Report on the Deliberation Results

September 7, 2012

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

[Brand name]	Tresiba FlexTouch, Tresiba Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination) (JAN*)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	December 22, 2011

[Results of deliberation]
In the meeting held on August 31, 2012, the First Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

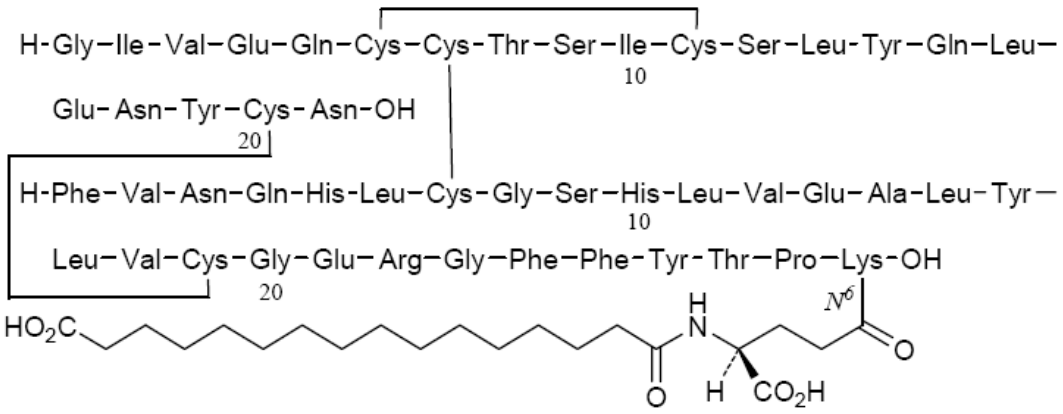
**Japanese Accepted Name (modified INN)*

Review Report

August 16, 2012
Pharmaceuticals and Medical Devices Agency

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

[Brand name] (a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name] Insulin Degludec (Genetical Recombination)
[Name of applicant] Novo Nordisk Pharma Ltd.
[Date of application] December 22, 2011
[Dosage form/Strength] (a) Solution for injection: One pre-filled pen (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).
(b) Solution for injection: One cartridge (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).
[Application classification] Prescription drug (1) Drug with a new active ingredient
[Chemical structure]



Molecular formula: $C_{274}H_{411}N_{65}O_{81}S_6$
Molecular weight: 6103.97
Chemical name: Insulin Degludec (Genetical Recombination)

[Items warranting special mention] None
[Reviewing office] Office of New Drug I

Review Results

August 16, 2012

[Brand name] (a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name] Insulin Degludec (Genetical Recombination)
[Name of applicant] Novo Nordisk Pharma Ltd.
[Date of application] December 22, 2011
[Results of review]
Based on the submitted data, the efficacy of the product in patients with diabetes mellitus who require insulin has been demonstrated and its safety is acceptable in view of its observed benefits. The occurrence of hypoglycaemia, injection site reactions, and anaphylactic reactions etc. and the safety of the product in elderly patients, patients with renal impairment, and patients with hepatic impairment need to be further investigated via post-marketing surveillance.

As a result of its regulatory review, the Pharmaceuticals and Medical Devices Agency has concluded that the product may be approved for the following indication and dosage and administration.

[Indication]
Diabetes mellitus where treatment with insulin is required

[Dosage and administration]
(a) The usual initial adult dosage is 4 to 20 units of Insulin Degludec administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.
(b) The usual initial adult dosage is 4 to 20 units of Insulin Degludec administered subcutaneously once daily, using a specific insulin pen device. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

Review Report (1)

July 9, 2012

I. Product Submitted for Registration

[Brand name] (a) Tresiba FlexTouch, (b) Tresiba Penfill

[Non-proprietary name] Insulin Degludec (Genetical Recombination)

[Name of applicant] Novo Nordisk Pharma Ltd.

[Date of application] December 22, 2011

[Dosage form/Strength] (a) Solution for injection: One pre-filled pen (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).

(b) Solution for injection: One cartridge (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).

[Proposed indication] Diabetes mellitus where treatment with insulin is required

[Proposed dosage and administration]

(a) Insulin Degludec should be injected subcutaneously once daily. It may be used in combination with other insulin products. The usual initial adult dosage is 4 to 20 units of Insulin Degludec administered once daily. The dose should be adjusted according to the patient's symptoms and test results. Typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

(b) Insulin Degludec should be injected subcutaneously once daily, using a specific insulin pen device. It may be used in combination with other insulin products. The usual initial adult dosage is 4 to 20 units of Insulin Degludec administered once daily. The dose should be adjusted according to the patient's symptoms and test results. Typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

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

The data submitted in the application and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

The proposed product is a solution for injection containing a long-acting insulin analog, Insulin Degludec (Genetical Recombination) (hereinafter, "insulin degludec") as an active ingredient

(hereinafter, the drug product is referred to as "IDeg"). Removal of threonine at position 30 of the B chain of human insulin and the addition of hexadecanedioic acid attached to lysine at position 29 of the B chain of human insulin via a γ-glutamic acid spacer result in the insulin degludec molecule. Insulin degludec has a partially modified structure of insulin detemir (genetical recombination), the active ingredient of a long-acting insulin analog product marketed by the applicant, and forms soluble and stable multi-hexamers in the subcutaneous tissue after injection. Monomers gradually dissociate from the multi-hexamers and are continuously absorbed into the blood circulation. The fatty acid moiety of insulin degludec is able to bind to albumin, thereby further contributing to a prolonged action profile. As described above, insulin degludec was developed, expecting that it would have a longer and more stable action profile than current long-acting insulin analogs. The applicant claims that the efficacy and safety of insulin degludec in patients with diabetes mellitus who require insulin have now been demonstrated, and have filed a marketing application for the product.

Insulin degludec is unlicensed overseas as of June 2012 and under regulatory review in the EU, the US (filed in September 2011 both in the EU and the US), and [redacted] other countries.

In Japan, as long-acting insulin analogs, insulin glargine (genetical recombination) was approved in October 2003 and insulin detemir (genetical recombination) in October 2007.

2. Data relating to quality

2.A *Summary of the submitted data*

2.A.(1) Drug substance

2.A.(1).1) Generation and control of the cell substrate

Saccharomyces cerevisiae (*S. cerevisiae*) was transformed with a plasmid constructed for the expression of a precursor-insulin, and an initial cell clone (ICC), a master cell bank (MCB), and a working cell bank (WCB) were prepared.

The MCB and WCB were characterized (specification tests: microbiological purity, viability, identity [phenotype], identity [HPLC], restriction endonuclease mapping; supplementary tests [[redacted] only]: DNA sequence analysis, plasmid copy number, plasmid loss, strain identification) and found to meet their acceptance criteria for all tests conducted. The appropriate storage conditions for the MCB and WCB have been established. A new MCB or WCB is generated as needed.

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

The drug substance manufacturing process comprises inoculation and growth, seed fermentation, main fermentation, clarification of fermentation broth ([redacted]), [redacted] chromatography, cleavage, [redacted] crystallization ([redacted]), [redacted] liquid chromatography ([redacted] and [redacted]), [redacted] crystallization ([redacted]), acylation, [redacted] chromatography,

[redacted] liquid chromatography ([redacted]), precipitation, [redacted] filtration, [redacted] drying, and mixing. The concentrate is filtered and [redacted] dried to obtain the drug substance, which is transferred to plastic containers and stored frozen.

Cleavage, [redacted] liquid chromatography ([redacted] and [redacted]), acylation, [redacted] chromatography, and [redacted] liquid chromatography ([redacted]) have been defined as critical steps. Process validation (PV) of the commercial-scale manufacturing process for the drug substance has demonstrated that each process step is adequately controlled.

2.A.(1).3) Manufacturing process development (Comparability)

Major changes made to the drug substance manufacturing process during development are as shown in Table 1 and Process [redacted] is the proposed commercial production process.

Table 1. Major changes made to the manufacturing process

Manufacturing process	Process changes
Process [redacted] → Process [redacted]	• Purification process ・Solvent for dilution after the completion of [redacted] ・Load for [redacted] chromatography ・Load for [redacted] liquid chromatography
Process [redacted] → Process [redacted]	• Cell strain • Precursor-insulin • Plasmid • Medium [redacted] • Recovery process ・Addition of [redacted] step to [redacted] ・Type of [redacted] chromatography ・Cleavage step [redacted] ・[redacted] crystallization and [redacted] filtration → [redacted] crystallization
Process [redacted] → Process [redacted]	• Purification process ・Introduction of [redacted] crystals at [redacted] in [redacted] step ・Solvent and conditions for [redacted] chromatography ・[redacted] ([redacted]) fillers ・Introduction of [redacted] filtration
Process [redacted] → Process [redacted]	• Recovery process ・Omission of [redacted] ・Omission of [redacted] chromatography ・Type of [redacted] chromatography ・Cleavage step [redacted] ・[redacted] filtration and [redacted] crystallization • Purification process ・Conditions for [redacted] step

In the clinical and non-clinical studies submitted in the application, the drug products derived from the drug substances produced from Process [redacted] through Process [redacted] were used. The quality attributes of the drug substances before and after changes made in the manufacturing process were evaluated, which demonstrated comparability between pre-change and post-change drug substances.

2.A.(1).4) Characterization

(a) Structure/Composition

The primary structure of insulin degludec was elucidated by N-terminal sequencing by Edman degradation, which confirmed that insulin degludec has the amino acid sequence identical to the theoretical sequence and that a side chain is attached to the amino acid residue at position B29 via an

amino acid spacer. As expected, four peaks corresponding to peptides after enzymatic digestion were detected by peptide MS mapping, confirming the correct primary structure and the positions of disulfide bonds. The theoretical monoisotopic mass as determined by matrix-assisted laser desorption-ionization time-of-flight mass spectrometry (MALDI-TOF MS) was [redacted] Da.

The higher-order (secondary and tertiary) structure of the protein was confirmed by far- and near-ultraviolet circular dichroism spectra.

(b) Physicochemical properties

The solubility of the drug substance in water, methanol, and ethanol and the pH of a high-concentration drug substance aqueous solution used in solubility tests were determined.

The isoelectric point of insulin degludec was approximately [redacted] as determined by isoelectric focusing. The ultraviolet absorption spectrum of the drug substance showed a maximum absorption at [redacted] nm and no absorption at wavelengths longer than [redacted] nm, confirming that the protein has a high purity.

According to the determination of water absorption properties, insulin degludec is hygroscopic and its equilibrium water content was [redacted]% to [redacted]% at [redacted]°C/[redacted]%RH. Also, water absorption increased in a linear fashion at [redacted]% to [redacted]%RH and increased slightly more than linearly at ≥[redacted]%RH.

The hydrophobic properties of insulin degludec were confirmed by RP-HPLC using two different solid supports. The hydrodynamic properties of insulin degludec were confirmed by gel permeation chromatography.

(c) Biological properties

Biological activity assay using [redacted] ([redacted]) showed that human insulin [redacted].

(d) Product-related substances

Hydrophobic related substances that are measured by RP-HPLC ([redacted] isomers of insulin degludec, insulin degludec with [redacted] side chain, [redacted] insulin degludec, [redacted] insulin degludec, [redacted] insulin degludec) were identified as product-related substances.

(e) Impurities

i) Process-related impurities

Host cell proteins (HCP), host cell DNA, [redacted] peptide, [redacted] peptide, [redacted] peptide, [redacted], acylation reagent ([redacted]), [redacted] acylation reagent ([redacted]), [redacted] ([redacted]), [redacted] ([redacted]), ethanol, [redacted],

ammonium, [redacted], potassium, sulfate, Tris, [redacted], [redacted], total microbial counts, and endotoxins were identified as process-related impurities. It has been confirmed that all of the process-related impurities are consistently and adequately removed in the manufacturing process. HCP content is controlled by [redacted] for the drug substance.

ii) Product-related impurities

Insulin [redacted], [redacted] insulin, [redacted] insulin, [redacted] form of [redacted] insulin, [redacted] insulin [redacted], a compound with [redacted] peptide ([redacted]), [redacted] insulin, [redacted] insulin, [redacted] insulin, [redacted] insulin, other [redacted] insulin related impurities, [redacted] insulin, and [redacted] insulin (up to Step [redacted]) and [redacted] insulin, [redacted] of insulin degludec, [redacted] insulin degludec, [redacted] form of insulin degludec, [redacted] and [redacted] insulin degludec, and [redacted] of insulin degludec (from Step [redacted] through Step [redacted]) were identified as product-related impurities. It has been confirmed that all of the product-related impurities are consistently and adequately removed in the manufacturing process.

2.A.(1).5) Control of drug substance

The proposed specifications for the drug substance include content (substance content), description, identification (peptide mapping, RP-HPLC), purity ([redacted] impurities,[1] [redacted] impurities,[2] [redacted] related substances [RP-HPLC], high molecular weight proteins [gel permeation chromatography]), loss on drying, bacterial endotoxins (chromogenic technique), microbial limits (pour plate method), biological activity ([redacted]), and assay (RP-HPLC).

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

Primary stability studies on the drug substance are as shown in Table 2.

Table 2. Overview of primary stability studies on drug substance

Study	Manufacturing process	No. of lots	Storage condition	Storage package	Storage period
Long-term	Process [redacted]	3	[redacted]±[redacted]°C	Plastic containers with plastic screw-caps	[redacted] months[redacted]
Accelerated	Process [redacted]	3	[redacted]±[redacted]°C		[redacted] months

a) Long-term stability studies on 3 drug substance lots produced by Process [redacted], 3 drug substance lots for PV, and 3 drug substance lots for PV have been completed up to [redacted] months, [redacted] months, and [redacted] months, respectively.
b) Accelerated stability studies on 3 drug substance lots produced by Process [redacted], 3 drug substance lots for PV, and 3 drug substance lots for PV have been completed up to [redacted] months, [redacted] months, and [redacted] months, respectively.
c) The stability studies are ongoing.

Using 6 commercial-scale drug substance lots produced by Process [redacted] (Campaign [redacted]) and Process [redacted] (Campaign [redacted]), long-term ([redacted]±[redacted]°C, [redacted] months) and accelerated ([redacted]±[redacted]°C, [redacted] months) stability studies were performed on 3 lots as studies [redacted] and long-term ([redacted]±[redacted]°C, [redacted] months) and accelerated ([redacted]±[redacted]°C, [redacted] months) stability studies were performed on 3 lots as studies [redacted].

[1] [redacted] of insulin degludec, [redacted] insulin degludec, [redacted] insulin degludec, [redacted] insulin degludec, insulin degludec with [redacted] and [redacted], [redacted] insulin degludec, and [redacted] insulin degludec

[2] Impurities of insulin degludec with high [redacted], [redacted], [redacted], and [redacted]

The attributes tested include appearance, assay (substance), [redacted] impurities, [redacted] related substances, [redacted] impurities (RP-HPLC), high molecular weight proteins (gel permeation chromatography), biological activity ([redacted]), and loss on drying. As a result, at the long-term and accelerated conditions, the acceptance criteria were met for all attributes tested, except that 1 lot failed to meet the specification for biological activity at [redacted] months in the accelerated study. There were also no changes in content or loss on drying.

Based on the above, a shelf-life of [redacted] months was established for the proposed drug substance when stored in tight containers at [redacted]±[redacted]°C, protected from light. The long-term stability study on the proposed drug substance will continue for up to [redacted] months.

2.A.(2) Drug product

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

The insulin degludec 100 U/mL formulation (the drug product) is a clear colorless solution for subcutaneous injection containing 600 nmol/mL of the drug substance. The drug product contains an isotonizing agent (glycerol), a stabilizer (zinc acetate), preservatives (phenol and m-cresol), and a solvent (water for injection). The drug product is packaged in a 3 mL Penfill cartridge made of glass (primary packaging). One end of the cartridge is closed with a latex-free [redacted] rubber/synthetic [redacted] rubber disc and the other end is closed with a red [redacted] rubber plunger. The 3 mL Penfill cartridge is assembled into a pre-filled disposable device, a PDS290 pen-injector (secondary packaging), or used in the approved Novo Nordisk pen-injector device (replaceable cartridge type).

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

The drug product manufacturing process comprises formulation, sterile filtration, filling, inspection, testing, storage, assembly, labeling, packaging, inspection, and storage. Formulation, sterile filtration, and filling have been defined as critical steps. Process validation of the commercial-scale manufacturing process has demonstrated that each process step is adequately controlled.

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

Formulation and manufacturing site changes occurred during the drug product development. Based on the results from releases testing, stability studies, and clinical trials, pre-change and post-change drug products were determined to be comparable.

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

The proposed specifications for the drug product include content (insulin degludec content, [redacted]), description, identification (insulin degludec, m-cresol, phenol [RP-HPLC]), pH, purity ([redacted] impurities, [redacted] related substances, and [redacted] impurities [RP-HPLC], high molecular weight

proteins [gel permeation chromatography]), m-cresol and phenol (RP-HPLC), bacterial endotoxins, sterility, foreign insoluble matter, insoluble particulate matter, dose accuracy[3] (measured by weighing), and assay (insulin degludec [RP-HPLC], [ ]).

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

Primary stability studies on the drug product are as shown in Table 3.

Table 3. Overview of primary stability studies on drug product

Stability study	Manufacturing process for drug substance	No. of lots	Storage condition	Storage package	Storage period
Long-term	Process	3	5 ± 3°C	Primary packaging (3 mL Penfill cartridge) and carton	36 months
	Process	3	5 ± 3°C		months[a)]
Accelerated	Process	3	25 ± 2°C		6 months
	Process	3	25 ± 2°C		6 months
Photostability	Process	1	25 ± 2°C, an overall illumination of approximately lx·hr and an integrated near ultraviolet energy of W·h/m^2	Primary packaging (3 mL Penfill cartridge), Secondary packaging (PDS290 pre-filled pen, blister pack, carton)	—
	Process	1			—

a) The stability study is ongoing.

At the long-term conditions (5 ± 3°C/ambient humidity/dark place, 36 months and months), there were no major changes for all attributes tested throughout the study period.

At the accelerated conditions (25 ± 2°C/ambient humidity/dark place, 6 months), while in high molecular weight proteins, impurities, related substances, and impurities were observed, there were no changes for other attributes tested.

In the photostability studies (25 ± 2°C, an overall illumination of approximately lx·hr and an integrated near ultraviolet energy of W·h/m^2), the primary packaged drug product was not sufficiently stable when exposed to light, compared with when protected from light.

Based on the above, a shelf-life of 30 months was established for the proposed drug product when stored in sealed containers at 2°C to 8°C (avoid freezing), protected from light. The long-term stability study on the proposed drug product will continue for up to months.

2.A.(3) Reference materials

As a primary reference material, the drug substance is weighed into containers, sealed with closures, and stored at ≤°C. The shelf-life of the primary reference material and the procedures for extending the shelf-life based on stability studies and statistical evaluation have been established. The proposed specifications for the primary reference material are identification (and), impurities, related substances,

[3] Tresiba FlexTouch only

impurities, [redacted], homogeneity (relative standard deviation of area between containers), and content (insulin degludec Substance Content, [redacted]% confidence interval [CI] for the mean content).

