Report on the Deliberation Results

June 4, 2024

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

Brand Name Awiqli Injection FlexTouch 300 Units, Awiqli Injection FlexTouch 700 Units
Non-proprietary Name Insulin Icodec (Genetical Recombination) (JAN*)
Applicant Novo Nordisk Pharma Ltd.
Date of Application August 10, 2023

Results of Deliberation

In its meeting held on May 31, 2024, the First Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

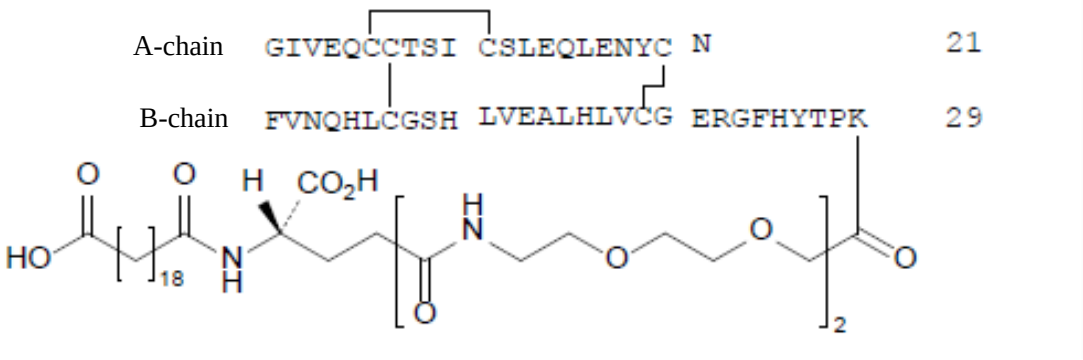
May 20, 2024
Pharmaceuticals and Medical Devices Agency

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

Brand Name	(a) Awiqli Injection FlexTouch 300 Units (b) Awiqli Injection FlexTouch 700 Units
Non-proprietary Name	Insulin Icodec (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 10, 2023
Dosage Form/Strength	(a) Solution for injection: One pre-filled pen (0.43 mL) contains 300 units of insulin icodec (genetical recombination). (b) Solution for injection: One pre-filled pen (1 mL) contains 700 units of insulin icodec (genetical recombination).
Application Classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Insulin Icodec is a recombinant human insulin analogue, in which amino acid residues are substituted at 3 positions (A-chain: Y14E, B-chain: Y16H, F25H), C-terminal T30 of B-chain is deleted, and the ε-amino group of K29 of B-chain is acylated with (22*S*)-22,42-dicarboxy-10,19,24-trioxo-3,6,12,15-tetraoxa-9,18,23-triazadotetracontan-1-oyl group. Insulin Icodec is a modified peptide composed of an A-chain consisting of 21 amino acid residues and a B-chain consisting of 29 amino acid residues.

Structure

Amino acid sequence and main disulfide bonds:



Disulfide bonds: Solid line

Molecular formula:

$C_{280}H_{435}N_{71}O_{87}S_6$ (A-chain, $C_{95}H_{151}N_{25}O_{36}S_4$: B-chain, $C_{185}H_{288}N_{46}O_{51}S_2$ [including modifications])

Molecular weight: 6,380.26 (including modifications, 2 chains)

Items Warranting Special Mention None

Reviewing Office Office of New Drug I

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of diabetes mellitus where treatment with insulin is required, and that the product has acceptable safety in view of its benefits (see Attachment).

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

Indication

Diabetes mellitus where treatment with insulin is required

Dosage and Administration

Usually, for adults, insulin icodec should be injected subcutaneously once weekly. The starting dose is typically 30 to 140 units followed by dose adjustments according to the patient's condition. Insulin icodec may be combined with other insulin products and typically, the weekly total insulin maintenance dose is 30 to 560 units. However, a higher dose than stated above may be used as needed.

Approval Condition

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

Attachment

Review Report (1)

March 29, 2024

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

Product Submitted for Approval

Brand Name	(a) Awiqli Injection 300 Units FlexTouch, (b) Awiqli Injection 700 Units FlexTouch [The brand names will be modified to (a) Awiqli Injection FlexTouch 300 Units and (b) Awiqli Injection FlexTouch 700 Units.]
Non-proprietary Name	Insulin Icodec (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 10, 2023
Dosage Form/Strength	(a) Solution for injection: One pre-filled pen (0.43 mL) contains 300 units of insulin icodec (genetical recombination). (b) Solution for injection: One pre-filled pen (1 mL) contains 700 units of insulin icodec (genetical recombination).
Proposed Indication	Diabetes mellitus where treatment with insulin is required
Proposed Dosage and Administration	The usual adult starting dosage is 30 to 140 units of insulin icodec injected subcutaneously once weekly (corresponding to 4-20 units/day). The dose should be adjusted according to the patient's condition. Insulin icodec may be combined with other insulin products and typically, the weekly total insulin maintenance dose is 30 to 560 units (corresponding to 4-80 units/day). However, a higher dose than stated above may be used as needed.

Table of Contents

List of Abbreviations

See Appendix.

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

The proposed product is presented as a solution for injection containing insulin icodec (genetical recombination) (hereinafter referred to as insulin icodec) as active substance. Insulin icodec is an insulin analog for once-weekly subcutaneous administration, developed by Novo Nordisk (Denmark).

The insulin icodec molecule consists of a modified insulin peptide backbone and a fatty acid-containing sidechain. Threonine at position 30 of the B-chain has been deleted, and 3 amino acids have been substituted. The fatty acid-containing sidechain is attached to the lysine at position 29 of the B-chain. The extension of the half-life of insulin icodec is achieved by reversible binding of the fatty acid-containing sidechain to plasma albumin and lower binding affinity to the insulin receptor due to the amino acid substitutions. Thus, insulin icodec has a longer duration of action than human insulin.

In the treatment of diabetes mellitus with basal insulin, it requires daily injections to maintain glycemic control. Moreover, ≥4 daily injections are required for patients on a basal-bolus regimen. The initiation of insulin therapy is associated with a significant treatment burden for patients and physicians (*Diabet Med*. 2012; 29: 682-9). The burden of multiple daily injections may be a barrier to insulin therapy initiation especially in type 2 diabetes patients (*Prim Care Diabetes*. 2017; 11: 3-12, *Adv Ther*. 2018; 35: 1735-45). Thus, fewer injections with a once weekly insulin product are expected to reduce treatment burden and improve patient adherence, leading to better clinical outcomes (*Int J Clin Pract*. 2021; 75: e13731, *Diabetes Obes Metab*. 2011; 13: 144-9).

Claiming that clinical trial results etc. demonstrated the efficacy and safety of insulin icodec in the treatment of diabetes mellitus where treatment with insulin is required, the applicant has now filed a marketing application for insulin icodec.

Outside Japan, insulin icodec was approved in Switzerland and Canada in March 2024. US and EU applications were filed in April 2023 and are currently under review as of March 2024.

2. Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

The insulin icodec precursor is a modified human insulin where threonine at position 30 of the B-chain has been deleted, tyrosine at position 14 of the A-chain has been substituted with glutamic acid, tyrosine at position 16 of the B-chain and phenylalanine at position 25 of the B-chain have been substituted with histidine, and a binding sequence ([redacted]) and an extension sequence ([redacted]) have been linked to the N-termini of the A-chain and B-chain, respectively. DNA fragments containing the coding sequences for the insulin icodec precursor and [redacted] derived from *S.cerevisiae* [redacted] were prepared. The DNA fragments were inserted into an expression vector to generate the expression construct for the insulin icodec precursor. The expression construct was transfected into *S.cerevisiae*,

and a clone most suitable for the manufacture of the insulin icodec precursor was selected from the cell line and was used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, end of production cells (EPC), and late extended culture (LEC) were characterized and subjected to purity tests in accordance with the ICH Q5B and Q5D guidelines. The test results demonstrated genetic stability during production, and none of the tests revealed microbial contamination other than *S.cerevisiae*.

The MCB and WCB are stored at −80°C. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: inoculation and cell propagation, seed fermentation, main fermentation, clarification, capture (chromatography), ultrafiltration, cleavage,[1)] chromatography, ultrafiltration, acylation,[2)] cleavage, chromatography, chromatography, concentration (chromatography), and spray-drying. Seed fermentation, main fermentation, the first chromatography, cleavage, and chromatography have been defined as critical steps.

Process validation of the commercial-scale drug substance manufacturing process has been performed.

2.1.3 Safety evaluation of adventitious agents

No raw materials of biological origin etc. are used in the drug substance manufacturing process.

The MCB, WCB, EPC, and LEC were subjected to purity tests [see Section "2.1.1 Generation and control of cell substrate"]. Test for microbiological purity is included as in-process controls for culture broth after fermentation.

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, the proposed commercial process). The drug product derived from the drug substance manufactured by Process A was used in phase I and II trials, and the drug products derived from the drug substances manufactured by Process B or the proposed commercial process were used in phase III trials [see Section "6.1 Summary of biopharmaceutic studies and associated analytical methods"].

[1)] The insulin icodec precursor that has a circular structure, is modified into the open precursor through cleavage.

[2)] A sidechain is attached to the lysine at position 29 of the B-chain of the open precursor by acylation.

- Process A → Process B: introduction of a new production strain, introduction of a concentration step and [redacted] cleavage step, changes in the final concentration step and the drying process, manufacturing site and scale changes
- Process B → the proposed commercial process: change of [redacted] and [redacted]/[redacted] steps to [redacted] only, manufacturing site change

For these process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 1.

Table 1. Characterization attributes

Primary/higher order structure	amino acid sequence, the position of the sidechain, the positions of disulfide bonds, secondary structure, tertiary structure
Physicochemical properties	molecular weight, appearance, solubility, pH, isoelectric point, ultraviolet spectrum, hygroscopicity, molecular variants (hydrophilic impurities or related substances, hydrophobic impurities or related substances, HMWPs)
Biological properties	Binding affinity for hIR-A and hIR-B, Akt activation via hIR

As to biological properties, competitive receptor binding studies using [redacted] [redacted] demonstrated the binding affinity of insulin icodec for human insulin receptor type A (hIR-A) and human insulin receptor type B (hIR-B). An assay using [redacted] cells expressing the human insulin receptor demonstrated the phosphorylation of protein kinase B (Akt) by binding of insulin icodec to the IR.

2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc. in Section "2.1.5.1 Structure and properties," sidechain [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted] sequence ([redacted]) [redacted], and [redacted] were considered product-related substances. [redacted], [redacted], [redacted], [redacted], Impurity A, and, high molecular weight proteins (HMWPs) were considered product-related impurities. The product-related impurities are appropriately controlled by the drug substance and drug product specifications.

2.1.5.3 Process-related impurities

Host cell protein (HCP), bacterial endotoxins, microorganisms, host cell DNA, [redacted], [redacted], residual solvents, residual salt ([redacted] salt), impurities derived from acylating reaction, and elemental impurities were considered process-related impurities. All of the process-related impurities have been demonstrated to be adequately removed by the manufacturing process. Bacterial endotoxins and microbial limits are controlled by the drug substance specification.

2.1.6 Control of drug substance

The proposed specifications for the drug substance include content, appearance, identity ([redacted], [redacted]-ultra high performance liquid chromatography [UHPLC]), purity ([redacted]-UHPLC, [redacted]-UHPLC, HCP [redacted]), microbial limits, bacterial endotoxins, loss on drying, bioactivity (Akt activation), and assay ([redacted]-UHPLC).

2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 2.

Table 2. Overview of primary stability studies on drug substance

Study	Manufacturing process	Number of batches	Storage conditions	Testing period	Storage package
Long-term	Process B	3	−20 ± 5°C	36 months[a)]	Low-density polyethylene bag and laminated aluminum bag
	Proposed commercial process	3		18 months[a)]	
Accelerated	Process B	3	5 ± 3°C	12 months	
	Proposed commercial process	3		12 months	
Photostability	Process B	1	An overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/m^2		Glass container

a) The stability studies are ongoing up to [redacted] months.

Under the long-term and accelerated conditions, no significant changes in quality attributes occurred throughout the testing period.

Photostability data showed that the drug substance is photosensitive.

Based on the above, a shelf-life of 36 months was proposed for the drug substance when packaged in a low-density polyethylene bag and stored in a laminated aluminum bag to protect from light, at −20 ± 5°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection. Each glass cartridge contains 300 units (0.43 mL of 700 units/mL) or 700 units (1 mL of 700 units/mL) of insulin icodec and the following excipients: phenol, glycerol, zinc acetate, m-cresol, sodium chloride, hydrochloric acid, sodium hydroxide, and water for injection. The final to-be-marketed drug product is a combination product containing a drug solution in a cartridge assembled into a dedicated pen-injector.

2.2.2 Manufacturing process

The drug product is manufactured through a process comprised of formulation (dissolution of the drug substance/preparation of a drug solution), filling (sterile filtration/filling), assembly into pen-injectors, packaging/labeling/testing, and storage. Formulation and filling have been defined as critical steps.

Process validation of the commercial-scale drug product manufacturing process has been performed.

2.2.3 Manufacturing process development

The major changes made to the drug product manufacturing process during development were changes in the method of dissolution/mixing of the drug substance and the excipients and manufacturing site and scale changes.

For these process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

2.2.4 Control of drug product

The proposed specifications for the drug product include strength, appearance, identity ([redacted]-UHPLC, [redacted]), pH, purity ([redacted]-UHPLC, [redacted]-UHPLC), zinc content ([redacted] method), identity and content of phenol and m-cresol ([redacted]-UHPLC), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, dose accuracy, and assay ([redacted]-UHPLC).

2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 3.

Table 3. Overview of primary stability studies on drug product

Study	Number of primary batches[a]		Storage conditions	Testing period	Storage package
Long-term	300 units variant	3	5 ± 3°C	24 months[b]	Glass cartridge with an aluminum cap with a laminated rubber[c] disc and [redacted] rubber plunger
	700 units variant	3		30 months[b]	
Accelerated	3 each		25 ± 2°C	6 months	
Photostability	1 each		An overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/m^2		

a) Pilot-scale batches derived from the drug substance manufactured by Process B at a manufacturing site different from the commercial manufacturing site
b) The stability studies are ongoing up to [redacted] months.
c) Consisting of 2 layers of [redacted] rubber (in contact with a drug solution) and [redacted] rubber.

Under the long-term condition, hydrophilic related substances and hydrophobic impurities, based on [redacted]-UHPLC, tended to increase, and HMWPs based on [redacted]-UHPLC tended to increase. In the 300 units variant batches, the m-cresol and phenol contents tended to decrease. In the 700 units variant batches, the content tended to decrease. However, no significant changes in other quality attributes occurred.

Under the accelerated condition, in both the 300 and 700 units variant batches, the content and the contents of m-cresol and phenol tended to decrease. In addition to the changes observed in the long-term testing, hydrophilic impurities and hydrophobic related substances, based on [redacted]-UHPLC, tended to increase.

In the photostability testing, the drug product was photosensitive when stored in a cartridge alone. When the cartridge was assembled into a dedicated pen-injector, the pen-injector provided protection from light, and the drug product was photostable.

Based on the above, a shelf-life of 30 months was proposed for the 700 units variant of the drug product when primary packaged in a glass cartridge with an aluminum cap with a laminated rubber disc ([redacted] rubber in contact with a drug solution) and [redacted] rubber plunger and stored in a dedicated pen-injector to protect from light at 2°C to 8°C.

The applicant's explanation:

The additional 30-month long-term stability data on 3 batches will be submitted, and the shelf-life of the 300 units variant of the drug product will be established based on these data.

2.3 Quality control strategy

The following critical quality attributes (CQAs) were identified. The process parameters that impact CQAs, etc., were characterized through design of experiments, quality risk assessment, etc. Critical process parameters (CPPs) were identified, and a control strategy was established.

- Identification of CQAs

  The CQAs of the drug substance: protein structure and bioactivity, content, identity, hydrophilic impurities, hydrophilic related substances, hydrophobic impurities, hydrophobic related substances, HMWPs, leachables, HCP, host cell DNA, residual solvents, residual [redacted], residual [redacted], microbial limits, bacterial endotoxins, appearance

  The CQAs of the drug product: protraction, oligomerization, extractable volume, dose accuracy, appearance, foreign insoluble matter, insoluble particulate matter, strength, HMWPs, hydrophilic impurities, hydrophilic related substances, hydrophobic impurities, hydrophobic related substances, leachables, pH, isotonicity, sterility, preservative content, pyrogens including bacterial endotoxins

2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations etc., PMDA concluded that the quality of the drug substance and the drug product is adequately controlled. The shelf-life of the 300 units variant of the drug product will be established after reviewing the additional long-term stability data to be submitted, and will be described in the Review Report (2).

2.R.1 Control of bioactivity of drug product

The applicant's explanation:

Using the bioactivity assay included in the drug substance specification (measuring Akt phosphorylation in the presence of human serum albumin in [redacted] cells expressing the human insulin receptor), the correlation between the insulin icodec bioactivity and the content (assay [[redacted]-UHPLC]) was investigated. Based on the data from batch analyses and stability studies, except for the samples in [redacted] studies in which [redacted] degraded, the ratio of bioactivity/content ranged from [redacted] to [redacted]. Thus, taking also account of variability in bioactivity assay results, these results indicated that there is a

correlation between the bioactivity and the content. [redacted] in the bioactivity/content ratio were observed at some time points in accelerated studies, which was considered attributable to the formation of Impurity A containing molecular species resulting from [redacted] degradation of [redacted], i.e., degradation products with [redacted] relative potency against insulin icodec. Since the sidechain of insulin icodec reversibly binds to albumin, the relative potency of Impurity A against insulin icodec may have exhibited a [redacted] value than the apparent level in the bioactivity assay performed in the presence of human serum albumin. Although Impurity A is considered to act as [redacted] in the patient's body, Impurity A was not detected in long-term studies, and up to [redacted]% of Impurity A was detected in accelerated studies. Thus, even if Impurity A at a level detected under the accelerated conditions is administered to humans, there should be no clinical concerns. Under the actual production conditions for the drug product and the long-term and accelerated conditions, the bioactivity was maintained. Based on the above, bioactivity assay was not included in the drug product specification, and it was decided to control the bioactivity of the drug product by the strength. Impurity A containing molecular species resulting from [redacted] degradation of [redacted] is controlled by purity test ([redacted]-UHPLC) included in the drug product specification.

PMDA's view:

Taking account of the results of accelerated and forced degradation studies in addition to the results of long-term studies, it cannot be concluded that a correlation between the bioactivity and the content (assay) was shown. However, given that there were no changes in the bioactivity under the actual production conditions and the long-term and accelerated conditions etc., and that Impurity A, which is considered the cause of a trend towards [redacted] in the bioactivity/content ratio under the accelerated conditions, is controlled by purity test ([redacted]-UHPLC), etc., there is no problem with controlling the bioactivity of the drug product by the content and purity test ([redacted]-UHPLC).

2.R.2 Novel excipients

The drug product contains zinc acetate, a novel excipient, in an amount higher than the amounts present in the existing subcutaneous formulations.

PMDA's conclusion:

Zinc acetate conforms to the Japanese Pharmaceutical Excipients (JPE), and there is no problem with the specification or stability. Regarding safety, based on the submitted data, there is no safety problem with the clinical use of insulin icodec.

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

Primary pharmacodynamic studies were conducted to determine the binding affinities of insulin icodec for the insulin receptors, etc., *in vitro* and investigate the blood glucose-lowering effect etc. of insulin icodec in animal models of diabetes *in vivo*. Secondary pharmacodynamic studies were conducted to evaluate the potential off-target binding of insulin icodec to various receptors etc. Safety pharmacology studies were conducted to assess the effects of insulin icodec on the central nervous, cardiovascular, and

respiratory systems. No pharmacodynamic drug interaction studies were conducted. The results from the main studies are described below.

3.1 Primary pharmacodynamics

3.1.1 *In vitro* studies

3.1.1.1 Binding affinities for insulin receptors (CTD4.2.1.1-1 to 4.2.1.1-3, 4.2.1.1-6)

Using the membrane fractions of baby hamster kidney (BHK) cells expressing hIR-A or hIR-B, competitive inhibition of binding of ^{125}I-human insulin to the IR by insulin icodec (approximately 1 pmol/L to 100 nmol/L) or human insulin (approximately 1 pmol/L to 10 nmol/L) was determined by scintillation proximity assay (SPA), and the relative IC_{50}[3)] of insulin icodec compared with human insulin was calculated. The relative IC_{50} values of insulin icodec compared with human insulin for hIR-A and hIR-B were 0.50% and 0.78%, respectively, in the absence of human serum albumin (HSA) and 0.03% and 0.03%, respectively, in the presence of 1.5% HSA.

Using the membrane fractions of BHK cells expressing human, porcine, and rat IR-A or IR-B, competitive inhibition of binding of ^{125}I-human insulin to the IR by insulin icodec (approximately 100 pmol/L to 10 µmol/L) or human insulin (approximately 1 pmol/L to 1 µmol/L) in the presence of 0.1% HSA was determined by SPA. The relative IC_{50}[3)] values of insulin icodec compared with human insulin for IR-A and IR-B were 0.05% and 0.06%, respectively, in the human, 0.07% and 0.06%, respectively, in the pig, and 0.05% and 0.06%, respectively, in the rat.

Using the membrane fractions of human, porcine, canine, and rat liver homogenates, competitive inhibition of binding of ^{125}I-human insulin to the IR by insulin icodec (approximately 100 pmol/L to 10 µmol/L) or human insulin (approximately 1 pmol/L to 1 µmol/L) in the presence of 0.1% HSA was determined by SPA. The relative IC_{50}[3)] values of insulin icodec against human insulin were 0.06% in the human, 0.04% in the pig, 0.05% in the dog, and 0.04% in the rat.

^{3}H-insulin icodec (approximately 5.4 nmol/L) or ^{3}H-human insulin (approximately 8.4 nmol/L) was added to hIR-A-expressing BHK cell culture medium and incubated for varying time periods (0-150 minutes). Then, the cells were lysed, and radioactivity (counts per minute) was measured to calculate the association rate constant. ^{3}H-insulin icodec (approximately 5.4 nmol/L) or ^{3}H-human insulin (approximately 8.4 nmol/L) was added to hIR-A-expressing BHK cell culture medium and incubated for 150 minutes. Then, an excess amount of unlabeled human insulin (1 µmol/L) was added and incubated for varying time periods (0-150 minutes). The cells were lysed, and radioactivity (counts per minute) was measured to calculate the dissociation rate constant. The association rate constant values (mean ± standard error [SE]) of insulin icodec and human insulin were 0.198 ± 0.016 min^{-1} and 0.246 ± 0.004 min^{-1}, respectively. The dissociation rate constant values (mean ± SE) of insulin icodec and human insulin were 0.226 ± 0.044 min^{-1} and 0.071 ± 0.010 min^{-1}, respectively.

[3)] IC_{50} of human insulin/IC_{50} of insulin icodec × 100

3.1.1.2 Activation of insulin receptors (CTD4.2.1.1-7 and 4.2.1.1-8)

Chinese hamster ovary (CHO) cells overexpressing hIR-A or hIR-B were incubated in the medium supplemented with insulin icodec (approximately 100 pmol/L to 10 µmol/L) or human insulin (approximately 10 pmol/L to 1 µmol/L) in the presence of 0.01% ovalbumin for 10 minutes. Then, the cells were lysed, and IR phosphorylation in the cell lysate was measured by an enzyme-linked immune sorbent assay (ELISA) to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec induced autophosphorylation of hIR-A and hIR-B in a concentration-dependent manner, and the relative EC_{50} values of insulin icodec against human insulin were 0.25% and 0.31%, respectively.

CHO cells overexpressing hIR were incubated in the medium supplemented with insulin icodec (1 pmol/L to 10 µmol/L) or human insulin (1 pmol/L to 1 µmol/L) in the presence of 0.1% HSA for 30 minutes. Then, the cells were lysed, and phosphorylation of endogenous Akt in the cell lysate was measured by an ELISA to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec stimulated Akt phosphorylation in a concentration-dependent manner, and the relative EC_{50} of insulin icodec against human insulin was 0.19%.

3.1.1.3 Metabolic effects

3.1.1.3.1 Glucose uptake in adipocytes (CTD4.2.1.1-9 and 4.2.1.1-10)

Primary adipocytes isolated from male SD rat epididymal fat pads were incubated with insulin icodec (approximately 0.1 pmol/L to 1 µmol/L) or human insulin (approximately 0.1 pmol/L to 1 nmol/L), with ^{3}H-glucose, for 2 hours in the presence of 0.1% or 1% HSA. Radioactivity in the lipid fraction extracted from the cells was measured to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec activated glucose uptake in a concentration-dependent manner, and the relative EC_{50} values of insulin icodec against human insulin were 0.03% in the presence of 0.1% HSA and 0.02% in the presence of 1% HSA.

SGBS cells[5)] were exposed to rosiglitazone and subsequently differentiated into mature adipocytes. Then the cells were incubated with insulin icodec (approximately 100 pmol/L to 1 µmol/L) or human insulin (approximately 1 pmol/L to 1 nmol/L), with ^{3}H-glucose, for 4 hours in the presence of 1% HSA, and radioactivity in the cells was measured to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec activated glucose uptake in a concentration-dependent manner, and the relative EC_{50} of insulin icodec against human insulin was 0.06%.

3.1.1.3.2 Glycogen accumulation in hepatocytes (CTD4.2.1.1-11)

Primary male SD rat hepatocytes were incubated with insulin icodec (10 pmol/L to 1 µmol/L) or human insulin (approximately 10 pmol/L to 10 nmol/L) for 18 to 24 hours in the presence or absence of 0.1% HSA. Cellular glycogen content was determined to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec induced glycogen accumulation in a concentration-dependent manner,

[4)] EC_{50} of human insulin/EC_{50} of insulin icodec × 100
[5)] A cell strain derived from stromal cells in the subcutaneous adipose tissue of an infant with Simpson-Golabi-Behmel syndrome. SGBS cells retain high capacity to differentiate into adipocytes.

and the relative EC_{50} values of insulin icodec against human insulin were 4.42% in the absence of HSA and 0.34% in the presence of 0.1% HSA.

3.1.1.3.3 Glycogen synthesis in muscle cells (CTD4.2.1.1-12 and 4.2.1.1-13)

L6 cells (rat skeletal myoblast cell line) overexpressing hIR-A, i.e., L6-hIR cells were cultured in starvation medium containing 0.1% HSA for 3 hours. Then, the cells were incubated with insulin icodec (approximately 100 pmol/L to 1 µmol/L) or human insulin (approximately 10 pmol/L to 100 nmol/L), with ^{14}C-glucose, for 1 hour.

MCF-7 cells (human mammary adenocarcinoma cell line) (insulin increases the proliferation of MCF-7 cells) were cultured in starvation medium containing 0.1% fetal bovine serum (FBS) for 24 hours and subsequently cultured in the medium containing 0.1% FBS and 500 µmol/L glucose for 3 hours. Then, the cells were incubated with insulin icodec (approximately 100 pmol/L to 10 µmol/L) or human insulin (approximately 100 pmol/L to 1 µmol/L), with ^{14}C-glucose, for 3 hours.

In both test systems, the cells were lysed after incubation, and radioactivity in glycogen in the cell lysate was measured to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Insulin icodec stimulated glycogen synthesis in L6-hIR cells and MCF-7 cells in a concentration-dependent manner, and the relative EC_{50} values of insulin icodec against human insulin were 0.52% and 0.26%, respectively.

3.1.1.3.4 Mitogenic effects (CTD4.2.1.1-14 to 4.2.1.1-17)

Insulin icodec (approximately 10 pmol/L to 100 µmol/L) or human insulin (0.1 pmol/L to 1 µmol/L) was added to human mammary epithelial cells (HMECs), COLO-205 cells (human colon adenocarcinoma cell line), MCF-7 cells, and L6-hIR cells. After addition of ^{3}H-thymidine, the cells were incubated. Then, the cellular incorporation of ^{3}H-thymidine was measured to calculate the relative EC_{50}[4)] of insulin icodec against human insulin. Concentration-dependent thymidine incorporation in all cell types was observed, and the relative EC_{50} values of insulin icodec against human insulin in HMECs, COLO-205 cells, MCF-7 cells, and L6-hIR cells were 0.2%, 2.0%, 0.5%, and 0.6%, respectively.

3.1.2 *In vivo* studies

3.1.2.1 Investigation of blood glucose lowering effect in rat model of diabetes (CTD4.2.1.1-18)

Male Zucker diabetic fatty (ZDF) rats (12 weeks of age, 6-7/group) were dosed subcutaneously with insulin icodec (122 or 245 nmol), neutral protamine Hagedorn insulin (NPH insulin) (18 nmol), or vehicle[6)] for 24 days (insulin icodec Q4D, NPH insulin and vehicle BID), and HbA1c was measured on Days −5, −1, 8, 16, and 24. There was a decline in HbA1c over time in the insulin icodec and NPH insulin groups compared with the vehicle group, and the changes in HbA1c from baseline to Day 24 were −1.18% in the insulin icodec 245 nmol group, −0.65% in the insulin icodec 122 nmol group, and −1.58% in the NPH insulin group.

[6)] 7 mmol/L Tris, 30 mmol/L phenol, 1.6% glycerol (pH 7.4)

Male ZDF rats (12 weeks of age, 5/group) were dosed subcutaneously with insulin icodec (15, 31, or 122 nmol), NPH insulin (18 nmol), or vehicle[6)] for 8 days (insulin icodec 122 nmol Q4D, insulin icodec 15 nmol, insulin icodec 31 nmol, NPH insulin, and vehicle BID), and HbA1c was measured on Days 0, 4, and 8. The changes in HbA1c from baseline to Day 8 were −0.70% in the insulin icodec (122 nmol, Q4D) group, −0.96% in the insulin icodec (15 nmol, BID) group, −1.00% in the insulin icodec (31 nmol, BID) group, and −1.32% in the NPH insulin group.

3.1.2.2 Investigation of blood glucose lowering effect in dogs (CTD4.2.1.1-19)

A single subcutaneous dose of insulin icodec 30 nmol/kg was administered to male beagle dogs (approximately 2-2.5 years of age, 5/group) immediately before feeding or 12 hours after feeding, and plasma glucose concentrations were measured from Day 0 to Day 7. Regardless of the timing of dosing, plasma glucose reached a nadir at approximately 24 hours after dosing and gradually recovered over the 7 days after dosing.

3.1.2.3 Hyperinsulinemic euglycemic clamp study in dogs (CTD4.2.1.1-20)

Male beagle dogs (approximately 1-2 years of age, 3/group) were dosed subcutaneously with insulin icodec or insulin glargine (genetical recombination) (IGlar) (2.1 nmol/kg/day, QD) for 7 days (Study Days 0-6) followed by insulin icodec or IGlar 1.05 nmol/kg BID on Study Days 7 to 11. A catheter was inserted into the jugular vein on Study Day 11, and a 12-hour clamp was started immediately after the last injection on the same day. A 20% glucose solution was infused through the jugular vein catheter at a variable rate to maintain euglycemia for 12 hours, and the area under the glucose infusion rate-time curve from time 0 to 12 hours ($AUC_{GIR,\ 0\text{-}12\ h}$) was calculated. Moreover, the doses of insulin icodec and IGlar were increased on Study Days 14 to 25 (4.2 nmol/kg/day QD on Study Days 14-20, 2.1 nmol/kg BID on Study Days 21-25), and then a clamp was conducted on Study Day 25, and the $AUC_{GIR,\ 0\text{-}12\ h}$ was calculated in the same manner. A 3-week washout period was included after Study Day 25, followed by crossover to the other treatment, and the study was repeated in the same manner. Table 4 shows the $AUC_{GIR,\ 0\text{-}12\ h}$ values of insulin icodec and IGlar, and the insulin potency of insulin icodec relative to IGlar determined using a linear regression model developed from $AUC_{GIR,\ 0\text{-}12\ h}$ values etc., with its 95% confidence interval was 190% [124%, 291%].

Table 4. Results of hyperinsulinemic glucose clamps in dogs

Compound	Dose (nmol/kg/day)	$AUC_{GIR,\ 0\text{-}12\ h}$ (mg/kg)[a)]
Insulin icodec	2.1	3060 ± 693
	4.2	4043 ± 647
IGlar	2.1	1477 ± 508
	4.2	3272 ± 1039

Mean ± SD
a) Results of n = 6 (3/group, crossed over)

3.1.2.4 Hyperinsulinemic euglycemic clamp study in pigs (CTD4.2.1.1-21 and 4.2.1.1-22)

Female pigs with a catheter inserted into the jugular vein (approximately 3.5-5 months of age, 6/group) were dosed subcutaneously with insulin icodec (97 nmol or 128 nmol) or IGlar (114 nmol or 150 nmol) once daily for 11 days. A clamp was conducted after the last injection, and a 20% glucose solution was

infused through the jugular vein catheter at a variable rate to maintain euglycemia for 24 hours. The area under the glucose infusion rate-time curve from time 2 to 24 hours[7)] ($AUC_{GIR,\ 2\text{-}24\ h}$) was calculated (Experiment 1).

A similar experiment as Experiment 1 was performed with equimolar doses of insulin icodec and IGlar (114 nmol or 150 nmol) (Experiment 2).

In both experiments, a linear regression model was developed from the obtained data etc., and the insulin potencies of insulin icodec and IGlar were determined using this model. Table 5 shows the $AUC_{GIR,\ 2\text{-}24\ h}$ values of insulin icodec or IGlar in Experiments 1 and 2. The potency of insulin icodec relative to IGlar with its 95% confidence interval was 191% [57%, 645%] in Experiment 1 and 181% [113%, 291%] in Experiment 2.

Table 5. Results of hyperinsulinemic glucose clamps in pigs

Experiment	Compound	Dose (nmol)	$AUC_{GIR,\ 2\text{-}24\ h}$ (mg/kg)
Experiment 1	Insulin icodec	97	4884 ± 1717
		128	5719 ± 1510
	IGlar	114	2792 ± 1761
		150	3753 ± 1811
Experiment 2	Insulin icodec	114	4573 ± 981
		150	6006 ± 1878
	IGlar	114	2494 ± 855
		150	3264 ± 686

Mean ± SD

3.2 Secondary pharmacodynamics

3.2.1 Off-target selectivity (CTD4.2.1.2-1 and 4.2.1.2-2)

The potential off-target binding of insulin icodec (10 µmol/L, approximately 49-fold the C_{max}[8)] following administration of 150 units of insulin icodec) to 67 receptors etc. was evaluated. Insulin icodec inhibited agonist binding at the $GABA_A$ receptor (the binding site for muscimol) by 79% and at the thyroid hormone receptor by 67%.

In a functional follow-up study in the guinea pig ileum, no signs of inhibition or stimulation of the $GABA_A$ receptor by insulin icodec (30 µmol/L) were detected.

3.3 Safety pharmacology

Table 6 shows the effects of insulin icodec on the central nervous, cardiovascular, and respiratory systems.

[7)] Since it was difficult to maintain plasma glucose levels during the initial phase of the clamp (0-2 hours), GIR-AUC data from 2-24 hours were used.

[8)] Steady-state insulin icodec exposure (C_{max} = 204.5 nmol/L) following once weekly administration of 150 units of insulin icodec (the median dose of insulin icodec in Japanese subjects in global phase III trials [Trials 4478, 4480, and 4625]) predicted from a population pharmacokinetic analysis [see Section "6.2.5 Population pharmacokinetic analysis"] was used.

Table 6. Overview of safety pharmacology studies

Organ systems evaluated	Test system	Endpoints/Method of assessment, etc.	Doses of insulin icodec	Route of administration	Findings	CTD
CNS	SD rat (6M/group)	Modified Irwin's test	0,[a] 25, 75, 150 nmol/kg	SC	No effects	4.2.1.3-1
Cardiovascular	HEK293 cells (n = 4/group)	hERG current	0,[b] 10 µmol/L	*In vitro*	7% inhibition of hERG tail current as compared with negative control	4.2.1.3-3
	Isolated rabbit cardiac Purkinje fibers (n = 6/group)	resting membrane potential, action potential duration, action potential amplitude, maximal depolarization velocity	0,[b] 1, 3, 10 µmol/L	*In vitro*	No effects	4.2.1.3-4
	Beagle dog (6M)	arterial blood pressure, heart rate, ECG	0,[a] 7, 14, 21 nmol/kg [c]	SC	No effects	4.2.1.3-5
	Beagle dog (3/sex [a total of 6]/group)	ECG	0,[a] 7, 14, 21/18 [d] nmol/kg	SC	No effects	4.2.3.2-7
	Beagle dog (3/sex [a total of 6]/group)	ECG	0,[a] 6, 12/9,[e] 18/12[e] nmol/kg	SC	No effects	4.2.3.2-8
Respiratory	SD rat (8M/group)	respiratory rate, inspiratory time, expiratory time, relaxation time, tidal volume, minute volume, peak inspiratory flow, peak expiratory flow, airway resistance	0,[a] 25, 75, 150 nmol/kg	SC	No effects	4.2.1.3-2

a) 16 mg/mL glycerol, 2.35 mg/mL phenol, 2.70 mg/mL m-cresol, 1.17 mg/mL sodium chloride, pH 7.4
b) Water for injection
c) Single ascending doses of vehicle, insulin icodec 7 nmol/kg, insulin icodec 14 nmol/kg, and insulin icodec 21 nmol/kg were administered on Days 0, 7, 14, and 21, respectively.
d) The dose level was reduced from 21 nmol/kg to 18 nmol/kg on Day 33 due to adverse clinical signs of severe hypoglycemia in some animals.
e) The dose level was reduced from 18 nmol/kg to 12 nmol/kg on Day 25 due to hypoglycemia in some animals. Accordingly, the intermediate dose was reduced from 12 nmol/kg to 9 nmol/kg.

3.R Outline of the review conducted by PMDA

3.R.1 Pharmacological effect of insulin icodec

The applicant's explanation:

Insulin icodec is an insulin analog, where the amino acid sequence of human insulin is modified, and a fatty acid-containing sidechain is added to prolong the action of insulin icodec compared with human insulin. In *in vitro* studies, insulin icodec bound to the IR and stimulated post-IR signaling pathways and cellular metabolic responses. Insulin icodec demonstrated lower binding affinity for the IR than human insulin. In *in vivo* studies, insulin icodec lowered HbA1c levels in the rat model of diabetes. In a study that investigated the blood glucose lowering effect of insulin icodec and a hyperinsulinemic euglycemic clamp study in dogs, etc., insulin icodec decreased plasma glucose levels. Based on the above, the pharmacology studies conducted showed the glucose-lowering effect of insulin icodec, and its efficacy in the treatment of diabetes is expected. Although a weak inhibition of hERG channel current was observed at 10 µmol/L of insulin icodec (49-fold the C_{max}[8]) following administration of 150 units of insulin icodec) in a safety pharmacology study, there were no effects of insulin icodec on QT interval in single and repeated dose studies in dogs. Thus, no effects of insulin icodec on the central nervous, cardiovascular, and respiratory systems were identified in the safety pharmacology studies conducted.

PMDA's view:

Given the results of the primary pharmacodynamic studies conducted, though insulin icodec demonstrated lower binding affinity for the IR than human insulin, as with human insulin, insulin icodec was shown to bind to the IR and stimulate cellular metabolic responses etc. As with NPH insulin and IGlar, insulin icodec lowered blood glucose in *in vivo* studies, indicating the potential efficacy of insulin icodec in treating diabetes. The results of safety pharmacology studies raised no safety concerns about the effects of insulin icodec on the central nervous, cardiovascular, and respiratory systems. The protraction of the glucose lowering action of insulin icodec and the efficacy of insulin icodec in clinical use will be discussed in Sections "6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec" and "7.R.1 Efficacy."

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

The pharmacokinetics following a single subcutaneous administration of insulin icodec or ^{3}H-insulin icodec in rats, rabbits, or dogs were characterized. The pharmacokinetics following repeated subcutaneous administration of insulin icodec were characterized based on toxicokinetics in toxicity studies in rats, rabbits, or dogs. Insulin icodec in plasma was quantified by luminescent oxygen channeling immunoassay (LOCI), and the lower limit of quantification (LLOQ) was 266 to 300 pmol/L in rats and dogs and 300 pmol/L in rabbits. Radioactivity in biological samples was measured using high performance liquid chromatography-radioactivity detection (HPLC-RAD). The results from the main studies are described below. In the following sections, unless otherwise specified, ^{3}H-insulin icodec, where the fatty acid sidechain was ^{3}H-labelled, was used.

4.1 Absorption

4.1.1 Single-dose studies (CTD4.2.1.3-1, 4.2.3.1-1)

Table 7 shows the pharmacokinetic parameters following a single subcutaneous administration of insulin icodec in rats or rabbits.

Table 7. Pharmacokinetic parameters following a single subcutaneous administration of insulin icodec

Animal species	Dose (nmol/kg)	Sex	Number of animals	C_{max} (nmol/L)	AUC [a)] (nmol·h/L)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)	V_z/F (mL/kg)
Rat	25	M	3/time point	92.1	3340	24	—	—	—
	75	M	3/time point	333.0	11400	24	—	—	—
	150	M	3/time point	662.0	23900	24	—	—	—
Rabbit	10	F	5	68.6 ± 5.3	3280 ± 205	8 [8, 12]	25 ± 2 [b)]	3.08 ± 0.15 [b)]	113 ± 12 [b)]

Mean ± SD (Calculated from the mean concentration data at each time point in rats.), Median [Range] (Median in rats) for t_{max}, —, Not calculated
C_{max}: maximum plasma concentration, AUC: area under the plasma concentration-time curve, t_{max}: time to reach the maximum plasma concentration, $t_{1/2}$: elimination half-life, CL/F: apparent clearance, V_z/F: apparent volume of distribution during terminal phase
a) area under the plasma concentration-time curve from time 0 to 48 hours in rats, area under the plasma concentration-time curve from time 0 to the last measurable concentration sampling time in rabbits
b) n = 4

4.1.2 Repeated-dose studies (CTD4.2.3.2-3, 4.2.3.2-8, 4.2.3.5.2-1)

Table 8 shows the pharmacokinetic parameters following once daily subcutaneous administration of insulin icodec in rats and pregnant rabbits and twice weekly subcutaneous administration of insulin icodec in dogs.

Table 8. Pharmacokinetic parameters following repeated subcutaneous administration of insulin icodec

Animal species	Dose (nmol/kg)	Number of animals	Sampling time point	C_{max} (nmol/L)		AUC[a] (nmol·h/L)		t_{max} (h)		$t_{1/2}$ (h)	
				M	F	M	F	M	F	M	F
Rat	20	3/time point	Day −5[b]	82.8	75.6	1430	1340	4	8	15.5	16.1
		3/time point	Week 13	175	180	3490	3600	4	8	—	—
		3/time point	Week 26	210	170	4340	3290	8	2	25.0	21.2
	40	3/time point	Day −5[b]	194	153	3250	2730	8	4	15.7	16.9
		3/time point	Week 13	397	532	8520	7800	8	4	—	—
		3/time point	Week 26	392	445	8920	8000	4	4	27.3	21.3
	60	3/time point	Day −5[b]	259	238	4750	4210	8	8	16.0	15.6
		3/time point	Week 13	621	547	12700	12000	8	8	—	—
		3/time point	Week 26	581	573	12500	12400	4	8	26.5	19.4
	80	3/time point	Day −5[b]	331	—	5680	—	8	—	17.0	—
		3/time point	Week 13	892	—	17800	—	8	—	—	—
		3/time point	Week 26	897	—	18600	—	8	—	26.0	—
Pregnant rabbit[c]	12	3/time point	Day 1	—	75.3	—	1410	—	24	—	—
		3/time point	Day 18	—	221	—	4670	—	8	—	—
	18	3/time point	Day 1	—	108	—	2150	—	24	—	—
		3/time point	Day 18	—	325	—	7320	—	4	—	—
	24	3/time point	Day 1	—	145	—	2930	—	24	—	—
		3/time point	Day 18	—	429	—	9370	—	4	—	—
Dog	6	4	Day 1	37.9	46.6	2610	3080	18.0	18.0	56.5	49.9
		4	Day 88	66.9	79.4	4680	5100	15.0	11.0	—	—
		4	Day 190	67.1	68.5	4680	4870	18.0	21.0	—	—
	12/9 [d]	7	Day 1	78.3	113	5510	6050	24.0	18.0	55.9	47.4
		7	Day 88	109	123	7320	7970	12.0	18.0	—	—
		7	Day 190	113	116	7930	7970	18.0	12.0	61.1 [f]	60.7 [f]
	18/12 [e]	7	Day 1	119	143	8110	8960	24.0	18.0	52.6	47.5
		7	Day 88	154	182	10500	12400	24.0	18.0	—	—
		7	Day 190	155	170	11000	11400	12.0	8.00	58.2 [f]	62.2 [f]

Mean (Calculated from the mean concentration data at each time point in rats and rabbits), Median for t_{max}, —, Not calculated

C_{max}: maximum plasma concentration, AUC: area under the plasma concentration-time curve, t_{max}: time to reach the maximum plasma concentration, $t_{1/2}$: elimination half life

a) area under the plasma concentration-time curve from time 0 to 24 hours in rats and rabbits, area under the plasma concentration-time curve from time 0 to 96 hours in dogs

b) A single dose was administered 5 days before the initiation of 26-week administration.

c) Insulin icodec was administered from gestation day 2 to gestation day 19.

d) The dose level was reduced from 12 nmol/kg to 9 nmol/kg on Day 25.

e) The dose level was reduced from 18 nmol/kg to 12 nmol/kg on Day 25.

f) n = 3

In the above studies, anti-insulin icodec antibodies were detected in 3 of 39 rats (1 of 20 males, 2 of 19 females) in the 20 nmol/kg group, 4 of 39 rats (3 of 20 males, 1 of 19 females) in the 40 nmol/kg group, 2 of 39 rats (1 of 20 males, 1 of 19 females) in the 60 nmol/kg group, and 2 of 20 rats (males only) in the 80 nmol/kg group at Week 27. Anti-insulin icodec antibodies were detected in 2 of 8 dogs (0 of 4 males, 2 of 4 females) in the 6 nmol/kg group, 3 of 14 dogs (0 of 7 males, 3 of 7 females) in the 12/9 nmol/kg group, and 3 of 14 dogs (1 of 7 males, 2 of 7 females) in the 18/12 nmol/kg group at Day 194. No anti-insulin icodec antibodies were detected in rabbits.

4.2 Distribution

4.2.1 Plasma protein binding (CTD5.3.2.1-1)

The mean fraction unbound of insulin icodec (1.57 µmol/L) to plasma protein (surface plasmon resonance [SPR]) was 0.017% to 0.023% in mice, 0.006% to 0.011% in rats, 0.014% in rabbits, and 0.019% to 0.033% in dogs [for human data, see Section "6.2.1 Studies using human biomaterials"].

4.2.2 Tissue distribution (CTD4.2.2.3-1)

Tissue distribution was investigated up to 168 hours following a single subcutaneous administration of ^{3}H-insulin icodec 75 nmol/kg to male albino rats (n = 9, 1/time point). Maximum radioactivity concentrations were noted in most tissues at 12 to 24 hours post-dose, and the tissue to blood radioactivity concentration ratio based on the $AUC_{0\text{-}168\ h}$ was high in the tooth pulp (1.53), kidney cortex (outer cortex) (1.31), and bile duct (1.27). The lowest radioactivity levels were detected in the meninges (0.276), choroid plexus (0.194), spinal cord (0.012), and brain (0.009). Little radioactivity was detected in each tissue at 168 hours post-dose.

4.3 Metabolism

4.3.1 *In vitro* metabolism (CTD5.3.2.2-1)

Using mouse, rat, rabbit, and dog hepatocytes, the metabolism of insulin icodec was investigated *in vitro*. Hepatocytes were incubated with ^{3}H-insulin icodec (10 nmol/L or 1.0 µmol/L) for 4 hours at 37°C. ^{3}H-insulin icodec that remained unchanged was undetectable in mouse, rat, and dog hepatocytes, and the mean percentage of ^{3}H-insulin icodec that remained unchanged was 3.82% in rabbit hepatocytes, at 10 nmol/L. At 1.0 µmol/L, the mean percentage of ^{3}H-insulin icodec that remained unchanged was 28.5% in mouse hepatocytes, 47.5% in rat hepatocytes, 61.2% in rabbit hepatocytes, and 53.4% in dog hepatocytes. In total, 14 metabolites were identified.

4.3.2 *In vivo* metabolism

4.3.2.1 Plasma metabolites (CTD4.2.2.4-5 and 4.2.2.4-6)

Following a single subcutaneous dose of ^{3}H-insulin icodec[9)] 75 nmol/kg in male rats (n = 8, 1/time point), 1 metabolite was found in plasma, and insulin icodec and the metabolite accounted for 97.7% and 2.3% of the $AUC_{0\text{-}168\ h}$ of plasma radioactivity, respectively.

Following a single subcutaneous dose of ^{3}H-insulin icodec[9)] 18 nmol/kg in male dogs (n = 2), 8 metabolites were identified in plasma, and insulin icodec and the metabolites accounted for 74.1% and 0.66% to 8.71% of the $AUC_{0\text{-}336\ h}$ of plasma radioactivity, respectively.

4.3.2.2 Urinary, fecal, and biliary metabolites (CTD4.2.2.4-2, 4.2.2.4-6)

Following a single subcutaneous dose of ^{3}H-insulin icodec 75 nmol/kg in male rats (n = 3), no unchanged insulin icodec was detected in urine up to 168 hours post-dose, and 11 metabolites were identified, which represented 0.04% to 0.23% of the administered radioactivity. No unchanged insulin icodec was detected in feces up to 168 hours post-dose, and 9 metabolites were identified, which represented 0.24% to 7.49% of the administered radioactivity. Following a single subcutaneous dose of ^{3}H-insulin icodec 75 nmol/kg in bile duct cannulated male rats (n = 2), no unchanged insulin icodec was detected in bile up to 48 hours post-dose, and 13 metabolites were identified, which represented 0.06% to 2.52% of the administered radioactivity.

[9)] The linker to the fatty acid sidechain was ^{3}H-labelled.

Following a single subcutaneous dose of ^{3}H-insulin icodec[9)] 18 nmol/kg in male dogs (n = 2), 5.62% of the administered radioactivity was found in urine as unchanged compound over 336 hours, and 15 metabolites were identified in urine, which represented 0.13% to 12.5% of the administered radioactivity. No unchanged insulin icodec was detected in feces up to 336 hours post-dose, and 17 metabolites were identified in feces, which represented 0.11% to 3.82% of the administered radioactivity.

4.4 Excretion (CTD4.2.2.5-1 and 4.2.2.5-2)

Following a single subcutaneous dose of ^{3}H-insulin icodec 75 nmol/kg in male rats (n = 3), the mean cumulative recoveries of the administered radioactivity in urine, feces, and carcass over 168 hours were 21.7%, 31.0%, and 39.0%,[10)] respectively. Following a single subcutaneous dose of ^{3}H-insulin icodec 75 nmol/kg in bile duct cannulated male rats (n = 4), the mean cumulative recovery of the administered radioactivity in bile over 48 hours was 10.4%.

Following a single subcutaneous dose of ^{3}H-insulin icodec[9)] 18 nmol/kg in male dogs (n = 2), the mean cumulative recoveries of the administered radioactivity in urine, feces, and carcass over 336 hours were 44.0%, 26.7%, and 6.2%, respectively.

4.R Outline of the review conducted by PMDA

PMDA's view:

The submitted non-clinical pharmacokinetic data raised no particular concerns about the clinical use of insulin icodec, though the pharmacokinetics of insulin icodec were not compared with those of the existing insulin products such as human insulin. The pharmacokinetic and pharmacodynamic characteristics of insulin icodec in humans will be discussed in Section "6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec."

5. Toxicity and Outline of the Review Conducted by PMDA

As toxicity studies of insulin icodec, repeated-dose toxicity, reproductive and developmental toxicity, and local tolerance studies were conducted. The results from the main studies are described below.

5.1 Single-dose toxicity

No single-dose toxicity studies were conducted, and the acute toxicity of insulin icodec was assessed based on the findings after the first dose in repeated-dose toxicity studies in rats and dogs (Table 9). No deaths or signs of acute toxicity were observed, and the approximate lethal dose of insulin icodec by subcutaneous route was determined to be >150 nmol/kg in rats and >21 nmol/kg in dogs.

[10)] Radioactivity in the carcass was considered attributable to tritiated water produced from β-oxidation of ^{3}H-fatty acid sidechain.

