in these combination therapies.

PMDA asked the applicant to explain why the change in HbA1c in the imeglimin + GLP-1 receptor agonist group was smaller than that in the imeglimin monotherapy group or any other combination therapy groups in the long-term monotherapy and combination therapy study (Study 019).

The applicant's explanation:
Table 48 shows the HbA1c, fasting blood glucose, and duration of diabetes mellitus at baseline in Study 019. These suggest that patients enrolled in the imeglimin + GLP-1 receptor agonist group had more advanced diabetes mellitus than those in other combination therapy groups.

Table 48. Patient characteristics in each combination therapy group of Study 019 (safety analysis set)

		Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
HbA1c (%)		8.63 ± 0.90	8.48 ± 0.84	8.16 ± 0.61	8.37 ± 0.77	8.72 ± 0.94	8.23 ± 0.75	8.50 ± 0.75	8.66 ± 0.85
Fasting blood glucose (mg/dL)		185.1 ± 37.7	179.8 ± 33.5	174.9 ± 30.7	173.9 ± 31.3	171.6 ± 32.2	180.1 ± 33.0	165.6 ± 27.7	191.0 ± 39.7
Duration of diabetes (years)	Mean ± standard deviation	10.59 ± 6.59	7.90 ± 4.89	8.96 ± 6.27	7.47 ± 6.83	9.27 ± 6.60	7.96 ± 5.60	9.55 ± 5.65	10.73 ± 5.90
	Patients with a ≥10 years of duration[a)]	42.5 (54)	28.1 (18)	42.2 (27)	25.0 (16)	40.0 (26)	30.2 (19)	39.7 (25)	52.9 (37)

Mean ± standard deviation
a) % (n)

Although the change in HbA1c in the imeglimin + GLP-1 receptor agonist group was smaller than that in the other combination therapy groups, the HbA1c values at all post-baseline timepoints, including Week 52 (LOCF), were lower than the baseline HbA1c value in the imeglimin + GLP-1 receptor agonist group. This indicates that the efficacy of the combination therapy was maintained over the long term. In the imeglimin + GLP-1 receptor agonist group, the proportion of patients with a ≥0.5% decrease in HbA1c from baseline to Week 52 (LOCF) was 31.4%, while that of patients with a ≥1.0% decrease was 12.9%, and the proportion of patients who achieved HbA1c of <7.0% was 8.6%. Thus, a certain proportion of patients in the imeglimin + GLP receptor agonist group gained an evident improvement in blood glucose control. In view of these results, combination therapy with imeglimin and a GLP-1 receptor agonist is expected to improve blood glucose control.

PMDA's view:
The phase III long-term monotherapy and combination therapy study (Study 019) evaluated the combination of imeglimin with the following hypoglycemic agents: SU, glinide, BG, α-GI, TZD, DPP-4 inhibitor, SGLT2 inhibitor, and GLP-1 receptor agonist. In the study, HbA1c decreased regardless of the type of concomitant hypoglycemic agent and remained low over 52 weeks. The small decrease in HbA1c in the imeglimin + GLP-1 receptor agonist group, as compared with the other combination therapy groups, was likely to be primarily attributable to the larger number of patients with prolonged diabetes mellitus who would presumably have poor blood glucose control in the group. However, given a certain proportion of patients in the combination treatment group showing a clinically relevant improvement in blood glucose control, the combination therapy of imeglimin with a GLP-1 receptor agonist is expected to have efficacy as well. The imeglimin + insulin

combination therapy study (Study 020) showed that the combination of imeglimin with insulin was superior to insulin alone (i.e., placebo + insulin) in the decrease in HbA1c from baseline to Week 16 and that the decreased HbA1c was sustained over 52 weeks of administration. Based on these study results, PMDA concluded that the efficacy of imeglimin in these combination therapies is promising.

7.R.2 Safety

The applicant's explanation:

Table 49 shows the incidences of adverse events in the imeglimin monotherapy groups of the phase II monotherapy study (Study 014), the phase III monotherapy study (Study 018), and the long-term monotherapy and combination therapy study (Study 019). Tables 50 and 51 show the incidences of adverse events in the combination therapy groups of the long-term monotherapy and combination therapy study (Study 019) and the imeglimin + insulin combination therapy study (Study 020). In the phase II and III monotherapy studies (Studies 014 and 018, respectively), the incidences of adverse events and the type of common adverse events in the imeglimin 1000 mg groups did not differ substantially from those in the placebo groups. Table 52 shows the incidences of adverse events in patients receiving imeglimin monotherapy by time to onset (pooled data from Studies 014 and 018). The data showed no tendency for adverse events to develop at particular timepoints in the imeglimin group. In addition, the results from the imeglimin monotherapy group of the long-term monotherapy and combination therapy study (Study 019) showed no adverse events of which the incidence increased remarkably with prolonged treatment and identified no late-onset adverse events. The results of the long-term monotherapy and combination therapy study (Study 019) and the imeglimin + insulin combination therapy (Study 020) showed no substantial differences in the incidences of adverse events except for hypoglycemia, across combination therapies with existing hypoglycemic agents or insulin products. The results also identified no adverse events of which incidence remarkably increased with prolonged treatment or late-onset adverse events. Thus, no relevant safety concerns have been posed in association with the use of imeglimin in patients with type 2 diabetes mellitus, and no clear differences in the safety of imeglimin have been identified between use as a monotherapy and use in combination therapies.

Table 49. Incidences of adverse events in patients receiving imeglimin monotherapy
(Studies 014, 018, and 019; safety analysis sets)

		Study 014				Study 018		Study 019
		Placebo (N = 75)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 74)	Imeglimin 1500 mg (N = 75)	Placebo (N = 107)	Imeglimin 1000 mg (N = 106)	Imeglimin 1000 mg (N = 134)
All adverse events		68.0 (51)	68.0 (51)	62.2 (46)	73.3 (55)	44.9 (48)	44.3 (47)	73.1 (98)
All adverse drug reactions		8.0 (6)	5.3 (4)	5.4 (4)	24.0 (18)	6.5 (7)	4.7 (5)	9.7 (13)
Deaths		0 (0)	0 (0)	0 (0)	1.3 (1)	0 (0)	0 (0)	0.7 (1)
Serious adverse events		1.3 (1)	0 (0)	5.4 (4)	1.3 (1)	0.9 (1)	3.8 (4)	3.0 (4)
Adverse events leading to drug discontinuation		10.7 (8)	2.7 (2)	4.1 (3)	6.7 (5)	5.6 (6)	2.8 (3)	3 (2.2)
Severity	Mild	65.3 (49)	68.0 (51)	59.5 (44)	69.3 (52)	43.0 (46)	41.5 (44)	70.9 (95)
	Moderate	8.0 (6)	4.0 (3)	5.4 (4)	12.0 (9)	3.7 (4)	4.7 (5)	6.7 (9)
	Severe	0 (0)	0 (0)	5.4 (4)	1.3 (1)	0.9 (1)	1.9 (2)	1.5 (2)

Incidence, % (n)

Table 50. Incidences of adverse events in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

		Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
All adverse events		80.3 (102)	84.4 (54)	75.0 (48)	51.6 (33)	76.9 (50)	79.4 (50)	76.2 (48)	80.0 (56)
All adverse drug reactions		21.3 (27)	15.6 (10)	37.5 (24)	9.4 (6)	9.2 (6)	22.2 (14)	11.1 (7)	11.4 (8)
Deaths		0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Serious adverse events		8.7 (11)	1.6 (1)	6.3 (4)	6.3 (4)	6.2 (4)	4.8 (3)	6.3 (4)	7.1 (5)
Adverse events leading to drug discontinuation		7.1 (9)	1.6 (1)	10.9 (7)	3.1 (2)	6.2 (4)	7.9 (5)	1.6 (1)	21.4 (15)
Severity	Mild	78.7 (100)	82.8 (53)	70.3 (45)	50.0 (32)	73.8 (48)	79.4 (50)	74.6 (47)	78.6 (55)
	Moderate	11.8 (15)	7.8 (5)	6.3 (4)	6.3 (4)	18.5 (12)	12.7 (8)	6.3 (4)	5.7 (4)
	Severe	3.9 (5)	0 (0)	6.3 (4)	1.6 (1)	1.5 (1)	1.6 (1)	1.6 (1)	2.9 (2)

Incidence, % (n)

Table 51. Incidences of adverse events in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set)

		Double-blind phase (16 weeks)		Entire treatment phase (52 weeks)	
		Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[a)] (N = 101)	Imeglimin/imeglimin (N = 108)
All adverse events		47.7 (51)	52.8 (57)	76.2 (77)	85.2 (92)
All adverse drug reactions		12.1 (13)	14.8 (16)	15.8 (16)	25.9 (28)
Deaths		0 (0)	0 (0)	1.0 (1)	0 (0)
Serious adverse events		2.8 (3)	0.9 (1)	5.9 (6)	5.6 (6)
Adverse events leading to drug discontinuation		3.7 (4)	0.9 (1)	3.0 (3)	4.6 (5)
Severity	Mild	43.9 (47)	50.0 (54)	75.2 (76)	84.3 (91)
	Moderate	3.7 (4)	5.6 (6)	5.9 (6)	10.2 (11)
	Severe	1.9 (2)	0 (0)	3.0 (3)	0.9 (1)

Incidence, % (n)

a) Events that developed after the start of treatment with imeglimin

Table 52. Incidences of adverse events in patients receiving imeglimin monotherapy by time to onset (Studies 014 and 018 combined, safety analysis set)

	Placebo	Imeglimin 500 mg	Imeglimin 1000 mg	Imeglimin 1500 mg
Weeks 1 to 4	13.7% (25/182)	16.0% (12/75)	13.9% (25/180)	32.0% (24/75)
Weeks 5 to 8	12.2% (22/181)	20.0% (15/75)	14.0% (25/179)	20.0% (14/70)
Weeks 9 to 12	16.9% (30/178)	18.9% (14/74)	11.9% (21/177)	24.6% (17/69)
Weeks 13 to 16	15.0% (26/173)	11.1% (8/72)	13.8% (24/174)	8.8% (6/68)
Weeks 17 to 20	11.9% (20/168)	19.4% (14/72)	12.9% (22/171)	27.9% (19/68)
Weeks 21 to 24	14.3% (24/168)	29.6% (21/71)	17.0% (29/171)	29.9% (20/67)

Incidence, % (No. of patients with the event/No. of patients evaluated)

PMDA's view:

The results of Studies 014 and 018, which evaluated imeglimin monotherapy, showed no substantial differences in the occurrence of adverse events between the imeglimin 1000 mg groups and the placebo group. The results of Studies 019 and 020, which evaluated imeglimin administered in combination therapies, showed no substantial differences across the combination therapies in the incidences of adverse events, except for hypoglycemia and gastrointestinal symptom-related events mentioned below. The studies also identified no particular safety concerns in association with the use of imeglimin in combination therapies. In Study 020, particularly among those receiving imeglimin in combination with insulin, those receiving premixed/combination insulin tended to present a higher incidence of hypoglycemia than those receiving basal insulin, but without substantial differences in the types of reported events by type of insulin product.

In addition, adverse events deserving special attention in the use of imeglimin were respectively evaluated as summarized below, with the action mechanisms of imeglimin and the clinical study results, etc. taken into account. Consequently, PMDA concluded that the safety of imeglimin is acceptable with appropriate caution given.

7.R.2.1 Hypoglycemia

The applicant's explanation:

Table 53 shows the incidences of hypoglycemia in the imeglimin monotherapy groups of the phase II monotherapy study (Study 014), the phase III monotherapy study (Study 018), and the long-term monotherapy and combination therapy study (Study 019). In all studies, most reported cases of SMBG-based hypoglycemia were asymptomatic,[43)] with no cases assessed as severe.[33)]

Table 53. Incidences of hypoglycemia in patients receiving imeglimin monotherapy (Studies 014, 018, and 019; safety analysis sets)

	Study 014				Study 018		Study 019
	Placebo (N = 75)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 74)	Imeglimin 1500 mg (N = 75)	Placebo (N = 107)	Imeglimin 1000 mg (N = 106)	Imeglimin 1000 mg (N = 134)
Any hypoglycemia[a)]	1.3 (1)	6.7 (5)	2.7 (2)	5.3 (4)	0.9 (1)	2.8 (3)	3.7 (5)
	0.157 [5]	0.150 [5]	0.063 [2]	0.222 [7]	0.043 [2]	0.148 [7]	0.062 [8]
Severe hypoglycemia[b)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Documented symptomatic hypoglycemia[c)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (1)	0 (0)
	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0.042 [2]	0 [0]
Asymptomatic hypoglycemia[d)]	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Asymptomatic hypoglycemia reported from SMBG[e)]	1.3 (1)	6.7 (5)	1.4 (1)	4.0 (3)	0.9 (1)	1.9 (2)	3.7 (5)
	0.157 [5]	0.150 [5]	0.032 [1]	0.190 [6]	0.043 [2]	0.106 [5]	0.062 [8]
Probable symptomatic hypoglycemia[f)]	0 (0)	0 (0)	1.4 (1)	1.3 (1)	0 (0)	0 (0)	0 (0)
	0 [0]	0 [0]	0.032 [1]	0.032 [1]	0 [0]	0 [0]	0 [0]

Upper row, incidence, % (No. of patients with the event); lower row, No. of events per unit time (events/patient-year) [No. of events]
a) Adverse events coded to the preferred term (PT) "hypoglycaemia"
b) Hypoglycemia requiring third-party assistance for the intake of carbohydrates or glucagon administration, or other procedures
c) Symptomatic, with a blood glucose concentration of <70 mg/dL
d) Asymptomatic, with a laboratory-documented blood glucose concentration of <70 mg/dL
e) Asymptomatic, with SMBG of <70 mg/dL
f) Symptomatic, with no blood glucose concentration data

Tables 54 and 55 show the incidences of hypoglycemia by concomitant therapy in the long-term monotherapy and combination therapy study (Study 019) and the insulin-combination therapy study (Study 020). In Study 019, the incidence of hypoglycemia was higher in the imeglimin + SU group and the imeglimin + glinide group than in other combination therapy groups. However, all reported cases of hypoglycemia in both groups were mild in severity, and most of the events were SMBG-based asymptomatic hypoglycemia. In the double-blind phase of Study 020, the incidence of hypoglycemia tended to be higher in the imeglimin group than in the placebo group. However, all reported cases of hypoglycemia in the imeglimin group were mild in severity, and most cases were SMBG-based asymptomatic hypoglycemia. Some patients in the imeglimin group of Study 020 reported hypoglycemia repeatedly. Some patients in the imeglimin group reported hypoglycemia repeatedly also in the placebo run-in phase, suggesting an imbalance in patient characteristics between the placebo group and the imeglimin group. Concomitant insulin products were required to be administered at a

[43)] Asymptomatic, with an SMBG of <70 mg/dL

fixed dose (within the range of ± <10% of the baseline daily dose) throughout the double-blind phase. Thus the dose of insulin could not be changed even if blood glucose concentration was lowered by the imeglimin combination therapy, consequently causing the same patient to report multiple episodes of hypoglycemia. The incidences of hypoglycemia by type of concomitant insulin in the placebo group during the double-blind phase were 14.1% (11 of 78 patients) in patients receiving basal insulin and 20.7 % (6 of 29 patients) in patients receiving premixed/combination insulin, while those in the imeglimin group were 13.7% (10 of 73 patients) and 37.1% (13 of 35 patients), respectively. Thus, hypoglycemia tended to occur more frequently in patients receiving premixed/combination insulin than in those receiving basal insulin, particularly in the imeglimin group. Basal insulin is thought to be associated with a low risk of hypoglycemia as compared to premixed/combination insulin (*Diabetes Technol Ther.* 2011;13 Suppl 1:S85-92). This might have affected the results of the insulin-combination therapy study.