As a secondary reference material, a drug substance solution is filled into [redacted] mL cartridges that serve as primary packaging and stored [redacted] at ≤[redacted]°C. The specifications for the secondary reference material are the same as those for the primary reference material, but [redacted]. The shelf life of the secondary reference material is also extended based on stability studies and statistical evaluation.

2.B *Outline of the review by PMDA*

2.B.(1) Comparability of drug substances before and after manufacturing process changes during development

PMDA asked the applicant to explain whether the tests conducted were adequate to assess the comparability of drug substances before and after manufacturing process changes.

The applicant responded as follows:

As a result of drug substance comparability studies for manufacturing process changes, the theoretical structure and expected physicochemical properties of the drug substance were confirmed by N-terminal sequencing, peptide MS map, [redacted] spectrum ([redacted] spectrum), biological activity, mass spectrum, isoelectric focusing, RP-HPLC, gel permeation chromatography, and [redacted] chromatography. The impurity profiles of different campaign lots were evaluated for comparability assessment. As a result, purity was improved on the whole and no new impurities were detected in drug substance lots produced for phase [redacted] trials (Campaign [redacted] using Process [redacted], Campaigns [redacted] and [redacted] using Process [redacted]) compared with drug substance lots used in phase [redacted] and phase [redacted] trials and non-clinical studies (Campaign [redacted] using Process [redacted], Campaign [redacted] using Process [redacted], Campaign [redacted] using Process [redacted]). Also when analyzed by [redacted] different RP-HPLC methods, the impurity profile of [redacted] insulin intermediate was similar among different campaign lots. In addition to comparison of impurity profiles, in-process control data for process-related impurities and purified [redacted] insulin intermediate and release batch data on drug substance were evaluated, which demonstrated comparability with Campaign [redacted] drug substance lots. Similar outcomes were obtained also in stability studies on purified [redacted] insulin intermediate and drug substance.

PMDA considers that it may be concluded that comparability between pre-change and post-change drug substances has been demonstrated by comparison of structural characterization, physicochemical properties, impurity profiles, etc.

2.B.(2) Biological activity

The applicant claims that the biological activity ([redacted]) of the drug substance is [redacted] and biological activity can be assured by measuring Substance Content. PMDA asked the applicant to explain a correlation between biological activity ([redacted]) and Substance Content and a relationship between biological activity and insulin degludec content.

The applicant responded as follows:

Using the samples of drug substance subjected to forced degradation under extreme conditions of [redacted], [redacted], [redacted], [redacted], [redacted], or [redacted] treatment, the correlation between biological activity and Substance Content was investigated. As a result, the correlation coefficient (biological activity/Substance Content) was around [redacted], demonstrating [redacted] correlation. As to a relationship between biological activity and the content of insulin degludec excluding [redacted], as with Substance Content, insulin degludec content was [redacted] correlated with biological activity when purity was high and correlation [redacted] with decreasing purity. The impurities and degradation products of insulin degludec were [redacted] and assayed for biological activity, which demonstrated [redacted]. Therefore, the result suggested that the content of insulin degludec only, excluding [redacted], does not properly reflect biological activity and Substance Content is more [redacted] correlated with biological activity. Based on the above investigations, and taking into account that [redacted] limits for the impurities and degradation products of insulin degludec will be controlled separately by the specifications, it is appropriate to assure biological activity by measuring substance content.

PMDA considers as follows:

There is a correlation between biological activity and Substance Content. Since biological activity can be assured by measuring Substance Content and performing purity tests, biological activity may be [redacted].

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

Primary pharmacodynamic studies investigated the mode of action *in vitro* and the blood glucose-lowering effect etc. of insulin degludec *in vivo* in animal models of diabetes. A secondary pharmacodynamic study investigated the receptor selectivity of insulin degludec. Safety pharmacology studies to assess the effects of insulin degludec on the central nervous system, cardiovascular system, and respiratory system were conducted in compliance with GLP. Study 204275 that assessed the effects of insulin degludec on the cardiovascular system in conscious dogs was a non-GLP study. No pharmacodynamic drug interaction studies have been performed.

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

3.(i).A.(1).1) *In vitro* studies

3.(i).A.(1).1).(a) Insulin receptor binding affinity (4.2.1.1.1, 4.2.1.1.3-6)

The binding affinity of insulin degludec or human insulin against [^{125}I]-human insulin in membranes from baby hamster kidney (BHK) cells expressing the two solubilized human insulin receptor (hIR) isoforms (hIR-A and hIR-B) was determined in the absence of human serum albumin (HSA). As a result, the K_d values of insulin degludec for hIR-A and hIR-B (mean ± standard deviation [SD]) were 150 ± 20 and 60 ± 21 pmol/L, respectively, and the K_d values of human insulin were 19 ± 4 and 9 ± 3 pmol/L, respectively. The binding affinities of insulin degludec were 13% and 15%, respectively, relative to human insulin.

The binding affinity of insulin degludec or human insulin against [^{125}I]-human insulin in membranes from BHK cells expressing recombinant human, porcine, and rat IR-A and IR-B was determined in the presence of 0.1% HSA. As a result, the IC_{50} values of insulin degludec for human IR-A and IR-B with their 95% confidential intervals (CIs) were 7.5 [5.6, 10] and 13 [11, 15] nmol/L, respectively, and the IC_{50} values of human insulin with their 95% CIs were 0.31 [0.21, 0.48] and 0.40 [0.33, 0.49] nmol/L, respectively. The IC_{50} values of insulin degludec for porcine IR-A and IR-B with their 95% CIs were 7.5 [3.3, 17] and 8.6 [4.5, 16] nmol/L, respectively, and the IC_{50} values of human insulin with their 95% CIs were 0.32 [0.28, 0.35] and 0.39 [0.20, 0.75] nmol/L, respectively. The IC_{50} values of insulin degludec for rat IR-A and IR-B with their 95% CIs were 30 [28, 31] and 22 [15, 31] nmol/L, respectively, and the IC_{50} values of human insulin with their 95% CIs were 0.68 [0.48, 0.97] and 0.65 [0.25, 1.7] nmol/L, respectively. The human IR-A and IR-B binding affinities of insulin degludec were 4.2% and 3.2%, respectively, relative to human insulin; the porcine IR-A and IR-B binding affinities of insulin degludec were 4.2% and 4.5 %, respectively, relative to human insulin; and the rat IR-A and IR-B binding affinities of insulin degludec were 2.3% and 3.0%, respectively, relative to human insulin.

Furthermore, using human, canine, porcine, and rat liver membrane IRs, the binding affinity of insulin degludec or human insulin against [^{125}I]-human insulin was determined in the presence of 0.1% HSA. As a result, the binding affinities of insulin degludec with its 95% CIs were 3.5% [1.5, 8.2], 7.0% [4.2, 11], 3.6% [2.3, 3.8], and 3.3% [1.3, 4.8], respectively, relative to human insulin.

The association constants of [^{125}I]-insulin degludec and [^{125}I]-human insulin for IR (mean ± standard error [SE]) in BHK cells expressing hIR-A were 0.0222 ± 0.0026 and 0.0239 ± 0.0024 min^{-1}, respectively, and for two binding sites, the fast dissociation constants were 0.1055 ± 0.0255 and 0.1232 ± 0.0557 min^{-1}, respectively, and the slow dissociation constants were 0.0139 ± 0.0081 and 0.0181 ± 0.0081 min^{-1}, respectively.

3.(i).A.(1).1).(b) IGF-1R binding affinity (4.2.1.1.1-2, 4.2.1.1.19)

The binding affinities of insulin degludec, hIGF-1, and human insulin against [^{125}I]-hIGF-1 in membranes from BHK cells expressing the human IGF-1 receptor (hIGF-1R) were determined in the absence of HSA. As a result, the K_d values (mean ± SD) were 102,000 ± 62,000, 50 ± 11, and 2100 ± 600 pmol/L, respectively, and the binding affinities of insulin degludec were 0.05% relative to hIGF-1 and 2.0% relative to human insulin. When the hIGF-1R binding affinities of insulin degludec, IGF-1, and human insulin were determined in the presence of 0.1% HSA, the IC_{50} values with their 95% CIs were 51,700 [20,000, 126,000], 0.43 [0.18, 1.0], and 212 [123, 372] nmol/L, respectively, and the binding affinity of insulin degludec was 0.4% relative to human insulin. When the binding affinities of insulin degludec in membranes from BHK cells expressing rat and dog IGF-1R were determined in the presence of 0.1% HSA, the binding affinities of insulin degludec were 1.2% and 0.7%, respectively, relative to human insulin.

3.(i).A.(1).1).(c) Receptor activation (4.2.1.1.7, 4.2.1.1.9)

In order to examine IR tyrosine autophosphorylation and protein kinase B (PKB) phosphorylation, one of the signaling cascades after stimulation of the insulin receptor, L6-myoblasts over-expressing hIR (L6-hIR cells) were stimulated with insulin degludec or human insulin in the presence of 0.1% HSA for 10 minutes. As a result, insulin degludec dose-dependently increased the hIR autophosphorylation and PKB phosphorylation effect, and its dose-response curves were similar to those of human insulin, but shifted to higher doses compared with those of human insulin. The potencies of insulin degludec in stimulating hIR autophosphorylation and PKB phosphorylation relative to human insulin with their 95% CIs were 15.5% [10.6, 22.6] and 24.5% [20.7, 29.2], respectively. Since insulin degludec had the same maximum response as human insulin, it was inferred that insulin degludec is a full agonist.

CHO cells over-expressing hIR were stimulated with 1000 nmol/L of insulin degludec or 10 nmol/L of human insulin for 30 minutes. As a result, the initial value of phosphorylation immediately after hIR stimulation was comparable between human insulin and insulin degludec and the rate of activation signal decline (% of the initial value over time) was similar between insulin degludec and human insulin.

3.(i).A.(1).1).(d) Biological response (4.2.1.1.8, 4.2.1.1.10-14)

i) Metabolism in adipocytes

Isolated primary adipocytes prepared from the epididymal fat pads of rats were stimulated with both [^{3}H]-glucose and insulin degludec or human insulin, in the presence of 1% HSA, for 2 hours. Then, lipids were extracted and [^{3}H]-glucose incorporation was measured. As a result, lipogenesis was promoted and the EC_{50} values of insulin degludec and human insulin (mean ± SD) were 3782.9 ± 1363.8 and 21.4 ± 6.0 pmol/L, respectively. The potency of insulin degludec in stimulating lipogenesis

with its 95% CI was 0.55% [0.52, 0.58] relative to human insulin. Since insulin degludec had similar maximum response as human insulin, it was inferred that insulin degludec is a full agonist.

Adipocytes derived from the stromal fraction of subcutaneous adipose tissue of an infant with Simpson-Golabi-Behmel syndrome (SGBS cells[4]) were stimulated with [^{14}C]-glucose and insulin degludec or human insulin, in the presence of 1% HSA and in the presence or absence of cytochalasin B, for 4 hours, and then [^{14}C]-glucose uptake into cells was measured. Insulin-dependent glucose uptake was calculated by subtracting insulin-independent glucose uptake in the presence of cytochalasin B from glucose uptake in the absence of cytochalasin B. As a result, insulin degludec and human insulin promoted glucose uptake and the EC_{50} values of insulin degludec and human insulin with their 95% CIs were 6683 [4870, 9171] and 98 [75, 128] pmol/L, respectively, and the potency of insulin degludec in promoting glucose uptake with its 95% CI was 1.47% [1.07, 2.01] relative to human insulin.

SGBS cells were stimulated with isoproterenol (10 nmol/L) and insulin degludec or human insulin, in the presence of 1% HSA for 4 hours and then, in order to measure the amount of glycerol released into the medium from the cells, the amount of ATP consumed when glycerol was converted to glycerophosphate by glycerol kinase was measured. In addition, free fatty acids released into the medium were measured. As a result, insulin degludec and human insulin inhibited glycerol release and free fatty acid release, and the IC_{50} values of insulin degludec and human insulin with their 95% CIs were 760 [534, 1083] and 14 [10, 19] pmol/L, respectively, for the inhibition of glycerol release and 1164 [909, 1491] and 20 [16, 25] pmol/L, respectively, for the inhibition of free fatty acid release. The potencies of insulin degludec in inhibiting glycerol release and free fatty acid release with their 95% CIs were 1.81% [1.27, 2.58] and 1.73% [1.35, 2.22], respectively, relative to human insulin.

ii) Metabolism in hepatocytes

Primary hepatocytes isolated from male rats were stimulated with insulin degludec or human insulin in the presence of various concentrations of HSA (0%, 0.1%, 0.5%, 1%) for 18 to 24 hours, and then, glycogen content in hepatocytes was determined. Primary hepatocytes isolated from male rats were preincubated with glucagon (0.1 nmol/L) and glucose (1.5 mmol/L) in the presence of 0.1% HSA for 2 hours, and then, stimulated with insulin degludec or human insulin in the presence of 0.1% HSA for 2 hours to measure the mRNA level of phosphoenolpyruvate carboxykinase (PEPCK), a rate-limiting enzyme in gluconeogenesis.[5] As a result, like human insulin, insulin degludec promoted glycogen accumulation and the EC_{50} values of insulin degludec for promotion of glycogen accumulation in the presence of 0%, 0.1%, 0.5%, and 1% HSA (mean ± SE) were 2.6 ± 0.3, 8.0 ± 1.3, 13.5 ± 4.2, and 92.4 ± 61 nmol/L, respectively, and the EC_{50} values of human insulin were 0.50 ± 0.08, 0.67 ± 0.18, 0.55 ±

[4] Fully-differentiated adipocytes

[5] The relative abundance of PEPCK mRNA in rat liver RNA was determined and normalized to 18srRNA.

0.14, and 0.62 ± 0.12 nmol/L, respectively. The potencies of insulin degludec in stimulating glycogen accumulation were 21.3 ± 4.4%, 10.1 ± 4.5%, 4.5 ± 1.2%, and 3.3 ± 1.6%, respectively, relative to human insulin. Since insulin degludec had similar maximum response as human insulin, it was inferred that insulin degludec is a full agonist.

As with human insulin, insulin degludec inhibited PEPCK expression, and the IC_{50} values of insulin degludec and human insulin in the presence of 0.1% HSA were 0.11 and 0.01 nmol/L, respectively, and the potency of insulin degludec in inhibiting PEPCK expression (mean ± SE) was 13.4 ± 2.1% relative to human insulin.

iii) Metabolism in muscle cells

Immortalized human skeletal muscle cells and primary skeletal muscle cells prepared from rats (satellite cells) were stimulated with [^{14}C]-glucose and insulin degludec or human insulin in the presence of 0.1% HSA for 2 hours, and then, glycogen synthesis was measured. As a result, the potencies of insulin degludec in stimulating glycogen synthesis in human and primary rat skeletal muscle cells with their 95% CIs, were 4.39% [3.20, 6.03] and 3.86% [2.58, 5.77], respectively, relative to human insulin.

Immortalized human skeletal muscle cells were stimulated with [^{14}C]-glucose and insulin degludec or human insulin in the presence of 0.1% or 0.5% HSA for 2 hours and then glycogen synthesis was measured. As a result, the EC_{50} values of insulin degludec and human insulin with their 95% CIs were 793 [646, 1291] and 50 [36, 71] nmol/L, respectively, in the presence of 0.1% HSA and 3479 [2258, 5360] and 26 [17, 39] nmol/L, respectively, in the presence of 0.5% HSA. The potencies of insulin degludec in stimulating glycogen synthesis were 5.5% [3.9, 7.8] relative to human insulin in the presence of 0.1% HSA and 0.7% [0.4, 1.0] relative to human insulin in the presence of 0.5% HSA. Since insulin degludec had similar maximum response as human insulin in human and primary rat skeletal muscle cells, it was inferred that insulin degludec is a full agonist.

Moreover, L6-hIR cells over-expressing hIR were stimulated with [^{14}C]-glucose and various concentrations of insulin degludec or human insulin in the presence of 0.1% HSA for 2 hours, and then, incorporation of glucose into glycogen was measured. As a result, the EC_{50} values of insulin degludec and human insulin for promotion of glycogen synthesis (mean ± SE) were 51.5 ± 15.0 and 6.7 ± 1.3 pmol/L, respectively, and the potency of insulin degludec in stimulating glycogen synthesis with its 95% CI, was 11.5% [8.8, 15.2] relative to human insulin. Insulin degludec had similar maximum response as human insulin.

iv) Metabolism in MCF-7 cells

For comparison of the metabolic and mitogenic potencies of insulin degludec, the MCF-7 human breast cancer cell line, which proliferates in response to insulin, was stimulated with [^{14}C]-glucose and various concentrations of insulin degludec or human insulin in the presence of 0.1% fetal calf serum (FCS) for 3 hours, and then, incorporation of [^{14}C]-glucose into glycogen was measured. As a result, insulin degludec and human insulin dose-dependently stimulated glycogen synthesis in MCF-7 cells. While insulin degludec had similar maximum response as human insulin, the EC_{50} values of insulin degludec and human insulin for stimulation of glycogen synthesis with their 95% CIs were 101.0 [63.25, 161.3] and 7.592 [4.674, 12.33] nmol/L, respectively, which showed that the dose-response curve of insulin degludec was shifted to higher doses. The potency of insulin degludec in stimulating glycogen synthesis with its 95% CI was 7.7% [5.1, 11.8] relative to human insulin.

3.(i).A.(1).1).(e) Mitogenicity (4.2.1.1.20-38)

i) MCF-7 cells

MCF-7 cells were stimulated with various concentrations of insulin degludec, human insulin, insulin X10 (positive control), or human IGF-1 (positive control) in the presence of 0.1% FCS for approximately 24 hours, and then, added with [^{3}H]-thymidine and its incorporation was measured. As a result, the mitogenic potency of insulin degludec was 8.5% (mean) relative to human insulin.

ii) Human mammary epithelial cells

Primary human mammary epithelial cells were stimulated with various concentrations of insulin degludec, human insulin, insulin X10, or human IGF-1 in the absence of albumin for 24 hours, and then, added with [^{3}H]-thymidine and its incorporation was measured. As a result, the mitogenic potency of insulin degludec was 6.6% (mean) relative to human insulin.

iii) Colon adenocarcinoma cells

Human colon adenocarcinoma cells were stimulated with various concentrations of insulin degludec, human insulin, insulin X10, or human IGF-1 in the presence of 0.1% FCS for 24 hours, and then, added with [^{3}H]-thymidine and its incorporation was measured. As a result, the mitogenic potency of insulin degludec was 5.4% (mean) relative to human insulin.

iv) L6-hIR myoblasts

L6-hIR cells were stimulated with various concentrations of insulin degludec, human insulin, insulin X10, or human IGF-1 in the presence of 0.1% FCS for 18 to 20 hours, and then, added with [^{3}H]-thymidine and its incorporation was measured. As a result, the mitogenic potency of insulin degludec was 9.6% (mean) relative to human insulin.