Table 9. Overview of the findings after the first dose in repeated-dose toxicity studies

Test system	Route of administration	Dose (nmol/kg)	Noteworthy findings	Approximate lethal dose (nmol/kg)	Attached document CTD
Male and female rats (SD)	SC	0,[a] 25, 75, 150	None	>150	4.2.3.2-2
Male and female dogs (Beagle)	SC	0,[b] 7, 14, 21	None	>21	4.2.3.2-7

a) 2.35 mg/mL phenol, 2.7 mg/mL m-cresol, 1.17 mg/mL sodium chloride, 16 mg/mL glycerol, pH 7.4
b) 0.067 mg/mL phenol, 0.077 mg/mL m-cresol, 1.17 mg/mL sodium chloride, 20.9 mg/mL glycerol, pH 7.4

5.2 Repeated-dose toxicity

Repeated-dose toxicity studies of up to 52 weeks duration in rats and of up to 26 weeks duration in dogs were conducted (Table 10). Toxicological findings were observed primarily in the pancreas, sciatic/tibial nerve, skeletal muscle, brown fat, myocardial muscle, and testes. The applicant explained that all findings were attributable to an exaggerated pharmacodynamic effect of insulin in normal animals (hypoglycemia).

The $C_{average}$ (408.8 nmol/L in rats, 116.7 nmol/L in dogs) at the no observed adverse effect level (NOAEL) following 52-week administration in rats or following 26-week administration in dogs (40 nmol/kg [once daily] in rats, 12 nmol/kg [twice weekly] in dogs) was 2.6-fold or 0.7-fold the $C_{average}$[11)] in humans following administration of insulin icodec 150 units, respectively.

[11)] Steady-state insulin icodec exposure ($C_{average}$ = 157.4 nmol/L) following once weekly administration of 150 units of insulin icodec (the median dose of insulin icodec in Japanese subjects in global phase III trials [Trials 4478, 4480, and 4625]) predicted from a population pharmacokinetic analysis [see Section "6.2.5 Population pharmacokinetic analysis"] was used to calculate exposure ratios.

Table 10. Overview of repeated-dose toxicity studies

Test system	Route of administration	Duration of dosing	Dose (nmol/kg)	Noteworthy findings	NOAEL (nmol/kg)	Attached document CTD
Male and female rats (SD)	SC	8 weeks (once daily) + 6-week recovery period	0,[a] 25, 75, 150/100[b]	Mortalities: 75 (1 of 20 males, 2 of 20 females), 150/100 (6 of 20 females)[c] ≥25: increased prostate gland weights, decreased kidney weights (male), increased ovary weights, vacuolation in brown fat ≥75: decreased white blood cells, increased AST, increased blood creatine kinase (female), decreased liver weights, decreased spleen weights, islet atrophy, axonal degeneration of the sciatic nerve, degeneration/necrosis/axonal degeneration of the myofibers in skeletal muscle, increased fat content of the bone marrow (female), increased urine volume (female), increased urine protein (female) 150/100: decreased body weight, increased ALT (female), vacuolation in the zona fasciculata of the adrenal cortex (male) These findings were reversible.	100	4.2.3.2-2
Male and female rats (SD)	SC	26 weeks (once daily) + 12-week recovery period	Males: 0,[a] 20, 40, 60, 80 Females: 0,[a] 20, 40, 60	Mortalities: 20 (1 of 20 males, 1 of 20 females), 40 (1 of 20 females), 60 (1 of 20 females)[c] ≥20: islet atrophy, vacuolation in brown fat, ≥40: increased urine volume, increased urine potassium concentrations, increased urine volume (female), decreased liver weights (female) ≥60: increased body weight gain, increased plasma urea concentrations (female), increased urine chloride concentrations, axonal degeneration of the sciatic nerve (female), degeneration/necrosis/axonal degeneration of the myofibers in skeletal muscle (female) 80: increased plasma sodium concentrations (male) These findings were reversible.	80 (males) 60 (females)	4.2.3.2-3
Male and female rats (SD)	SC	52 weeks (once daily)	Males: 0,[d] 20, 40, 60 Females: 0,[d] 20, 30, 40 HI: 40	Mortalities: 20 (6 of 40 males, 1 of 40 females), 40 (1 of 40 males, 4 of 48 females), 60 (2 of 48 males)[c] ≥20: increased plasma fibrinogen concentrations, decreased liver weights (male), small/soft testis, axonal degeneration of the sciatic nerve ≥30: increased plasma urea/creatinine concentrations (female), increased plasma sodium/chloride concentrations (female), prolongation of activated partial thromboplastin time, decreased kidney weights (female), myocardial fibrosis (female) ≥40: reduced prothrombin time, islet atrophy, degeneration/necrosis of the myofibers in skeletal muscle, vacuolation in brown fat (male) HI: reduced prothrombin time, prolongation of activated partial thromboplastin time, increased plasma chloride concentrations (female), decreased liver weights, small/soft testis, axonal degeneration of the sciatic nerve (female), myocardial fibrosis (female)	60 (males) 40 (females)	4.2.3.2-4

Male and female dogs (Beagle)	SC	8 weeks (twice weekly) + 6-week recovery period	0,[a)] 7, 14, 21/18 [e)]	≥7: soft/watery feces, decreased endogenous insulin concentrations ≥14: increased plasma phosphorus concentrations (male) 21: tremor, abnormal gait, increased body weight gain, increased plasma sodium concentrations (female) These findings were reversible.	18	4.2.3.2-7
Male and female dogs (Beagle)	SC	26 weeks (twice weekly) + 12-week recovery period	0,[a)] 6, 12/9 [f)], 18/12 [f)]	≥6: decreased liver weights (female) 18: tremor, ataxia These findings were reversible.	12	4.2.3.2-8

a) 2.35 mg/mL phenol, 2.7 mg/mL m-cresol, 1.17 mg/mL sodium chloride, 16 mg/mL glycerol, pH 7.4
b) The dose level was reduced from 150 nmol/kg to 100 nmol/kg on Day 28 because 3 females in the 150 nmol/kg/day group died.
c) Mortalities were considered related to an exaggerated pharmacodynamic effect of insulin icodec (hypoglycemia) or unrelated to insulin icodec.
d) 5.65 mg/mL phenol, 1.08 mg/mL m-cresol, 1.17 mg/mL sodium chloride, 15 mg/mL glycerol, 0.53 mg/mL disodium phosphate dihydrate, pH 7.4
e) The dose level was reduced from 21 nmol/kg to 18 nmol/kg on Day 33 due to adverse clinical signs of severe hypoglycemia in some animals.
f) The dose level was reduced from 18 nmol/kg to 12 nmol/kg on Day 25 due to hypoglycemia in some animals. Accordingly, the intermediate dose was reduced from 12 nmol/kg to 9 nmol/kg.

5.3 Genotoxicity

Since insulin icodec is a peptide produced by recombinant DNA technology, it is not expected that insulin icodec would interact directly with DNA or other chromosomal material. Thus, no genotoxicity studies with insulin icodec were conducted. *In silico* (Q)SAR analysis and a bacterial reverse mutation assay (Ames assay) were performed on the fatty acid sidechain of insulin icodec, both of which produced negative results. The sidechain was considered to have no mutagenic potential.

5.4 Carcinogenicity

Since insulin icodec is a peptide produced by recombinant DNA technology, no carcinogenicity studies were conducted. The applicant concluded that the carcinogenic risk of insulin icodec is low because insulin icodec shows lower mitogenic activity than human insulin [see Section "3.1.1.3.4 Mitogenic effects"], and there were no insulin icodec-related hyperplastic or neoplastic lesions in repeated-dose toxicity studies in rats and dogs [see Section "5.2 Repeated-dose toxicity"].

5.5 Reproductive and developmental toxicity

A fertility and embryo-fetal development study in rats, an embryo-fetal development study in rabbits, and a rat study for effects on pre- and postnatal development, including maternal function, were conducted (Table 11).

There were no particular effects on fertility, embryo-fetal development, or pups in these studies.

Table 11. Overview of reproductive and developmental toxicity studies

Type of study	Test system	Route of administration	Duration of dosing	Dose (nmol/kg/day)	Noteworthy findings	NOAEL (nmol/kg/day)	Attached document CTD
Fertility and embryo-fetal development	Male rat (SD)	SC	from 4 weeks prior to mating until the day before necropsy (once daily)	0,[a] 40, 60, 100	Mortality[b]: 100 (1 of 22 animals) ≥60: increased body weight gain 100: increased body weight, decreases in epididymis/testis weights	General toxicity: 100 Reproductive function: 100	4.2.3.5.1-2
	Female rat (SD)		from 2 weeks prior to mating until gestation day 17 (once daily)	0,[a] 10, 30, 60	Dams 60: decreased body weight gain Fetuses: None	General toxicity: 60 Reproductive function: 60 Early embryonic development: 60	
Embryo-fetal development	Female rabbit (NZW)	SC	Gestation days 2-19 (once daily)	0,[a] 6, 12, 18	Dams: Mortalities[b]: 12 (1 of 22 animals), 18 (1 of 22 animals) 18: abortion [c] Fetuses: None	Maternal general toxicity: 18 Embryo-fetal development: 18	4.2.3.5.2-2
Pre- and postnatal development, including maternal function	Female rat (SD)	SC	Dams: from gestation day 6 until lactation day 20 (once daily)	0,[d] 20, 35, 50	Dams: Mortalities[b]: 50 (4 of 22 animals) 50: decreases in body weight/body weight gain, decreased food consumption, an increase in the duration of gestation F1 pups (pre-weaning): 50: decreased survival, decreased body weight gain F1 pups (post-weaning): None	Maternal general toxicity: 35 F1 offspring pre- and post-natal development: 35	4.2.3.5.3-1

a) 2.35 mg/mL phenol, 2.70 mg/mL m-cresol, 1.17 mg/mL sodium chloride, 16 mg/mL glycerol, pH 7.4
b) Mortalities were considered related to an exaggerated pharmacodynamic effect of insulin icodec (hypoglycemia) or unrelated to insulin icodec.
c) The finding was considered related to an exaggerated pharmacodynamic effect of insulin icodec in dams (hypoglycemia and decreased food consumption).
d) 5.65 mg/mL phenol, 1.08 m-cresol, 1.17 mg /mL sodium chloride, 15 mg/mL glycerol, 0.53 mg/mL disodium phosphate dihydrate, pH 7.4

5.6 Local tolerance

Local tolerance studies of insulin icodec were conducted in pigs and minipigs (Table 12). The applicant concluded that there were no differences in local reactions between the insulin icodec and vehicle groups.

Table 12. Overview of local tolerance studies

Test system	Route of administration	Test method	Noteworthy findings	Attached document CTD
Female pig (LYD)	SC	Repeated administration of insulin icodec (4200 nmol/mL), vehicle[a)] A or B, or saline 100 µL (28 days, once weekly)	Inflammatory cell infiltration, adipocyte necrosis, and activated fibroblasts were observed. There were no differences in the findings between the insulin icodec and vehicle groups.	4.2.3.6-1
Female minipig (Göttingen)	SC	Repeated administration of insulin icodec (4200 nmol/mL) or vehicle[b)] 30 µL using pen-injector (13 weeks, once weekly)	Focal hemorrhage and inflammatory cell infiltration were observed. There were no differences in the findings between the insulin icodec and vehicle groups.	4.2.3.6-3

a) Composition of vehicle A: 2.35 mg/mL phenol, 2.7 mg/mL m-cresol, 16 mg/mL glycerol, 1.17 mg/mL sodium chloride, pH 7.4
Composition of vehicle B: 1.5 mg/mL phenol, 1.73 mg/mL m-cresol, 16 mg/mL glycerol, 1.17 mg/mL sodium chloride, pH 7.4
b) 5.65 mg/mL phenol, 0.53 mg/mL disodium phosphate dihydrate, 1.08 mg/mL m-cresol, 15 mg/mL glycerol, 1.17 mg/mL sodium chloride, pH 7.4

5.R Outline of the review conducted by PMDA

PMDA's view:

The submitted toxicity study data raised no particular concerns about the clinical use of insulin icodec as compared with the existing insulin products, from a toxicological point of view. The safety of insulin icodec in humans will be discussed in Section "7.R.2 Safety."

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 of insulin icodec, the drug products derived from the drug substances manufactured by different processes (Process A, Process B, the proposed commercial process) were used. Table 13 shows the drug products used in clinical trials. In the sections below, trial numbers are abbreviated, e.g., Trial NN1436-4422 is Trial 4422.

Table 13. Drug products used in clinical trials

Drug substance manufacturing process	Development phase (Trial Number)	
	Japanese or global trials	Foreign trials
Process A	Phase I (Trial 4422)	Phase I (Trials 4225, 4226, 4314, and 4462) Phase II (Trials 4383, 4465, and 4466)
Process B	Phase III (Trials 4477, 4478, 4480, and 4625)	Phase I (Trials 4462, 4569, 4570, 4571, and 4572) Phase III (Trials 4479 and 4481)
Proposed commercial process	Phase III (Trials 4477 and 4625)	—

—, Not applicable

Insulin icodec in human serum was quantified by LOCI, and the LLOQ was 500 pmol/L. Anti-insulin icodec antibodies in human serum were analyzed by radioimmunoassay (RIA).

The applicant submitted the results from a foreign phase I trial investigating the pharmacokinetic properties of insulin icodec after administration in different injection regions (Trial 4572) as reference data on biopharmaceutics.

6.1.1 Phase I trial investigating the pharmacokinetic properties of insulin icodec after administration in different injection regions (CTD5.3.1.1-1, Trial 4572 [October 2020 to September 2021] Reference data)

A randomized, open-label, 3-period crossover trial was conducted to investigate the pharmacokinetic and pharmacodynamic properties of insulin icodec after administration in different injection regions (the abdomen, the upper arm, the thigh) in non-Japanese patients with type 2 diabetes mellitus (target sample size, 24 subjects).

Subjects were to receive single subcutaneous injections of insulin icodec 5.6 units/kg in the abdomen, upper arm, or thigh, and a 4- to 8-week washout period was included between the periods. A glucose clamp (target of 135 mg/dL) was conducted at 36 to 60 hours after administration of insulin icodec.

All of 25 treated subjects were included in the safety analysis set and the full analysis set (FAS), and the FAS was used for pharmacokinetic and pharmacodynamic analyses.

Table 14 shows the pharmacokinetic parameters following a single subcutaneous dose of insulin icodec. The geometric mean ratios of C_{max} and $AUC_{0\text{-}inf}$ with their 95% confidence intervals were 1.17 [1.07, 1.29] and 1.02 [0.96, 1.09], respectively, for abdomen vs. thigh and 1.24 [1.14, 1.35] and 1.04 [0.98, 1.10], respectively, for upper arm vs. thigh.

Table 14. Pharmacokinetic parameters following single subcutaneous injection of insulin icodec 5.6 units/kg in the abdomen, upper arm, or thigh

Parameter	Abdomen (N = 24)	Upper arm (N = 23)	Thigh (N = 23)
C_{max} (nmol/L)	337.8 (23.8)	364.8 (19.6)	291.9 (24.3)
$AUC_{0\text{-}inf}$ (nmol·h/L)	69541.0 (22.2)	71324.2 (17.1)	68164.7 (18.6)
t_{max} (h)	24.0 [12.0, 48.0]	24.0 [12.0, 30.0]	27.0 [21.0, 96.0]

Geometric mean (coefficient of variation %), Median [Range] for t_{max}
C_{max}: maximum serum concentration, $AUC_{0\text{-}inf}$: area under the serum concentration-time curve from time 0 to infinity
t_{max}: time to reach the maximum serum concentration

Regarding pharmacodynamic effects, the geometric mean (coefficient of variation %) of the area under the glucose infusion rate-time curve (AUC_{GIR}) was 2130 mg/kg (51.6%) following injection in the abdomen, 2391 mg/kg (39.6%) following injection in the upper arm, and 1961 mg/kg (51.3%) following injection in the thigh.

Regarding safety, the incidences of adverse events and adverse drug reactions were 26.1% (6 of 23 subjects) and 13.0% (3 of 23 subjects), respectively, following injection in the abdomen, 37.5% (9 of 24 subjects) and 12.5% (3 of 24 subjects), respectively, following injection in the upper arm, and 26.1% (6 of 23 subjects) and 13.0% (3 of 23 subjects), respectively, following injection in the thigh. There were no deaths, serious adverse events, or adverse events leading to treatment discontinuation.

6.2 Clinical pharmacology

The applicant submitted the results from 1 Japanese trial (Trial 4422) as evaluation data and the results from 8 foreign trials (Trials 4225, 4226, 4314, 4462, 4569, 4570, 4571, and 4572) and the results of a

population pharmacokinetic analysis and a population pharmacokinetic/pharmacodynamic analysis as reference data. The applicant also submitted the results from studies using human biomaterials. The results from the main studies are described below.

6.2.1 Studies using human biomaterials (CTD5.3.2.1-1 and 5.3.2.1-2, 5.3.2.2-1)

The mean fraction unbound of insulin icodec (1.57 μmol/L) to plasma protein in humans (SPR) was 0.015% to 0.017%, and the mean fraction unbound to serum albumin was 0.013% to 0.014%.

The metabolism of ^{3}H-insulin icodec (10 nmol/L and 1.0 μmol/L) was investigated *in vitro* in human hepatocytes. Following 4-hour incubation, the mean percentage of ^{3}H-insulin icodec that remained unchanged was undetectable at 10 nmol/L and 61.1% at 1.0 μmol/L. Eight metabolites at 10 nmol/L and 4 metabolites at 1.0 μmol/L were identified.

6.2.2 Patient trials

6.2.2.1 Foreign phase I trial in patients with type 2 diabetes mellitus (CTD5.3.4.2-3, Trial 4314 [November 2016 to December 2017] Reference data)

A randomized, double-blind trial was conducted to investigate the pharmacokinetics, pharmacodynamics, and safety of multiple subcutaneous doses of insulin icodec or insulin degludec (genetical recombination) (IDeg) in non-Japanese patients with type 2 diabetes mellitus (target sample size, 48 subjects [16 per cohort]).

Key inclusion criteria: Type 2 diabetes mellitus patients aged 18 to 64 years who (1) were treated with 0.3-1.0 units/kg/day of insulin and had (2) HbA1c of ≤9.0% and (3) BMI of 20.0 to 34.9 kg/m^2.

Once weekly insulin icodec (2.0, 3.3, or 4.0 units/kg) or once daily IDeg 0.4 units/kg was to be administered subcutaneously in the thigh for 5 weeks. A glucose clamp (target of 100 mg/dL) was conducted at Week 5.[12)]

All of 50 treated subjects (13 in the insulin icodec 2.0 units/kg group, 13 in the insulin icodec 3.3 units/kg group, 12 in the insulin icodec 4.0 units/kg group, 12 in the IDeg group) were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic and pharmacodynamic analyses.

Figure 1 shows serum insulin icodec concentration-time profiles following multiple subcutaneous administration of insulin icodec and serum IDeg concentration-time profiles following multiple subcutaneous administration of IDeg, and Table 15 shows the pharmacokinetic parameters.

[12)] A glucose clamp was conducted at 24-48 hours (Day 30) and 144-168 hours (Day 35) after dosing at Week 5 in the insulin icodec group and on Days 2 and 7 of Week 5 (at 0-24 hours after dosing on Days 30 and 35) in the IDeg group.

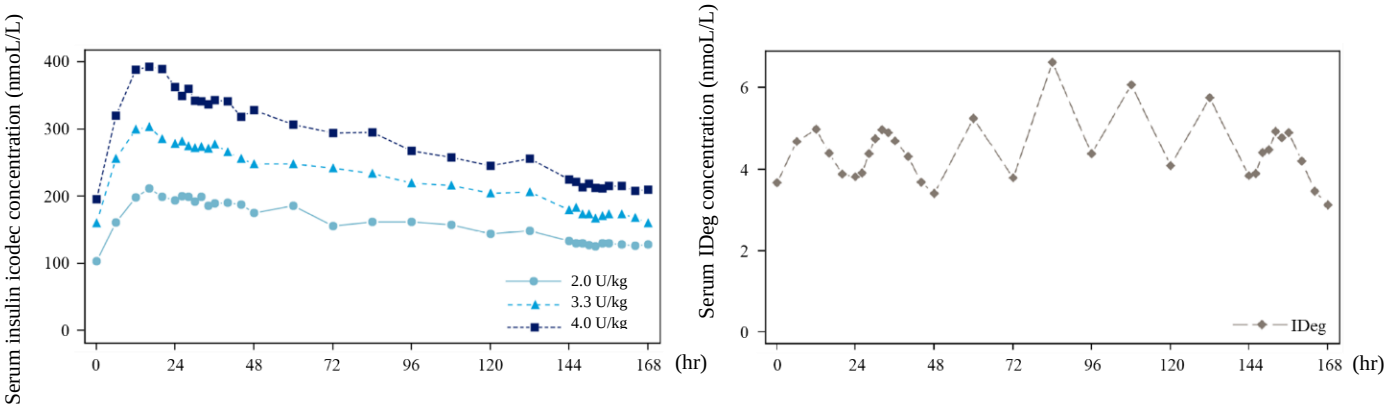


Figure 1. Serum insulin icodec or IDeg concentration-time profiles at Week 5 (Insulin icodec group [Left figure], IDeg group [Right figure]) (Mean)

Table 15. Pharmacokinetic parameters following multiple subcutaneous administration of insulin icodec or IDeg

Time point	Treatment group	Dose (units/kg)	N	C_{max} (nmol/L)	AUC (nmol·h/L)	t_{max} (h)	$t_{1/2}$ (h)	CL/F (mL/h/kg)	V_{ss}/F (mL/kg)
After dosing at Week 1[a)]	Insulin icodec	2.0	13	100.4 (16.1)	11848.4 (12.3)	23.9 [10.0, 108.0]	—	—	—
		3.3	13	159.6 (24.6)	18874.2 (16.6)	18.0 [16.0, 71.9]	—	—	—
		4.0	12	196.0 (11.2)	22504.8 (10.4)	20.0 [10.0, 47.9]	—	—	—
	IDeg	0.4	12	2.6 (28.4)	45.4 (34.3)	14.0 [10.0, 18.0]	—	—	—
After dosing at Week 5[b)]	Insulin icodec	2.0	13	223.9 (22.0)[c)]	26254.4 (27.8)[c)]	16.0 [12.0, 40.0][c)]	238 (27.6)[c)]	0.461 (26.5)[c)]	169 (28.2)[c)]
		3.3	13	309.9 (19.3)[d)]	37602.2 (22.9)[d)]	16.0 [12.0, 36.0][d)]	170 (19.8)[d)]	0.528 (17.8)[d)]	142 (13.3)[d)]
		4.0	12	414.5 (21.2)	46918.7 (24.1)	16.0 [12.0, 84.0]	188 (20.8)	0.511 (19.0)	148 (13.2)
	IDeg	0.4	12	5.1 (24.3)	99.1 (25.8)	8.0 [6.0, 20.0]	27 (25.0)[c)]	24.0 (22.3)	1339 (23.2)

Geometric mean (coefficient of variation %), Median [Range] for t_{max}, —, Not calculated
C_{max}: maximum serum concentration, AUC: area under the serum concentration-time curve from time 0 to 168 hours after dosing in the insulin icodec group and area under the serum concentration-time curve from time 0 to 24 hours after dosing in the IDeg group
t_{max}: time to reach the maximum serum concentration, $t_{1/2}$: elimination half-life, CL/F: apparent clearance, V_{ss}/F: apparent volume of distribution at steady state
a) Calculated from the serum concentrations on Day 1 in the IDeg group.
b) In the IDeg group, the C_{max}, AUC, and t_{max} were calculated from serum concentrations on Day 30, and the $t_{1/2}$, CL/F, and V_{ss}/F were calculated from serum concentrations on Day 35.
c) N = 11, d) N = 12

Table 16 shows the pharmacodynamic parameters following multiple subcutaneous administration of insulin icodec or IDeg.

Table 16. Pharmacodynamic parameters following multiple subcutaneous administration of insulin icodec or IDeg

Parameter	Time point	Insulin icodec 2.0 units/kg (N = 12)	Insulin icodec 3.3 units/kg (N = 11)	Insulin icodec 4.0 units/kg (N = 12)	IDeg 0.4 units/kg (N = 12)
$AUC_{GIR,0\text{-}24\ h}$ (mg/kg)	Day 30	796 (52.9)	2092 (64.9)	1924 (62.3)	1086 (56.6)
	Day 35	724 (62.4)[a)]	1560 (54.6)	1468 (53.8)[b)]	1295 (57.3)
GIR_{max} (mg/kg/min)	Day 30	1.0 (32.8)	2.0 (52.9)	2.0 (50.5)	1.3 (38.0)
	Day 35	0.9 (38.2)[a)]	1.7 (46.4)	1.7 (43.2)[b)]	1.4 (48.6)

Geometric mean (coefficient of variation %)
$AUC_{GIR,0\text{-}24\ h}$: area under the glucose infusion rate-time curve from time 0 to 24 hours after initiation of glucose infusion
GIR_{max}: maximum glucose infusion rate
a) N = 11, b) N = 10

The proportions of subjects who were positive for anti-insulin icodec antibodies at any time after treatment initiation were 30.8% (4 of 13 subjects) in the insulin icodec 2.0 units/kg group, 53.8% (7 of

13 subjects) in the insulin icodec 3.3 units/kg group, and 58.3% (7 of 12 subjects) in the insulin icodec 4.0 units/kg group.

Regarding safety, the incidences of adverse events and adverse drug reactions were 100% (13 of 13 subjects) and 53.8% (7 of 13 subjects), respectively, in the insulin icodec 2.0 units/kg group, 69.2% (9 of 13 subjects) and 7.7% (1 of 13 subjects), respectively, in the insulin icodec 3.3 units/kg group, 75.0% (9 of 12 subjects) and 0% (0 of 12 subjects), respectively, in the insulin icodec 4.0 units/kg group, and 100% (12 of 12 subjects) and 8.3% (1 of 12 subjects), respectively, in the IDeg 0.4 units/kg group. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported. There were no clinically relevant changes in laboratory parameters, vital signs, or ECG.

6.2.2.2 Japanese phase I trial in patients with type 1 diabetes mellitus (CTD5.3.4.2-1, Trial 4422 [December 2018 to December 2019] Evaluation data)

A randomized, open-label, 2-period crossover trial was conducted to investigate the pharmacokinetics, pharmacodynamics, and safety of multiple subcutaneous doses of insulin icodec or IGlar (100 units/mL) in Japanese type 1 diabetes mellitus patients (target sample size, 24 subjects).

Key inclusion criteria: Type 1 diabetes mellitus patients aged 20 to 64 years who (1) were treated with ≥0.2 units/kg/day of basal insulin and had (2) HbA1c of ≤9.0% and (3) BMI of 18.5 kg/m^2 to 28.0 kg/m^2.

The doses of insulin icodec and IGlar were individualized.[13)] Once weekly insulin icodec was to be administered subcutaneously in the thigh for 8 weeks, or once daily IGlar (100 units/mL) was to be administered subcutaneously in the thigh for 2 weeks. Treatment periods were separated by approximately 2 weeks (optional for subjects who received insulin icodec first), and subjects were to receive IGlar during this period. A glucose clamp (target of 120 mg/dL) was conducted at Week 8 of treatment with insulin icodec and on Day 14 of treatment with IGlar.[14)]

All of 24 treated subjects were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic and pharmacodynamic analyses.

Table 17 shows the pharmacokinetic parameters following multiple subcutaneous administration of insulin icodec or IGlar. After dosing of insulin icodec at Week 8, the $t_{1/2}$ was 164 hours (11.4%), the CL/F was 0.553 mL/h/kg (10.6%), and the V_{ss}/F was 137 mL/kg (17.7%) [geometric mean (coefficient of variation %)].

[13)] Subjects were to receive IGlar during the run-in period. IGlar was titrated to a pre-breakfast SMBG target of 80-130 mg/dL to establish the individual IGlar dose. The dose of insulin icodec was 7 times the individual IGlar dose established during the run-in period.
[14)] A glucose clamp was conducted at 24-48 hours and 150-168 hours after dosing of insulin icodec at Week 8 and at 0-24 hours after dosing of IGlar on Day 14.

Table 17. Pharmacokinetic parameters following subcutaneous administration of once weekly insulin icodec or once daily IGlar

Parameter	Insulin icodec		IGlar
	After dosing at Week 1 (N = 24)	After dosing at Week 8 (N = 24)	After dosing on Day 14 (N = 24)
Dose (units/kg)	1.71 [1.2, 3.1]	1.69 [1.2, 3.1]	0.24 [0.2, 0.4]
Dose-normalized C_{max} (nmol/L/(units/kg))	52.2 (19.0)	91.2 (14.7)	0.399 (38.9)
Dose-normalized AUC (nmol·h/L/(units/kg))	6108.5 (12.8)	10849.0 (10.6)	7.36 (38.2)
t_{max} (h)	12.0 [12.0, 36.0]	16.0 [12.0, 18.0]	4.0 [2.0, 16.0]

Geometric mean (coefficient of variation %), Mean [Range] for dose, Median [Range] for t_{max}
C_{max}: maximum serum concentration
AUC: area under the serum concentration-time curve from time 0 to 168 hours after dosing of insulin icodec and area under the serum concentration-time curve from time 0 to 24 hours after dosing of IGlar
t_{max}: time to reach the maximum serum concentration

Regarding pharmacodynamic effects, the geometric means (coefficient of variation %) of the area under the glucose infusion rate-time curve (AUC_{GIR}) and the maximum glucose infusion rate (GIR_{max}) were 1505 mg/kg (42.7%) and 1.6 mg/kg/min (30.4%), respectively, at 24 to 48 hours after dosing of insulin icodec at Week 8, 512 mg/kg (45.3%) and 1.4 mg/kg/min (27.2%), respectively, at 150 to 168 hours after dosing of insulin icodec at Week 8, and 1136 mg/kg (36.7%) and 1.3 mg/kg/min (22.0%), respectively, at 0 to 24 hours after dosing of IGlar on Day 14.

The proportion of subjects who were positive for anti-insulin icodec antibodies at any time after treatment initiation was 62.5% (15 of 24 subjects).

Regarding safety, the incidences of adverse events and adverse drug reactions were 45.8% (11 of 24 subjects) and 4.2% (1 of 24 subjects), respectively, after administration of insulin icodec and 8.3% (2 of 24 subjects) and 0% (0 of 24 subjects), respectively, after administration of IGlar. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported. There were no clinically relevant changes in laboratory parameters, vital signs, or ECG.

6.2.2.3 Foreign phase I trial in patients with type 1 diabetes mellitus (CTD5.3.4.2-2, Trial 4225 [November 2018 to June 2020] Reference data)

A randomized, open-label, 2-period crossover trial was conducted to investigate the pharmacokinetics, pharmacodynamics, and safety of multiple subcutaneous doses of insulin icodec or IGlar (100 units/mL) in non-Japanese type 1 diabetes mellitus patients (target sample size, 66 subjects).

Key inclusion criteria: Type 1 diabetes mellitus patients aged 18 to 64 years who (1) were treated with ≥0.2 units/kg/day of basal insulin and had (2) HbA1c of ≤9.0% and (3) BMI of 18.5 kg/m^2 to 29.0 kg/m^2.

The doses of insulin icodec and IGlar were individualized.[13)] Once weekly insulin icodec was to be administered subcutaneously in the thigh for 8 weeks, or once daily IGlar (100 units/mL) was to be administered subcutaneously in the thigh for 2 weeks. Treatment periods were separated by approximately 2 weeks (optional for subjects who received insulin icodec first), and subjects were to

receive IGlar during this period. A glucose clamp (target of 120 mg/dL) was conducted at Week 8 of treatment with insulin icodec and on Day 14 of treatment with IGlar.[15)]

All of 66 treated subjects were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic and pharmacodynamic analyses.

Table 18 shows the pharmacokinetic parameters following multiple subcutaneous administration of insulin icodec or IGlar. After dosing of insulin icodec at Week 8, the $t_{1/2}$ was 175 hours (19.3%), the CL/F was 0.479 mL/h/kg (23.0%), and the V_{ss}/F was 128 mL/kg (14.5%) [geometric mean (coefficient of variation %)].

Table 18. Pharmacokinetic parameters following subcutaneous administration of once weekly insulin icodec or once daily IGlar

Parameter	Insulin icodec		IGlar
	After dosing at Week 1 (N = 65)	After dosing at Week 8 (N = 65)	After dosing on Day 14 (N = 65)
Dose (units/kg)	1.92 [1.2, 3.2]	1.91 [1.1, 3.3]	0.27 [0.2, 0.5]
Dose-normalized C_{max} (nmol/L/(units/kg))	54.4 (18.1)	99.3 (23.2)	0.526 (76.0)
Dose-normalized AUC (nmol·h/L/(units/kg))	6503.1 (13.9)	12524.8 (23.0)	9.81 (78.9)
t_{max} (h)	18.0 [12.0, 119.9]	18.1 [6.0, 96.0]	6.0 [2.0, 16.0]

Geometric mean (coefficient of variation %), Mean [Range] for dose, Median [Range] for t_{max}
C_{max}: maximum serum concentration
AUC: area under the serum concentration-time curve from time 0 to 168 hours after dosing of insulin icodec and area under the serum concentration-time curve from time 0 to 24 hours after dosing of IGlar
t_{max}: time to reach the maximum serum concentration

Regarding pharmacodynamic effects, the geometric means (coefficient of variation %) of the area under the glucose infusion rate-time curve (AUC_{GIR}) and the maximum glucose infusion rate (GIR_{max}) were 2589 mg/kg (45.7%) and 1.7 mg/kg/min (38.6%), respectively, at 16 to 52 hours after dosing of insulin icodec at Week 8, 983 mg/kg (67.3%) and 1.1 mg/kg/min (48.9%), respectively, at 138 to 168 hours after dosing of insulin icodec at Week 8, and 1040 mg/kg (81.0%) and 1.3 mg/kg/min (58.8%), respectively, at 0 to 24 hours after dosing of IGlar on Day 14.

The proportion of subjects who were positive for anti-insulin icodec antibodies at any time after treatment initiation was 76.9% (50 of 65 subjects).

Regarding safety, the incidences of adverse events and adverse drug reactions were 50.8% (33 of 65 subjects) and 3.1% (2 of 65 subjects), respectively, after administration of insulin icodec and 16.7% (11 of 66 subjects) and 0% (0 of 66 subjects), respectively, after administration of IGlar. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported. There were no clinically relevant changes in laboratory parameters, vital signs, or ECG.

[15)] A glucose clamp was conducted at 16-52 hours and 138-168 hours after dosing of insulin icodec at Week 8 and at 0-24 hours after dosing of IGlar on Day 14.

6.2.2.4 Foreign phase I trial in patients with type 2 diabetes mellitus (CTD5.3.4.2-5, Trial 4569 [October 2020 to April 2022] Reference data)

An open-label trial was conducted to investigate the pharmacokinetics and pharmacodynamics of multiple subcutaneous doses of insulin icodec in non-Japanese type 2 diabetes mellitus patients (target sample size, 45 subjects).

Key inclusion criteria: Type 2 diabetes mellitus patients aged 18 to 75 years who (1) were treated with ≥0.2 units/kg/day of basal insulin and had (2) HbA1c of ≤9.0% and (3) BMI of 18.0 kg/m^2 to 38.0 kg/m^2.

Once weekly insulin icodec was to be administered at an individualized dose[16)] subcutaneously in the thigh for 8 weeks.[17)] A glucose clamp (target of 135 mg/dL) was conducted at Weeks 6, 7, and 8.[18)]

All of 46 treated subjects were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic and pharmacodynamic analyses.

Table 19 shows the pharmacokinetic parameters following multiple subcutaneous administration of insulin icodec. After dosing of insulin icodec at Week 8, the $t_{1/2}$ was 155 hours (15.3%), the CL/F was 0.47 mL/h/kg (20.0%), and the V_{ss}/F was 112 mL/kg (16.5%) [geometric mean (coefficient of variation %)].

Table 19. Pharmacokinetic parameters following once weekly subcutaneous administration of insulin icodec

Parameter	After dosing at Week 1 (N = 46)	After dosing at Week 8 (N = 42)
Dose (units/kg)	2.56 [1.21, 5.27]	2.91 [1.53, 5.64]
Dose-normalized C_{max} (nmol·kg/L/(units/kg))	50.8 (22.5)	105.8 (21.0)[a)]
Dose-normalized $AUC_{0\text{-}168\ h}$ (nmol·h/L/(units/kg))	6064.5 (15.8)	12748.4 (20.0)[a)]
t_{max} (h)	21.2 [11.6, 59.9]	15.1 [12.0, 42.0][a)]

Geometric mean (coefficient of variation %), Mean [Range] for dose, Median [Range] for t_{max}
C_{max}: maximum serum concentration, $AUC_{0\text{-}168\ h}$: area under the serum concentration-time curve from time 0 to 168 hours after dosing
t_{max}: time to reach the maximum serum concentration
a) N = 41

Regarding pharmacodynamic effects, the geometric mean (coefficient of variation %) of the area under the glucose infusion rate-time curve (AUC_{GIR}) was 4763 mg/kg (29.1%) at 0 to 36 hours after dosing of insulin icodec at Week 6, 3393 mg/kg (26.5%) at 40 to 64 hours after dosing of insulin icodec at Week 7, and 2602 mg/kg (36.4%) at 144 to 168 hours after dosing of insulin icodec at Week 8.

The proportion of subjects who were positive for anti-insulin icodec antibodies at any time after treatment initiation was 87.0% (40 of 46 subjects).

16) Subjects were to receive IDeg during the run-in period. IDeg was titrated to a pre-breakfast SMBG target of 80-126 mg/dL to establish the individual IDeg dose. The dose of insulin icodec was 7 times the individual IDeg dose established during the run-in period.
17) Patients who had been treated with stable doses of metformin, DPP-4 inhibitor, SGLT2 inhibitor, oral antidiabetic combination therapy, or GLP-1 receptor agonist for ≥90 days prior to screening could be enrolled in the trial. These patients were to continue these hypoglycemic drugs using the same dosing regimens as those used at screening throughout the trial period.
18) A glucose clamp was conducted at 0-36 hours after dosing at Week 6, at 40-64 hours after dosing at Week 7, and at 144-168 hours after dosing at Week 8.

Regarding safety, the incidences of adverse events and adverse drug reactions were 52.2% (24 of 46 subjects) and 15.2% (7 of 46 subjects), respectively. No deaths or serious adverse events were reported. Adverse events leading to treatment discontinuation occurred in 3 subjects (pruritic rash; rash; and pruritus and angioedema, 1 subject each), all of which were classified as adverse drug reactions. There were no clinically relevant changes in laboratory parameters, vital signs, or ECG.

6.2.3 Intrinsic factor pharmacokinetic trials

6.2.3.1 Pharmacokinetic trial in subjects with renal impairment (CTD5.3.3.3-1, Trial 4226 [November 2018 to September 2019] Reference data)

An open-label, parallel-group trial was conducted to investigate the pharmacokinetics and safety of insulin icodec by the degree of renal impairment (glomerular filtration rate [GFR] [mL/min],[19] normal, ≥90; mild, ≥60 and <90; moderate, ≥30 and <60; severe, <30; and end-stage renal disease requiring hemodialysis [ESRD]) in non-Japanese adult male and female subjects (target sample size, 60 subjects).

A single subcutaneous dose of insulin icodec 1.5 units/kg was to be administered.

All of 58 treated subjects (12 subjects with normal renal function, 12 subjects with mild renal impairment, 12 subjects with moderate renal impairment, 12 subjects with severe renal impairment, 10 ESRD subjects) were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic analysis.

Table 20 shows the pharmacokinetic parameters in subjects with normal renal function or renal impairment. The geometric mean ratio of C_{max} with its 95% confidence interval was 1.05 [0.85, 1.30] for mild renal impairment vs. normal renal function, 1.05 [0.85, 1.30] for moderate renal impairment vs. normal renal function, 0.91 [0.74, 1.13] for severe renal impairment vs. normal renal function, and 1.02 [0.81, 1.29] for ESRD vs. normal renal function. The geometric mean ratio of $AUC_{0\text{-}840\ h}$ with its 95% confidence interval was 1.12 [0.96, 1.31], 1.21 [1.04, 1.41], 1.16 [0.99, 1.36], and 1.13 [0.95, 1.33], respectively.

Table 20. Pharmacokinetic parameters in subjects with normal renal function or renal impairment

Parameter	Normal renal function (N = 12)	Mild renal impairment (N = 12)	Moderate renal impairment (N = 12)	Severe renal impairment (N = 12)	ESRD (N = 10)
C_{max} (nmol/L)	84.7 (17.1)	90.7 (14.6)	91.1 (24.9)	76.9 (48.1)	80.4 (18.4)
$AUC_{0\text{-}840\ h}$ (nmol·h/L)	17390.9 (14.3)	19888.3 (9.8)	21366.4 (8.2)	19857.0 (36.6)	18590.8 (16.2)
t_{max} (h)	15.0 [6.0, 62.0]	15.0 [12.2, 18.0]	21.0 [15.0, 72.1]	21.1 [14.8, 63.8]	18.1 [12.0, 83.7]
$t_{1/2}$ (h)	139 (11.2)	160 (9.0)	169 (7.6)	178 (18.6)	171 (9.0)
CL/F (mL/h/kg)	0.507 (14.2)	0.442 (9.8)	0.408 (8.2)	0.437 (36.8)	0.466 (15.6)
V_z/F (mL/kg)	102 (8.7)	102 (9.4)	99 (9.9)	112 (45.1)	115 (16.5)

Geometric mean (coefficient of variation %), Median [Range] for t_{max}
C_{max}: maximum serum concentration, $AUC_{0\text{-}840\ h}$: area under the serum concentration-time curve from time 0 to 840 hours after dosing
t_{max}: time to reach the maximum serum concentration, $t_{1/2}$: elimination half-life, CL/F: apparent clearance
V_z/F: apparent volume of distribution during terminal phase

[19] Classified based on the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) equation using iohexol.

The proportion of subjects who were positive for anti-insulin icodec antibodies after treatment initiation was 33.3% (4 of 12 subjects) in subjects with normal renal function, 41.7% (5 of 12 subjects) in subjects with mild renal impairment, 16.7% (2 of 12 subjects) in subjects with moderate renal impairment, 8.3% (1 of 12 subjects) in subjects with severe renal impairment, and 20.0% (2 of 10 subjects) in ESRD subjects.

Regarding safety, the incidences of adverse events and adverse drug reactions were 25.0% (3 of 12 subjects) and 16.7% (2 of 12 subjects), respectively, in subjects with normal renal function, 41.7% (5 of 12 subjects) and 16.7% (2 of 12 subjects), respectively, in subjects with mild renal impairment, 50.0% (6 of 12 subjects) and 16.7% (2 of 12 subjects), respectively, in subjects with moderate renal impairment, 50.0% (6 of 12 subjects) and 25.0% (3 of 12 subjects), respectively, in subjects with severe renal impairment, and 50.0% (5 of 10 subjects) and 10.0% (1 of 10 subjects), respectively, in ESRD subjects. Serious adverse events occurred in 1 ESRD subject (fall, skin laceration, and craniocerebral injury), but a causal relationship to insulin icodec was denied for all those events. No deaths or adverse events leading to trial discontinuation were reported.

6.2.3.2 Pharmacokinetic trial in subjects with hepatic impairment (CTD5.3.3.3-2, Trial 4570 [December 2020 to March 2022] Reference data)

An open-label, parallel-group trial was conducted to investigate the pharmacokinetics of insulin icodec by the degree of hepatic impairment (Classification of hepatic impairment based on the Child-Pugh scores: score 5-6 [mild], score 7-9 [moderate], score 10-15 [severe]) in non-Japanese adult male and female subjects (target sample size, 24 subjects).

A single subcutaneous dose of insulin icodec 1.5 units/kg was to be administered.

All of 25 treated subjects (6 subjects with normal hepatic function, 6 subjects with mild hepatic impairment, 6 subjects with moderate hepatic impairment, 7 subjects with severe hepatic impairment) were included in the safety analysis set and FAS, and the FAS was used for pharmacokinetic analysis.

Table 21 shows the pharmacokinetic parameters in subjects with normal hepatic function or hepatic impairment. The geometric mean ratio of C_{max} with its 95% confidence interval was 1.13 [0.90, 1.42] for mild hepatic impairment vs. normal hepatic function, 1.05 [0.83, 1.31] for moderate hepatic impairment vs. normal hepatic function, and 0.97 [0.77, 1.21] for severe hepatic impairment vs. normal hepatic function, and the geometric mean ratio of $AUC_{0\text{-}inf}$ with its 95% confidence interval was 1.13 [1.00, 1.28], 1.15 [1.02, 1.29], and 0.97 [0.86, 1.09], respectively.

Table 21. Pharmacokinetic parameters in subjects with normal hepatic function or hepatic impairment

Parameter	Normal hepatic function (N = 6)	Mild hepatic impairment (N = 6)	Moderate hepatic impairment (N = 6)	Severe hepatic impairment (N = 7)
C_{max} (nmol/L)	78.6 (13.4)	82.6 (24.1)	80.4 (27.8)	73.2 (19.8)[a)]
$AUC_{0\text{-}inf}$ (nmol·h/L)	17153.5 (8.8)	18326.4 (18.8)	19100.2 (14.5)	16118.2 (18.7)[a)]
t_{max} (h)	22.5 [14.9, 26.9]	17.9 [11.9, 24.0]	25.5 [15.0, 60.0]	27.0 [15.0, 35.9][a)]
$t_{1/2}$ (h)	134 (12.3)	134 (7.1)	148 (14.5)	161 (6.8)[b)]
CL/F (mL/h/kg)	0.52 (9.5)	0.50 (20.4)	0.47 (14.8)	0.56 (17.3)[a)]
V_z/F (mL/kg)	101 (12.0)	96 (14.3)	102 (22.9)	130 (19.6)[b)]

Geometric mean (coefficient of variation %), Median [Range] for t_{max}
C_{max}: maximum serum concentration, $AUC_{0\text{-}inf}$: area under the serum concentration-time curve from time 0 to infinity
t_{max}: time to reach the maximum serum concentration, $t_{1/2}$: elimination half-life, CL/F: apparent clearance
V_z/F: apparent volume of distribution during terminal phase
a) N = 6, b) N = 5

Regarding safety, the incidences of adverse events and adverse drug reactions were 0% (0 of 6 subjects) and 0% (0 of 6 subjects), respectively, in subjects with normal hepatic function, 16.7% (1 of 6 subjects) and 16.7% (1 of 6 subjects), respectively, in subjects with mild hepatic impairment, 16.7% (1 of 6 subjects) and 0% (0 of 6 subjects), respectively, in subjects with moderate hepatic impairment, and 57.1% (4 of 7 subjects) and 28.6% (2 of 7 subjects), respectively, in subjects with severe hepatic impairment. Serious adverse events occurred in 3 subjects with severe hepatic impairment (intestinal haemorrhage and pleural effusion; loss of consciousness; and hypokalaemia, 1 subject each), and intestinal haemorrhage and pleural effusion; and loss of consciousness were classified as adverse drug reactions. Adverse events leading to trial discontinuation occurred in 2 subjects with severe hepatic impairment (pleural effusion; and loss of consciousness, 1 subject each), both of which were classified as adverse drug reactions. No deaths were reported.

6.2.4 Pharmacodynamic trial

6.2.4.1 Trial investigating hypoglycemic response (CTD5.3.4.2-4, Trial 4462 [May 2019 to September 2021] Reference data)

A randomized, open-label, 2-period crossover trial was conducted to compare the counterregulatory response to hypoglycemia induced by overdosing of insulin icodec or IGlar (100 units/mL) in non-Japanese type 2 diabetes mellitus patients (target sample size, 43 subjects).

Key inclusion criteria: Type 2 diabetes mellitus patients aged 18 to 72 years who (1) were treated with basal insulin (total insulin dose of 0.2-1.0 units/kg/day) and had (2) HbA1c of ≤9.0% and (3) BMI of 18.5 kg/m^2 to 37.9 kg/m^2.

The doses of insulin icodec and IGlar were individualized.[20)] Once weekly insulin icodec was to be administered subcutaneously in the thigh for 6 weeks, or once daily IGlar was to be administered subcutaneously in the thigh for 12 days. During 6-week treatment with insulin icodec, based on the individual dose of insulin icodec (a normal dose), a double dose was to be administered at Week 1, followed by a normal dose at Week 2, a double dose at Week 3, no dose at Week 4, a normal dose at

[20)] The individual dose of insulin icodec or IGlar was determined based on the IGlar dose optimized during the run-in period. Subjects were to receive IGlar during the run-in period. IGlar was titrated to a pre-breakfast SMBG target of 80-130 mg/dL to establish the individual IGlar dose. A normal dose of insulin icodec was defined as 7 times the individual IGlar dose established during the run-in period, and a normal dose of IGlar was defined as the individual IGlar dose established during the run-in period.

Week 5, and a triple dose at Week 6. During 12-day treatment with IGlar, based on the individual dose of IGlar (a normal dose), IGlar was to be administered at a normal dose for 3 days followed by a double dose on Day 4, no dose on Day 5, a normal dose for 5 days, a triple dose on Day 11, and no dose on Day 12. Treatment periods were separated by 35 to 49 days of washout following insulin icodec and 4 to 11 days of washout following IGlar, and subjects received IGlar during this period. A glucose clamp (target of 100 mg/dL) was conducted[21)] at Weeks 3 and 6 of treatment with insulin icodec and on Days 4 and 11 of treatment with IGlar. Hypoglycemia induction was initiated by terminating glucose infusion after a double dose of insulin icodec at Week 3 and a triple dose of insulin icodec at Week 6 and after a double dose of IGlar on Day 4 and a triple dose of IGlar on Day 11 to assess the hypoglycemic response. Specifically, at 44 hours after dosing of insulin icodec and at 7 hours after dosing of IGlar, plasma glucose was allowed to decline towards <45 mg/dL, which was maintained for 15 minutes, and the hypoglycemic response was assessed during this period. Subsequently, glucose was infused at a constant rate (5.5 mg/kg/min) until plasma glucose was 100 mg/dL, and then the plasma glucose target was maintained by variable infusion of glucose.

All of 43 treated subjects were included in the safety analysis set and FAS, and the FAS was used for pharmacodynamic analysis.

Table 22 shows the pharmacodynamic parameters following a double or triple dose of insulin icodec or IGlar. The proportion of subjects who experienced level 2 hypoglycemia (plasma glucose <54 mg/dL) was 39.5% (17 of 43 subjects) following a double dose of insulin icodec, 52.6% (20 of 38 subjects) following a triple dose of insulin icodec, 35.7% (15 of 42 subjects) following a double dose of IGlar, and 70.0% (28 of 40 subjects) following a triple dose of IGlar. The changes in hypoglycemic symptoms score[22)] from the termination of glucose infusion to PG_{nadir} (mean ± SD) were 5.85 ± 7.30 following a double dose of insulin icodec, 5.30 ± 5.34 following a triple dose of insulin icodec, 6.37 ± 7.83 following a double dose of IGlar, and 5.07 ± 5.11 following a triple dose of IGlar.

Table 22. Pharmacodynamic parameters following a double or triple dose of insulin icodec or IGlar

Parameter	Double dose of insulin icodec (N = 43)	Triple dose of insulin icodec (N = 38)	Double dose of IGlar (N = 42)	Triple dose of IGlar (N = 40)
PG_{nadir} (mg/dL)	57.63 (12.35)	55.97 (13.40)	59.31 (16.65)	51.89 (13.98)
$t_{decline,\ PG54\ mg/dL}$ (h)	4.81 ± 4.59 [a)]	3.65 ± 4.08 [b)]	5.68 ± 3.20 [c)]	3.07 ± 2.91 [d)]
$t_{decline,\ PGnadir}$ (h)	5.53 ± 4.74 [b)]	6.20 ± 5.27 [b)]	7.51 ± 4.15 [e)]	4.37 ± 3.19 [f)]
$t_{recovery}$ (min)	29.40 ± 9.23 [c)]	24.89 ± 8.52 [g)]	22.15 ± 6.01 [h)]	24.41 ± 7.41 [i)]
$AUC_{GIR,\ recovery}$ (mg/kg)	139.30 (33.81)[c)]	116.19 (31.77)[g)]	110.71 (27.25)[h)]	114.84 (29.11)[i)]

Geometric mean (coefficient of variation %), Arithmetic mean ± SD for $t_{declice}$ and $t_{recovery}$
PG_{nadir}: Plasma glucose concentration at nadir
$t_{decline,\ PG54\ mg/dL}$: time from termination of glucose infusion to plasma glucose of 54 mg/dL
$t_{decline,\ PGnadir}$: time from termination of glucose infusion to PG_{nadir}
$t_{recovery}$: time to recovery from PG_{nadir} to plasma glucose of 100 mg/dL
$AUC_{GIR,\ recovery}$: area under the glucose infusion rate-time curve from PG_{nadir} to plasma glucose of 100 mg/dL
a) N = 17, b) N = 20, c) N = 15, d) N = 28, e) N = 19, f) N = 29, g) N = 18, h) N = 13, i) N = 22

Table 23 shows the blood concentrations of counterregulatory hormones at PG_{nadir}.