Table 54. Incidences of hypoglycemia in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
Any hypoglycemia[a)]	16.5 (21)	14.1 (9)	9.4 (6)	3.1 (2)	3.1 (2)	7.9 (5)	6.3 (4)	2.9 (2)
	0.546 [64]	0.695 [42]	0.138 [8]	0.048 [3]	0.032 [2]	0.139 [8]	0.065 [4]	0.034 [2]
Severe hypoglycemia[b)]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Documented symptomatic hypoglycemia[c)]	3.9 (5)	3.1 (2)	3.1 (2)	0 (0)	0 (0)	1.6 (1)	0 (0)	0 (0)
	0.068 [8]	0.116 [7]	0.052 [3]	0 [0]	0 [0]	0.017 [1]	0 [0]	0 [0]
Asymptomatic hypoglycemia[d)]	0.8 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	0.034 [4]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]
Asymptomatic hypoglycemia reported from SMBG[e)]	13.4 (17)	12.5 (8)	6.3 (4)	3.1 (2)	3.1 (2)	7.9 (5)	4.8 (3)	2.9 (2)
	0.384 [45]	0.579 [35]	0.086 [5]	0.048 [3]	0.032 [2]	0.122 [7]	0.048 [3]	0.034 [2]
Probable symptomatic hypoglycemia[f)]	3.1 (4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1.6 (1)	0 (0)
	0.060 [7]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0.016 [1]	0 [0]

Upper row, incidence, % (No. of patients with the event); lower row, No. of events per unit time (events/patient-year) [No. of events]
a) to f), same as footnotes a) to f) in Table 53

Table 55. Incidences of hypoglycemia in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set)

	Double-blind phase (16 weeks)		Entire treatment phase (52 weeks)	
	Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[h)] (N = 101)	Imeglimin/imeglimin (N = 108)
Any hypoglycemia[a)]	15.9 (17)	21.3 (23)	35.6 (36)	36.1 (39)
	0.782 [25]	2.883 [95]	2.399 [161]	3.589 [379]
Severe hypoglycemia[b)]	0 (0)	0 [0]	0 [0]	0 [0]
	0 [0]	0 [0]	0 [0]	0 [0]
Documented symptomatic hypoglycemia[c)]	4.7 (5)	7.4 (8)	19.8 (20)	20.4 (22)
	0.219 [7]	0.637 [21]	0.551 [37]	1.288 [136]
Asymptomatic hypoglycemia[d)]	2.8 (3)	1.9 (2)	3.0 (3)	3.7 (4)
	0.125 [4]	0.061 [2]	0.075 [5]	0.066 [7]
Asymptomatic hypoglycemia reported from SMBG[e)]	5.6 (6)	15.7 (17)	19.8 (20)	27.8 (30)
	0.344 [11]	2.094 [69]	1.758 [118]	2.140 [226]
Probable symptomatic hypoglycemia[f)]	1.9 (2)	0.9 (1)	0 (0)	3.7 (4)
	0.063 [2]	0.030 [1]	0 [0]	0.057 [6]
Symptomatic hypoglycemia with a blood glucose of ≥70 mg/dL[g)]	0.9 (1)	1.9 (2)	1.0 (1)	2.8 (3)
	0.031 [1]	0.061 [2]	0.015 [1]	0.038 [4]

Upper row, incidence, % (No. of patients with the event); lower row, No. of events per unit time (events/patient-year) [No. of events]
a) to f), same as footnotes a) to f) in Table 53
g) Symptomatic, and diagnosed as hypoglycemia, despite a blood glucose concentration of ≥70 mg/dL
h) Events that developed after the start of treatment with imeglimin

Table 56 shows the incidences of hypoglycemia in patients receiving imeglimin monotherapy (Studies 014 and 018 combined) by time to onset. Hypoglycemia did not tend to occur frequently at specific times in the imeglimin group. Also in Studies 019 and 020, hypoglycemia did not tend to occur frequently at specific times.

Table 56. Incidences of hypoglycemia in patients receiving imeglimin monotherapy by time to onset (Studies 014 and 018 combined, safety analysis set)

	Placebo	Imeglimin 500 mg	Imeglimin 1000 mg	Imeglimin 1500 mg
Weeks 1 to 4	1.1% (2/182)	1.3% (1/75)	2.2% (4/180)	1.3% (1/75)
	0.038 [3]	0.030 [1]	0.051 [4]	0.032 [1]
Weeks 5 to 8	0.6% (1/181)	2.7% (2/75)	0.6% (1/179)	1.4% (1/70)
	0.026 [2]	0.060 [2]	0.013 [1]	0.032 [1]
Weeks 9 to 12	0.6% (1/178)	0% (0/74)	0% (0/177)	2.9% (2/69)
	0.013 [1]	0 [0]	0 [0]	0.096 [3]
Weeks 13 to 16	0.6% (1/173)	0% (0/72)	1.1% (2/174)	1.5% (1/68)
	0.013 [1]	0 [0]	0.026 [2]	0.032 [1]
Weeks 17 to 20	0% (0/168)	1.4% (1/72)	0.6% (1/171)	1.5% (1/68)
	0 [0]	0.030 [1]	0.013 [1]	0.032 [1]
Weeks 21 to 24	0% (0/168)	1.4% (1/71)	0.6% (1/171)	0% (0/67)
	0 [0]	0.031 [1]	0.013 [1]	0 [0]

Upper row: incidence, % (No. of patients with the event/No. of patients evaluated); lower row: No. of events per unit time (events/patient-year) [No. of events]

These clinical study results indicated that the risk of hypoglycemia associated with imeglimin monotherapy does not largely differ from placebo or increase with prolonged treatment. On the other hand, the results revealed a higher incidence of hypoglycemia and more reported cases of hypoglycemia in combination therapies of imeglimin with SUs glinide, or insulin than other combination therapies. Accordingly, patients should be monitored for hypoglycemia in the use of imeglimin in combination with medications which may increase the risk of hypoglycemia, such as SU, glinide, and insulin products, and the doses of these concomitant medications need to be adjusted as necessary. This cautionary advice will be provided. The risk of hypoglycemia is considered low in the use of imeglimin in combination with a hypoglycemic drug other than the above-mentioned medications. Nonetheless, these drugs may also have a risk to enhance blood glucose-lowering effect of imeglimin as with similar drugs. Thus, caution should be advised against the onset of hypoglycemia.

PMDA's view:

In the phase II and III monotherapy studies (Studies 014 and 018, respectively), imeglimin monotherapy showed no tendency to increase the incidence of hypoglycemia in a dose-dependent manner or no tendency toward significantly increasing incidence even as compared with placebo. In the long-term monotherapy and combination therapy study (Study 019) as well as in the insulin-combination study (Study 020), the incidence of hypoglycemia in patients receiving imeglimin in combination with SU or glinide tended to be higher than that in patients receiving imeglimin in combination with other oral hypoglycemic agents or GLP-1 receptor agonists. Although in a comparison of different studies, the incidence of hypoglycemia in patients receiving imeglimin in combination with insulin in Study 020 tended to be higher than that in patients receiving imeglimin in combination with other oral hypoglycemic agents or GLP-1 receptor agonists in Study 019. In addition, given that no severe hypoglycemia was reported in any of these studies, etc., the risk of hypoglycemia associated with the use of imeglimin monotherapy or in combination therapies is considered acceptable. However, the applicant should give appropriate cautionary advice via the package insert on the risk of

hypoglycemia associated with imeglimin used particularly in combination with insulin, SU, or glinide, and continue to closely monitor for hypoglycemia-related events in the use of imeglimin in the post-marketing setting.

7.R.2.2 Gastrointestinal symptoms

The applicant's explanation:

Table 57 shows the incidences of gastrointestinal symptoms[44)] in patients receiving imeglimin 1500 mg monotherapy. Gastrointestinal symptoms were reported more frequently in the 1500 mg group than in other dose groups. Common gastrointestinal symptoms were diarrhea, abdominal discomfort, vomiting, nausea, and abdominal pain upper. The incidences of all these events in the 500 mg or 1000 mg group were similar to those in the placebo group, but lower than those in the 1500 mg group (Table 33). All reported cases of gastrointestinal symptoms were mild or moderate in severity. A serious gastrointestinal symptom was reported in 1 patient in the 1000 mg group of Study 018 (ileus). Gastrointestinal symptoms led to drug discontinuation in 1 patient in the 1000 mg group of Study 018 (diarrhoea/vomiting) and 3 patients in the 1500 mg group of Study 014 (vomiting in 2 patients and stomatitis in 1 patient).

Table 57. Incidences of gastrointestinal symptoms in patients receiving imeglimin monotherapy (Studies 014, 018, and 019; safety analysis sets)

	Study 014				Study 018		Study 019
	Placebo (N = 75)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 74)	Imeglimin 1500 mg (N = 75)	Placebo (N = 107)	Imeglimin 1000 mg (N = 106)	Imeglimin 1000 mg (N = 134)
All gastrointestinal symptoms	14.7 (11)	14.7 (11)	18.9 (14)	32.0 (24)	8.4 (9)	11.3 (12)	22.4 (30)
Serious gastrointestinal symptoms	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.9 (1)	0 (0)
Gastrointestinal symptoms leading to drug discontinuation	0 (0)	0 (0)	0 (0)	4.0 (3)	0 (0)	0.9 (1)	0 (0)

Incidence, % (n)

Table 58 shows the incidences of gastrointestinal symptoms in the long-term monotherapy and combination therapy study (Study 019). The incidences of gastrointestinal symptoms were similar across the combination therapy groups, except for the imeglimin + BG group, in which the incidence (40.6% [26 of 64 patients]) was higher than in any of the other combination therapy groups. Table 38 shows common gastrointestinal symptoms reported in the combination therapy groups. Most gastrointestinal symptoms were mild or moderate in severity, except for a severe case reported by 1 patient in the imeglimin + BG group (nausea). Serious gastrointestinal symptoms were reported in 1 patient in the imeglimin + SU group (lower gastrointestinal haemorrhage), 1 patient in the imeglimin + BG group (large intestine polyp), 1 patient in the imeglimin + TZD group (enterovesical fistula), 1 patient in the imeglimin + DPP-4 inhibitor group (large intestine polyp), and 1 patient in the imeglimin + SGLT2 inhibitor group (large intestine polyp). Gastrointestinal symptoms led to drug discontinuation in 5 patients in the imeglimin + BG group (nausea, decreased appetite, abdominal pain upper, vomiting, and diarrhoea in 1 patient each), 1 patient in the imeglimin + α-GI group (gastritis), 3 patients in the imeglimin + TZD group (vomiting, nausea, and enterovesical fistula in 1 patient each), 2 patients in the imeglimin + DPP-4 inhibitor group (nausea and decreased appetite in 1 patient each), and 4 patients in the

[44)] Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

imeglimin + GLP-1 receptor agonist group (decreased appetite, nausea, abdominal pain upper, and dyspepsia in 1 patient each).

Table 59 shows the incidences of gastrointestinal symptoms in the insulin-combination therapy study (Study 020). Common gastrointestinal symptoms are presented in Tables 41 and 42, and they were all mild or moderate in severity. No serious gastrointestinal symptoms were reported. Only 1 gastrointestinal symptom led to drug discontinuation in the 1000 mg group during the double-blind phase (nausea).

Table 58. Incidences of gastrointestinal symptoms in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
All gastrointestinal symptoms	22.0 (28)	18.8 (12)	40.6 (26)	7.8 (5)	15.4 (10)	33.3 (21)	23.8 (15)	21.4 (15)
Serious gastrointestinal symptoms	0.8 (1)	0 (0)	1.6 (1)	0 (0)	1.5 (1)	1.6 (1)	1.6 (1)	0 (0)
Gastrointestinal symptoms leading to drug discontinuation	0 (0)	0 (0)	7.8 (5)	1.6 (1)	4.9 (3)	3.2 (2)	0 (0)	5.7 (4)

Incidence, % (n)

Table 59. Incidences of gastrointestinal symptoms in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set)

	Double-blind phase (16 weeks)		Entire treatment phase (52 weeks)	
	Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[a)] (N = 101)	Imeglimin/imeglimin (N = 108)
All gastrointestinal symptoms	6.5 (7)	9.3 (10)	9.9 (10)	18.5 (20)
Serious gastrointestinal symptoms	0 (0)	0 (0)	0 (0)	0 (0)
Gastrointestinal symptoms leading to drug discontinuation	0 (0)	0.9 (1)	0 (0)	0.9 (1)

Incidence, % (n)

a) Events that developed after the start of treatment with imeglimin

Table 60 shows the incidences of gastrointestinal symptoms in patients receiving imeglimin monotherapy (pooled data from Studies 014 and 018) by time to onset. Meanwhile, the results from Studies 019 and 020 also indicated frequent occurrence of gastrointestinal symptoms at an early stage of treatment (over the 4 weeks after the start of treatment) in the 1500 mg group of Study 014 and the imeglimin + BG group[45)] of Study 019, whereas the incidence of gastrointestinal symptoms did not tend to increase in a particular period in the imeglimin monotherapy 500 and 1000 mg groups, or in other combination therapy groups.

Table 60. Incidences of gastrointestinal symptoms by time to onset in patients receiving imeglimin monotherapy (Studies 014 and 018 combined; safety analysis set)

	Placebo	Imeglimin 500 mg	Imeglimin 1000 mg	Imeglimin 1500 mg
Weeks 1 to 4	2.7% (5/182)	2.7% (2/75)	4.4% (8/180)	20.0% (15/75)
Weeks 5 to 8	1.1% (2/181)	2.7% (2/75)	4.5% (8/179)	5.7% (4/70)
Weeks 9 to 12	3.4% (6/178)	1.4% (1/74)	2.8% (5/177)	4.3% (3/69)
Weeks 13 to 16	1.7% (3/173)	1.4% (1/72)	1.7% (3/174)	0% (0/68)
Weeks 17 to 20	1.2% (2/168)	2.8% (2/72)	0.6% (1/171)	8.8% (6/68)
Weeks 21 to 24	2.4% (4/168)	4.2% (3/71)	2.3% (4/171)	1.5% (1/67)

Incidence, % (No. of patients with the event/No. of patients evaluated)

45) The incidences of gastrointestinal symptoms by time to onset were 25.0% (16 of 64 patients) from Weeks 1 to 4, 6.3% (4 of 64 patients) from Weeks 5 to 8, 12.5% (8 of 64 patients) from Weeks 9 to 16, 9.4% (6 of 64 patients) from Weeks 17 to 24, 6.3% (4 of 63 patients) from Weeks 25 to 32, 0% (0 of 60 patients) from Weeks 33 to 40, 6.7% (4 of 60 patients) from Weeks 41 to 48, and 1.7% (1 of 58 patients) from Weeks 48 to 52.