3.(i).A.(1).2) *In vivo* studies

(a) Hyperinsulinemic glucose clamp in rats (4.2.1.1.15)

Normal male rats (n = 5 per group) were catheterized 7 to 9 days before clamp experiments and after overnight fasting, data in the unrestrained state ("basal state") were recorded for 90 minutes. Rats in the insulin degludec group received an intravenous bolus of insulin degludec (2.7 nmol/kg) followed by a 300-minute continuous intravenous infusion of insulin degludec at 15 or 30 pmol/kg/min, while rats in the human insulin group received an intravenous bolus of vehicle[6] (2 mL/kg) followed by a 300-minute continuous intravenous infusion of human insulin at 15 or 30 pmol/kg/min. Likewise, for male Zucker obese rats (n = 4 per insulin degludec dose group, n = 5 per human insulin dose group), data in the basal state were recorded for 90 minutes. After that, rats in the insulin degludec group received an intravenous bolus of insulin degludec (2.7 nmol/kg) followed by a 300-minute continuous intravenous infusion of insulin degludec at 90 or 180 pmol/kg/min, while rats in the human insulin group received an intravenous bolus of vehicle followed by a 300-minute continuous intravenous infusion of human insulin at 45 or 90 pmol/kg/min. In all animals, plasma glucose was continuously measured at 10-minute intervals, the glucose infusion rate (GIR) was adjusted to maintain euglycemia, and GIR during the last hour of the clamp (mean) was assessed. [^{3}H]-glucose was intravenously infused at 0.8 μCi/kg/min and glucose production rate[7] (Ra) and glucose disappearance rate[8] (Rd) were calculated. After 2-deoxy-D-[1-^{14}C]-glucose ([^{14}C]-2DG) was intravenously administered 45 minutes prior to the end of the clamp, blood was sampled repeatedly over time until the end of the clamp. Epididymal and subcutaneous white adipose tissues and muscle tissues (soleus and red and white gastrocnemius muscles) were isolated at the end of the clamp, and glucose uptake in the tissues was measured. Immediately before the start of infusion of insulin degludec or human insulin (0 minutes) and at the end of the clamp (300 minutes), plasma concentrations of insulin degludec and human insulin were determined by enzyme-linked immunosorbent assay (ELISA method) and plasma C-peptide levels were determined by radioimmunoassay (RIA method).

The steady-state GIRs after 300-minute infusions of human insulin at 15 and 30 pmol/kg/min in normal rats (mean ± SE) were 13.6 ± 1.1 and 23.0 ± 1.0 mg/kg/min, respectively, and the steady-state GIRs after 300-minute infusions of insulin degludec at 15 and 30 pmol/kg/min were 8.3 ± 1.8 and 16.0 ± 1.2 mg/kg/min, respectively. The steady-state GIRs after 300-minute infusions of human insulin at 45 and 90 pmol/kg/min in Zucker obese rats were 7.8 ± 0.8 and 13.3 ± 1.7 mg/kg/min, respectively, and the steady-state GIRs after 300-minute infusions of insulin degludec at 90 and 180 pmol/kg/min were 8.3 ± 0.9 and 13.1 ± 2.7 mg/kg/min, respectively. The molar potency of insulin degludec relative to human insulin on GIR, calculated as the horizontal distance between the linear regressions fitted to dose-response semi-log plots, was 65% in normal rats and 47% in Zucker obese rats.

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[6] 0.007% polysorbate 20, 5 mmol/L sodium phosphate (pH 7.4), and 0.1 mol/L sodium chloride

[7] (Sum of endogenous glucose production rate and exogenous glucose infusion rate) − GIR (basal state)

[8] (Sum of endogenous glucose production rate and exogenous glucose infusion rate) − [0.65 (pooled fraction taken) × 270 mL/kg (distribution volume of glucose) × dG/dt (G; plasma glucose concentration [mg/mL])]

As to Ra measured using [^{3}H]-glucose, the difference of clamp state Ra and basal state Ra (ΔRa) in normal rats was -4.9 ± 0.7 and -4.7 ± 0.9 mg/kg/min after infusions of human insulin at 15 and 30 pmol/kg/min, respectively, and -2.7 ± 0.3 and -4.1 ± 0.5 mg/kg/min after infusions of insulin degludec at 15 and 30 pmol/kg/min, respectively. The difference of clamp state Rd and basal state Rd (ΔRd) was 8.3 ± 1.5 and 18.0 ± 1.3 mg/kg/min after infusions of human insulin at 15 and 30 pmol/kg/min, respectively, and 5.6 ± 1.6 and 11.8 ± 1.5 mg/kg/min after infusions of insulin degludec at 15 and 30 pmol/kg/min, respectively. ΔRa in Zucker obese rats was -1.6 ± 0.2 and -2.5 ± 0.4 mg/kg/min after infusions of human insulin at 45 and 90 pmol/kg/min, respectively, and -1.1 ± 1.0 and -2.8 ± 1.0 mg/kg/min after infusions of insulin degludec at 90 and 180 pmol/kg/min, respectively. ΔRd was 6.1 ± 0.7 and 10.1 ± 1.5 mg/kg/min after infusions of human insulin at 45 and 90 pmol/kg/min, respectively, and 7.4 ± 1.5 and 9.7 ± 2.2 mg/kg/min after infusions of insulin degludec at 90 and 180 pmol/kg/min, respectively.

There were no differences in [^{14}C]-2DG uptake in the various skeletal muscle and adipose tissues between human insulin and insulin degludec.

(b) Euglycemic glucose clamp in pigs (4.2.1.1.16-18)

Female pigs fasted overnight (n = 6 in [redacted] insulin degludec hexamer group, n = 7 in the insulin detemir [IDet] group) received a single subcutaneous injection of 216 nmol/pig of [redacted] insulin degludec hexamer ([redacted] mmol/L) or IDet. At the same time, the intravenous infusion rate of a 20% glucose aqueous solution was adjusted for 24 hours to maintain euglycemia and plasma glucose was measured at regular intervals for 60 minutes before and for 24 hours after the start of infusion, and GIR was calculated. As a result, the time to peak activity for [redacted] insulin degludec hexamer was about 6 hours and the duration of action was 18 hours. The blood concentration reached its maximum level at about 5 hours after the start of infusion, and low but quantifiable levels were present between 18 and 24 hours.

Female pigs fasted overnight (n = 8) received a single subcutaneous injection of 216 nmol/pig of [redacted] insulin degludec hexamer ([redacted] or [redacted] mmol/L) or insulin glargine (genetical recombination) (IGlar) (0.6 mmol/L) in a crossover design. The intravenous infusion rate of a 20% glucose aqueous solution was adjusted for 24 hours to maintain fasting plasma glucose levels and plasma glucose was measured at regular intervals for 60 minutes before and for 24 hours after the start of infusion, and GIR was calculated. A 1-week washout period was included between treatments. As a result, the glucose level (mean ± SE) was similar when [redacted] insulin degludec hexamer [redacted] and [redacted] mmol/L and IGlar 0.6 mmol/L were compared, i.e. 4.46 ± 0.13, 4.46 ± 0.07, and 4.40 ± 0.10 mmol/L, respectively, and the GIR profile of [redacted] insulin degludec

hexamer was flatter and more prolonged at [redacted] mmol/L compared with [redacted] mmol/L. The blood concentration profile was also flatter and more prolonged at [redacted] mmol/L compared with [redacted] mmol/L.

Furthermore, female pigs fasted overnight (n = 7) received a single subcutaneous injection of 324 nmol/pig of [redacted] insulin degludec hexamer ([redacted] mmol/L) or [redacted] insulin degludec hexamer ([redacted] mmol/L) (two formulations with different [redacted] contents) in a crossover design, and another 4 female pigs received a single subcutaneous injection of 324 nmol/pig of [redacted] insulin degludec hexamer ([redacted] mmol/L). The intravenous infusion rate of a 20% glucose aqueous solution was adjusted for 24 hours to maintain fasting plasma glucose levels and plasma glucose was measured at regular intervals for 60 minutes before and for 24 hours after the start of infusion, and GIR was calculated. As a result, the glucose level was similar when [redacted] insulin degludec hexamer and [redacted] insulin degludec hexamer were compared, i.e., 4.24 ± 0.14 and 4.22 ± 0.11 mmol/L, respectively, and the glucose level after the injection of [redacted] insulin degludec hexamer was 4.33 ± 0.18 mmol/L. The GIR profiles of [redacted] insulin degludec hexamer and [redacted] insulin degludec hexamer were different and the action profile of [redacted] insulin degludec hexamer was flatter and less peaked than that of [redacted] insulin degludec hexamer. Glucose utilization during the 24 hours after the start of infusion (mean ± SE) was 8037 ± 4319 mg/kg for [redacted] insulin degludec hexamer and 6002 ± 2391 mg/kg for the injection of [redacted] insulin degludec hexamer. The action profile of [redacted] insulin degludec hexamer was found to lie in between those of [redacted] insulin degludec hexamer and [redacted] insulin degludec hexamer and glucose utilization during the 24 hours after the start of infusion was 7529 ± 4576 mg/kg.

3.(i).A.(2) Secondary pharmacodynamics

Receptor selectivity (4.2.1.2.1)

Insulin degludec at 1000 nmol/L did not cause ≥50% inhibition of ligand binding effect (up to 34% inhibition) in 67 different assays of receptors, ion channels, and transporters.

3.(i).A.(3) Safety pharmacology

3.(i).A.(3).1) Effects on central nervous system (4.2.1.3.1)

Male rats (n = 6 per group) received a single subcutaneous injection of insulin degludec (3, 30, 300 nmol/kg), chlorpromazine 5 mg/kg (positive control), or vehicle[9] and behavior was assessed by Irwin test at 2, 4, 6, and 24 hours post-dose. As a result, while treatment-related effects, e.g. hypoactivity and lethargy were observed in the chlorpromazine group, there were no significant behavioral changes during a 24-hour observation period at any dose level of insulin degludec.

[9] 16 mmol/L (1.50 mg/mL) phenol, 16 mmol/L (1.72 mg/mL) m-cresol, 16.0 mg/mL glycerol, 7 mmol/L (1.25 mg/mL) disodium hydrogen phosphate dihydrate, and 10 mmol/L (0.58 mg/mL) sodium chloride (pH = 7.5)

3.(i).A.(3).2) Effects on cardiovascular system (4.2.1.3.2-4)

(a) *In vitro* study

The effects of insulin degludec (10, 100, 1000 nmol/L) or vehicle[10], on action potential parameters in isolated rabbit Purkinje fibers electrically stimulated at frequencies of 0.5 and 1 Hz, were assessed. As a result, insulin degludec at any concentration had no effect on resting membrane potential (RMP), maximum rate of depolarization (MRD), upstroke amplitude (UA), or action potential duration (APD).

(b) *In vivo* studies

Conscious female dogs (n = 5) received a single subcutaneous injection of 24 nmol/kg of insulin degludec or vehicle[9] in a crossover design. At least a 3-day washout period was included between treatments. Blood pressure and electrocardiogram (ECG) were measured at pre-dose and 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, and 24 hours post-dose to obtain systolic blood pressure, diastolic blood pressure, mean arterial pressure, heart rate, and PQ, QRS, and QT intervals. As a result, insulin degludec had no effects on systolic blood pressure, diastolic blood pressure, mean arterial pressure, or ECG parameters (PQ, QRS, and QT intervals) up to 24 hours post-dose. Heart rate tended to increase after the injection of insulin degludec, which was considered associated with decreased blood glucose, but there was no significant difference compared with the control group. While there were no changes in blood glucose at 24 hours after the injection of vehicle, blood glucose was lowered after the injection of insulin degludec (blood glucose level [mean ± SE] was 4.92 ± 0.09 mmol/L before vehicle injection and 5.38 ± 0.12 mmol/L after vehicle injection and blood glucose level was 4.74 ± 0.17 mmol/L before the injection of insulin degludec and 3.04 ± 0.46 mmol/L after the injection of insulin degludec).

Anesthetized, mechanically ventilated, glucose-clamped male dogs (n = 4 in the insulin degludec group, n = 2 in the control group) were treated with three intravenous doses of insulin degludec (4, 8, and 12 nmol/kg, in this order) or vehicle[9] at 60-minute intervals and the effects on ECG (RR, PR, QT, QRS, QTcB, QTcF, QTcV[11]) and arterial pressure, heart rate, and left ventricular pressure were assessed. The cumulative dose of insulin degludec was 24 nmol/kg and the total volume administered was 1.5 mL. As a result, insulin degludec had no effect on ECG or systemic hemodynamics.

3.(i).A.(3).3) Effects on respiratory system (4.2.1.3.5)

Male rats (n = 8 per group) received a single subcutaneous injection of insulin degludec (3, 30, 300 nmol/kg) or vehicle[9] and the effects on respiratory rate, tidal volume, and minute volume were assessed. As a result, insulin degludec at 3 or 30 nmol/kg had no statistically significant effects on the respiratory parameters. At 300 nmol/kg, severe clinical symptoms including decreased respiratory rate

[10] Salt solution containing 0.1% HSA (108.2 mmol/L sodium chloride, 4.0 mmol/L potassium chloride, 1.8 mmol/L calcium chloride, 1.8 mmol/L sodium dihydrogenphosphate, 1.0 mmol/L magnesium chloride, 25 mmol/L sodium bicarbonate, 55 mmol/L D-glucose)

[11] A value calculated using Van de Water's formula (QT interval − 0.087 [RR interval − 1000]).

were observed in 1 rat, 3 rats, and 8 rats before the measurement at 5, 6, and 24 hours post-dose, respectively.Therefore, the study was discontinued for this dose group without performing observation at 24 hours post-dose. The respiratory rate per minute (least square mean) was 74 at 5 hours post-dose and 72 at 6 hours post-dose in the insulin degludec 300 nmol/kg group, showing a significant reduction compared with 111 (at both timepoints) in the control group. The tidal volume (least square mean) was 2.1 mL at 5 hours post-dose and 2.0 mL at 6 hours post-dose, showing a significant increase compared with 1.5 mL (at both timepoints) in the control group. The respiratory minute volume was 136 mL at 6 hours post-dose, showing a significant reduction compared with 158 mL in the control group. The blood glucose levels after the 300 nmol/kg injection, which were measured before the study discontinuation, were 1.3 to 5.4 mmol/L. The values were lower than the normal laboratory background levels (6.7-14.5 mmol/L) and inferred to be severe hypoglycaemia. The applicant considered that the effects on the respiratory parameters observed in 300 nmol/kg of insulin degludec were likely to be related to the pharmacological action of insulin degludec on blood glucose, and also resulted from increased stress due to restricted food intake in the restrained state and the situation where hypoglycaemia was not resolved by feeding.

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

3.(i).B.(1) Mechanism of action of insulin degludec

PMDA asked the applicant to present any studies (electron microscopy etc.) confirming that insulin degludec forms multi-hexamers and that the release of zinc ions leads to the release of monomers and then explain the mechanism of the prolonged actin of insulin degludec.

The applicant responded as follows:

Formation of insulin degludec multi-hexamers and zinc-dependent dissociation were confirmed by *in vitro* studies using size exclusion chromatography and transmission electron microscopy. In order to confirm the formation of soluble insulin degludec multi-hexamers, samples of insulin degludec were subjected to size exclusion chromatography under conditions mimicking the pharmaceutical formulation for clinical trials (in the presence of phenol and zinc) and under physiological conditions mimicking the subcutaneous tissue (phenol-free Tris buffer[12] in the presence of zinc) to characterize the molecular size of soluble structures of insulin degludec. While insulin degludec eluted with a molecular weight corresponding to the size of a dihexamer in the presence of phenol, the elution time was further reduced in the absence of phenol, indicating that insulin degludec forms very large molecular-size structures (>5000 kD). Examination of these large molecular-size structures under physiological conditions in the absence of phenol by transmission electron microscopy revealed elongated structures with a uniform width of 6.3 ± 0.9 nm, which was close to the diameter of zinc-containing insulin hexamers. Thus, the structures were determined to be multi-hexamers. No such elongated structures were seen in the presence of phenol.

[12] 140 mmol/L sodium chloride, 1.54 mmol/L sodium azide, and 10 mmol/L trishydroxymethylaminomethane (pH = 7.4)

Dissociation into insulin degludec monomers with depletion of zinc was studied by performing size exclusion chromatography in phenol-free Tris buffer[13] in an environment of varying zinc content. While insulin degludec eluted mainly as high molecular weight multi-hexamers in the presence of high concentrations of zinc, dissociation into low molecular weight insulin degludec monomers increased as the zinc concentration decreased, and insulin degludec eluted exclusively as monomers in the absence of zinc. These results supported the mechanism that high zinc content in the formulation enables the formation of insulin degludec multi-hexamers at the injection site and monomers dissociate from the multi-hexamers with decreasing zinc concentration due to simple diffusion. Furthermore, in order to demonstrate that multi-hexamer formation is reversible and insulin degludec monomers are released, insulin degludec solution in the absence of phenol was added with EDTA to chelate zinc ions and examined by transmission electron microscopy. As a result, no elongated structures were visible, demonstrating that multi-hexamer formation is zinc-dependent and reversible (Jonassen I, *et al*., *Pharm. Res*, 2012; Apr 7 [Epub ahead of print]).

Based on the above, it was shown that insulin degludec is dihexameric in pharmaceutical formulation and becomes multihexameric under physiological conditions, and it was inferred that insulin degludec multi-hexamers dissociate into monomers with decreasing zinc concentration, providing slow and stable subcutaneous absorption of insulin degludec. Albumin is also involved in the prolonged duration of action. In the animal species tested in non-clinical studies (rat, dog, pig), the $t_{1/2}$ of insulin degludec was different between subcutaneous and intravenous administration and the $t_{1/2}$ after subcutaneous administration was longer than the $t_{1/2}$ after intravenous administration. In light of the different $t_{1/2}$ values between subcutaneous and intravenous administration, the *in vivo* rate-limiting (prolongation) step in the elimination of insulin degludec should be the absorption process itself, not the elimination of absorbed insulin degludec via insulin receptors. The $t_{1/2}$ of a compound exhibiting absorption rate-limited pharmacokinetics is determined by the absorption rate and the absorption rate of insulin molecules is very much dependent on the molecular size. Insulin monomers (~6 kD) are absorbed rapidly while albumin-bound insulin (~72 kD) is absorbed more slowly. Since soluble insulin degludec multi-hexamers (>5000 kD) are so large that they can not be absorbed into the circulation, the dissociation of monomers from the multi-hexamers is the rate-limiting step in the absorption of insulin degludec. Athough albumin binding in the subcutaneous tissue also contributes to the overall prolongation of the absorption of insulin degludec, its degree should be small.

In conclusion, slow absorption due to multi-hexamer formation following subcutaneous injection of insulin degludec is the rate-limiting step in the elimination of insulin degludec, which is considered to contribute to the prolonged action of insulin degludec.

[13] 10 mol/L trishydroxymethylaminomethane hydrochloride, 140 mmol/L sodium chloride (pH = 7.4)

PMDA accepted the response.

3.(i).B.(2) Comparison with insulin detemir

Concerning differences in pharmacological action between insulin degludec and IDet (both *in vitro* and *in vivo*), PMDA asked the applicant to explain how different fatty acid side chains affect multi-hexamer formation and albumin binding etc., and are reflected in pharmacological action.