[21)] A glucose clamp was conducted at 26-61 hours after dosing of insulin icodec at Weeks 3 and 6 and from 30 minutes prior to until 24 hours after dosing of IGlar on Days 4 and 11.
[22)] Based on the Edinburgh Hypoglycemia Scale, 11 symptoms were scored on a 7-point scale (1 = not at all, 7 = a great deal).

Table 23. Blood hormone concentrations at PG_{nadir} following a double or triple dose of insulin icodec or IGlar

Endpoint	Double dose of insulin icodec (N = 20)	Triple dose of insulin icodec (N = 20)	Double dose of IGlar (N = 19)	Triple dose of IGlar (N = 29)
Plasma glucagon concentration (pg/mL)	48.59 (78.34)[a)]	59.92 (53.02)	54.00 (60.30)	58.88 (53.38)
Plasma adrenaline concentration (pg/mL)	102.37 (121.49)	157.52 (47.79)	118.44 (108.83)	104.16 (114.09)
Plasma noradrenaline concentration (pg/mL)	188.55 (80.32)	166.22 (79.77)	164.81 (83.70)	148.67 (72.72)
Serum cortisol concentration (ng/mL)	116.41 (68.65)[a)]	119.93 (49.38)[a)]	108.34 (85.45)	69.74 (94.34)
Serum growth hormone concentration (ng/mL)	4.69 (112.44)[a)]	3.57 (84.89)[a)]	3.69 (121.75)	3.36 (178.42)

Geometric mean (coefficient of variation %)
a) N = 19

The proportion of subjects who were positive for anti-insulin icodec antibodies at any time after treatment initiation was 72.1% (31 of 43 subjects).

Regarding safety, the incidences of adverse events and adverse drug reactions were 55.8% (24 of 43 subjects) and 14.0% (6 of 43 subjects), respectively, after administration of insulin icodec and 31.0% (13 of 42 subjects) and 9.5% (4 of 42 subjects), respectively, after administration of IGlar. No deaths, serious adverse events, or adverse events leading to treatment discontinuation were reported. There were no clinically relevant changes in vital signs or ECG.

6.2.5 Population pharmacokinetic analysis (CTD5.3.3.5-2)

Using 6939 serum insulin icodec concentrations obtained from 1244 subjects (sex, 724 male subjects and 520 female subjects; population, 957 type 2 diabetes patients and 287 type 1 diabetes patients; race/ethnicity, 127 Japanese subjects and 1117 non-Japanese subjects; anti-insulin icodec antibody status, 942 antibody-positive subjects and 302 antibody-negative subjects) in 5 Japanese and foreign clinical trials (a foreign phase II trial, Trial 4383; global phase III trials, Trials 4478, 4480, and 4625; a foreign phase III trial, Trial 4479), a population pharmacokinetic analysis was performed (software used: NONMEM [ver.7.3]).

As to the characteristics of subjects included in the PPK analysis, the mean age [range] was 56.1 [18, 86] years, the mean body weight was 84.1 [39.6, 160.3] kg, and the mean BMI was 29.4 [16.6, 46.6] kg/m^2.

A 1-compartment model with first-order absorption and elimination was developed as the base model. Age (18-64 years, 65-74 years, ≥75 years), body weight, ethnicity (Not Hispanic, Hispanic), race (White, Black, Chinese, Japanese, other Asian), sex, antibody titer, albumin, and population (type 2 diabetes, type 1 diabetes) were investigated as potential covariates on CL/F, and body weight as a potential covariate on V/F, using a full model approach. All covariates were included in the final model. Body weight is the primary source of variability in the PK of insulin icodec, and the predicted $C_{average}$ in subjects weighing 55.8 kg or 116.2 kg is 1.34-fold or 0.78-fold that in subjects weighing 83 kg, respectively.

6.R Outline of the review conducted by PMDA

6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec

The applicant's explanation:

Insulin icodec is an insulin analog, where the amino acid sequence of human insulin is modified, and a fatty acid-containing sidechain is added to prolong the action of insulin icodec compared with human insulin. Regarding the pharmacokinetics of insulin icodec, the serum concentration-time profiles and pharmacokinetic parameters of insulin icodec or IDeg following subcutaneous administration of once weekly insulin icodec or once daily IDeg in Trial 4314 in type 2 diabetes patients are shown in Figure 1 and Table 15, respectively. The geometric mean terminal elimination half-life was 170 to 238 hours in the insulin icodec group and 27 hours in the IDeg group. Trials 4422 and 4225 in type 1 diabetes patients also demonstrated a longer half-life of insulin icodec compared with IGlar (The geometric mean half-life of insulin icodec was 164 hours in Trial 4422 and 175 hours in Trial 4425). As to the pharmacodynamic effects of insulin icodec, the following results indicated that the duration of the glucose-lowering effect of insulin icodec is 1 week after dosing.

- In Trials 4422 and 4225 in type 1 diabetes patients and Trial 4569 in type 2 diabetes patients, glucose clamps were conducted at 150 to 168 hours, 138 to 168 hours, or 144 to 168 hours after dosing of insulin icodec, respectively, and glucose infusion was continued during the glucose clamps.
- Using the serum insulin icodec concentrations and glucose infusion rates in Trials 4422, 4225, and 4569, a population pharmacokinetic/pharmacodynamic analysis[23)] was performed by trial. Based on the AUC_{GIR} for each day as a percentage of the predicted steady-state AUC_{GIR} following once weekly administration of insulin icodec, the glucose-lowering effect of insulin icodec seemed to be distributed fairly evenly across the dosing interval of 1 week (Figure 2)

[23)] NONMEM (ver.7.3) was used for population pharmacokinetic/pharmacodynamic modeling of insulin icodec. A population PK/PD model consisted of an effect compartment for insulin action turnover, and a direct link between insulin action and GIR. GIR-time profiles were simulated based on this model.

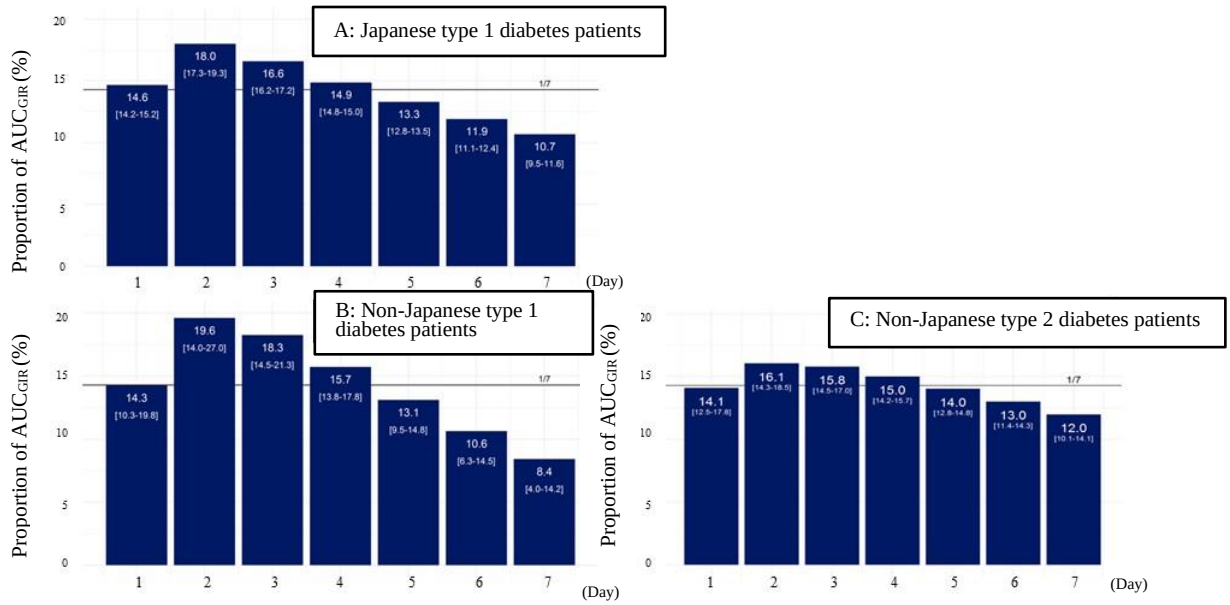


Figure 2. Predicted steady-state area under the glucose infusion rate-time curve (AUC_{GIR}) following once weekly administration of insulin icodec (A: Trial 4422, B: Trial 4225, C: Trial 4569)

PMDA's view:

The serum concentration-time profiles of insulin icodec and IDeg/IGlar and the results from clinical trials that evaluated the duration of the glucose lowering effect of insulin icodec, etc., demonstrated the pharmacokinetic and pharmacodynamic characteristics of insulin icodec as explained by the applicant. The effects of full-week pharmacokinetic and pharmacodynamic profiles of once weekly insulin icodec in clinical use on the efficacy and safety of insulin icodec will be discussed in the subsequent sections.

6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations

The applicant's explanation:

Based on the data from Trial 4422 in Japanese type 1 diabetes patients, Trial 4225 in non-Japanese type 1 diabetes patients, and Trial 4569 in non-Japanese type 2 diabetes patients, the pharmacokinetics following once weekly subcutaneous administration of insulin icodec for 8 weeks were compared. Table 24 shows the dose-normalized pharmacokinetic parameters (C_{max} and $AUC_{0\text{-}168\,h}$). The pharmacokinetics of insulin icodec were similar between the trials in Japanese and non-Japanese type 1 diabetes patients. The pharmacokinetics of insulin icodec were similar also between the trials in non-Japanese type 1 and type 2 diabetes patients.

Table 24. Pharmacokinetic parameters following once weekly subcutaneous administration of insulin icodec

Population	Trial	N	Dose-normalized C_{max} (nmol/L/(units/kg))		Dose-normalized $AUC_{0\text{-}168\ h}$ (nmol·h/L/(units/kg))	
			Week 1	Week 8	Week 1	Week 8
Japanese type 1 diabetes patients	4422	24	52.2 (19.0)	91.2 (14.7)	6108.5 (12.8)	10849.0 (10.6)
Non-Japanese type 1 diabetes patients	4225	65	54.4 (18.1)	99.3 (23.2)	6503.1 (13.9)	12524.8 (23.0)
Non-Japanese type 2 diabetes patients	4569	46	50.8 (22.5)	105.8 (21.0)[a)]	6064.5 (15.8)	12748.4 (20.0)[a)]

Geometric mean (coefficient of variation %)
C_{max}: maximum serum concentration, $AUC_{0\text{-}168\ h}$: area under the serum concentration-time curve from time 0 to 168 hours after dosing
a) N = 41

Table 25 shows the steady-state pharmacokinetic parameters following once weekly subcutaneous administration of insulin icodec in global phase III trials (Trials 4478, 4480, and 4625), predicted from a population pharmacokinetic analysis. In both type 1 and type 2 diabetes, the geometric means of the predicted pharmacokinetic parameters of insulin icodec tended to be slightly higher in Japanese patients than in non-Japanese patients. However, given that the ranges of the predicted values largely overlapped, and that phase I trials in type 1 diabetes patients showed no differences in the pharmacokinetic parameters of insulin icodec normalized to dose per kg body weight between the Japanese and non-Japanese populations (Table 24), there should be no major differences in the pharmacokinetics of insulin icodec between Japanese and non-Japanese patients with type 1 or type 2 diabetes.

Table 25. Predicted steady-state pharmacokinetic parameters following once weekly subcutaneous administration of insulin icodec

Population	Trial	Subgroup	N	Dose-normalized C_{max} (nmol/L/unit)	Dose-normalized AUC_{tau} (nmol·h/L/unit)
Type 2 diabetes patients	4478	Japanese	51	1.31 [0.85, 2.42]	167.9 [101.4, 367.0]
		Non-Japanese	209	1.11 [0.50, 1.90]	141.2 [68.9, 249.8]
	4480	Japanese	44	1.22 [0.71, 1.72]	157.4 [86.6, 227.8]
		Non-Japanese	240	1.11 [0.66, 3.66]	143.7 [82.8, 448.4]
Type 1 diabetes patients	4625	Japanese	32	1.43 [1.07, 1.91]	190.4 [136.1, 254.3]
		Non-Japanese	255	1.24 [0.66, 2.56]	166.1 [85.0, 370.4]

Geometric mean [Min., Max.]
C_{max}: maximum serum concentration, AUC_{tau}: area under the serum concentration-time curve from time 0 to 168 hours after dosing

Regarding pharmacodynamic effects, Table 26 shows the predicted steady-state pharmacodynamic parameters based on glucose infusion rates following once weekly administration of insulin icodec in Trials 4422 and 4425 in type 1 diabetes patients. There were no major differences in the pharmacodynamic parameters between the trials in Japanese and non-Japanese patients. It was difficult to compare the pharmacodynamic parameters between the trials in non-Japanese type 1 and type 2 diabetes patients because the trials used individualized dosing, instead of fixed dose, the clamp target level differed between the trials, etc. However, the duration of glucose-lowering effect covered 1 week in type 2 diabetes patients as in type 1 diabetes patients [see Section "6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec"].

Table 26. Predicted steady-state pharmacodynamic parameters following once weekly administration of insulin icodec

Population	Trial	N	Dose (units/kg)	$AUC_{GIR,\ tau}$ (mg/kg)	GIR_{max} (mg/kg/min)	$t_{GIR,\ max}$ (h)
Japanese type 1 diabetes patients	4422	13	1.6 [1.2, 2.3]	8330 (40.7)	1.5 (31.1)	24 [23, 28]
Non-Japanese type 1 diabetes patients	4225	49	2.0 [1.2, 3.3]	8668 (52.7)	1.5 (40.6)	46 [20, 94]

Geometric mean (coefficient of variation %), Mean [Range] for dose, Median [Range] for $t_{GIR,\ max}$
$AUC_{GIR,\ tau}$: area under the glucose infusion rate-time curve from time 0 to 168 hours after dosing, GIR_{max}: maximum glucose infusion rate
$t_{GIR,\ max}$: time to reach GIR_{max}

Comparison between Japanese and non-Japanese type 2 diabetes patients was made using blood glucose parameters in global phase III trials in type 2 diabetes patients (Trials 4477, 4478, and 4480). There were no major differences in the results of fasting plasma glucose and continuous glucose monitoring (CGM) endpoints between the Japanese subgroup and the entire trial population (Tables 32, 41, and 48).

Based on the above, there were no major differences in the pharmacokinetics or pharmacodynamics of insulin icodec between the Japanese and non-Japanese populations with type 1 or type 2 diabetes.

PMDA's view:
Regarding pharmacokinetics, although the pharmacokinetic parameters normalized to dose per kg body weight were similar between Japanese and non-Japanese patients in phase I trials (Trials 4422, 4225, and 4569), the predicted dose-normalized pharmacokinetic parameters were slightly higher in Japanese patients than in non-Japanese patients in global phase III trials in type 1 and type 2 diabetes patients. Body weight may have affected insulin icodec exposure. Regarding pharmacodynamic effects, there were no major differences in the pharmacodynamic parameters based on glucose infusion rates between Japanese and non-Japanese type 1 diabetes patients. Although the pharmacodynamic parameters based on glucose infusion rates were not compared among type 2 diabetes patients, the results of global phase III trials showed no major differences in fasting plasma glucose or CGM endpoints following administration of insulin icodec between the entire trial population and the Japanese subgroup. Based on the above, there should be no clinically meaningful differences in the pharmacokinetics or pharmacodynamics of insulin icodec between the Japanese and non-Japanese populations with type 1 or type 2 diabetes.

6.R.3 Effect of antibody formation on pharmacokinetics

The applicant's explanation:
Antibody test was performed in global phase III trials in patients with type 2 diabetes (Trials 4478 and 4480) and a global phase III trial in patients with type 1 diabetes (Trial 4625). Among subjects tested for antibodies in the insulin icodec group, the proportion of subjects who were positive for anti-insulin icodec antibodies at baseline and the proportion of subjects who tested positive for anti-insulin icodec antibodies at least once after treatment initiation were 15.4% (40 of 259 subjects) and 70.2% (184 of 262 subjects), respectively, in Trial 4478, 31.5% (91 of 289 subjects) and 71.2% (205 of 288 subjects), respectively, in Trial 4480, and 50.2% (145 of 289 subjects) and 75.3% (217 of 288 subjects), respectively, in Trial 4625 (the main phase). Table 27 shows the steady-state pharmacokinetic parameters following once weekly administration of insulin icodec by anti-insulin icodec antibody status, predicted from a population pharmacokinetic analysis [see Section "6.2.5 Population pharmacokinetic analysis"]. There were no major differences in insulin icodec exposure between anti-insulin icodec antibody-negative and -positive subjects.

Table 27. Predicted steady-state pharmacokinetic parameters by anti-insulin icodec antibody status

Population	Trial	Antibody status[a)]	N	Dose-normalized C_{max} (nmol/L/unit)	Dose-normalized AUC_{tau} (nmol·h/L/unit)
Type 2 diabetes patients	4478	Negative	76	1.14 (20.5)	144.1 (22.6)
		Positive	184	1.15 (24.2)	146.9 (26.1)
	4480	Negative	79	1.12 (22.8)	143.7 (25.2)
		Positive	205	1.13 (25.9)	146.5 (27.5)
Type 1 diabetes patients	4625	Negative	61	1.23 (23.5)	162.3 (25.7)
		Positive	226	1.27 (22.6)	170.4 (24.9)

Geometric mean (coefficient of variation %)
C_{max}: maximum serum concentration, AUC_{tau}: area under the serum concentration-time curve from time 0 to 168 hours after dosing
a) Subjects who tested positive for anti-insulin icodec antibodies at least once were classified as "positive" and other subjects were classified as "negative."

Based on the above, anti-insulin icodec antibody formation had no clinically meaningful effect on the pharmacokinetics of insulin icodec.

PMDA's view:

Although anti-insulin icodec antibody formation was common in Trials 4478, 4480, and 4625, the results of a population pharmacokinetic analysis raised no particular concerns about the effect of anti-insulin icodec antibodies on the pharmacokinetics of insulin icodec. The effect of anti-insulin icodec antibodies on the efficacy and safety of insulin icodec will be further discussed in Section "7.R.2.11 Antibody formation."

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

The applicant submitted efficacy and safety evaluation data, in the form of the results from 4 global phase III trials presented in Table 28. The applicant also submitted the results from 2 foreign phase III trials (Trials 4479 and 4481) as reference data.

Table 28. Listing of efficacy and safety evaluation data

Data category	Geographical location	Trial Number	Phase	Trial population	No. of treated subjects	Dosing regimen	Main endpoints
Evaluation	Global	4477	III	Insulin-naïve type 2 diabetes mellitus patients	984	Once weekly insulin icodec or once daily IGlar (100 units/mL) administered subcutaneously	Efficacy Safety
	Global	4478	III	Type 2 diabetes mellitus patients treated with basal insulin	525	Once weekly insulin icodec or once daily IDeg administered subcutaneously	Efficacy Safety
	Global	4480	III	Type 2 diabetes mellitus patients treated with basal-bolus regimen	582	Once weekly insulin icodec or once daily IGlar (100 units/mL) administered subcutaneously	Efficacy Safety
	Global	4625	III	Type 1 diabetes mellitus patients treated with basal-bolus regimen	582	Once weekly insulin icodec or once daily IDeg administered subcutaneously	Efficacy Safety

The results from the main studies are described below. Subcutaneous interstitial fluid glucose measured by CGM is also referred to as blood glucose.

7.1 Global phase III trial in insulin-naïve patients with type 2 diabetes mellitus (CTD5.3.5.1-4 and 5.3.5.1-5, Trial 4477 [November 2020 to December 2022])

A randomized, open-label, IGlar (100 units/mL)-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of insulin icodec in insulin-naïve adult patients with type 2 diabetes mellitus including Japanese patients[24] (target sample size, 970 subjects[25] [485 per group]).

Key inclusion criteria: Adult type 2 diabetes mellitus patients who (1) had been treated with stable doses of non-insulin glucose-lowering treatment(s) or combination regimen(s) for ≥90 days prior to screening and had (2) HbA1c of 7.0% to 11.0% at screening and (3) BMI of ≤40.0 kg/m^2. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The trial consisted of a screening period (2 weeks), a main phase (52 weeks), an extension phase (26 weeks), and a follow-up period (5 weeks).

Once weekly insulin icodec[26] or once daily IGlar (100 units/mL) was to be administered subcutaneously in the thigh, upper arm, or abdomen for 78 weeks (self-injection). The starting dose was 70 units for insulin icodec or 10 units for IGlar (100 units/mL), and then the doses of insulin icodec and IGlar were to be adjusted once weekly or every other week according to the titration algorithms presented in Table 29. Non-insulin glucose-lowering treatments that subjects had been receiving at screening were to be continued throughout the trial period, except for sulphonylureas (SU) and glinides, which were to be discontinued at randomization.

Table 29. Titration algorithms (Trial 4477)

Pre-breakfast SMBG (mg/dL)[a]	Dose adjustment of insulin icodec	Dose adjustment of IGlar
<80	−20 units	−3 units
80-130	0	0
>130	+20 units	+3 units

a) Dose adjustments were based on the pre-breakfast SMBG values measured on 2 days prior to and on the day of titration. If the lowest of the 3 pre-breakfast SMBG values was <80 mg/dL, the dose was reduced. Otherwise, a decision to not change or increase the dose was made based on the mean of the 3 pre-breakfast SMBG values.

All of 984 randomized subjects (492 in the insulin icodec group [including 78 Japanese subjects], 492 in the IGlar group [including 86 Japanese subjects]) were included in the FAS, and the FAS was the primary efficacy analysis population. All of the 984 subjects received trial product and were included in the safety analysis set. During the main phase, 17 subjects discontinued the trial, including 10 subjects in the insulin icodec group (consent withdrawal [3 subjects], lost to follow-up [2 subjects], investigator

[24] Japan, US, UK, Spain, Slovakia, Russia, Poland, Mexico, Italy, Israel, India, Croatia

[25] With respect to the true difference in the primary endpoint of the change in HbA1c from baseline to Week 52 between the insulin icodec and IGlar groups, it was assumed that there would be no between-group difference in the change in HbA1c among subjects who completed randomized treatment without treatment with bolus insulin for more than 2 weeks and a difference of 0.3 percentage points in favor of the comparator among subjects having an intercurrent event (subjects who discontinued treatment prematurely, initiated bolus insulin treatment for more than 2 weeks, or withdrew from the trial). Thus, with 10% expected to experience an intercurrent event, this would lead to an assumption of a mean between-group difference of 0.03 percentage point in favor of the comparator in the overall population. Assuming a standard deviation of 1.0%, 1:1 randomization, and a non-inferiority margin of 0.3%, a total of 970 subjects would provide 99% power.

[26] Insulin icodec was to be administered once weekly on the same day of the week, at any time of day. If an insulin icodec dose was missed for ≤3 days after the planned dosing day, subjects were to inject the planned dose as soon as possible. If the missing dose was missed for >3 days, the subject was to await the next planned day of injection. If necessary, the day of weekly administration could be changed by up to 3 days, as long as a minimum of 4 days between doses was maintained.

decision [2 subjects], death [2 subjects], site closure [1 subject]) and 7 subjects in the IGlar group (consent withdrawal [5 subjects], death [2 subjects] [including 1 Japanese subject]). During the extension phase, 18 subjects discontinued the trial, including 8 subjects in the insulin icodec group (consent withdrawal [3 subjects], lost to follow-up [2 subjects], investigator decision [2 subjects], death [1 subject]) and 10 subjects in the IGlar group (lost to follow-up [4 subjects], consent withdrawal [3 subjects], death [2 subjects], investigator decision [1 subject]).

The primary efficacy endpoint of the change in HbA1c from baseline to Week 52 is shown in Table 30. Since the upper limit of the 95% confidence interval for the treatment difference between insulin icodec and IGlar fell below the pre-specified non-inferiority margin of 0.3%,[27] the non-inferiority of insulin icodec to IGlar was demonstrated.

Table 30. Change in HbA1c from baseline to Week 52 (Trial 4477 [main phase]: FAS)

	Treatment group	Baseline	Week 52	Change from baseline[a), b)]	Treatment difference [95% CI][a), b)]
Entire trial population	Insulin icodec (N = 492)	8.50 ± 0.99 (492)	6.93 ± 0.78 (479)	−1.55 ± 0.06	−0.19 [−0.36, −0.03]
	IGlar (N = 492)	8.44 ± 1.02 (492)	7.09 ± 0.82 (479)	−1.35 ± 0.05	
Japanese subgroup	Insulin icodec (N = 78)	8.06 ± 0.83 (78)	6.86 ± 0.61 (78)	−1.18 ± 0.07	−0.09 [−0.30, 0.12]
	IGlar (N = 86)	8.01 ± 0.84 (86)	6.91 ± 0.62 (85)	−1.09 ± 0.08	

Unit: %, Mean ± SD (Number of evaluable subjects), Least-squares mean ± SE for change, Least-squares mean [95% CI] for treatment difference

a) Missing values were imputed using multiple imputation based on the change from LAOT-WOB value (last available on-treatment without initiation of bolus insulin for more than 2 weeks) to Week 52 for subjects who had an intercurrent event but had a measurement at Week 52.

b) Calculated using an ANCOVA model with treatment, region, and baseline HbA1c as explanatory variables.

Table 31 shows the results of the key secondary endpoints during the main phase (52 weeks of treatment).

[27] Chosen based on the recommendation in the FDA guidance (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER). Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention. Draft Guidance. Feb 2008.) etc.

Table 31. Results of key secondary endpoints (Trial 4477 [main phase]: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 78)	IGlar (N = 86)
Fasting plasma glucose (mg/dL)	Baseline	185.31 ± 48.96 (480)	185.71 ± 51.66 (474)	164.26 ± 34.64 (78)	163.84 ± 32.38 (86)
	Change at Week 52	−63.69 ± 50.27 (452)	−63.63 ± 55.55 (450)	−48.35 ± 37.06 (76)	−44.35 ± 35.46 (85)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]		71.94 ± 18.23 (439)	66.90 ± 18.19 (440)	68.05 ± 15.70 (77)	63.65 ± 15.93 (82)
Time spent below range <70 mg/dL (TBR) (%)[a)]		1.20 ± 1.98 (439)	0.83 ± 2.12 (440)	0.55 ± 0.96 (77)	0.31 ± 0.63 (82)
Time spent above range >180 mg/dL (TAR) (%)[a)]		26.86 ± 18.74 (439)	32.27 ± 18.66 (440)	31.40 ± 16.12 (77)	36.04 ± 16.11 (82)
Proportion of subjects who achieved an HbA1c <7.0% (%)		57.6 (276/479)	47.4 (227/479)	60.3 (47/78)	54.1 (46/85)
Proportion of subjects who achieved an HbA1c ≤6.5% (%)		33.6 (161/479)	26.5 (127/479)	34.6 (27/78)	28.2 (24/85)
Proportion of subjects who achieved an HbA1c <7.0% without level 3 hypoglycemia (%)[b)]		57.0 (273/479)	47.2 (226/479)	59.0 (46/78)	54.1 (46/85)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]		54.7 (262/479)	46.1 (221/479)	59.0 (46/78)	54.1 (46/85)
Insulin dose (units/week)[c)]		230.0 (10.0, 980.0) (472)	221.5 (14.0, 1022.7) (477)	130.0 (10.0, 840.0) (77)	154.0 (14.0, 427.0) (84)
Body weight (kg)	Baseline	85.17 ± 17.74 (492)	84.31 ± 17.63 (492)	73.42 ± 15.48 (78)	73.28 ± 13.24 (86)
	Change at Week 52	2.32 ± 3.96 (478)	1.84 ± 4.56 (478)	2.31 ± 2.82 (78)	1.53 ± 3.49 (85)

Mean ± SD (Number of evaluable subjects), Proportion % (Number of subjects in category/Number of evaluable subjects)
Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 48 to Week 52.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 50 to Week 52

Table 32 shows the results of the key secondary endpoints during the extension phase (78 weeks of treatment). Figure 3 shows the change in HbA1c over time from baseline to Week 78.

Table 32. Results of key secondary endpoints (Trial 4477 [main + extension phases]: FAS)

Endpoint	Entire trial population		Japanese subgroup	
	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 78)	IGlar (N = 86)
Change in HbA1c (%)	−1.62 ± 1.01 (467)	−1.42 ± 1.07 (472)	−1.28 ± 0.83 (77)	−1.17 ± 0.82 (85)
Change in fasting plasma glucose (mg/dL)	−65.66 ± 54.15 (435)	−63.67 ± 54.85 (442)	−50.12 ± 37.15 (75)	−40.63 ± 35.99 (82)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]	70.18 ± 18.69 (428)	64.83 ± 19.41 (432)	68.45 ± 17.48 (74)	62.08 ± 16.78 (80)
Proportion of subjects who achieved an HbA1c <7.0% (%)	58.9 (275/467)	51.5 (243/472)	66.2 (51/77)	64.7 (55/85)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]	57.8 (270/467)	50.4 (238/472)	64.9 (50/77)	62.4 (53/85)
Insulin dose (units/week)[c)]	230.0 (10.0, 1320.0) (459)	238.0 (22.5, 1206.0) (466)	130.0 (10.0, 1020.0) (75)	175.0 (22.5, 532.0) (83)
Change in body weight (kg)	2.38 ± 4.62 (468)	1.64 ± 4.77 (472)	2.11 ± 3.21 (78)	1.07 ± 3.96 (85)

Mean ± SD (Number of evaluable subjects), Proportion % (Number of subjects in category/Number of evaluable subjects)
Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 74 to Week 78.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 76 to Week 78

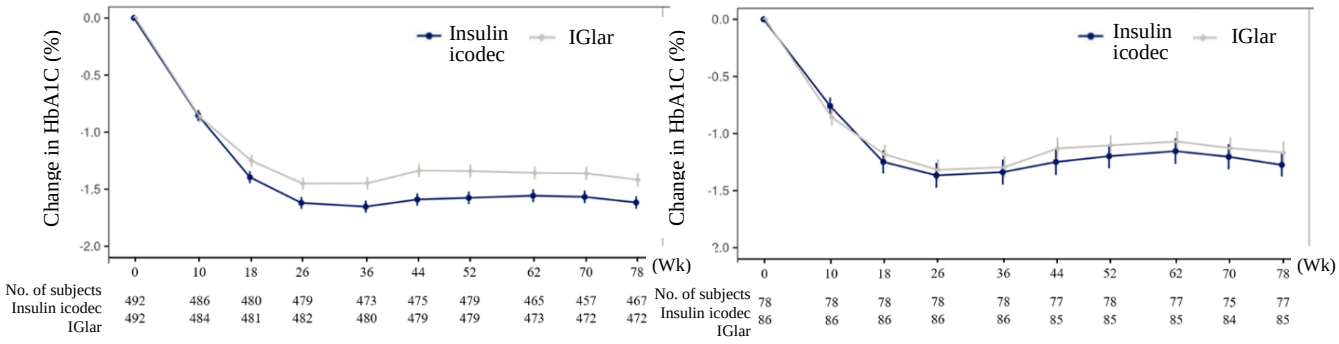


Figure 3. Change in HbA1c over time from baseline to Week 78
(Trial 4477 [main + extension phases]: Entire trial population [Left figure], Japanese subgroup [Right figure], FAS) (Mean ± SE)

Regarding safety, adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population during the main phase (52 weeks of treatment) are shown in Table 33, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 34.

Table 33. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group
(Trial 4477 [main phase], Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 492)		IGlar (N = 492)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	71.3 (351)	9.8 (48)	68.1 (335)	11.2 (55)
COVID-19	10.0 (49)	0 (0)	12.4 (61)	0 (0)
Diarrhoea	6.3 (31)	0.4 (2)	4.3 (21)	0.6 (3)
Nasopharyngitis	6.1 (30)	0 (0)	6.9 (34)	0 (0)
Back pain	5.5 (27)	0 (0)	4.9 (24)	0 (0)
Upper respiratory tract infection	4.7 (23)	0 (0)	2.6 (13)	0 (0)
Arthralgia	4.7 (23)	0 (0)	3.5 (17)	0 (0)
Pyrexia	3.5 (17)	0 (0)	4.3 (21)	0 (0)
Headache	3.3 (16)	0.2 (1)	3.5 (17)	0.2 (1)
Pain in extremity	3.0 (15)	0.2 (1)	2.2 (11)	0 (0)
Nausea	3.0 (15)	0.8 (4)	1.0 (5)	0.2 (1)
Urinary tract infection	1.4 (7)	0 (0)	3.3 (16)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Table 34. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group
(Trial 4477 [main phase], Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 78)		IGlar (N = 86)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	76.9 (60)	24.4 (19)	74.4 (64)	23.3 (20)
Nasopharyngitis	11.5 (9)	0 (0)	14.0 (12)	0 (0)
Back pain	7.7 (6)	0 (0)	4.7 (4)	0 (0)
Arthralgia	7.7 (6)	0 (0)	3.5 (3)	0 (0)
Pyrexia	6.4 (5)	0 (0)	12.8 (11)	0 (0)
Diarrhoea	6.4 (5)	0 (0)	5.8 (5)	1.2 (1)
Nausea	6.4 (5)	1.3 (1)	0 (0)	0 (0)
Vaccination complication	6.4 (5)	0 (0)	8.1 (7)	0 (0)
Headache	6.4 (5)	1.3 (1)	7.0 (6)	0 (0)
Cystitis	5.1 (4)	0 (0)	5.8 (5)	0 (0)
Malaise	5.1 (4)	2.6 (2)	4.7 (4)	3.5 (3)
Hunger	5.1 (4)	5.1 (4)	1.2 (1)	1.2 (1)
Dental caries	5.1 (4)	0 (0)	0 (0)	0 (0)
Dizziness	2.6 (2)	1.3 (1)	5.8 (5)	4.7 (4)
Dry eye	1.3 (1)	0 (0)	5.8 (5)	0 (0)
Hypoglycemia	1.3 (1)	1.3 (1)	8.1 (7)	8.1 (7)
Medical device site dermatitis	0 (0)	0 (0)	7.0 (6)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Through the extension phase (78 weeks of treatment), adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population are shown in Table 35, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 36.

Table 35. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group (Trial 4477 [main + extension phases], Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 492)		IGlar (N = 492)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	80.7 (397)	14.2 (70)	79.1 (389)	13.4 (66)
COVID-19	18.5 (91)	0 (0)	21.1 (104)	0 (0)
Back pain	8.1 (40)	0.2 (1)	6.5 (32)	0 (0)
Diarrhoea	7.9 (39)	0.4 (2)	5.3 (26)	0.6 (3)
Nasopharyngitis	7.7 (38)	0 (0)	9.6 (47)	0 (0)
Diabetic retinopathy	7.3 (36)	1.8 (9)	6.5 (32)	0.6 (3)
Arthralgia	6.1 (30)	0 (0)	4.5 (22)	0 (0)
Upper respiratory tract infection	5.7 (28)	0 (0)	4.5 (22)	0 (0)
Pyrexia	5.5 (27)	0 (0)	4.7 (23)	0 (0)
Headache	4.5 (22)	0.2 (1)	4.3 (21)	0.2 (1)
Nausea	4.1 (20)	1.0 (5)	1.8 (9)	0.2 (1)
Osteoarthritis	3.9 (19)	0 (0)	2.8 (14)	0 (0)
Pain in extremity	3.7 (18)	0.2 (1)	2.8 (14)	0 (0)
Cataract	3.7 (18)	0.2 (1)	2.4 (12)	0 (0)
Fatigue	3.3 (16)	0.2 (1)	1.4 (7)	0.4 (2)
Pharyngitis	3.0 (15)	0 (0)	2.4 (12)	0 (0)
Dizziness	3.0 (15)	0.6 (3)	3.0 (15)	1.2 (6)
Hypertension	3.0 (15)	0 (0)	3.3 (16)	0 (0)
Vaccination complication	2.4 (12)	0 (0)	3.3 (16)	0 (0)
Urinary tract infection	1.8 (9)	0 (0)	4.3 (21)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Table 36. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group (Trial 4477 [main + extension phases], Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 78)		IGlar (N = 86)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	89.7 (70)	28.2 (22)	82.6 (71)	26.7 (23)
Pyrexia	15.4 (12)	0 (0)	14.0 (12)	0 (0)
Back pain	15.4 (12)	0 (0)	7.0 (6)	0 (0)
Nasopharyngitis	14.1 (11)	0 (0)	18.6 (16)	0 (0)
Diarrhoea	10.3 (8)	0 (0)	5.8 (5)	1.2 (1)
Arthralgia	9.0 (7)	0 (0)	4.7 (4)	0 (0)
Vaccination complication	9.0 (7)	0 (0)	11.6 (10)	0 (0)
Diabetic retinopathy	9.0 (7)	2.6 (2)	11.6 (10)	1.2 (1)
Nausea	7.7 (6)	1.3 (1)	1.2 (1)	0 (0)
Dental caries	7.7 (6)	0 (0)	0 (0)	0 (0)
Headache	7.7 (6)	1.3 (1)	7.0 (6)	0 (0)
COVID-19	6.4 (5)	0 (0)	7.0 (6)	0 (0)
Malaise	6.4 (5)	2.6 (2)	7.0 (6)	3.5 (3)
Cystitis	5.1 (4)	0 (0)	5.8 (5)	0 (0)
Vaccination site pain	5.1 (4)	0 (0)	1.2 (1)	0 (0)
Hunger	5.1 (4)	5.1 (4)	1.2 (1)	1.2 (1)
Insomnia	5.1 (4)	0 (0)	1.2 (1)	0 (0)
Contusion	2.6 (2)	0 (0)	11.6 (10)	0 (0)
Dizziness	2.6 (2)	1.3 (1)	5.8 (5)	4.7 (4)
Hypoglycemia	2.6 (2)	2.6 (2)	9.3 (8)	9.3 (8)
Hypertension	2.6 (2)	0 (0)	8.1 (7)	0 (0)
Dry eye	1.3 (1)	0 (0)	5.8 (5)	0 (0)
Medical device site dermatitis	0 (0)	0 (0)	8.1 (7)	0 (0)
Tenosynovitis	0 (0)	0 (0)	5.8 (5)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

During the main phase, 4 deaths occurred in the insulin icodec group (COVID-19; metastases to liver and pancreatic neoplasm; glioblastoma multiforme; and acute coronary syndrome, 1 subject each) and 2 deaths occurred in the IGlar group (angina pectoris and post procedural infection [Japanese subject]; and death, 1 subject each), and the event reported by 1 subject in the IGlar group (death) was classified as an adverse drug reaction. During the extension phase, 1 death occurred in the insulin icodec group (intestinal sepsis and intestinal obstruction) and 2 deaths occurred in the IGlar group (adult failure to thrive, cardio-respiratory arrest, hepatocellular carcinoma, and metastatic renal cell carcinoma; and arteriosclerosis), but no adverse drug reactions were reported. Serious adverse events occurred in 51 subjects in the insulin icodec group (including 4 Japanese subjects) and 49 subjects in the IGlar group (including 7 Japanese subjects) during the main phase, and new serious adverse events occurred in 13 subjects in the insulin icodec group (including 3 Japanese subjects) and 22 subjects in the IGlar group (including 1 Japanese subject) during the extension phase. Table 37 shows serious adverse events reported by ≥3 subjects in either treatment group, and the events reported by 2 subjects in the IGlar group during the main phase (diabetic retinal oedema; and death, 1 subject each) and the events reported by 2 subjects in the IGlar group during the extension phase (hypoglycemic unconsciousness [Japanese subject]; and hypoglycemia, 1 subject each) were classified as adverse drug reactions.

Table 37. Serious adverse events reported by ≥3 subjects in either treatment group (Trial 4477, Entire trial population: Safety analysis set)

Event term	Main phase (52 weeks of treatment)		Main + extension phases (78 weeks of treatment)	
	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 492)	IGlar (N = 492)
Any serious adverse event	10.4 (51)	10.0 (49)	13.0 (64)	14.4 (71)
Atrial fibrillation	1.0 (5)	0.4 (2)	1.0 (5)	0.4 (2)
Coronary artery disease	0.8 (4)	0.2 (1)	0.8 (4)	0.4 (2)
COVID-19	0.8 (4)	0.4 (2)	0.8 (4)	0.6 (3)
COVID-19 pneumonia	0.8 (4)	0.4 (2)	0.8 (4)	0.4 (2)
Myocardial infarction	0.6 (3)	0.4 (2)	0.6 (3)	0.6 (3)
Angina unstable	0.4 (2)	0.2 (1)	0.8 (4)	0.2 (1)
Acute myocardial infarction	0.4 (2)	0.8 (4)	0.8 (4)	1.0 (5)
Pneumonia	0.4 (2)	0.2 (1)	0.4 (2)	0.6 (3)
Osteoarthritis	0.2 (1)	0.2 (1)	0.2 (1)	0.6 (3)

Incidence % (n), MedDRA/J ver.24.1

Adverse events leading to treatment discontinuation occurred in 6 subjects in the insulin icodec group (weight increased [2 subjects]; obesity; pancreatic neoplasm and metastases to liver; glioblastoma multiforme; and glycosylated haemoglobin increased, 1 subject each) and 4 subjects in the IGlar group (angina pectoris [Japanese subject]; death; rib fracture, lower limb fracture, pneumothorax, and upper limb fracture; and mood swings, 1 subject each) during the main phase, and the events reported by 3 subjects in the insulin icodec group (weight increased [2 subjects]; and obesity [1 subject]) and the events reported by 2 subjects in the IGlar group (death; and mood swings, 1 subject each) were classified as adverse drug reactions. During the extension phase, adverse events leading to treatment discontinuation occurred in 3 subjects in the insulin icodec group (abdominal distension and constipation [Japanese subject]; psychotic disorder; and hip fracture, 1 subject each) and 2 subjects in the IGlar group (adult failure to thrive, haematoma, and metabolic encephalopathy; and ovarian cancer metastatic [Japanese subject]), and the event reported by 1 subject in the insulin icodec group (abdominal distension) was classified as an adverse drug reaction.

The incidence and rate of hypoglycemia are shown in Table 38.

Table 38. Incidence and rate of hypoglycemia (Trial 4477: Safety analysis set)

Endpoint	Main phase (52 weeks of treatment)				Main + extension phases (78 weeks of treatment)			
	Entire trial population		Japanese subgroup		Entire trial population		Japanese subgroup	
	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 78)	IGlar (N = 86)
Level 2 or 3 hypoglycemia	9.8 (48)	10.6 (52)	3.8 (3)	5.8 (5)	12.4 (61)	14.2 (70)	6.4 (5)	8.1 (7)
	29.64 [144]	16.08 [78]	6.45 [5]	9.30 [8]	29.65 [227]	15.78 [121]	7.32 [9]	8.13 [11]
Level 3 hypoglycemia	0.2 (1)	0.6 (3)	0 (0)	0 (0)	0.2 (1)	1.2 (6)	0 (0)	1.2 (1)
	0.21 [1]	0.62 [3]	0 [0]	0 [0]	0.13 [1]	0.91 [7]	0 [0]	0.74 [1]
Level 2 or 3 nocturnal hypoglycemia	1.8 (9)	2.2 (11)	0 (0)	2.3 (2)	1.8 (9)	3.3 (16)	0 (0)	2.3 (2)
	4.12 [20]	3.09 [15]	0 [0]	4.65 [4]	3.40 [26]	3.13 [24]	0 [0]	3.69 [5]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]
Level 2 hypoglycemia, blood glucose <54 mg/dL
Level 3 hypoglycemia (severe hypoglycemia), hypoglycemia requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Nocturnal hypoglycemia, hypoglycemic episodes occurring between 0:01 a.m. and 5:59 a.m.

There were no clinically relevant changes in laboratory parameters, vital signs, or ECG in the insulin icodec group compared with the IGlar group.

7.2 Global phase III trial in patients with type 2 diabetes mellitus treated with basal insulin (CTD5.3.5.1-6, Trial 4478 [March 2021 to March 2022])

A randomized, open-label, IDeg-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of insulin icodec in adult patients with type 2 diabetes mellitus treated with basal insulin including Japanese patients[28)] (target sample size, 520 subjects[29)] [260 per group]).

Key inclusion criteria: Adult type 2 diabetes mellitus patients who (1) had been treated with stable doses of once daily or twice daily basal insulin[30)] for ≥90 days prior to screening, (2) with or without stable doses of non-insulin glucose-lowering agents for ≥90 days prior to screening, and had (3) HbA1c of 7.0% to 10.0% at screening and (4) BMI of ≤40.0 kg/m^2. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The trial consisted of a screening period (2 weeks), a treatment period (26 weeks), and a follow-up period (5 weeks).

Once weekly insulin icodec[26)] or once daily IDeg was to be administered subcutaneously in the thigh, upper arm, or abdomen for 26 weeks (self-injection). The starting dose of insulin icodec was 7 times the daily basal insulin dose before randomization, increased by a one-time additional 50% dose, and the

[28)] Japan, US, Ukraine, Portugal, Poland, Korea, Germany, Bulgaria, South Africa
[29)] With respect to the true difference in the primary endpoint of the change in HbA1c from baseline to Week 26 between the insulin icodec and IDeg groups, it was assumed that there would be no between-group difference in the change in HbA1c among subjects who completed randomized treatment without treatment with bolus insulin for more than 2 weeks and a difference of 0.3 percentage points in favor of the comparator among subjects having an intercurrent event (subjects who discontinued treatment prematurely, initiated bolus insulin treatment for more than 2 weeks, or withdrew from the trial). Thus, with 5% expected to experience an intercurrent event, this would lead to an assumption of a mean between-group difference of 0.015 percentage point in favor of the comparator in the overall population. Assuming a standard deviation of 1.0%, 1:1 randomization, and a non-inferiority margin of 0.3%, a total of 520 subjects would provide 90% power.
[30)] NPH insulin, IDeg, IDet, IGlar (100 units/mL or 300 units/mL)

second once-weekly dose of insulin icodec was 7 times the daily basal insulin dose before randomization.[31)] When switching to IDeg, the starting dose of IDeg was determined based on the daily basal insulin dose before randomization, in accordance with the local label. Then, the doses of insulin icodec and IDeg were to be adjusted once weekly according to the titration algorithms presented in Table 39. Non-insulin glucose-lowering agents that subjects had been receiving at screening were to be continued throughout the trial period, except for SU and glinides, which were to be discontinued at randomization.

Table 39. Titration algorithms (Trial 4478)

Pre-breakfast SMBG (mg/dL)[a)]	Dose adjustment of insulin icodec	Dose adjustment of IDeg
<80	−20 units	−3 units
80-130	0	0
>130	+20 units	+3 units

a) Dose adjustments were based on the pre-breakfast SMBG values measured on 2 days prior to and on the day of titration. If the lowest of the 3 pre-breakfast SMBG values was <80 mg/dL, the dose was reduced. Otherwise, a decision to not change or increase the dose was made based on the mean of the 3 pre-breakfast SMBG values.

All of 526 randomized subjects (263 in the insulin icodec group [including 51 Japanese subjects] and 263 in the IDeg group [including 49 Japanese subjects]) were included in the FAS, and the FAS was the primary efficacy analysis population. Of whom, 525 subjects (262 in the insulin icodec group [including 51 Japanese subjects] and 263 in the IDeg group [including 49 Japanese subjects]) received trial product and were included in the safety analysis set. Eight subjects discontinued the trial, including 3 subjects in the insulin icodec group (death [2 subjects]; and investigator decision [1 subject]) and 5 subjects in the IDeg group (consent withdrawal [3 subjects]; and death [2 subjects] [including 1 Japanese subject]).

The primary efficacy endpoint of the change in HbA1c from baseline to Week 26 is shown in Table 40. Since the upper limit of the 95% confidence interval for the treatment difference between insulin icodec and IDeg fell below the pre-specified non-inferiority margin of 0.3%,[27)] the non-inferiority of insulin icodec to IDeg was demonstrated.

Table 40. Change in HbA1c from baseline to Week 26 (Trial 4478: FAS)

	Treatment group	Baseline	Week 26	Change from baseline[a), b)]	Treatment difference [95% CI][a), b)]
Entire trial population	Insulin icodec (N = 263)	8.17 ± 0.77 (263)	7.21 ± 0.74 (256)	−0.93 ± 0.05	−0.22 [−0.37, −0.08]
	IDeg (N = 263)	8.10 ± 0.77 (263)	7.39 ± 0.78 (253)	−0.71 ± 0.06	
Japanese subgroup	Insulin icodec (N = 51)	8.10 ± 0.70 (51)	7.24 ± 0.78 (51)	−0.83 ± 0.09	0.05 [−0.22, 0.33]
	IDeg (N = 49)	7.98 ± 0.74 (49)	7.10 ± 0.68 (48)	−0.89 ± 0.10	

Unit: %, Mean ± SD (Number of evaluable subjects); Least-squares mean ± SE for change; Least-squares mean [95% CI] for treatment difference
a) Missing values were imputed using multiple imputation based on the change from LAOT-WOB value (last available on-treatment without initiation of bolus insulin for more than 2 weeks) to Week 26 for subjects who had an intercurrent event but had a measurement at Week 26.
b) Calculated using an ANCOVA model with treatment, personal CGM device use, region, and baseline HbA1c as explanatory variables.

Table 41 shows the results of the key secondary endpoints at Week 26.

[31)] The doses were rounded to the nearest 10 units.

Table 41. Results of key secondary endpoints (Trial 4478: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Insulin icodec (N = 263)	IDeg (N = 263)	Insulin icodec (N = 51)	IDeg (N = 49)
Fasting plasma glucose (mg/dL)	Baseline	152.24 ± 47.47 (260)	150.70 ± 40.92 (257)	143.91 ± 39.24 (51)	151.22 ± 32.41 (49)
	Change at Week 26	−30.95 ± 47.63 (243)	−30.85 ± 44.51 (239)	−30.71 ± 39.50 (49)	−37.58 ± 36.30 (48)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]		63.13 ± 17.40 (238)	59.50 ± 18.92 (239)	57.90 ± 16.50 (50)	59.07 ± 18.14 (48)
Time spent below range <70 mg/dL (TBR) (%)[a)]		1.35 ± 2.23 (238)	0.79 ± 1.12 (239)	0.75 ± 1.17 (50)	0.41 ± 0.49 (48)
Time spent above range >180 mg/dL (TAR) (%)[a)]		35.52 ± 17.95 (238)	39.71 ± 19.34 (239)	41.35 ± 16.54 (50)	40.52 ± 18.25 (48)
Proportion of subjects who achieved an HbA1c <7.0% (%)		39.8 (102/256)	28.9 (73/253)	43.1 (22/51)	45.8 (22/48)
Proportion of subjects who achieved an HbA1c ≤6.5% (%)		17.2 (44/256)	10.7 (27/253)	21.6 (11/51)	18.8 (9/48)
Proportion of subjects who achieved an HbA1c <7.0% without level 3 hypoglycemia (%)[b)]		39.5 (101/256)	28.9 (73/253)	41.2 (21/51)	45.8 (22/48)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]		35.9 (92/256)	28.5 (72/253)	39.2 (20/51)	45.8 (22/48)
Insulin dose (units/week)[c)]		280.0 (10.0, 980.0) (249)	253.97 (49.0, 1364) (252)	120.0 (60.0, 740.0) (50)	181.5 (49.0, 728.0) (48)
Body weight (kg)	Baseline	83.72 ± 18.47 (262)	81.54 ± 17.14 (263)	67.51 ± 12.81 (51)	70.16 ± 14.16 (49)
	Change at Week 26	1.51 ± 3.69 (258)	−0.02 ± 4.96 (253)	0.84 ± 2.23 (51)	0.38 ± 2.01 (48)

Mean ± SD (Number of evaluable subjects); Proportion % (Number of subjects in category/Number of evaluable subjects)
Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 22 to Week 26.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 24 to Week 26

Regarding safety, adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population through Week 26 are shown in Table 42, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 43.