Based on the above results, the incidence of gastrointestinal symptoms in the monotherapy 1000 mg group was similar to that in the placebo group, with no trend toward a clear increase in incidence by prolonged treatment. The incidence of gastrointestinal symptoms tended to be higher in the imeglimin + BG group than in other combination therapy groups. One patient in the imeglimin + BG group reported a severe gastrointestinal symptom (nausea). However, most of the reported symptoms were mild or moderate in severity, and there were no events of clinically significant concerns. Accordingly, the risk of gastrointestinal symptoms associated with imeglimin monotherapy or combination therapies is unlikely to raise any particular concerns.

PMDA's view:

Most gastrointestinal events reported in the phase II and III monotherapy or combination therapy studies of imeglimin (Studies 014, 018, 019, and 020) were mild. Given this, the risk of gastrointestinal symptoms associated with imeglimin is acceptable. However, it should be noted that gastrointestinal symptoms were observed at a certain frequency in patients receiving imeglimin, the incidence of gastrointestinal symptoms increased in a dose-dependent manner in Study 014, and gastrointestinal symptoms were reported more frequently in the imeglimin + BG group than in other combination therapy groups. The applicant, therefore, should provide information on the occurrence of these gastrointestinal events in clinical studies along with cautionary advice against gastrointestinal symptoms that often develop in the early phase of combination therapy with imeglimin and BG. Furthermore, the incidences of gastrointestinal symptoms leading to drug discontinuation and overall gastrointestinal symptoms tended to be relatively high when imeglimin was used with a GLP-1 receptor agonist or DPP-4 inhibitor, as compared with combination use with any other hypoglycemic agents. Thus, the applicant should continue to collect information on the occurrence of gastrointestinal symptoms associated with imeglimin monotherapy or combination therapies through the post-marketing surveillance.

7.R.2.3 Lactic acidosis-related adverse events

The applicant's explanation:

No lactic acidosis-related events[46)] were reported in the monotherapy studies (Studies 014 and 018). Increased blood lactic acid was reported in 2 patients in the imeglimin + SU group of the long-term monotherapy and combination therapy study (Study 019) as well as in 1 patient during the open-label phase in the imeglimin/imeglimin group of the insulin-combination therapy study (Study 020). However, all these events were mild in severity.

Markedly abnormal blood lactate levels, i.e., blood lactate concentrations of >5 mmol/L, were found in 1 patient in the 1000 mg group and 1 patient in the 1500 mg group of the monotherapy studies (Studies 014 and 018). In the monotherapy group of the long-term monotherapy and combination therapy study (Study 019), markedly abnormal blood lactate levels were not reported in the monotherapy group but were reported in 1 patient each in the imeglimin + SU group and the imeglimin + SGLT2 inhibitor group. The markedly abnormal blood lactate level in the imeglimin + SU group was reported as an adverse event (blood lactic acid increased).

[46)] Adverse events coded to PTs included in the SMQ "lactic acidosis (broad)"

In the insulin-combination therapy study (Study 020), 1 patient in the imeglimin group had a markedly abnormal blood lactate level in the double-phase phase, and the patient also reported abnormal blood lactate in the open-label phase, which was the sole case in the phase. Of the 5 patients with markedly abnormal blood lactate levels, a patient in the imeglimin + SU group of Study 019 had a baseline blood lactate concentration of 0.9 mmol/L, which increased to 1.3 mmol/L at Week 24. When the increasing lactate concentration reached 5.5 mmol/L at the end of the treatment period (Week 52), it was reported as an adverse event (blood lactic acid increased) and assessed as an adverse drug reaction. This event resolved without being treated, and the blood lactate concentration lowered to 2.5 mmol/L a month after the completion of the study treatment. The remaining 4 patients had baseline blood lactate concentrations above the upper limit of the normal range, and the effect of imeglimin on their blood lactate values was thus considered insignificant.

Tables 61 to 63 show changes from baseline in lactate concentration in the monotherapy studies (pooled data from Studies 014 and 018), and Studies 019 and 020.

Table 61. Changes from baseline in lactate concentration in pooled data from Studies 014 and 018 (safety analysis set)

	Placebo	Imeglimin 500 mg	Imeglimin 1000 mg	Imeglimin 1500 mg
Baseline	1.26 ± 0.54 (n = 181)	1.21 ± 0.51 (n = 75)	1.27 ± 0.59 (n = 179)	1.28 ± 0.45 (n = 75)
Week 12	0.00 ± 0.48 (n = 168)	0.06 ± 0.50 (n = 72)	-0.05 ± 0.40 (n = 172)	0.01 ± 0.31 (n = 67)
Week 24	-0.01 ± 0.48 (n = 167)	0.13 ± 0.60 (n = 69)	-0.03 ± 0.47 (n = 169)	-0.04 ±0.47 (n = 67)

mmol/L; Mean ± standard deviation

Table 62. Changes from baseline in lactate concentration in Study 019 (safety analysis set)

	Imeglimin monotherapy	Imeglimin + SU	Imeglimin + glinide	Imeglimin + BG	Imeglimin + α-GI	Imeglimin + TZD	Imeglimin + DPP-4 inhibitor	Imeglimin + SGLT2 inhibitor	Imeglimin + GLP-1 receptor agonist
Baseline	1.22 ± 0.53 (n = 134)	1.32 ± 0.60 (n = 127)	1.23 ± 0.56 (n = 64)	1.33 ± 0.47 (n = 64)	1.15 ± 0.37 (n = 64)	1.27 ± 0.51 (n = 65)	1.15 ± 0.47 (n = 62)	1.43 ± 0.69 (n = 63)	1.31 ± 0.51 (n = 70)
Week 24	-0.02 ± 0.45 (n = 128)	0.00 ± 0.50 (n = 122)	-0.03 ± 0.42 (n = 62)	0.09 ± 0.49 (n = 61)	-0.02 ± 0.43 (n = 63)	0.00 ± 0.51 (n = 65)	-0.02 ± 0.34 (n = 59)	0.02 ± 0.66 (n = 62)	0.03 ± 0.41 (n = 69)
Week 52	0.00 ± 0.48 (n = 126)	0.12 ± 0.65 (n = 116)	-0.04 ± 0.50 (n = 59)	0.06 ± 0.51 (n = 58)	-0.05 ± 0.43 (n = 62)	-0.01 ± 0.51 (n = 65)	0.03 ± 0.38 (n = 60)	-0.05 ± 0.44 (n = 61)	0.01 ± 0.51 (n = 66)

mmol/L; Mean ± standard deviation

Table 63. Changes from baseline in lactate concentration in Study 020 (Long-term Safety Population)

	Placebo or placebo/imeglimin	Imeglimin or imeglimin/imeglimin
Baseline	1.15 ± 0.47 (n = 101)	1.22 ± 0.88 (n = 108)
Week 16	-0.01 ± 0.47 (n = 101)	0.07 ± 0.40 (n = 108)
Week 52	0.08 ± 0.43 (n = 98)	0.00 ± 0.42 (n = 107)

mmol/L; Mean ± standard deviation

In the monotherapy or combination therapy studies of imeglimin (Studies 014, 018, 019, and 020), there were no lactic acidosis reported as adverse events or no clinically significant increases in blood lactate concentration induced by imeglimin treatment. Although in limited number of patients, the results suggested no risk of lactic acidosis associated with imeglimin monotherapy or combination therapies with hypoglycemic agents or insulin products. At present, imeglimin therapy is thus unlikely to induce lactic acidosis.

PMDA's view:

BG is known to carry the risk of lactic acidosis. Because imeglimin has action mechanisms partially in common with BG, the risk of imeglimin-associated lactic acidosis was assessed. The results of studies on imeglimin monotherapy or combination therapies (Studies 014, 018, 019, and 020) revealed few cases of lactic acidosis-

related events and few number of patients experiencing a marked increase in blood lactate concentration. In addition, no clinical studies of imeglimin reported lactic acidosis, thus providing no clear evidence of a risk of lactic acidosis associated with imeglimin. However, the following facts deserve attention: the generally small number of cases with lactic acidosis precludes an adequate risk assessment of the event in clinical studies of that scale; in some study participants, blood lactate concentration kept increasing throughout the treatment with imeglimin and decreased after the completion of treatment; and the studies excluded patients who would likely be at high risk of lactic acidosis, such as those with renal impairment, hepatic impairment, and impaired cardiac function. The non-clinical pharmacology studies suggested that imeglimin and metformin affect lactate concentration differently. However, the studies also showed that imeglimin inhibits mitochondrial Complex I activity and suppresses glucose production as does metformin, which should also be taken into consideration. All these findings indicate the importance of continual collection of information relevant to the risk of imeglimin-associated lactic acidosis in the post-marketing setting. Through a use results survey, the occurrence of lactic acidosis, particularly in patients with a risk factor of lactic acidosis, including a history of lactic acidosis as well as hepatic impairment, susceptibility to hypoxic conditions, or dehydration, should be closely monitored, and available blood lactate concentration data should be collected. In addition, the applicant should observe over-time change in blood lactate concentrations in the post-marketing clinical study that is scheduled to be conducted in patients with renal impairment, who have increased exposure to imeglimin.

7.R.2.4 Hepatic dysfunction

The applicant's explanation:

The incidences of hepatic function-related adverse events[47)] in the monotherapy double-blind comparative studies (Studies 014 and 018 combined) were 2.2% (4 of 182 patients) in the placebo group, 1.3% (1 of 75 patients) in the imeglimin 500 mg group, 1.1% (2 of 180 patients) in the 1000 mg group, and 4.0% (3 of 75 patients) in the 1500 mg group, with no large differences between the placebo group and imeglimin groups. No hepatic function-related adverse events were reported in the imeglimin monotherapy group of the long-term monotherapy and combination therapy study (Study 019).

The incidences of hepatic function-related adverse events in the combination therapy groups of the long-term monotherapy and combination therapy study (Study 019) were 2.4% (3 of 127 patients) in the imeglimin + SU group, 1.6% (1 of 64 patients) in the imeglimin + glinide group, 0% (0 of 64 patients) in the imeglimin + BG group, 1.6% (1 of 64 patients) in the imeglimin + α-GI group, 4.6% (3 of 65 patients) in the imeglimin + TZD group, 1.6% (1 of 63 patients) in the imeglimin + DPP4-inhibitor group, 4.8% (3 of 63 patients) in the imeglimin + SGLT2 inhibitor group, and 2.9% (2 of 70 patients) in the imeglimin + GLP-1 receptor agonist group, with no large differences across the combination therapy groups. One patient in the imeglimin + α-GI group reported serious drug-induced liver injury, and concomitant tazobactam/piperacillin was suspected to be associated with the event, while its causal relationship to imeglimin was ruled out. One patient each in the imeglimin + TZD group and the imeglimin + SGLT2 inhibitor group reported non-serious drug-induced liver injury. The concomitant medications were suspected to be associated with the events, and a causal relationship

[47)] Adverse events coded to PTs included in the SMQ "hepatic disorders (broad)"

to imeglimin was ruled out. In the insulin-combination therapy study (Study 020), hepatic function-related adverse events were not reported in the placebo group or the imeglimin group during the double-blind phase, but reported in 2.4% (5 of 209 patients) of patients during the open-label phase (2 in the placebo/imeglimin group and 3 in the imeglimin/imeglimin group). The event reported in 1 patient in the placebo/imeglimin group (hepatic function abnormal) was assessed as a serious adverse event, for which a causal relationship to the study drug was ruled out.

No clinically relevant changes in liver function tests (bilirubin, ASL, ALT, ALP, and γ-GTP) were seen in the monotherapy double-blind comparative studies or the long-term monotherapy and combination therapy study. These results indicated a low risk of hepatic dysfunction associated with imeglimin monotherapy or combination therapies.

PMDA's view:
Patients receiving imeglimin monotherapy or combination therapies in the clinical studies (Studies 014, 018, 019, and 020) showed low incidences of hepatic dysfunction-related adverse events. Currently available information, including the results of comparisons with placebo, indicates that the effects of imeglimin on hepatic functions are unlikely to pose a clinically relevant problem.

7.R.2.5 Cardiovascular risk

The applicant's explanation:
No cardiovascular events[48)] were observed in the monotherapy double-blind comparative studies (Studies 014 and 018). In the long-term monotherapy and combination therapy study (Study 019), cardiovascular events were reported in 1 patient in the imeglimin + SU group (acute myocardial infarction), 1 patient in the imeglimin + BG group (myocardial infarction), 1 patient in the imeglimin + SGLT2 inhibitor group (lacunar infarction), and 1 patient in the imeglimin + GLP-1 receptor agonist group (cerebral infarction). All events were serious, and their causal relationship to the study drug was ruled out. In the insulin-combination therapy study (Study 020), no reported events were categorized as cardiovascular events.

Table 64 shows the incidences of cardiovascular-related events[49)] in the monotherapy double-blind comparative studies (pooled data from Studies 014 and 018), and the monotherapy group of the long-term monotherapy and combination therapy study (Study 019). In the monotherapy double-blind comparative studies, the incidence of cardiovascular-related events tended to be higher in the 1500 mg group than in the placebo, 500 mg, and 1000 mg groups, while the incidence in the 500 mg and 1000 mg groups was similar to that in the placebo group. Cardiovascular-related events reported by ≥2 patients in the pooled imeglimin group of the monotherapy double-blind comparative studies were hypertension (4 of 330 patients) and palpitations (2 of 330 patients). A severe cardiovascular-related event reported in 1 patient in the 1000 mg group (bradycardia) was assessed as

[48)] Adverse events reported by the investigators as cardiovascular events
[49] Adverse events coded to PTs included in the SMQ "central nervous system vascular disorders (broad)," the SMQ "ischaemic heart disease (broad)," the SMQ "cardiac arrhythmias (broad)," the SMQ "cardiac failure (broad)," the HLGT "arteriosclerosis, stenosis, vascular insufficiency and necrosis," the HLGT "embolism and thrombosis," the HLGT "aneurysms and artery dissections," the HLGT "vascular disorders NEC," the HLGT "vascular haemorrhagic disorders, the HLGT "vascular injuries," the HLGT "venous varices," or the HLGT "vascular hypertensive disorders," or the PT "cardiac aneurysm"

serious, but a causal relationship to imeglimin was ruled out for the event. In the monotherapy group of the long-term monotherapy and combination therapy study (Study 019), no cardiovascular-related events were reported by ≥2 patients. However, a severe event (subarachnoid haemorrhage) that was also assessed as serious, was reported in 1 patient, for which a causal relationship to imeglimin was ruled out.