The applicant responded as follows:

Insulin degludec and IDet have a similar molecular structure and both differ from human insulin in that threonine at position B30 has been omitted, and a fatty acid side chain has been attached to lysine at position B29. Insulin degludec has a 16-carbon fatty acid (hexadecanedioic acid) side chain attached via a γ-glutamic acid spacer and IDet has a 14-carbon fatty acid (tetradecanoic acid) side chain. When *in vitro* biological properties are compared between insulin degludec and IDet, the potencies of insulin degludec with their 95% CIs in human and rat hepatocyte membrane preparations were 3.5% [1.5, 8.2] and 3.3% [1.3, 4.8], respectively, relative to human insulin and the potencies of IDet were 7.0% [5.2, 9.4] and 4.9% [4.3, 5.5], respectively, relative to human insulin. Insulin degludec and IDet both had a low affinity for the human insulin receptor (Sørensen AR, *et al*., *Diabetes Obes Metab*, 2010;12: 665-73). Although insulin degludec and IDet bind to albumin, insulin degludec has a 2.5-fold higher affinity for albumin than IDet. Regarding the albumin binding capacities of insulin degludec and IDet, the dose-response curve is shifted to higher doses with increasing albumin concentration in a metabolic reaction system using cells. In a study on stimulation of lipogenesis in rat adipocytes, the potencies of insulin degludec and IDet relative to human insulin decrease with increasing albumin concentration. Based on the above, the binding properties of insulin degludec and IDet to the insulin receptor and albumin are considered to be similar.

However, the presence of a discrepant fatty acid side chain from that of IDet confers insulin degludec with its ability to form multi-hexamers in the absence of phenol, whereas IDet is unable to form multi-hexamers under the same physiological conditions (Jonassen I, *et al*., *Pharm. Res*, 2012;Apr 7 [Epub ahead of print]). Multi-hexamer formation at the injection site contributes to slow absorption of insulin degludec and insulin degludec shows a flat and stable pharmacokinetic profile compared with IDet. In normal rats, the potency of insulin degludec is 65% relative to human insulin while the potency of IDet is very weak and only about 10% relative to human insulin. The weaker pharmacological action of IDet compared with insulin degludec is considered attributable to [redacted] ([redacted]). The hydrophobicities of insulin degludec and IDet relative to human insulin were determined to be 0.87% and 113%, respectively, showing a higher hydrophobicity of IDet compared with human insulin. Following [redacted] ([redacted]) treatment, the $AUC_{170\text{-}210\ min}$ of IDet was increased from 7313 to 22,210 pmol/L and the $GIR_{10\text{-}210\ min}$ was increased from 6.6 to 17.9 mg/kg/min. Therefore, since IDet is

[redacted] ([redacted]), the *in vivo* potency of IDet is weaker than that of insulin degludec in rats.

PMDA accepted the response.

3.(i).B.(3) Mitogenic potential

PMDA asked the applicant to explain the relevance of mitogenic effects of insulin degludec in humans, in relation to its metabolic effects.

The applicant responded as follows:

Since cells in the body that express high levels of insulin receptors (e.g., liver, muscle, fat) do not proliferate in response to insulin, L6-hIR cells over-expressing human insulin receptors that hardly respond to IGF-1, in addition to MCF-7 cells etc., were used to compare the mitogenic potency of insulin degludec with that of human insulin. As a result, although the mitogenic potency of insulin degludec was shown to be lower than that of human insulin, the affinity of insulin degludec for the insulin receptor was also lower than that of human insulin. Taking also account of albumin concentrations, the mitogenic potency of insulin degludec was not different from that of human insulin at concentrations producing metabolic effects. Therefore, the balance between the metabolic and mitogenic potencies should be similar between insulin degludec and human insulin. None of the cell lines were highly sensitive to the mitogenic effects of insulin degludec. With respect to human relevance, while there are a number of reports on investigations of the relationship between insulin analog therapy and malignant tumors/neoplasms, there is no definite consensus about the influence of insulin therapy on cancer risk or whether there are clear differences in cancer risk between insulin analogs and human insulin. According to the global pooled data on IDeg and a coformulation of insulin degludec and rapid-acting insulin aspart (genetical recombination) (IDegAsp),[14] there were no differences in the incidence rate (or person-time rate) of malignant neoplasms between the pooled IDeg/IDegAsp group and the pooled comparator group (0.9 events/100 patient-years in the pooled IDeg/IDegAsp group, 0.8 events/100 patient-years in the pooled comparator group). The incidence rates of some types of malignant neoplasms were different between the groups, which is considered incidental due to low incidence rates of each type of malignancies.

In conclusion, insulin degludec acted via the same mechanism as human insulin and there were no findings suggesting the possibility of increased mitogenicity with insulin degludec compared with human insulin in non-clinical studies. In clinical trials, there were no differences in the overall rate of

[14] Pooled data from 17 confirmatory trials with administration of IDeg or IDegAsp completed by January 31, 2011 (IDeg, Multinational trial [3585, type 1], Multinational trial [3586, type 2], Trial 3579 [type 2], Trial 3580 [type 2], Trial 3582 [type 2], Trial 3583 [type 1], Trial 3668 [type 2], Trial 3672 [type 2], Trial 3718 [type 2], Trial 3724 [type 2], and Trial 3770 [type 1]; IDegAsp, Multinational trial [3597, type 2], Trial 3590 [type 2], Trial 3592 [type 2], Trial 3593 [type 2], and Trial 3594 and its extension [3645]) (Safety Analysis Set, 5635 subjects in the pooled IDeg/IDegAsp group and 3306 subjects in the pooled comparator group).

malignant neoplasms between the pooled IDeg/IDegAsp group and the pooled comparator group. Therefore, there should be no safety concern about malignant neoplasms associated with insulin degludec.

PMDA accepts the applicant's response pertaining to non-clinical studies, but will continue to review human relevance in the clinical data section [see "4.(iii).B.(4).4) Neoplasms"].

3.(ii) Summary of pharmacokinetic studies

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

Pharmacokinetics were determined after intravenous administration of insulin degludec or radiolabeled insulin degludec in rats, dogs, and pigs or subcutaneous administration of insulin degludec or radiolabeled insulin degludec in mice, rats, dogs, rabbits, and pigs. Pharmacokinetics after repeated subcutaneous administration of insulin degludec were determined based on toxicokinetics in toxicity studies in mice, rats, rabbits, and dogs. Serum and plasma levels of insulin degludec were determined by an ELISA method. The lower limit of quantification for insulin degludec in mouse serum was 37.8 pmol/L, the lower limits of quantification for insulin degludec in rat serum and plasma were 320 and 63.5 pmol/L, respectively, the lower limit of quantification for insulin degludec in rabbit serum was 20 pmol/L, and the lower limits of quantification for insulin degludec in dog serum and plasma were 27 and 19.6 pmol/L, respectively. Radioactivity in biological samples was measured by liquid scintillation counter or quantitative whole-body autoradiography. Metabolites were determined by high performance liquid chromatography (HPLC). The results from the main studies are described below.

3.(ii).A.(1) Absorption (4.2.2.4.4, 4.2.3.2.2, 4.2.3.2.5-9, 4.2.3.5.2.1, 4.2.3.7.7.2-3)

The pharmacokinetic parameters of insulin degludec in male and female mice following a single subcutaneous administration were as shown in Table 4.

Table 4. Pharmacokinetic parameters of insulin degludec in male and female mice following a single subcutaneous administration

Study No.	209388[a)]			209479[b)]		
Dose (nmol/kg/day)	25	150	250	15	40	75
N (male/female)	12/12	12/12	12/12	12/12	12/12	12/12
t_{max} (h)	1 1	1 3	1 1	1 1	1 1	1 1
C_{max} (nmol/L)	25.0 24.4	151 135	301 248	24.4 21.3	54.2 55.0	98.6 86.8
$AUC_{0\text{-}24h}$ (nmol·h/L)	85.1 82.2	658 624	1380 1160	55.8 58.8[c)]	188 175	312 265
$t_{1/2}$ (h)	— 3.2	3.3 2.8	2.7 3.0	4.3 1.4	— —	3.4 —

Upper row: males, Lower row: females, —: not reported

t_{max}: time to maximum serum concentration, C_{max}: maximum serum concentration,
$AUC_{0\text{-}24h}$: area under the serum concentration-time curve up to 24 hours post-dose,
$t_{1/2}$: half-life

a) Data on Day 1 in a 4-week repeated subcutaneous dose toxicity study (Study 209388). Blood was collected at 6 timepoints (n = 2/timepoint) to calculate parameters.
b) Data on Day 1 in a 13-week repeated subcutaneous dose toxicity study (Study 209479).

Blood was collected at 6 timepoints (n = 2/timepoint) to calculate parameters.

c) Calculated based on $AUC_{0\text{-}12h}$ as 24 h sample was not available.

The pharmacokinetic parameters of insulin degludec in male and female rats following a single subcutaneous administration were as shown in Table 5.

Table 5. Pharmacokinetic parameters of insulin degludec in male and female rats following a single subcutaneous administration

Study No.	205239[a]			206538[b]		206315[c]			206539[d]		
Dose (nmol/kg/day)	25	150	250	100	200	20	50	125	20	65	100
N (male/female)	9/9	9/9	9/9	12/12	12/12	9/9	9/9	9/9	20/20	20/20	20/20
t_{max} (h)	1 1	3 3	3 3	3 3	3 3	2 2	2 2	3 3	1 1	3 1	3 3
C_{max} (nmol/L)	35.5 43.2	285 295	380 443	235 204	510 586	38.7 46.2	110 144	310 292	56.6 46.6	179 178	233 241
AUC_{inf} (nmol·h/L)	199 230	1610 1720	2450 2910	1260 1160	2530 2760	207 226	488 505	1480 1460	248 224[e]	859 974	1290 1310
$t_{1/2}$ (h)	3.5 3.7	3.2 2.9	2.9 2.7	2.7 3.0	2.8 2.6	4.0 3.8	3.2 3.5	3.1 2.9	2.6 —	2.6 2.6	2.9 2.7
CL/f (L/h/kg)	0.13 0.11	0.09 0.09	0.10 0.09	—	—	—	—	—	—	—	—

Upper row: males, Lower row: females, —: not reported

t_{max}: time to maximum serum concentration, C_{max}: maximum serum concentration,

AUC_{inf}: area under the serum concentration-time curve extrapolated to infinity,

$t_{1/2}$: half-life, CL/f: apparent body clearance

a) Data on Day 1 in a 4-week repeated subcutaneous dose toxicity study (Study 205239).
Blood was collected at 6 timepoints (n = 3/two timepoints) to calculate parameters.

b) Data on Day 1 in a 13-week repeated subcutaneous dose toxicity study (Study 206538).
Blood was collected at 4 timepoints (n = 3/timepoint) to calculate parameters.

c) Data on Day 1 in a 26-week repeated subcutaneous dose toxicity study (Study 206315).
Blood was collected at 6 timepoints (n = 3/two timepoints) to calculate parameters.

d) Data on Day 1 in a 52-week repeated subcutaneous dose toxicity study (Study 206539).
Blood was collected at 5 timepoints (n = 4/timepoint) to calculate parameters.

e) $AUC_{0\text{-}9h}$

The pharmacokinetic parameters of insulin degludec in female rabbits following a single subcutaneous administration were as shown in Table 6.

Table 6. Pharmacokinetic parameters of insulin degludec in female rabbits following a single subcutaneous administration

Study No.	206073[a]		
Dose (nmol/kg/day)	5	15	25
N	6	6	6
t_{max}[b] (h)	6	4.5	6
C_{max} (nmol/L)	20.1	78.2	122
AUC_{inf} (nmol·h/L)	301	1010	1420
$t_{1/2}$ (h)	7.2	4.9	5.5

Mean

t_{max}: time to maximum serum concentration, C_{max}: maximum serum concentration,

AUC_{inf}: area under the serum concentration-time curve extrapolated to infinity, $t_{1/2}$: half-life

a) Data on Day 1 (gestation day 6) in a preliminary embryo-fetal developmental toxicity study (Study 206073)

b) Median

The pharmacokinetic parameters of insulin degludec in male and female dogs following a single intravenous or subcutaneous administration were as shown in Table 7.

Table 7. Pharmacokinetic parameters of insulin degludec in male and female dogs following a single intravenous (i.v.) or subcutaneous (s.c.) administration

Study No.	207374		205238[a)]			206314[b)]		
Route of administration	i.v.	s.c.	s.c.			s.c.		
Dose (nmol/kg/day)	4	4	4	8	12	4	8	12
N (male/female)	3/0	3/0	3/3	3/3	3/3	4/4	4/4	4/4
t_{max} (h)	—	8	4 2	6 3	3 6	5 7	6 7	6 8
C_{max} (nmol/L)	40	5.8	5.6 4.4	7.9 9.5	10 15	6.9 6.7	12 9.7	11 12
AUC_{inf} (nmol·h/L)	95	68	61 36	125 93	163 200	71 77	130 118	139 182
$t_{1/2}$ (h)	3.4	4.0	4.3 3.7	6.9 5.1	8.8 4.5	—	—	—
Vz (L/kg)	0.2	—	—	—	—	—	—	—
CL (L/h/kg)	0.04	—	—	—	—	—	—	—
CL/f (L/h/kg)	—	—	0.07 0.11	0.06 0.09	0.07 0.06	0.06 0.05	0.06 0.06	0.07 0.06
BA (%)	—	74	—	—	—	—	—	—

Mean (Upper row: males, Lower row: females), —: not reported
t_{max}: time to maximum serum concentration, C_{max}: maximum serum concentration,
AUC_{inf}: area under the serum concentration-time curve extrapolated to infinity,
$t_{1/2}$: half-life, Vz: volume of distribution, CL: body clearance, CL/f: apparent body clearance, BA: bioavailability
a) Data on Day 1 in a 4-week repeated subcutaneous dose toxicity study (Study 205238)
b) Data on Day 1 in a 26-week repeated subcutaneous dose toxicity study (Study 206314)

Regarding pharmacokinetics after repeated subcutaneous administration, the accumulation factors were 0.95 to 1.5 in a mouse 13-week repeated subcutaneous dose toxicity study (4.2.3.7.7.3), 0.82 to 1.2 in a rat 4-week repeated subcutaneous dose toxicity study (4.2.3.2.5), 2.2 to 2.9 in a rat 26-week repeated subcutaneous dose toxicity study (4.2.3.2.6), 1.0 to 1.6 in a rat 52-week repeated subcutaneous dose toxicity study (4.2.3.2.7), 1.2 to 1.4 in a rabbit preliminary embryo-fetal developmental toxicity study (4.2.3.5.2.1), 1.0 to 1.9 in a dog 4-week repeated subcutaneous dose toxicity study (4.2.3.2.8), and 1.6 to 2.8 in a dog 26-week repeated subcutaneous dose toxicity study (4.2.3.2.9).

3.(ii).A.(2) Distribution (4.2.2.3.1, 4.2.2.3.4, 4.2.2.4.4, 5.3.2.1.1-3)

Following a single subcutaneous administration of 25 nmol/kg of ^{3}H-insulin degludec to male rats (n = 12), tissue distribution was determined by quantitative whole-body autoradiography. As a result, radioactivity levels peaked at 2 to 5 hours post-dose in most tissues. The tissues with higher radioactivity than plasma at any timepoint (the tissue to plasma radioactivity ratio >1) were kidney cortex (1.790 at 2 hours post-dose, 3.060 at 5 hours post-dose, 3.680 at 8 hours post-dose) and liver (1.420 at 5 hours post-dose, 2.570 at 8 hours post-dose) only. In other tissues, the tissue to plasma radioactivity ratio was mostly <0.2.

Following a single subcutaneous administration of 4 nmol/kg of ^{3}H-insulin degludec to male dogs (n = 3), radioactivity was measured by liquid scintillation counter. As a result, the whole blood to plasma radioactivity ratio was approximately 0.6.

Following subcutaneous administration of 125 nmol/kg/day of insulin degludec to pregnant rats (n = 4) from 6 to 20 days after mating, the fetal serum exposure was 1/247 (3 hours after dosing) and 1/124 (9 hours after dosing[15]) of the maternal serum exposure.

The dissociation constants (K_d) of insulin degludec to rat, rabbit, canine, and porcine plasma protein, as determined by surface plasmon resonance (SPR method), were 9.3, 4.2, 6.4, and 13 μmol/L, respectively. The K_d of fatty acids to free human serum albumin was 13 μmol/L.

The binding affinity of insulin degludec to serum albumin was determined using Mini-Leak™ Sepharose beads. As a result, the K_d values (mean) of insulin degludec to rat, rabbit, canine, and porcine serum albumins were 0.56, 0.08, 0.44, and 0.25 μmol/L, respectively, and these results corresponded to a serum albumin binding of ≥99% [for human data, see "4.(ii).A.(1) Studies using human biomaterials"].

3.(ii).A.(3) Metabolism (4.2.2.4.1, 4.2.2.4.3-4, 4.2.2.4.6-7)

Following a single subcutaneous administration of 25 or 250 nmol/kg of ^{3}H-insulin degludec to male and female rats (12 males, 5 females), the plasma exposures (AUC_{0-12h}) of insulin degludec and metabolites[16] P1, P2, and P3 were 46% to 63%, 18% to 33%, 10% to 11%, and 10% to 13%, respectively, relative to the total exposure (the sum of AUCs of parent compound and metabolites). The relative ratios of the metabolites, P1, P2, and P3 were similar regardless of dose level or gender.

Following a single intravenous or subcutaneous administration of 4 nmol/kg of ^{3}H-insulin degludec to male dogs (n = 3), the serum exposures of insulin degludec and metabolites S1, S2, S3, and S4 (intravenous administration, AUC_{0-12h}; subcutaneous administration, AUC_{0-30h}) relative to the total exposure were 64%, 7%, 9%, 11%, and 10%, respectively, after intravenous administration and 48%, 17%, 13%, 11%, and 12%, respectively, after subcutaneous administration.

Following a single subcutaneous administration of 25 nmol/kg of ^{3}H-insulin degludec to normal and bile duct cannulated male rats (n = 3), more than 10 radioactive components were present in the urine (up to 72 hours post-dose), feces (up to 72 hours post-dose), and bile (up to 24 hours post-dose), but none of the components accounted for ≥6% of the administered radioactivity.

Following a single subcutaneous administration of 25 nmol/kg of ^{3}H-insulin degludec to lactating rats (n = 12), insulin degludec and metabolites Mi1, Mi2, and Mi3 were detected in milk and the exposures

[15] Data from three rats because one rat died in necropsy.

[16] According to structural characterization of circulating metabolites in rat plasma (4.2.2.4.3), P1 was identified as tritiated water, P2 was identified as a component having the same molecular weight as insulin degludec, and P3 was identified as the complete B chain of insulin degludec, resulting from breakage of disulfide bridges.

($AUC_{0\text{-}8h}$) of insulin degludec and Mi1, Mi2, and Mi3 relative to the total exposure were 26%, 46%, 26%, and 2%, respectively. Seven radioactive components were detected in plasma and the main components were the parent compound, P1, and P3, which accounted for 49%, 21%, and 15% of the total exposure, respectively. The $AUC_{0\text{-}8h}$ of the parent compound in milk and plasma were 19.9 and 65.2 nmol·h/L, respectively.