Table 42. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group (Trial 4478, Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 262)		IDeg (N = 263)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	61.5 (161)	9.2 (24)	51.0 (134)	4.6 (12)
Nasopharyngitis	8.4 (22)	0 (0)	3.8 (10)	0 (0)
Diarrhoea	5.3 (14)	1.1 (3)	3.4 (9)	0.4 (1)
Headache	5.3 (14)	0.8 (2)	3.4 (9)	0.4 (1)
Diabetic retinopathy	3.8 (10)	0.4 (1)	6.1 (16)	0.4 (1)
COVID-19	3.4 (9)	0 (0)	2.7 (7)	0 (0)
Muscle spasms	3.4 (9)	0.4 (1)	0.4 (1)	0 (0)
Upper respiratory tract infection	3.1 (8)	0 (0)	1.5 (4)	0 (0)
Back pain	2.7 (7)	0 (0)	4.2 (11)	0 (0)
Arthralgia	2.3 (6)	0 (0)	3.8 (10)	0 (0)
Dizziness	1.5 (4)	0.4 (1)	3.4 (9)	0.8 (2)

Incidence % (n), MedDRA/J ver.24.1

Table 43. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group (Trial 4478, Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 51)		IDeg (N = 49)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	70.6 (36)	3.9 (2)	59.2 (29)	10.2 (5)
Nasopharyngitis	13.7 (7)	0 (0)	8.2 (4)	0 (0)
Pyrexia	9.8 (5)	0 (0)	4.1 (2)	0 (0)
Muscle spasms	5.9 (3)	0 (0)	2.0 (1)	0 (0)
Vaccination site pain	3.9 (2)	0 (0)	6.1 (3)	0 (0)
Diabetic retinopathy	3.9 (2)	2.0 (1)	6.1 (3)	2.0 (1)
Vaccination complication	2.0 (1)	0 (0)	6.1 (3)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Two deaths occurred in the insulin icodec group (acute respiratory failure and COVID-19; and COVID-19, 1 subject each) and 2 deaths occurred in the IDeg group (thrombotic stroke; and metastatic pancreatic carcinoma [Japanese subject], 1 subject each), but no adverse drug reactions were reported. Serious adverse events occurred in 22 subjects in the insulin icodec group (including 4 Japanese subjects) and 16 subjects in the IDeg group (including 2 Japanese subjects). Those reported by ≥2 subjects in either treatment group were pneumonia (2 subjects in the insulin icodec group), COVID-19 (2 subjects in the insulin icodec group), COVID-19 pneumonia (2 subjects in the insulin icodec group), and arthritis (2 subjects in the IDeg group). A serious adverse event reported by 1 subject in the IDeg group (anaphylactic reaction) was classified as an adverse drug reaction.

Adverse events leading to treatment discontinuation occurred in 5 subjects in the insulin icodec group (alopecia; urticaria; COVID-19; nephrotic syndrome (Japanese subject); and acute respiratory failure, 1 subject each) and 3 subjects in the IDeg group (anaphylactic reaction; metastatic pancreatic carcinoma (Japanese subject); and thrombotic stroke, 1 subject each), and the event reported by 1 subject in the insulin icodec group (urticaria) and the event reported by 1 subject in the IDeg group (anaphylactic reaction) were classified as adverse drug reactions.

The incidence and rate of hypoglycemia are shown in Table 44.

Table 44. Incidence and rate of hypoglycemia (Trial 4478: Safety analysis set)

Endpoint	Entire trial population		Japanese subgroup	
	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 51)	IDeg (N = 49)
Level 2 or 3 hypoglycemia	14.1 (37)	7.2 (19)	5.9 (3)	0 (0)
	72.79 [113]	27.49 [42]	9.93 [3]	0 [0]
Level 3 hypoglycemia	0 (0)	0.4 (1)	0 (0)	0 (0)
	0 [0]	0.65 [1]	0 [0]	0 [0]
Level 2 or 3 nocturnal hypoglycemia	6.1 (16)	3.4 (9)	3.9 (2)	0 (0)
	20.61 [32]	8.51 [13]	6.62 [2]	0 [0]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
See Table 38 for the classification of hypoglycemia.

The proportion of subjects who developed treatment-induced anti-insulin icodec antibodies was 70.2% (184 of 262 subjects).

There were no clinically relevant changes in laboratory parameters, vital signs, or ECG in the insulin icodec group compared with the IDeg group.

7.3 Global phase III trial in patients with type 2 diabetes mellitus treated with basal-bolus regimen (CTD5.3.5.1-7, Trial 4480 [May 2021 to June 2022])

A randomized, open-label, IGlar (100 units/mL)-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of insulin icodec in adult patients with type 2 diabetes mellitus treated with a basal-bolus regimen including Japanese patients[32] (target sample size, 580 subjects[33] [290 per group]).

Key inclusion criteria: Adult type 2 diabetes mellitus patients who (1) had been treated with stable doses of once daily basal insulin[30] and 2 to 4 daily injections of bolus insulin analog[34] for ≥90 days prior to screening, (2) with or without stable doses of non-insulin anti-diabetic drugs/regimens for ≥90 days prior to screening and (3) had HbA1c of 7.0% to 10.0% at screening and (4) BMI of ≤40.0 kg/m^2. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The trial consisted of a screening period (2 weeks), a treatment period (26 weeks), and a follow-up period (5 weeks).

Once weekly insulin icodec[26] or once daily IGlar (100 units/mL) was to be administered subcutaneously in the thigh, upper arm, or abdomen for 26 weeks (self-injection). As bolus insulin, insulin aspart (genetical recombination) (IAsp) was to be administered subcutaneously with meals 2 to 4 times daily for 26 weeks. The starting dose of insulin icodec was 7 times the daily basal insulin dose before randomization, increased by a one-time additional 50% dose, and the second once-weekly dose of insulin icodec was 7 times the daily basal insulin dose before randomization.[31] When switching to IGlar, the starting dose of IGlar was determined based on the daily basal insulin dose before randomization, in accordance with the local label. Then, the doses of insulin icodec and IGlar were to be adjusted once weekly, according to the titration algorithms presented in Table 45. When switching to IAsp, the starting dose of IAsp was determined based on the bolus insulin dose per meal before randomization, in accordance with the local label. During the first 8 weeks of treatment, IAsp dose adjustments were only permitted for safety reasons. Then the dose of IAsp was to be adjusted at intervals of 3 to 4 days, according to the titration algorithm presented in Table 46. Non-insulin anti-diabetic drugs that subjects had been receiving at screening were to be continued throughout the trial period, except for SU and glinides, which were to be discontinued at randomization.

[32] Japan, US, Belgium, India, Italy, Mexico, Netherlands, Romania, Russia

[33] With respect to the true difference in the primary endpoint of the change in HbA1c from baseline to Week 26 between the insulin icodec and IGlar groups, it was assumed that there would be no between-group difference in the change in HbA1c among subjects who completed randomized treatment and a difference of 0.3 percentage points in favor of the comparator among subjects having an intercurrent event (subjects who discontinued treatment prematurely or withdrew from the trial). Thus, with 10% expected to experience an intercurrent event, this would lead to an assumption of a mean between-group difference of 0.03 percentage point in favor of the comparator in the overall population. Assuming a standard deviation of 1.0%, 1:1 randomization, and a non-inferiority margin of 0.3%, a total of 580 subjects would provide 90% power.

[34] IAsp, insulin lispro (genetical recombination), insulin glulisine (genetical recombination)

Table 45. Titration algorithms for insulin icodec and IGlar (100 units/mL) (Trial 4480)

Pre-breakfast SMBG (mg/dL)[a)]	Dose adjustment of insulin icodec	Dose adjustment of IGlar
<80	−20 units	−3 units
80-130	0	0
>130	+20 units	+3 units

a) Dose adjustments were based on the pre-breakfast SMBG values measured on 2 days prior to and on the day of titration. If the lowest of the 3 pre-breakfast SMBG values was <80 mg/dL, the dose was reduced. Otherwise, a decision to not change or increase the dose was made based on the mean of the 3 pre-breakfast SMBG values.

Table 46. Titration algorithm for IAsp (Trial 4480)

Pre-prandial or bedtime SMBG[a)]	Dose adjustment
≥1 SMBG below 80 mg/dL	−1 unit
No SMBG below 80 mg/dL 0-1 SMBG above 130 mg/dL	0
No SMBG below 80 mg/dL ≥2 SMBGs above 130 mg/dL	+1 unit

a) Dose adjustments were based on the SMBG values measured on 3 days prior to titration, with adjustments to breakfast dose based on pre-lunch SMBG values, adjustments to lunch dose based on pre-dinner SMBG values, and adjustments to dinner dose based on bedtime SMBG values.

All of 582 randomized subjects (291 in the insulin icodec group [including 44 Japanese subjects] and 291 in the IGlar group [including 41 Japanese subjects]) were included in the FAS, and the FAS was the primary efficacy analysis population. All of the 582 subjects received trial product and were included in the safety analysis set. Thirty-four subjects discontinued the trial, including 16 subjects in the insulin icodec group (consent withdrawal [9 subjects], lost to follow-up [3 subjects], investigator decision [2 subjects] [including 1 Japanese subject], death [2 subjects]) and 18 subjects in the IGlar group (consent withdrawal [10 subjects], lost to follow-up [6 subjects], investigator decision [1 subject], death [1 subject]).

The primary efficacy endpoint of the change in HbA1c from baseline to Week 26 is shown in Table 47. Since the upper limit of the 95% confidence interval for the treatment difference between insulin icodec and IGlar fell below the pre-specified non-inferiority margin of 0.3%,[27)] the non-inferiority of insulin icodec to IGlar was demonstrated.

Table 47. Change in HbA1c from baseline to Week 26 (Trial 4480: FAS)

	Treatment group	Baseline	Week 26	Change from baseline[a)]	Treatment difference [95% CI][a)]
Entire trial population	Insulin icodec (N = 291)	8.29 ± 0.86 (291)	7.06 ± 0.73 (275)	−1.16 ± 0.05 [b)]	0.02 [−0.11, 0.15][b)]
	IGlar (N = 291)	8.31 ± 0.90 (291)	6.99 ± 0.71 (264)	−1.18 ± 0.05 [b)]	
Japanese subgroup	Insulin icodec (N = 44)	7.90 ± 0.70 (44)	6.90 ± 0.62 (44)	−1.08 ± 0.08	0.19 [−0.04, 0.43]
	IGlar (N = 41)	8.15 ± 0.83 (41)	6.79 ± 0.59 (41)	−1.27 ± 0.09	

Unit: %, Mean ± SD (Number of evaluable subjects); Least-squares mean ± SE for change; Least-squares mean [95% CI] for treatment difference
a) Calculated using an ANCOVA model with treatment, personal CGM device use, region, and baseline HbA1c as explanatory variables.
b) Missing values were imputed by baseline HbA1c value plus a random error using multiple imputation. This random error was generated from a normal distribution with a mean of 0 and a variance equal to the estimated residual variance from the regression model with the last observed HbA1c value on randomized treatment as a criterion variable and personal CGM device use, treatment, and baseline HbA1c as explanatory variables.

Table 48 shows the results of the key secondary endpoints at Week 26.

Table 48. Results of key secondary endpoints (Trial 4480: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 44)	IGlar (N = 41)
Fasting plasma glucose (mg/dL)	Baseline	166.59 ± 54.10 (283)	173.05 ± 63.46 (284)	155.87 ± 32.37 (44)	170.40 ± 60.24 (41)
	Change at Week 26	−31.39 ± 61.25 (263)	−34.55 ± 73.40 (258)	−18.79 ± 35.23 (42)	−38.28 ± 57.34 (41)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]		66.88 ± 15.62 (244)	66.44 ± 16.17 (237)	64.66 ± 14.77 (40)	67.63 ± 15.73 (40)
Time spent below range <70 mg/dL (TBR) (%)[a)]		2.65 ± 2.92 (244)	2.26 ± 2.62 (237)	1.73 ± 2.32 (40)	1.07 ± 1.47 (40)
Time spent above range >180 mg/dL (TAR) (%)[a)]		30.47 ± 15.90 (244)	31.30 ± 16.67 (237)	33.61 ± 14.68 (40)	31.30 ± 15.70 (40)
Proportion of subjects who achieved an HbA1c <7.0% (%)		46.9 (129/275)	53.0 (140/264)	56.8 (25/44)	65.9 (27/41)
Proportion of subjects who achieved an HbA1c ≤6.5% (%)		25.8 (71/275)	29.2 (77/264)	38.6 (17/44)	34.1 (14/41)
Proportion of subjects who achieved an HbA1c <7.0% without level 3 hypoglycemia (%)[b)]		46.5 (128/275)	52.7 (139/264)	54.5 (24/44)	65.9 (27/41)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]		30.5 (84/275)	29.9 (79/264)	34.1 (15/44)	46.3 (19/41)
Basal insulin dose (units/week)[c)]		360.0 (45.0, 1450.0) (261)	294.0 (52.0, 1116.5) (264)	177.5 (45.0, 840.0) (42)	161.0 (52.5, 800.0) (41)
Bolus insulin dose (units/week)[c)]		209.0 (3.5, 1064.5) (271)	281.1 (28.0, 1250.0) (266)	178.8 (42.0, 769.0) (42)	185.5 (70.0, 593.0) (41)
Total insulin dose (units/week)[c)]		537.0 (58.7, 2259.5) (273)	567.0 (145.0, 2133.0) (266)	342.5 (138.5, 1599.0) (42)	403.0 (175.0, 1377.7) (41)
Body weight (kg)	Baseline	85.51 ± 17.63 (291)	83.08 ± 17.29 (291)	74.61 ± 15.44 (44)	74.70 ± 13.69 (41)
	Change at Week 26	2.84 ± 4.51 (277)	2.20 ± 4.06 (270)	2.52 ± 2.73 (44)	1.13 ± 3.09 (41)

Mean ± SD (Number of evaluable subjects); Proportion % (Number of subjects in category/Number of evaluable subjects); Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 22 to Week 26.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 24 to Week 26

Regarding safety, adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population through Week 26 are shown in Table 49, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 50.

Table 49. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group (Trial 4480, Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 291)		IGlar (N = 291)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	58.8 (171)	10.3 (30)	57.4 (167)	7.6 (22)
COVID-19	8.9 (26)	0 (0)	7.9 (23)	0 (0)
Diarrhoea	5.2 (15)	0.3 (1)	3.1 (9)	0.3 (1)
Diabetic retinopathy	4.1 (12)	1.0 (3)	5.2 (15)	0 (0)
Nasopharyngitis	2.7 (8)	0 (0)	4.1 (12)	0 (0)
Back pain	2.7 (8)	0 (0)	3.8 (11)	0 (0)
Headache	2.7 (8)	0 (0)	3.1 (9)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Table 50. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group (Trial 4480, Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 44)		IGlar (N = 41)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	65.9 (29)	15.9 (7)	63.4 (26)	12.2 (5)
Diarrhoea	13.6 (6)	0 (0)	0 (0)	0 (0)
Diabetic retinopathy	9.1 (4)	2.3 (1)	9.8 (4)	0 (0)
Headache	9.1 (4)	0 (0)	4.9 (2)	0 (0)
Vaccination site pain	6.8 (3)	0 (0)	4.9 (2)	0 (0)
Back pain	6.8 (3)	0 (0)	7.3 (3)	0 (0)
Nasopharyngitis	4.5 (2)	0 (0)	9.8 (4)	0 (0)
Pyrexia	4.5 (2)	0 (0)	7.3 (3)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Two deaths occurred in the insulin icodec group (chronic kidney disease, multiple organ dysfunction syndrome, and acute kidney injury; and COVID-19 pneumonia, 1 subject each) and 1 death occurred in the IGlar group (gastrointestinal haemorrhage), but no adverse drug reactions were reported. Serious adverse events occurred in 22 subjects in the insulin icodec group (including 5 Japanese subjects) and 25 subjects in the IGlar group (including 2 Japanese subjects). Those reported by ≥2 subjects in either treatment group are shown in Table 51, and the events reported by 2 subjects in the insulin icodec group (hypoglycemia [2 subjects] [including 1 Japanese subject]) and the events reported by 2 subjects in the IGlar group (coronary artery disease; and diabetic retinal oedema, 1 subject each) were classified as adverse drug reactions.

Table 51. Serious adverse events reported by ≥2 subjects in either treatment group (Trial 4480, Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 291)	IGlar (N = 291)
Any serious adverse event	7.6 (22)	8.6 (25)
COVID-19 pneumonia	1.4 (4)	0.3 (1)
Hypoglycemia	1.0 (3)	0 (0)
Pneumonia	0.7 (2)	0 (0)
Myocardial infarction	0.7 (2)	0 (0)
Coronary artery disease	0.3 (1)	0.7 (2)
Cardiac failure congestive	0 (0)	0.7 (2)
Diabetic retinal oedema	0 (0)	0.7 (2)

Incidence % (n), MedDRA/J ver.24.1

Adverse events leading to treatment discontinuation occurred in 3 subjects in the insulin icodec group (COVID-19 pneumonia; pneumonia (Japanese subject); and urticaria (Japanese subject), 1 subject each) and 3 subjects in the IGlar group (upper gastrointestinal haemorrhage; lung adenocarcinoma; and hydrocalyx, cognitive disorder, diabetic neuropathy, and liver disorder, 1 subject each), and the event reported by 1 subject in the insulin icodec group (urticaria) was classified as an adverse drug reaction.

The incidence and rate of hypoglycemia are shown in Table 52.

Table 52. Incidence and rate of hypoglycemia (Trial 4480: Safety analysis set)

Endpoint	Entire trial population		Japanese subgroup	
	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 44)	IGlar (N = 41)
Level 2 or 3 hypoglycemia	51.5 (150)	55.7 (162)	47.7 (21)	39.0 (16)
	564.05 [944]	562.36 [938]	374.30 [96]	225.82 [55]
Level 3 hypoglycemia	1.4 (4)	0.7 (2)	2.3 (1)	0 (0)
	4.18 [7]	1.80 [3]	3.90 [1]	0 [0]
Level 2 or 3 nocturnal hypoglycemia	18.6 (54)	24.7 (72)	20.5 (9)	7.3 (3)
	78.27 [131]	103.72 [173]	62.38 [16]	12.32 [3]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]
See Table 38 for the classification of hypoglycemia.

The proportion of subjects who developed treatment-induced anti-insulin icodec antibodies was 70.8% (204 of 288 subjects).

There were no clinically relevant changes in laboratory parameters, vital signs, or ECG in the insulin icodec group compared with the IGlar group.

7.4 Global phase III trial in patients with type 1 diabetes mellitus treated with basal-bolus regimen (CTD5.3.5.1-8 and 5.3.5.1-9, Trial 4625 [April 2021 to December 2022])

A randomized, open-label, IDeg-controlled, parallel group trial was conducted to evaluate the efficacy and safety of insulin icodec in adult patients with type 1 diabetes mellitus treated with a basal-bolus regimen including Japanese patients[35] (target sample size, 580 subjects[36] [290 per group]).

Key inclusion criteria: Adult type 1 diabetes mellitus patients who (1) had been treated with multiple daily insulin injections (basal[37]-bolus[34] insulin analog regimens) for ≥1 year prior to screening and (2) had HbA1c of <10.0% at screening. Patients with eGFR <30 mL/min/1.73 m^2 were excluded.

The trial consisted of a screening period (2 weeks), a main phase (26 weeks), an extension phase (26 weeks), and a follow-up period (5 weeks).

Once-weekly insulin icodec[38] or once-daily IDeg was to be administered subcutaneously in the thigh, upper arm, or abdomen for 52 weeks (self-injection). As bolus insulin, IAsp was to be administered subcutaneously with meals 2 to 4 times daily for 52 weeks. For the first injection only, the insulin icodec dose was the daily basal insulin dose before randomization multiplied by 7, increased by (1) a 100% one-time additional dose for subjects with screening HbA_{1c} ≥8% or (2) a 50% one-time additional dose for subjects with screening HbA_{1c} <8%. Subjects previously treated with IGlar (300 units/mL) or twice-

[35] Japan, US, Austria, Canada, Germany, India, Italy, Netherlands, Russia, Spain, Turkey, UK
[36] With respect to the true difference in the primary endpoint of the change in HbA1c from baseline to Week 26 between the insulin icodec and IDeg groups, it was assumed that there would be no between-group difference in the change in HbA1c among subjects who completed randomized treatment and a difference of 0.3 percentage points in favor of the comparator among subjects having an intercurrent event (subjects who discontinued treatment prematurely or withdrew from the trial). Thus, with 10% expected to experience an intercurrent event, this would lead to an assumption of a mean between-group difference of 0.03 percentage point in favor of the comparator in the overall population. Assuming a standard deviation of 1.0%, 1:1 randomization, and a non-inferiority margin of 0.3%, a total of 580 subjects would provide 90% power.
[37] IDeg, IDet, IGlar (100 units/mL or 300 units/mL)
[38] Insulin icodec was to be administered once weekly on the same day of the week, at any time of day. If an insulin icodec dose was missed for ≤3 days after the planned dosing day, subjects were to inject the planned dose as soon as possible. If the missing dose was missed for >3 days, the subject was to await the next planned day of injection. While awaiting the next planned dose, subjects were to perform frequent SMBG measurements to closely monitor their glycaemic control and adjust bolus doses, if needed.

daily basal insulin were to receive a 50% one-time additional dose regardless of their screening HbA_{1c}. For the second injection, subjects (1) (2) were to receive the calculated once-weekly dose (calculated by multiplying the daily basal insulin dose before randomization by 7).[31)] When switching to IDeg, the starting dose of IDeg was determined based on the daily basal insulin dose before randomization, in accordance with the local label. Then, the doses of insulin icodec and IDeg were to be adjusted once weekly according to the titration algorithms presented in Table 53. When switching to IAsp, the starting dose of IAsp was determined based on the bolus insulin dose per meal before randomization, in accordance with the local label. Then, IAsp doses were to be adjusted once weekly according to the titration algorithm presented in Table 54 or carbohydrate counting. For subjects using the titration algorithm, IAsp dose adjustments were only permitted during the first 8 weeks of treatment for safety reasons.

Table 53. Titration algorithms for insulin icodec and IDeg (Trial 4625)

Pre-breakfast SMBG (mg/dL)[a)]	Dose adjustment of insulin icodec	Dose adjustment of IDeg
<80	−20 units	−3 units
80-130	0	0
>130	+20 units	+3 units

a) Dose adjustments were based on the lowest of the pre-breakfast SMBG values measured on 2 days prior to and on the day of titration.

Table 54. Titration algorithm for IAsp (Trial 4625)

Pre-prandial or bedtime SMBG (mg/dL)[a)]	Dose adjustment
<80	−1 unit
80-130	0
>130	+1 unit

a) Dose adjustments were based on the lowest of the SMBG values measured in the week prior to titration, with adjustments to breakfast dose based on pre-lunch SMBG values, adjustments to lunch dose based on pre-dinner SMBG values, and adjustments to dinner dose based on bedtime SMBG values.

All of 582 randomized subjects (290 in the insulin icodec group [including 32 Japanese subjects], 292 in the IDeg group [including 48 Japanese subjects]) were included in the FAS, and the FAS was the primary efficacy analysis population. All of 582 subjects received trial product and were included in the safety analysis set. During the main phase, 19 subjects discontinued the trial, including 11 subjects in the insulin icodec group (consent withdrawal [9 subjects], lost to follow-up [1 subject], death [1 subject]) and 8 subjects in the IDeg group (consent withdrawal [7 subjects], lost to follow-up [1 subject]). During the extension phase, 8 subjects discontinued the trial, including 5 subjects in the insulin icodec group (consent withdrawal [4 subjects], investigator decision [1 subject]) and 3 subjects in the IDeg group (consent withdrawal [2 subjects], lost to follow-up [1 subject]).

The primary efficacy endpoint of the change in HbA1c from baseline to Week 26 is shown in Table 55. Since the upper limit of the 95% confidence interval for the treatment difference between insulin icodec and IDeg fell below the pre-specified non-inferiority margin of 0.3%,[27)] the non-inferiority of insulin icodec to IDeg was demonstrated.

Table 55. Change in HbA1c from baseline to Week 26 (Trial 4625 [main phase]: FAS)

	Treatment group	Baseline	Week 26	Change from baseline[a)]	Treatment difference [95% CI][a)]
Entire trial population	Insulin icodec (N = 290)	7.59 ± 0.96 (290)	7.11 ± 0.88 (274)	−0.47 ± 0.07 [b)]	0.05 [−0.13, 0.23][b)]
	IDeg (N = 292)	7.63 ± 0.93 (292)	7.08 ± 0.79 (283)	−0.51 ± 0.06 [b)]	
Japanese subgroup	Insulin icodec (N = 32)	7.49 ± 0.65 (32)	7.46 ± 0.78 (32)	−0.07 ± 0.10	0.26 [0.01, 0.51]
	IDeg (N = 48)	7.63 ± 0.74 (48)	7.27 ± 0.67 (48)	−0.33 ± 0.08	

Unit: %, Mean ± SD (Number of evaluable subjects), Least-squares mean ± SE for change, Least-squares mean [95% CI] for treatment difference
a) Calculated using an ANCOVA model with treatment, region, screening HbA1c (<8%, ≥8%), pre-trial basal insulin treatment, and baseline HbA1c (continuous quantity) as explanatory variables.
b) Missing values were imputed using multiple imputation based on the change from LAOT value (last available on-treatment) to Week 26 for subjects who discontinued treatment prematurely but had a measurement at Week 26.

Table 56 shows the results of the key secondary endpoints during the main phase (26 weeks of treatment).

Table 56. Results of key secondary endpoints (Trial 4625 [main phase]: FAS)

Endpoint		Entire trial population		Japanese subgroup	
		Insulin icodec (N = 290)	IDeg (N = 292)	Insulin icodec (N = 32)	IDeg (N = 48)
Fasting plasma glucose (mg/dL)	Baseline	179.17 ± 73.86 (276)	172.31 ± 72.30 (287)	188.53 ± 66.50 (32)	188.23 ± 73.29 (48)
	Change at Week 26	−19.24 ± 90.08 (256)	−32.42 ± 83.31 (274)	−12.67 ± 71.71 (31)	−35.03 ± 70.97 (48)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]		59.10 ± 15.66 (261)	60.85 ± 15.03 (272)	50.65 ± 13.70 (30)	53.37 ± 13.60 (47)
Time spent below range <70 mg/dL (TBR) (%)[a)]		3.86 ± 3.56 (261)	2.90 ± 2.91 (272)	2.94 ± 2.36 (30)	1.85 ± 2.86 (47)
Time spent above range >180 mg/dL (TAR) (%)[a)]		37.03 ± 16.21 (261)	36.25 ± 15.61 (272)	46.41 ± 14.53 (30)	44.78 ± 14.61 (47)
Proportion of subjects who achieved an HbA1c <7.0% (%)		42.3 (116/274)	45.6 (129/283)	28.1 (9/32)	31.2 (15/48)
Proportion of subjects who achieved an HbA1c ≤6.5% (%)		29.9 (82/274)	23.7 (67/283)	9.4 (3/32)	14.6 (7/48)
Proportion of subjects who achieved an HbA1c <7.0% without level 3 hypoglycemia (%)[b)]		41.6 (114/274)	44.9 (127/283)	28.1 (9/32)	31.2 (15/48)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]		14.2 (39/274)	20.8 (59/283)	12.5 (4/32)	12.5 (6/48)
Basal insulin dose (units/week)[c)]		170.0 (50.0, 720.0) (263)	147.0 (14.4, 686.0) (282)	132.5 (50.0, 460.0) (32)	101.5 (14.4, 343.0) (48)
Bolus insulin dose (units/week)[c)]		131.0 (9.8, 742.5) (268)	158.8 (13.0, 546.0) (278)	124.0 (35.0, 487.7) (32)	151.8 (43.5, 414.0) (48)
Total insulin dose (units/week)[c)]		301.0 (12.2, 1259.0) (269)	310.8 (89.9, 1007.0) (282)	269.0 (85.0, 947.7) (32)	265.0 (91.0, 675.0) (48)
Body weight (kg)	Baseline	78.65 ± 17.62 (290)	77.10 ± 16.78 (292)	64.49 ± 12.11 (32)	64.98 ± 13.27 (48)
	Change at Week 26	1.25 ± 3.11 (277)	1.06 ± 2.88 (284)	1.04 ± 2.42 (32)	0.86 ± 1.93 (48)

Mean ± SD (Number of evaluable subjects); Proportion % (Number of subjects in category/Number of evaluable subjects);
Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 22 to Week 26.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 24 to Week 26

Table 57 shows the results of the key secondary endpoints during the extension phase (52 weeks of treatment). Figure 4 shows the change in HbA1c over time from baseline to Week 52.

Table 57. Results of key secondary endpoints (Trial 4625 [main + extension phases]: FAS)

Endpoint	Entire trial population		Japanese subgroup	
	Insulin icodec (N = 290)	IDeg (N = 292)	Insulin icodec (N = 32)	IDeg (N = 48)
Change in HbA1c (%)	−0.39 ± 0.80 (270)	−0.56 ± 0.71 (278)	0.05 ± 0.90 (32)	−0.44 ± 0.52 (48)
Change in fasting plasma glucose (mg/dL)	−15.31 ± 86.95 (239)	−34.67 ± 83.67 (257)	−6.22 ± 77.51 (31)	−38.37 ± 80.02 (48)
Time spent in range 70-180 mg/dL (TIR) (%)[a)]	57.26 ± 15.97 (241)	59.60 ± 15.08 (264)	48.12 ± 14.19 (30)	53.07 ± 14.01 (46)
Proportion of subjects who achieved an HbA1c <7.0% (%)	40.4 (109/270)	41.7 (116/278)	31.2 (10/32)	33.3 (16/48)
Proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia (%)[b)]	14.8 (40/270)	20.5 (57/278)	12.5 (4/32)	12.5 (6/48)
Basal insulin dose (units/week)[c)]	180.0 (35.0, 900.0) (250)	147.0 (21.0, 770.0) (272)	130.0 (40.0, 430.0) (31)	101.5 (21.0, 422.0) (48)
Bolus insulin dose (units/week)[c)]	123.0 (9.3, 688.5) (249)	150.2 (15.8, 641.7) (271)	132.5 (41.5, 472.5) (31)	145.3 (45.0, 393.0) (48)
Total insulin dose (units/week)[c)]	295.5 (10.5, 1352.5) (258)	311.0 (77.0, 1180.7) (272)	287.0 (91.5, 902.5) (31)	258.5 (77.0, 799.0) (48)
Change in body weight (kg)	1.41 ± 4.10 (273)	1.25 ± 3.61 (279)	0.65 ± 3.46 (32)	0.79 ± 2.77 (48)

Mean ± SD (Number of evaluable subjects); Proportion % (Number of subjects in category/Number of evaluable subjects);
Median (Min., Max.) for insulin dose
a) Calculated based on CGM data from Week 48 to Week 52.
b) Based on the occurrence of hypoglycemia in the preceding 12 weeks
c) Mean insulin dose from Week 50 to Week 52

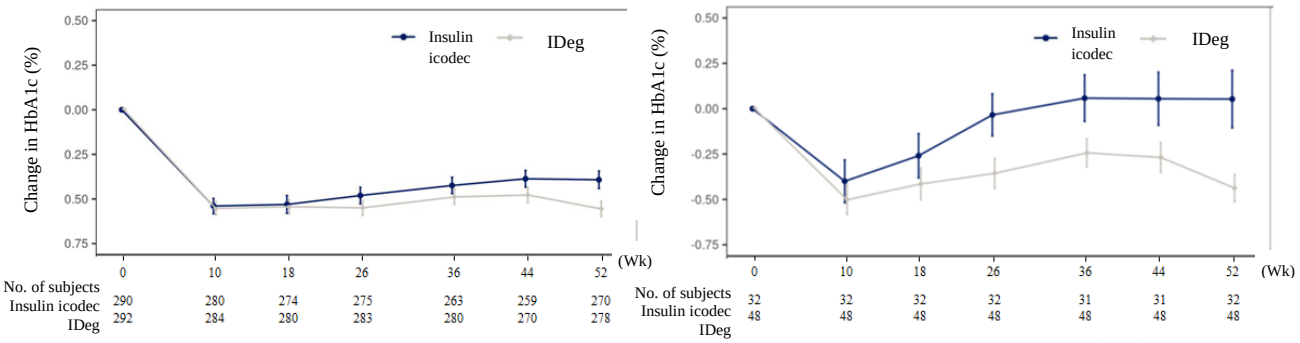


Figure 4. Change in HbA1c over time from baseline to Week 52
(Trial 4625 [main + extension phases]: Entire trial population [Left figure], Japanese subgroup [Right figure], FAS) (Mean ± SE)

Regarding safety, adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population during the main phase (26 weeks of treatment) are shown in Table 58, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 59.

Table 58. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group
(Trial 4625 [main phase], Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 290)		IDeg (N = 292)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	65.2 (189)	12.8 (37)	65.1 (190)	7.2 (21)
Nasopharyngitis	11.7 (34)	0 (0)	12.3 (36)	0 (0)
COVID-19	10.0 (29)	0 (0)	11.0 (32)	0 (0)
Headache	4.5 (13)	1.0 (3)	3.4 (10)	0 (0)
Diabetic retinopathy	4.1 (12)	1.4 (4)	4.8 (14)	0.3 (1)
Pyrexia	3.1 (9)	0 (0)	2.1 (6)	0 (0)
Arthralgia	2.1 (6)	0 (0)	3.1 (9)	0 (0)
Back pain	1.0 (3)	0 (0)	3.8 (11)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Table 59. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group (Trial 4625 [main phase], Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 32)		IDeg (N = 48)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	78.1 (25)	18.8 (6)	77.1 (37)	20.8 (10)
Diabetic retinopathy	15.6 (5)	6.2 (2)	6.2 (3)	0 (0)
Medical device site rash	9.4 (3)	0 (0)	8.3 (4)	0 (0)
Pyrexia	9.4 (3)	0 (0)	8.3 (4)	0 (0)
Dermatitis	9.4 (3)	0 (0)	2.1 (1)	0 (0)
Medical device site dermatitis	6.2 (2)	0 (0)	4.2 (2)	0 (0)
Cataract	6.2 (2)	0 (0)	2.1 (1)	0 (0)
Nasopharyngitis	6.2 (2)	0 (0)	8.3 (4)	0 (0)
Ventricular extrasystoles	6.2 (2)	0 (0)	0 (0)	0 (0)
Pain in extremity	6.2 (2)	0 (0)	2.1 (1)	0 (0)
Hepatic steatosis	6.2 (2)	0 (0)	0 (0)	0 (0)
Hypertension	6.2 (2)	0 (0)	2.1 (1)	0 (0)
Malaise	3.1 (1)	0 (0)	6.2 (3)	2.1 (1)
Myalgia	3.1 (1)	0 (0)	6.2 (3)	0 (0)
Cold sweat	0 (0)	0 (0)	10.4 (5)	4.2 (2)
Contact dermatitis	0 (0)	0 (0)	8.3 (4)	0 (0)
Headache	0 (0)	0 (0)	8.3 (4)	0 (0)
Vaccination complication	0 (0)	0 (0)	6.2 (3)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group in the entire trial population through the extension phase (52 weeks of treatment) are shown in Table 60, and adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group in the Japanese subgroup are shown in Table 61.

Table 60. Adverse events and/or adverse drug reactions reported by ≥3% of subjects in either treatment group (Trial 4625 [main + extension phases], Entire trial population: Safety analysis set)

Event term	Insulin icodec (N = 290)		IDeg (N = 292)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	82.8 (240)	15.2 (44)	80.8 (236)	10.3 (30)
COVID-19	25.9 (75)	0 (0)	28.8 (84)	0 (0)
Nasopharyngitis	16.6 (48)	0 (0)	20.9 (61)	0 (0)
Diabetic retinopathy	8.3 (24)	2.1 (6)	8.9 (26)	0.7 (2)
Headache	5.9 (17)	1.0 (3)	5.5 (16)	0 (0)
Pyrexia	5.5 (16)	0 (0)	6.8 (20)	0 (0)
Upper respiratory tract infection	5.2 (15)	0 (0)	3.8 (11)	0 (0)
Sinusitis	4.8 (14)	0 (0)	3.1 (9)	0 (0)
Gastroenteritis	4.5 (13)	0 (0)	1.7 (5)	0 (0)
Urinary tract infection	4.1 (12)	0 (0)	2.7 (8)	0 (0)
Arthralgia	4.1 (12)	0 (0)	5.1 (15)	0 (0)
Vomiting	3.8 (11)	0.3 (1)	3.4 (10)	0.3 (1)
Diarrhoea	3.4 (10)	0 (0)	2.1 (6)	0 (0)
Hypoglycemia	3.4 (10)	2.4 (7)	1.4 (4)	1.4 (4)
Nausea	3.1 (9)	0 (0)	3.4 (10)	0 (0)
Cough	3.1 (9)	0 (0)	3.8 (11)	0 (0)
Pain in extremity	2.8 (8)	0 (0)	4.5 (13)	0 (0)
Oropharyngeal pain	2.8 (8)	0 (0)	3.4 (10)	0 (0)
Medical device site rash	2.4 (7)	0 (0)	3.8 (11)	0 (0)
Back pain	1.7 (5)	0 (0)	5.8 (17)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

Table 61. Adverse events and/or adverse drug reactions reported by ≥5% of subjects in either treatment group (Trial 4625 [main + extension phases], Japanese subgroup: Safety analysis set)

Event term	Insulin icodec (N = 32)		IDeg (N = 48)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	90.6 (29)	18.8 (6)	91.7 (44)	20.8 (10)
Diabetic retinopathy	28.1 (9)	6.2 (2)	10.4 (5)	0 (0)
Pyrexia	21.9 (7)	0 (0)	29.2 (14)	0 (0)
Cataract	12.5 (4)	0 (0)	4.2 (2)	0 (0)
Hypertension	12.5 (4)	0 (0)	6.2 (3)	0 (0)
Medical device site rash	9.4 (3)	0 (0)	14.6 (7)	0 (0)
Nasopharyngitis	9.4 (3)	0 (0)	14.6 (7)	0 (0)
Dermatitis	9.4 (3)	0 (0)	2.1 (1)	0 (0)
Pain in extremity	9.4 (3)	0 (0)	4.2 (2)	0 (0)
Medical device site dermatitis	6.2 (2)	0 (0)	8.3 (4)	0 (0)
Gastroenteritis	6.2 (2)	0 (0)	4.2 (2)	0 (0)
Palpitations	6.2 (2)	0 (0)	4.2 (2)	0 (0)
Ventricular extrasystoles	6.2 (2)	0 (0)	0 (0)	0 (0)
Hepatic steatosis	6.2 (2)	0 (0)	0 (0)	0 (0)
Malaise	3.1 (1)	0 (0)	10.4 (5)	6.2 (3)
Myalgia	3.1 (1)	0 (0)	8.3 (4)	0 (0)
Tremor	3.1 (1)	0 (0)	6.2 (3)	4.2 (2)
Dizziness	3.1 (1)	0 (0)	6.2 (3)	2.1 (1)
Headache	3.1 (1)	0 (0)	10.4 (5)	0 (0)
Vaccination complication	3.1 (1)	0 (0)	6.2 (3)	0 (0)
Cold sweat	0 (0)	0 (0)	10.4 (5)	4.2 (2)
Contact dermatitis	0 (0)	0 (0)	8.3 (4)	0 (0)
Arthralgia	0 (0)	0 (0)	6.2 (3)	0 (0)

Incidence % (n), MedDRA/J ver.24.1

One death occurred in the insulin icodec group (intracranial haemorrhage) during the main phase, but no adverse drug reactions were reported. There were no deaths during the extension phase. Serious adverse events occurred in 11 subjects in the insulin icodec group (including 1 Japanese subject) and 7 subjects in the IDeg group (including 2 Japanese subjects) during the main phase. New serious adverse events occurred in 13 subjects in the insulin icodec group and 13 subjects in the IDeg group during the extension phase. Serious adverse events reported by ≥2 subjects in either treatment group were hypoglycemia (4 subjects in the insulin icodec group during the main phase, 4 subjects in the insulin icodec group and 1 subject in the IDeg group during the extension phase) and unstable angina (2 subjects in the IDeg group during the extension phase). Those classified as adverse drug reactions were hypoglycemia (4 subjects), product administration error (1 subject), and hypoglycemic seizure (1 subject) in the insulin icodec group and obesity (1 subject) (Japanese subject) and hypoglycemic seizure (1 subject) in the IDeg group during the main phase and hypoglycemia (3 subjects) and spontaneous abortion (1 subject) in the insulin icodec group and hypoglycemia (1 subject) and hypoglycemic unconsciousness (1 subject) in the IDeg group during the extension phase.

Adverse events leading to treatment discontinuation occurred in 1 subject in the IDeg group (insulin resistance) during the main phase and 1 subject in the insulin icodec group (cerebral haemorrhage) during the extension phase, but no adverse drug reactions were reported.

The incidence and rate of hypoglycemia are shown in Table 62.

Table 62. Incidence and rate of hypoglycemia (Trial 4625: Safety analysis set)

Endpoint	Main phase (26 weeks of treatment)				Main + extension phases (52 weeks of treatment)			
	Entire trial population		Japanese subgroup		Entire trial population		Japanese subgroup	
	Insulin icodec (N = 290)	IDeg (N = 292)	Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)	Insulin icodec (N = 32)	IDeg (N = 48)
Level 2 or 3 hypoglycemia	85.2 (247)	76.4 (223)	87.5 (28)	60.4 (29)	90.7 (263)	85.6 (250)	96.9 (31)	75.0 (36)
	1992.86 [2836]	1037.33 [1495]	2068.63 [332]	951.02 [229]	1700.10 [5103]	916.07 [2836]	1913.99 [661]	789.54 [414]
Level 3 hypoglycemia	3.1 (9)	3.1 (9)	0 (0)	0 (0)	4.5 (13)	4.1 (12)	0 (0)	0 (0)
	33.03 [47]	11.80 [17]	0 [0]	0 [0]	18.66 [56]	8.08 [25]	0 [0]	0 [0]
Level 2 or 3 nocturnal hypoglycemia	46.6 (135)	33.6 (98)	43.8 (14)	33.3 (16)	59.0 (171)	47.9 (140)	59.4 (19)	43.8 (21)
	338.00 [481]	157.51 [227]	542.08 [87]	178.58 [43]	289.85 [870]	149.23 [462]	498.04 [172]	162.10 [85]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]
See Table 38 for the classification of hypoglycemia.

The proportion of subjects who developed treatment-induced anti-insulin icodec antibodies was 80.6% (232 of 288 subjects).

There were no clinically relevant changes in laboratory parameters, vital signs, or ECG in the insulin icodec group compared with the IDeg group.

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy in patients with type 2 diabetes mellitus

The applicant's explanation:

Three global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480) demonstrated the non-inferiority of insulin icodec to IGlar (100 units/mL) or IDeg in the primary endpoint of the change from baseline in HbA1c (Tables 30, 40, and 47). Trial 4477 in insulin-naïve patients evaluated the efficacy of insulin icodec through Week 78, and the reduction in HbA1c with insulin icodec at Week 52 (the timing of the primary endpoint) was maintained to Week 78 (Table 32 and Figure 3). Secondary endpoints of the proportion of subjects who achieved an HbA1c <7.0% and the proportion of subjects who achieved an HbA1c <7.0% without hypoglycemia were higher in the insulin icodec group than in the control group (IGlar or IDeg) in Trial 4477 in insulin-naïve patients and Trial 4478 in basal insulin-treated patients, and there were no major differences between the insulin icodec and IGlar groups in Trial 4480 in basal-bolus regimen-treated patients. The change from baseline in fasting plasma glucose was similar between the insulin icodec and control groups in all of the 3 trials. As to CGM endpoints, the percentage of TIR (time spent in the glycemic range of 70-180 mg/dL) was higher in the insulin icodec group than in the IGlar group, and the percentage of TAR (time spent above range >180 mg/dL) was lower in the insulin icodec group than in the IGlar group in Trial 4477 in insulin-naïve patients. In Trials 4478 and 4480, there were no major differences in the percentages of TIR and TAR between the insulin icodec and control groups. In all of the 3 trials, there were no major differences in the percentage of TBR (time spent below range <70 mg/dL) between the insulin icodec and control groups (Tables 31, 41, and 48).

The efficacy of insulin icodec in the Japanese subgroup was evaluated as follows:
Type 2 diabetes mellitus is characterized by relative insulin deficiency due to reduced insulin secretion and insulin resistance resulting in chronic hyperglycemia. With regard to the extrinsic and intrinsic ethnic factors relating to type 2 diabetes mellitus, the pathogenesis of type 2 diabetes mellitus differs from region to region. Impaired insulin secretion is considered to contribute more to the disease than insulin resistance in patients in East Asian countries including Japan compared with the Western population, and the body size and diet composition also differ from region to region. On the other hand, there are no major differences in the diagnostic criteria or treatment goals for type 2 diabetes between Japan and overseas. In insulin therapy, insulin doses are adjusted according to the individual patient's condition including self-measured blood glucose. Also from this standpoint, there are no major ethnic differences. In addition, there were no major differences in the pharmacokinetics or pharmacodynamics of insulin icodec between the Japanese and non-Japanese populations [see Section "6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations"].

Tables 63 to 65 show baseline subject characteristics in Trials 4477, 4478, and 4480, respectively. In all of the 3 trials, body weight, BMI, and eGFR were lower in the Japanese subgroup than in the entire trial population. In Trials 4478 and 4480, the basal insulin dose was lower in the Japanese subgroup than in the entire trial population. In Trial 4480, the total insulin dose and the proportion of female subjects were lower in the Japanese subgroup than in the entire trial population. In Trial 4480, the difference in the total insulin dose was attributable to the difference in the basal insulin dose. With respect to other baseline subject characteristics, there were no major differences between the entire trial population and the Japanese subgroup.

Table 63. Baseline subject characteristics (Trial 4477: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 492)	IGlar (N = 492)
Age (years)		58.72 ± 10.40	58.97 ± 10.16	59.06 ± 10.05	58.85 ± 9.85
Sex[a)]	Male	70.5 (55)	65.1 (56)	60.0 (295)	53.5 (263)
	Female	29.5 (23)	34.9 (30)	40.0 (197)	46.5 (229)
Body weight (kg)		73.42 ± 15.48	73.28 ± 13.24	85.17 ± 17.74	84.31 ± 17.63
BMI (kg/m^2)		26.62 ± 4.41	27.01 ± 4.22	29.98 ± 4.78	30.13 ± 5.05
Diabetes duration (years)		13.13 ± 7.61	12.17 ± 6.87	11.62 ± 6.66	11.46 ± 6.75
HbA1c (%)		8.06 ± 0.83	8.01 ± 0.84	8.50 ± 0.99	8.44 ± 1.02
Fasting plasma glucose (mg/dL)		164.26 ± 34.64	163.84 ± 32.38	185.31 ± 48.96 [b)]	185.71 ± 51.66 [c)]
eGFR ($mL/min/1.73\ m^2$)		72.51 ± 13.41	70.22 ± 14.09	86.05 ± 18.19	84.90 ± 19.58

Mean ± SD
a) Proportion % (Number of subjects in category)
b) N = 480, c) N = 474

Table 64. Baseline subject characteristics (Trial 4478: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 51)	IDeg (N = 49)	Insulin icodec (N = 263)	IDeg (N = 263)
Age (years)		61.94 ± 10.33	62.90 ± 9.00	62.35 ± 9.79	62.60 ± 8.42
Sex[a)]	Male	64.7 (33)	63.3 (31)	61.6 (162)	53.2 (140)
	Female	35.3 (18)	36.7 (18)	38.4 (101)	46.8 (123)
Body weight (kg)		67.51 ± 12.81	70.16 ± 14.16	83.72 ± 18.44	81.54 ± 17.14
BMI (kg/m^2)		25.05 ± 3.81	25.75 ± 3.90	29.52 ± 5.20	29.17 ± 4.89
Diabetes duration (years)		18.21 ± 9.81	16.24 ± 8.05	16.54 ± 8.36	16.93 ± 7.92
HbA1c (%)		8.10 ± 0.70	7.98 ± 0.74	8.17 ± 0.77	8.10 ± 0.77
Fasting plasma glucose (mg/dL)		143.91 ± 39.24	151.22 ± 32.41	152.24 ± 47.47 [b)]	150.70 ± 40.92 [c)]
eGFR (mL/min/1.73 m^2)		69.12 ± 13.60	69.39 ± 11.70	81.02 ± 18.81	80.23 ± 19.86
Basal insulin dose (Upper row: units/day, Lower row: units/day/kg)		13.0 (4.0, 50.0)	15.0 (4.0, 66.0)	25.0 (4.0, 150.0)	28.0 (4.0, 180.0)
		0.19 (0.04, 0.67)	0.21 (0.06, 0.80)	0.31 (0.04, 1.98)	0.34 (0.06, 1.68)

Mean ± SD, Median (Min., Max.) for insulin dose
a) Proportion % (Number of subjects in category)
b) N = 260, c) N = 257

Table 65. Baseline subject characteristics (Trial 4480: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 44)	IGlar (N = 41)	Insulin icodec (N = 291)	IGlar (N = 291)
Age (years)		61.16 ± 11.49	60.24 ± 11.20	59.67 ± 10.13	59.91 ± 9.92
Sex[a)]	Male	75.0 (33)	73.2 (30)	52.9 (154)	51.5 (150)
	Female	25.0 (11)	26.8 (11)	47.1 (137)	48.5 (141)
Body weight (kg)		74.61 ± 15.44	74.70 ± 13.69	85.51 ± 17.63	83.08 ± 17.29
BMI (kg/m^2)		26.63 ± 3.72	26.74 ± 3.55	30.55 ± 5.02	29.98 ± 5.02
Diabetes duration (years)		20.87 ± 9.75	17.36 ± 9.67	17.97 ± 9.09	16.33 ± 7.65
HbA1c (%)		7.90 ± 0.70	8.15 ± 0.83	8.29 ± 0.86	8.31 ± 0.90
Fasting plasma glucose (mg/dL)		155.87 ± 32.37	170.40 ± 60.24	166.59 ± 54.10 [c)]	173.05 ± 63.46 [d)]
eGFR (mL/min/1.73 m^2)		72.34 ± 13.75	72.85 ± 13.59	81.92 ± 20.48	81.88 ± 20.27
Insulin dose[b)] (Upper row: units/week) (Lower row: units/week/kg)	Basal	100.0 (15.0, 420.0)[e)]	97.0 (35.0, 407.0)	220.0 (15.0, 1050.0)[f)]	224.0 (29.0, 819.0)[c)]
		1.24 (0.28, 3.91)[e)]	1.40 (0.48, 5.75)	2.75 (0.21, 12.16)[f)]	2.79 (0.36, 11.99)[c)]
	Bolus	168.0 (70.0, 960.0)[e)]	140.0 (28.0, 464.0)	196.0 (28.0, 960.0)[g)]	204.0 (28.0, 1467.7)[c)]
		2.25 (0.97, 7.02)[e)]	1.92 (0.39, 5.99)	2.36 (0.34, 10.65)[g)]	2.49 (0.22, 17.83)[c)]
	Total	270.0 (100.0, 1380.0)[e)]	275.0 (63.0, 706.0)	422.5 (70.0, 1970.0)[g)]	450.0 (63.0, 1832.9)[d)]
		3.59 (1.39, 10.60)[e)]	3.86 (0.88, 9.96)	5.13 (0.63, 22.81)[g)]	5.33 (0.70, 22.27)[d)]

Mean ± SD, Median (Min., Max.) for insulin dose
a) Proportion % (Number of subjects in category)
b) Bolus insulin doses collected at screening, especially in subjects using carbohydrate counting, may have been incomplete compared with the actual doses during the trial period. Thus, the doses at Week 2 were used as baseline values.
c) N = 283, d) N = 284, e) N = 43, f) N = 278, g) N = 286

The primary endpoint of the change from baseline in HbA1c showed a similar trend between the Japanese subgroup and the entire trial population in all of Trials 4477, 4478, and 4480 (Tables 30, 40, and 47). Secondary endpoints of fasting plasma glucose, TIR using CGM, etc., also showed a similar trend between the Japanese subgroup and the entire trial population (Tables 31, 41, and 48).

Subgroup analyses of the change from baseline in HbA1c were performed according to the baseline subject characteristics that differed between the Japanese subgroup and the entire trial population, i.e., sex, BMI, eGFR, and basal insulin dose per body weight. There were no major differences across the subgroups (Table 66 to Table 68). Thus, the differences in baseline subject characteristics between the Japanese subgroup and the entire trial population are considered to have no clinically meaningful effects on the assessment of the trial results, and there were consistent trends in the efficacy results from these trials between the Japanese subgroup and the entire trial population.