Table 65 shows the incidences of cardiovascular-related events in the combination therapy groups of the long-term monotherapy and combination therapy study (Study 019). The incidences did not differ substantially across the combination therapy groups. Cardiovascular-related events reported by a total of ≥2 patients in the combination therapy groups were hypertension in 20 patients, carotid arteriosclerosis in 4 patients, atrial fibrillation in 3 patients, and angina unstable, coronary artery stenosis, palpitations, sinus bradycardia, loss of consciousness, and blood creatine phosphokinase increased in 2 patients each. Severe cardiovascular-related events reported were acute myocardial infarction and subdural haematoma in 1 patient each in the imeglimin + SU group, myocardial infarction in 1 patient in the imeglimin + BG group, cardiac failure in 1 patient in the imeglimin + SGLT2 inhibitor group, and coronary artery stenosis and cerebral infarction in 1 patient each in the imeglimin + GLP-1 receptor agonist group. Serious cardiovascular-related events reported were angina unstable, acute myocardial infarction, and subdural haematoma in 1 patient each in the imeglimin + SU group, myocardial infarction in 1 patient in the imeglimin + BG group, cardiac failure and lacunar infarction in 1 patient each in the imeglimin + SGLT2 inhibitor group, and coronary artery stenosis/cerebral infarction and coronary artery stenosis in 1 patient each in the imeglimin + GLP-1 receptor agonist group. A causal relationship to the study drug was ruled out for all events.

Table 66 shows the incidences of cardiovascular-related events reported in the double-blind phase of the insulin-combination therapy study (Study 020). No cardiovascular-related events were reported by ≥2 patients, and no severe events were reported. Cardiovascular-related events reported by ≥2 patients in the open-label phase (52 weeks) of the study were hypertension in 7 patients and blood creatine phosphokinase increased in 3 patients. One serious severe event (sudden death), for which a causal relationship to the study drug was ruled out, was also reported.

Table 64. Incidences of cardiovascular-related adverse events in patients receiving imeglimin monotherapy (Studies 014 and 018 combined, and Study 019, safety analysis sets)

Studies 014 and 018 combined				Study 019
Placebo (N = 182)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 180)	Imeglimin 1500 mg (N = 75)	Imeglimin 1000 mg (N = 134)
3.8 (7)	2.7 (2)	1.7 (3)	8.0 (6)	3.0 (4)

Incidence, % (n)

Table 65. Incidences of cardiovascular-related events in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
8.7 (11)	4.7 (3)	9.4 (6)	9.4 (6)	12.3 (8)	4.8 (3)	6.3 (4)	7.1 (5)

Incidence, % (n)

Table 66. Incidences of cardiovascular-related events in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set)

Double-blind phase (16 weeks)		Entire treatment phase (52 weeks)	
Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[a)] (N = 101)	Imeglimin/imeglimin (N = 108)
0.9 (1)	3.7 (4)	6.9 (7)	7.4 (8)

Incidence, % (n)
a) Events that developed after the start of treatment with imeglimin

The proportion of patients with each electrocardiographic parameter result beyond the normal range was assessed in the phase II and III monotherapy and combination therapy studies (Studies 014, 018, 019, and 020). The results showed no clear trend toward increasing abnormal electrocardiographic findings in patients receiving imeglimin. Among patients who had "normal" electrocardiographic results at baseline, only 0 or 1 patient in each treatment group was assessed as having "abnormal, clinically relevant" electrocardiographic findings at the end of treatment. Tables 67 to 69 show the changes in body weight, vital signs, and lipid parameters in the clinical studies. No clinically relevant changes were observed in any parameters.

Table 67. Changes in body weight, vital signs, and lipid parameters (Studies 014, 018, and 019; safety analysis sets or FAS)

	Study 014				Study 018		Study 019
	Placebo (N = 75)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 74)	Imeglimin 1500 mg (N = 75)	Placebo (N = 107)	Imeglimin 1000 mg (N = 106)	Imeglimin 1000 mg (N = 134)
Body weight (kg)[a)]	-0.74 ± 1.99	0.11 ± 2.05	-0.22 ± 1.38	-0.03 ± 1.97	-0.29 ± 1.40	-0.20 ± 1.67	-0.78 ± 2.45
Pulse rate (beats/minute)[a)]	0.6 ± 7.5	1.6 ± 8.2	0.4 ± 11.1	0.2 ± 8.5	0.4 ± 7.9	0.3 ± 8.1	1.2 ± 9.3
Systolic blood pressure (mmHg)[a)]	0.7 ± 11.6	2.5 ± 12.2	1.8 ± 14.9	-0.9 ± 13.3	2.5 ± 11.3	3.1 ± 11.0	-0.02 ± 11.0
Diastolic blood pressure (mmHg)[a)]	0.1 ± 6.6	0.6 ± 8.4	0.7 ± 10.0	-2.5 ± 9.0	1.6 ± 7.8	1.9 ± 7.6	-0.3 ± 7.0
TC (%)[b)]	3.35 ± 11.47 (n = 66)	6.21 ± 13.65 (n = 72)	4.88 ± 11.98 (n = 68)	0.22 ± 13.22 (n = 68)	-1.38 ± 12.60 (n = 103)	2.85 ± 11.77 (n = 105)	0.96 ± 11.90 (n = 132)
LDL-C (%)[b)]	1.21 ± 16.42 (n = 61)	8.28 ± 22.47 (n = 69)	5.20 ± 17.47 (n = 66)	2.79 ± 24.99 (n = 64)	-1.12 ± 18.07 (n =103)	7.21 ± 19.63 (n = 105)	1.58 ± 19.74 (n = 132)
HDL-C (%)[b)]	7.90 ± 15.49 (n = 66)	5.49 ± 14.52 (n = 72)	4.87 ± 15.56 (n = 68)	3.31 ± 13.61 (n = 68)	-0.49 ± 13.84 (n = 103)	-1.26 ± 13.65 (n = 105)	-2.68 ± 12.14 (n = 132)
TG (%)[b)]	10.68 ± 39.37 (n = 66)	7.30 ± 39.51 (n =72)	6.81 ± 35.49 (n = 68)	-0.71 ± 36.47 (n = 68)	2.56 ± 43.21 (n = 103)	6.69 ± 41.98 (n = 105)	12.26 ± 50.90 (n = 132)

a) Change from baseline (LOCF), mean ± standard deviation, (b) percent change from baseline (LOCF), mean ± standard deviation
TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides

Table 68. Changes in body weight, vital signs, and lipid parameters in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
Body weight (kg)[a)]	0.28 ± 2.08	-0.39 ± 4.03	-0.07 ± 1.96	-0.65 ± 3.18	0.79 ± 2.79	-0.07 ± 1.83	-0.10 ± 2.01	-0.30 ± 2.36
Pulse rate (beats/minute)[a)]	0.4 ± 7.7	0.3 ± 7.9	-1.0 ± 7.4	1.2 ± 10.3	1.3 ± 9.1	0.4 ± 6.5	-1.8 ± 7.5	0.3 ± 6.8
Systolic blood pressure (mmHg)[a)]	0.77 ± 11.43	1.42 ± 10.35	0.43 ± 10.37	1.75 ± 11.47	0.87 ± 11.50	1.14 ± 13.13	0.027 ± 11.55	-1.55 ± 12.12
Diastolic blood pressure (mmHg)[a)]	0.20 ± 7.37	0.76 ± 5.90	0.17 ± 6.68	0.49 ± 7.00	-0.32 ± 8.24	-0.20 ± 8.87	-0.063 ± 6.57	-1.78 ± 6.75
TC (%)[b)]	0.49 ± 12.88 (n = 122)	3.15 ± 11.59 (n = 62)	-3.47 ± 11.52 (n = 62)	0.25 ± 12.09 (n = 64)	-0.015 ± 11.79 (n = 63)	-1.53 ± 12.02 (n = 59)	0.70 ± 11.59 (n = 63)	2.49 ± 14.18 (n = 64)
LDL-C (%)[b)]	4.95 ± 20.15 (n = 122)	6.65 ± 16.43 (n = 62)	-1.57 ± 17.81 (n = 62)	1.66 ± 16.90 (n = 64)	-0.45 ± 18.10 (n = 63)	-0.006 ± 17.96 (n = 59)	5.36 ± 21.92 (n = 63)	6.90 ± 21.58 (n = 64)
HDL-C (%)[b)]	-0.86 ± 12.42 (n = 122)	3.35 ± 12.04 (n = 62)	-4.07 ± 12.58 (n = 62)	-1.95 ± 13.75 (n = 64)	-0.55 ± 12.55 (n = 63)	-0.91 ± 14.63 (n = 59)	-0.99 ± 13.41 (n = 63)	1.46 ± 12.83 (n = 64)
TG (%)[b)]	-0.46 ± 40.49 (n = 122)	-0.35 ± 38.47 (n = 62)	-3.59 ± 30.01 (n = 62)	21.76 ± 147.92 (n = 64)	2.53 ± 36.18 (n = 63)	-0.58 ± 29.93 (n = 59)	8.63 ± 47.78 (n = 63)	2.68 ± 40.61 (n = 64)

a) Change from baseline (LOCF), mean ± standard deviation, (b) percent change from baseline (LOCF), mean ± standard deviation
TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides

Table 69. Changes in body weight, vital signs, and lipid parameters in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set or FAS)

	Double-blind phase (16 weeks)		Open-label phase (52 weeks)	
	Placebo (N = 106)	Imeglimin (N = 108)	Placebo/imeglimin (N = 101)	Imeglimin/imeglimin (N = 108)
Body weight (kg)[a)]	-0.18 ± 1.48	0.48 ± 1.47	0.35 ± 2.09	0.66 ± 2.40
Pulse rate (beats/minute)[a)]	0.2 ± 8.9	-0.7 ± 7.4	0.5 ± 8.2	0.3 ± 7.6
Systolic blood pressure (mmHg)[a)]	-0.33 ± 10.20	2.74 ± 11.38	0.97 ± 11.77	1.17 ± 11.83
Diastolic blood pressure (mmHg)[a)]	0.32 ± 6.54	1.14 ± 8.03	1.46 ± 6.52	0.75 ± 7.86
TC (%)[b)]	3.14 ± 13.42 (n = 102)	4.33 ± 14.09 (n = 107)	4.12 ± 12.28 (n = 98)	3.37 ± 14.46 (n = 107)
LDL-C (%)[b)]	6.41 ± 22.90 (n = 102)	9.78 ± 23.51 (n = 107)	7.16 ± 20.99 (n = 98)	7.92 ± 23.21 (n = 107)
HDL-C (%)[b)]	2.32 ± 14.40 (n = 102)	0.40 ± 12.08 (n = 107)	-2.63 ± 11.55 (n = 98)	-0.51 ± 13.06 (n = 107)
TG (%)[b)]	3.32 ± 42.55 (n = 102)	4.03 ± 42.04 (n = 107)	19.61 ± 78.03 (n = 98)	9.84 ± 55.11 (n = 107)

a) Change from baseline (LOCF), mean ± standard deviation
b) Percent change from baseline (LOCF), mean ± standard deviation
TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; TG, triglycerides

Accordingly, the risk of cardiovascular events is considered low in monotherapy or combination therapies with imeglimin.

PMDA's view:
The available information indicates no tendency toward an increase in cardiovascular risk associated with imeglimin.

7.R.2.6 Association with tumor development

The applicant's explanation:
In the monotherapy or combination therapy studies of imeglimin (Studies 014, 018, 019, and 020), none of 289 patients receiving placebo reported tumor-related adverse events.[50)] A total of 23 of 1253 patients receiving imeglimin reported relevant events, but a causal relationship to imeglimin was ruled out for all events. The tumor-related adverse events reported in the monotherapy studies (pooled data from the Studies 014 and 018 combined, 330 patients in total) were bladder cancer, pancreatic carcinoma metastatic, prostate cancer, seborrhoeic keratosis, and solid pseudopapillary tumor of the pancreas in 1 patient each, those reported in the monotherapy and combination therapy study (Study 019) were benign neoplasm of spinal cord, cholangiocarcinoma, colon adenoma, colon cancer stage I, endometrial cancer stage III, hemangioma of liver, invasive ductal breast carcinoma, rectal cancer, skin papilloma, testis cancer, thyroid neoplasm, and uterine leiomyoma in 1 patient each, and those reported in the insulin-combination therapy study (Study 020) were lipoma in 1 patient during the double-blind phase (108 patients), and papillary thyroid cancer in 2 patients, and benign neoplasm of thyroid gland, intraductal papillary mucinous neoplasm, lipoma, pancreatic carcinoma, and uterine leiomyoma in 1 patient each during the open-label phase (209 patients). Thus, most of these events were reported by 1 patient, except for uterine leiomyoma and papillary thyroid cancer, which were reported by 2 patients.

[50)] Adverse events coded to PTs included in the SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)"

These study results suggest that a low risk of tumor development is associated with imeglimin therapy

PMDA's view:
The results of the clinical studies showed no particular tendency, with respect to the types of tumor-related events reported in patients receiving imeglimin. In addition, a causal relationship to imeglimin was ruled out for all events. Also, in view of the past history, progression, etc. of reported serious tumor-related events, no currently available data suggest an increase in the risk of tumor-related events in association with imeglimin therapy.

7.R.3 Clinical positioning

The applicant's explanation:
The main causes of type 2 diabetes mellitus are decreased insulin secretion and increased insulin resistance. Imeglimin has the ability to both increase insulin secretion and reduce insulin resistance. The mechanisms of these actions of imeglimin were evaluated in 2 foreign phase II studies; by hyperglycemic clamp test in Study 006 and by OGTT in Study 009. Study 006 investigated change in insulin secretion in patients with type 2 diabetes mellitus receiving imeglimin 1500 mg or placebo for 7 days by hyperglycemic clamp test. When glucose was infused so that blood glucose would be constantly maintained at a high concentration (360 mg/dL), the insulin secretion over 45 minutes after the start of glucose injection tended to be high in the imeglimin 1500 mg group as compared with the placebo group as shown in Table 43. Study 009, the effects of imeglimin on glucose tolerance in patients with type 2 diabetes mellitus who received imeglimin 1500 mg or placebo for 18 weeks by OGTT. The change (least squares mean) from baseline in the insulinogenic index, an indicator of insulin secretion, tended to improve in the 1500 mg group (2.55) as compared with the placebo group (0.76). These results suggested that imeglimin increases insulin secretion.

In Study 009, the ability of imeglimin to reduce insulin resistance was assessed through the Stumvoll index, an indicator of insulin resistance. The change (least squares mean) from baseline in the Stumvoll index improved in the imeglimin 1500 mg group (0.0182) as compared with the placebo group (0.0049). The change from baseline in the Matsuda index, another indicator of insulin resistance, tended to improve in the imeglimin 1500 mg group (1.54) as compared with the placebo group (-0.02). These results suggested that the reduction in insulin resistance imparted by imeglimin contributes to the improvement of glucose tolerance. Thus, imeglimin is expected to reduce blood glucose, regardless of the cause of type 2 diabetes mellitus.

The results of the Japanese phase II and III studies (Studies 014, 018, 019, and 020) showed that imeglimin administered alone or in combination therapies with existing hypoglycemic agents improves blood glucose control without requiring dose adjustment. Although elderly patients with type 2 diabetes mellitus are likely to be on concomitant medications for their other underlying diseases or complications, the possibility is low that imeglimin causes pharmacokinetic drug interactions with such medications. Thus the dose of imeglimin needs not be adjusted according to concomitant medications for other diseases. For patients with type 2 diabetes mellitus who have renal impairment, dose adjustment can control blood glucose.