Male and female rats (n = 5 per group) were subcutaneously administered 0, 25, 100, or 150 nmol/kg/day of insulin degludec or 100 nmol/kg/day of neutral protamine Hagedorn (NPH) insulin for 2 weeks to investigate the effect of insulin degludec on cytochrome P450 enzyme activity. As a result, the effect of insulin degludec was similar to that of NPH insulin.

3.(ii).A.(4) Excretion (4.2.2.5.1-2)

Following a single subcutaneous administration of 25 nmol/kg of ^{3}H-insulin degludec to normal and bile duct cannulated male rats (n = 3 each), the cumulative urinary and fecal excretion rates (% of the dose) up to 168 hours post-dose in normal rats were 37.4% and 22.3%, respectively, and the cumulative urinary, biliary, and fecal excretion rates up to 96 hours post-dose in bile duct cannulated rats were 24.6%, 18.1%, and 8.9%, respectively. At later timepoints (≥48 hours post-dose), most of the radioactivity was found to be due to tritiated water.

Following a single subcutaneous administration of 25 nmol/kg of ^{3}H-insulin degludec to lactating rats (n = 17), the radioactivity concentration in milk was lower than the radioactivity concentration in plasma at all timepoints and the milk to plasma radioactivity ratio ranged from 0.07 (1 hour post-dose) to 0.67 (8 hours post-dose).

3.(ii).B *Outline of the review by PMDA*

3.(ii).B.(1) Effect of serum albumin concentration on pharmacokinetics

The albumin binding of insulin degludec was ≥99% both in the human and in all animal species studied. PMDA asked the applicant to explain the effect of serum albumin concentration on the pharmacokinetics of insulin degludec and interactions between albumin-binding drugs and insulin degludec.

The applicant responded as follows:

The concentration of insulin degludec at the estimated clinical dose[17] is very low in human plasma (<0.01 μmol/L) compared with the serum albumin concentration (normally, around 600 μmol/L) and insulin degludec will occupy less than 0.01% of the circulating albumin molecules. Thus, even in

[17] Since the mean dose of IDeg in the Japanese subgroup in multinational clinical trials in which Japanese patients participated (patients with type 1 diabetes mellitus, Trial 3585; patients with type 2 diabetes mellitus, Trial 3586) was 0.26 U/kg/day, the estimated clinical dose was considered 0.26 U/kg/day.

patients with hypoalbuminemia, the circulating albumin molecules are unlikely to be completely saturated with insulin degludec. Likewise, the potential of insulin degludec to competitively displace albumin-binding drugs should be low. In a pharmacokinetic trial in foreign subjects with hepatic impairment (Trial 1989) and a pharmacokinetic trial in foreign subjects with renal impairment (Trial 1990), subjects with varying degrees of chronic hypoalbuminemia were enrolled and the effect of serum albumin concentration on the pharmacokinetics of insulin degludec was investigated. As a result, in Trial 1989, an analysis including serum albumin concentration as an explanatory variable showed that serum albumin concentration had no effect on $AUC_{0\text{-}120h,SD}$ and there was also no correlation between $C_{max,SD}$ and serum albumin concentration. Also in Trial 1990, there was no correlation between serum albumin concentration and $AUC_{0\text{-}120h,SD}$, $C_{max,SD}$, or CL/F_{SD}. Although examples of cases that could result in acute serum albumin concentration changes in humans include trauma with massive bleeding or burns, acute changes in the ratio of albumin to insulin degludec are unlikely to occur, as both albumin and insulin degludec fractions are reduced simultaneously. Based on the above, the applicant considers that patients with hypoalbuminemia are not at an increased safety risk of hypoglycaemia or hyperglycaemia associated with insulin degludec.

PMDA accepted the response.

3.(ii).B.(2) Effect of antibody formation on the pharmacokinetics of insulin degludec

PMDA asked the applicant to explain the effect of anti-insulin degludec antibody (anti-degludec antibody) formation on the pharmacokinetics of insulin degludec.

The applicant responded as follows:

In a non-clinical setting, anti-degludec antibodies were measured in the pivotal repeat-dose toxicity studies. Due to a limitation on the volume of blood that could be collected from each rat, serial measurements of serum insulin degludec in the same rat could not be obtained. Thus, rats with positive anti-degludec antibodies were identified and serum concentrations of insulin degludec were compared between antibody positive and negative rats at the same sampling point within the same dose group. In a rat 4-week repeated subcutaneous dose toxicity study (205239), 2 of 18 rats in the low-dose group (25 nmol/kg/day), 3 of 18 rats in the mid-dose group (150 nmol/kg/day), and 2 of 18 rats in the high-dose group (250 nmol/kg/day) were tested positive for anti-degludec antibodies. The serum concentrations of insulin degludec were similar between antibody positive and negative rats at the same sampling point. Also in a rat 26-week repeated subcutaneous dose toxicity study (206315), 2 of 18 rats in the low-dose group (20 nmol/kg/day), 1 of 18 rats in the mid-dose group (50 nmol/kg/day), and 4 of 15 rats in the high-dose group (125 nmol/kg/day) were tested positive for anti-degludec antibodies. The serum concentrations of insulin degludec were similar between antibody positive and negative rats at the same sampling point, except for the 2 rats in the low-dose group. The reason for

higher serum concentrations of insulin degludec in the 2 antibody-positive rats in the low-dose group is unknown. No anti-degludec antibodies were detected in dogs.

In conclusion, only a very small number of animals were tested positive for anti-degludec antibodies and there were generally no differences in serum concentration of insulin degludec between antibody positive and negative animals in non-clinical toxicity studies. Therefore, anti-degludec antibody formation has no effect on the pharmacokinetics of insulin degludec.

PMDA accepts the response, but will continue to review the effect of anti-degludec antibody formation in humans in the clinical data section [see "4.(iii).B.(3) Efficacy and 4.(iii).B.(4).6) Antibody formation"].

3.(iii) Summary of toxicology studies

3.(iii).A *Summary of the submitted data*

Single-dose toxicity, repeat-dose toxicity, reproductive and developmental toxicity, and local tolerance studies and a repeat-dose toxicity study with insulin degludec subjected to forced degradation were conducted to assess the toxicity of insulin degludec. No carcinogenicity studies of insulin degludec have been performed and the carcinogenic potential of insulin degludec was assessed based on the results from the repeat-dose toxicity studies and the pharmacological properties of insulin degludec.

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1, 4.2.3.2.4)

Male and female rats (Wistar, n = 1/sex/group) received a single subcutaneous escalating dose of 3000, 9000, 18,000, or 24,000 nmol/kg of insulin degludec and male and female rats (Wistar, n = 5/sex/group) received a single subcutaneous dose of 24,000 nmol/kg of insulin degludec. As a result, although 1 female in the 18,000 nmol/kg group exhibited piloerection, no death occurred at up to the highest dose tested. The approximate lethal dose was determined to be >24,000 nmol/kg.

A subcutaneous dose escalation study of insulin degludec at doses of 1.5, 3, 6, 12/18 (dosed at 12 nmol/kg for 2 days and at 18 nmol/kg for 2 days), and 30 nmol/kg was conducted. Male and female dogs (1 male and 1 female) were dosed for 4 consecutive days and underwent a 3-day treatment-free period and then were escalated to the next dose level. As a result, no death occurred at up to the highest dose tested. The approximate lethal dose was determined to be >30 nmol/kg.

3.(iii).A.(2) Repeat-dose toxicity

Rat 4-, 26-, and 52-week repeated subcutaneous dose toxicity studies and dog 4- and 26-week repeated subcutaneous dose toxicity studies were conducted. In rats, anti-degludec antibodies were detected in a small number of rats in most of these studies, but antibody formation had no effect on the exposure or glucose-lowering effect of insulin degludec. No anti-degludec antibodies were detected in dogs. Blood

glucose was lowered by insulin degludec or human insulin and findings such as bleeding at the injection site were observed in almost all groups including the control groups in these studies.

3.(iii).A.(2).1) Rat 4-week repeated subcutaneous dose toxicity study (4.2.3.2.5)

Male and female rats (Wistar, n = 10/sex/group) were subcutaneously administered 0 (vehicle[9]), 25, 150, or 250 nmol/kg/day of insulin degludec for 4 weeks and a 1-week treatment-free period was included. One female in the 150 nmol/kg/day group and 1 male and 4 females in the 250 nmol/kg/day group died due to hypoglycaemia. A decrease in relative liver weight (% of body weight) in the insulin degludec groups, hypoglycemic symptoms (piloerection, staggering gait, convulsion, etc.), increased food consumption, and a reduction in the area not stained by HE, suggesting liver glycogen depletion, at ≥150 nmol/kg/day, and a trend towards increased body weight gain etc. at 250 nmol/kg/day were observed, and all of these findings were considered related to the pharmacological effect of insulin degludec. Based on the above, the no observed adverse effect level (NOAEL) was determined to be 250 nmol/kg/day.

3.(iii).A.(2).2) Rat 26-week repeated subcutaneous dose toxicity study (4.2.3.2.6)

Male and female rats (Wistar, n = 20/sex/group) were subcutaneously administered 0 (vehicle[18]), 20, 50, or 125 nmol/kg/day of insulin degludec or 80/50 nmol/kg/day[19] of NPH insulin for 26 weeks. In the insulin degludec 0 and 125 nmol/kg/day groups (n = 10/sex/group), 26-week subcutaneous administration was followed by a 4-week recovery period. Three females in the 50 nmol/kg/day group, 3 males and 7 females in the 125 nmol/kg/day group, and 3 males and 7 females in the NPH insulin group died or were euthanized due to hypoglycaemia. Hypoglycemic symptoms at ≥50 nmol/kg/day of insulin degludec and in the NPH insulin group and decreases in absolute liver weight and relative liver weight (% of body weight) and a reduction in PAS-stained area (performed on liver sections from the vehicle control group and the 125 nmol/kg/day group), suggesting a reduction in glycogen accumulation in the liver, at 125 nmol/kg/day of insulin degludec, were observed. At 125 nmol/kg/day of insulin degludec, there were changes in hematological parameters (increases in hemoglobin and hematocrit, etc.) and changes in urine parameters (an increase in urine specific gravity, a decrease in urine pH, etc.), indicative of dehydration. Changes in clinical chemistry parameters (decreases in alkaline phosphatase, urea, and albumin, etc.) were also noted. There were effects on liver weight, hematological parameters, urine parameters, and clinical chemistry parameters in the NPH insulin group as well. All findings were considered related to the pharmacological effect of insulin degludec, but these findings were reversible. Based on the above, the NOAEL was determined to be 125 nmol/kg/day.

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[18] 16 mg/mL glycerol, 0.58 mg/mL sodium chloride, 1.50 mg/mL phenol, 1.72 mg/mL m-cresol (pH = 7.4)

[19] The NPH insulin dose equipotent to 125 nmol/kg/day of insulin degludec was chosen. However, from Day 130, the NPH insulin dose was reduced to 50 nmol/kg/day due to hypoglycaemic symptoms and hypoglycaemia-related mortality.

3.(iii).A.(2).3) Rat 52-week repeated subcutaneous dose toxicity study (4.2.3.2.7)

Male and female rats (Sprague-Dawley, n = 40 or 50/sex/group) were subcutaneously administered 0 (vehicle[20]), 20 (low-dose), 65/50/40[21] (mid-dose), or 100/80/60[21] nmol/kg/day (high-dose) of IDeg[22] or 65/50/40[21] nmol/kg/day of NPH insulin for 52 weeks. Seven females in the mid-dose IDeg group, 4 males and 22 females in the high-dose IDeg group, and 6 males and 10 females in the NPH insulin group died or were euthanized due to hypoglycaemia. Changes in clinical chemistry parameters (e.g., decreases in ALAT, ASAT, urea, total protein, albumin, and globulin), changes in urine parameters (e.g., an increase in ketones), and decreases in absolute kidney weight and absolute liver weight and relative liver weight (% of body weight) in the mid-dose and high-dose IDeg groups and changes in hematological parameters (increases in red blood cell parameters, e.g. hematocrit, MCV, and MCH) in the high-dose IDeg group were observed. Histopathologic examination revealed extramedullary hematopoiesis and hemosiderin deposition in the spleen in the mid-dose and high-dose IDeg groups and lymphoid atrophy in the thymus and an increased incidence of basophilic changes in renal tubular epithelium, etc. in the high-dose IDeg group. There were effects on liver and kidney weights, hematological parameters, urine parameters, clinical chemistry parameters, and histopathology in the NPH insulin group as well. All of these findings were likely to be related to the pharmacological effect of insulin degludec or seen as background findings in rats and considered of little toxicological significance. Based on the above, the NOAEL was determined to be 60 nmol/kg/day. The exposure ($AUC_{0\text{-}24h}$) in the high-dose IDeg group at Week 52 was 883 nmol·h/L, which was 17 times the clinical exposure.[23] Although neoplastic or hyperplastic lesions such as mammary gland neoplasia were also observed in this study, the incidence of such lesions with IDeg was similar to that with vehicle control or NPH insulin and the proliferative activity of mammary gland epithelial cells (bromodeoxyuridine [BrdU] labeling index) was also similar between IDeg and vehicle control or NPH insulin.

3.(iii).A.(2).4) Dog 4-week repeated subcutaneous dose toxicity study (4.2.3.2.8)

Male and female dogs (beagle, n = 3/sex/group) were subcutaneously administered 0 (vehicle[9]), 4, 8, or 12 nmol/kg/day of insulin degludec for 4 weeks. As a result, no toxicological findings were observed and the NOAEL was determined to be 12 nmol/kg/day.

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[20] 1.50 mg/mL phenol, 1.72 mg/mL m-cresol, 19.6 mg/mL glycerol (pH = 7.6)

[21] The dose level from Day 1 to Day 75/the dose level from Day 76 to Day 224/the dose level from Day 225 to the end of treatment. Due to hypoglycaemic symptoms and hypoglycaemia-related mortality in the high-dose and positive control groups, the doses for the mid-dose, high-dose, and positive control groups were reduced on Day 76 and again on Day 225. Treatment was interrupted for 3 to 4 days in the animals with hypoglycaemic symptoms.

[22] Formulation E

[23] The multiple-dose C_{max} and $AUC_{0\text{-}24h}$ in a Japanese phase I trial (Trial 1996) were dose-normalized and the exposure at 0.26 U/kg/day, i.e. the mean dose of IDeg in the Japanese subgroup in multinational trials in which Japanese patients participated (patients with type 1 diabetes mellitus, Trial 3585; patients with type 2 diabetes mellitus, Trial 3586), was calculated.

3.(iii).A.(2).5) Dog 26-week repeated subcutaneous dose toxicity study (4.2.3.2.9)

Male and female dogs (beagle, n = 3-4/sex/group) were subcutaneously administered 0 (vehicle[18]), 4, 8, or 12/10/8[24] nmol/kg/day of insulin degludec or 8 nmol/kg/day of NPH insulin for 26 weeks. In the 12/10/8 nmol/kg/day group (2 males and 2 females), 26-week subcutaneous administration was followed by a 4-week recovery period. One female in the insulin degludec 8 nmol/kg/day group and 2 males and 1 female in the 12/10/8 nmol/kg/day group died or were euthanized due to hypoglycemic symptoms. Hypoglycemic symptoms and a decrease in triglycerides at ≥8 nmol/kg/day of insulin degludec and a reduction in the area not stained by HE, suggesting liver glycogen depletion, at 12/10/8 nmol/kg/day were observed. All of these findings were considered related to the pharmacological effect of insulin degludec. Based on the above, the NOAEL was determined to be 8 nmol/kg/day. The exposure ($AUC_{0\text{-}24h}$) in the 8 nmol/kg/day group at Week 26 was 227.5 nmol·h/L, which was 4.3 times the clinical exposure.[23]

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

It is expected that none of the components of insulin degludec (desB30 human insulin, glutamic acid, 1,16-hexadecanedioic acid) would interact directly with DNA or other chromosomal material. Thus, no genotoxicity studies with insulin degludec have been conducted.

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

No carcinogenicity studies of insulin degludec have been performed. According to insulin receptor and IGF-1 receptor binding assays, intracellular signaling via insulin receptor, dissociation rate from the insulin receptor and the rate of activation signal decline, and *in vitro* mitogenicity studies, the mitogenic activity of insulin degludec was similar to that of human insulin [see "3.(i).A *Summary of the submitted data*"]. There were no insulin degludec-related effects on the incidence of hyperplastic or neoplastic lesions in repeat-dose toxicity studies of up to 52 weeks in rats and up to 26 weeks in dogs. In a rat 52-week repeat-dose toxicity study, there were no insulin degludec-related effects on the proliferative activity of mammary gland epithelial cells as measured by BrdU uptake [see "3.(iii).A.(2) Repeat-dose toxicity"]. Therefore, the applicant considered that the carcinogenic risk of insulin degludec is similar to that of human insulin.

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

3.(iii).A.(5).1) Rat study of fertility and embryo-fetal development (4.2.3.5.1.2)

Male and female rats (Wistar, n = 22/sex/group) were subcutaneously administered 0 (vehicle[25]), 20, 80, or 125 nmol/kg/day of insulin degludec or 80 nmol/kg/day of NPH insulin. Males were dosed from 4 weeks prior to mating until necropsy and females were dosed from 2 weeks prior to mating until

[24] Due to severe hypoglycaemic symptoms and hypoglycaemia-related mortality at 12 nmol/kg/day, the dose was reduced to 10 nmol/kg/day on Day 48 and again to 8 nmol/kg/day on Day 108.

[25] 1.50 mg/mL phenol, 1.72 mg/mL m-cresol, 16 mg/mL glycerol, 0.58 mg/mL sodium chloride (pH = 7.4)

gestation day 17. Rats were mated within the same dose group. In the parent animals, there were no insulin degludec-related effects on clinical observations or reproductive performance (copulation index, fertility index, number of implantation sites, pre- and post-implantation loss, etc.). Fetal skeletal examination revealed increased incidences of minor skeletal abnormalities (extra ribs, extra thoracolumbar vertebrae, offset alignment of pelvic girdle, etc.) in the insulin degludec groups and increased incidences of major skeletal abnormalities (short/bent/thickened humerus, bent scapula) at ≥80 nmol/kg/day, but the incidences of skeletal abnormalities except for offset alignment of pelvic girdle were within the background control range. Offset alignment of pelvic girdle was considered an incidental finding because its incidence only in the 80 nmol/kg/day group was higher than the background control data. Based on the above, the NOAELs for parental general and reproductive toxicity and embryo-fetal development were all determined to be 125 nmol/kg/day. The exposures ($AUC_{0\text{-}24h}$) in the 125 nmol/kg/day group were 2814 nmol·h/L[26] in males and 866 nmol·h/L[27] in females, which were 53 times and 16 times the clinical exposure,[23] respectively.