Table 66. Change in HbA1c from baseline to Week 52 by subject characteristics (Trial 4477: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 492)	IGlar (N = 492)
BMI (kg/m^2)	<25	−1.18 ± 0.11 (32)	−1.14 ± 0.16 (31)	−1.42 ± 0.12 (87)	−1.16 ± 0.12 (80)
	≥25 and <30	−1.19 ± 0.11 (32)	−1.04 ± 0.11 (33)	−1.57 ± 0.09 (164)	−1.31 ± 0.08 (171)
	≥30 and <35	−1.08 ± 0.21 (9)	−1.08 ± 0.15 (18)	−1.64 ± 0.09 (162)	−1.42 ± 0.09 (146)
	≥35	−1.35 ± 0.29 (5)	−1.33 ± 0.32 (4)	−1.45 ± 0.11 (79)	−1.49 ± 0.11 (95)
eGFR ($mL/min/1.73\ m^2$)	≥90	−0.97 ± 0.45 (2)	−1.09 ± 0.29 (5)	−1.53 ± 0.08 (224)	−1.37 ± 0.08 (222)
	≥60 and <90	−1.14 ± 0.08 (63)	−1.06 ± 0.10 (58)	−1.55 ± 0.07 (223)	−1.35 ± 0.07 (213)
	<60	−1.41 ± 0.18 (13)	−1.18 ± 0.13 (23)	−1.64 ± 0.21 (45)	−1.30 ± 0.14 (57)

Unit: %, Least-squares mean ± SE (Number of evaluable subjects)

Table 67. Change in HbA1c from baseline to Week 26 by subject characteristics (Trial 4478: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 51)	IDeg (N = 49)	Insulin icodec (N = 263)	IDeg (N = 263)
BMI (kg/m^2)	<25	−0.75 ± 0.13 (27)	−0.78 ± 0.17 (21)	−0.84 ± 0.11 (54)	−0.75 ± 0.13 (56)
	≥25 and <30	−0.93 ± 0.16 (17)	−0.98 ± 0.14 (23)	−0.94 ± 0.09 (93)	−0.70 ± 0.08 (104)
	≥30 and <35	−0.94 ± 0.26 (7)	−0.91 ± 0.30 (5)	−0.94 ± 0.10 (69)	−0.76 ± 0.10 (63)
	≥35			−1.01 ± 0.11 (47)	−0.59 ± 0.13 (40)
eGFR ($mL/min/1.73\ m^2$)	≥90	−0.74 ± 0.47 (2)	−0.26 ± 0.68 (1)	−0.98 ± 0.08 (94)	−0.65 ± 0.08 (109)
	≥60 and <90	−0.76 ± 0.11 (39)	−1.00 ± 0.12 (38)	−0.86 ± 0.07 (135)	−0.84 ± 0.08 (108)
	≥30 and <60	−1.11 ± 0.21 (10)	−0.55 ± 0.21 (10)	−1.11 ± 0.15 (34)	−0.53 ± 0.12 (46)
Basal insulin dose (units/day/kg)	≤0.3	−0.89 ± 0.11 (39)	−0.93 ± 0.12 (36)	−1.05 ± 0.07 (125)	−0.82 ± 0.08 (108)
	>0.3	−0.64 ± 0.20 (12)	−0.77 ± 0.19 (13)	−0.83 ± 0.07 (138)	−0.64 ± 0.07 (155)

Unit: %, Least-squares mean ± SE (Number of evaluable subjects)

Table 68. Change in HbA1c from baseline to Week 26 by subject characteristics (Trial 4480: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 44)	IGlar (N = 41)	Insulin icodec (N = 291)	IGlar (N = 291)
Sex	Male	−1.08 ± 0.10 (33)	−1.25 ± 0.10 (30)	−1.11 ± 0.06 (154)	−1.20 ± 0.07 (150)
	Female	−1.07 ± 0.16 (11)	−1.32 ± 0.16 (11)	−1.21 ± 0.07 (137)	−1.16 ± 0.07 (141)
BMI (kg/m^2)	<25	−0.93 ± 0.15 (14)	−1.33 ± 0.13 (16)	−0.94 ± 0.13 (42)	−1.14 ± 0.12 (49)
	≥25 and <30	−1.13 ± 0.11 (22)	−1.10 ± 0.14 (15)	−1.15 ± 0.08 (95)	−1.07 ± 0.08 (96)
	≥30 and <35	−1.15 ± 0.19 (8)	−1.45 ± 0.17 (10)	−1.26 ± 0.08 (93)	−1.25 ± 0.08 (99)
	≥35			−1.17 ± 0.11 (61)	−1.28 ± 0.12 (47)
eGFR ($mL/min/1.73\ m^2$)	≥90	−1.03 ± 0.25 (5)	−1.33 ± 0.25 (5)	−1.22 ± 0.07 (123)	−1.11 ± 0.07 (127)
	≥60 and <90	−1.04 ± 0.10 (30)	−1.27 ± 0.10 (30)	−1.06 ± 0.07 (121)	−1.27 ± 0.07 (120)
	≥30 and <60	−1.22 ± 0.19 (9)	−1.20 ± 0.22 (6)	−1.25 ± 0.12 (47)	−1.11 ± 0.12 (44)
Basal insulin dose (units/week/kg)[a)]	≤2.8	−1.10 ± 0.09 (36)	−1.37 ± 0.09 (31)	−1.23 ± 0.06 (146)	−1.22 ± 0.06 (145)
	>2.8	−1.17 ± 0.19 (7)	−0.93 ± 0.17 (10)	−1.10 ± 0.07 (133)	−1.20 ± 0.07 (138)

Unit: %, Least-squares mean ± SE (Number of evaluable subjects)
a) Doses at Week 2 were used as baseline values.

PMDA's view:

Three global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes patients (Trials 4477, 4478, and 4480) demonstrated the non-inferiority of insulin icodec to IGlar (100 units/mL) or IDeg in the primary endpoint of the change from baseline in HbA1c. There were no major differences in secondary endpoints of the proportion of subjects who achieved an HbA1c <7.0% without hypoglycemia, fasting plasma glucose, and CGM endpoints between the control and insulin icodec groups. In Trials 4477 and 4478, there was a trend towards greater improvement in some endpoints of glycemic control in the insulin icodec group compared with the control group. Regarding the long-term efficacy of insulin icodec, as the reduction in HbA1c with insulin icodec at Week 52 was maintained to Week 78 in Trial 4477, clinically meaningful efficacy will be maintained through ≥1 year of continuous treatment in insulin icodec-treated patients with type 2 diabetes mellitus.

Regarding the efficacy of insulin icodec in the Japanese subgroup, though some baseline subject characteristics differed between the Japanese subgroup and the entire trial population in these trials, those differences had no major impact on the efficacy assessment of insulin icodec. Also with respect to the primary endpoint of the change from baseline in HbA1c, the proportion of subjects achieving HbA1c target, fasting plasma glucose, CGM endpoints, etc., the consistent results were obtained between the Japanese subgroup and the entire trial population.

Based on the above, the efficacy of insulin icodec in Japanese patients can be explained by the results from the global phase III trials. Those trial results etc. indicated that insulin icodec has clinically meaningful efficacy in Japanese patients with type 2 diabetes mellitus.

7.R.1.2 Efficacy in patients with type 1 diabetes mellitus

The applicant's explanation:

A global phase III trial in patients with type 1 diabetes mellitus treated with a basal-bolus regimen (Trial 4625) demonstrated the non-inferiority of insulin icodec to IDeg in the primary endpoint of the change in HbA1c from baseline to Week 26 (Table 55). As to the change in HbA1c over time up to Week 52, the change tended to be slightly smaller from Week 26 onwards in both the insulin icodec and IDeg groups, but the reduction in HbA1c with insulin icodec was maintained to Week 52 (Table 57 and Figure 4). With respect to secondary endpoints of the proportion of subjects who achieved an HbA1c <7.0% and the proportion of subjects who achieved an HbA1c <7.0% without level 3 hypoglycemia, there were no major differences between the insulin icodec and IDeg groups, whereas the proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia was lower in the insulin icodec group than in the IDeg group (Table 56). The change from baseline in fasting plasma glucose (FPG) tended to be smaller in the insulin icodec group than in the IDeg group. This may be explained by FPG collected at the last day of the weekly dosing interval, and this difference potentially could reflect a higher variability of the FPG lowering effect throughout the insulin icodec dosing interval in type 1 diabetes mellitus patients compared with type 2 diabetes mellitus patients, given the full-week pharmacodynamic profile of insulin icodec [see Section "6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec"]. With respect to CGM endpoints of the percentages of TIR (time spent in the glycemic range of 70-180 mg/dL), TBR (time spent below range <70 mg/dL), and TAR (time spent above range >180 mg/dL), there were no major differences between the insulin icodec and IDeg groups (Table 56).

The efficacy of insulin icodec in the Japanese subgroup was evaluated as follows:

With regard to the extrinsic and intrinsic ethnic factors relating to type 1 diabetes mellitus, the pathogenesis of type 1 diabetes mellitus is characterized by a lack of endogenous insulin secretion from pancreatic β cells. Insulin therapy is required for survival, and in terms of this point, there are no ethnic differences. In insulin therapy, insulin doses are adjusted according to the individual patient's condition including self-measured blood glucose, and also from this standpoint, there are no differences between Japan and overseas. In addition, there were no major differences in the pharmacokinetics or pharmacodynamics of insulin icodec between the Japanese and non-Japanese populations [see Section

"6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations"].

Table 69 shows the baseline subject characteristics in Trial 4625. eGFR and the weekly basal insulin dose were lower, and the weekly bolus insulin dose was higher in the Japanese subgroup than in the entire trial population, but there were no major differences in other baseline subject characteristics between the entire trial population and the Japanese subgroup.

Table 69. Baseline subject characteristics (Trial 4625: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)
Age (years)		51.31 ± 13.08	52.56 ± 11.92	44.08 ± 14.07	44.28 ± 14.07
Sex[a)]	Male	43.8 (14)	50.0 (24)	56.9 (165)	58.9 (172)
	Female	56.2 (18)	50.0 (24)	43.1 (125)	41.1 (120)
Body weight (kg)		64.49 ± 12.11	64.98 ± 13.27	78.65 ± 17.62	77.10 ± 16.78
BMI (kg/m^2)		24.14 ± 3.58	24.17 ± 3.75	26.84 ± 5.03	26.19 ± 4.53
Diabetes duration (years)		23.39 ± 12.58	19.62 ± 10.95	20.05 ± 13.20	18.98 ± 12.88
HbA1c (%)		7.49 ± 0.65	7.63 ± 0.74	7.59 ± 0.96	7.63 ± 0.93
Fasting plasma glucose (mg/dL)		188.53 ± 66.50	188.23 ± 73.29	179.17 ± 73.86 [c)]	172.31 ± 72.30 [d)]
eGFR (mL/min/1.73 m^2)		80.75 ± 10.77	80.79 ± 11.45	98.50 ± 18.71	97.02 ± 19.62
Insulin dose[b)] (Upper row: units/week) (Lower row: units/week/kg)	Basal	110.0 (20.0, 300.0)	89.5 (14.0, 270.0)	170.0 (20.0, 550.0)[e)]	143.0 (14.0, 644.0)[f)]
		1.70 (0.44, 3.62)	1.55 (0.26, 3.35)	2.17 (0.44, 6.30)[e)]	1.95 (0.26, 6.65)[f)]
	Bolus	190.5 (72.0, 588.0)	165.0 (46.0, 415.0)	159.0 (18.0, 930.0)[g)]	164.0 (42.0, 567.0)[h)]
		2.85 (1.47, 7.35)	2.61 (0.85, 5.36)	2.04 (0.28, 10.25)[g)]	2.23 (0.59, 6.58)[h)]
	Total	322.0 (119.0, 848.0)	260.0 (95.0, 625.0)	325.0 (39.7, 1226.0)[i)]	312.0 (95.0, 1019.0)[f)]
		4.57 (2.52, 10.60)	4.24 (1.65, 8.07)	4.29 (0.51, 13.23)[i)]	4.19 (1.37, 9.82)[f)]

Mean ± SD, Median (Min., Max.) for insulin dose
a) Proportion % (Number of subjects in category)
b) Bolus insulin doses collected at screening, especially in subjects using carbohydrate counting, may have been incomplete compared with the actual doses during the trial period. Thus, the doses at Week 2 were used as baseline values.
c) N = 276, d) N = 287, e) N = 285, f) N = 291, g) N = 286, h) N = 288, i) N = 289

Regarding the primary endpoint of the change in HbA1c from baseline to Week 26, though HbA1c decreased from baseline to Week 10 in both treatment groups of the Japanese subgroup and the entire trial population, the change in HbA1c from baseline to Week 26 in the insulin icodec group was smaller in the Japanese subgroup than in the entire trial population (Table 55), and the change in HbA1c in the insulin icodec group tended to gradually get smaller over weeks even in the entire trial population. Moreover, HbA1c in the insulin icodec group tended to increase towards baseline through Week 52 in the Japanese subgroup (Table 57 and Figure 4). With respect to secondary endpoints of fasting plasma glucose, TIR using CGM, etc., the relationship between the IDeg and insulin icodec groups in the Japanese subgroup showed a similar trend to that in the entire trial population (Tables 56 and 57).

Subgroup analyses of the change from baseline in HbA1c were performed according to the baseline subject characteristics that differed between the Japanese subgroup and the entire trial population, i.e., eGFR and the basal and bolus insulin doses per kg body weight. Although there was no reduction in HbA1c in the Japanese subgroup with normal eGFR, it should be noted that the number of Japanese subjects with normal eGFR was limited. There were no major differences in the change in HbA1c across the subgroups according to eGFR in the entire trial population. There was no trend towards reduced HbA1c in the insulin icodec group compared with the control group in the Japanese subgroup with the weekly basal insulin dose of ≤2.1 units/kg or the Japanese subgroup with the weekly bolus insulin dose

of ≤2.2 units/kg, while there were no major differences in the change in HbA1c across the subgroups according to the weekly basal or bolus insulin doses in the entire trial population (Table 70).

Table 70. Change in HbA1c from baseline to Week 26 by subject characteristics (Trial 4625: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)
eGFR (mL/min/1.73 m^2)	≥90	0.22 ± 0.23 (6)	−0.37 ± 0.19 (9)	−0.52 ± 0.08 (197)	−0.56 ± 0.08 (190)
	≥60 and <90	−0.14 ± 0.11 (26)	−0.32 ± 0.09 (39)	−0.32 ± 0.11 (88)	−0.42 ± 0.09 (93)
	≥30 and <60			−0.75 ± 0.36 (5)	−0.57 ± 0.27 (9)
Basal insulin dose (units/week/kg)[a)]	≤2.1	−0.00 ± 0.12 (21)	−0.30 ± 0.09 (40)	−0.47 ± 0.10 (136)	−0.49 ± 0.08 (175)
	>2.1	−0.21 ± 0.17 (11)	−0.46 ± 0.20 (8)	−0.49 ± 0.08 (150)	−0.56 ± 0.09 (116)
Bolus insulin dose (units/week/kg)[a)]	≤2.2	0.08 ± 0.20 (8)	−0.27 ± 0.14 (17)	−0.37 ± 0.10 (152)	−0.46 ± 0.08 (142)
	>2.2	−0.12 ± 0.11 (24)	−0.37 ± 0.10 (31)	−0.59 ± 0.08 (134)	−0.58 ± 0.08 (147)

Unit: %, Least-squares mean ± SE (Number of evaluable subjects)
a) Doses at Week 2 were used as baseline values.

The applicant's explanation about the reason for the above findings (The primary endpoint of the change in HbA1c from baseline to Week 26 in the insulin icodec group was smaller in the Japanese subgroup than in the entire trial population, and HbA1c tended to increase towards baseline through Week 52):
In order to assess the impact of baseline subject characteristics on HbA1c change in Trial 4625, subjects were divided into subgroups with a reduction in HbA1c from baseline to Week 52 or no change or an increase in HbA1c, and subject characteristics that may impact HbA1c change were identified. In the entire trial population, there were no major differences in subject characteristics between the subgroups with a reduction in HbA1c or no change or an increase in HbA1c. On the other hand, in the insulin icodec group of the Japanese subgroup, subjects with no change or an increase in HbA1c tended to have a longer duration of diabetes and a lower basal insulin dose and a lower basal to total insulin dose ratio (basal insulin dose/total insulin dose) at baseline[39)] than subjects with a reduction in HbA1c.

Table 71 shows the change in HbA1c from baseline to Week 52 in the subgroups according to the basal insulin dose and the basal to total insulin dose ratio at baseline (the subject characteristics that differed between the subjects with a reduction in HbA1c from baseline to Week 52 and the subjects with no change or an increase in HbA1c from baseline to Week 52 in the insulin icodec group of the Japanese subgroup). In the Japanese subgroup, HbA1c tended to increase from baseline to Week 52 in the subjects with a lower basal insulin dose at baseline and the subjects with a lower basal to total insulin dose ratio at baseline. In the entire trial population, there were no major difference across the subgroups.

Table 71. Change in HbA1c from baseline to Week 52 by insulin dose at baseline [a)] (Trial 4625: FAS)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)
Basal insulin dose (units/week/kg)	≤2.1	0.26 ± 0.14 (21)	−0.42 ± 0.10 (40)	−0.39 ± 0.07 (136)	−0.54 ± 0.07 (174)
	>2.1	−0.43 ± 0.20 (11)	−0.39 ± 0.23 (8)	−0.37 ± 0.07 (150)	−0.55 ± 0.07 (117)
Basal to total insulin dose ratio	≤0.5	0.09 ± 0.14 (25)	−0.46 ± 0.10 (42)	−0.43 ± 0.07 (142)	−0.60 ± 0.06 (184)
	>0.5	−0.22 ± 0.26 (7)	−0.13 ± 0.28 (6)	−0.32 ± 0.07 (144)	−0.46 ± 0.08 (107)

Unit: %, Least-squares mean ± SE (Number of evaluable subjects)
a) Doses at Week 2 were used as baseline values.

[39)] Bolus insulin doses collected at screening, especially in subjects using carbohydrate counting, may have been incomplete compared with the actual doses during the trial period. Thus, both doses at screening and at Week 2 were used as baseline values for analyses.

In the Japanese subgroup, there were 4 subjects who had a >1% point increase in HbA1c from baseline to the end of treatment in the insulin icodec group and none in the IDeg group. Thus, these 4 cases may have affected the change in HbA1 over time up to Week 52 observed in the insulin icodec group of the Japanese subgroup. In the entire trial population, 7 subjects in the insulin icodec group and 4 subjects in the IDeg group had a >1% point increase in HbA1c from baseline to the end of treatment. In the 4 Japanese subjects who had a >1% point increase in HbA1c from baseline to the end of treatment in the insulin icodec group, the basal insulin dose at screening was relatively low, i.e., 0.066 to 0.217 units/kg. In 3 of the 4 subjects, the basal insulin dose was lower, and the bolus insulin dose was higher, compared with the mean values in the Japanese subgroup, throughout the trial period. The basal to total insulin dose ratio at screening was relatively low, i.e., 0.120 to 0.286, and the basal to total insulin dose ratio was generally lower than the mean value in the Japanese subgroup throughout the trial period. Since the actual basal insulin doses at screening in the 4 subjects were relatively low, i.e., 3 units/day, 7 units/day, 8 units/day, and 16 units/day, respectively, dose adjustments of ±20 units according to the titration algorithm are considered to result in a large change in the basal to total insulin dose ratio. Indeed, the basal to total insulin dose ratios in the 4 subjects kept changing instead of remaining constant, throughout the trial period. This was considered a contributing factor to an increase in HbA1c from baseline to Week 52 in the subjects with a lower basal insulin dose at baseline and the subjects with a lower basal to total insulin dose ratio at baseline in the Japanese subgroup. There was no particular trend in other subject characteristics or blood glucose parameters other than HbA1c in the 4 subjects with a >1% point increase in HbA1c.

Based on the above, the primary endpoint of the change in HbA1c from baseline to Week 26 in the insulin icodec group was smaller in the Japanese subgroup than in the entire trial population, and HbA1c tended to increase towards baseline through Week 52, which was considered attributable to the results in the 4 Japanese subjects with deteriorated glycemic control. In the 4 subjects, there was no consistent trend in subject characteristics, except for a lower basal insulin dose and a lower basal to total insulin dose ratio. Even when compared with the mean values in the Japanese subgroup, TIR using CGM was lower, and TAR using CGM was higher. Thus, the titration algorithm used in Trial 4625 may have been inadequate for glycemic control in the 4 subjects. With respect to secondary endpoints of fasting plasma glucose, TIR using CGM, etc., the relationship between the IDeg and insulin icodec groups in the Japanese subgroup showed a similar trend to that in the entire trial population. In clinical pharmacology trials in type 1 diabetes mellitus patients, the pharmacokinetic parameters of insulin icodec normalized to dose per kg body weight and the pharmacodynamic parameters based on glucose infusion rates were similar between Japanese and non-Japanese patients [see Section "6.R.2 Comparison of pharmacokinetics and pharmacodynamics between Japanese and non-Japanese populations"]. Thus, the trend in HbA1c change observed in the insulin icodec group of the Japanese subgroup in Trial 4625 does not indicate limited efficacy of insulin icodec in Japanese type 1 diabetes mellitus patients compared with non-Japanese type 1 diabetes mellitus patients, but shows difficulty of balanced dose titration suitable for the individual patient’s insulin requirements and lifestyle in type 1 diabetes mellitus

patients, and a consistent trend in the efficacy results of Trial 4625 was observed between the Japanese subgroup and the entire trial population.

PMDA's view:
A global phase III trial in patients with type 1 diabetes mellitus treated with a basal-bolus regimen (Trial 4625) demonstrated the non-inferiority of insulin icodec to IDeg in the primary endpoint of the change in HbA1c from baseline to Week 26. As to the change in HbA1c over time up to Week 52, there was a trend towards a slight reduction in efficacy in both the insulin icodec and IDeg groups, but the reduction in HbA1c with insulin icodec was maintained to Week 52. With respect to secondary endpoints of CGM endpoints and the proportion of subjects who achieved an HbA1c <7.0%, there were no major differences between the insulin icodec and IDeg groups. Although the change from baseline in fasting plasma glucose tended to be smaller in the insulin icodec group than in the IDeg group, as explained by the applicant, given the full-week pharmacodynamic profile of insulin icodec (Figure 2) and no major differences in CGM endpoints between the insulin icodec and IDeg groups, this may be explained by FPG collected at the last day of the weekly dosing interval. Thus, the efficacy of insulin icodec was demonstrated throughout the trial period, and given that once-weekly insulin icodec is expected to reduce treatment burden due to fewer injections, compared with the existing daily basal insulin products, it can be concluded that insulin icodec has clinically meaningful efficacy.

As to the efficacy of insulin icodec in the Japanese subgroup, the primary endpoint of the change in HbA1c from baseline to Week 26 in the insulin icodec group was smaller in the Japanese subgroup than in the entire trial population, and HbA1c tended to increase towards baseline through Week 52. The applicant explained that 4 subjects with a >1% point increase in HbA1c from baseline to the end of treatment in the Japanese subgroup was a contributing factor to this trend. Seven subjects in the insulin icodec group and 4 subjects in the IDeg group had a >1% point increase in HbA1c from baseline to the end of treatment in the entire trial population while 4 subjects in the insulin icodec group only had a >1% point increase in HbA1c from baseline to the end of treatment in the Japanese subgroup. Taking also account of this finding, the results in these 4 subjects may have affected the results of HbA1c in the insulin icodec group of the Japanese subgroup, but the cause for failure to achieve good glycemic control in these 4 subjects could not be identified. The applicant's explanation (With respect to secondary endpoints of fasting plasma glucose, TIR using CGM etc., and the proportion of subjects who achieved an HbA1c <7.0%, the relationship between the IDeg and insulin icodec groups in the Japanese subgroup was similar to the relationship between the IDeg and insulin icodec groups in the entire trial population) is appropriate. Thus, as the overall efficacy of insulin icodec is considered consistent between the Japanese subgroup and the entire trial population, the efficacy of insulin icodec confirmed in the entire trial population is expected also in Japanese patients.

Based on the above, the results from Trial 4625 demonstrated the efficacy of insulin icodec in type 1 diabetes mellitus patients. In the entire trial population, the proportion of subjects who achieved an HbA1c <7.0% without level 2 or 3 hypoglycemia was lower in the insulin icodec group than in the IDeg

group. This finding will be discussed in Section “7.R.2.3 Hypoglycemia.” Especially in the Japanese subgroup, there were subjects who had a >1% point increase from baseline in HbA1c, suggesting that some type 1 diabetes mellitus patients may not be able to optimize glycemic control. Thus, taking also account of the safety results such as hypoglycemia, the need for a precautionary statement regarding the use of insulin icodec in type 1 diabetes mellitus patients will be discussed in Section “7.R.4 Indication.”

7.R.2 Safety

7.R.2.1 Safety in patients with type 2 diabetes mellitus

The applicant’s explanation:

Tables 72 to 74 show the incidence and rate of adverse events in 3 global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480), respectively. In the entire trial population, there were no major differences in the incidences and rates of adverse events, adverse drug reactions, serious adverse events, and adverse events leading to treatment discontinuation between the insulin icodec and control groups (IGlar [100 units/mL] or IDeg) in all trials, except that the incidences and rates of adverse events and adverse drug reactions were higher in the insulin icodec group than in the IDeg group in Trial 4478. With regard to the trend of occurrence of adverse events and adverse drug reactions in the insulin icodec and IDeg groups in Trial 4478, adverse events occurred more frequently in the insulin icodec group, which is considered attributable to a higher incidence of nasopharyngitis in the insulin icodec group than in the IDeg group. Although adverse drug reactions occurred more frequently in the insulin icodec group, those events were reported across multiple system organ classes, and there was no trend towards a higher incidence of particular events in the insulin icodec group. The reported deaths are described in Sections "7.1 Global phase III trial in insulin-naïve patients with type 2 diabetes mellitus" to "7.3 Global phase III trial in patients with type 2 diabetes mellitus treated with basal-bolus regimen." Except for 1 case (death) in the IGlar group of Trial 4477, no adverse drug reactions were reported. Among the events of special interest, the incidence and rate of level 2 or 3 hypoglycemia were higher in the insulin icodec group than in the IDeg group in Trial 4478, whereas there were no major differences between the insulin icodec and control groups in all trials with respect to the incidences of other hypoglycemic episodes and other events of special interest. In Trial 4477, there were no clear differences in the occurrence of adverse events in the insulin icodec and IGlar groups between the main phase (52 weeks of treatment) and the main + extension phases (78 weeks of treatment). Thus, the safety profile of insulin icodec was similar to that of the existing daily basal insulin products.

As to the occurrence of adverse events in the Japanese subgroup and the entire trial population, although the incidence of hypersensitivity reactions was higher in the Japanese subgroup than in the entire trial population in Trial 4477, there were no major differences in the incidence between the insulin icodec and IGlar groups in the Japanese subgroup. Although the incidences and rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia were slightly higher in the insulin icodec group than in the control group in the Japanese subgroup relative to the entire trial population in Trial 4480, the rates in the insulin icodec group were lower in the Japanese subgroup than in the entire trial population.

Otherwise, there were no major differences in the occurrence of adverse events between the Japanese subgroup and the entire trial population in all trials. No subjects in the Japanese subgroup experienced level 3 nocturnal hypoglycemia.

Table 72. Incidence and rate of adverse events (Trial 4477: Safety analysis set)

	Japanese subgroup				Entire trial population			
	Main phase (52 weeks of treatment)		Main + extension phases (78 weeks of treatment)		Main phase (52 weeks of treatment)		Main + extension phases (78 weeks of treatment)	
	Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 492)	IGlar (N = 492)
All adverse events	76.9 (60)	74.4 (64)	89.7 (70)	82.6 (71)	71.3 (351)	68.1 (335)	80.7 (397)	79.1 (389)
	269.78 [209]	316.36 [272]	277.27 [341]	306.55 [415]	252.53 [1227]	239.57 [1162]	245.85 [1882]	237.75 [1823]
All adverse drug reactions	24.4 (19)	23.3 (20)	28.2 (22)	26.7 (23)	9.8 (48)	11.2 (55)	14.2 (70)	13.4 (66)
	40.02 [31]	48.85 [42]	34.15 [42]	36.93 [50]	15.02 [73]	18.76 [91]	14.37 [110]	14.48 [111]
Death	0 (0)	1.2 (1)	0 (0)	1.2 (1)	0.8 (4)	0.4 (2)	1.0 (5)	0.6 (3)
	0 [0]	2.33 [2]	0 [0]	1.48 [2]	1.03 [5]	0.62 [3]	0.91 [7]	0.91 [7]
Serious adverse events	5.1 (4)	8.1 (7)	9.0 (7)	9.3 (8)	10.4 (51)	10.0 (49)	13.0 (64)	14.4 (71)
	5.16 [4]	11.63 [10]	5.69 [7]	10.34 [14]	15.23 [74]	15.05 [73]	12.41 [95]	15.52 [119]
Adverse events leading to treatment discontinuation	0 (0)	1.2 (1)	1.3 (1)	2.3 (2)	1.2 (6)	0.8 (4)	1.8 (9)	1.2 (6)
	0 [0]	1.16 [1]	1.63 [2]	1.48 [2]	1.44 [7]	0.82 [4]	1.44 [11]	1.43 [11]
Level 2 or 3 hypoglycemia[a)]	3.8 (3)	5.8 (5)	6.4 (5)	8.1 (7)	9.8 (48)	10.6 (52)	12.4 (61)	14.2 (70)
	6.45 [5]	9.30 [8]	7.32 [9]	8.13 [11]	29.64 [144]	16.08 [78]	29.65 [227]	15.78 [121]
Level 3 hypoglycemia[a)]	0 (0)	0 (0)	0 (0)	1.2 (1)	0.2 (1)	0.6 (3)	0.2 (1)	1.2 (6)
	0 [0]	0 [0]	0 [0]	0.74 [1]	0.21 [1]	0.62 [3]	0.13 [1]	0.91 [7]
Level 2 or 3 nocturnal hypoglycemia[a)]	0 (0)	2.3 (2)	0 (0)	2.3 (2)	1.8 (9)	2.2 (11)	1.8 (9)	3.3 (16)
	0 [0]	4.65 [4]	0 [0]	3.69 [5]	4.12 [20]	3.09 [15]	3.40 [26]	3.13 [24]
Diabetic retinopathy or maculopathy[b)]	2.6 (2)	7.0 (6)	10.3 (8)	18.6 (16)	1.2 (6)	2.0 (10)	9.8 (48)	10.2 (50)
	2.58 [2]	6.98 [6]	7.32 [9]	17.73 [24]	1.65 [8]	2.27 [11]	7.71 [59]	9.00 [69]
Injection site reactions[c)]	0 (0)	3.5 (3)	0 (0)	3.5 (3)	1.2 (6)	2.4 (12)	1.4 (7)	2.4 (12)
	0 [0]	3.49 [3]	0 [0]	2.22 [3]	1.23 [6]	2.47 [12]	0.91 [7]	1.57 [12]
Hypersensitivity reactions[d)]	7.7 (6)	11.6 (10)	16.7 (13)	16.3 (14)	4.7 (23)	6.5 (32)	6.7 (33)	7.9 (39)
	10.33 [8]	19.77 [17]	14.64 [18]	19.94 [27]	5.97 [29]	9.28 [45]	6.27 [48]	7.96 [61]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events], MedDRA/J ver.24.1

a) Classification of hypoglycemia is shown below:
Level 2 hypoglycemia: blood glucose <54 mg/dL
Level 3 hypoglycemia (severe hypoglycemia): hypoglycemia requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Nocturnal hypoglycemia is hypoglycemic episodes occurring between 0:01 a.m. and 5:59 a.m.

b) Events in SMQ "retinal disorders (narrow)" or HLT "visual impairment and blindness (excl colour blindness)"

c) Events in HLTs "administration site reactions NEC," "application and instillation site reactions," "infusion site reactions," or "injection site reactions"

d) Events in SMQs "anaphylactic reaction (narrow)," "angioedema (narrow)," " severe cutaneous adverse reactions (narrow)," "anaphylactic/anaphylactoid shock conditions (narrow)," or "hypersensitivity (narrow)"

Table 73. Incidence and rate of adverse events (Trial 4478: Safety analysis set)

	Japanese subgroup		Entire trial population	
	Insulin icodec (N = 51)	IDeg (N = 49)	Insulin icodec (N = 262)	IDeg (N = 263)
All adverse events	70.6 (36)	59.2 (29)	61.5 (161)	51.0 (134)
	291.17 [88]	235.20 [68]	300.17 [466]	214.70 [328]
All adverse drug reactions	3.9 (2)	10.2 (5)	9.2 (24)	4.6 (12)
	6.62 [2]	34.59 [10]	22.54 [35]	13.09 [20]
Death	0 (0)	2.0 (1)	0.8 (2)	0.8 (2)
	0 [0]	3.46 [1]	1.93 [3]	1.31 [2]
Serious adverse events	7.8 (4)	4.1 (2)	8.4 (22)	6.1 (16)
	13.23 [4]	6.92 [2]	19.32 [30]	13.09 [20]
Adverse events leading to treatment discontinuation	2.0 (1)	2.0 (1)	1.9 (5)	1.1 (3)
	3.31 [1]	3.46 [1]	3.22 [5]	1.96 [3]
Level 2 or 3 hypoglycemia[a)]	5.9 (3)	0 (0)	14.1 (37)	7.2 (19)
	9.93 [3]	0 [0]	72.79 [113]	27.49 [42]
Level 3 hypoglycemia[a)]	0 (0)	0 (0)	0 (0)	0.4 (1)
	0 [0]	0 [0]	0 [0]	0.65 [1]
Level 2 or 3 nocturnal hypoglycemia[a)]	3.9 (2)	0 (0)	6.1 (16)	3.4 (9)
	6.62 [2]	0 [0]	20.61 [32]	8.51 [13]
Diabetic retinopathy or maculopathy[b)]	5.9 (3)	8.2 (4)	6.5 (17)	6.8 (18)
	9.93 [3]	13.84 [4]	13.53 [21]	13.75 [21]
Injection site reactions[c)]	0 (0)	0 (0)	1.1 (3)	0.4 (1)
	0 [0]	0 [0]	1.93 [3]	0.65 [1]
Hypersensitivity reactions[d)]	5.9 (3)	4.1 (2)	3.4 (9)	1.9 (5)
	9.93 [3]	6.92 [2]	5.80 [9]	3.27 [5]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]; MedDRA/J ver.24.1
a) to d) See notes a) to d) of Table 72.

Table 74. Incidence and rate of adverse events (Trial 4480: Safety analysis set)

	Japanese subgroup		Entire trial population	
	Insulin icodec (N = 44)	IGlar (N = 41)	Insulin icodec (N = 291)	IGlar (N = 291)
All adverse events	65.9 (29)	63.4 (26)	58.8 (171)	57.4 (167)
	354.80 [91]	402.37 [98]	271.87 [455]	329.74 [550]
All adverse drug reactions	15.9 (7)	12.2 (5)	10.3 (30)	7.6 (22)
	58.48 [15]	102.64 [25]	28.08 [47]	30.58 [51]
Death	0 (0)	0 (0)	0.7 (2)	0.3 (1)
	0 [0]	0 [0]	2.39 [4]	0.60 [1]
Serious adverse events	11.4 (5)	4.9 (2)	7.6 (22)	8.6 (25)
	19.49 [5]	8.21 [2]	20.91 [35]	19.78 [33]
Adverse events leading to treatment discontinuation	4.5 (2)	0 (0)	1.0 (3)	1.0 (3)
	7.80 [2]	0 [0]	1.79 [3]	3.60 [6]
Level 2 or 3 hypoglycemia[a)]	47.7 (21)	39.0 (16)	51.5 (150)	55.7 (162)
	374.30 [96]	225.82 [55]	564.05 [944]	562.36 [938]
Level 3 hypoglycemia[a)]	2.3 (1)	0 (0)	1.4 (4)	0.7 (2)
	3.90 [1]	0 [0]	4.18 [7]	1.80 [3]
Level 2 or 3 nocturnal hypoglycemia[a)]	20.5 (9)	7.3 (3)	18.6 (54)	24.7 (72)
	62.38 [16]	12.32 [3]	78.27 [131]	103.72 [173]
Diabetic retinopathy or maculopathy[b)]	11.4 (5)	17.1 (7)	7.9 (23)	8.9 (26)
	31.19 [8]	61.59 [15]	17.93 [30]	23.98 [40]
Injection site reactions[c)]	0 (0)	0 (0)	0.7 (2)	0.7 (2)
	0 [0]	0 [0]	1.20 [2]	1.20 [2]
Hypersensitivity reactions[d)]	6.8 (3)	2.4 (1)	2.1 (6)	2.4 (7)
	11.70 [3]	4.11 [1]	3.59 [6]	4.20 [7]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]; MedDRA/J ver.24.1
a) to d) See notes a) to d) of Table 72.

Subgroup analyses of the incidence and rate of adverse events in Trials 4477, 4478, and 4480 were performed according to the subject characteristics that differed between the Japanese subgroup and the entire trial population. Though it should be noted that the number of subjects was limited in some subgroups, there were no major differences across the subgroups in each treatment group (Table 75 to Table 77). Thus, the differences in baseline subject characteristics between the Japanese subgroup and the entire trial population are considered to have no clinically meaningful effects on the assessment of

the trial results, and based on the occurrence of adverse events in these trials, there were no clear differences in the safety profile of insulin icodec between the Japanese subgroup and the entire trial population.

Table 75. Incidence and rate of adverse events by subject characteristics (Trial 4477 [main phase]: Safety analysis set)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 78)	IGlar (N = 86)	Insulin icodec (N = 492)	IGlar (N = 492)
BMI (kg/m^2)	<25	75.0 (24/32) [225.50]	61.3 (19/31) [203.42]	74.7 (65/87) [228.93]	63.8 (51/80) [187.61]
	≥25 and <30	78.1 (25/32) [318.94]	75.8 (25/33) [381.57]	71.3 (117/164) [253.61]	68.4 (117/171) [232.77]
	≥30 and <35	77.8 (7/9) [266.61]	88.9 (16/18) [316.88]	68.5 (111/162) [269.31]	71.2 (104/146) [261.63]
	≥35	80.0 (4/5) [239.90]	100.0 (4/4) [650.45]	73.4 (58/79) [241.81]	66.3 (63/95) [260.88]
eGFR ($mL/min/1.73\ m^2$)	≥90	100.0 (2/2) [100.07]	60.0 (3/5) [120.41]	69.6 (156/224) [241.13]	65.8 (146/222) [202.55]
	≥60 and <90	81.0 (51/63) [272.04]	82.8 (48/58) [351.88]	74.0 (165/223) [263.81]	70.9 (151/213) [254.05]
	<60	53.8 (7/13) [285.05]	56.5 (13/23) [269.33]	66.7 (30/45) [253.38]	66.7 (38/57) [334.16]

Incidence % (Number of subjects with event/Number of evaluable subjects) [Rate (Number of events/100 PYE)]

Table 76. Incidence and rate of adverse events by subject characteristics (Trial 4478: Safety analysis set)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 51)	IDeg (N = 49)	Insulin icodec (N = 262)	IDeg (N = 263)
BMI (kg/m^2)	<25	63.0 (17/27) [298.11]	61.9 (13/21) [236.22]	55.6 (30/54) [254.78]	42.9 (24/56) [155.44]
	≥25 and <30	88.2 (15/17) [271.52]	56.5 (13/23) [248.97]	59.8 (55/92) [237.39]	48.1 (50/104) [174.54]
	≥30 and <35	50.0 (3/6) [251.13]	50.0 (2/4) [167.74]	58.0 (40/69) [324.44]	60.3 (38/63) [270.18]
	≥35	100.0 (1/1) [673.27]	100.0 (1/1) [168.32]	76.6 (36/47) [437.40]	55.0 (22/40) [310.58]
eGFR ($mL/min/1.73\ m^2$)	≥90	100.0 (2/2) [503.79]	100.0 (1/1) [168.32]	61.7 (58/94) [298.05]	47.7 (52/109) [205.63]
	≥60 and <90	69.2 (27/39) [303.29]	60.5 (23/38) [214.51]	59.7 (80/134) [309.83]	54.6 (59/108) [210.00]
	≥30 and <60	70.0 (7/10) [201.61]	50.0 (5/10) [319.80]	67.6 (23/34) [267.08]	50.0 (23/46) [247.14]
Basal insulin dose (units/day/kg)	≤0.3	66.7 (26/39) [303.54]	61.1 (22/36) [198.48]	56.8 (71/125) [303.41]	50.0 (54/108) [214.92]
	>0.3	83.3 (10/12) [251.32]	53.8 (7/13) [335.45]	65.7 (90/137) [297.20]	51.6 (80/155) [214.55]

Incidence % (Number of subjects with event/Number of evaluable subjects) [Rate (Number of events/100 PYE)]

Table 77. Incidence and rate of adverse events by subject characteristics (Trial 4480: Safety analysis set)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 44)	IGlar (N = 41)	Insulin icodec (N = 291)	IGlar (N = 291)
Sex	Male	57.6 (19/33) [337.34]	60.0 (18/30) [314.29]	55.2 (85/154) [278.57]	58.0 (87/150) [285.27]
	Female	90.9 (10/11) [410.95]	72.7 (8/11) [642.40]	62.8 (86/137) [264.38]	56.7 (80/141) [377.34]
BMI (kg/m^2)	<25	71.4 (10/14) [414.36]	62.5 (10/16) [379.59]	45.2 (19/42) [204.61]	53.1 (26/49) [250.27]
	≥25 and <30	63.6 (14/22) [315.62]	60.0 (9/15) [425.10]	50.5 (48/95) [208.60]	54.2 (52/96) [297.13]
	≥30 and <35	71.4 (5/7) [407.43]	70.0 (7/10) [404.52]	66.7 (62/93) [342.55]	62.6 (62/99) [349.96]
	≥35	0 (0/1) [0]	—	68.9 (42/61) [311.46]	57.4 (27/47) [437.16]
eGFR ($mL/min/1.73\ m^2$)	≥90	40.0 (2/5) [234.56]	20.0 (1/5) [100.99]	52.0 (64/123) [262.92]	44.9 (57/127) [307.26]
	≥60 and <90	70.0 (21/30) [376.01]	70.0 (21/30) [415.38]	62.0 (75/121) [282.28]	67.5 (81/120) [330.34]
	≥30 and <60	66.7 (6/9) [353.35]	66.7 (4/6) [588.21]	68.1 (32/47) [268.35]	65.9 (29/44) [396.01]
Basal insulin dose (units/week/kg)[a)]	≤2.8	61.1 (22/36) [351.20]	61.3 (19/31) [364.11]	60.3 (88/146) [261.97]	57.2 (83/145) [287.26]
	>2.8	85.7 (6/7) [359.26]	70.0 (7/10) [520.59]	60.2 (80/133) [294.16]	59.4 (82/138) [370.87]

Incidence % (Number of subjects with event/Number of evaluable subjects) [Rate (Number of events/100 PYE)], —, Not applicable
a) Doses at Week 2 were used as baseline values.

PMDA's view:

In 3 global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480), there were no major differences in the occurrence of adverse events between the insulin icodec and control groups (IGlar or IDeg). Although the incidence and rate of level 2 or 3 hypoglycemia were higher in the insulin icodec group than in the IDeg group in Trial 4478, Trial 4477 or Trial 4480 showed no similar trend relative to the control group, and there were no major differences in the incidence and rate of level 3 hypoglycemia between the insulin icodec and control groups in all trials. Thus, there should be no major differences in the safety profile including the risk of hypoglycemia between the insulin icodec and control groups. Some differences in baseline subject characteristics between the Japanese subgroup and the entire trial

population have no major impact on the safety assessment of insulin icodec, and there was no trend towards differences in the occurrence of adverse events in the insulin icodec and control groups between the Japanese subgroup and the entire trial population. Taking account of the mechanism of action of insulin icodec, clinical trial results, etc., in addition to the above analyses, adverse events of special interest such as hypoglycemia following administration of insulin icodec were assessed individually in Sections "7.R.2.3 Hypoglycemia" to "7.R.2.11 Antibody formation," and it was concluded that as with the existing daily basal insulin products, the safety of insulin icodec in type 2 diabetes mellitus patients is manageable, provided that appropriate precautionary statements are included in the package insert.

7.R.2.2 Safety in patients with type 1 diabetes mellitus

The applicant's explanation:

Table 78 shows the incidence and rate of adverse events in a global phase III trial in patients with type 1 diabetes mellitus treated with a basal-bolus regimen (Trial 4625). In the entire trial population, the incidence and rate of serious adverse events were higher in the insulin icodec group than in the IDeg group, which is considered attributable to serious hypoglycemic episodes reported as adverse events more frequently in the insulin icodec group than in the IDeg group. There were no major differences in the incidences and rates of adverse events, adverse drug reactions, and adverse events leading to treatment discontinuation between the insulin icodec and IDeg groups. There was 1 death (intracranial haemorrhage) in the insulin icodec group during the main phase, but no adverse drug reactions were reported. Among the events of special interest, the incidence and rate of hypoglycemia were higher in the insulin icodec group than in the IDeg group, whereas there were no major differences in the incidence of other events of special interest between the insulin icodec and IDeg groups. In Trial 4625, there were no clear differences in the occurrence of adverse events in the insulin icodec and IDeg groups between the main phase (26 weeks of treatment) and the main + extension phases (52 weeks of treatment). Thus, the safety profile of insulin icodec was similar to that of the existing daily basal insulin products, except for the frequency of hypoglycemia.

As to the occurrence of adverse events in the Japanese subgroup and the entire trial population, although the incidence of hypersensitivity reactions was higher in the Japanese subgroup than in the entire trial population, there were no major differences in the incidence between the insulin icodec and IDeg groups in the Japanese subgroup. Otherwise, there were no major differences in the occurrence of adverse events between the Japanese subgroup and the entire trial population. No subjects in the Japanese subgroup experienced level 3 nocturnal hypoglycemia.

Table 78. Incidence and rate of adverse events (Trial 4625: Safety analysis set)

Event term	Japanese subgroup				Entire trial population			
	Main phase (26 weeks of treatment)		Main + extension phases (52 weeks of treatment)		Main phase (26 weeks of treatment)		Main + extension phases (52 weeks of treatment)	
	Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)	Insulin icodec (N = 290)	IDeg (N = 292)
All adverse events	78.1 (25)	77.1 (37)	90.6 (29)	91.7 (44)	65.2 (189)	65.1 (190)	82.8 (240)	80.8 (236)
	442.39 [71]	843.04 [203]	361.95 [125]	703.72 [369]	356.27 [507]	429.50 [619]	321.50 [965]	370.18 [1146]
All adverse drug reactions	18.8 (6)	20.8 (10)	18.8 (6)	20.8 (10)	12.8 (37)	7.2 (21)	15.2 (44)	10.3 (30)
	49.85 [8]	145.35 [35]	26.06 [9]	114.43 [60]	32.32 [46]	34.00 [49]	20.32 [61]	27.13 [84]
Death	0 (0)	0 (0)	0 (0)	0 (0)	0.3 (1)	0 (0)	0.3 (1)	0 (0)
	0 [0]	0 [0]	0 [0]	0 [0]	0.70 [1]	0 [0]	0.33 [1]	0 [0]
Serious adverse events	3.1 (1)	4.2 (2)	3.1 (1)	4.2 (2)	3.8 (11)	2.4 (7)	8.3 (24)	6.8 (20)
	6.23 [1]	8.31 [2]	2.90 [1]	3.81 [2]	10.54 [15]	6.24 [9]	12.99 [39]	8.08 [25]
Adverse events leading to treatment discontinuation	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0.3 (1)	0.3 (1)	0.3 (1)
	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0.69 [1]	0.67 [2]	0.32 [1]
Level 2 or 3 hypoglycemia[a)]	87.5 (28)	60.4 (29)	96.9 (31)	75.0 (36)	85.2 (247)	76.4 (223)	90.7 (263)	85.6 (250)
	2068.63 [332]	951.02 [229]	1913.99 [661]	789.54 [414]	1992.86 [2836]	1037.33 [1495]	1700.10 [5103]	916.07 [2836]
Level 3 hypoglycemia[a)]	0 (0)	0 (0)	0 (0)	0 (0)	3.1 (9)	3.1 (9)	4.5 (13)	4.1 (12)
	0 [0]	0 [0]	0 [0]	0 [0]	33.03 [47]	11.80 [17]	18.66 [56]	8.08 [25]
Level 2 or 3 nocturnal hypoglycemia[a)]	43.8 (14)	33.3 (16)	59.4 (19)	43.8 (21)	46.6 (135)	33.6 (98)	59.0 (171)	47.9 (140)
	542.08 [87]	178.58 [43]	498.04 [172]	162.10 [85]	338.00 [481]	157.51 [227]	289.85 [870]	149.23 [462]
Diabetic retinopathy or maculopathy[b)]	15.6 (5)	8.3 (4)	31.2 (10)	12.5 (6)	7.6 (22)	7.2 (21)	12.8 (37)	12.0 (35)
	31.15 [5]	20.76 [5]	34.75 [12]	17.16 [9]	18.27 [26]	17.35 [25]	15.66 [47]	14.54 [45]
Injection site reactions[c)]	0 (0)	0 (0)	0 (0)	0 (0)	0.3 (1)	0.7 (2)	0.3 (1)	0.7 (2)
	0 [0]	0 [0]	0 [0]	0 [0]	1.41 [2]	1.39 [2]	0.67 [2]	0.65 [2]
Hypersensitivity reactions[d)]	25.0 (8)	25.0 (12)	28.1 (9)	39.6 (19)	8.3 (24)	8.6 (25)	12.4 (36)	14.0 (41)
	49.85 [8]	58.14 [14]	28.96 [10]	43.86 [23]	17.57 [25]	18.73 [27]	14.66 [44]	15.50 [48]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]; MedDRA/J ver.24.1

a) to d) See notes a) to d) of Table 72.

Subgroup analyses of the incidence and rate of adverse events in Trial 4625 were performed according to the subject characteristics that differed between the Japanese subgroup and the entire trial population. Though it should be noted that the number of subjects was limited in some subgroups, there were no major differences across the subgroups in each treatment group (Table 79). Thus, the differences in baseline subject characteristics between the Japanese subgroup and the entire trial population are considered to have no clinically meaningful effects on the assessment of the trial results, and based on the occurrence of adverse events in the trial, there were no clear differences in the safety profile of insulin icodec between the Japanese subgroup and the entire trial population.

Table 79. Incidence and rate of adverse events by subject characteristics (Trial 4625 [main phase]: Safety analysis set)

Item		Japanese subgroup		Entire trial population	
		Insulin icodec (N = 32)	IDeg (N = 48)	Insulin icodec (N = 290)	IDeg (N = 292)
eGFR (mL/min/1.73 m^2)	≥90	100.0 (6/6) [332.95]	88.9 (8/9) [398.45]	62.9 (124/197) [327.67]	62.1 (118/190) [347.65]
	≥60 and <90	76.0 (19/25) [486.26]	73.7 (28/38) [965.33]	70.5 (62/88) [429.07]	69.9 (65/93) [609.18]
	≥30 and <60	0 (0/1) [0]	100.0 (1/1) [199.59]	60.0 (3/5) [236.66]	77.8 (7 /9) [288.30]
Basal insulin dose (units/week/kg)[a)]	≤2.1	71.4 (15/21) [550.68]	77.5 (31/40) [682.85]	61.0 (83/136) [368.46]	64.6 (113/175) [441.33]
	>2.1	90.9 (10/11) [235.65]	75.0 (6/8) [1643.25]	70.0 (105/150) [350.11]	66.4 (77/116) [412.64]
Bolus insulin dose (units/week/kg)[a)]	≤2.2	75.0 (6/8) [398.64]	76.5 (13/17) [551.45]	67.8 (103/152) [368.68]	66.9 (95/142) [402.59]
	>2.2	79.2 (19/24) [456.98]	77.4 (24/31) [1002.80]	61.9 (83/134) [340.11]	63.9 (94/147) [460.67]

Incidence % (Number of subjects with event/Number of evaluable subjects) [Rate (Number of events/100 PYE)]

a) Doses at Week 2 were used as baseline values.

PMDA's view:

In a global phase III trial in patients with type 1 diabetes mellitus treated with a basal-bolus regimen (Trial 4625), there were no major differences in the occurrence of adverse events between the insulin

icodec and IDeg groups, except for the incidence and rate of hypoglycemia. A higher incidence and rate of hypoglycemia in the insulin icodec group than in the IDeg group can be managed appropriately, as long as adequate precautionary statements are included in the package insert, as discussed in Section "7.R.2.3 Hypoglycemia." Some differences in baseline subject characteristics between the Japanese subgroup and the entire trial population have no major impact on the safety assessment of insulin icodec, and there was no trend towards differences in the occurrence of adverse events in the insulin icodec and control groups between the Japanese subgroup and the entire trial population. Taking account of the mechanism of action of insulin icodec, clinical trial results, etc., in addition to the above analyses, adverse events of special interest etc. other than hypoglycemia following administration of insulin icodec were also assessed individually in Sections "7.R.2.4 Neoplasms" to "7.R.2.11 Antibody formation," and it was concluded that as with the existing daily basal insulin products, the safety of insulin icodec in type 1 diabetes mellitus patients is manageable, provided that appropriate precautionary statements are included in the package insert.

7.R.2.3 Hypoglycemia

The applicant's explanation:

Table 80 shows the incidence and rate of hypoglycemia[40)] in 3 global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480) and a global phase III trial in patients with type 1 diabetes mellitus treated with a basal-bolus regimen (Trial 4625).