Based on the above, imeglimin is expected to offer a new treatment option that would be beneficial for patients with type 2 diabetes mellitus in the early to advanced stages.

PMDA's view:
The efficacy of imeglimin monotherapy was demonstrated by its superiority over placebo in change from baseline in HbA1c shown in the Japanese phase III study (Study 018). Imeglimin has raised no major concerns in its efficacy in combination therapies [see Section "7.R.1 Efficacy"]. The safety of imeglimin is acceptable in view of the clinical study results [see Section "7.R.2 Safety"].

Because imeglimin and existing BGs share a common structural feature, differences and similarities between imeglimin and metformin, a BG, in their action mechanisms, etc. were reviewed. The applicant has claimed that imeglimin has the abilities to both increase insulin secretion and reduce insulin resistance. In terms of the insulinotropic effect of imeglimin, the results of the non-clinical pharmacology studies did not necessarily elucidate how imeglimin exerts its effect, but indicated the possibility that imeglimin is influential to insulin secretion. Further, the results from 2 foreign phase II studies in patients with type 2 diabetes mellitus, i.e., the results of the hyperglycemic clamp test in Study 006 and the OGTT in Study 009, showed that insulin secretion tended to increase by imeglimin treatment, also suggesting that imeglimin may have the ability to increase insulin secretion. In contrast, imeglimin has promising effect to improve insulin resistance based on the results of non-clinical pharmacology studies, in which imeglimin normalized liver mitochondrial functions, decreased hepatic glucose production, and improved glucose uptake in skeletal muscles, and based on the results of the foreign phase II study (Study 009). In terms of the differences between the 2 drugs, metformin is considered to suppress hepatic glucose production primarily through the inhibition of mitochondrial Complex I, which may be in common with imeglimin. However, metformin are known to have multiple actions and was not always chosen as a control drug in the non-clinical or clinical studies conducted. Given these, it is difficult at present to clearly determine differences and similarities between metformin and imeglimin in their action mechanisms or degree of effects.

Based on the above discussions, etc., imeglimin can be recognized as a novel oral hypoglycemic drug for type 2 diabetes mellitus. The results of Study 019 demonstrated promising efficacy of the combination therapy of imeglimin with metformin and indicated its acceptable safety. However, gastrointestinal symptoms, which were more frequently reported in the imeglimin + metformin group than in other combination therapy groups, warrant extra attention. Therefore, the package insert should provide cautionary advice against gastrointestinal symptoms occurring in the use of imeglimin in combination with metformin. Possible some common action mechanisms of these drugs should also be communicated.

7.R.4 Indication

PMDA's view:
The results of the clinical studies of imeglimin in patients with type 2 diabetes mellitus demonstrated the promising efficacy of imeglimin both in monotherapy and combination therapies [see Section "7.R.1 Efficacy"],

and indicated its acceptable safety [see Section "7.R.2 Safety"]. Based on these results, the proposed indication of "type 2 diabetes mellitus" is acceptable.

7.R.5 Dosage and administration

The applicant's explanation:

In the phase II study, in which Japanese patients with type 2 diabetes mellitus received oral imeglimin 500, 1000, or 1500 mg, or placebo twice daily for 24 weeks (Study 014), changes in HbA1c from baseline to Week 24 (MMRM-based least squares mean ± standard error) were 0.43 ± 0.09% in the placebo group, -0.09 ± 0.09% in the imeglimin 500 mg group, -0.51 ± 0.09% in the 1000 mg group, and -0.57 ± 0.09% in the 1500 mg group, indicating significant decreases in HbA1c in all the imeglimin groups as compared with the placebo group. However, the 1500 mg group showed a higher incidence of gastrointestinal disorder-related adverse drug reaction than in other groups, and therefore imeglimin was administered at 1000 mg twice daily in the phase III monotherapy study (Study 018), the long-term monotherapy and combination therapy study (Study 019), and the insulin-combination therapy study (Study 020). The results of all these studies demonstrated the promising efficacy and acceptable safety of imeglimin 1000 mg administered twice daily.

In these 4 main Japanese studies (Studies 014, 018, 019, and 020), imeglimin was orally administered twice daily in the morning and evening, preferably during or closely after breakfast and dinner. The food effect study in Japanese healthy adult men (Study DD401101) identified no clinically significant food effects on the C_{max} or AUC of imeglimin.

Based on the above results, the dosage regimen of imeglimin was proposed as "The usual adult dosage is 1000 mg of imeglimin administered orally twice daily in the morning and evening."

PMDA's view:

The phase II monotherapy study (Study 014) showed a significant decrease in HbA1c in all the imeglimin 500 mg, 1000 mg, and 1500 mg groups, as compared with the placebo group. However, the 1500 mg group showed a higher incidence of gastrointestinal symptoms than the 1000 mg group, despite no substantial difference in change from baseline in HbA1c between the dose groups. The proposed dosage regimen, "1000 mg twice daily in the morning and evening" is acceptable in view of the results of the phase III monotherapy study with imeglimin 1000 mg, which demonstrated the superiority of imeglimin over placebo in change in HbA1c (Study 018), and of Studies 019 and 020, which demonstrated the efficacy of imeglimin administered in combination therapies, as well as the acceptable safety of imeglimin demonstrated both in monotherapy and combination therapies. The phase II and III studies recommended imeglimin dosing during or closely after breakfast and dinner, in light of the fact that a fasting dose of imeglimin is expected to increase C_{max} as compared with a fed dose [see Section "6.R.1 Food effects"]. However, the extent of increase in C_{max} by a fasting dose is not significant. Accordingly, while the "Dosage and Administration" section needs not to specify the dosing timing relative to meals, the food effect on the pharmacokinetics of imeglimin should be communicated.

7.R.6 Special populations

7.R.6.1 Patients with renal impairment

The applicant's explanation:

Tables 70 to 72 show the incidences of adverse events in the phase II and III studies (Studies 014, 018, 019, and 020), by severity of renal impairment (baseline CKD 1, eGFR of ≥90 mL/min/1.73 m^2; baseline CKD 2, eGFR of ≥60 to <90 mL/min/1.73 m^2; baseline CKD 3a, eGFR of ≥45 to <60 mL/min/1.73 m^2). The incidences of adverse events did not substantially differ among the groups treated with imeglimin alone or in combination therapies regardless of the severity of renal impairment. During both the double-blind and open-label phases of the insulin-combination therapy study (Study 020), the number of events of hypoglycemia per unit time (events/patient-year) tended to be larger in patients with baseline CKD 2 than in those with baseline CKD 1 in the imeglimin group. However, all reported cases were mild in severity. The incidence of gastrointestinal symptoms tended to be higher in patients with CKD 3a than in those with CKD 1 or 2 in the imeglimin + BG group, all events were, however, mild in severity.

Table 70. Incidences of adverse events in patients receiving imeglimin monotherapy by severity of renal impairment (Studies 014 and 018 pooled, and Study 019; safety analysis sets)

	Severity of renal impairment	Studies 014 and 018 combined				Study 019
		Placebo (N = 182)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 180)	Imeglimin 1500 mg (N = 75)	Imeglimin 1000 mg (N = 134)
Number. of patients	CKD 1	16	9	21	14	24
	CKD 2	137	56	131	52	91
	CKD 3a	29	10	28	9	19
All adverse events	CKD 1	68.8 (11)	55.6 (5)	47.6 (10)	85.7 (12)	66.7 (16)
	CKD 2	51.8 (71)	69.6 (39)	51.9 (68)	69.2 (36)	74.7 (68)
	CKD 3a	58.6 (17)	70.0 (7)	53.6 (15)	77.8 (7)	73.7 (14)
All adverse drug reactions	CKD 1	12.5 (2)	0 (0)	0 (0)	35.7 (5)	12.5 (3)
	CKD 2	7.3 (10)	5.4 (3)	6.1 (8)	23.1 (12)	9.9 (9)
	CKD 3a	3.4 (1)	10.0 (1)	3.6 (1)	11.1 (1)	5.3 (1)
Serious adverse events	CKD 1	0 (0)	0 (0)	0 (0)	0 (0)	4.2 (1)
	CKD 2	1.5 (2)	0 (0)	6.1 (8)	1.9 (1)	2.2 (2)
	CKD 3a	0 (0)	0 (0)	0 (0)	0 (0)	5.3 (1)
Adverse events leading to drug discontinuation	CKD 1	6.3 (1)	0 (0)	0 (0)	7.1 (1)	0 (0)
	CKD 2	7.3 (10)	3.6 (2)	4.6 (6)	7.7 (4)	3.3 (3)
	CKD 3a	10.3 (3)	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycaemia	CKD 1	0 (0)	11.1 (1)	0 (0)	7.1 (1)	8.3 (2)
		0 [0]	0.263 [1]	0 [0]	0.334 [2]	0.226 [5]
	CKD 2	0.7 (1)	5.4 (3)	2.3 (3)	5.8 (3)	2.2 (2)
		0.034 [2]	0.119 [3]	0.071 [4]	0.229 [5]	0.023 [2]
	CKD 3a	3.4 (1)	10.0 (1)	7.1 (2)	0 (0)	5.3 (1)
		0.403 [5]	0.228 [1]	0.388 [5]	0 [0]	0.055 [1]
Gastrointestinal symptoms[a)]	CKD 1	37.5 (6)	0 (0)	19.0 (4)	21.4 (3)	25.0 (6)
	CKD 2	8.0 (11)	16.1 (9)	14.5 (19)	32.7 (17)	19.8 (18)
	CKD 3a	10.3 (3)	20.0 (2)	10.7 (3)	44.4 (4)	31.6 (6)

Incidence, % (Number. of patients with the event); Number of events per unit time (events/patient-year) [Number. of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 71. Incidences of adverse events in patients receiving imeglimin in combination therapies by severity of renal impairment (Study 019; safety analysis set)

	Severity of renal impairment	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
Number of patients	CKD 1	22	12	18	13	16	9	21	16
	CKD 2	96	50	42	49	44	47	40	51
	CKD 3a	9	2	4	2	5	7	2	3
All adverse events	CKD 1	90.9 (20)	75.0 (9)	83.3 (15)	46.2 (6)	81.3 (13)	77.8 (7)	81.0 (17)	93.8 (15)
	CKD 2	78.1 (75)	86.0 (43)	71.4 (30)	51.0 (25)	77.3 (34)	78.7 (37)	75.0 (30)	76.5 (39)
	CKD 3a	77.8 (7)	100 (2)	75.0 (3)	100 (2)	60.0 (3)	85.7 (6)	50.0 (1)	66.7 (2)
All adverse drug reactions	CKD 1	27.3 (6)	16.7 (2)	38.9 (7)	7.7 (1)	6.3 (1)	11.1 (1)	9.5 (2)	18.8 (3)
	CKD 2	18.8 (18)	14.0 (7)	33.3 (14)	10.2 (5)	9.1 (4)	25.5 (12)	10.0 (4)	7.8 (4)
	CKD 3a	33.3 (3)	50.0 (1)	75.0 (3)	0 (0)	20.0 (1)	14.3 (1)	50.0 (1)	33.3 (1)
Serious adverse events	CKD 1	18.2 (4)	0 (0)	0 (0)	7.7 (1)	0 (0)	0 (0)	0 (0)	6.3 (1)
	CKD 2	6.3 (6)	2.0 (1)	9.5 (4)	6.1 (3)	6.8 (3)	6.4 (3)	10.0 (4)	7.8 (4)
	CKD 3a	11.1 (1)	0 (0)	0 (0)	0 (0)	20.0 (1)	0 (0)	0 (0)	0 (0)
Adverse events leading to drug discontinuation	CKD 1	22.7 (5)	0 (0)	11.1 (2)	7.7 (1)	6.3 (1)	0 (0)	0 (0)	18.8 (3)
	CKD 2	4.2 (4)	2.0 (1)	9.5 (4)	2.0 (1)	4.5 (2)	10.6 (5)	2.5 (1)	23.5 (12)
	CKD 3a	0 (0)	0 (0)	25.0 (1)	0 (0)	20.0 (1)	0 (0)	0 (0)	0 (0)
Hypoglycaemia	CKD 1	31.8 (7)	8.3 (1)	22.2 (4)	7.7 (1)	6.3 (1)	0 (0)	0 (0)	6.3 (1)
		0.558 [10]	1.914 [21]	0.370 [6]	0.081 [1]	0.063 [1]	0 [0]	0 [0]	0.078 [1]
	CKD 2	12.5 (12)	14.0 (7)	4.8 (2)	2.0 (1)	2.3 (1)	8.5 (4)	7.5 (3)	2.0 (1)
		0.558 [51]	0.400 [19]	0.052 [2]	0.042 [2]	0.024 [1]	0.168 [7]	0.077 [3]	0.023 [1]
	CKD 3a	22.2 (2)	50.0 (1)	0 (0)	0 (0)	0 (0)	14.3 (1)	50.0 (1)	0 (0)
		0.376 [3]	1.005 [2]	0 [0]	0 [0]	0 [0]	0.144 [1]	0.500 [1]	0 [0]
Gastrointestinal symptoms[a)]	CKD 1	31.8 (7)	25.0 (3)	33.3 (6)	7.7 (1)	25.0 (4)	33.3 (3)	28.6 (6)	18.8 (3)
	CKD 2	20.8 (20)	18.0 (9)	40.5 (17)	8.2 (4)	9.1 (4)	31.9 (15)	20.0 (8)	21.6 (11)
	CKD 3a	11.1 (1)	0 (0)	75.0 (3)	0 (0)	40.0 (2)	42.9 (3)	50.0 (1)	33.3 (1)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 72. Incidences of adverse events in patients receiving imeglimin in combination with insulin by severity of renal impairment (Study 020; safety analysis set)

	Severity of renal impairment	Double-blind phase (16 weeks)		Entire treatment period (52 weeks)	
		Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[a)] (N = 101)	Imeglimin/imeglimin (N = 108)
Number of patients	CKD 1	14	16	13	16
	CKD 2	93	92	88	92
All adverse events	CKD 1	50.0 (7)	56.3 (9)	84.6 (11)	81.3 (13)
	CKD 2	47.3 (44)	52.2 (48)	75.0 (66)	85.9 (79)
All adverse drug reactions	CKD 1	7.1 (1)	12.5 (2)	23.1 (3)	18.8 (3)
	CKD 2	12.9 (12)	15.2 (14)	14.8 (13)	27.2 (25)
Serious adverse events	CKD 1	0 (0)	0 (0)	0 (0)	12.5 (2)
	CKD 2	3.2 (3)	1.1 (1)	6.8 (6)	4.3 (4)
Adverse events leading to drug discontinuation	CKD 1	0 (0)	6.3 (1)	0 (0)	12.5 (2)
	CKD 2	4.3 (4)	0 (0)	3.4 (3)	3.3 (3)
Hypoglycaemia	CKD 1	7.1 (1)	25.0 (4)	53.8 (7)	37.5 (6)
		0.234 [1]	1.066 [5]	2.672 [24]	1.638 [24]
	CKD 2	17.2 (16)	20.7 (19)	33.0 (29)	35.9 (33)
		0.867 [24]	3.184 [90]	2.357 [137]	3.904 [355]
Gastrointestinal symptoms[b)]	CKD 1	7.1 (1)	25.0 (4)	15.4 (2)	31.3 (5)
	CKD 2	6.5 (6)	6.5 (6)	9.1 (8)	16.3 (15)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Events that developed after the start of treatment with imeglimin
b) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

As shown above, despite the small number of patients with moderate or severe renal impairment evaluated, the results of the phase II and III studies showed no consistent tendency in the safety profile of imeglimin to be affected by the severity of renal impairment or identified no major safety problems with the use of imeglimin in patients with renal impairment. Further, the analysis of the efficacy of imeglimin by the severity of renal impairment based on the pooled data from the phase II and III monotherapy studies (Studies 014 and 018) showed that the changes in HbA1c (mean ± standard deviation) in patients with baseline CKD 1, CKD 2, and CKD 3a were 0.16 ± 0.31%, 0.27 ± 0.84%, and 0.09 ± 0.61%, respectively, in the placebo group, and -0.47 ± 0.77%, -0.66 ± 0.58%, and -0.58 ± 0.67% in the imeglimin 1000 mg group, with no clear tendencies attributable to the severity of renal impairment.