3.(iii).A.(5).2) Embryo-fetal development study in rabbits (4.2.3.5.2.2)

Pregnant rabbits (NZW, n = 22/group) were subcutaneously administered 0 (vehicle[25]), 5, 10, or 20 nmol/kg/day of insulin degludec or 20 nmol/kg/day of NPH insulin from gestation day 6 to gestation day 19. Two rabbits in the vehicle control group, 2 rabbits in the insulin degludec 10 nmol/kg/day group, 1 rabbit in the insulin degludec 20 nmol/kg/day group, and 1 rabbit in the NPH insulin group failed to become pregnant. While increases in maternal body weight gain and food consumption and an increased percentage of post-implantation loss were observed in the NPH insulin group, there were no effects in the insulin degludec groups. The incidence of extra ribs in the fetuses was higher in the insulin degludec 20 nmol/kg/day group than in the vehicle control group, which was within the background control range. Based on the above, the NOAELs for parental general and reproductive toxicity and embryo-fetal development were all determined to be 20 nmol/kg/day. The exposure ($AUC_{0\text{-}24h}$) in the 20 nmol/kg/day group was 1658 nmol·h/L,[28] which was 31 times the clinical exposure.[23]

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.2)

Pregnant rats (Wistar, n = 22/group) were subcutaneously administered 0 (vehicle[20]), 20, 80, or 125 nmol/kg/day of IDeg[29] or 80 nmol/kg/day of NPH insulin from gestation day 6 to lactation day 20. In order to prevent hypoglycaemia, glucose was concomitantly administered to rats during the

[26] The exposure in the 125 nmol/kg/day group at Week 13 in a rat 26-week repeated subcutaneous dose toxicity study (4.2.3.2.6)

[27] Estimated as the mean exposure of the 100 nmol/kg/day and 150 nmol/kg/day groups on gestation day 17 in a rat preliminary fertility and embryo-fetal development study (4.2.3.5.1.1).

[28] Estimated as the mean exposure of the 15 nmol/kg/day and 25 nmol/kg/day groups on gestation day 19 in a rabbit preliminary embryo-fetal development study (4.2.3.5.2.1).

[29] The to-be-marketed drug product (Formulation M)

periparturient period. Since severe hypoglycaemia occurred at ≥80 nmol/kg/day of IDeg and in the NPH insulin group, treatment was interrupted during the periparturient period from gestation day 21 to lactation day 2 in subsequent animals and no death or hypoglycemic symptom occurred in these animals. Due to hypoglycaemia, 3 rats in the IDeg 80 nmol/kg/day group died and 3 rats in the IDeg 125 nmol/kg/day group died or were euthanized. One rat in the IDeg 125 nmol/kg/day group had total litter loss and was euthanized. In the dams, decreases in body weight gain and food consumption during the lactation period were observed at ≥80 nmol/kg/day of IDeg. In the F_1 litters, there were pups cold to touch, pups with little milk in the stomach or who appeared unfed in the IDeg groups, and a trend towards decreased live birth index at ≥80 nmol/kg/day of IDeg, and increased dead pups and a trend towards decreased postnatal survival to Day 4 and decreases in body weight and body weight gain at 125 nmol/kg/day were observed. As effects on the F_1 offspring development, there was a slight delay in the mean age of preputial separation in males in the 125 nmol/kg/day group while there were no effects on motor activity or learning. There were no effects on the reproductive performance of the F_1 generation or effects on F_2 fetuses. All findings were considered related to the pharmacological effect of insulin degludec. Based on the above, the NOAELs for maternal general and reproductive toxicity and offspring development were all determined to be 125 nmol/kg/day. The exposure ($AUC_{0\text{-}24h}$) in the 125 nmol/kg/day group was 866 nmol·h/L,[27] which was 16 times the clinical exposure.[23]

3.(iii).A.(6) Local tolerance (4.2.3.6.1-3)

Local reactions following subcutaneous injection of 600 or 1200 nmol/mL of IDeg[29] or vehicle were histopathologically compared with those with NPH insulin or saline in minipigs. Two days after injection, local reactions observed after injection of IDeg were comparable to those seen after injection of vehicle and less pronounced than those seen after injection of NPH insulin. Five days after injection, local reactions observed after injection of IDeg were comparable to those observed after injection of saline or NPH insulin. No difference was seen between 600 and 1200 nmol/mL. The early development drug product was also studied in pigs in the same manner. As a result, the reactions were comparable to those seen after injection of vehicle or saline and less pronounced than those observed after injection of NPH insulin.

Local reactions following intramuscular, intravenous, or intraarterial injection of 600 or 1200 nmol/mL of IDeg[29] or vehicle were histopathologically compared with those with NPH insulin or its vehicle in rabbits. As a result, the reactions after intramuscular, intravenous, or intraarterial injection of IDeg were not different from those of vehicle or NPH insulin.

Based on the above, the applicant considered the local tolerance of IDeg is unlikely to become a more significant problem than that of NPH insulin in clinical use.

3.(iii).A.(7) Immunogenicity

Anti-degludec antibodies were measured in rat and dog repeat-dose toxicity studies. As a result, the applicant considered that anti-degludec antibody formation has little effect on the exposure and blood glucose-lowering effect of insulin degludec.

3.(iii).A.(8) Rat 4-week administration study with insulin degludec subjected to forced degradation (4.2.3.7.6.1)

A rat 4-week repeated subcutaneous dose toxicity study with insulin degludec degraded by long-term storage at 37°C for 5 months from manufacture was conducted. As a result, there were no differences in findings between the forced-degraded insulin degludec and non-degraded insulin degludec groups.

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

Since no carcinogenicity studies of insulin degludec have been performed, PMDA asked the applicant to explain the possibility of increased carcinogenic risk with insulin degludec compared to current insulin products.

The applicant responded as follows:

The *in vivo* carcinogenic potential of insulin degludec was assessed based on hyperplasic and neoplastic lesions observed in a rat 26-week repeated subcutaneous dose toxicity study, a dog 26-week repeated subcutaneous dose toxicity study, and a rat 52-week repeated subcutaneous dose toxicity study. In these studies, intermediate-acting NPH insulin was used as a comparator. As a result, hyperplasic lesions were observed in the IDeg groups, but its incidence was similar to that with vehicle control or NPH insulin and there were no IDeg-related effects on hyperplasic lesions in any animal species or strain, regardless of duration of study. In the rat 52-week repeated subcutaneous dose toxicity study, there was no increase in the incidence of mammary gland hyperplasia in females with IDeg compared with vehicle control or NPH insulin and there was also no increase in the proliferative activity of mammary gland epithelial cells as measured by BrdU labeling. The incidence of neoplastic lesions with IDeg was similar to that with vehicle or NPH insulin and there was also no increase in the incidence of benign or malignant neoplasia in the mammary gland in females. Based on the above study results, the applicant considered that the carcinogenic risk of IDeg is similar to that of NPH insulin.

PMDA accepted the response.

4. Clinical data

In this section, trial numbers are abbreviated, e.g. Trial NN5401-1778 is Trial 1778 and Trial NN1250-1996 is Trial 1996.

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

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

In clinical development, Formulation B (1200 nmol/mL), Formulation D (900 nmol/mL), Formulation E (600 nmol/mL [100 U/mL]), and Formulation M (600 nmol/mL [100 U/mL]) proposed for marketing, using a different *S. cerevisiae* strain from that used in the production of the drug substance for Formulation E (unless otherwise specified, "IDeg" refers to Formulation M in this section), were primarily used. The formulations used in the main clinical trials were as shown in Table 8. Human serum and urine concentrations of insulin degludec were determined by an enzyme-linked immunosorbent assay (ELISA method) and the lower limit of quantification was 20 pmol/L or 32 pmol/L, respectively. Serum anti-degludec antibodies were detected by a radioimmunoassay (RIA method). As the reference data on biopharmaceutics, the results from Foreign Trials 1988, 3769, and 1992 were submitted. The results from the main studies are described below.

Table 8. Formulations used in main clinical trials

Formulation	Concentration	Development phase (Trial No.)	
		Japanese subjects	Foreign subjects
Formulation B[a)]	1200 nmol/mL	Phase I (Trial 1788, Evaluation data)	—
Formulation D[b)]	900 nmol/mL	Phase I (Trial 1790, Evaluation data)	—
Formulation E[b)]	600 nmol/mL (100 U/mL)	Phase I (Trial 1790, Evaluation data) Phase II (Trial 3569, Evaluation data)	Phase I (Trial 1988)
To-be-marketed drug product (Formulation M[c)])	600 nmol/mL (100 U/mL)	Phase I (Trial 1996, Evaluation data)	Phase I (Trials 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, and 3538)
		Phase III (Trials 3585, 3725, and 3586, Evaluation data)	

—: Not applicable
a) [redacted] insulin degludec hexamer formulation containing sodium chloride
b) [redacted] insulin degludec hexamer formulation
c) [redacted] insulin degludec hexamer formulation proposed for marketing. Drug substance production capacity has been improved compared with Formulation E.

(1) Bioequivalence trial

Bioequivalence trial between formulations with different strains for production of drug substance (5.3.1.2.1, Trial 1988 [August to October 2009], Reference data)

A randomized, double-blind, two-period, crossover trial in foreign healthy adult male and female subjects (Target sample size of 26) was conducted to test for bioequivalence between Formulation E and Formulation M.

A single dose of 0.4 U/kg of Formulation E or Formulation M was to be administered subcutaneously. A 13- to 21-day washout period was included between treatments.

All of 26 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.[30]

Pharmacokinetic analysis showed that the estimated geometric mean ratios of $AUC_{0\text{-}120h,SD}$ and $C_{max,SD}$ of insulin degludec (Formulation M/Formulation E) with their 90% CIs were 1.00 [0.94, 1.05] and 0.97 [0.89, 1.05], respectively, which met the bioequivalence criterion established based on "Guideline for Bioequivalence Studies of Generic Products" (PMSB/ELD Notification No. 487 dated December 22, 1997, the Guideline was partially revised by PFSB/ELD Notification No. 1124004 dated November 24, 2006).

Pharmacodynamic analysis showed that the geometric mean area under the glucose infusion rate (GIR) curve ($AUC_{GIR,0\text{-}24h,SD}$) (coefficient of variation [CV] %) was 1892.2 mg/kg (50.4) for Formulation E and 1907.4 mg/kg (54.4) for Formulation M, the maximum glucose infusion rate ($GIR_{max,SD}$) was 2.2 mg/kg/min (42.1) and 2.3 mg/kg/min (47.7), respectively, and the time to the maximum glucose infusion rate ($tGIR_{max,SD}$, median [Min.-Max.]) was 14.6 hours (6.0-24.0) and 13.9 hours (5.3-24.0), respectively.

Regarding safety, adverse events occurred in 9 of the 26 subjects (5 subjects after administration of Formulation E, 5 subjects after administration of Formulation M). Adverse events reported by at least 2 subjects were headache (3 subjects [2 subjects after administration of Formulation E and 2 subjects after administration of Formulation M]) and injection site pain (2 subjects [1 subject after administration of Formulation E and 1 subject after administration of Formulation M]) and these events were all mild in severity. Injection site pain reported by 1 subject after administration of Formulation M was the only event classified as those for which a causal relationship to trial drug could not be denied (hereinafter referred to as "an adverse drug reaction"). While 1 subject experienced one episode of confirmed hypoglycaemia[31] after administration of Formulation E, no nocturnal confirmed hypoglycaemia[32] or severe hypoglycaemia[33] was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

[30] Twenty-five subjects excluding 1 subject who did not complete the second glucose clamp (after administration of Formulation E) were included in the analyses for Formulation E.

[31] "Severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"

[32] "Severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms" occurring between 0:01 a.m. and 5:59 a.m.

[33] Hypoglycaemia requiring the assistance of another person for treatment

(2) Trial comparing different injection sites (5.3.1.1.1, Trial 1992 [June to October 2010], Reference data)

A randomized, open-label, five-period, crossover trial in foreign healthy adult male and female subjects (Target sample size of 18) was conducted to compare the pharmacokinetics and pharmacodynamics after administration of IDeg in the thigh, abdomen, and upper arm.

A single dose of 0.04 U/kg of IDeg was to be administered intravenously,[34] a single dose of 0.4 U/kg of IDeg was to be administered subcutaneously in the thigh, abdomen, or upper arm, or a single dose of 0.4 U/kg of IDeg was to be administered intramuscularly in the thigh. A 13- to 21-day washout period was included between treatments.

All of 20 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.

Pharmacokinetic parameters following a single subcutaneous administration of 0.4 U/kg of IDeg in the thigh, abdomen, or upper arm or a single intramuscular administration of 0.4 U/kg of IDeg in the thigh were as shown in Table 9.

Table 9. Pharmacokinetic parameters following a single subcutaneous administration of 0.4 U/kg of IDeg in the thigh, abdomen, or upper arm or a single intramuscular administration of 0.4 U/kg of IDeg in the thigh

Parameter	Subcutaneous administration			Intramuscular administration
	Thigh (n = 19)	Abdomen (n = 20)	Upper arm (n = 20)	Thigh (n = 19)
$AUC_{0\text{-}120h,SD}$ (pmol·h/L)	75,853 (19)	82,059 (17)	81,135 (20)	81,521 (18)
$C_{max,SD}$ (pmol/L)	1945 (22)	2388 (24)	2462 (25)	3067 (21)
$t_{max,SD}$[a)] (h)	15.0 (11.0-30.0)	13.0 (7.0-20.0)	12.0 (8.0-20.0)	11.0 (7.0-15.0)

Geometric mean (CV%)
$AUC_{0\text{-}120h,SD}$: area under the serum concentration-time curve from 0 to 120 hours after dosing, $C_{max,SD}$: maximum serum concentration, $t_{max,SD}$: time to maximum serum concentration
a) Median (Min.-Max.)

After subcutaneous administration of IDeg, the estimated geometric mean ratio of $AUC_{0\text{-}120h,SD}$ with its 95% CI was 1.07 [1.03, 1.11] for abdomen/thigh, 1.06 [1.01, 1.10] for upper arm/thigh, and 1.01 [0.96, 1.06] for abdomen/upper arm and the estimated geometric mean ratio of $C_{max,SD}$ with its 95% CI was 1.23 [1.07, 1.42], 1.27 [1.08, 1.49], and 0.97 [0.84, 1.12], respectively. When subcutaneous administration was compared with intramuscular administration, the estimated geometric mean ratio of $AUC_{0\text{-}120h,SD}$ (intramuscular administration in the thigh/subcutaneous administration in the thigh) with its 95% CI was 1.07 [1.02, 1.13] and the estimated geometric mean ratio of $C_{max,SD}$ with its 95% CI was 1.58 [1.36, 1.84].

[34] Due to an inappropriate diluent for intravenous administration, although IDeg was administered intravenously, the absolute bioavailability of insulin degludec was not calculated.

Pharmacodynamic parameters following a single subcutaneous administration of 0.4 U/kg of IDeg in the thigh, abdomen, or upper arm or a single intramuscular administration of 0.4 U/kg of IDeg in the thigh were as shown in Table 10.

Table 10. Pharmacodynamic parameters following a single subcutaneous administration of 0.4 U/kg of IDeg in the thigh, abdomen, or upper arm or a single intramuscular administration of 0.4 U/kg of IDeg in the thigh

Parameter	Subcutaneous administration			Intramuscular administration
	Thigh (n = 19)	Abdomen (n = 20)	Upper arm (n = 20)	Thigh (n = 19)
$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	2572 (38)	2833 (42)	2960 (43)	3269 (25)
$GIR_{max,SD}$ (mg/kg/min)	2.7 (32)	3.0 (37)	3.0 (42)	3.4 (24)
$tGIR_{max,SD}$ [a)] (h)	13.2 (7.5-24.0)	11.1 (6.4-24.0)	12.4 (7.0-24.0)	12.4 (8.8-24.0)

Geometric mean (CV%)
$AUC_{GIR,0\text{-}24h,SD}$: area under the glucose infusion rate curve from 0 to 24 hours after dosing, $GIR_{max,SD}$: maximum GIR, $tGIR_{max}$: time to $GIR_{max,SD}$
a) Median (Min.-Max.)

Regarding safety, adverse events occurred in 8 of the 20 subjects. Adverse events reported by at least 2 subjects were headache (3 subjects [1 subject after subcutaneous administration in the thigh, 3 subjects after subcutaneous administration in the abdomen, 1 subject after intramuscular administration, and 1 subject after intravenous administration]) and nasopharyngitis (2 subjects [2 subjects after subcutaneous administration in the upper arm and 1 subject after intramuscular administration]). Headache/diarrhoea reported by 1 subject after intramuscular administration were classified as adverse drug reactions. No injection site reaction was reported. While confirmed hypoglycaemia[31] occurred in 2 subjects (2 episodes) (1 episode in 1 subject after subcutaneous administration in the thigh and 1 episode in 1 subject after subcutaneous administration in the upper arm), no nocturnal confirmed hypoglycaemia[32] or severe hypoglycaemia[33] was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the results from a single-dose trial in Japanese healthy adult subjects (Trial 1788), a multiple-dose trial in Japanese healthy adult subjects (Trial 1790), and a multiple-dose trial in Japanese patients with type 1 diabetes mellitus (Trial 1996) and the results of population pharmacokinetic (PPK) analysis of a phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586) (5.3.3.5.1) were submitted. As the reference data, the results from foreign clinical trials (Trials 1987, 1989, 1990, 1991, 1993, 1994, 1995, and 3538) were submitted. The results from studies using human biomaterials were also submitted. The results from the main studies are described below. In this section, HbA1c results are reported in National Glycohemoglobin Standardization Program (NGSP) units.

4.(ii).A.(1) Studies using human biomaterials (5.3.2.1.3, 5.3.2.2.2-3)

The binding affinity of insulin degludec to serum albumin was determined using Mini-Leak™

Sepharose beads. As a result, the dissociation constant, K_d (mean), of insulin degludec binding to human serum albumin was 0.56 μmol/L. This result corresponded to a serum albumin binding of ≥99%.

^{125}I-insulin degludec 0.8 nmol/L and human serum albumin (10 μmol/L) immobilized to Mini-Leak™ Sepharose beads were incubated with palmitate, warfarin, acetylsalicylate, or ibuprofen (0-100 times the albumin concentration). As a result, the IC_{50} values were 125,[35] >1000, >5000, and >5000 μmol/L, respectively.

^{125}I-insulin degludec 25 pmol/L and human serum albumin (0.3 μmol/L) immobilized to Mini-Leak™ Sepharose beads were incubated with palmitate, oleate, linoleate, ibuprofen, glimepiride, metformin, sitagliptin, liraglutide, warfarin, acetylsalicylate, or salicylate (0-1000 times the albumin concentration). As a result, the IC_{50} values were 3.2, 5.5, 4.1, 11, >100, >500, >500, >100, >100, >500, and >100 μmol/L, respectively.

4.(ii).A.(2) Healthy adult subject studies

4.(ii).A.(2).1) Single-dose trial (5.3.4.1.1, Trial 1788 [December 2006 to March 2007])

A randomized, placebo-controlled, double-blind, parallel-group, comparative trial in Japanese healthy adult male subjects living in Europe (Target sample size of 32) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single doses of Formulation B and a coformulation of insulin degludec and rapid-acting insulin aspart (genetical recombination, IAsp) (IDegAsp) [for trial design and safety data, see "4.(iii).A.(1).1) Single-dose trial in Japanese healthy adult subjects"].

Pharmacokinetic parameters following a single subcutaneous dose of 0.3, 0.6, or 1.2 U/kg of Formulation B were as shown in Table 11.