Table 80. Incidence and rate of hypoglycemia (Safety analysis set)

	Trial 4477 (Insulin-naïve patients with type 2 diabetes mellitus)		Trial 4478 (Basal insulin-treated patients with type 2 diabetes mellitus)		Trial 4480 (Basal-bolus regimen-treated patients with type 2 diabetes mellitus)		Trial 4625 (Basal-bolus regimen-treated patients with type 1 diabetes mellitus)	
	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 290)	IDeg (N = 292)
Level 3 hypoglycemia	0.2 (1)	1.2 (6)	0 (0)	0.4 (1)	1.4 (4)	0.7 (2)	4.5 (13)	4.1 (12)
	0.13	0.91	0	0.65	4.18	1.80	18.66	8.08
Level 2 or 3 hypoglycemia	12.4 (61)	14.2 (70)	14.1 (37)	7.2 (19)	51.5 (150)	55.7 (162)	90.7 (263)	85.6 (250)
	29.65	15.78	72.79	27.49	564.05	562.36	1700.10	916.07
Level 1 hypoglycemia	56.5 (278)	48.6 (239)	55.3 (145)	44.9 (118)	83.8 (244)	86.3 (251)	99.3 (288)	99.0 (289)
	301.50	139.16	778.76	385.54	3145.28	2485.04	6798.40	4786.77
Level 3 nocturnal hypoglycemia	0 (0)	0.2 (1)	0 (0)	0 (0)	0 (0)	0.3 (1)	1.4 (4)	1.4 (4)
	0	0.13	0	0	0	1.20	3.00	1.29
Level 2 or 3 nocturnal hypoglycemia	1.8 (9)	3.3 (16)	6.1 (16)	3.4 (9)	18.6 (54)	24.7 (72)	59.0 (171)	47.9 (140)
	3.40	3.13	20.61	8.51	78.27	103.72	289.85	149.23

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE)
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
Level 1 hypoglycemia: blood glucose ≥54 mg/dL and <70 mg/dL
Level 2 hypoglycemia: blood glucose <54 mg/dL
Level 3 hypoglycemia (severe hypoglycemia): hypoglycemia requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Nocturnal hypoglycemia: hypoglycemic episodes occurring between 0:01 a.m. and 5:59 a.m.

[40)] Classification of hypoglycemia is shown below. Nocturnal hypoglycemia was defined as hypoglycemic episodes occurring between 0:01 a.m. and 5:59 a.m..
Level 1 hypoglycemia: blood glucose ≥54 mg/dL and <70 mg/dL
Level 2 hypoglycemia: blood glucose <54 mg/dL
Level 3 hypoglycemia (severe hypoglycemia): hypoglycemia requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions

In Trials 4477, 4478, and 4480 in patients with type 2 diabetes mellitus, the rate of level 2 or 3 hypoglycemia was slightly higher in the insulin icodec group than in the control group in Trials 4477 and 4478, and the rate was similar between the insulin icodec and control groups in Trial 4480. The rate of level 1 hypoglycemia was higher in the insulin icodec group than in the control group in all of the 3 trials. There were no major differences in the incidence and rate of level 3 hypoglycemia (severe hypoglycemia) between the insulin icodec and control groups in Trials 4477 and 4478, and the incidence and rate were slightly higher in the insulin icodec group than in the control group in Trial 4480. There were no major differences in the incidence and rate of level 2 or 3 nocturnal hypoglycemia between the insulin icodec and control groups in Trials 4477 and 4480, and the incidence and rate were slightly higher in the insulin icodec group than in the control group in Trial 4478. Level 3 nocturnal hypoglycemia was not reported in the insulin icodec group of any trial. No subjects experienced hypoglycemia leading to treatment discontinuation in the insulin icodec group of Trial 4477, 4478, or 4480.

In Trial 4625 in type 1 diabetes mellitus patients, the incidences and rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia were higher in the insulin icodec group than in the IDeg group. The rate of level 1 hypoglycemia was also higher in the insulin icodec group than in the IDeg group. Although the rate of level 3 hypoglycemia was slightly higher in the insulin icodec group than in the IDeg group, the incidence was similar between the treatment groups. One subject in the insulin icodec group had 33 of the 47 reported level 3 hypoglycemic episodes during the main phase, which was considered to be a cause for the higher rate in the insulin icodec group. A minority of subjects accounted for the majority of hypoglycemic episodes also in a clinical study of the currently approved insulin products in type 1 diabetes mellitus patients (*Acta Diabetol*. 2015; 52: 845-53). The subject who had 33 level 3 hypoglycemic episodes (a 2[redacted]-year-old woman, BMI of 3[redacted] kg/m^2) had lifestyle changes and lost weight during the trial period. Although 32 of the 33 episodes occurred during the first 12 weeks of treatment, all of the hypoglycemic episodes were non-serious and did not lead to hospitalization or discontinuation of insulin icodec. With regard to level 3 nocturnal hypoglycemia, there were no major differences between the IDeg and insulin icodec groups. One subject in the insulin icodec group had hypoglycemia leading to treatment discontinuation. This subject experienced 14 level 2 hypoglycemic episodes by the day of the last dose of insulin icodec (Day 71) and then initiated treatment with Insulin Detemir (genetical recombination) (IDet) on Day 84, but the subject experienced 4 level 2 hypoglycemic episodes (including 2 nocturnal episodes) by Day 106.

In Trial 4625 (main phase), the proportion of subjects with ≥20 level 2 or 3 hypoglycemic episodes was 14.8% (43 of 290 subjects) in the insulin icodec group, which was higher than 5.8% (17 of 292 subjects) in the IDeg group, but none of the subjects with ≥20 level 2 or 3 hypoglycemic episodes discontinued treatment in either treatment group. The subgroup of subjects with a higher number of hypoglycemic episodes tended to have a higher baseline HbA1c, longer duration of diabetes, lower body weight, higher blood glucose fluctuations during the early phase of treatment, etc. than the subgroup of subjects with a lower number of hypoglycemic episodes in the insulin icodec group, and these factors have been

reported as the risk factors for hypoglycemia (*Acta Diabetol.* 2015; 52: 845-53).

Figures 5 and 6 show the cumulative numbers of level 2 or 3 hypoglycemic episodes and nocturnal hypoglycemic episodes over time in each trial. In type 2 diabetes mellitus patients, the number of hypoglycemic episodes per subject in Trial 4477 and the numbers of hypoglycemic episodes and nocturnal hypoglycemic episodes per subject in Trial 4478 were similar between the insulin icodec and control groups during the first 4 to 12 weeks of treatment, but were higher in the insulin icodec group than in the control group thereafter. With regard to the number of nocturnal hypoglycemic episodes per subject in Trial 4477 and the numbers of hypoglycemic episodes and nocturnal hypoglycemic episodes per subject in Trial 4480, there were no major differences between the insulin icodec and IGlar groups. In Trial 4625 in type 1 diabetes mellitus patients, the numbers of hypoglycemic episodes and nocturnal hypoglycemic episodes per subject were similar between the insulin icodec and control groups during the first several weeks of treatment, but were higher in the insulin icodec group than in the control group thereafter. In any of the trials, the frequency of hypoglycemia did not tend to increase with prolonged treatment.

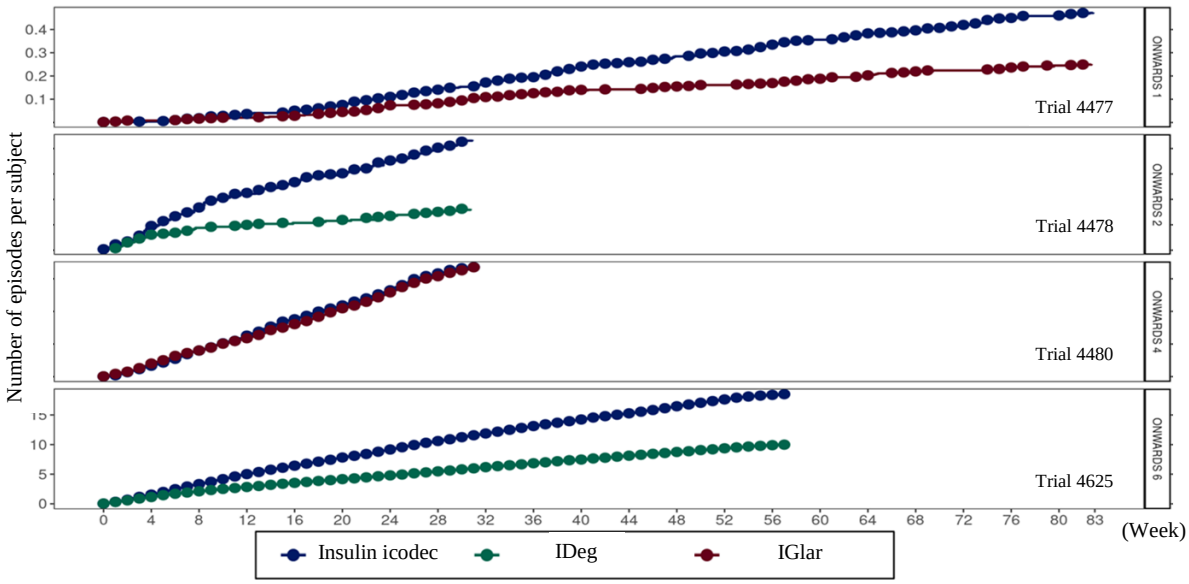


Figure 5. Cumulative number of level 2 or 3 hypoglycemic episodes over time (Safety analysis set)

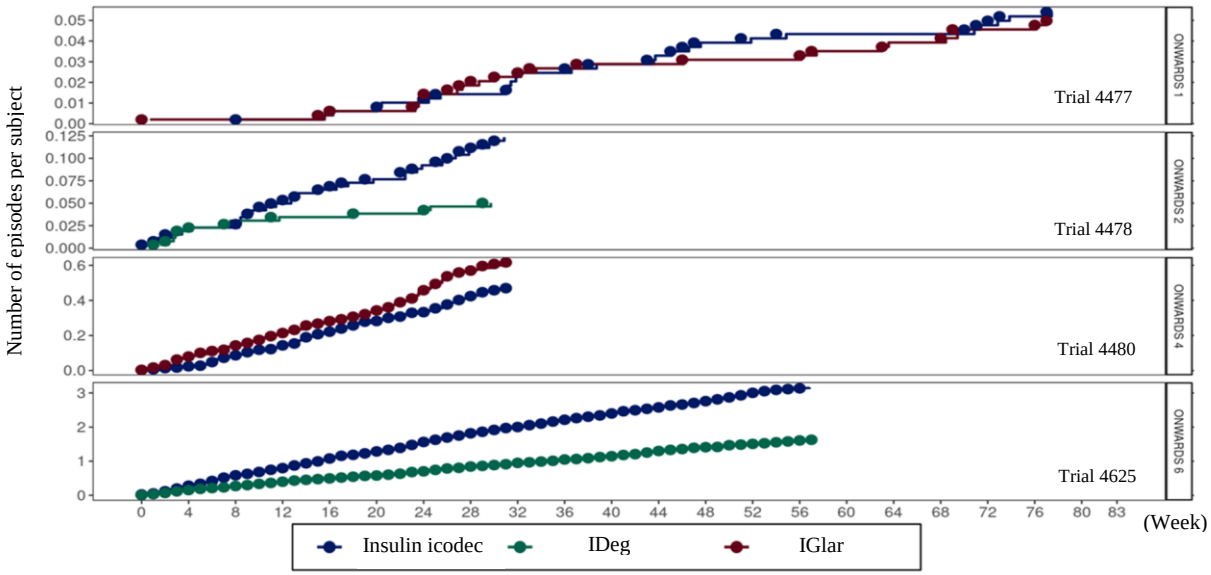


Figure 6. Cumulative number of level 2 or 3 nocturnal hypoglycemic episodes over time (Safety analysis set)

Figure 7 shows the occurrence of level 2 or 3 hypoglycemic episodes during the week. In all trials in type 2 or type 1 diabetes mellitus patients, the highest rates of level 2 or 3 hypoglycemic episodes were observed on Days 2 to 4 after the weekly administration in the insulin icodec group, and the trend in the time of onset of hypoglycemia in the insulin icodec group was as per the pharmacodynamic profile of insulin icodec (Figure 2).

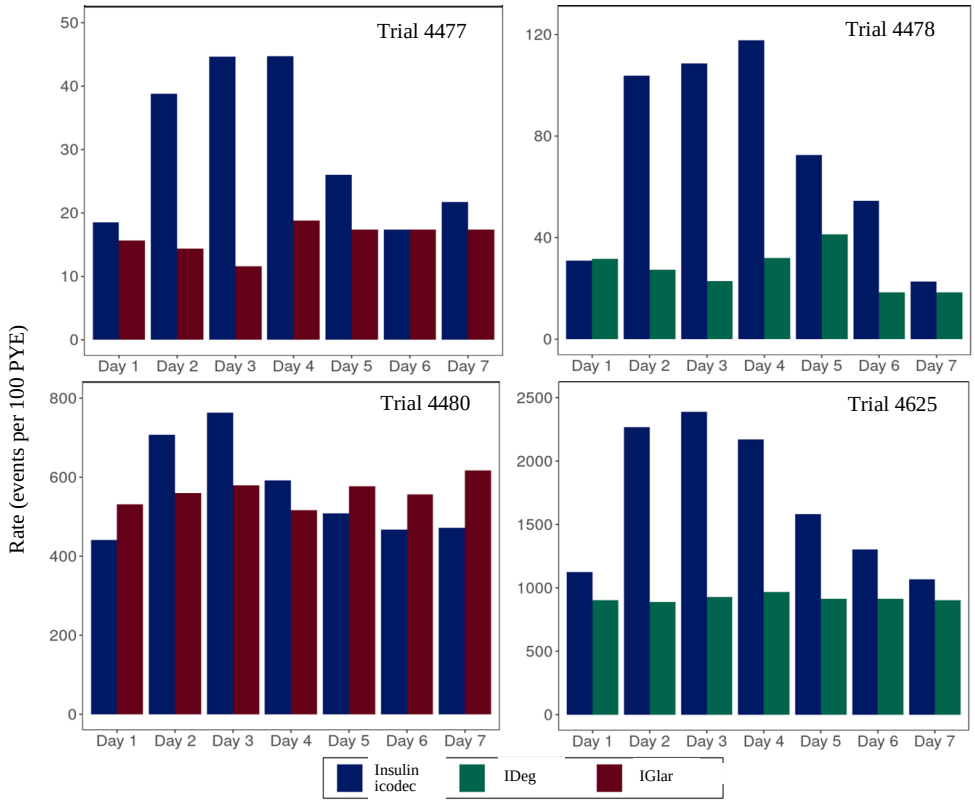


Figure 7. Occurrence of level 2 or 3 hypoglycemic episodes during the week (Safety analysis set)

Table 81 shows the percentage of time below 70 mg/dL or 54 mg/dL using CGM in each trial. There were no major differences between the insulin icodec and control groups in 3 trials in type 2 diabetes patients, and the percentage of time below 54 mg/dL was slightly higher in the insulin icodec group than in the IDeg group in Trial 4625 in type 1 diabetes patients.

Table 81. Percentage of time below 70 mg/dL or 54 mg/dL (FAS)

Blood glucose	Trial 4477 (Insulin-naïve patients with type 2 diabetes mellitus)		Trial 4478 (Basal insulin-treated patients with type 2 diabetes mellitus)		Trial 4480 (Basal-bolus regimen-treated patients with type 2 diabetes mellitus)		Trial 4625 (Basal-bolus regimen-treated patients with type 1 diabetes mellitus)	
	Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
Time below 70 mg/dL (%)	1.20 ± 1.98 (439)	0.83 ± 2.12 (440)	1.35 ± 2.23 (238)	0.79 ± 1.12 (239)	2.65 ± 2.92 (244)	2.26 ± 2.62 (237)	3.86 ± 3.56 (261)	2.90 ± 2.91 (272)
Time below 54 mg/dL (%)	0.27 ± 0.57 (439)	0.21 ± 0.63 (440)	0.34 ± 0.88 (238)	0.22 ± 0.45 (239)	0.73 ± 1.14 (244)	0.61 ± 1.07 (237)	1.02 ± 1.64 (261)	0.68 ± 1.27 (272)

Mean ± SD (Number of evaluable subjects)
Calculated based on CGM data from Week 48 to Week 52 in Trial 4477 and CGM data from Weeks 22 to Week 26 in Trials 4478, 4480, and 4625.

In order to assess the severity of the symptoms of hypoglycemia associated with insulin icodec, the duration of hypoglycemic episodes was determined retrospectively using the SMBG data collected from patient diaries. Though the results should be interpreted with care due to many missing values, the duration of level 2 or 3 hypoglycemic episodes is shown in Table 82. In all trials, there were no major differences in the median duration between the insulin icodec and control groups, and the majority of hypoglycemic episodes had a duration of <60 minutes in both the insulin icodec and control groups.

The hypoglycemic response to overdosing of insulin icodec or IGlar (100 units/mL) was investigated in type 2 diabetes mellitus patients [see Section "6.2.4.1 Trial investigating hypoglycemic response"]. The time to hypoglycemia and the severity of hypoglycemic symptoms, the time to recovery from hypoglycemia, the amount of glucose required to recover from hypoglycemia, etc., after double or triple doses of IGlar were similar to those after double or triple doses of insulin icodec, and the mean duration of level 2 hypoglycemic episodes was 25.3 minutes for insulin icodec and 37.7 minutes for IGlar. Blood concentrations of counterregulatory hormones increased with both insulin icodec and IGlar.

Table 82. Duration of level 2 or 3 hypoglycemic episodes (Safety analysis set)

Duration	Trial 4477 (Insulin-naïve patients with type 2 diabetes mellitus)		Trial 4478 (Basal insulin-treated patients with type 2 diabetes mellitus)		Trial 4480 (Basal-bolus regimen-treated patients with type 2 diabetes mellitus)		Trial 4625 (Basal-bolus regimen-treated patients with type 1 diabetes mellitus)	
	Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
Duration (minutes)	27.0 (1, 1436)	16.5 (1, 505)	30.0 (1, 1407)	22.0 (1, 63)	22.0 (1, 1418)	18.0 (1, 877)	23.0 (1, 1357)	20.0 (1, 1343)
Duration of <30 minutes	52.9 (83/157)	67.1 (47/70)	48.4 (31/64)	65.6 (21/32)	64.8 (444/685)	71.9 (420/584)	59.6 (1990/3341)	68.5 (1374/2005)
Duration of ≥30 minutes and <60 minutes	18.5 (29/157)	18.6 (13/70)	32.8 (21/64)	28.1 (9/32)	21.3 (146/685)	16.1 (94/584)	15.0 (500/3341)	16.9 (339/2005)
Duration of ≥60 minutes and <90 minutes	5.1 (8/157)	1.4 (1/70)	6.2 (4/64)	6.2 (2/32)	6.0 (41/685)	4.8 (28/584)	12.2 (408/3341)	6.9 (139/2005)

Median (Min., Max.); Proportion % (Number of events in category/Number of evaluable events)
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
The duration of level 2 or 3 hypoglycemic episodes could not be evaluated for 70 episodes in the insulin icodec group and 51 episodes in the IGlar group of Trial 4477, 49 episodes in the insulin icodec group and 10 episodes in the IDeg group of Trial 4478, 259 episodes in the insulin icodec group and 354 episodes in the IGlar group of Trial 4480, and 1762 episodes in the insulin icodec group and 831 episodes in the IDeg group of Trial 4625.

As described in the above, in the 3 trials in type 2 diabetes mellitus patients, though the rate of level 2 or 3 hypoglycemia tended to be slightly higher in the insulin icodec group than in the control group, depending on the trial, the number of level 3 hypoglycemic episodes was low. An efficacy endpoint of the proportion of subjects who achieved an HbA1c <7% without level 2 or 3 hypoglycemia in the insulin icodec group was similar to or higher than that in the control group in all trials. Given these findings etc., the hypoglycemic risk associated with insulin icodec in type 2 diabetes mellitus patients should be clinically acceptable. In type 1 diabetes mellitus patients, the rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia were higher in the insulin icodec group than in the IDeg group, and an efficacy endpoint of the proportion of subjects who achieved an HbA1c <7% without level 2 or 3 hypoglycemia was also lower in the insulin icodec group than in the IDeg group. On the other hand, with respect to the duration of hypoglycemic episodes in the phase III trials and the recovery from hypoglycemia etc. in the trial investigating the hypoglycemic response to overdosing in patients with type 2 diabetes, there were no major differences between insulin icodec and the existing daily basal insulin products. Given these findings, the nature of hypoglycemic episodes reported with insulin icodec is not different from the nature of hypoglycemic episodes known with the existing daily basal insulin products, and the risk of hypoglycemia associated with insulin icodec can be managed in the same way as patients manage the hypoglycemia risk with the existing insulin products. In clinical trials of insulin icodec, hypoglycemic episodes were managed in the same way as patients manage the hypoglycemia risk with the existing daily basal insulin products, and a very few subjects experienced hypoglycemia leading to treatment discontinuation. Thus, hypoglycemia is manageable in type 1 diabetes mellitus patients, provided that the following precautionary statements are included in the package insert: a precautionary statement about hypoglycemia included in the package inserts for the existing daily basal insulin products; a higher risk of hypoglycemia occurred on Days 2 to 4 after the weekly administration of insulin icodec; the patient's condition should be closely observed while monitoring blood glucose in type 1 diabetes mellitus patients; and switching from insulin icodec to daily basal insulin should be considered if it is difficult to optimize the glycemic control, e.g., if a patient experiences recurrent hypoglycemia. Close monitoring of blood glucose using SMBG or CGM, etc., in type 1 diabetes mellitus patients will be

recommended in the information material for healthcare professionals.

PMDA's view:
In Trials 4477, 4478, and 4480 in type 2 diabetes mellitus patients, although the rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia tended to be higher in the insulin icodec group than in the control group in some trials, there were no major differences in the rate of level 3 hypoglycemia or nocturnal hypoglycemia between the control and insulin icodec groups in all trials. In Trial 4625 in type 1 diabetes mellitus patients, though the rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia were higher in the insulin icodec group than in the control group, given the applicant's explanation, it is presumed that there were no substantial differences in the number of level 3 hypoglycemic episodes between the treatment groups. In Trial 4462 investigating the hypoglycemic response to overdosing in type 2 diabetes mellitus patients, there were no major differences in the severity of hypoglycemia or the time to recovery from hypoglycemia between insulin icodec and IGlar. In clinical trials of insulin icodec in which hypoglycemic episodes were managed in the same way as patients manage the hypoglycemic risk with daily basal insulin products, no events with a serious outcome were reported, and a very few subjects experienced hypoglycemia leading to treatment discontinuation. Thus, based on the clinical trial results, the way to manage hypoglycemia, including patient guidance, for the existing insulin products, is effective also for insulin icodec. As with the existing basal insulin products, the risk of hypoglycemia associated with insulin icodec is manageable in both type 2 and type 1 diabetes mellitus patients, provided that appropriate precautionary statements are included in the package insert. Furthermore, the following precautionary statements about hypoglycemia should be included in the package insert: a precautionary statement about hypoglycemia included in the package inserts for the existing daily basal insulin products; information on when a higher risk of hypoglycemia occurred after the weekly administration of insulin icodec; and especially when insulin icodec is used in type 1 diabetes mellitus patients, given the clinical trials in which hypoglycemia occurred frequently, the use of CGM etc. should also be considered, and then the patient's condition should be closely observed while carefully monitoring blood glucose over time, and insulin icodec should be switched to the existing daily basal insulin products if glycemic control cannot be optimized. A final conclusion on the appropriateness of the above precautionary statements about hypoglycemia in the package insert will be made, taking account of comments from the Expert Discussion.

7.R.2.4 Neoplasms

The applicant's explanation:
Table 83 shows the incidence of neoplasm-related events[41)] in 4 global phase III trials (Trials 4477, 4478, 4480, and 4625), and there were no major differences between the insulin icodec and control groups. In

[41)] Events in SMQs "biliary neoplasms," "breast neoplasms, malignant and unspecified," "liver neoplasms, benign (incl cysts and polyps)," "liver neoplasms, malignant and unspecified," "malignancies," "malignant lymphomas," "oropharyngeal neoplasms," "ovarian neoplasms, malignant and unspecified," "premalignant disorders," "prostate neoplasms, malignant and unspecified," "skin neoplasms, malignant and unspecified," or "uterine and fallopian tube neoplasms, malignant and unspecified," or SOC "neoplasms benign, malignant and unspecified (incl cysts and polyps)"

the phase III pool,[42] the incidences of neoplasm-related events[43] were 2.9% (62 subjects) in the insulin icodec group and 3.0% (66 subjects) in the control group, showing no major differences between the insulin icodec and control groups. The events reported by ≥0.2% of subjects in either treatment group were large intestine polyp (0.2% in the insulin icodec group, 0.3% in the control group), gastric polyps (0.1% in the insulin icodec group, 0.2% in the control group), renal cyst (0.3% in the insulin icodec group, 0.2% in the control group), and dermal cyst (0.0% in the insulin icodec group, 0.2% in the control group), and there was no particular trend in the organs and tissues in which the observed neoplasms developed. The events leading to death occurred in 3 subjects in the insulin icodec group (metastases to liver and pancreatic neoplasm; glioblastoma multiforme; and adenocarcinoma pancreas) and 2 subjects in the control group (pancreatic carcinoma metastatic; and breast cancer metastatic), but a causal relationship to trial product was denied for all those events.

Based on the above, there were no differences in the frequency of neoplasms between insulin icodec and the existing daily basal insulin products.

Table 83. Incidence of neoplasm-related events (Safety analysis set)

Trial 4477		Trial 4478		Trial 4480		Trial 4625	
Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 290)	IDeg (N = 292)
6.9 (34)	4.5 (22)	2.7 (7)	3.0 (8)	2.1 (6)	3.1 (9)	5.2 (15)	4.8 (14)

Incidence % (Number of subjects with event), MedDRA/J ver.24.1
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625

PMDA's view:
The submitted clinical trial data showed no trend towards an increased risk of neoplasms with insulin icodec compared with the existing daily basal insulin products.

7.R.2.5 Diabetic retinopathy or maculopathy

The applicant's explanation:
Subjects with uncontrolled and potentially unstable diabetic retinopathy or maculopathy were excluded from 4 global phase III trials (Trials 4477, 4478, 4480, and 4625). In these trials, there were no major differences in the incidence of diabetic retinopathy or maculopathy-related events[44] between the insulin icodec and control groups (Table 72 to Table 74 and Table 78). In the Japanese subgroup of Trial 4625 (main + extension phases), the incidence was higher in the insulin icodec group than in the IDeg group. However, after excluding 1 subject who experienced colour blindness and recovered within 1 day, 9 of the 10 subjects in the insulin icodec group had a long duration of diabetes or a history of diabetic retinopathy or experienced abrupt improvement in glycemic control during the trial period, and these

[42] Pooled data from 4 global phase III trials (Trials 4477, 4478, 4480, and 4625) and foreign phase III trials in insulin-naïve patients with type 2 diabetes mellitus (Trials 4479 and 4481) (Total exposure was 1681.2 PYE [n = 2170] in the insulin icodec group and 1680.6 PYE [n = 2170] in the control group). The comparators were IDeg, IGlar (100 units/mL), and daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL]). Data from the extension phases of Trials 4477 and 4625 are not included.
Trial 4479: A 26-week, double-blind, IDeg-controlled, parallel-group trial in insulin-naïve type 2 diabetes mellitus patients with HbA1c of 7.0% to 11.0% at screening
Trial 4481: A 52-week, open-label, daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL])-controlled, parallel-group trial in insulin-naïve type 2 diabetes mellitus patients with HbA1c >7.0% at screening

[43] Adjusted incidences and rates for the phase III pool were calculated using Cochran-Mantel-Haenszel weights to account for differences between trials.

[44] Events in SMQ "retinal disorders (narrow)" or HLT "visual impairment and blindness (excl colour blindness)"

factors are known to be generally associated with the risk of onset or worsening of diabetic retinopathy. Thus, compared with IDeg, insulin icodec itself should not increase the risk of onset or worsening of diabetic retinopathy. Among foreign phase III trials, Trial 4481 in insulin-naïve patients with type 2 diabetes mellitus[45)] did not have an exclusion criterion as to diabetic retinopathy or maculopathy. There were no major differences in the incidence of diabetic retinopathy or maculopathy-related events between the insulin icodec and control groups, i.e., 3.9% (21 of 542 subjects) in the insulin icodec group and 5.4% (29 of 538 subjects) in the control group, and no serious events were reported. With regard to the incidence of diabetic retinopathy or maculopathy-related events in subjects with or without diabetic retinopathy or maculopathy in Trial 4481, the incidences were 8.0% (2 of 25 subjects) in the insulin icodec group and 23.8% (10 of 42 subjects) in the control group in the subgroup with diabetic retinopathy or maculopathy and 3.7% (19 of 517 subjects) in the insulin icodec group and 3.8% (19 of 496 subjects) in the control group in the subgroup without diabetic retinopathy or maculopathy, and there was no trend towards a higher incidence in the insulin icodec group than in the control group. In the phase III pool,[42)] the incidences of diabetic retinopathy or maculopathy-related events[43)] were 5.1% (111 subjects) in the insulin icodec group and 5.3% (116 subjects) in the control group, showing no major differences between the insulin icodec and control groups. Serious events occurred in 2 subjects in the insulin icodec group (hypertensive retinopathy; and retinal vein occlusion) and 3 subjects in the control group (all diabetic retinal oedema), and the majority of the events were non-serious and mild in severity.

In phase III trials, funduscopy and fundusphotography were performed at baseline and at the end of treatment. In 4 global phase III trials (Trials 4477, 4478, 4480, and 4625) and a foreign trial (Trial 4481), the proportion of subjects whose findings from funduscopy and fundusphotography shifted from "normal" at baseline to "abnormal, clinically relevant" at the end of treatment is shown in Table 84. There were no major differences between the insulin icodec and control groups in all trials.

Table 84. Fundus status (Safety analysis set)

	"Abnormal, clinically relevant" at screening				"Normal" at screening and "abnormal, clinically relevant" at the end of treatment			
	Insulin icodec		Comparator		Insulin icodec		Comparator	
	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye	Left eye	Right eye
Trial 4477	8.5 (42/492)	6.7 (33/492)	8.3 (41/492)	7.7 (38/492)	2.6 (13/492)	2.2 (11/492)	2.2 (11/492)	2.6 (13/492)
Trial 4478	11.1 (29/262)	10.7 (28/262)	10.6 (28/263)	10.3 (27/263)	1.9 (5/262)	1.1 (3/262)	1.5 (4/263)	2.3 (6/263)
Trial 4480	7.6 (22/291)	7.6 (22/291)	7.9 (23/291)	7.9 (23/291)	0.7 (2/291)	1.0 (3/291)	0.7 (2/291)	1.4 (4/291)
Trial 4481	3.0 (16/542)	3.9 (21/542)	3.9 (21/538)	4.3 (23/538)	0.7 (4/542)	0.6 (3/542)	0.9 (5/538)	0.7 (4/538)
Trial 4625	4.5 (13/290)	4.8 (14/290)	5.1 (15/292)	5.1 (15/292)	1.7 (5/290)	1.4 (4/290)	1.7 (5/292)	2.1 (6/292)

Proportion of subjects in category % (Number of subjects in category/Number of evaluable subjects)
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
Comparators: IGlar in Trials 4477 and 4480, IDeg in Trials 4478 and 4625, daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL]) in Trial 4481

[45)] A 52-week, open-label, daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL])-controlled, parallel-group trial in insulin-naïve type 2 diabetes mellitus patients with HbA1c >7.0% at screening

Based on the above, the clinical trial data did not show the potential of insulin icodec to increase the risk of diabetic retinopathy or maculopathy, compared with the existing daily basal insulin products. As with the existing daily basal insulin products, a precautionary statement about the risk of diabetic retinopathy will be included in the package insert.

PMDA's view:

In clinical trials including Trial 4481 without an exclusion criterion as to diabetic retinopathy or maculopathy, there were no major differences in the incidence of diabetic retinopathy or maculopathy-related events between the insulin icodec and control groups, and assessment of the findings from funduscopy and fundusphotography also showed no trend towards an increased risk of retinopathy in the insulin icodec group than in the control group. The applicant's explanation (In the Japanese subgroup of Trial 4625, although the incidence of diabetic retinopathy or maculopathy-related events was higher in the insulin icodec group than in the IDeg group, as all those subjects had factors generally associated with the risk of onset or worsening of diabetic retinopathy, insulin icodec should not increase the risk of onset or worsening of diabetic retinopathy, compared with IDeg, in Japanese patients) is appropriate. Based on the above, as with the existing daily basal insulin products, the risk of diabetic retinopathy associated with insulin icodec is manageable, provided that as with the existing daily basal insulin products, a precautionary statement about the risk of diabetic retinopathy is included in the package insert.

7.R.2.6 Hyperglycemia

The applicant's explanation:

Table 85 shows the incidence of hyperglycemia or diabetic ketoacidosis-related events[46)] in 4 global phase III trials (Trials 4477, 4478, 4480, and 4625), and there were no major differences between the insulin icodec and control groups. In the phase III pool,[42)] the incidences of hyperglycemia or diabetic ketoacidosis-related events[43)] were 0.5% (10 subjects) in the insulin icodec group and 1.0% (21 subjects) in the control group, showing no major differences between the insulin icodec and control groups. The events reported by ≥0.2% of subjects in either treatment group were hyperglycemia (0.3% in the insulin icodec group, 0.6% in the control group). No diabetic ketoacidosis was reported. All of the events reported in the insulin icodec group were mild or moderate in severity. There were no serious events in the insulin icodec group, and serious events occurred in 3 subjects in the control group (hyperglycemia [2 subjects], blood glucose increased [1 subject]).

Table 85. Incidence of hyperglycemia or diabetic ketoacidosis-related events (Safety analysis set)

Trial 4477		Trial 4478		Trial 4480		Trial 4625	
Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 290)	IDeg (N = 292)
1.0 (5)	2.2 (11)	0.8 (2)	0.8 (2)	0 (0)	1.7 (5)	0.3 (1)	0.7 (2)

Incidence % (Number of subjects with event), MedDRA/J ver.24.1
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625

[46)] Events in the SMQ "hyperglycaemia/new onset diabetes mellitus (narrow)"

Regarding hyperglycemia, the percentage of TAR (time above 180 mg/dL) using CGM was lower in the insulin icodec group than in the IGlar group in Trial 4477 (Table 31), and there were no major differences between the insulin icodec and control groups (IGlar or IDeg) in Trials 4478, 4480, and 4625 (Tables 41, 48, and 56).

Based on the above, the clinical trial data raised no concerns about an increased risk of hyperglycemia and diabetic ketoacidosis with insulin icodec compared with the existing daily basal insulin products.

PMDA's view:
The submitted clinical trial data showed no trend towards an increased risk of hyperglycemia and diabetic ketoacidosis with insulin icodec compared with the existing daily basal insulin products.

7.R.2.7 Peripheral oedema

The applicant's explanation:
Table 86 shows the incidence of peripheral oedema[47)] in 4 global phase III trials (Trials 4477, 4478, 4480, and 4625), and there were no major difference between the insulin icodec and control groups. In the phase III pool,[42)] the incidences of peripheral oedema[43)] were 1.1% (24 subjects) in the insulin icodec group and 0.6% (14 subjects) in the control group, showing no major differences between the insulin icodec and control groups. Most of the events were mild in severity. No serious adverse events were reported in the insulin icodec group, and a serious adverse event occurred in 1 subject in the control group (peripheral swelling).

Table 86. Incidence of clinically relevant peripheral oedema (Safety analysis set)

Trial 4477		Trial 4478		Trial 4480		Trial 4625	
Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 290)	IDeg (N = 292)
2.2 (11)	3.5 (17)	0.8 (2)	0 (0)	0.7 (2)	1.4 (4)	1.0 (3)	1.0 (3)

Incidence % (Number of subjects with event), MedDRA/J ver.24.1
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625

Thus, the clinical trial data did not show the potential of insulin icodec to increase the risk of peripheral oedema, compared with the existing daily basal insulin products.

PMDA's view:
In the phase III pool, though the frequency of peripheral oedema tended to be slightly higher in the insulin icodec group than in the control group, most of the reported events were mild in severity, and no serious events were reported in the insulin icodec group. Given these findings, there was no trend towards an increased risk of peripheral oedema with insulin icodec compared with the existing daily basal insulin products.

7.R.2.8 Cardiovascular disorders

The applicant's explanation:

[47)] PTs peripheral oedema or peripheral swelling

Table 87 shows the incidence of cardiovascular events (acute coronary syndrome, stroke, heart failure, or CV death) confirmed by an independent event adjudication committee established by the sponsor in 4 global phase III trials (Trials 4477, 4478, 4480, and 4625). There were no major differences between the insulin icodec and control groups.

Table 87. Incidence of cardiovascular disorders confirmed by the event adjudication committee (Safety analysis set)

	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
	Insulin icodec (N = 492)	IGlar (N = 492)	Insulin icodec (N = 262)	IDeg (N = 263)	Insulin icodec (N = 291)	IGlar (N = 291)	Insulin icodec (N = 290)	IDeg (N = 292)
Acute coronary syndrome	2.2 (11)	1.4 (7)	0.8 (2)	0.4 (1)	1.4 (4)	0.3 (1)	0.3 (1)	0.7 (2)
Stroke	0.4 (2)	0.8 (4)	0.8 (2)	0.8 (2)	0 (0)	0.3 (1)	0.7 (2)	0.3 (1)
Heart failure	0.4 (2)	0.4 (2)	0 (0)	0 (0)	0 (0)	0.7 (2)	0.3 (1)	0 (0)
CV death	0.2 (1)	0.4 (2)	0 (0)	0.4 (1)	0.3 (1)	0 (0)	0 (0)	0 (0)

Incidence % (Number of subjects with event)
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
Acute coronary syndrome: acute myocardial infarction, unstable angina pectoris requiring hospitalization
Stroke: ischemic stroke, hemorrhagic stroke, undetermined stroke
Heart failure: heart failure requiring hospitalization, urgent heart failure visit

In the phase III pool (for analysis of MACE),[48] the incidences of major adverse cardiovascular events (MACE-3: CV death, acute myocardial infarction, stroke)[43] were 1.0% (22 subjects) in the insulin icodec group and 1.2% (26 subjects) in the control group, and the estimated hazard ratio from the analysis of time to first occurrence of MACE for insulin icodec vs. daily basal insulins with its 95% confidence interval[49] was 0.84 [0.48, 1.49], and there were no major differences between the insulin icodec and control groups.

With respect to ECG findings in the phase III pool,[42] the proportion of subjects with normal ECG at baseline was 64.0% (1389 subjects) in the insulin icodec group and 64.1% (1392 subjects) in the control group, and the proportion of those subjects with "abnormal, clinically relevant" at the end of treatment was comparable between the groups, i.e. 0.1% (2 subjects) in the insulin icodec group and 0.6% (13 subjects) in the control group.

Based on the above, the clinical trial data did not show the potential of insulin icodec to increase the risk of cardiovascular events, compared with the existing daily basal insulin products.

PMDA's view:
The submitted clinical trial data showed no trend towards an increased risk of cardiovascular events with insulin icodec compared with the existing daily basal insulin products.

7.R.2.9 Injection site reactions

The applicant’s explanation:
In 4 global phase III trials (Trials 4477, 4478, 4480, and 4625), there were no major differences in the

[48] Pooled data from 4 global phase III trials (Trials 4477, 4478, 4480, and 4625) and foreign phase III trials in insulin-naïve patients with type 2 diabetes mellitus (Trials 4479 and 4481) (Total exposure was 1707.1 PYE [n = 2170] in the insulin icodec group and 1702.1 PYE [n = 2170] in the control group). The comparators were IDeg, IGlar (100 units/mL), and daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL]).
[49] Calculated using a Cox proportional hazard model stratified by trial and with treatment as an explanatory variable.

incidence of injection site reaction-related events[50)] between the insulin icodec and control groups (Table 72 to Table 74 and Table 78). In the phase III pool,[42)] the incidence and rate of injection site reaction-related events[43)] were 1.9% and 6.04 events/100 patient-years of exposure (PYE), respectively, in the insulin icodec group and 1.7% and 3.97 events/100 PYE, respectively, in the control group, showing a higher rate in the insulin icodec group than in the control group. A foreign phase III trial (Trial 4479) was conducted as a double-dummy, double-blind trial, and 56.8% (84 of 148) of the observed events were reported in this trial. In Trial 4479, the incidences of injection site reaction-related events were 8.5% (25 of 293 subjects, 62 events) in the insulin icodec group and 4.4% (13 of 294 subjects, 22 events) in the control group. Twenty-four of the 62 events occurring in the insulin icodec group were reported by 2 subjects, which was considered a cause for the higher rate in the insulin icodec group than in the control group. In the phase III pool, the events reported by ≥0.5% of subjects in either treatment group were injection site reactions (0.7% and 2.23 events/100 PYE in the insulin icodec group, 0.3% and 0.46 events/100 PYE in the control group) and injection site pain (0.1% and 0.24 events/100 PYE in the insulin icodec group, 0.6% and 1.67 events/100 PYE in the control group). There were no serious or severe events, and most of the events were mild in severity with an outcome of recovered or recovering.

In the phase III pool,[42)] the incidence and rate[43)] of lipodystrophy[51)] were 0.0% and 0.05 events/100 PYE, respectively, in the insulin icodec group and 0.1% and 0.13 events/100 PYE, respectively, in the control group, showing no major differences between the insulin icodec and control groups. No serious events were reported, and all events were mild in severity. In the phase III pool, localized amyloidosis[52)] was not reported.

Based on the above, according to the clinical trial data, the limited number of subjects had injection site reactions or lipodystrophy, and insulin icodec was not shown to have the potential to increase the risk of injection site reactions, compared with the existing daily basal insulin products. As with the existing daily basal insulin products, a precautionary statement about the risk of lipodystrophy etc. will be included in the package insert.

PMDA's view:
In the phase III pool, although the rate of injection site reaction-related events tended to be slightly higher in the insulin icodec group than in the control group, there were no serious or severe events, and most of the events were mild in severity with an outcome of recovered or recovering. There were no major differences in the frequency of lipodystrophy between the insulin icodec and control groups. Thus, as with the existing daily basal insulin products, the risk of injection site reactions and lipodystrophy associated with insulin icodec is manageable, provided that as with the existing daily basal insulin products, a precautionary statement about the risk of lipodystrophy etc. is included in the package insert.

[50)] Events in HLTs "administration site reactions NEC," "application and instillation site reactions," "infusion site reactions," or "injection site reactions"
[51)] Events in HLT "lipodystrophies"
[52)] PTs cutaneous amyloidosis or amyloidosis

7.R.2.10 Hypersensitivity reactions

The applicant's explanation:

In 4 global phase III trials (Trials 4477, 4478, 4480, and 4625), there were no major differences in the incidence of hypersensitivity reaction-related events[53)] between the insulin icodec and control groups (Table 72 to Table 74 and Table 78). In the phase III pool,[42)] the incidence and rate of hypersensitivity reaction-related events[43)] were 3.8% and 6.20 events/100 PYE, respectively, in the insulin icodec group and 4.4% and 7.47 events/100 PYE, respectively, in the control group, showing no major differences between the insulin icodec and control groups. The events reported by ≥0.5% of subjects in either treatment group were rash (0.6% and 0.95 events/100 PYE in the insulin icodec group, 0.5% and 0.62 events/100 PYE in the control group), eczema (0.5% and 0.56 events/100 PYE in the insulin icodec group, 0.3% and 0.50 events/100 PYE in the control group), contact dermatitis (0.3% and 0.47 events/100 PYE in the insulin icodec group, 0.6% and 1.00 event/100 PYE in the control group), urticaria (0.3% and 0.45 events/100 PYE in the insulin icodec group, 0.6% and 0.72 events/100 PYE in the control group), and medical device site dermatitis (0.3% and 0.67 events/100 PYE in the insulin icodec group, 0.5% and 1.03 events/100 PYE in the control group). Most of the events were mild in severity, and 2 serious events occurred in 2 subjects in the insulin icodec group (anaphylactic reaction; and urticaria) and 1 serious event occurred in 1 subject in the control group (anaphylactic reaction). The event reported by 1 subject in the insulin icodec group (anaphylactic reaction) was related to the use of an analgesic, and therefore its causal relationship to trial product was denied. In the other subject in the insulin icodec group (urticaria), generalized urticaria led to treatment discontinuation with an outcome of recovered and was classified as an adverse drug reaction. The event reported by 1 subject in the control group (anaphylactic reaction) led to treatment discontinuation with an outcome of recovered and was classified as an adverse drug reaction.

Systemic hypersensitivity reactions were to be reported as adverse events and were to be reported by the investigator using a dedicated form. In the phase III pool,[42)] the incidence and rate of systemic hypersensitivity reactions[43)] were 0.6% and 0.89 events/100 PYE, respectively, in the insulin icodec group and 0.4% and 0.52 events/100 PYE, respectively, in the control group, showing no major differences between the insulin icodec and control groups. The events classified as serious systemic hypersensitivity reactions were the same as serious hypersensitivity reaction-related events reported by 2 subjects in the insulin icodec group and 1 subject in the control group. Except for the event reported by 1 subject in the insulin icodec group (urticaria, non-serious and severe in severity) and the event reported by 1 subject in the control group (allergic rhinitis, non-serious and mild in severity), all events had an outcome of recovered or resolved. There were no events with a fatal outcome. After excluding 5 subjects with systemic hypersensitivity reactions for which a causal relationship to trial product was denied, 7 of the 12 subjects with systemic hypersensitivity reactions in the insulin icodec group underwent antibody test.[54)] After excluding 2 subjects from whom blood samples were taken too

[53)] Events in SMQs "anaphylactic reaction," "angioedema," "severe cutaneous adverse reactions," "anaphylactic/anaphylactoid shock conditions," or "hypersensitivity"

[54)] Anti-insulin icodec IgE antibodies, anti-human insulin IgE antibodies, total IgE antibodies, and anti-insulin icodec antibodies were measured.

late, 2 of the 5 subjects were considered to develop systemic reactions related to insulin icodec. Antibody testing was not planned in the control group.

According to the clinical trial data, systemic hypersensitivity reactions were reported in the insulin icodec group, but there were no major differences in the incidence of hypersensitivity reaction-related events or investigator-reported systemic hypersensitivity reactions between the insulin icodec and control groups. Thus, insulin icodec was not shown to have the potential to increase the risk of hypersensitivity reactions compared with the existing daily basal insulin products. As with the existing daily basal insulin products, a precautionary statement about the risk of hypersensitivity reactions including anaphylactic shock will be included in the package insert.

PMDA's view:
Systemic hypersensitivity reactions including urticaria that were considered related to insulin icodec were reported, and this is a risk that requires attention following administration of insulin icodec. However, most events had an outcome of recovered or resolved, and there were no major differences in the incidence of hypersensitivity reactions or systemic hypersensitivity reactions between the insulin icodec and control groups in clinical trials. Given the above findings, as with the existing daily basal insulin products, the risk of hypersensitivity reactions associated with insulin icodec is manageable, provided that as with the existing daily basal insulin products, a precautionary statement about the risk of hypersensitivity reactions including anaphylactic shock is included in the package insert.

7.R.2.11 Antibody formation

The applicant's explanation:
Antibody testing was performed in 4 (Trials 4478, 4479, 4480, and 4625) of 6 phase III trials. Table 88 shows the formation of anti-insulin icodec antibodies after treatment initiation in the insulin icodec group of Trials 4478, 4480, and 4625 in which Japanese patients participated.

Table 88. Formation of anti-insulin icodec antibodies after treatment initiation (Safety analysis set)

	Trial 4478 (N = 262)	Trial 4480 (N = 288)	Trial 4625 (N = 288)
Positive for anti-insulin icodec antibodies	70.2 (184)	71.2 (205)	75.3 (217)
Positive for cross-reacting antibodies towards human insulin	67.9 (178)	66.7 (192)	72.2 (208)
Negative for anti-insulin icodec antibodies at baseline and then positive	54.2 (142)	41.0 (118)	28.1 (81)
Positive for anti-insulin icodec antibodies at baseline and a titer increase by ≥4-fold during the trial	11.1 (29)	19.1 (55)	27.8 (80)

Proportion % (Number of subjects in category)
Main phase (26 weeks of treatment) for Trial 4625

Table 89 shows the incidences and rates of injection site reaction-related events[50)] and hypersensitivity reaction-related events[53)] by antibody status in Trials 4478, 4480, and 4625. There were no major differences in the incidences across the subgroups.

Table 89. Incidences and rates of injection site reactions and hypersensitivity reactions by anti-insulin icodec antibody status

	Trial 4478		Trial 4480		Trial 4625	
	Negative (N = 79)	Positive (N = 183)	Negative (N = 85)	Positive (N = 202)	Negative (N = 72)	Positive (N = 216)
Injection site reactions	0 (0)	1.6 (3)	1.2 (1)	0.5 (1)	1.4 (1)	0 (0)
	0 [0]	2.75 [3]	2.04 [1]	0.85 [1]	5.55 [2]	0 [0]
Hypersensitivity reactions	5.1 (4)	2.7 (5)	1.2 (1)	2.5 (5)	13.9 (10)	6.5 (14)
	8.66 [4]	4.58 [5]	2.04 [1]	4.24 [5]	30.53 [11]	13.18 [14]

Upper row, Incidence % (Number of subjects with event); Lower row, Rate (Number of events/100 PYE) [Number of events]; MedDRA/J ver.24.1
Main phase (26 weeks of treatment) for Trial 4625

In Trials 4478, 4480, and 4625, subjects were divided into 5 subgroups: the anti-insulin icodec antibody-negative subgroup and the 4 antibody-positive subgroups of quartiles according to antibody titer. Tables 90 and 91 show the incidence and rate of level 2 or 3 hypoglycemia and the change in HbA1c from baseline to Week 26 by subgroup, respectively. There were no major differences in the incidence and rate of hypoglycemia or the change in HbA1c across the subgroups.

Table 90. Incidence and rate of level 2 or 3 hypoglycemia by anti-insulin icodec antibody status

		Trial 4478 (N = 262)	Trial 4480 (N = 288)	Trial 4625 (N = 288)
Negative		20.5 (16/78)	55.4 (46/83)	92.9 (52/56)
		47.27 [22]	533.87 [260]	1707.13 [1029]
Positive	1st quartile	5.3 (3/57)	52.5 (32/61)	94.9 (74/78)
		64.88 [22]	567.99 [203]	1645.49 [1396]
	2nd quartile	16.0 (8/50)	54.5 (24/44)	85.2 (52/61)
		103.74 [31]	635.62 [166]	1456.33 [935]
	3rd quartile	8.1 (3/37)	55.1 (27/49)	94.9 (37/39)
		17.97 [4]	482.13 [140]	2000.49 [837]
	4th quartile	17.5 (7/40)	41.2 (21/51)	88.9 (48/54)
		141.63 [34]	601.28 [181]	1634.75 [913]

Upper row: Incidence % (Number of subjects with event/Number of evaluable subjects)
Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (52 weeks of treatment) for Trial 4625

Table 91. Change in HbA1c from baseline to Week 26 by anti-insulin icodec antibody status

		Trial 4478 (N = 262)	Trial 4480 (N = 288)	Trial 4625 (N = 288)
Negative		−0.94 ± 0.96 (76)	−1.11 ± 0.70 (80)	−0.49 ± 0.74 (69)
Positive	1st quartile	−0.95 ± 0.74 (56)	−1.19 ± 0.73 (56)	−0.38 ± 0.86 (80)
	2nd quartile	−1.08 ± 0.92 (48)	−1.28 ± 0.88 (43)	−0.52 ± 0.57 (47)
	3rd quartile	−0.89 ± 0.95 (36)	−1.13 ± 0.78 (46)	−0.59 ± 0.79 (36)
	4th quartile	−0.90 ± 0.90 (40)	−1.42 ± 1.08 (50)	−0.52 ± 0.86 (42)

Mean ± SD (Number of evaluable subjects)
Main phase (26 weeks of treatment) for Trial 4625

Based on the above, according to the clinical trial data, the proportion of subjects who were positive for anti-insulin icodec antibodies after treatment initiation was high, but anti-insulin icodec antibodies had no clinically relevant effects on the safety and efficacy of insulin icodec.

PMDA's view:

In clinical trials from which the results on antibody formation were submitted, antibodies were detected after treatment initiation. However, when analyzed by antibody status etc., antibody formation had no major effects on the safety and efficacy of insulin icodec. Thus, at present, the trial results have raised no concerns about clinically relevant effects of anti-insulin icodec antibodies on the safety and efficacy of insulin icodec.