Imeglimin is excreted primarily through the kidneys. Thus the recommended dosage regimens for patients with renal impairment will be modified to 500 mg twice daily for patients with CKD 3b or 4 (CKD 3b, eGFR of ≥30 to <45 mL/min/1.73 m^2; CKD 4, eGFR of ≥15 to <30 mL/min/1.73 m^2), and 500 mg once daily for patients with CKD 5 (eGFR of <15 mL/min/1.73 m^2), based on the results of pharmacokinetic assessment. Healthcare professionals will be advised that the use of imeglimin in patients with CKD 5 is allowed only when the potential benefits of imeglimin are expected to outweigh its potential risks, because of no clinical studies conducted targeting this patient population and only 4 patients with CKD 5 who have ever been treated with imeglimin.

PMDA's view:
Exposure to imeglimin increases with decreasing renal function. Meanwhile, patients with CKD 3b to 5 (eGFR <45 mL/min/1.73 m^2) were not enrolled in the phase II or III studies (Studies 014, 018, 019, and 020), and all patients with CKD 5 (eGFR <15 mL/min/1.73 m^2) treated with imeglimin in the clinical studies had an eGFR of ≥14 mL/min/1.73 m^2. The clinical experience of imeglimin in patents with CKD 5 (eGFR <15 mL/min/1.73 m^2) was thus limited. The applicant explained that no dose adjustment would be necessary for patients with

CKD 2 or 3a and that the dosage of oral imeglimin for patients with CKD 3b or 4 should be modified to 500 mg twice daily and to 500 mg once daily for patients with CKD 5. In view of the discussion in Section "6.R.2 Patients with renal impairment" and the results of the applicant's PPK model-based assessment showing no large inconsistencies with the results obtained from patients with renal impairment who were treated with multiple doses of imeglimin in the clinical pharmacology studies, patients with CKD 2 or 3a can be treated with oral imeglimin 1000 mg twice daily. Patients with CKD 3b or 4 treated with oral imeglimin 500 mg twice daily are expected to have exposure equivalent to that obtained in the phase II and III studies. It is thus acceptable to present this reduced dose as guidelines for clinical recommended dose for the relevant patients. On the other hand, patients with CKD 5 are likely to have an even higher exposure than patients with CKD 3b or 4, and the extent of the increase in exposure is unpredictable. Available information is thus not adequate enough to provide guidelines for an exposure-based clinical recommended dose for patients with CKD5. The use of imeglimin in this patient population is thus not recommended at present.

The clinical dose to be recommended for patients with CKD 5 should be discussed when the pharmacokinetic, safety, and efficacy data of imeglimin are made available from this patient population in the future. In addition, in the phase II and III studies, among those in combination therapy groups, patients with renal impairment showed high incidences of hypoglycemia and gastrointestinal symptoms as compared with those with normal renal function. Given this, the applicant should continue to collect information about safety, etc. in patients with renal impairment in the post-marketing setting. The PMDA's conclusions will be finalized taking into account comments from the Expert Discussion.

7.R.6.2 Patients with hepatic impairment

The applicant's explanation:

Tables 73 to 75 show the incidences of adverse events by presence or absence of hepatic impairment in patients receiving imeglimin alone or in combination therapies in the phase II and III studies (Studies 014, 018, 019, and 020).[51)] In all treatment groups, the incidences of adverse events did not differ substantially by presence or absence of hepatic impairment.

[51)] Defined as having hepatic impairment if any of the following 4 criteria were met, and defined as having no hepatic impairment if none of the following were met; (a) total bilirubin of ≥1.6 mg/dL, (b) AST or ALT of ≥1.25 × the ULN or ≥50 IU, (c) ALP of ≥1.25 × the ULN, and (d) γ-GTP of ≥1.5 × the ULN

Table 73. Incidences of adverse events in patients receiving imeglimin monotherapy by presence or absence of hepatic impairment (pooled data from Studies 014 and 018, and Study 019; safety analysis sets)

	Underlying hepatic impairment	Studies 014 and 018 pooled				Study 019
		Placebo (N = 182)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 180)	Imeglimin 1500 mg (N = 75)	Imeglimin 1000 mg (N = 134)
Number of patients	Present	31	14	24	14	18
	Absent	151	61	156	61	116
All adverse events	Present	45.2 (14)	64.3 (9)	58.3 (14)	85.7 (12)	55.6 (10)
	Absent	56.3 (85)	68.9 (42)	50.6 (79)	70.5 (43)	75.9 (88)
All adverse drug reactions	Present	6.5 (2)	7.1 (1)	4.2 (1)	28.6 (4)	11.1 (2)
	Absent	7.3 (11)	4.9 (3)	5.1 (8)	23.0 (14)	9.5 (11)
Serious adverse events	Present	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
	Absent	1.3 (2)	0 (0)	5.1 (8)	1.6 (1)	3.4 (4)
Adverse events leading to drug discontinuation	Present	6.5 (2)	0 (0)	0 (0)	7.1 (1)	0 (0)
	Absent	7.9 (12)	3.3 (2)	3.8 (6)	6.6 (4)	2.6 (3)
Hypoglycaemia	Present	0 (0)	7.1 (1)	4.2 (1)	14.3 (2)	0 (0)
		0 [0]	0.166 [1]	0.094 [1]	0.830 [5]	0 [0]
	Absent	1.3 (2)	6.6 (4)	2.6 (4)	3.3 (2)	4.3 (5)
		0.107 [7]	0.147 [4]	0.117 [8]	0.079 [2]	0.072 [8]
Gastrointestinal symptoms[a)]	Present	3.2 (1)	28.6 (4)	8.3 (2)	28.6 (4)	16.7 (3)
	Absent	12.6 (19)	11.5 (7)	15.4 (24)	32.8 (20)	23.3 (27)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 74. Incidences of adverse events in patients receiving imeglimin in combination therapies by presence or absence of hepatic impairment (Study 019, safety analysis set)

	Underlying hepatic impairment	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
Number of patients	Present	16	11	10	9	9	12	13	20
	Absent	111	53	54	55	56	51	50	50
All adverse events	Present	75.0 (12)	81.8 (9)	70.0 (7)	55.6 (5)	100 (9)	91.7 (11)	92.3 (12)	65.0 (13)
	Absent	81.1 (90)	84.9 (45)	75.9 (41)	50.9 (28)	73.2 (41)	76.5 (39)	72.0 (36)	86.0 (43)
All adverse drug reactions	Present	12.5 (2)	27.3 (3)	40.0 (4)	11.1 (1)	11.1 (1)	16.7 (2)	15.4 (2)	15.0 (3)
	Absent	22.5 (25)	13.2 (7)	37.0 (20)	9.1 (5)	8.9 (5)	23.5 (12)	10.0 (5)	10.0 (5)
Serious adverse events	Present	6.3 (1)	0 (0)	10.0 (1)	11.1 (1)	11.1 (1)	0 (0)	7.7 (1)	5.0 (1)
	Absent	9.0 (10)	1.9 (1)	5.6 (3)	5.5 (3)	5.4 (3)	5.9 (3)	6.0 (3)	8.0 (4)
Adverse events leading to drug discontinuation	Present	6.3 (1)	0 (0)	0 (0)	0 (0)	11.1 (1)	0 (0)	0 (0)	25.0 (5)
	Absent	7.2 (8)	1.9 (1)	7 (13.0)	3.6 (2)	5.4 (3)	9.8 (5)	2.0 (1)	20.0 (10)
Hypoglycaemia	Present	12.5 (2)	18.2 (2)	20.0 (2)	11.1 (1)	11.1 (1)	16.7 (2)	0 (0)	5.0 (1)
		0.659 [10]	2.293 [22]	0.447 [4]	0.112 [1]	0.113 [1]	0.167 [2]	0 [0]	0.065 [1]
	Absent	17.1 (19)	13.2 (7)	7.4 (4)	1.8 (1)	1.8 (1)	5.9 (3)	8.0 (4)	2.0 (1)
		0.529 [54]	0.393 [20]	0.082 [4]	0.038 [2]	0.019 [1]	0.131 [6]	0.081 [4]	0.023 [1]
Gastrointestinal symptoms[a)]	Present	31.3 (5)	18.2 (2)	50.0 (5)	0 (0)	0 (0)	16.7 (2)	30.8 (4)	25.0 (5)
	Absent	20.7 (23)	18.9 (10)	38.9 (21)	9.1 (5)	17.9 (10)	37.3 (19)	22.0 (11)	20.0 (10)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 75. Incidences of adverse events in patients receiving imeglimin in combination with insulin by presence or absence of hepatic impairment (Study 020, safety analysis set)

	Underlying hepatic impairment	Double-blind phase (16 weeks)		Entire treatment phase (52 weeks)	
		Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[b] (N = 101)	Imeglimin/imeglimin (N = 108)
Number of patients	Present	15	17	14	17
	Absent	92	91	87	91
All adverse events	Present	46.7 (7)	58.8 (10)	85.7 (12)	82.4 (14)
	Absent	47.8 (44)	51.6 (47)	74.7 (65)	85.7 (78)
All adverse drug reactions	Present	13.3 (2)	11.8 (2)	28.6 (4)	23.5 (4)
	Absent	12.0 (11)	15.4 (14)	13.8 (12)	26.4 (24)
Serious adverse events	Present	6.7 (1)	0 (0)	7.1 (1)	5.9 (1)
	Absent	2.2 (2)	1.1 (1)	5.7 (5)	5.5 (5)
Adverse events leading to drug discontinuation	Present	6.7 (1)	0 (0)	7.1 (1)	5.9 (1)
	Absent	3.3 (3)	1.1 (1)	2.3 (2)	4.4 (4)
Hypoglycaemia	Present	6.7 (1)	23.5 (4)	50.0 (7)	29.4 (5)
		0.231 [1]	3.656 [19]	1.835 [17]	2.565 [43]
	Absent	17.4 (16)	20.9 (19)	33.3 (29)	37.4 (34)
		0.868 [24]	2.738 [76]	2.490 [144]	3.782 [336]
Gastrointestinal symptoms[a]	Present	6.7 (1)	5.9 (1)	0 (0)	11.8 (2)
	Absent	6.5 (6)	9.9 (9)	11.5 (10)	19.8 (18)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"
b) Events that developed after the start of treatment with imeglimin

The above clinical study results identified no marked safety problems with the use of imeglimin in patients with hepatic impairment. The efficacy analysis of imeglimin monotherapy by presence or absence of hepatic impairment was performed based on the pooled data from the phase II and III monotherapy studies (Studies 014 and 018). The results revealed that changes in HbA1c (mean ± standard deviation) were 0.14 ± 0.92% in patients with hepatic impairment and 0.25 ± 0.74% in patients without hepatic impairment in the placebo group, and -0.54 ± 0.46% in the former and -0.64 ± 0.64% in the latter, in the imeglimin 1000 mg group, indicating no clear tendency for the efficacy of imeglimin to be affected by underlying hepatic impairment. The package insert will provide the results of the pharmacokinetic study in patients with moderate hepatic impairment along with a caution to the effect that no clinical studies have been conducted in patients with severe hepatic impairment.

PMDA's view:

The applicant's observation is acceptable that the phase II and II studies showed no obvious tendency for markedly increasing safety risk associated with the use of imeglimin by presence or absence of hepatic impairment. The package insert should present the data of exposure to imeglimin in patients with moderate haptic impairment and highlight that no clinical studies have been conducted in patients with severe hepatic impairment.

7.R.6.3 Elderly patients

The applicant's explanation:

Tables 76 to 78 show the incidences of adverse events by age in the phase II and III studies (Studies 014, 018, 019, and 020). In all these studies, the incidences of adverse events, adverse drug reactions, serious adverse events, adverse events leading to drug discontinuation, and gastrointestinal symptoms showed no clear differences in safety profiles across age categories. Although the small number of study participants aged ≥75 years precluded precise comparisons, no age-related tendencies were noted. The number of events of

hypoglycemia per unit time in patients receiving imeglimin in combination with insulin tended to be greater in patients aged ≥65 to <75 years than in those aged <65 years. However, all hypoglycemia reported by patients aged ≥75 years were mild in severity; thus, hypoglycemia did not tend to become more severe with aging. The package insert will provide appropriate cautionary statements about the combination of imeglimin with insulin therapy in the "Clinically Significant Adverse Reactions" and "Precautions for Coadministration" sections. Therefore, no additional cautionary advice will be necessary for elderly patients.