Table 11. Pharmacokinetic parameters following a single subcutaneous dose of 0.3, 0.6, or 1.2 U/kg of Formulation B

Parameter	0.3 U/kg (n = 6)	0.6 U/kg (n = 6)	1.2 U/kg (n = 6)
$AUC_{0\text{-}inf}$ (pmol·h/L)	74,667 (11)	134,935 (14)	248,735 (13)
C_{max} (pmol/L)	2058 (31)	4279 (24)	6860 (33)
t_{max} [a)] (h)	17.0 (10.0-36.0)	13.0 (10.0-18.0)	15.0 (8.0-20.0)
$t_{1/2}$ [b)] (h)	15.9 (30.7)	13.5 (18.3)	12.9 (26.0)

Geometric mean (CV%)
$AUC_{0\text{-}inf}$: area under the serum concentration-time curve extrapolated to infinity
C_{max}: maximum serum concentration
t_{max}: time to maximum serum concentration, $t_{1/2}$: elimination half-life
a) Median (Min.-Max.)
b) Harmonic mean (CV%)

Pharmacodynamic parameters following a single subcutaneous dose of placebo or 0.3, 0.6, or 1.2 U/kg of Formulation B were as shown in Table 12.

[35] Adjusted for human serum albumin concentration.

Table 12. Pharmacodynamic parameters following a single subcutaneous dose of placebo or 0.3, 0.6, or 1.2 U/kg of Formulation B

Parameter	Placebo (n = 8)	0.3 U/kg (n = 6)	0.6 U/kg (n = 6)	1.2 U/kg (n = 6)
$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	954 (30)	1241 (46)	2853 (31)	5002 (32)
$GIR_{max,SD}$ (mg/kg/min)	1.5 (30)	1.6 (35)	3.1 (24)	5.8 (19)
$tGIR_{max,SD}$ [a] (h)	13.1 (5.7-24.0)	10.1 (3.8-24.0)	16.5 (10.5-20.3)	12.0 (6.0-24.0)
$AUC_{GIR,12\text{-}24h}/AUC_{GIR,0\text{-}24h}$ [b]	0.59 (0.14)	0.54 (0.21)	0.65 (0.05)	0.66 (0.09)

Geometric mean (CV%)
$AUC_{GIR,0\text{-}24h}$: area under the GIR curve from 0 to 24 hours after dosing, GIR_{max}: maximum GIR, $tGIR_{max}$: time to GIR_{max}
$AUC_{GIR,12\text{-}24h}/AUC_{GIR,0\text{-}24h}$: ratio of the area under the GIR curve from 12 to 24 hours after dosing to the area under the GIR curve from 0 to 24 hours after dosing
a) Median (Min.-Max.)
b) Arithmetic mean (SD)

4.(ii).A.(2).2) Multiple-dose trial (5.3.4.1.2, Trial 1790 [December 2007 to February 2008])

A randomized, double-blind, placebo-controlled, parallel-group, comparative trial in Japanese healthy adult male subjects (Target sample size of 32) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of Formulation D or Formulation E or IDegAsp [for trial design and safety data, see "4.(iii).A.(1).2) Multiple-dose trial in Japanese healthy adult subjects"].

Pharmacokinetic parameters following once daily subcutaneous administration of 0.1 U/kg of Formulation D or Formulation E for 6 days were as shown in Table 13.

Table 13. Pharmacokinetic parameters following once daily subcutaneous administration of 0.1 U/kg of Formulation D or Formulation E for 6 days

Parameter	Sampling day	Formulation D 0.1 U/kg (n = 6)	Formulation E 0.1 U/kg (n = 6)
$AUC_{0\text{-}inf}$ (pmol·h/L)	—	16,419 (19.1)	18,959 (21.9)
$AUC_{0\text{-}24h}$ (pmol·h/L)	Day 1	11,797 (19.2)	12,885 (8.1)
	Day 6	13,738 (17.1)	16,009 (13.0)
C_{max} (pmol/L)	Day 1	891 (25.7)	932 (23.4)
	Day 6	1030 (13.1)	1180 (9.7)
t_{max} (h) [a]	Day 1	8.0 (8.0-10.0)	8.0 (8.0-18.0)
	Day 6	8.0 (4.0-8.0)	8.0 (4.0-8.0)
$t_{1/2}$ (h) [b]	Day 1	—	—
	Day 6	10.1 (31.2)	9.1 (58.0)

Geometric mean (geometric coefficient of variation %), —: not applicable
$AUC_{0\text{-}inf}$: area under the serum concentration-time curve extrapolated to infinity
$AUC_{0\text{-}24h}$: area under the serum concentration-time curve from 0 to 24 hours after dosing
C_{max}: maximum serum concentration, t_{max}: time to maximum serum concentration, $t_{1/2}$: elimination half-life
a) Median (Min.-Max.)
b) Harmonic mean (CV%)

Pharmacodynamic analysis showed that the profiles of serum endogenous insulin and plasma glucose were similar between Days 1 and 6.

4.(ii).A.(3) Patient studies

4.(ii).A.(3).1) Multiple-dose trial in Japanese patients with type 1 diabetes mellitus (5.3.4.2.1, Trial 1996 [June to October 2010])

A randomized, double-blind, insulin detemir (IDet)-controlled, two-period, crossover trial in Japanese patients with type 1 diabetes mellitus (Target sample size of 20) was conducted to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg [for trial design and safety data, see "4.(iii).A.(1).3) Multiple-dose trial in Japanese patients with type 1

diabetes mellitus"].

Pharmacokinetic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg or IDet for 6 days were as shown in Table 14.

Table 14. Pharmacokinetic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg or IDet for 6 days

Parameter	IDeg 0.4 U/kg (n = 21)	IDet 0.4 U/kg (n = 22)
$AUC_{\tau,SS}$ (pmol·h/L)	81,270 (28)	61,777 (21)
$C_{max,SS}$ (pmol/L)	4311 (27)	4774 (19)
$t_{max,SS}$ [a)] (h)	8.0 (5.0-12.0)	7.0 (4.0-11.0)
$t_{1/2,SS}$ [b)] (h)	18.3 (34.3)	6.3 (44.7)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state
$C_{max,SS}$: maximum steady-state serum concentration, $t_{max,SS}$: time to maximum serum concentration at steady state
$t_{1/2,SS}$: elimination half-life at steady state
a) Median (Min.-Max.)
b) Harmonic mean (CV%)

A steady-state was reached after 2 to 3 days with IDeg dosing, and both IDeg and IDet were detectable in serum until at least 120 and 48 hours after administration of the dose, respectively.

The geometric mean ratio of the exposure from 0 to 12 hours after dosing ($AUC_{0\text{-}12h,SS}$) to the exposure during one dosing interval (24 hours) ($AUC_{\tau,SS}$) ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$) (CV%) was 0.53 (5.8) for IDeg and 0.65 (12.5) for IDet.

The geometric mean ratios of the exposure at steady state to the exposure after the first dose ($AUC_{\tau,SS}/AUC_{0\text{-}24h,SD}$ and $C_{max,SS}/C_{max,SD}$) (CV%) were 1.73 (34.0) and 1.51 (36.6), respectively.

Pharmacodynamic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg or IDet for 6 days were as shown in Table 15.

Table 15. Pharmacodynamic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg or IDet for 6 days

Parameter	IDeg 0.4 U/kg (n = 21)	IDet 0.4 U/kg (n = 22)
$AUC_{GIR,\tau,SS}$ (mg/kg)	1446 (55)	1093 (61)
$GIR_{max,SS}$ (mg/kg/min)	1.7 (43)	1.8 (48)
$tGIR_{max,SS}$ [a)] (h)	10.6 (0.0-26.0)	8.9 (4.4-21.2)

Geometric mean (CV%)
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state, $GIR_{max,SS}$: maximum GIR at steady state
$tGIR_{max,SS}$: time to maximum GIR at steady state
a) Median (Min.-Max.)

The geometric mean ratio of glucose-lowering effect from 0 to 12 hours after dosing ($AUC_{GIR,0\text{-}12h,SS}$) to glucose-lowering effect during one dosing interval (24 hours) ($AUC_{GIR,\tau,SS}$) ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,\tau,SS}$) (CV%) was 0.48 (29.9) for IDeg and 0.66 (27.7) for IDet.

The geometric mean of fluctuations of the GIR curve of IDeg and IDet ($AUCF_{GIR,\tau,SS}$) (CV%) were 0.28 (46) and 0.49 (54), respectively.

As to the duration of action,[36] blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 26-hour clamp period for any subjects dosed with IDeg.

4.(ii).A.(3).2) Multiple-dose trial in foreign patients with type 1 diabetes mellitus (5.3.4.2.3, Trial 1993 [May to August 2010], Reference data)

A randomized, double-blind, incomplete block crossover trial in foreign patients with type 1 diabetes mellitus [37] (Target sample size of 60) was conducted to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg.

Subjects were to receive one of the three doses of 0.4, 0.6, and 0.8 U/kg of IDeg and insulin glargine (IGlar) once daily for 8 days in one of the two sequences (IDeg was administerd first and then IGlar or vice versa). IDeg and IGlar were to be administered subcutaneously in the thigh. A 7- to 21-day washout period was included between treatments.

All of 66 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses. Two subjects were withdrawn from the trial due to serious adverse events (intraspinal abscess, gastrointestinal haemorrhage).

Pharmacokinetic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar for 8 days were as shown in Table 16.

Table 16. Pharmacokinetic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar for 8 days (No clamp)

Parameter	0.4 U/kg		0.6 U/kg		0.8 U/kg	
	IDeg (n = 21)	IGlar (n = 22)	IDeg (n = 21)	IGlar (n = 22)	IDeg (n = 22)	IGlar (n = 22)
$AUC_{\tau,SS}$ (pmol·h/L)	90,941 (25)	2411 (31)	13,7497 (43)	3744 (21)	179,606 (23)	4747 (27)
$C_{max,SS}$ (pmol/L)	5376 (28)	150 (32)	7389 (38)	235 (23)	9731 (21)	300 (31)
$t_{max,SS}$ [a)] (h)	8.0 (0.0-12.0)	6.0 (0.5-13.0)	8.0 (5.0-18.0)	5.5 (0.5-12.0)	8.0 (0.5-11.2)	5.5 (0.5-10.0)
$t_{1/2,SS}$ [b)] (h)	25.9 (26.3)	11.8 (52.2)	27.0 (27.0)	14.0 (33.8)	23.6 (29.3)	11.9 (46.7)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state, $C_{max,SS}$: maximum serum concentration
$t_{max,SS}$: time to maximum serum concentration
$t_{1/2,SS}$: elimination half-life
a) Median (Min.-Max.)
b) Harmonic mean (CV%), Clamp periods (Not calculated for no clamp)

A steady-state was reached within 2 to 3 days with IDeg dosing and IDeg and IGlar were detectable in serum until at least 120 and 36 to 48 hours after administration of the dose, respectively.

The geometric mean ratios of the exposure from 0 to 12 hours after dosing ($AUC_{0\text{-}12h,SS}$) to the exposure during one dosing interval (24 hours) ($AUC_{\tau,SS}$) for IDeg and IGlar ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$)

[36] Duration of action was defined as the time from trial drug administration until the blood glucose concentration was consistently above 8.3 mmol/L (150 mg/dL) in the setting of a glucose clamp procedure.

[37] Key inclusion criteria: treated with insulin therapy for ≥12 months (<1.2 U/kg/day); HbA1c ≤10.0%; BMI ≥18.0 and ≤28.0 kg/m^2; fasting C-peptide <0.3 nmol/L; and patients with type 1 diabetes mellitus aged ≥18 and ≤65 years.

(CV%) were 0.53 (4.6) and 0.60 (10.6), respectively, at 0.4 U/kg, 0.52 (5.2) and 0.59 (9.9), respectively, at 0.6 U/kg, and 0.54 (5.5) and 0.61 (6.4), respectively, at 0.8 U/kg.

The geometric mean ratios of the exposure at steady state to the exposure after the first dose for IDeg ($AUC_{\tau,SS}/AUC_{0\text{-}24h,SD}$ and $C_{max,SS}/C_{max,SD}$) (CV%) were 1.91 (28.4) and 1.86 (30.5), respectively, at 0.4 U/kg, 1.98 (25.2) and 1.78 (28.5), respectively, at 0.6 U/kg, and 2.14 (24.0) and 1.93 (23.4), respectively, at 0.8 U/kg.

Pharmacodynamic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar for 8 days were as shown in Table 17.

Table 17. Pharmacodynamic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar for 8 days

Parameter	0.4 U/kg		0.6 U/kg		0.8 U/kg	
	IDeg (n = 21)	IGlar (n = 22)	IDeg (n = 21)	IGlar (n = 22)	IDeg (n = 22)	IGlar (n = 22)
$AUC_{GIR,\tau,SS}$ (mg/kg)	1948 (54)	1725 (58)	3854 (31)	3501 (29)	4766 (27)	5093 (34)
$GIR_{max,SS}$ (mg/kg/min)	2.0 (49)	2.2 (49)	3.6 (30)	3.5 (28)	4.2 (29)	5.1 (34)
$tGIR_{max,SS}$[a)] (h)	11.6 (4.8-42.0)	8.1 (0.0-27.3)	12.4 (3.1-23.7)	5.5 (2.8-11.5)	12.3 (0.0-18.3)	8.6 (0.0-32.0)

Geometric mean (CV%)
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state, $GIR_{max,SS}$: maximum GIR at steady state
$tGIR_{max,SS}$: time to maximum GIR at steady state
a) Median (Min.-Max.)

The geometric mean ratios of glucose-lowering effect from 0 to 12 hours after dosing ($AUC_{GIR,0\text{-}12h,SS}$) to glucose-lowering effect during one dosing interval (24 hours) ($AUC_{GIR,\tau,SS}$) for IDeg and IGlar ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,\tau,SS}$) (CV%) were 0.45 (27.4) and 0.60 (16.0), respectively, at 0.4 U/kg, 0.50 (8.7) and 0.59 (8.2), respectively, at 0.6 U/kg, and 0.49 (4.9) and 0.57 (10.0), respectively, at 0.8 U/kg.

The geometric mean fluctuations of the GIR curve of IDeg and IGlar ($AUCF_{GIR,\tau,SS}$) (CV%) were 0.25 (76) and 0.39 (65), respectively, at 0.4 U/kg, 0.37 (49) and 0.54 (42), respectively, at 0.6 U/kg, and 0.38 (43) and 0.73 (54), respectively, at 0.8 U/kg.

As to the duration of action,[36] blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 42-hour clamp period for any subjects dosed with 0.6 or 0.8 U/kg IDeg and only for 3 subjects on 0.4 U/kg.[38]

Regarding safety, adverse events occurred in 15 of the 66 subjects (7 subjects after administration of IDeg, 13 subjects after administration of IGlar). Adverse events reported by at least 3 subjects were headache (10 subjects [1 subject after administration of 0.4 U/kg of IDeg, 3 subjects after administration of 0.6 U/kg of IDeg, 2 subjects after administration of 0.4 U/kg of IGlar, 4 subjects after administration of 0.6 U/kg of IGlar, and 2 subjects after administration of 0.8 U/kg of IGlar]) and phlebitis (3 subjects [1 subject after administration of 0.4 U/kg of IGlar, 1 subject after administration

[38] In the 3 subjects in which blood glucose exceeded 8.3 mmol/L (150 mg/dL) within the clamp period, the duration of action was 32.9, 36.8, and 38.5 hours, respectively.

of 0.6 U/kg of IGlar, and 1 subject after administration of 0.8 U/kg of IGlar]), which were all mild or moderate in severity. These events were classified as adverse drug reactions except for phlebitis after administration of 0.6 U/kg of IGlar. Serious adverse events occurred in 1 subject after administration of 0.4 U/kg of IGlar (gastrointestinal haemorrhage, severe) and 1 subject after administration of 0.6 U/kg of IGlar (intraspinal abscess, severe), which led to trial discontinuation, but their causal relationship to trial drug was denied. No injection site reaction was reported. Confirmed hypoglycaemia[31] occurred in 40 subjects (82 episodes) after administration of IDeg (0.4, 0.6, and 0.8 U/kg) (13 subjects [24 episodes], 13 subjects [26 episodes], and 14 subjects [32 episodes], respectively) and 40 subjects (102 episodes) after administration of IGlar (7 subjects [16 episodes], 15 subjects [41 episodes], and 18 subjects [45 episodes], respectively), nocturnal confirmed hypoglycaemia[32] occurred in 13 subjects (17 episodes) after administration of IDeg (5 subjects [6 episodes], 3 subjects [5 episodes], and 5 subjects [6 episodes], respectively) and 16 subjects (25 episodes) after administration of IGlar (2 subjects [2 episodes], 8 subjects [11 episodes], and 6 subjects [12 episodes], respectively), and severe hypoglycaemia[33] occurred in 1 subject after administration of 0.4 U/kg of IGlar. No deaths occurred and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(3).3) Multiple-dose trial in foreign patients with type 2 diabetes mellitus (5.3.4.2.9, Trial 1987 [June to November 2010], Reference data)

A randomized, double-blind, incomplete block, two-period, crossover trial in foreign patients with type 2 diabetes mellitus [39] (Target sample size of 45) was conducted to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg.

IDeg (100 U/mL) at a dose of 0.4, 0.6, or 0.8 U/kg or the 200 U/mL formulation at a dose of 0.6 U/kg was to be subcutaneously administered in the thigh once daily for 6 days. Subjects were to receive two of these treatments in their assigned sequence. A 13- to 21-day washout period was included between treatments.

All of 49 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses. One subject was withdrawn from the trial for a personal reason.

Pharmacokinetic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg (100 U/mL) for 6 days were as shown in Table 18.

[39] Key inclusion criteria: treated with insulin therapy for ≥12 months (basal insulin ≥0.2 U/kg/day and total daily insulin <1.2 U/kg/day); HbA1c ≤10.0%; BMI ≤35.0 kg/m^2; fasting C-peptide <1.0 nmol/L; and patients with type 2 diabetes mellitus aged ≥18 and ≤70 years.

Table 18. Pharmacokinetic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg (100 U/mL) for 6 days

Parameter	0.4 U/kg (n = 22)	0.6 U/kg (n = 37)	0.8 U/kg (n = 21)
$AUC_{\tau,SS}$ (pmol·h/L)	89,643 (35)	13,0164 (23)	177,408 (27)
$C_{max,SS}$ (pmol/L)	4534 (37)	6592 (23)	8987 (28)
$t_{max,SS}$[a] (h)	8.5 (4.0-15.0)	9.0 (1.0-36.0)	8.0 (3.0-11.0)
$t_{1/2,SS}$ (h)[b]	24.6 (26.7)	24.4 (28.2)	26.8 (38.1)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state
$C_{max,SS}$: maximum serum concentration
$t_{max,SS}$: time to maximum serum concentration, $t_{1/2,SS}$: elimination half-life
a) Median (Min.-Max.)
b) Harmonic mean (CV%)

A steady state was reached within 2 to 3 days after dosing.