7.R.3 Clinical positioning

The applicant's explanation:

The key goal in the treatment of diabetes is to achieve normoglycemia or near-normoglycemia to prevent the development of diabetic complications (*Diabetes Care*. 2018; 41: S1-S159). Approximately one third of insulin-treated diabetes patients report poor adherence and do not reach clinically meaningful targets of HbA1c (*Diabet Med*. 2012; 29: 682-9). As the degree of adherence to insulin treatment is a predictor of reductions in HbA1c (*QJM*. 2007; 100: 345-50), improved adherence should lead to better glycemic control. Though insulin therapy is recommended upon progression of type 2 diabetes mellitus, a high number of injections may be a barrier to insulin therapy initiation especially in type 2 diabetes mellitus patients (*Prim Care Diabetes*. 2017; 11: 3-12, *Adv Ther*. 2018; 35: 1735-45). Patients are reluctant to initiate and intensify insulin therapy, which is associated with a failure to achieve glycemic targets for the prevention of complications (*N Engl J Med*. 2013; 368: 1613-24, *Diabetes Metab*. 2012; 38 Suppl 3: S27-8). Furthermore, ≥4 injections per day are generally required for patients on a basal-bolus regimen, which is a burden to patients and physicians (*Diabet Med*. 2012; 29: 682-9).

Insulin icodec is a once-weekly basal insulin, and fewer injections compared with daily basal insulins, are expected to reduce treatment burden and improve patient adherence, leading to better clinical outcomes (*Int J Clin Pract*. 2021; 75: e13731, *Diabetes Obes Metab*. 2011; 13: 144-9). Clinical trials of insulin icodec showed that the duration of action is 1 week after dosing, and the results from global phase III trials etc. demonstrated the efficacy of insulin icodec in both type 2 and type 1 diabetes mellitus patients. The safety profile of insulin icodec was largely similar to that of the existing daily basal insulin products. Though the incidence and rate of hypoglycemia were higher with insulin icodec than with IDeg in type 1 diabetes mellitus patients, as the nature of hypoglycemic episodes reported with insulin icodec is not different from the nature of hypoglycemic episodes known with the existing daily basal insulin products, as with the existing basal insulin products, the risk of hypoglycemia associated with insulin icodec is manageable, provided that appropriate precautionary statements are included in the package insert. Based on the above, insulin icodec can become a new treatment option for patients who require basal insulin therapy.

PMDA's view:

Clinical trials demonstrated the efficacy of insulin icodec [see Section "7.R.1 Efficacy"]. Except for the incidence and rate of hypoglycemia in type 1 diabetes mellitus patients, the safety profile of insulin icodec was similar to that of the existing daily basal insulin products. Insulin icodec has acceptable safety, given its expected efficacy, provided that appropriate precautionary statements about hypoglycemia etc. are included in the package insert [see Section "7.R.2 Safety"]. Given that frequent injections is a barrier to the initiation of insulin therapy, and that new insulin therapies with fewer injections are required to reduce treatment burden, once-weekly insulin icodec can become a new treatment option for diabetes patients who require insulin therapy.

7.R.4 Indication

The applicant's explanation:

Three global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480) and a global phase III trial in type 1 diabetes mellitus patients treated with a basal-bolus regimen (Trial 4625) demonstrated the efficacy of insulin icodec based on the primary endpoint of the change from baseline in HbA1c and other blood glucose parameters [see Section "7.R.1 Efficacy"], and the safety profile of insulin icodec was largely similar to that of the existing daily basal insulin products [see Section "7.R.2 Safety"]. Although the results from Trial 4625 indicated that the risk of hypoglycemia is higher with insulin icodec than with IDeg in type 1 diabetes mellitus patients, a higher rate of hypoglycemia in the insulin icodec group than in the IDeg group was mainly attributable to some subjects with ≥20 hypoglycemic episodes, and the nature of hypoglycemic episodes reported with insulin icodec and the characteristics of subjects with a high number of hypoglycemic episodes were similar to those with the existing daily basal insulin products. Thus, as with the existing daily basal insulin products, the risk of hypoglycemia associated with insulin icodec is manageable, provided that appropriate precautionary statements about hypoglycemia are included in the package insert [see Section "7.R.2.3 Hypoglycemia"].

In clinical practice, insulin-treated diabetes patients have reported poor adherence. Treatment with once-weekly insulin icodec with fewer injections compared with daily basal insulins is expected to reduce treatment burden and improve patient adherence, leading to better clinical outcomes [see Section "7.R.3 Clinical positioning"]. In Trial 4625 in type 1 diabetes mellitus patients, there were subjects who had a >1% point increase in HbA1c from baseline especially in the Japanese subgroup. Given the pathogenesis of type 1 diabetes mellitus, regardless of either insulin icodec or the existing daily basal insulin products, basal and bolus insulin titration suitable for the individual patient's insulin requirements and lifestyle may be difficult in some type 1 diabetes mellitus patients. Insulin icodec may not be a basal insulin useful for all type 1 diabetes mellitus patients. Although the results from Trial 4625 could not identify the insulin icodec-specific factors characterizing patients for whom dose titration was difficult, individual doses of insulin icodec can be optimized in clinical practice by individualizing the frequency of dose adjustments and the glycemic target, according to not only the titration algorithm specified in clinical trials, but also the individual patient's blood glucose profile and lifestyle.

Based on the above, the benefit-risk balance of insulin icodec is favorable in type 2 diabetes mellitus patients and a certain number of type 1 diabetes mellitus patients. The indication should be "diabetes mellitus where treatment with insulin is required," and then the package insert should advise that switching from insulin icodec to the existing daily basal insulin products should be considered in type 1 diabetes mellitus patients if it is difficult to optimize the glycemic control, e.g., if a patient experiences recurrent hypoglycemia.

PMDA's view:

The applicant's explanation (Based on the results from global phase III trials [Trials 4477, 4478, and

4480], the benefit-risk balance of insulin icodec is favorable in type 2 diabetes mellitus patients) is appropriate. Trial 4625 in type 1 diabetes mellitus patients demonstrated the efficacy of insulin icodec in the primary endpoint [see Section "7.R.1 Efficacy"]. Regarding safety, although there were no major differences in the occurrence of adverse events between the insulin icodec and IDeg groups, the incidence and rate of hypoglycemia were higher in the insulin icodec group than in the IDeg group [see Section "7.R.2 Safety"]. The results from Trial 4625 suggested the presence of type 1 diabetes mellitus patients who cannot achieve good glycemic control with insulin icodec compared with IDeg. Although the proportion of subjects with ≥20 level 2 or 3 hypoglycemic episodes was higher in the insulin icodec group than in the IDeg group, which was considered a reason for the higher rate of hypoglycemia in the insulin icodec group than in the IDeg group, predictive factors for patients who are difficult to achieve good glycemic control with insulin icodec or patients who experience a high number of hypoglycemic episodes with insulin icodec could not be identified. Thus, the benefit-risk balance of insulin icodec in type 1 diabetes mellitus patients may be slightly different from that in type 2 diabetes mellitus patients, but a new treatment option with fewer injections is required to reduce treatment burden also for type 1 diabetes mellitus patients. Given the above points, the indication of “diabetes mellitus where treatment with insulin is required” as that for the currently approved basal insulin products is acceptable, provided that precautionary statements about hypoglycemia (e.g., especially when insulin icodec is used in type 1 diabetes mellitus patients who are susceptible to hypoglycemia, close blood glucose monitoring should be performed, and switching to the existing daily insulin products should be considered if it is difficult to optimize the glycemic control) are included in the package insert, and that information materials etc. are used to ensure proper use of insulin icodec. However, the package insert should advise that a decision to use insulin icodec in type 1 diabetes mellitus patients should be made on an individual patient basis, with a full understanding of the glycemic control to be achieved with insulin icodec and the risk of hypoglycemia, after also considering the use of daily basal insulin etc. A final conclusion on the appropriateness of the statements in the INDICATION and PRECAUTIONS CONCERNING INDICATION sections will be made, taking account of comments from the Expert Discussion.

7.R.5 Dosage and administration

7.R.5.1 Dosing regimen

The applicant’s explanation:

As to the regimen, clinical pharmacology trials with glucose clamps in type 1 and type 2 diabetes mellitus patients demonstrated that insulin icodec has a pharmacokinetic profile suitable for once weekly administration and that the glucose-lowering effect of insulin icodec covers the full weekly dosing interval [see Section "6.R.1 Pharmacokinetic and pharmacodynamic characteristics of insulin icodec"]. As to dose selection, insulin icodec is a human insulin analog, and based on the results of the aforementioned clinical pharmacology trials etc., 1 unit of insulin icodec corresponds to 6 nmol, as with insulin human (genetical recombination). In phase I trials in type 1 or type 2 diabetes mellitus patients, the molar dose-normalized area under the glucose infusion rate-time curve during 1 week (AUC_{GIR}) was similar between IDeg or IGlar and insulin icodec, according to a population pharmacokinetic/pharmacodynamic analysis[23)] (the ratio of insulin icodec to IDeg or IGlar with its 95%

CI was 103% [74%, 144%] in Trial 4314, 119% [100%, 143%] in Trial 4225, and 101% [82%, 124%] in Trial 4422).

Thus, in phase III trials, insulin icodec was to be administered once weekly. When switching from the existing daily basal insulin products to insulin icodec, the dose of insulin icodec was 7 times the daily basal insulin dose. In insulin-naïve patients, the dose of insulin icodec was 70 units based on the starting doses of the existing daily basal insulin products of 10 units. Since the pen-injectors of the drug products and the to-be-marketed drug product used in phase III trials deliver doses in steps of 10 units, the dose of insulin icodec calculated by multiplying the daily basal insulin dose by 7 was rounded to the nearest 10 units.

All of 3 global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480) and a global phase III trial in basal-bolus regimen-treated patients with type 1 diabetes mellitus (Trial 4625) demonstrated the non-inferiority of insulin icodec to IGlar (100 units/mL) or IDeg in the primary endpoint of the change from baseline in HbA1c (Tables 30, 40, 47, and 55). With respect to the dose at the end of trial, there were no major differences between the insulin icodec and IGlar groups in Trial 4477 (Table 32), and the dose was higher in the insulin icodec group than in the IDeg group in Trial 4478 (Table 41). The total insulin dose was lower in the insulin icodec group than in the IGlar group in Trial 4480 (Table 48), and there were no major differences in the total insulin dose between the insulin icodec and IDeg groups in Trial 4625 (Table 57). The insulin doses per kg body weight in these trials are shown in Table 92. The basal insulin doses in Trials 4477 and 4478 and the total insulin doses in Trials 4480 and 4625 were similar between the insulin icodec and control groups or were slightly lower in the insulin icodec group than in the control group. In Trial 4480 in basal-bolus regimen-treated patients with type 2 diabetes mellitus and Trial 4625 in basal-bolus regimen-treated patients with type 1 diabetes mellitus, the basal insulin dose was higher in the insulin icodec group than in the control group, and the bolus insulin dose was lower in the insulin icodec group than in the control group. This trend was possibly attributable to the action profile of insulin icodec suitable for once weekly administration, the use of the titration algorithm based on the SMBG values measured on 2 days prior to and on the day of titration, bolus insulin dose adjustments only permitted during the first 8 weeks of treatment for safety reasons, etc. Although the basal to total insulin dose ratio with insulin icodec may be different from that with the existing daily basal insulin products, the individual patient’s insulin requirements should remain unchanged.

Table 92. Insulin dose per kg body weight during the last 2 weeks of treatment

		Japanese subgroup		Entire trial population	
		Insulin icodec	Comparator	Insulin icodec	Comparator
Trial 4477 (Insulin-naïve patients with type 2 diabetes mellitus)	Basal insulin	1.84 (81.49) (75)	1.96 (65.60) (83)	2.63 (75.49) (459)	2.75 (70.97) (466)
Trial 4478 (Basal insulin-treated patients with type 2 diabetes mellitus)	Basal insulin	2.21 (56.35) (50)	2.71 (60.70) (48)	3.10 (69.15) (249)	3.21 (63.48) (252)
Trial 4480 (Basal-bolus regimen-treated patients with type 2 diabetes mellitus)	Total	4.77 (53.78) (42)	5.28 (47.56) (41)	5.97 (58.52) (273)	6.85 (50.05) (266)
	Basal insulin	2.34 (67.79) (42)	2.38 (62.76) (41)	3.79 (58.08) (261)	3.41 (60.76) (264)
	Bolus insulin	2.24 (65.20) (42)	2.69 (54.47) (41)	2.26 (81.75) (271)	3.15 (66.79) (266)
Trial 4625 (Basal-bolus regimen-treated patients with Type 1 diabetes mellitus)	Total	4.14 (40.75) (31)	4.00 (40.91) (48)	3.87 (52.06) (258)	4.10 (40.68) (272)
	Basal insulin	2.01 (52.33) (31)	1.54 (56.06) (48)	2.29 (48.11) (250)	1.95 (50.22) (272)
	Bolus insulin	1.95 (53.28) (31)	2.31 (50.94) (48)	1.61 (68.83) (249)	1.99 (56.37) (271)

Unit: units/week/kg, Geometric mean (coefficient of variation %) (Number of evaluable subjects)
Comparators: IGlar in Trials 4477 and 4480, IDeg in Trials 4478 and 4625

Table 93 shows the proportion of subjects with a total insulin dose during the last 2 weeks of treatment of ≤560 units/week (80 units/day), and there were no major differences between the insulin icodec and control groups in the entire trial population and the Japanese subgroup. In all trials, the insulin dose was lower, and the proportion of subjects with a total insulin dose of ≤560 units/week was also higher in the Japanese subgroup than in the entire trial population.

Table 93. Proportion of subjects with total insulin dose during the last 2 weeks of treatment of ≤560 units/week (%)

	Japanese subgroup		Entire trial population	
	Insulin icodec	Comparator	Insulin icodec	Comparator
Trial 4477	98.7 (74/75)	100.0 (83/83)	89.8 (412/459)	90.3 (421/466)
Trial 4478	96.0 (48/50)	93.8 (45/48)	86.7 (221/255)	87.7 (221/252)
Trial 4480	71.4 (30/42)	75.6 (31/41)	51.6 (141/273)	48.1 (128/266)
Trial 4625	96.8 (30/31)	95.8 (46/48)	88.8 (229/258)	89.7 (245/273)

Proportion % (Number of subjects in category/Number of evaluable subjects)
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
Comparators: IGlar in Trials 4477 and 4480, IDeg in Trials 4478 and 4625

Based on the above, the appropriate dosage and administration statement is as follows: Insulin icodec should be administered once weekly. The once-weekly starting dose of insulin icodec is 30 to 140 units so that the dose of insulin icodec is 7 times the existing daily basal insulin dose. Typically, the weekly total insulin maintenance dose is 30 to 560 units. However, a higher dose than stated above may be used as needed.

Given the precautionary statements included in the package inserts for the existing daily basal insulin products, the following precautionary statements will be included in the package insert: Note the action profile of insulin icodec and the patient's condition, and administer insulin icodec if the patient's condition is suitable for the pharmaceutical properties of insulin icodec; and the doses and timing of concurrent bolus insulin products or other concomitant antidiabetic treatment may need to be adjusted, etc.

The starting dose of insulin icodec in patients not on basal insulin or when switching from another basal insulin will be described in Sections “7.R.5.2 Starting dose in diabetes patients not on basal insulin” and “7.R.5.3 Starting dose when switching from another basal insulin.”

Regarding the switch from insulin icodec to post-trial basal insulin, given an extended duration of action even after the last injection of insulin icodec due to its longer half-life compared with the existing daily basal insulin products, the new basal insulin was to be initiated 2 weeks after the last injection of insulin icodec, and if pre-breakfast SMBG exceeded 180 mg/dL, initiation of the daily basal insulin dose earlier than 2 weeks after the last dose of insulin icodec was to be considered in Trials 4477, 4478, and 4480 in type 2 diabetes mellitus patients. In Trial 4625 in type 1 diabetes mellitus patients, when pre-breakfast SMBG exceeded 180 mg/dL, the new basal insulin was to be initiated. In all trials, the new daily basal insulin dose was calculated by dividing the latest insulin icodec dose by 7, and then the basal insulin was to be titrated once or twice weekly according to the pre-breakfast SMBG values and the local label.

The following precautionary statements will be included in the package insert: When switching from insulin icodec to another basal insulin, the timing of initiation of the basal insulin should be considered, taking account of the action profile of insulin icodec and referring to the pre-breakfast self-measured blood glucose values; and close glucose monitoring is recommended during the switch and in the following weeks.

PMDA’s view:
Given the clinical trial data, a once-weekly regimen of insulin icodec is appropriate. As to dose selection, insulin icodec is a human insulin analog, and 1 unit of insulin icodec corresponds to 6 nmol, as with insulin human (genetical recombination). Although there was variation in the results of glucose clamp trials, the molar dose-normalized weekly pharmacodynamic effect was largely similar between IGlar (100 units/mL) or IDeg and insulin icodec. Phase III trials in which the starting dose of insulin icodec was 7 times the existing daily basal insulin dose demonstrated the non-inferiority of insulin icodec to IGlar (100 units/mL) or IDeg [see Section "7.R.1 Efficacy"]. With respect to the insulin dose at the end of treatment, there were no major differences in the range of insulin dose or the insulin dose per kg body weight between insulin icodec and daily basal insulin in Trial 4477 in insulin-naïve patients with type 2 diabetes mellitus and Trial 4478 in basal-insulin-treated patients with type 2 diabetes mellitus. In Trial 4480 in basal-bolus regimen-treated patients with type 2 diabetes mellitus and Trial 4625 in basal-bolus regimen-treated patients with type 1 diabetes mellitus, the basal insulin dose tended to be higher, and the bolus insulin dose tended to be lower in the insulin icodec group than in the control group, but there were no major differences in the range of the total insulin dose between the insulin icodec and control groups. As explained by the applicant, the action profile of insulin icodec suitable for once weekly administration may have affected the dose adjustments of insulin icodec and bolus insulin. Thus, based on the recommended doses of the existing daily basal insulin products (the once-daily starting dose is 4-20 units, and typically, the total insulin maintenance dose is 4-80 units/day), the once-weekly starting dose of insulin icodec should be 30 to 140 units; the total insulin maintenance dose should be stated;

and typically, the weekly total insulin maintenance dose should be 30 to 560 units. The package insert should also mention that a higher dose than stated above may be used as needed. Although the precautionary statements in the package insert proposed by the applicant are appropriate, regarding the switch from insulin icodec to another basal insulin, the recommended dose of the basal insulin should also be stated in the package insert.

A final conclusion on the appropriateness of the statements in the DOSAGE AND ADMINISTRATION and PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION sections will be made, taking account of comments from the Expert Discussion.

7.R.5.2 Starting dose in diabetes patients not on basal insulin

The applicant's explanation:
In Trial 4477 in insulin-naïve patients with type 2 diabetes mellitus, the starting dose was 70 units for insulin icodec or 10 units for IGlar (100 units/mL), and then the doses of insulin icodec and IGlar were to be adjusted once weekly or every other week according to the titration algorithms.

As to the actual starting doses of insulin icodec in Trial 4477, the starting doses were <70 units in 8 of 78 Japanese subjects (40 units in 1 subject, 50 units in 5 subjects, 60 units in 2 subjects) and 70 units in other subjects. The investigator could change the doses including the starting dose to avoid safety hazards. Among the 8 subjects who received a starting dose of <70 units, 7 subjects were enrolled at the same trial site, but there was no particular trend in patient characteristics including sex, age, body weight, BMI, and blood glucose levels. The percentages of TIR (time spent in 70-180 mg/dL) based on CGM data from Week 0 to Week 4 (mean ± SD) were 50.12 ± 26.83% (n = 470) in the insulin icodec group and 52.51 ± 26.13% (n = 463) in the IGlar group, showing no major differences between the treatment groups, and fasting plasma glucose also decreased similarly in the both groups. The rates of level 2 or 3 hypoglycemia during the first month of treatment were 4.87 events/100 PYE in the insulin icodec group and 9.77 events/100 PYE in the IGlar group, showing no major differences between the treatment groups. Thus, there were no safety or efficacy problems with a starting dose of insulin icodec of 70 units, i.e. 7 times the IGlar dose of 10 units, in insulin-naïve patients with type 2 diabetes mellitus. As the potency of 1 unit of insulin icodec should be equivalent to that of other basal insulins, starting doses of insulin icodec higher than 70 units were not evaluated in Trial 4477. However, given the starting dose ranges of the existing daily basal insulin products, insulin icodec may need to be initiated at >70 units in clinical practice, and therefore the DOSAGE AND ADMINISTRATION section should be drafted so that a starting dose of insulin icodec can be selected according to the patient's condition, within the weekly dose range of 30 to 140 units, which corresponds to the daily starting dose range of 4 to 20 units of the existing daily basal insulin products. As with the existing daily basal insulin products, the package insert will advise that when switching from non-insulin anti-diabetic treatment to insulin icodec or when combining with non-insulin anti-diabetic treatment, insulin icodec should be administered with caution, e.g., insulin icodec should be initiated at a low dose, taking account of the action profile of insulin icodec.

PMDA's view:

In Trial 4477, the starting dose of insulin icodec was 70 units, and there were no safety or efficacy problems during early phase of treatment in the insulin icodec group compared with the IGlar group. The applicant explained that as with the existing daily basal insulin products, insulin icodec may need to be initiated at >70 units within the starting dose range in clinical practice. In clinical practice, as with the existing daily basal insulin products, the starting dose is determined according to the individual patient's condition. However, given that the starting dose of insulin icodec was 70 units in Trial 4477, and that there were Japanese subjects who received a starting dose of <70 units, the package insert should advise that the recommended starting dose of insulin icodec is ≤70 units in patients not on basal insulin. A final conclusion on the above point will be made, taking account of comments from the Expert Discussion.

7.R.5.3 Starting dose when switching from another basal insulin

The applicant's explanation:

In Trial 4478 in basal insulin-treated patients with type 2 diabetes mellitus and Trial 4480 in basal-bolus regimen-treated patients with type 2 diabetes mellitus, the starting dose of insulin icodec was 7 times the daily basal insulin dose before randomization, increased by a one-time additional 50% dose, and the second once-weekly dose of insulin icodec was 7 times the daily basal insulin dose before randomization. Then, the dose of insulin icodec was to be adjusted once weekly according to the titration algorithm. In Trial 4625 in basal-bolus regimen-treated patients with type 1 diabetes mellitus, in addition to the dosing rules in Trials 4478 and 4480, for the first injection only, the insulin icodec dose was the daily basal insulin dose before randomization multiplied by 7, increased by a 100% one-time additional dose for subjects with screening HbA_{1c} ≥8% (excluding subjects previously treated with IGlar [300 units/mL] or twice-daily basal insulin).

When switching from the existing daily basal insulin products to insulin icodec, it is important to ensure good glycemic control without the risk of transient hyperglycemia. Subjects received a higher single starting dose of insulin icodec to avoid blood glucose elevation during transition from daily basal insulin to insulin icodec with a long half-life. In a foreign phase II trial in basal insulin-treated patients with type 2 diabetes mellitus (Trial 4466[55)]), the results with 2 different switch approaches (once-weekly insulin icodec with no loading dose [NLD] [the insulin icodec starting dose was 7 times the daily basal insulin dose before randomization] and once-weekly insulin icodec with an initial 100% loading dose [LD] [the insulin icodec starting dose was 7 times the daily basal insulin dose before randomization,

[55)] A 16-week, randomized, open-label, IGlar (100 units/mL)-controlled, parallel-group trial in basal insulin-treated patients with type 2 diabetes mellitus. Key inclusion criteria: Type 2 diabetes mellitus patients aged 18-75 years who (1)(2) had been treated with stable doses of metformin, with or without concomitant use of DPP-4 inhibitor and/or SGLT2 inhibitor, along with 10-50 units/day of basal insulin (IDeg, IDet or IGlar [100 units/mL or 300 units/mL]) once daily or twice daily, for ≥90 days prior to screening, and (3) had HbA1c of 7.0% to 10.0% at screening and (4) BMI of ≤40.0 kg/m^2. Once weekly insulin icodec or once daily IGlar (100 units/mL) was to be administered subcutaneously. Based on the daily basal insulin dose before randomization (For those who had been receiving twice-daily basal insulin or once-daily IGlar [300 units/mL], the daily basal insulin dose before randomization decreased by 20%), the insulin icodec dose was the daily dose multiplied by 7, and the IGlar dose was the daily dose. In the insulin icodec group in which the first weekly dose was doubled, the insulin icodec starting dose was 7 times the daily basal insulin dose before randomization, increased by a 100% one-time additional dose. Titration was based on pre-breakfast SMBG values. If the upper limit of the pre-breakfast SMBG target (80-130 mg/dL) was exceeded, doses were uptitrated by 28 units (insulin icodec) or 4 units (IGlar). If pre-breakfast SMBG was <80 mg/dL, doses were downtitrated by 28 units (insulin icodec) or 4 units (IGlar).

increased by a 100% one-time additional dose]) are shown in Table 94 and Figure 8. Adding a loading dose of insulin icodec to the first dose prevented elevation of blood glucose levels during the immediate post-switch period. Although the incidence and rate of level 2 or 3 hypoglycemia were higher in the insulin icodec LD group than in the insulin icodec NLD group, there were no major differences between the insulin icodec LD group and the IGlar group. There were no major differences in the incidence and rate of level 2 or 3 nocturnal hypoglycemia between the insulin icodec NLD group and the insulin icodec LD group, and the incidence and rate were lower in either insulin icodec group than in the IGlar group. Based on these results etc., adding a one-time additional dose of insulin icodec to the first dose when switching from another basal insulin was considered useful. Thus, based on the results of a population pharmacokinetic/pharmacodynamic analysis using the data from clinical trials that were obtained before the conduct of phase III trials, the sizes of one-time additional doses in Trials 4477, 4480, and 4625 were determined.

Table 94. Blood glucose parameters and incidence and rate of hypoglycemia at Week 16 (Trial 4466)

		Insulin icodec (NLD) (N = 50)	Insulin icodec (LD) (N = 54)	IGlar (N = 50)
Time spent in range 70-180 mg/dL (%)[a)]		64.78 ± 17.69 (45)	73.98 ± 15.28 (53)	65.45 ± 18.76 (48)
Change from baseline in HbA1c (%)		−0.53 ± 0.60 (48)	−0.73 ± 0.92 (52)	−0.59 ± 0.78 (49)
Change from baseline in fasting plasma glucose (mg/dL)	Week 8	3.72 ± 43.63 (48)	−8.73 ± 40.57 (51)	−14.87 ± 44.56 (48)
	Week 16	−15.00 ± 46.01 (46)	−10.96 ± 33.21 (50)	−11.81 ± 42.22 (47)
Insulin dose (units/week)[b)]		224.0 (70.0, 714.0) (49)	196.0 (70.0, 616.0) (53)	204.6 (21.0, 518.0) (49)
Level 2 or 3 hypoglycemia		4.0 (2)	7.4 (4)	12.0 (6)
		19.34 [3]	101.91 [17]	102.98 [16]
Level 2 or 3 nocturnal hypoglycemia		4.0 (2)	3.7 (2)	8.0 (4)
		12.89 [2]	11.99 [2]	70.80 [11]

Mean ± SD (Number of evaluable subjects), Median (Min., Max.) for insulin dose
For hypoglycemia, Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
a) Calculated based on CGM data from Week 15 to Week 16.
b) Mean insulin dose from Week 15 to Week 16

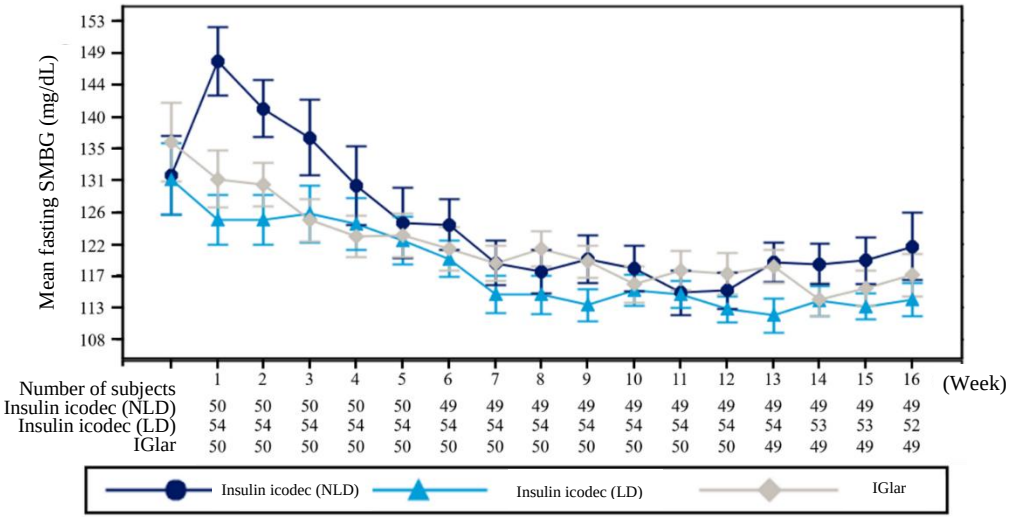


Figure 8. Mean fasting SMBG levels over time (Trial 4466: FAS, Mean ± SE)

Table 95 shows the actual insulin doses at Weeks 1 and 2 in Trials 4478, 4480, and 4625. In most subjects in the insulin icodec group, the actual dose corresponded to the planned dose, and there were no major differences between the insulin dose at Week 2 in the insulin icodec group and the doses at Weeks 1 and 2 in the control group in each trial. Table 96 shows the results of CGM endpoints during

the early phase of treatment in each trial. Figure 9 shows fasting SMBG levels over time and the number of hypoglycemic episodes per subject. In Trials 4478 and 4480 in type 2 diabetes mellitus patients, there were no major differences in CGM endpoints, fasting SMBG levels, or the number of level 2 or 3 hypoglycemic episodes per subject between the insulin icodec and control groups. In Trial 4625 in type 1 diabetes mellitus patients, fasting SMBG levels decreased in both the insulin icodec and IDeg groups, and there were no major differences in CGM endpoints from Week 0 to Week 4 between the insulin icodec and IDeg groups. The number of level 2 or 3 hypoglycemic episodes per subject was similar between the insulin icodec and IDeg groups through Week 2, but was higher in the insulin icodec group thereafter.

Table 95. Insulin doses at Weeks 1 and 2

			Japanese subgroup		Entire trial population	
			Insulin icodec	Comparator	Insulin icodec	Comparator
Trial 4478 (Basal insulin-treated patients with type 2 diabetes mellitus)	Basal insulin	Week 1	130.0 (8.3, 530.0) (50)	105.0 (28.0, 448.0) (49)	250.0 (8.3, 950.0) (253)	182.0 (28.0, 945.0) (263)
		Week 2	80.0 (8.6, 350.0) (51)	123.0 (19.8, 462.0) (49)	180.0 (8.6, 880.0) (258)	189.0 (19.8, 1102.5) (260)
Trial 4480 (Basal-bolus regimen-treated patients with type 2 diabetes mellitus)	Total	Week 1	293.5 (106.0, 1470.0) (44)	272.0 (38.3, 744.0) (41)	504.5 (84.0, 1960.0) (290)	448.0 (38.3, 1750.0) (291)
		Week 2	270.0 (100.0, 1380.0) (43)	275.0 (63.0, 706.0) (41)	422.5 (70.0, 1970.0) (286)	450.0 (63.0, 1832.9) (284)
	Basal insulin	Week 1	130.0 (25.0, 630.0) (43)	84.0 (12.3, 392.0) (41)	320.0 (25.0, 1260.0) (282)	210.0 (12.3, 840.0) (290)
		Week 2	100.0 (15.0, 420.0) (43)	97.0 (35.0, 407.0) (41)	220.0 (15.0, 1050.0) (278)	224.0 (29.0, 819.0) (283)
	Bolus insulin	Week 1	160.0 (66.0, 840.0) (44)	140.0 (26.0, 452.0) (41)	190.2 (4.2, 848.0) (290)	210.0 (26.0, 1180.0) (289)
		Week 2	168.0 (70.0, 960.0) (43)	140.0 (28.0, 464.0) (41)	196.0 (28.0, 960.0) (286)	204.0 (28.0, 1467.7) (283)
Trial 4625 (Basal-bolus regimen-treated patients with type 1 diabetes mellitus)	Total	Week 1	394.5 (145.0, 930.0) (32)	253.0 (101.0, 548.0) (48)	410.0 (9.0, 1574.0) (289)	307.0 (92.0, 1055.0) (291)
		Week 2	322.0 (119.0, 848.0) (32)	260.0 (95.0, 625.0) (48)	325.0 (39.7, 1226.0) (289)	312.0 (95.0, 1019.0) (291)
	Basal insulin	Week 1	190.0 (30.0, 600.0) (32)	84.0 (16.0, 294.0) (48)	250.0 (30.0, 980.0) (282)	142.0 (16.0, 644.0) (291)
		Week 2	110.0 (20.0, 300.0) (32)	89.5 (14.0, 270.0) (48)	170.0 (20.0, 550.0) (285)	143.0 (14.0, 644.0) (291)
	Bolus insulin	Week 1	178.0 (59.0, 540.0) (32)	162.0 (44.0, 364.0) (48)	161.0 (3.5, 918.0) (286)	163.0 (12.0, 586.0) (289)
		Week 2	190.5 (72.0, 588.0) (32)	165.0 (46.0, 415.0) (48)	159.0 (18.0, 930.0) (286)	164.0 (42.0, 567.0) (288)

Median (Min., Max.) (Number of evaluable subjects)
Comparators: IDeg in Trials 4478 and 4625, IGlar in Trial 4480

Table 96. Results of CGM endpoints from Week 0 to Week 4

		Japanese subgroup		Entire trial population	
		Insulin icodec	Comparator	Insulin icodec	Comparator
Trial 4478	TIR	43.50 ± 16.99 (50)	49.00 ± 22.00 (46)	51.17 ± 21.42 (252)	53.42 ± 20.16 (244)
	TBR	0.28 ± 1.28 (50)	0.17 ± 0.37 (46)	0.76 ± 1.77 (252)	0.69 ± 1.91 (244)
	TAR	56.21 ± 17.28 (50)	50.83 ± 22.08 (46)	48.08 ± 21.89 (252)	45.89 ± 20.76 (244)
Trial 4480	TIR	58.67 ± 16.85 (41)	52.15 ± 23.34 (40)	56.58 ± 20.96 (268)	56.14 ± 20.11 (262)
	TBR	0.97 ± 1.79 (41)	0.54 ± 1.05 (40)	1.87 ± 3.18 (268)	1.68 ± 2.62 (262)
	TAR	40.36 ± 17.26 (41)	47.31 ± 23.58 (40)	41.55 ± 21.90 (268)	42.18 ± 20.82 (262)
Trial 4625	TIR	54.18 ± 12.09 (32)	56.75 ± 15.81 (48)	60.73 ± 14.78 (284)	63.20 ± 14.66 (284)
	TBR	3.04 ± 2.46 (32)	2.37 ± 3.63 (48)	3.56 ± 3.15 (284)	3.19 ± 3.16 (284)
	TAR	42.77 ± 13.20 (32)	40.88 ± 17.24 (48)	35.70 ± 15.31 (284)	33.62 ± 15.34 (284)

Mean ± SD (Number of evaluable subjects)
Comparators: IDeg in Trials 4478 and 4625, IGlar in Trial 4480
TIR: Time in range 70-180 mg/dL (%), TBR: Time below range <70 mg/dL (%), TAR: Time above range >180 mg/dL (%)

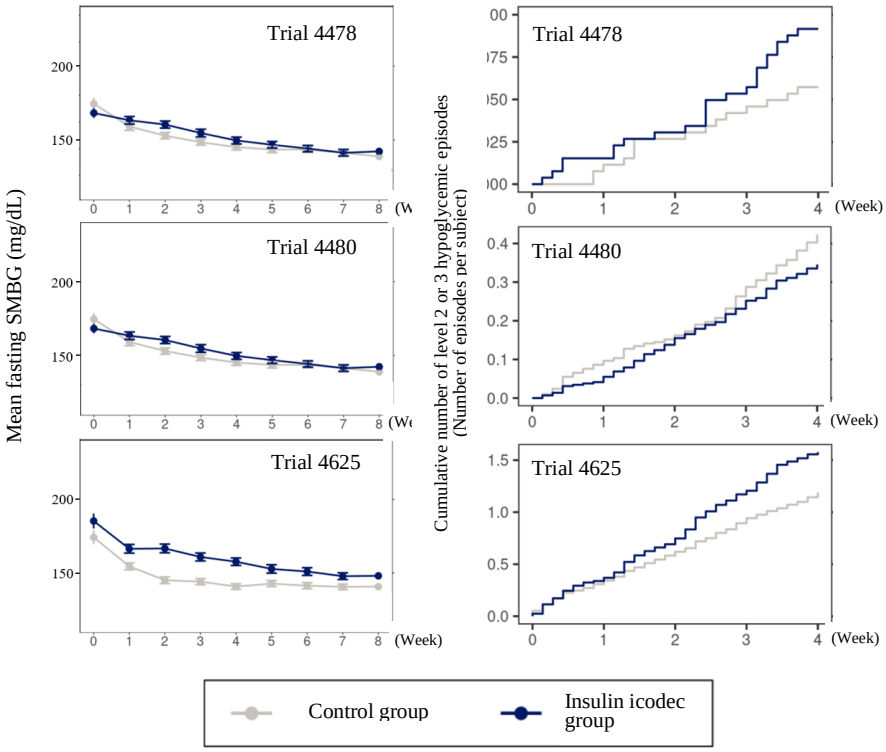


Figure 9. Mean fasting SMBG levels and number of hypoglycemic episodes per subject over time
(Left figure: Mean ± SE of fasting SMBG levels, Right figure: Cumulative number of level 2 or 3 hypoglycemic episodes)

Based on the above, there were no safety or efficacy problems with initiating insulin icodec with a one-time additional dose of 50% with the first dose (the existing daily basal insulin dose multiplied by 7) when switching from another basal insulin to insulin icodec in type 2 diabetes mellitus patients. In Trials 4478 and 4480, all subjects were to receive a one-time additional 50% dose with the first dose. Using the data obtained from these trials, the effect of the use of a one-time additional dose on the mean pre-breakfast SMBG levels etc. was evaluated by modelling.[56)] Based on the mean pre-breakfast SMBG levels from Week 2 to Week 3, transient hyperglycemia was not observed even without a one-time additional dose. Thus, there should be no clinically relevant problem with glycemic control even without a one-time additional dose in type 2 diabetes mellitus patients, whereas adding a one-time additional 50% dose to the first dose should be useful if seeking faster optimization of glycemic control. The package insert will advise that adding a one-time additional 50% dose to the first dose is recommended, but the need for a one-time additional dose should be determined, taking account of the patient's glycemic control and the risk of hypoglycemia.

In Trial 4625 in type 1 diabetes mellitus patients, a one-time additional 50% dose or a one-time additional 100% dose was to be added to the first dose. The appropriateness of the size of a one-time additional dose was assessed as follows:

Figure 10 shows the mean fasting SMBG levels over time in the subgroup of subjects with screening HbA1c ≥8% (excluding subjects previously treated with IGlar [300 units/mL] or twice-daily basal

[56)] A population pharmacokinetic/pharmacodynamic model developed based on the data from 5 phase III trials in type 2 diabetes mellitus patients (Trials 4477, 4478, 4479, 4480, and 4625)

insulin) (the subgroup with a one-time additional 100% dose) and the subgroup of the other subjects (the subgroup with a one-time additional 50% dose). The one-time additional 100% dose led to a very steep decease in the mean fasting SMBG from Week 0 to Week 1, but no further decrease during the next 5 weeks. The one-time additional 50% dose led to a steadier decrease of the mean fasting SMBG during the initial 6 weeks. The change in HbA1c over time from baseline to Week 26 was similar between the insulin icodec and control groups in each subgroup. The rate of level 2 or 3 hypoglycemia in the insulin icodec group was similar between the subgroups, i.e., 2091.70 events/100 PYE in the subgroup with a one-time additional 100% dose and 2086.34 events/100 PYE in the subgroup with a one-time additional 50% dose.

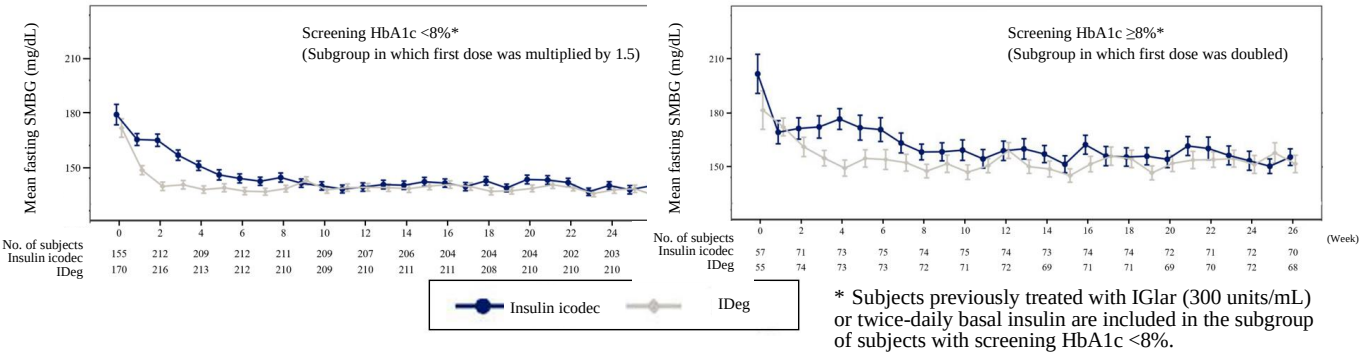


Figure 10. Mean fasting SMBG levels over time (Trial 4625: FAS, Mean ± SE)

On the other hand, as to CGM endpoints at Weeks 1 and 2, the percentage of time spent below range <54 mg/dL was higher in the insulin icodec group than in the IDeg group on a few days in the subgroup in which the first dose of insulin icodec was doubled. Taking also account of the mean fasting SMBG levels over time, the one-time additional 100% dose may have been higher than needed to prevent transient elevation of blood glucose levels.

Based on the above, when switching from another basal insulin to insulin icodec in type 1 diabetes mellitus patients, there were no safety or efficacy problems with initiating insulin icodec with a one-time additional 50% or 100% dose with the first dose (the existing daily basal insulin dose multiplied by 7). On the other hand, given the results on blood glucose levels, a one-time additional 100% dose in subjects with HbA1c ≥8% may have been higher than needed to prevent transient elevation of blood glucose levels, and 2 different one-time additional doses for type 1 diabetes mellitus patients unnecessarily complicate the dosing recommendation. Thus, a single 50% one-time additional dose in alignment with the dosing recommendation for type 2 diabetes mellitus patients on a basal-bolus regimen is proposed. A one-time additional 50% dose should be added to the first dose in type 1 diabetes mellitus patients, as a rule, also in clinical practice, as in Trial 4625. Meanwhile, in patients with good glycemic control, recurrent hypoglycemia, or high blood glucose fluctuations, a higher single starting dose may increase the risk of hypoglycemia. Thus, the package insert will advise that the need for a one-time additional 50% dose should be determined carefully, taking account of the balance between the patient's glycemic control and the risk of hypoglycemia.

The median times to reach the fasting SMBG target (80-130 mg/dL) were 5 weeks in the insulin icodec group and 3 weeks in the IDeg group in Trial 4478, 8 weeks in the insulin icodec group and 4 weeks in the IGlar group in Trial 4480, and 6 weeks in the insulin icodec group and 3 weeks in the IDeg group in Trial 4625. The median time to reach the target was longer in the insulin icodec group than in the control group. This trend was possibly due to the following: In all trials, the insulin icodec dose was not titrated at Week 2, while doses were titrated in the control group; and insulin icodec needs 3 to 4 weeks to reach a steady state. The package insert will advise that close glucose monitoring is recommended during the switch and in the following weeks.

PMDA's view:
Given the results of Trial 4466 in basal insulin-treated patients with type 2 diabetes mellitus, adding a supplemental dose of insulin icodec to the first dose is useful to prevent transient elevation of blood glucose levels when switching from daily basal insulin to insulin icodec. In Trials 4478, 4480, and 4625, subjects were to receive a one-time additional 50% dose (a one-time additional 100% dose in some subjects in Trial 4625) with the first dose (the existing daily basal insulin dose multiplied by 7), and there were no major problems with glycemic control or the occurrence of hypoglycemia during the early phase of treatment with insulin icodec. Thus, a one-time additional 50% dose of insulin icodec should be added to the first dose (calculated based on the daily basal insulin dose) when switching to insulin icodec in type 2 diabetes mellitus patients on daily basal insulin. When switching to insulin icodec in basal-bolus regimen-treated patients with type 1 diabetes mellitus, 2 different one-time additional doses of insulin icodec were used in the clinical trial. Given fasting blood glucose levels over time etc., the one-time additional 100% dose may be higher than needed to prevent transient elevation of blood glucose levels. Given the risk of hypoglycemia associated with insulin icodec in type 1 diabetes mellitus patients, a single 50% one-time additional dose in alignment with the dosing recommendation for type 2 diabetes mellitus patients on a basal-bolus regimen is appropriate.

As to whether adding a one-time additional dose of insulin icodec to the first dose is mandatory when switching to insulin icodec in daily basal insulin-treated patients, all subjects received a one-time additional dose with the first dose in Trials 4478, 4480, and 4625. Although the applicant explained that based on a population pharmacokinetic/pharmacodynamic model developed based on the data from phase III trials, transient hyperglycemia was not observed even without a one-time additional dose in type 2 diabetes patients, it is difficult to predict with due precision fasting SMBG levels over time etc. without a one-time additional dose from this model developed based only on the data from subjects who received a one-time additional dose with the first dose. On the other hand, given that the incidence and rate of level 2 or 3 hypoglycemia were higher in the insulin icodec LD group in which the first dose was doubled than in the insulin icodec NLD group in Trial 4466, a one-time additional dose may be associated with the risk of hypoglycemia. In addition, given the degree of fasting SMBG elevation during the early phase of treatment in the insulin icodec NLD group in Trial 4466, a one-time additional dose with the first dose based on the dosing rules in clinical trials is recommended for type 2 diabetes

mellitus patients, and the need for a one-time additional dose should be determined on an individual patient basis, taking account of the patient's glycemic control and the occurrence of hypoglycemia. In type 1 diabetes mellitus patients, given fasting SMBG levels over time etc. during the early phase of treatment in Trial 4625, a one-time additional dose should be added to the first dose, as a rule. However, since the number of hypoglycemic episodes is higher with insulin icodec than with IDeg in type 1 diabetes patients, and a one-time additional dose may be associated with the risk of hypoglycemia, when insulin icodec is administered after careful consideration of the appropriateness of its use, as explained by the applicant, the need for a one-time additional dose should be determined carefully, taking account of the patient's glycemic control and the risk of hypoglycemia. Although recommending close glucose monitoring during the switch from another basal insulin and in the following weeks is appropriate, the following information should also be provided: Insulin icodec may need time to achieve the optimal glycemic control compared with the existing daily basal insulin products.

A final conclusion on the above will be made, taking account of comments from the Expert Discussion.

7.R.6 Special populations

7.R.6.1 Patients with renal impairment

The applicant's explanation:

In a clinical pharmacology trial in subjects with renal impairment, there were no major differences in insulin icodec exposure following subcutaneous administration of 1.5 units/kg of insulin icodec according to the degree of renal impairment [see Section "6.2.3.1 Pharmacokinetic trial in subjects with renal impairment"]. Tables 97 and 98 show the incidence and rate of adverse events by the degree of renal impairment (eGFR[57)] [mL/min/1.73 m^2] at baseline, normal ≥90; mild ≥60 and <90; moderate ≥30 and <60; and severe <30) in global phase III trials (Trials 4477, 4478, 4480, and 4625) and in the phase III pool,[42)] respectively. Though evaluation has limitations due to fewer subjects in the subgroup with moderate renal impairment compared with other subgroups, there were no major differences in the incidence and rate of adverse events or serious adverse events between the insulin icodec group and the control group in each subgroup. Patients with eGFR <30 mL/min/1.73 m^2 were excluded from the phase III trials, except for Trial 4481.

[57)] Calculated using the CKD-EPI equation.

Table 97. Incidence and rate of adverse events by degree of renal impairment in each global phase III trial (Safety analysis set)

	Renal function	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	Normal	224	222	94	109	123	127	197	190
	Mild	223	213	134	108	121	120	88	93
	Moderate	45	57 [a)]	34	46	47	44	5	9
All adverse events	Normal	78.1 (175)	77.9 (173)	61.7 (58)	47.7 (52)	52.0 (64)	44.9 (57)	81.7 (161)	77.9 (148)
		229.58 [801]	201.71 [704]	298.05 [165]	205.63 [129]	262.92 [186]	307.26 [223]	303.20 [623]	299.25 [598]
	Mild	83.0 (185)	80.8 (172)	59.7 (80)	54.6 (59)	62.0 (75)	67.5 (81)	85.2 (75)	86.0 (80)
		258.44 [902]	254.28 [845]	309.83 [248]	210.00 [133]	282.28 [197]	330.34 [232]	368.75 [329]	518.62 [518]
	Moderate	82.2 (37)	77.2 (44)	67.6 (23)	50.0 (23)	68.1 (32)	65.9 (29)	80.0 (4)	88.9 (8)
		264.87 [179]	320.70 [274]	267.08 [53]	247.14 [66]	268.35 [72]	396.01 [95]	237.89 [13]	303.95 [30]
Serious adverse events	Normal	9.8 (22)	11.7 (26)	6.4 (6)	3.7 (4)	4.9 (6)	7.9 (10)	7.1 (14)	6.8 (13)
		9.46 [33]	10.03 [35]	19.87 [11]	11.16 [7]	24.03 [17]	23.42 [17]	12.17 [25]	8.01 [16]
	Mild	13.9 (31)	16.4 (35)	8.2 (11)	6.5 (7)	9.9 (12)	6.7 (8)	11.4 (10)	4.3 (4)
		12.61 [44]	19.26 [64]	14.99 [12]	11.05 [7]	20.06 [14]	11.39 [8]	15.69 [14]	5.01 [5]
	Moderate	24.4 (11)	17.5 (10)	14.7 (5)	10.9 (5)	8.5 (4)	15.9 (7)	0 (0)	33.3 (3)
		26.63 [18]	23.41 [20]	35.28 [7]	22.47 [6]	14.91 [4]	33.35 [8]	0 [0]	40.53 [4]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
a) Including 1 subject with severe renal impairment

Table 98. Incidence and rate of adverse events by degree of renal impairment in the phase III pool (Safety analysis set)

	Renal function	Insulin icodec	Comparator
N	Normal	1121	1137
	Mild	837	791
	Moderate or severe	211	241
All adverse events	Normal	59.2 (663)	56.5 (641)
		241.66 [1934]	233.04 [1870]
	Mild	63.9 (534)	60.7 (481)
		279.10 [1693]	267.73 [1513]
	Moderate or severe	62.2 (131)	58.5 (141)
		229.64 [358]	274.89 [495]
Serious adverse events	Normal	5.8 (65)	6.2 (70)
		11.84 [101]	11.51 [100]
	Mild	8.6 (72)	7.7 (61)
		15.85 [100]	11.36 [75]
	Moderate or severe	13.8 (29)	16.0 (38)
		27.39 [44]	32.49 [63]

Upper row: Incidence % (Number of subjects with event)
Lower row: Rate (Number of events/100 PYE) [Number of events]

Table 99 shows the incidence and rate of hypoglycemia by the degree of renal impairment in global phase III trials (Trials 4477, 4478, 4480, and 4625). Both treatment groups showed no trend towards clearly higher incidence and rate of hypoglycemia in the subgroups with mild or moderate renal impairment than in the subgroup with normal renal function.