Table 76. Incidences of adverse events by age in patients receiving imeglimin monotherapy (Studies 014 and 018 combined, and Study 019; safety analysis sets)

	Age (years)	Studies 014 and 018 pooled				Study 019
		Placebo (N = 182)	Imeglimin 500 mg (N = 75)	Imeglimin 1000 mg (N = 180)	Imeglimin 1500 mg (N = 75)	Imeglimin 1000 mg (N = 134)
Number of patients	<65	106	54	97	47	86
	≥65 to <75	63	21	74	28	41
	≥75	13	0	9	0	7
All adverse events	<65	59.4 (63)	74.1 (40)	50.5 (49)	78.7 (37)	67.4 (58)
	≥65 to <75	47.6 (30)	52.4 (11)	50.0 (37)	64.3 (18)	82.9 (34)
	≥75	46.2 (6)	-	77.8 (7)	-	85.7 (6)
All adverse drug reactions	<65	9.4 (10)	7.4 (4)	5.2 (5)	23.4 (11)	8.1 (7)
	≥65 to <75	4.8 (3)	0 (0)	5.4 (4)	25.0 (7)	9.8 (4)
	≥75	0 (0)	-	0 (0)	-	28.6 (2)
Serious adverse events	<65	0.9 (1)	0 (0)	3.1 (3)	0 (0)	1.2 (1)
	≥65 to <75	1.6 (1)	0 (0)	4.1 (3)	3.6 (1)	7.3 (3)
	≥75	0 (0)	-	22.2 (2)	-	0 (0)
Adverse events leading to drug discontinuation	<65	7.5 (8)	3.7 (2)	3.1 (3)	6.4 (3)	2.3 (2)
	≥65 to <75	7.9 (5)	0 (0)	2.7 (2)	7.1 (2)	2.4 (1)
	≥75	7.7 (1)	-	11.1 (1)	-	0 (0)
Hypoglycaemia	<65	1.9 (2)	7.4 (4)	5.2 (5)	8.5 (4)	3.5 (3)
		0.153 [7]	0.168 [4]	0.208 [9]	0.343 [7]	0.229 [6]
	≥65 to <75	0 (0)	4.8 (1)	0 (0)	0 (0)	4.9 (2)
		0 [0]	0.105 [1]	0 [0]	0 [0]	0.019 [2]
	≥75	0 (0)	-	0 (0)	-	0 (0)
		0 [0]	-	0 [0]	-	0 [0]
Gastrointestinal symptoms[a)]	<65	11.3 (12)	18.5 (10)	14.4 (14)	29.8 (14)	19.8 (17)
	≥65 to <75	12.7 (8)	4.8 (1)	14.9 (11)	35.7 (10)	24.4 (10)
	≥75	0 (0)	-	11.1 (1)	-	42.9 (3)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 77. Incidences of adverse events by age in patients receiving imeglimin in combination therapies (Study 019, safety analysis set)

	Age (years)	Imeglimin + SU (N = 127)	Imeglimin + glinide (N = 64)	Imeglimin + BG (N = 64)	Imeglimin + α-GI (N = 64)	Imeglimin + TZD (N = 65)	Imeglimin + DPP-4 inhibitor (N = 63)	Imeglimin + SGLT2 inhibitor (N = 63)	Imeglimin + GLP-1 receptor agonist (N = 70)
Number of patients	<65	76	42	47	41	44	28	45	46
	≥65 to <75	46	19	14	21	17	30	16	21
	≥75	5	3	3	2	4	5	2	3
All adverse events	<65	78.9 (60)	81.0 (34)	74.5 (35)	46.3 (19)	77.3 (34)	82.1 (23)	73.3 (33)	76.1 (35)
	≥65 to <75	84.8 (39)	89.5 (17)	78.6 (11)	57.1 (12)	76.5 (13)	80.0 (24)	81.3 (13)	85.7 (18)
	≥75	60.0 (3)	100 (3)	66.7 (2)	100 (2)	75.0 (3)	60.0 (3)	100 (2)	100 (3)
All adverse drug reactions	<65	21.1 (16)	14.3 (6)	31.9 (15)	4.9 (2)	6.8 (3)	17.9 (5)	6.7 (3)	6.5 (3)
	≥65 to <75	23.9 (11)	21.1 (4)	57.1 (8)	14.3 (3)	11.8 (2)	23.3 (7)	18.8 (3)	19.0 (4)
	≥75	0 (0)	0 (0)	33.3 (1)	50.0 (1)	25.0 (1)	40.0 (2)	50.0 (1)	33.3 (1)
Serious adverse events	<65	3.9 (3)	2.4 (1)	6.4 (3)	7.3 (3)	2.3 (1)	7.1 (2)	6.7 (3)	2.2 (1)
	≥65 to <75	15.2 (7)	0 (0)	7.1 (1)	4.8 (1)	11.8 (2)	3.3 (1)	6.3 (1)	14.3 (3)
	≥75	20.0 (1)	0 (0)	0 (0)	0 (0)	25.0 (1)	0 (0)	0 (0)	33.3 (1)
Adverse events leading to drug discontinuation	<65	9.2 (7)	2.4 (1)	8.5 (4)	2.4 (1)	4.5 (2)	10.7 (3)	2.2 (1)	19.6 (9)
	≥65 to <75	4.3 (2)	0 (0)	21.4 (3)	0 (0)	5.9 (1)	3.3 (1)	0 (0)	23.8 (5)
	≥75	0 (0)	0 (0)	0 (0)	50.0 (1)	25.0 (1)	20.0 (1)	0 (0)	33.3 (1)
Hypoglycaemia	<65	15.8 (12)	11.9 (5)	6.4 (3)	4.9 (2)	4.5 (2)	7.1 (2)	2.2 (1)	4.3 (2)
		0.397 [28]	0.856 [33]	0.093 [4]	0.074 [3]	0.047 [2]	0.153 [4]	0.023 [1]	0.051 [2]
	≥65 to <75	19.6 (9)	15.8 (3)	14.3 (2)	0 (0)	0 (0)	10.0 (3)	12.5 (2)	0 (0)
		0.843 [36]	0.423 [8]	0.166 [2]	0 [0]	0 [0]	0.146 [4]	0.125 [2]	0 [0]
	≥75	0 (0)	33.3 (1)	33.3 (1)	0 (0)	0 (0)	0 (0)	50.0 (1)	0 (0)
		0 [0]	0.336 [1]	0.704 [2]	0 [0]	0 [0]	0 [0]	0.500 [1]	0 [0]
Gastrointestinal symptoms[a)]	<65	21.1 (16)	26.2 (11)	38.3 (18)	2.4 (1)	18.2 (8)	28.6 (8)	15.6 (7)	17.4 (8)
	≥65 to <75	26.1 (12)	5.3 (1)	50.0 (7)	14.3 (3)	5.9 (1)	40.0 (12)	43.8 (7)	28.6 (6)
	≥75	0 (0)	0 (0)	33.3 (1)	50.0 (1)	25.0 (1)	20.0 (1)	50.0 (1)	33.3 (1)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"

Table 78. Incidences of adverse events by age in patients receiving imeglimin in combination with insulin (Study 020, safety analysis set)

	Age (years)	Double-blind phase (16 weeks)		Entire treatment period (52 weeks)	
		Placebo (N = 107)	Imeglimin (N = 108)	Placebo/imeglimin[b)] (N = 101)	Imeglimin/imeglimin (N = 108)
Number of patients	<65	76	68	72	68
	≥65 to <75	28	33	26	33
	≥75	3	7	3	7
All adverse events	<65	47.4 (36)	48.5 (33)	75.0 (54)	83.8 (57)
	≥65 to <75	46.4 (13)	57.6 (19)	80.8 (21)	84.8 (28)
	≥75	66.7 (2)	71.4 (5)	66.7 (2)	100 (7)
All adverse drug reactions	<65	10.5 (8)	11.8 (8)	12.5 (9)	26.5 (18)
	≥65 to <75	14.3 (4)	24.2 (8)	23.1 (6)	30.3 (10)
	≥75	33.3 (1)	0 (0)	33.3 (1)	0 (0)
Serious adverse events	<65	1.3 (1)	1.5 (1)	1.4 (1)	8.8 (6)
	≥65 to <75	7.1 (2)	0 (0)	15.4 (4)	0 (0)
	≥75	0 (0)	0 (0)	33.3 (1)	0 (0)
Adverse events leading to drug discontinuation	<65	3.9 (3)	0 (0)	1.4 (1)	4.4 (3)
	≥65 to <75	3.6 (1)	3.0 (1)	7.7 (2)	6.1 (2)
	≥75	0 (0)	0 (0)	0 (0)	0 (0)
Hypoglycaemia	<65	14.5 (11)	17.6 (12)	31.9 (23)	33.8 (23)
		0.742 [17]	1.770 [37]	1.672 [82]	2.401 [161]
	≥65 to <75	14.3 (4)	24.2 (8)	46.2 (12)	33.3 (11)
		0.736 [6]	4.941 [49]	4.254 [68]	5.700 [180]
	≥75	66.7 (2)	42.9 (3)	33.3 (1)	71.4 (5)
		2.174 [2]	4.209 [9]	5.266 [11]	5.451 [38]
Gastrointestinal symptoms[a)]	<65	5.3 (4)	5.9 (4)	11.1 (8)	14.7 (10)
	≥65 to <75	10.7 (3)	15.2 (5)	7.7 (2)	24.2 (8)
	≥75	0 (0)	14.3 (1)	0 (0)	28.6 (2)

Incidence, % (Number of patients with the event); Number of events per unit time (events/patient-year) [Number of events]
a) Adverse events coded to PTs included in the SOC "gastrointestinal disorders" or the HLT "appetite disorders"
b) Events that developed after the start of treatment with imeglimin

The efficacy of imeglimin was analyzed by age based on the pooled data from the phase II and III monotherapy studies (Studies 014 and 018). Changes in HbA1c (mean ± standard deviation) in patients aged <65 years and

those aged ≥65 years were 0.29 ± 0.88% and 0.15 ± 0.59%, respectively in the placebo group, and -0.55 ± 0.69% and -0.71 ± 0.50% in the imeglimin 1000 mg group, with no clear age-related tendency regarding efficacy.

PMDA's view:
The results of the clinical studies showed no tendency toward a consistently high risk associated with the use of imeglimin in elderly patients. However, because of the small number of patients aged ≥75 years enrolled in the studies, etc., safety information should be further collected from elderly patients receiving imeglimin in the post-marketing setting.

7.R.7 Post-marketing investigations

The applicant's explanation:
The clinical studies of imeglimin have identified no major safety concerns. However, a post-marketing clinical study will be conducted in patients with type 2 diabetes mellitus and renal impairment (defined as eGFR of <45 mL /min/1.73 m^2), i.e., the patient population excluded from the Japanese phase II or III studies (Studies 014, 018, 019, and 020), to evaluate the long-term safety and efficacy of imeglimin monotherapy. The treatment period of the study will be 52 weeks. The target sample size for patients with eGFR of ≥15 to <45 mL/min/1.73 m^2 is 50, while that for patients with eGFR of <15 mL/min/1.73 m^2 will not be set due to the rarity of such disease conditions. After the launch of Twymeeg, an additional dosage regimen will also be developed for pediatric patients with type 2 diabetes mellitus aged ≥[redacted] years, despite the small number of Japanese children suffering this disease. Currently, there are limited options in oral hypoglycemic agents for this patient population.

PMDA's view:
As far as seeing the clinical study results, there are no major safety concerns. Nevertheless, the safety profile of imeglimin including imeglimin-associated hypoglycemia, gastrointestinal symptoms, and lactic acidosis in observed in the clinical setting should be further investigated based on an extensive amount of information collected through a drug use-results survey. Exposure to imeglimin has been shown to increase as the severity of renal impairment increases. In view of the limited information available on the safety, efficacy, etc., of imeglimin, particularly in patients with eGFR of <45 mL/min/1.73 m^2, the applicant's plan to conduct a post-marketing clinical study in patients with renal impairment is appropriate. Information about the pharmacokinetics, safety, and efficacy of imeglimin in patients with eGFR of <15 mL/min/1.73 m^2 and patients on dialysis, an extremely rare patient population enrolled in the studies, will be helpful for healthcare professionals. It is thus advisable to collect data on these patients whenever possible. The above PMDA's conclusions will be finalized taking into account comments from the Expert Discussion. The applicant's development plan for the treatment of pediatric patients with type 2 diabetes mellitus aged ≥[redacted] years is meaningful in light of a certain proportion of children in this age group actually suffering from type 2 diabetes mellitus.

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

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

The new drug application data (CTD 5.3.5.1.02, 5.3.5.1.03, and 5.3.5.2.01) 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, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

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

On the basis of the data submitted, PMDA has concluded that imeglimin has efficacy in the treatment of type 2 diabetes mellitus, and that imeglimin has acceptable safety in view of its benefits. Imeglimin is clinically meaningful because of its actions unique from existing hypoglycemic agents, and it offers a new treatment option for patients with type 2 diabetes mellitus.

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

Review Report (2)

April 27, 2021

Product Submitted for Approval

Brand Name	Twymeeg Tablets 500 mg
Non-proprietary Name	Imeglimin Hydrochloride
Applicant	Sumitomo Dainippon Pharma Co., Ltd.
Date of Application	July 30, 2020

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

PMDA's view:

The results of the phase II monotherapy study (Study 014), the phase III monotherapy study (Study 018), and of the imeglimin monotherapy in the long-term monotherapy and combination therapy study (Study 019) demonstrated the efficacy of imeglimin monotherapy including that in long term treatment. The results of Study 019 also showed that imeglimin administered in combination therapies decreased HbA1c, regardless of the type of concomitant agent, and its effect was sustained up to 52 weeks. In Study 019, the change in HbA1c from baseline to Week 52 was smaller in the imeglimin + glucagon-like peptide-1 (GLP-1) receptor agonist group than that in other combination therapy groups. This may be partly attributed to the larger number of patients with presumed poor blood glucose control in the imeglimin + GLP-1 receptor agonist group than in other combination therapy groups. However, a certain proportion of patients in the imeglimin + GLP-1 receptor agonist group achieved a clinically significant improvement in blood glucose control, which suggests promising efficacy of combination therapy of imeglimin with a GLP-1 receptor agonist. In addition, the insulin-combination therapy (Study 020) demonstrated the efficacy of imeglimin in combination with insulin, including that in long term treatment. These results indicated that the efficacy of imeglimin administered in combination therapies is also promising.

At the Expert Discussion, the expert advisors made the following comment on the above PMDA's conclusions: The insulinotropic effect of imeglimin may be attenuated when GLP-1 signals are activated by a GLP-1

receptor agonist; the applicant should continue to collect efficacy data on imeglimin administered in combination with a GLP-1 receptor agonist, through a drug use-results survey, etc. Accordingly, PMDA asked the applicant for necessary actions, and the applicant agreed. PMDA has confirmed that the applicant took appropriate measures in their drug use-results survey plan.

1.2 Safety

PMDA's view:

The results of Studies 014 and 018, in which imeglimin was administered alone, identified no substantial differences in the incidences of adverse events between the imeglimin 1000 mg group and the placebo group. The results of Studies 019 and 020, in which imeglimin was administered in combination therapies, revealed no substantial differences in the incidences of adverse events, except those related to hypoglycemia and gastrointestinal symptoms, across the combination therapy groups. The clinical studies thus identified no particular safety concerns in the use of imeglimin. In terms of the incidences of adverse events by type of concomitant insulin therapy, hypoglycemia tended to occur at a higher percentage in patients receiving premixed/combination insulin than in those receiving basal insulin in the imeglimin group of Study 020, but with no substantial differences in the types of events reported by type of insulin therapy. Including hypoglycemia and gastrointestinal symptoms, adverse events warranting special attention in the use of imeglimin, namely, lactic acidosis-related events, hepatic dysfunction, cardiovascular risk, and the association with tumor development were separately assessed. According to the safety of imeglimin is acceptable where appropriate safety advice is given, etc.

While lactic acidosis is an adverse event warranting special attention, the incidence of lactic acidosis-related events was extremely low, and only a small number of patients experienced marked increases in blood lactate concentration in the phase II or III monotherapy or combination therapy studies of imeglimin (Studies 014, 018, 019, and 020). Further, no lactic acidosis was reported in any of the clinical studies of imeglimin. Thus, currently available clinical data provide no clear evidence for a risk of lactic acidosis associated with imeglimin. Furthermore, the non-clinical pharmacology studies suggested that the effect of imeglimin on lactate concentration differ from that of metformin. Nevertheless, the following should be noted: the incidence of lactic acidosis is generally low, and there is a limitation in assessing the risk of lactic acidosis in clinical studies of this size; the blood lactate concentration continued to increase during the treatment with imeglimin and declined after the completion of treatment in some patients in the studies; patients who were likely to be at high risk of lactic acidosis were excluded from the studies; and imeglimin, as with metformin, has been shown to inhibit mitochondrial Complex I activity and decrease hepatic glucose production. Based on the above, PMDA has made the following conclusions: the applicant should monitor the occurrence of lactic acidosis, particularly in patients with risk factors for lactic acidosis, and should also collect blood lactate concentration measurements, whenever possible in clinical practice; the changes in blood lactate concentration should be evaluated in the post-marketing clinical study planned to be conducted in patients with renal impairment; and the package insert should provide currently available findings and results, etc. on lactic acidosis associated with metformin or imeglimin.

At the Expert Discussion, the expert advisors generally supported the PMDA's conclusions, while raising the following comments: Imeglimin has the insulin resistance improvement effect, which is considered similar to that of metformin, and thus it should be noted that imeglimin has also been shown to reduce hepatic glucose production and that the possibility of lactic acidosis risk increased by the use of imeglimin in combination with high-dose metformin cannot be denied. These issues warrant further attention.

PMDA reviewed the safety results from the imeglimin + metformin group of Study 019 by dose of metformin (Table 79).

Table 79. Safety results in the imeglimin + metformin group by the dose of metformin (Study 019, safety analysis set)

	Dose of metformin (mg)				
	≥500 to <750 (N = 8)	≥750 to <1000 (N = 9)	≥1000 to <1500 (N = 19)	≥1500 to <2000 (N = 17)	≥2000 (N = 11)
Hypoglycaemia[a)]	12.5 (1)	0 (0)	5.3 (1)	11.8 (2)	18.2 (2)
Gastrointestinal symptoms[b)]	37.5 (3)	55.6 (5)	42.1 (8)	47.1 (8)	18.2 (2)
Cardiovascular-related events[c)]	12.5 (1)	11.1 (1)	10.5 (2)	11.8 (2)	0 (0)
Lactate concentration (mmol/L)[d)]	0.20 ± 0.56	0.01 ± 0.30	0.04 ± 0.36	0.09 ± 0.66	-0.01 ± 0.62
	0.00 [-0.5, 1.1]	0.00 [-0.5, 0.4]	0.10 [-0.8, 0.6]	-0.10 [-0.7, 1.8]	0.00 [-1.6, 0.8]
	7	8	17	15	11

Incidence, % (n)
a) Same as footnote a) in Table 53; b) same as footnote a) in Table 70; c) same as footnote 49
d) Change from baseline to Week 52; upper row, mean ± standard deviation; middle row, median [range], and lower row, n

The results of Study 019 showed no substantial differences in safety across the doses of metformin. However, safety information of imeglimin, including the risk of lactic acidosis associated with combination therapy with metformin, should be collected through the post-marketing surveillance.

1.3 Clinical positioning and indication

PMDA's view:

Imeglimin has been demonstrated to have promising efficacy for type 2 diabetes mellitus both alone and in combination therapies with acceptable safety. Therefore, the proposed indication for imeglimin of "type 2 diabetes mellitus" is acceptable, and imeglimin can be recognized as a novel oral hypoglycemic drug for type 2 diabetes mellitus.

The applicant investigated the mechanism of action, etc. of imeglimin, which chemical structure is partially in common with metformin. The mechanism of imeglimin's insulinotropic effect has not exactly been elucidated in light of the results of the non-clinical pharmacology studies. However, the results of the hyperglycemic clamp test conducted in the foreign phase II study in patients with type 2 diabetes mellitus (Study 006), etc. suggested the potential insulinotropic effect of imeglimin. The insulin resistance improvement by imeglimin, in contrast, was demonstrated in the results of non-clinical pharmacology studies that show normalized mitochondrial functions and suppressed glucose production in the liver as well as improved glucose uptake by skeletal muscles. Also, the results of the foreign phase II study (Study 009) indicate imeglimin's effect on insulin resistance improvement in humans as well. Imeglimin's suppressive effect on hepatic glucose production, which probably induced by the inhibition of mitochondrial Complex I, may be in common with

metformin. Nevertheless, metformin is known to have multiple actions, and metformin was not always used as control drug in the non-clinical and clinical studies conducted, precluding clear determination of differences in the action mechanisms or effectiveness between imeglimin and metformin from the clinical viewpoint. Based on the results of Study 019, the imeglimin + metformin combination therapy has been shown to have promising efficacy and acceptable safety. Even so, it should be noted that gastrointestinal symptoms were more frequently reported in the imeglimin + metformin group than in other combination therapy groups. The package insert should give caution against gastrointestinal symptoms in the use of the imeglimin + metformin combination therapy and communicate that the 2 drugs may have some overlapping pharmacological actions.

At the Expert Discussion, the expert advisors generally supported the above PMDA's conclusions, while raising the following comments:

- While imeglimin is considered to have action mechanisms different from metformin's, the majority of its actions can be in common with metformin.
- Metformin, a biguanide (BG), has been recognized as a first-line drug for the treatment of type 2 diabetes mellitus outside Japan, and increasingly so in Japan as well. While greater number of Japanese patients with type 2 diabetes mellitus presented with decreased insulin secretion more frequently than European and American patients, the number of patients with obesity-derived insulin resistance is also increasing in Japan. If proven to have abilities both to increase insulin secretion and to reduce insulin resistance, imeglimin can potentially be recognized as a drug to treat early-stage type 2 diabetes mellitus.
- The important tasks in the post-marketing setting will be an additional nonclinical studies for further elucidation of how imeglimin promotes insulin secretion, post-marketing surveillance, etc. for the clarification of clinical differences between imeglimin and metformin, and the risk assessment of lactic acidosis.

1.4 Dosage and administration

PMDA's view:

Based on the efficacy and safety results of Study 014, imeglimin was administered at 1000 mg twice daily in subsequent Studies 018, 019, and 020, and the results of these studies successfully demonstrated that imeglimin has efficacy for type 2 diabetes mellitus both alone or in combination therapies with acceptable safety. In view of these results, the dosage regimen of imeglimin should be 1000 mg twice daily. While, in the phase II and III studies, patients were encouraged to take imeglimin during or immediately after breakfast and dinner, food effects on the pharmacokinetics of imeglimin are insignificant. Therefore, the "Dosage and Administration" section needs not to specify the dosing timing relative to meals.

At the Expert Discussion, the expert advisors supported the PMDA's above conclusions.

1.5 Special populations

PMDA's view:

Imeglimin absorbed in the body is thought to be eliminated as unchanged imeglimin primarily via renal excretion, and exposure to imeglimin has been shown to increase with decreasing renal function. Although

patients with CKD 3b to 5 (eGFR of <45 mL/min/1.73 m^2) were excluded from all phase II or III studies of imeglimin (Studies 014, 018, 019, and 020), the applicant assessed the impact of renal impairment on exposure to imeglimin in multiple clinical pharmacology studies involving patients with renal impairment, and performed a PPK model-based analysis of exposure by severity of renal impairment. The results of the assessment and analysis suggested that patients with CKD 3b or 4 are expected to have a similar level of exposure to that observed in the Japanese phase II and III studies, when imeglimin is orally administered at a reduced dose of 500 mg twice daily. Therefore, giving the advice on "500 mg twice daily" as recommended clinical dose for patients with CKD 3b or 4 is acceptable. On the other hand, no data is available from patients with eGFR of <14 mL/min/1.73 m^2 who were treated with imeglimin for type 2 diabetes mellitus in clinical studies. This precludes the estimation of exposure to imeglimin using the above PPK model and the prediction of the degree of increase in exposure in patients with type 2 diabetes mellitus with CKD 5. Because of the lack of data sufficient to propose an exposure-based specific clinical dose for patients with CKD 5, the use of imeglimin cannot be recommended for this patient population at present. Meanwhile, no major safety concerns have been identified in the use of imeglimin in elderly patients or patients with hepatic impairment.

At the Expert Discussion, some expert advisors showed understanding for the exposure-based clinical dose for patients with CKD 3b and 4. However, others pointed out that the eligibility of patients with 3b to 5 for imeglimin therapy warrants careful discussion in view of the following points, and that the conclusion should be reached based on the results from the planned post-marketing clinical study in patients with renal impairment.

- None of the phase II or III studies (Studies 014, 018, 019, and 020) enrolled patients with CKD 3b to 5, and the foreign clinical pharmacology study in patients with type 2 diabetes with CKD 3b or 4 (Study RVT-1501-1002) was designed with a short treatment period and a small number of patients.
- Imeglimin's action mechanisms may partially differ from those of existing antidiabetic drugs.
- Only limited information is available about the potential risks associated with imeglimin, such as lactic acidosis.
- Imeglimin may be administered to patients with CKD 3b in combination with metformin.

Based on the above discussion, PMDA considers that the appropriateness of providing advice should be further discussed on the use of imeglimin in patients with CKD 3b to 5, including their eligibility for the treatment and dose adjustment, based on the pharmacokinetic, safety, and efficacy results from the planned post-marketing clinical study in patients with type 2 diabetes mellitus and renal impairment. Accordingly, PMDA has come to the conclusion that the package insert, until results from the post-marketing clinical study are available, should not mention the dose adjustment for patients with renal impairment in its "Precautions Concerning Dosage and Administration" section, while it should give caution in its "Precautions Concerning Indication" section that the use of imeglimin in patients with CKD 3b to 5 is not recommended.

Precautions Concerning the Indication

Because renal impairment can cause delayed excretion according to its severity, blood imeglimin concentration increases in patients with renal impairment. No clinical studies involving efficacy and safety endpoints have

been conducted in patients with moderate or severe (eGFR of <45 mL/min/1.73 m^2) renal impairment, and the use of imeglimin in such patients is not recommended.

PMDA asked the applicant to take appropriate actions for the "Precautions Concerning the Indication" section, etc. of the package insert, and the applicant agreed. PMDA has confirmed that the applicant responded appropriately.

1.6 Risk management plan (draft)

At the Expert Discussion, the expert advisors supported the PMDA's conclusions presented in Section "7.R.7 Post-marketing investigations" in the Review Report (1), and PMDA has concluded that the risk management plan (draft) for imeglimin should include the safety specifications presented in Table 80, and that the applicant should conduct the additional pharmacovigilance activities and additional risk minimization activities presented in Tables 81 to 83.

Table 80. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycemia • Gastrointestinal symptoms	• Lactic acidosis	• Safety in patients with renal impairment • Effects on cardiovascular risks
Efficacy specification		
None		

Table 81. 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 • Specified use-results survey • Post-marketing clinical study (patients with renal impairment)	• Disseminate data gathered during the early post-marketing phase vigilance

Table 82. Outline of the specified use-results survey (draft)

Objective	To evaluate the long-term safety and efficacy of imeglimin in clinical practice
Survey method	Central registration system
Study population	Patients with type 2 diabetes mellitus
Observation period	3 years
Planned sample size	3000
Main survey items	Patient characteristics, exposure to imeglimin, concomitant medications, safety evaluation (adverse events, clinical laboratory tests including blood lactate concentration, etc.), and efficacy evaluation (HbA1c, etc.)

Table 83. Outline of the post-marketing clinical study (draft)

Objective	To evaluate the long-term safety, efficacy, and pharmacokinetics of imeglimin in patients with renal impairment
Study design	An open-label, uncontrolled study
Study population	Patients with type 2 diabetes mellitus, with eGFR of <45 mL/min/1.73 m^2 (Imeglimin will be administered at a dose of 500 mg twice daily in patients with eGFR of ≥15 to <45 mL/min/1.73 m^2, and 500 mg once daily in patients with eGFR of <15 mL/min/1.73 m^2.)
Observation period	52 weeks
Planned sample size	50
Main endpoints	Patient characteristics, exposure to imeglimin, plasma drug concentrations, safety evaluation (adverse events, eGFR, clinical laboratory tests including blood lactate concentration, etc.), and efficacy evaluation (HbA1c, fasting blood glucose, etc.)

2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration as follows, with the approval conditions shown below. The product is a drug with a new active ingredient; accordingly, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

Indication

Type 2 diabetes mellitus

Dosage and administration

The usual adult dosage is 1000 mg of Imeglimin Hydrochloride administered orally twice daily, in the morning and evening.

Approval Condition

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

Appendix

List of Abbreviations

ADP	Adenosine diphosphate
Adverse drug reaction	An adverse event for which a causal relationship with the study drug cannot be ruled out
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the drug plasma concentration-time curve
BCRP	Breast cancer resistance protein
BG	Biguanide
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CKD	Chronic kidney disease
CL/F	Apparent total clearance
C_{max}	Maximum plasma concentration
CPP	Critical process parameter
CQA	Critical quality attribute
CYP	Cytochrome P450
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
FAS	Full analysis set
GC	Gas chromatography
GK rat	Goto-Kakizaki rat
glinide	
GLP-1	Glucagon-like peptide-1
HbA1c	Hemoglobin A1c
hERG	Human ether-a-go-go related gene
HFHS	High fat high sucrose
HLGT	High level group term
HLT	High level term
HPLC	High performance liquid chromatography
ICH Q1E Guidelines	Evaluation of stability data, PFSB/ELD Notification No. 0603004 dated June 3, 2003
IC_{50}	Half maximal inhibitory concentration
INHAND	International Harmonization of Nomenclature and Diagnostic Criteria
IR	Infrared absorption spectrum
ITT	Intent to treat
K_i	Inhibition constant
K_m	Michaelis-Menten constant
LC-MS/MS	Liquid chromatography-tandem mass spectrometry
LOCF	Last observation carried forward
MATE	Multidrug and toxin extrusion
MedDRA	Medical Dictionary for Regulatory Activities
MF	Master file
mGPDH	Mitochondrial glycerol 3-phosphate dehydrogenase
MMRM	Mixed-effects model repeated measures
MS	Mass spectrum
NAD^+	Oxidized form nicotinamide adenine dinucleotide

NADH	Reduced form nicotinamide adenine dinucleotide
NAMPT	Nicotinamide phosphoribosyltransferase
NGSP	National glycohemoglobin standardization program
NMR	Nuclear magnetic resonance spectrum
N0-STZ	Neonatal streptozotocin
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
OCT	Organic cation transporter
OGTT	Oral glucose tolerance test
P-gp	P-glycoprotein
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
PT	Preferred terms
PTP	Press through pack
QbD	Quality by design
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate according to Fridericia's formula
ROS	Reactive Oxygen species
RT-qPCR	Reverse transfection Quantitative polymerase chain reaction
SGLT2	Sodium glucose cotransporter 2
sitagliptin	Sitagliptin phosphate hydrate
SMBG	Self-Monitoring of Blood Glucose
SMQ	Standardised MedDRA queries
SOC	System organ class
SU	Sulfonylurea
S9	Supernatant fraction after 9000×g centrifugation
Tg	Transgenic
the drug product	Imeglimin hydrochloride
the product	Twymeeg Tablets 500 mg
t_{max}	Time to reach the maximum drug plasma concentration following drug administration
$t_{1/2}$	Elimination half life
TZD	Thiazolidinedione
UV	Ultraviolet absorption spectroscopy
UV-VIS	Ultraviolet-visible absorption spectroscopy
V_{max}	Maximum velocity
ZDF rat	Zucker diabetic fatty rat
α-GI	Alpha-glucosidase inhibitor
γ-GTP	Ganma-glutamyltranspeptidase