Table 99. Incidence and rate of hypoglycemia by degree of renal impairment in each global phase III trial (Safety analysis set)

	Renal function	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	Normal	224	222	94	109	123	127	197	190
	Mild	223	213	134	108	121	120	88	93
	Moderate	45	57 a)	34	46	47	44	5	9
Level 2 or 3 hypoglycemia	Normal	13.8 (31)	15.8 (35)	13.8 (13)	7.3 (8)	47.2 (58)	53.5 (68)	90.4 (178)	86.8 (165)
		16.62 [58]	19.20 [67]	75.87 [42]	28.69 [18]	585.21 [414]	509.80 [370]	1658.13 [3407]	915.76 [1830]
	Mild	10.8 (24)	11.7 (25)	11.2 (15)	6.5 (7)	53.7 (65)	58.3 (70)	93.2 (82)	82.8 (77)
		44.41 [155]	12.94 [43]	66.21 [53]	18.95 [12]	545.94 [381]	546.76 [384]	1822.44 [1626]	955.15 [954]
	Moderate	13.3 (6)	16.1 (9)	26.5 (9)	8.7 (4)	57.4 (27)	54.5 (24)	60.0 (3)	88.9 (8)
		20.72 [14]	11.93 [10]	90.71 [18]	44.94 [12]	555.33 [149]	767.02 [184]	1280.94 [70]	526.85 [52]
Level 3 hypoglycemia	Normal	0.4 (1)	0.9 (2)	0 (0)	0 (0)	1.6 (2)	0.8 (1)	5.1 (10)	4.7 (9)
		0.29 [1]	0.86 [3]	0 [0]	0 [0]	7.07 [5]	2.76 [2]	23.36 [48]	11.01 [22]
	Mild	0 (0)	0.9 (2)	0 (0)	0 (0)	1.7 (2)	0 (0)	3.4 (3)	2.2 (2)
		0 [0]	0.60 [2]	0 [0]	0 [0]	2.87 [2]	0 [0]	8.97 [8]	2.00 [2]
	Moderate	0 (0)	3.6 (2)	0 (0)	2.2 (1)	0 (0)	2.3 (1)	0 (0)	11.1 (1)
		0 [0]	2.39 [2]	0 [0]	3.74 [1]	0 [0]	4.17 [1]	0 [0]	10.13 [1]
Level 2 or 3 nocturnal hypoglycemia	Normal	3.1 (7)	3.2 (7)	7.4 (7)	3.7 (4)	16.3 (20)	20.5 (26)	60.4 (119)	50.0 (95)
		2.87 [10]	2.87 [10]	32.51 [18]	12.75 [8]	89.05 [63]	88.18 [64]	269.62 [554]	138.62 [277]
	Mild	0.9 (2)	3.3 (7)	5.2 (7)	2.8 (3)	19.0 (23)	30.8 (37)	58.0 (51)	46.2 (43)
		4.58 [16]	3.61 [12]	14.99 [12]	4.74 [3]	74.51 [52]	123.88 [87]	329.52 [294]	181.22 [181]
	Moderate	0 (0)	3.6 (2)	5.9 (2)	4.3 (2)	23.4 (11)	20.5 (9)	20.0 (1)	22.2 (2)
		0 [0]	2.39 [2]	10.08 [2]	7.49 [2]	59.63 [16]	91.71 [22]	402.58 [22]	40.53 [4]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
Level 2 hypoglycemia: blood glucose <54 mg/dL
Level 3 hypoglycemia (severe hypoglycemia): hypoglycemia requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Nocturnal hypoglycemia: hypoglycemic episodes occurring between 0:01 a.m. and 5:59 a.m.
a) Including 1 subject with severe renal impairment

In a foreign phase III trial in insulin-naïve patients with type 2 diabetes mellitus (Trial 4481[45]), which is a clinical trial without an exclusion criterion as to renal impairment, the incidence and rate of hypoglycemia by the degree of renal impairment are shown in Table 100. Though evaluation has limitations due to the limited number of subjects in the subgroup with severe renal impairment, there were no major differences in the incidence and rate of hypoglycemia between the insulin icodec group and the control group in each subgroup.

Table 100. Incidence and rate of hypoglycemia by degree of renal impairment in Trial 4481 (Safety analysis set)

	Treatment group	Renal function			
		Normal	Mild	Moderate	Severe
N	Insulin icodec	311	174	52	5
	Comparator	304	169	61	3
Level 2 or 3 hypoglycemia	Insulin icodec	11.3 (35)	11.5 (20)	15.4 (8)	20.0 (1)
		14.55 ［47]	25.15 [45]	20.93 [11]	19.75 [1]
	Comparator	8.2 (25)	7.1 (12)	13.1 (8)	0 (0)
		12.19 [39]	18.42 [32]	15.79 [10]	0 [0]
Level 3 hypoglycemia	Insulin icodec	0 (0)	0 (0)	0 (0)	0 (0)
		0 [0]	0 [0]	0 [0]	0 [0]
	Comparator	1.0 (3)	0 (0)	1.6 (1)	0 (0)
		1.25 [4]	0 [0]	1.58 [1]	0 [0]
Level 2 or 3 nocturnal hypoglycemia	Insulin icodec	2.3 (7)	1.7 (3)	1.9 (1)	0 (0)
		2.17 [7]	2.79 [5]	1.90 [1]	0 [0]
	Comparator	2.0 (6)	3.6 (6)	0 (0)	0 (0)
		2.19 [7]	6.91 [12]	0 [0]	0 [0]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Comparator: Daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL])
See Table 99 for the classification of hypoglycemia.

Based on the above, though the number of patients with severe renal impairment evaluated was limited, the degree of renal impairment did not tend to impact the incidence and rate of adverse events or

hypoglycemia in the insulin icodec group compared with the control group. However, as with the existing daily basal insulin products, a relevant precautionary statement should be included in the package insert. Thus, the package insert will advise that particularly hypoglycemia may occur in patients with severe renal impairment.

PMDA's view:
In a clinical pharmacology trial in subjects with renal impairment, there were no major differences in insulin icodec exposure according to the degree of renal impairment. When analyzed by the degree of renal impairment in phase III trials, the frequencies of adverse events and hypoglycemia did not tend to increase with increasing renal impairment relative to normal renal function in the insulin icodec group compared with the control group. However, as rigorous comparison is difficult due to limited clinical experience with insulin icodec in patients with severe renal impairment, at present, it is appropriate to include a precautionary statement about the use of insulin icodec in patients with severe renal impairment in the package insert, as with the existing basal insulin products.

7.R.6.2 Patients with hepatic impairment

The applicant's explanation:
In a clinical pharmacology trial in subjects with hepatic impairment, there were no major differences in insulin icodec exposure following subcutaneous administration of 1.5 units/kg of insulin icodec according to the degree of hepatic impairment [see Section "6.2.3.2 Pharmacokinetic trial in subjects with hepatic impairment"]. Table 101 shows the incidence and rate of adverse events in subjects with or without hepatic impairment (subjects with baseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) exceeding the upper limit of normal were defined as having hepatic impairment) in global phase III trials (Trials 4477, 4478, 4480, and 4625). There were no clear differences between subjects with and without hepatic impairment. Patients with ALT ≥2.5 times or bilirubin >1.5 times the upper limit of normal were excluded from phase III trials, except for Trial 4481. In the phase III pool,[42)] the number of subjects with a total score of >2 based on the Modified Child-Pugh classification according to bilirubin and albumin concentrations was very limited in both groups, i.e., 8 subjects in the insulin icodec group and 7 subjects in the control group. Thus, the frequency of adverse events in the subgroup of subjects in this category could not be compared with that in the subgroup of other subjects.

Table 101. Incidence and rate of adverse events in subjects with or without hepatic impairment in each global phase III trial (Safety analysis set)

	Hepatic impairment	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	No	381	401	224	227	245	259	271	278
	Yes	110	89	38	35	44	31	17	14
All adverse events	No	80.6 (307)	79.3 (318)	58.9 (132)	46.7 (106)	58.4 (143)	56.4 (146)	82.7 (224)	82.0 (228)
		243.51 [1451]	234.59 [1462]	288.21 [383]	202.55 [266]	278.53 [390]	297.15 [441]	321.22 [900]	376.55 [1115]
	Yes	80.9 (89)	78.7 (70)	76.3 (29)	77.1 (27)	61.4 (27)	64.5 (20)	82.4 (14)	57.1 (8)
		255.31 [429]	255.05 [358]	371.24 [83]	277.94 [58]	244.39 [64]	550.85 [98]	337.21 [60]	230.04 [31]
Serious adverse events	No	12.9 (49)	15.0 (60)	8.5 (19)	5.7 (13)	8.2 (20)	7.3 (19)	8.9 (24)	7.2 (20)
		12.08 [72]	16.69 [104]	19.57 [26]	12.94 [17]	23.57 [33]	14.15 [21]	13.92 [39]	8.44 [25]
	Yes	13.6 (15)	12.4 (11)	7.9 (3)	8.6 (3)	4.5 (2)	16.1 (5)	0 (0)	0 (0)
		13.69 [23]	10.69 [15]	17.89 [4]	14.38 [3]	7.64 [2]	44.97 [8]	0 [0]	0 [0]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625

Table 102 shows the incidence and rate of hypoglycemia in subjects with or without hepatic impairment in the global phase III trials (Trials 4477, 4478, 4480, and 4625). Both treatment groups showed no trend towards higher incidence and rate of hypoglycemia in the subgroup with hepatic impairment compared with the subgroup without hepatic impairment.

Table 102. Incidence and rate of hypoglycemia in subjects with or without hepatic impairment in each global phase III trial (Safety analysis set)

	Hepatic impairment	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	No	381	401	224	227	245	259	271	278
	Yes	110	89	38	35	44	31	17	14
Level 2 or 3 hypoglycemia	No	13.9 (53)	14.7 (59)	14.7 (33)	7.9 (18)	54.7 (134)	57.9 (150)	90.0 (244)	85.6 (238)
		26.85 [160]	17.01 [106]	78.26 [104]	31.22 [41]	609.19 [853]	613.85 [911]	1731.76 [4852]	929.06 [2751]
	Yes	7.3 (8)	12.4 (11)	10.5 (4)	2.9 (1)	34.1 (15)	35.5 (11)	100.0 (17)	85.7 (12)
		39.87 [67]	10.69 [15]	40.26 [9]	4.79 [1]	343.67 [90]	146.14 [26]	1343.20 [239]	630.76 [85]
Level 3 hypoglycemia	No	0.3 (1)	1.5 (6)	0 (0)	0.4 (1)	1.6 (4)	0.8 (2)	4.8 (13)	4.3 (12)
		0.17 [1]	1.12 [7]	0 [0]	0.76 [1]	5.00 [7]	2.02 [3]	19.99 [56]	8.44 [25]
	Yes	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]
Level 2 or 3 nocturnal hypoglycemia	No	2.1 (8)	3.5 (14)	6.7 (15)	4.0 (9)	20.0 (49)	27.0 (70)	59.0 (160)	48.9 (136)
		4.20 [25]	3.53 [22]	23.33 [31]	9.90 [13]	82.84 [116]	115.22 [171]	293.74 [823]	154.34 [457]
	Yes	0.9 (1)	2.2 (2)	2.6 (1)	0 (0)	11.4 (5)	3.2 (1)	64.7 (11)	28.6 (4)
		0.60 [1]	1.42 [2]	4.47 [1]	0 [0]	57.28 [15]	5.62 [1]	264.14 [47]	37.10 [5]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
See Table 99 for the classification of hypoglycemia.

In a foreign phase III trial in insulin-naïve patients with type 2 diabetes mellitus (Trial 4481[45]), which is a clinical trial without an exclusion criterion as to hepatic impairment, the incidences and rates of adverse events and hypoglycemia in subjects with or without hepatic impairment are shown in Table 103. Both treatment groups showed no trend towards higher incidence and rate of adverse events or hypoglycemia in the subgroup with hepatic impairment compared with the subgroup without hepatic impairment.

Table 103. Incidences and rates of adverse events and hypoglycemia in subjects with or without hepatic impairment in Trial 4481 (Safety analysis set)

	Hepatic impairment	Insulin icodec	Comparator
N	No	439	426
	Yes	95	98
All adverse events	No	51.7 (227)	49.1 (209)
		138.27 [627]	134.26 [597]
	Yes	50.5 (48)	54.1 (53)
		188.96 [186]	154.66 [158]
Serious adverse events	No	9.1 (40)	11.0 (47)
		14.11 [64]	14.39 [64]
	Yes	5.3 (5)	9.2 (9)
		5.08 [5]	12.73 [13]
Level 2 or 3 hypoglycemia	No	12.3 (54)	7.7 (33)
		19.63 [89]	13.27 [59]
	Yes	10.5 (10)	10.2 (10)
		15.24 [15]	16.64 [17]
Level 3 hypoglycemia	No	0 (0)	0.9 (4)
		0 [0]	1.12 [5]
	Yes	0 (0)	0 (0)
		0 [0]	0 [0]
Level 2 or 3 nocturnal hypoglycemia	No	1.8 (8)	2.1 (9)
		2.21 [10]	3.37 [15]
	Yes	3.2 (3)	2.0 (2)
		3.05 [3]	1.96 [2]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Comparator: Daily basal insulin (IDeg or IGlar [100 units/mL or 300 units/mL])
See Table 99 for the classification of hypoglycemia.

Based on the above, hepatic impairment had no clear impact on the incidence and rate of adverse events or hypoglycemia in the insulin icodec group or the control group in the phase III trials. As with the existing daily basal insulin products, the package insert will advise that particularly hypoglycemia may occur in patients with severe hepatic impairment.

PMDA's view:

In a clinical pharmacology trial in subjects with hepatic impairment, there were no major differences in insulin icodec exposure according to the degree of hepatic impairment. In phase III trials, both the insulin icodec and control groups showed no trend towards differences in the incidence and rate of adverse events or hypoglycemia between subjects with and without hepatic impairment. However, as it is difficult to rigorously evaluate the relationship between worsening of hepatic impairment and the safety of insulin icodec due to the limited number of patients with hepatic impairment enrolled in clinical trials, at present, it is appropriate to include a precautionary statement about the use of insulin icodec in patients with severe hepatic impairment in the package insert, as with the existing basal insulin products.

7.R.6.3 Elderly

The applicant's explanation:

Tables 104 and 105 show the incidence and rate of adverse events by age group in global phase III trials (Trials 4477, 4478, 4480, and 4625) and in the phase III pool,[42)] respectively. Though evaluation has limitations due to fewer subjects in the subgroup of ≥75 years of age compared with other subgroups, there were no major differences in the incidence and rate of adverse events or serious adverse events between the insulin icodec and control groups in each subgroup.

Table 104. Incidence and rate of adverse events by age group in each global phase III trial (Safety analysis set)

	Age (years)	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	<65	333	332	144	149	189	184	267	271
	≥65 and <75	134	144	99	99	92	96	20	18
	≥75	25	16	19	15	10	11	3	3
All adverse events	<65	80.2 (267)	77.7 (258)	64.6 (93)	55.7 (83)	52.9 (100)	53.3 (98)	82.4 (220)	80.1 (217)
		231.91 [1202	220.34 [1151	342.28 [292]	240.34 [211]	219.70 [239]	318.28 [336]	313.83 [870]	372.63 [1068
	≥65 and <75	79.1 (106)	81.9 (118)	54.5 (54)	43.4 (43)	68.5 (63)	64.6 (62)	85.0 (17)	88.9 (16)
		254.15 [530]	278.42 [613]	251.00 [148]	178.45 [100]	377.81 [201]	371.16 [203]	414.16 [84]	299.55 [59]
	≥75	96.0 (24)	81.3 (13)	73.7 (14)	53.3 (8)	80.0 (8)	63.6 (7)	100.0 (3)	100.0 (3)
		388.01 [150]	243.58 [59]	237.00 [26]	190.12 [17]	279.10 [15]	168.32 [11]	413.77 [11]	579.76 [19]
Serious adverse events	<65	8.1 (27)	12.3 (41)	9.0 (13)	4.0 (6)	3.7 (7)	9.2 (17)	7.9 (21)	7.0 (19)
		7.14 [37]	10.53 [55]	17.58 [15]	6.83 [6]	6.43 [7]	23.68 [25]	11.90 [33]	8.37 [24]
	≥65 and <75	21.6 (29)	18.1 (26)	7.1 (7)	9.1 (9)	15.2 (14)	8.3 (8)	10.0 (2)	0 (0)
		22.54 [47]	27.25 [60]	20.35 [12]	23.20 [13]	50.75 [27]	14.63 [8]	24.65 [5]	0 [0]
	≥75	32.0 (8)	25.0 (4)	10.5 (2)	6.7 (1)	10.0 (1)	0 (0)	33.3 (1)	33.3 (1)
		28.45 [11]	16.51 [4]	27.35 [3]	11.18 [1]	18.61 [1]	0 [0]	37.62 [1]	30.51 [1]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625

Table 105. Incidence and rate of adverse events by age group in the phase III pool (Safety analysis set)

	Age	Insulin icodec	Comparator
N	<65	1501	1498
	≥65 and <75	569	592
	≥75	100	80
All adverse events	<65	61.0 (915)	57.9 (868)
		249.05 [2649]	256.08 [2664]
	≥65 and <75	60.7 (345)	58.2 (345)
		267.51 [1119]	240.67 [1075]
	≥75	67.8 (68)	62.4 (50)
		266.38 [217]	227.07 [139]
Serious adverse events	<65	5.6 (84)	6.4 (96)
		9.81 [113]	10.63 [121]
	≥65 and <75	12.0 (68)	10.0 (59)
		27.16 [115]	18.95 [94]
	≥75	13.6 (14)	17.7 (14)
		20.80 [17]	33.81 [23]

Upper row: Incidence % (Number of subjects with event)
Lower row: Rate (Number of events/100 PYE) [Number of events]

Table 106 shows the incidence and rate of hypoglycemia by age group in the global phase III trials (Trials 4477, 4478, 4480, and 4625). Both treatment groups showed no trend towards markedly higher incidence and rate of level 3 or 2 hypoglycemia or nocturnal hypoglycemia or level 3 hypoglycemia in the subgroups of ≥65 and <75 years of age and ≥75 years of age compared with the subgroup of <65 years of age.

Table 106. Incidence and rate of hypoglycemia by age group in each global phase III trial (Safety analysis set)

	Age (years)	Trial 4477		Trial 4478		Trial 4480		Trial 4625	
		Insulin icodec	IGlar	Insulin icodec	IDeg	Insulin icodec	IGlar	Insulin icodec	IDeg
N	<65	333	332	144	149	189	184	267	271
	≥65 and <75	134	144	99	99	92	96	20	18
	≥75	25	16	19	15	10	11	3	3
Level 2 or 3 hypoglycemia	<65	12.6 (42)	15.7 (52)	13.2 (19)	6.7 (10)	47.6 (90)	54.3 (100)	90.6 (242)	86.3 (234)
		25.08 [130]	18.19 [95]	87.91 [75]	23.92 [21]	512.93 [558]	566.46 [598]	1730.40 [4797]	894.25 [2563]
	≥65 and <75	13.4 (18)	11.8 (17)	15.2 (15)	9.1 (9)	59.8 (55)	57.3 (55)	95.0 (19)	72.2 (13)
		44.60 [93]	10.90 [24]	55.97 [33]	37.47 [21]	652.23 [347]	585.07 [320]	1474.21 [299]	1203.28 [237]
	≥75	4.0 (1)	6.2 (1)	15.8 (3)	0 (0)	50.0 (5)	63.6 (7)	66.7 (2)	100.0 (3)
		10.35 [4]	8.26 [2]	45.58 [5]	0 [0]	725.66 [39]	306.03 [20]	263.31 [7]	1098.50 [36]
Level 3 hypoglycemia	<65	0.3 (1)	1.2 (4)	0 (0)	0 (0)	1.6 (3)	0.5 (1)	4.9 (13)	3.7 (10)
		0.19 [1]	0.96 [5]	0 [0]	0 [0]	5.52 [6]	1.89 [2]	20.20 [56]	8.02 [23]
	≥65 and <75	0 (0)	1.4 (2)	0 (0)	1.0 (1)	1.1 (1)	1.0 (1)	0 (0)	5.6 (1)
		0 [0]	0.91 [2]	0 [0]	1.78 [1]	1.88 [1]	1.83 [1]	0 [0]	5.08 [1]
	≥75	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	33.3 (1)
		0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	0 [0]	30.51 [1]
Level 2 or 3 nocturnal hypoglycemia	<65	2.7 (9)	3.9 (13)	5.6 (8)	4.0 (6)	20.1 (38)	24.5 (45)	59.9 (160)	48.3 (131)
		5.02 [26]	3.83 [20]	25.79 [22]	11.39 [10]	87.33 [95]	106.09 [112]	299.40 [830]	146.19 [419]
	≥65 and <75	0 (0)	2.1 (3)	7.1 (7)	3.0 (3)	16.3 (15)	27.1 (26)	55.0 (11)	38.9 (7)
		0 [0]	1.82 [4]	15.26 [9]	5.35 [3]	62.03 [33]	109.70 [60]	197.22 [40]	192.93 [38]
	≥75	0 (0)	0 (0)	5.3 (1)	0 (0)	10.0 (1)	9.1 (1)	0 (0)	66.7 (2)
		0 [0]	0 [0]	9.12 [1]	0 [0]	55.82 [3]	15.30 [1]	0 [0]	152.57 [5]

Upper row: Incidence % (Number of subjects with event), Lower row: Rate (Number of events/100 PYE) [Number of events]
Main + extension phases (78 weeks of treatment) for Trial 4477, Main + extension phases (52 weeks of treatment) for Trial 4625
See Table 99 for the classification of hypoglycemia.

Based on the above, age did not tend to impact the incidence and rate of adverse events or hypoglycemia in the insulin icodec group compared with the control group. However, as with the existing daily basal insulin products, the package insert will advise that as hypoglycemia is likely to occur in elderly patients due to reduced physiological function, insulin icodec should be administered with caution while monitoring the patient's condition.

PMDA's view:

When analyzed by age group in phase III trials, there was no trend towards higher risk of adverse events or hypoglycemia in the subgroup of ≥65 years of age compared with the subgroup of <65 years of age in the insulin icodec group compared with the control group. However, as it is difficult to rigorously evaluate the relationship between old age and the safety of insulin icodec due to limited clinical experience with insulin icodec in patients aged ≥75 years, at present, it is appropriate to include a precautionary statement about the use of insulin icodec in elderly patients in the package insert, as with the existing basal insulin products.

7.R.7 Post-marketing investigations

7.R.7.1 Post-marketing surveillance

The applicant's explanation:

The applicant plans to conduct a general use-results survey to evaluate the safety and efficacy of insulin icodec in clinical practice (central registry system, a 1-year observation period, a 3-year survey period, a target sample size of 500 patients [including approximately 100 patients with type 1 diabetes mellitus]). The survey is intended to collect information on hypoglycemia, systemic hypersensitivity reactions, and medication errors. The package insert etc. will advise about the risk of hypoglycemia, as a risk minimization activity. After implementing this risk minimization activity, the time to onset of

hypoglycemia, the frequency of hypoglycemia recurrence occurring within a short period of time, etc., in clinical practice, will be investigated. Information on the details of medication errors, the use of insulin icodec, and blood glucose parameters such as CGM data (if available) will also be collected to investigate the relationship between medication errors and hypoglycemia.

PMDA's view:
Although a clinical trial suggested the presence of type 1 diabetes mellitus patients who cannot achieve good glycemic control with insulin icodec compared with IDeg and showed a trend towards higher incidence and rate of hypoglycemia with insulin icodec than with IDeg, the results from the clinical trial could not identify factors characterizing patients who are difficult to achieve glycemic control with insulin icodec or patients who are at an increased risk of hypoglycemia with insulin icodec. Since insulin icodec has a pharmacokinetic profile substantially different from those of the existing basal insulin products, an evaluation using the existing data has limitations, and especially, the risk of hypoglycemia and systemic hypersensitivity reactions that can affect the benefit-risk balance of insulin icodec could not be assessed in a sufficient number of patients with diverse characteristics in whom the use of insulin icodec was expected in clinical practice. Given the above points, it is necessary to investigate the relationship between patient characteristics etc. and the occurrence of these events/glycemic control for post-marketing assessment of the benefit-risk balance of insulin icodec. As medication errors relate to the risk of hypoglycemia etc., a post-marketing investigation of the relationship between medication errors and hypoglycemia in clinical practice is important. Thus, it is appropriate to conduct a general use-results survey proposed by the applicant to investigate the relationship between patient characteristics and the safety of insulin icodec/glycemic control, including the safety specification (hypoglycemia, systemic hypersensitivity reactions, medication errors). The details of a post-marketing surveillance plan will be finalized, taking account of comments from the Expert Discussion.

7.R.7.2 Additional risk minimization activities

The applicant's explanation:
The proposed product is an insulin product containing 700 units/mL of insulin icodec for once-weekly administration. Since the recommended dose of insulin icodec is 7 times the existing daily basal insulin dose, medication errors due to mix-ups between insulin icodec and the existing daily basal insulin products are associated with the risk of hyperglycemia or hypoglycemia. As with the existing daily basal insulin products, the package insert will advise that patients must be instructed to always check the label on the product, etc., before each injection to avoid accidental mix-ups between insulin icodec and other insulin products. Then, this information will be disseminated also using materials for healthcare professionals and for patients. Since insulin icodec is for once-weekly administration, if insulin icodec is mistakenly administered daily, there will be a risk of hypoglycemia. Thus, "for once-weekly administration" will be displayed on the product label, and materials for healthcare professionals and for patients will be used to inform that insulin icodec is for once-weekly administration.

When switching patients from the existing daily basal insulin products to insulin icodec, for the first

injection only, the introduction of a one-time additional 50% dose of insulin icodec is recommended for type 2 diabetes mellitus patients, and a one-time additional 50% dose is added as a rule for type 1 diabetes mellitus patients. Thus, also in the case of forgetting to remove the one-time additional dose after the first injection, there will be a risk of hypoglycemia. Especially, type 1 diabetes mellitus patients are at an increased risk of hypoglycemia with insulin icodec compared with IDeg, and therefore, more careful monitoring of glycemic control and dose adjustments are needed. These precautionary statements will also be included in the package insert, and the relevant information will be disseminated using materials for healthcare professionals and for patients, to promote proper use of insulin icodec. The proposed product is a combination product containing a drug solution in a cartridge assembled into a dedicated pen-injector, and the pen-injector delivers doses in steps of 10 units. This precautionary statement will be included in the package insert, and the packaging materials and the materials for healthcare professionals and for patients will also be used to inform that the pen-injector delivers doses in steps of 10 units.

PMDA's view:
Regarding risk minimization activities against mix-ups or medication errors and the associated risk of hypoglycemia, it is important to include the relevant precautionary statements in the package insert and provide adequate information using materials for healthcare professionals and for patients, etc.

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 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 (CTD5.3.5.1-4, CTD5.3.5.1-8) 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 insulin icodec has efficacy in the treatment of diabetes mellitus where treatment with insulin is required, and that insulin icodec has acceptable safety in view of its benefits. Insulin icodec is clinically meaningful because it is an insulin product

allowing once-weekly dosing and offers a new treatment option for patients with diabetes mellitus who require insulin.

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

Review Report (2)

May 17, 2024

Product Submitted for Approval

Brand Name	(a) Awiqli Injection FlexTouch 300 Units
	(b) Awiqli Injection FlexTouch 700 Units
Non-proprietary Name	Insulin Icodec (Genetical Recombination)
Applicant	Novo Nordisk Pharma Ltd.
Date of Application	August 10, 2023

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:

Regarding the efficacy of insulin icodec in type 2 diabetes mellitus, all of 3 global phase III trials in insulin-naïve, basal insulin-treated, and basal-bolus regimen-treated patients with type 2 diabetes mellitus (Trials 4477, 4478, and 4480) demonstrated the non-inferiority of insulin icodec to the comparator in the primary endpoint of the change from baseline in HbA1c. As to the long-term efficacy of insulin icodec, the reduction in HbA1c with insulin icodec was maintained to Week 78 in Trial 4477. As to the efficacy of insulin icodec in Japanese patients, the consistent results were obtained between the Japanese subgroup and the entire trial population in all trials, and the efficacy of insulin icodec confirmed in the entire trial population is expected also in Japanese patients.

Regarding the efficacy of insulin icodec in type 1 diabetes mellitus, a global phase III trial in basal-bolus regimen-treated patients with type 1 diabetes mellitus (Trial 4625) demonstrated the non-inferiority of insulin icodec to IDeg in the primary endpoint of the change from baseline in HbA1c. As to the long-term efficacy of insulin icodec, the change in HbA1c over time up to Week 52 showed a trend towards decreasing efficacy over time in both the insulin icodec and IDeg groups, but the reduction in HbA1c with insulin icodec was maintained to Week 52. As to the efficacy of insulin icodec in Japanese patients, the change in HbA1c from baseline to Week 26 in the insulin icodec group was smaller in the Japanese

subgroup than in the entire trial population, and HbA1c tended to increase towards baseline through Week 52. A cause for this trend was subjects who were difficult to achieve glycemic control, i.e., subjects with a >1% point increase in HbA1c from baseline to the end of treatment, enrolled in the insulin icodec group more prevalently in the Japanese subgroup. Taking also into account that the secondary endpoints of fasting plasma glucose, CGM endpoints, etc. showed a similar trend between the Japanese subgroup and the entire trial population, the overall efficacy of insulin icodec is consistent between the Japanese subgroup and the entire trial population. Thus, the efficacy of insulin icodec confirmed in the entire trial population is expected also in Japanese patients.

Based on the above, insulin icodec has clinically meaningful efficacy in patients with diabetes mellitus who require insulin.

However, there was a trend towards lower efficacy in the insulin icodec group than in the IDeg group in type 1 diabetes mellitus patients, and especially in the Japanese subgroup, there were subjects who had a >1% point increase from baseline in HbA1c, suggesting that some type 1 diabetes mellitus patients may not be able to optimize glycemic control. The trial raised a safety concern about hypoglycemia etc. [see Section "7.R.2.3 Hypoglycemia" in the Review Report (1)]. Thus, a particular precautionary statement regarding the use of insulin icodec in type 1 diabetes mellitus patients is needed [see Section "1.3 Clinical positioning and indication"].

At the Expert Discussion, the expert advisors supported the above conclusions (the efficacy of insulin icodec is expected also in Japanese patients with type 1 diabetes mellitus; and the need for a precautionary statement regarding the use of insulin icodec in type 1 diabetes mellitus patients, etc.).

1.2 Safety

PMDA's view:

Trials 4477, 4478, and 4480 in type 2 diabetes mellitus patients and Trial 4625 in type 1 diabetes mellitus patients showed no major differences in the occurrence of adverse events between the insulin icodec and control groups, except for a higher incidence and rate of hypoglycemia in the insulin icodec group than in the control group in some trials. In all trials, there was no trend towards differences in the occurrence of adverse events in the insulin icodec and control groups between the Japanese subgroup and the entire trial population.

Taking account of the mechanism of action of insulin icodec, clinical trial results, etc., in addition to the above analyses, as with the existing daily basal insulin products, the safety of insulin icodec is manageable, provided that appropriate precautionary statements about adverse events of special interest including hypoglycemia following administration of insulin icodec are included in the package insert.

At the Expert Discussion, the expert advisors supported the above conclusion by PMDA.

1.2.1 Hypoglycemia

PMDA's view:

In Trials 4477, 4478, and 4480 in type 2 diabetes mellitus patients, although the rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia tended to be higher in the insulin icodec group than in the IDeg group in Trial 4478, the occurrence of hypoglycemia was similar between the insulin icodec and control groups in Trials 4477 and 4480. There were no major differences in the rate of level 3 hypoglycemia or nocturnal hypoglycemia between the treatment groups in all trials. In Trial 4625 in type 1 diabetes mellitus patients, the rates of level 2 or 3 hypoglycemia and nocturnal hypoglycemia were higher in the insulin icodec group than in the IDeg group. Given that 1 subject in the insulin icodec group had 33 of the 47 reported level 3 hypoglycemic episodes during the main phase (all non-serious episodes), etc., it is presumed that there were no substantial differences in the risk of level 3 hypoglycemia between the treatment groups. In Trial 4462 investigating the hypoglycemic response to overdosing in type 2 diabetes mellitus patients, there were no major differences in the severity of hypoglycemia or the time to recovery from hypoglycemia between insulin icodec and IGlar. In clinical trials of insulin icodec in which hypoglycemic episodes were managed in the same way as patients manage the hypoglycemic risk with daily basal insulin products, no events with a serious outcome were reported.

Given the above situation etc., based on the clinical trial results, the way to manage hypoglycemia, including patient guidance, for the existing insulin products, is effective also for insulin icodec. As with the existing basal insulin products, the risk of hypoglycemia associated with insulin icodec is manageable in type 1 and type 2 diabetes mellitus patients, provided that appropriate precautionary statements are included in the package insert. However, the following precautionary statements should be included in the package insert: a precautionary statement about hypoglycemia included in the package inserts for the existing daily basal insulin products; a higher risk of hypoglycemia occurred on Days 2 to 4 after the weekly administration of insulin icodec; and especially when insulin icodec is used in type 1 diabetes mellitus patients, the use of CGM etc. should also be considered, and then the patient's condition should be closely observed while carefully monitoring blood glucose over time, and insulin icodec should be switched to the existing daily basal insulin products if glycemic control cannot be optimized. Information materials should also be used to disseminate the above information.

At the Expert Discussion, the expert advisors supported the above conclusions and made the following comments.

- Patients are likely to be unaware of nocturnal hypoglycemia, which poses the risk of level 3 hypoglycemia. Thus, the package insert should appropriately advise that the rate of nocturnal hypoglycemia was higher with insulin icodec than with the comparator.
- As the risk of hypoglycemia is high in type 1 diabetes mellitus patients with high blood glucose fluctuations, an adequate precautionary statement about hypoglycemia is important particularly for type 1 diabetes mellitus patients. Attention should be paid to the possible occurrence of

hypoglycemia when switching from the existing basal insulin products to insulin icodec, and intensification of blood glucose monitoring using CGM etc. is also useful.

- Since insulin icodec has a long half-life, there is a potential risk of prolonged hypoglycemia with insulin icodec. Post-marketing information on the adequacy of the way to manage hypoglycemia for the existing insulin products should be collected.

Based on the above, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, that information on the incidences and rates of hypoglycemia and nocturnal hypoglycemia in clinical trials should be disseminated using the package insert and materials for healthcare professionals etc., and that information on the occurrence of prolonged hypoglycemia and its management should be collected via post-marketing surveillance. The applicant appropriately responded to these instructions.

Precautions Concerning Dosage and Administration (Relevant text only)

- Since especially type 1 diabetes mellitus patients are likely to experience blood glucose changes with lifestyle changes, the patient's condition should be closely observed while carefully monitoring blood glucose, and the doses of insulin icodec should be adjusted. Insulin icodec should be switched to daily basal insulin etc. if glycemic control cannot be optimized, e.g., if a patient experiences recurrent hypoglycemia.
- Close glucose monitoring is recommended at the start of treatment with insulin icodec and until stable glycemic control is achieved. When switching from daily basal insulin to insulin icodec, insulin icodec may need time to achieve the optimal glycemic control due to its action profile. The doses and timing of concurrent rapid-acting or short-acting insulin products or other concomitant antidiabetic treatment may need to be adjusted.

1.3 Clinical positioning and indication

PMDA's view:

Clinical positioning

Insulin therapy with fewer injections is expected to reduce treatment burden. Thus, a once-weekly insulin product is required as a new treatment option for patients who require insulin including type 1 diabetes mellitus patients.

Indication

The applicant's explanation is appropriate based on the results from Trials 4477, 4478, and 4480, the benefit-risk balance of insulin icodec is favorable in type 2 diabetes mellitus patients. On the other hand, Trial 4625 in type 1 diabetes mellitus patients demonstrated the efficacy of insulin icodec in the primary endpoint, but the incidence and rate of hypoglycemia were higher in the insulin icodec group than in the IDeg group, and the proportion of subjects with ≥20 level 2 or 3 hypoglycemic episodes was also higher in the insulin icodec group than in the IDeg group, suggesting the presence of type 1 diabetes mellitus patients who cannot achieve good glycemic control with insulin icodec. Thus, the benefit-risk balance

of insulin icodec in type 1 diabetes mellitus patients may be slightly different from that in type 2 diabetes mellitus patients, and especially when insulin icodec is used in type 1 diabetes mellitus patients who are susceptible to hypoglycemia, caution is needed. However, reducing treatment burden with fewer injections has its significance also in type 1 diabetes mellitus patients. The indication of "diabetes mellitus where treatment with insulin is required" as that for the currently approved basal insulin products is acceptable, provided that appropriate precautionary statements about hypoglycemia (e.g., close glucose monitoring is recommended; and switching to the existing daily insulin products should be considered if it is difficult to optimize the glycemic control) are included in the package insert.

At the Expert Discussion, the expert advisors supported the above conclusions and made the following comments.

- Insulin icodec should be useful particularly for elderly patients with type 1 diabetes mellitus who require daily basal insulin because treatment with daily basal insulin is sometimes difficult. Insulin icodec is useful also for elderly patients with type 2 diabetes mellitus who require insulin, for the following reasons: self-injection and self-management may be difficult, and such patients treated with insulin icodec also can achieve good glycemic control, which reduces a burden to patients, their families, and caregivers.
- Especially type 2 diabetes mellitus patients are psychologically reluctant to initiate injectables, instead of oral formulations, and tend to delay insulin therapy initiation. Once-weekly insulin icodec and daily basal insulin are expected to have comparable effects, which shows the great advantage of insulin icodec in terms of achieving good glycemic control with early initiation of insulin therapy.
- For example, on a sick day or in the case of a marked reduction in endogenous basal insulin secretion or unstable disease such as profound insulin resistance, treatment with daily basal insulin is recommended. The package insert should advise that treatment with daily basal insulin, instead of insulin icodec, should be considered for these patients.

Based on the above, PMDA concluded that the indication should be "diabetes mellitus where treatment with insulin is required" as that for the currently approved basal insulin products and then the following precautionary statements should be included in the package insert. The applicant responded appropriately.

Indication

Diabetes mellitus where treatment with insulin is required

Precautions Concerning Indication (Relevant text only)

In a clinical trial in type 1 diabetes mellitus patients, the incidence and rate of hypoglycemia were higher with insulin icodec than with daily basal insulin. The use of insulin icodec in type 1 diabetes mellitus patients should be considered carefully with a full understanding of the efficacy and safety of insulin icodec, after also considering the choice of daily basal insulin etc.

Precautions Concerning Dosage and Administration (Relevant text only)
Note the action profile of insulin icodec and the patient's condition, and administer insulin icodec if the patient's condition is suitable for the pharmaceutical properties of insulin icodec.

1.4 Dosage and administration

PMDA's view:
Given the clinical trial data, a once-weekly regimen of insulin icodec is appropriate.

As to dose selection, insulin icodec is a human insulin analog, and 1 unit of insulin icodec corresponds to 6 nmol, as with insulin human (genetical recombination). In clinical pharmacology trials with glucose clamps, the molar dose-normalized weekly pharmacodynamic effect was largely similar between insulin icodec and IGlar (100 units/mL) or IDeg. Trials 4478 and 4480 in which the starting dose of insulin icodec was 7 times the existing daily basal insulin dose demonstrated the non-inferiority of insulin icodec to IGlar (100 units/mL) or IDeg. In Trials 4477 and 4478, there were no major differences in the insulin dose at the end of treatment between the insulin icodec and control groups (Review Report (1), Table 92). In Trials 4480 and 4625 in basal-bolus regimen-treated patients, the basal insulin dose tended to be higher, and the bolus insulin dose tended to be lower in the insulin icodec group than in the control group, but there were no major differences in the range of the total insulin dose between the insulin icodec and control groups. The trend in the basal insulin dose differed from that in the bolus insulin dose because the action profile of insulin icodec suitable for once weekly administration affected the dose adjustments of insulin icodec and bolus insulin.

Based on the above, 1 unit of insulin icodec largely corresponds to 1 unit of the existing daily basal insulin products. Based on the recommended doses of the existing daily basal insulin products (the once-daily starting dose is 4-20 units, and typically, the total insulin maintenance dose is 4-80 units/day), the once-weekly starting dose of insulin icodec should be 30 to 140 units; the total insulin maintenance dose should be stated; and typically, the weekly total insulin maintenance dose should be 30 to 560 units. The package insert should also mention that a higher dose than stated above may be used as needed.

At the Expert Discussion, the expert advisors supported the above conclusions. PMDA concluded that the following statements should be included in the DOSAGE AND ADMINISTRATION section, and the applicant responded appropriately.

Dosage and Administration
Usually, for adults, insulin icodec should be injected subcutaneously once weekly. The starting dose is typically 30 to 140 units followed by dose adjustments according to the patient's condition. Insulin icodec may be combined with other insulin products and typically, the weekly total insulin maintenance dose is 30 to 560 units. However, a higher dose than stated above may be used as needed.

1.4.1 Starting dose in diabetes patients not on basal insulin

PMDA's view:

In Trial 4477 in insulin-naïve patients with type 2 diabetes mellitus, the starting dose of insulin icodec was 70 units. With respect to the rate of level 2 or 3 hypoglycemia, the percentage of TIR (time spent in 70-180 mg/dL) based on CGM data, etc., during the early phase of treatment (from Week 0 to Week 4), there were no major differences between the insulin icodec and IGlar groups. Thus, there were no safety or efficacy problems with a starting dose of insulin icodec of 70 units. In clinical practice, as with the existing daily basal insulin products, the starting dose of insulin icodec should be determined according to the individual patient's condition. However, given that the starting dose of insulin icodec was 70 units in Trial 4477, and that the starting doses were <70 units in 8 of 78 Japanese subjects, the package insert should advise that the recommended starting dose of insulin icodec is ≤70 units in patients not on basal insulin.

At the Expert Discussion, the expert advisors supported the above conclusions and made the following comments.

- In clinical practice, the starting dose of daily basal insulin is generally 4 to 6 units, and a starting dose of 10 units is uncommon. Thus, as a starting dose of insulin icodec of 70 units may be excessive, the package insert should advise that starting with a lower dose should also be considered.

Based on the above, PMDA concluded that the following statement should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and that materials for healthcare professionals etc. should advise that starting with a lower dose should be considered. The applicant responded appropriately.

Precautions Concerning Dosage and Administration (Relevant text only)

In patients not on basal insulin, the recommended starting dose of insulin icodec is ≤70 units, and insulin icodec should be initiated carefully, e.g., starting with a lower dose should be considered.

1.4.2 Starting dose when switching from another basal insulin

PMDA's view:

When switching from the existing daily basal insulin products to insulin icodec, as in Trials 4478 and 4480, a one-time additional 50% dose of insulin icodec should be added to the first dose (7 times the existing daily basal insulin dose) in type 2 diabetes mellitus patients on daily basal insulin to ensure good glycemic control.

When switching to insulin icodec in basal-bolus regimen-treated patients with type 1 diabetes mellitus, 2 different one-time additional doses of insulin icodec (a one-time additional 50% or 100% dose according to baseline HbA1c etc.) were used in Trial 4625. Given fasting blood glucose levels over time etc., a single 50% one-time additional dose is appropriate.

When switching to insulin icodec in patients on daily basal insulin, given fasting SMBG levels over time during the switch and the risk of hypoglycemia associated with a one-time additional dose, a one-time additional dose with the first dose is recommended for type 2 diabetes mellitus patients, and a one-time additional dose should be added to the first dose as a rule for type 1 diabetes mellitus patients. The package insert should advise that for both type 1 and 2 diabetes mellitus patients, the need for a one-time additional dose should be determined carefully, taking account of the patient's glycemic control and the risk of hypoglycemia.

Furthermore, the package insert should advise that close glucose monitoring is recommended at the start of treatment with insulin icodec and until stable glycemic control is achieved, and that insulin icodec may need time to achieve the optimal glycemic control compared with the existing daily basal insulin products.

At the Expert Discussion, the expert advisors supported the above conclusions.

Based on the above, PMDA concluded that the following statements should be included in the PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION section, and that materials for healthcare professionals etc. should provide appropriate dosing guidance when switching from the existing basal insulin products to insulin icodec for type 2 and type 1 diabetes mellitus patients. The applicant responded appropriately.

Precautions Concerning Dosage and Administration (Relevant text only)
When switching from daily basal insulin to insulin icodec, patients should be switched carefully, taking account of the action profile of insulin icodec, e.g., insulin icodec should be initiated as per the following guidance, followed by dose adjustments according to the patient's condition.

(1) The recommended once-weekly insulin icodec dose is the total daily basal insulin dose multiplied by 7.
(2) When switching from daily basal insulin to insulin icodec, blood glucose may be elevated. For the first injection only, a one-time additional 50% dose of insulin icodec is recommended for type 2 diabetes mellitus patients in order to prevent blood glucose elevation (The week 1 dose is the total daily basal insulin dose multiplied by 7 and then multiplied by 1.5). The need for a one-time additional dose should be determined carefully, taking account of the balance between the patient's glycemic control and the risk of hypoglycemia.
    For type 1 diabetes mellitus patients, a one-time additional 50% dose of insulin icodec should be added as a rule for the first injection only (The week 1 dose is the total daily basal insulin dose multiplied by 7 and then multiplied by 1.5). The need for a one-time additional dose should be determined carefully, taking account of the patient's glycemic control and the risk of hypoglycemia.
(3) If the one-time additional 50% dose is added to the first dose, the second once-weekly dose is the total daily basal insulin dose multiplied by 7. The third and subsequent once-weekly doses should

be adjusted, taking account of the action profile of insulin icodec, in addition to the patient's condition such as glycemic control and the occurrence of hypoglycemia.

1.5 Risk management plan (draft)

PMDA's view:

Although a clinical trial showed a trend that some type 1 diabetes mellitus patients could not achieve good glycemic control with insulin icodec, the results from the clinical trial could not identify factors characterizing the above patient group. Since insulin icodec has a pharmacokinetic profile substantially different from those of the existing basal insulin products, there are limitations to evaluation of the safety and efficacy of insulin icodec using the existing data on basal insulin products, and probably, especially, the risk of hypoglycemia and systemic hypersensitivity reactions that can affect the benefit-risk balance of insulin icodec have not been assessed in a sufficient number of patients with diverse characteristics in whom the use of insulin icodec was expected in clinical practice. Given the above points, it is necessary to investigate the relationship between patient characteristics etc. and the occurrence of these events/glycemic control for post-marketing assessment of the benefit-risk balance of insulin icodec. Since the dosing regimen and titration algorithm of insulin icodec are different from those of the existing basal insulin products, and there is a concern about medication errors relating to the risk of hypoglycemia etc., a post-marketing investigation of the relationship between medication errors and hypoglycemia in clinical practice is important. Thus, it is appropriate to conduct a general use-results survey proposed by the applicant to investigate the relationship between patient characteristics and the safety of insulin icodec/glycemic control, including the safety specification (hypoglycemia, systemic hypersensitivity reactions, medication errors).

At the Expert Discussion, the expert advisors supported the above conclusions and made the following comments.

- Since prolonged hypoglycemia may occur due to the pharmacokinetic profile of insulin icodec, a general use-results survey with a sufficient sample size should be conducted to collect information on the occurrence and management of such events especially in type 1 diabetes mellitus patients.
- Since insulin icodec displays protracted action due to reversible binding to albumin, information on the safety and efficacy of insulin icodec in patients with hepatic impairment or nephrotic syndrome who have low blood albumin levels and the safety and efficacy of insulin icodec in combination with drugs highly bound to albumin or in the presence of free fatty acid should also be collected.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for insulin icodec should include the safety and efficacy specifications presented in Table 107, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 108 and 109.

Table 107. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Hypoglycemia • Systemic hypersensitivity reactions	• Medication errors (mix-ups with other insulin products) • Medication errors (when switching from daily basal insulin) • Medication errors (inappropriate use associated with a higher concentration of insulin icodec compared with the existing insulin products)	None
Efficacy specification		
None		

Table 108. Summary of additional pharmacovigilance activities, efficacy survey and studies, and additional risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Efficacy survey and studies	Additional risk minimization activities
• Early post-marketing phase vigilance • General use-results survey	None	• Develop information materials for proper use to be distributed to healthcare professionals • Develop information materials for proper use to be distributed to patients • Disseminate data gathered during early post-marketing phase vigilance

Table 109. Outline of use-results survey (draft)

Objective	To evaluate the safety of insulin icodec in clinical practice.
Survey method	Central registry system
Population	Diabetes mellitus where treatment with insulin is required
Observation period	1 year
Planned sample size	630 patients
Main survey items	Patient characteristics (medical history, prior antidiabetic treatment, etc.), the use of insulin icodec, the use of concomitant medications, adverse events (including the occurrence of prolonged hypoglycemia), efficacy (HbA1c, fasting plasma glucose, etc.), treatment compliance status, etc.

1.6 Shelf-life of the 300 units variant of the drug product

The applicant submitted the additional 30-month long-term stability data on 3 batches of the 300 units variant, as planned in the Review Report (1), and explained about the shelf-life of the 300 units variant of the drug product as follows:

As with the 24-month data, the 30-month long-term stability data also showed that hydrophilic related substances and hydrophobic impurities, based on [redacted]-UHPLC, tended to increase; HMWPs based on [redacted]-UHPLC tended to increase; and the m-cresol and phenol contents tended to decrease, but no significant changes in other quality attributes occurred. Thus, as with the 700 units variant, a shelf-life of 30 months was proposed for the 300 units variant of the drug product when primary packaged in a glass cartridge with an aluminum cap with a laminated rubber disc ([redacted] rubber in contact with a drug solution) and [redacted] rubber plunger and stored in a dedicated pen-injector to protect from light at 2°C to 8°C.

PMDA concluded that the proposed shelf-life of the 300 units variant of the drug product is acceptable.

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 shown below, with the following condition. As the product is

a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Diabetes mellitus where treatment with insulin is required

Dosage and Administration

Usually, for adults, insulin icodec should be injected subcutaneously once weekly. The starting dose is typically 30 to 140 units followed by dose adjustments according to the patient's condition. Insulin icodec may be combined with other insulin products and typically, the weekly total insulin maintenance dose is 30 to 560 units. However, a higher dose than stated above may be used as needed.

Approval Condition

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

Appendix

List of Abbreviations

[redacted]	[redacted]
Akt	protein kinase B
[redacted]	[redacted]
ALT	Alanine aminotransferase
An adverse drug reaction	An adverse event for which a causal relationship to trial product cannot be ruled out
AST	Aspartate aminotransferase
AUC	Area under the drug plasma/serum concentration-time curve
BHK	Baby hamster kidney
BMI	Body mass index
CGM	Continuous glucose monitoring
[redacted]	[redacted]
CL/F	Apparent clearance
$C_{average}$	Average plasma/serum concentration
C_{max}	Maximum plasma/serum concentration
COVID-19	Coronavirus disease 2019
CQA	Critical quality attribute
[redacted]	insulin icodec [redacted]
[redacted]	insulin icodec [redacted]
[redacted]	insulin icodec [redacted]
DNA	Deoxyribonucleic acid
DPP-4	Dipeptidyl peptidase-4
EC_{50}	Effective concentration 50
ELISA	Enzyme-linked immune sorbent assay
EPC	End of production cells
FAS	Full analysis set
FBS	Fetal bovine serum
FTT	Failure to thrive
GABA	γ-aminobutyric acid
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
GIR	Glucose infusion rate
glinide	A rapid-acting insulin secretagogue
HbA1c	Hemoglobin A1c
HCP	Host cell protein
HEK293 cells	Human embryonic kidney 293 cells

hERG	Human ether-a-go-go related gene
HI	Human insulin
hIR	Human insulin receptor
hIR-A	Human insulin receptor type A
hIR-B	Human insulin receptor type B
HLT	High level terms
HMEC	Human mammary epithelial cell
HMWP	High molecular weight protein
HPLC-RAD	High performance liquid chromatography-radioactivity detection
HSA	Human serum albumin
IAsp	Insulin Aspart (genetical recombination)
ICH-Q5B guideline	Analysis of the Expression Construct in Cells Used for Production of r-DNA Derived Protein Products (PMSB/ELD Notification No. 3 dated January 6, 1998)
ICH-Q5D guideline	Derivation and Characterisation of Cell Substrates Used for Production of Biotechnological/Biological Products (PMSB/ELD Notification No. 873 dated July 14, 2000)
IC_{50}	Half maximal inhibitory concentration
IDeg	Insulin Degludec (genetical recombination)
IDet	Insulin Detemir (genetical recombination)
IGlar	Insulin Glargine (genetical recombination)
insulin icodec	Insulin Icodec (genetical recombination)
IR	insulin receptor
[redacted]	[redacted]
LEC	Late extended culture
LOCI	Luminescent oxygen channeling immunoassay
MACE	Major adverse cardiovascular events
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MCB	Master cell bank
[redacted]	[redacted]
NPH insulin	Neutral protamine Hagedorn insulin
NZW	New Zealand White
PG_{nadir}	Plasma glucose concentration at nadir
PMDA	Pharmaceuticals and Medical Devices Agency
PT	Preferred terms
(Q)SAR	(Quantitative) Structure-Activity Relationship
RIA	Radioimmunoassay
[redacted]	[redacted]
[redacted]-UHPLC	[redacted]-ultra high performance liquid chromatography
S. cerevisiae	*Saccharomyces cerevisiae*
SD	Sprague-Dawley
[redacted]-UHPLC	[redacted]-ultra high performance liquid chromatography

SGLT2	Sodium glucose co-transporter type 2
SMBG	Self-measured blood glucose
SMQ	Standardised MedDRA queries
SOC	System organ class
SPA	Scintillation proximity assay
SPR	Surface plasmon resonance
SU	Sulfonylurea
TAR	Time above the range
TBR	Time below the range
The product	Awiqli Injection FlexTouch
TIR	Time in range
t_{max}	Time to reach the maximum drug plasma/serum concentration following drug administration
$t_{1/2}$	Elimination half life
V/F	Apparent volume of distribution
WCB	Working cell bank
ZDF rat	Zucker diabetic fatty rat