After administration of IDeg, the geometric mean ratio of the exposure from 0 to 12 hours after dosing ($AUC_{0\text{-}12h,SS}$) to the exposure during one dosing interval (24 hours) ($AUC_{\tau,SS}$) ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$) (CV%) was 0.53 (4.1) at 0.4 U/kg, 0.52 (5.0) at 0.6 U/kg, and 0.53 (5.3) at 0.8 U/kg.

The geometric mean ratios of the exposure at steady state to the exposure after the first dose ($AUC_{\tau,SS}/AUC_{0\text{-}24h,SD}$ and $C_{max,SS}/C_{max,SD}$) (CV%) were 1.8 (28.1) and 1.4 (28.9), respectively, at 0.4 U/kg, 2.0 (22.7) and 1.7 (25.3), respectively, at 0.6 U/kg, and 2.0 (22.9) and 1.7 (30.8), respectively, at 0.8 U/kg.

Pharmacodynamic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg (100 U/mL) for 6 days were as shown in Table 19.

Table 19. Pharmacodynamic parameters following once daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg (100 U/mL) for 6 days

Parameter	0.4 U/kg (n = 22)	0.6 U/kg (n = 37)	0.6 U/kg (n = 21)
$AUC_{GIR,\tau,SS}$ (mg/kg)	828 (68)	1694 (56)	2482 (46)
$GIR_{max,SS}$ (mg/kg/min)	1.1 (52)	1.7 (49)	2.4 (54)
$tGIR_{max,SS}$[a] (h)	12.6 (0.0-26.0)	10.5 (0.0-26.0)	10.5 (0.0-26.0)

Geometric mean (CV%)
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state, $GIR_{max,SS}$: maximum GIR at steady state
$tGIR_{max,SS}$: time to maximum GIR at steady state
a) Median (Min.-Max.)

The geometric mean ratio of glucose-lowering effect from 0 to 12 hours after dosing ($AUC_{GIR,0\text{-}12h,SS}$) to glucose-lowering effect during one dosing interval (24 hours) ($AUC_{GIR,\tau,SS}$) for IDeg ($AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,\tau,SS}$) (CV%) was 0.47 (24) at 0.4 U/kg, 0.52 (16) at 0.6 U/kg, and 0.50 (12) at 0.8 U/kg.

As to the duration of action,[36] blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 26-hour clamp period for any subjects.

Regarding safety, adverse events occurred in 14 of the 49 subjects (13 of 49 subjects after administration of IDeg, 3 of 16 subjects after administration of the 200 U/mL formulation). Adverse events reported by at least 3 subjects were headache (7 subjects [2 subjects after administration of 0.4

U/kg of IDeg, 3 subjects after administration of 0.6 U/kg of IDeg, 1 subject after administration of 0.8 U/kg of IDeg, 1 subject after administration of the 200 U/mL formulation]), nasopharyngitis (3 subjects [1 subject after administration of 0.4 U/kg of IDeg, 1 subject after administration of 0.6 U/kg of IDeg, 1 subject after administration of the 200 U/mL formulation]), and back pain (3 subjects after administration of 0.6 U/kg of IDeg), which were all mild or moderate in severity. Five cases of headache (1 subject after administration of 0.4 U/kg of IDeg, 3 subjects after administration of 0.6 U/kg of IDeg, 1 subject after administration of the 200 U/mL formulation) were classified as adverse drug reactions. Two serious adverse events were reported by 1 subject after administration of 0.8 U/kg of IDeg (syncope and thoracic vertebral fracture, both severe), but their causal relationship to trial drug was denied. No injection site reaction was reported. Confirmed hypoglycaemia[40] occurred in 6 subjects (6 episodes) after administration of IDeg (0.4, 0.6, and 0.8 U/kg) (0 subjects [0 episodes], 3 subjects [3 episodes], and 3 subjects [3 episodes], respectively) and nocturnal hypoglycaemia[41] occurred in 2 subjects (2 episodes) (after administration of 0.6 U/kg), but no severe hypoglycaemia[33] was reported. No deaths or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(3).4) Trial investigating intra-subject variability at steady state in foreign patients with type 1 diabetes mellitus (5.3.4.2.2, Trial 1991 [July to October 2009] Reference data)

A randomized, double-blind, parallel-group, comparative trial in foreign patients with type 1 diabetes mellitus[42] (Target sample size of 50) was conducted to investigate the intra-subject pharmacodynamic variability after multiple-dose administration of IDeg.

IDeg or IGlar at a dose of 0.4 U/kg was to be subcutaneously administered in the thigh once daily for 12 days. Each subject underwent a glucose clamp on the 6th, 9th and 12th day of treatment (a total of three clamp procedures).

All of 54 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses. Two subjects withdrew consent during the trial period and were discontinued from the trial.

Pharmacokinetic analysis showed that the intra-subject variability (CV%) for $AUC_{ins,\tau,SS}$ during one dosing interval (24 hours) was 13% for IDeg and 24% for IGlar and the intra-subject variability for $AUC_{ins,0\text{-}12h,SS}$ over the first 12 hours was 14% and 23%, respectively.

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40 "Severe hypoglycaemia" and "hypoglycaemia with plasma glucose <50 mg/dL, regardless of symptoms"

41 "Severe hypoglycaemia" and "hypoglycaemia with plasma glucose <50 mg/dL, regardless of symptoms" occurring between 0:01 a.m. and 5:59 a.m.

42 Key inclusion criteria: treated with multiple daily insulin injections for ≥12 months (basal insulin ≥0.2 U/kg/day and total daily insulin <1.2 U/kg/day); HbA1c ≤10.0%; BMI ≥18.0 and ≤28.0 kg/m^2; fasting C-peptide <0.3 nmol/L; and patients with type 1 diabetes mellitus aged ≥18 and ≤65 years.

Pharmacodynamic analysis showed that the intra-subject day-to-day variability in glucose lowering effect of once daily subcutaneous administration of 0.4 U/kg of IDeg or IGlar for 12 days (CV%) was as shown in Table 20.

Table 20. Intra-subject day-to-day variability in glucose lowering effect after once daily subcutaneous administration of 0.4 U/kg of IDeg or IGlar for 12 days (CV%)

Parameter	IDeg 0.4 U/kg (n = 26)	IGlar 0.4 U/kg (n = 27)
$AUC_{GIR,\tau,SS}$ (mg/kg)	20	82
$AUC_{GIR,2\text{-}24h,SS}$ (mg/kg)	22	92
$GIR_{max,SS}$ (h)	18	60

$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state
$AUC_{GIR,2\text{-}24h,SS}$: area under the GIR curve from 2 to 24 hours after dosing at steady state, $GIR_{max,SS}$: maximum GIR
Calculated as the area under the smoothed GIR curve using the linear trapezoidal rule and analyzed in a linear mixed model with insulin type and period as fixed effects and subject as a random effect.
The difference in intra-subject variability between the two insulin types was assessed as the ratio between the error variances.

Regarding safety, adverse events occurred in 19 of the 54 subjects (11 subjects after administration of IDeg, 8 subjects after administration of IGlar). Adverse events reported by at least 3 subjects were headache (16 subjects [9 subjects after administration of IDeg and 7 subjects after administration of IGlar]) and these events were all mild or moderate in severity, but the events of headache reported by 8 subjects after administration of IDeg and 6 subjects after administration of IGlar were classified as adverse drug reactions. No injection site reaction was reported. Confirmed hypoglycaemia[31] occurred in 23 subjects (100 episodes) after administration of IDeg and 24 subjects (95 episodes) after administration of IGlar, nocturnal confirmed hypoglycaemia[32] occurred in 9 subjects (16 episodes) after administration of IDeg and 13 subjects (26 episodes) after administration of IGlar, but no severe hypoglycaemia[33] was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(3).5) Multiple-dose trial in foreign patients with type 1 diabetes mellitus (younger adult and geriatric patients) (5.3.3.3.3, Trial 1994 [August to November 2009] Reference data)

A randomized, double-blind, two-period, crossover trial in foreign younger adult and geriatric patients with type 1 diabetes mellitus[43] (Target sample size of 24 [12 subjects each]) was conducted to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg.

IDeg or IGlar at a dose of 0.4 U/kg was to be subcutaneously administered in the thigh once daily for 6 days. A 7- to 21-day washout period was included between treatments.

All of 27 treated subjects (13 younger adult subjects, 14 geriatric subjects) were included in the safety, pharmacokinetic, and pharmacodynamic analyses. One geriatric subject was withdrawn from the trial due to a serious adverse event (hypoglycaemia).

[43] Key inclusion criteria: diabetes duration ≥12 months; treated with insulin therapy (basal insulin ≥0.2 U/kg/day and total daily insulin <1.2 U/kg/day; HbA1c ≤10.0%; BMI ≥18.0 and ≤28.0 kg/m^2; fasting C-peptide <0.3 nmol/L; and geriatric (≥65 years of age) or young (≥18 and ≤35 years of age) patients with type 1 diabetes mellitus.

Pharmacokinetic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg for 6 days in younger adult and geriatric subjects were as shown in Table 21.

Table 21. Pharmacokinetic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg for 6 days in younger adult and geriatric subjects

Parameter	Younger adult subjects (n = 13)	Geriatric subjects (n = 14)
$AUC_{\tau,SS}$ (pmol·h/L)	82,998 (48)	85,953 (72)
$C_{max,SS}$ (pmol/L)	4425 (39)	4493 (66)
t_{maxSS}[a)] (h)	9.0 (5.0-14.0)	10.0 (0.0-16.0)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve at steady state, $C_{max,SS}$: maximum serum concentration
$t_{max,SS}$: time to maximum blood concentration
a) Median (Min.-Max.)

The estimated geometric mean ratios of $AUC_{\tau,SS}$ and $C_{max,SS}$ (geriatric subjects/younger adult subjects) with their 95% CIs were 1.04 [0.73, 1.47] and 1.02 [0.74, 1.39], respectively.

Pharmacodynamic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg for 6 days in younger adult and geriatric subjects were as shown in Table 22.

Table 22. Pharmacodynamic parameters following once daily subcutaneous administration of 0.4 U/kg of IDeg for 6 days in younger adult and geriatric subjects

Parameter	Younger adult subjects (n = 12)	Geriatric subjects (n = 14)
$AUC_{GIR,\tau,SS}$ (mg/kg)	2457 (33)	1906 (44)
$GIR_{max,SS}$ (mg/kg/min)	2.6 (32)	2.0 (45)
$tGIR_{max,SS}$[a)] (h)	13.3 (0.0-24.0)	12.3 (6.8-24.0)

Geometric mean (CV%)
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state, $GIR_{max,SS}$: maximum GIR at steady state
$tGIR_{max,SS}$: time to maximum GIR at steady state
a) Median (Min.-Max.)

The estimated geometric mean ratios of $AUC_{GIR,\tau,SS}$ and $GIR_{max,SS}$ (geriatric subjects/younger adult subjects) with their 95% CIs were 0.78 [0.47, 1.31] and 0.80 [0.54, 1.17], respectively.

Regarding safety, adverse events occurred in 16 of the 27 subjects (8 subjects after administration of IDeg, 11 subjects after administration of IGlar). Adverse events reported by at least 3 subjects were headache (9 subjects [1 younger adult subject after administration of IDeg, 3 geriatric subjects after administration of IDeg, and 5 younger adult subjects after administration of IGlar]) and these events were all mild in severity and their causal relationship to trial drug was denied. A serious adverse event occurred in 1 geriatric subject after administration of IDeg (severe hypoglycaemia), which led to trial discontinuation. This event was classified as an adverse drug reaction. Injection site reaction occurred in 1 geriatric subject after administration of IDeg and 1 younger adult subject after administration of IGlar, but their causal relationship to trial drug was denied. Confirmed hypoglycaemia[31] occurred in 23 subjects (74 episodes) after administration of IDeg (11 younger adult subjects [24 episodes], 12 geriatric subjects [50 episodes]) and 16 subjects (39 episodes) after administration of IGlar (8 younger adult subjects [16 episodes], 8 geriatric subjects [23 episodes]), nocturnal confirmed hypoglycaemia[32] occurred in 14 subjects (24 episodes) after administration of IDeg (7 younger adult subjects [9

episodes], 7 geriatric subjects [15 episodes]) and 10 subjects (14 episodes) after administration of IGlar (5 younger adult subjects [5 episodes], 5 geriatric subjects [9 episodes]), and severe hypoglycaemia[33] occurred in 2 subjects (2 episodes) after administration of IDeg (1 younger adult subject, 1 geriatric subject). No deaths occurred and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(3).6) Single-dose trial in foreign patients with type 1 diabetes mellitus (children, adolescents, adults) (5.3.3.3.4, Trial 1995 [December 2009 to May 2010], Reference data)

A randomized, double-blind, two-period, crossover trial in foreign pediatric, adolescent, and adult patients with type 1 diabetes mellitus[44] (Target sample size of 36) was conducted to evaluate the pharmacokinetics and safety of a single dose of IDeg.

A single dose of 0.4 U/kg of IDeg or IGlar was to be subcutaneously administered in the thigh. A 7- to 21-day washout period was included between treatments.

All of 38 treated subjects (13 children, 13 adolescents, 12 adults) were included in the safety analysis and 37 subjects (12 children, 13 adolescents**,** 12 adults), excluding 1 subject who withdrew consent after the first dose, were included in the pharmacokinetic analysis.

Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg in children, adolescents, and adults were as shown in Table 23.

Table 23. Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg in children, adolescents, and adults

Parameter	Children (n = 12)	Adolescents (n = 13)	Adults (n = 12)
$AUC_{inf,SD}$ (pmol·h/L)	145,891 (73)	130,713 (30)	98,594 (21)
$C_{max,SD}$ (pmol/L)	3350 (51)	3422 (33)	2792 (17)
$t_{max,SD}$ (h)[a)]	11.0 (4.0-17.8)	14.8 (9.0-21.1)	13.0 (9.0-21.0)

Geometric mean (CV%)
$AUC_{inf,SD}$: area under the serum concentration-time curve extrapolated to infinity, $C_{max,SD}$: maximum serum concentration
$t_{max,SD}$: time to maximum serum concentration
a) Median (Min.-Max.)

The estimated geometric mean ratios of $AUC_{inf,SD}$ and $C_{max,SD}$ (children/adults) with their 95% CIs were 1.48 [0.98, 2.24] and 1.20 [0.90, 1.60], respectively, and the estimated geometric mean ratios of $AUC_{inf,SD}$ and $C_{max,SD}$ (adolescents/adults) with their 95% CIs were 1.33 [1.08, 1.64] and 1.23 [1.00, 1.51], respectively.

Regarding safety, adverse events occurred in 7 of 37 subjects after administration of IDeg and 5 of 38 subjects after administration of IGlar. Adverse events reported by at least 2 subjects were headache (3 subjects [1 child after administration of IDeg, 1 adult after administration of IDeg, and 1 adolescent

[44] Key inclusion criteria: treated with insulin therapy for ≥12 months (total daily insulin 0.6-1.2 U/kg/day); HbA1c ≤10.0%; BMI ≥15.0 and ≤20.0 kg/m^2 for children (≥6 and ≤11 years of age), ≥18.0 and ≤28.0 kg/m^2 for adolescents (≥12 and ≤17 years of age), and ≥18.0 and ≤30.0 kg/m^2 for adults (≥18 and ≤65 years of age); and patients with type 1 diabetes mellitus.

after administration of IGlar]) and nasopharyngitis (2 subjects [1 child after administration of IDeg and 1 adolescent after administration of IGlar]). The events of headache were all classified as adverse drug reactions. A serious adverse event occurred in 1 adolescent after administration of IDeg (hypoglycaemia). The investigator inferred that this event was factitious hypoglycaemia due to a deliberate overdose of IAsp. Confirmed hypoglycaemia[31] occurred in 21 subjects (75 episodes) after administration of IDeg (7 children [30 episodes], 6 adolescents [23 episodes], 8 adults [22 episodes]) and 21 subjects (101 episodes) after administration of IGlar (8 children [32 episodes], 6 adolescents [29 episodes], 7 adults [40 episodes]) and nocturnal confirmed hypoglycaemia[32] occurred in 2 subjects (2 episodes) after administration of IDeg (1 child [1 episode], 1 adolescent [1 episode]) and 5 subjects (10 episodes) after administration of IGlar (2 children [4 episodes], 3 adults [6 episodes]), but no severe hypoglycaemia[33] was reported. No deaths or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(3).7) PPK analysis of data from phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586)

The plasma insulin degludec concentration data from Trial 3586 (690 sampling points) were used to perform a PPK analysis using non-linear mixed effect modeling (Software, NONMEM7.1.2). The basic model was a 1-compartment model. The PPK analysis included data on 259 subjects (119 male subjects and 140 female subjects [84 subjects in Japan, 16 subjects in Hong Kong, 81 subjects in Korea, 39 subjects in Malaysia, 21 subjects in Thailand, 20 subjects in Taiwan]), the mean body weight was 65.3 kg (Min.-Max., 37.4-99.8 kg), the mean age was 58.9 years (20-83.1 years), and BMI was 24.8 kg/m^2 (15.5-34.9 kg/m^2). The influence of covariates, i.e., age, body weight, BMI, country, and sex, on CL/F was analyzed using the stepwise method. Only body weight was selected as a covariate, but body weight and country were included in the final model to provide an estimate of the CL/F ratio between different ethnic groups within the Asian region and its corresponding confidence interval. As a result, the estimated geometric mean ratios of CL/F and dose-normalized AUC (Asian patients with type 2 diabetes mellitus/Japanese patients with type 2 diabetes mellitus) were as shown in Table 24.

Table 24. CL/F and dose-normalized AUC ratios
(Asian patients with type 2 diabetes mellitus/
Japanese patients with type 2 diabetes mellitus)

	CL/F	Dose-normalized AUC
Hong Kong/Japan	0.994 [0.916, 1.078]	1.006 [0.927, 1.091]
Korea/Japan	1.005 [0.948, 1.066]	0.995 [0.938, 1.055]
Malaysia/Japan	0.968 [0.903, 1.039]	1.033 [0.963, 1.108]
Thailand/Japan	1.009 [0.928, 1.097]	0.991 [0.912, 1.077]
Taiwan/Japan	1.052 [0.942, 1.176]	0.950 [0.850, 1.062]

Estimated geometric mean ratio with its 90% CI

4.(ii).A.(4) Intrinsic factor pharmacokinetic trials

4.(ii).A.(4).1) Pharmacokinetic trial in subjects with hepatic impairment (5.3.3.3.1, Trial 1989 [August 2009 to March 2010], Reference data)

An open-label, parallel-group, comparative trial in foreign healthy adult subjects and foreign subjects with hepatic impairment[45] (Target sample size of 24) was conducted to evaluate the pharmacokinetics and safety of IDeg.

A single dose of 0.4 U/kg of IDeg was to be subcutaneously administered in the thigh. Six subjects were assigned to each group.

All of 24 treated subjects were included in the safety and pharmacokinetic analyses.

Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg were as shown in Table 25.

Table 25. Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg

Parameter	Healthy adult (n = 6)	Mild hepatic impairment (n = 6)	Moderate hepatic impairment (n = 6)	Severe hepatic impairment (n = 6)
$AUC_{0\text{-}120h,SD}$ (pmol·h/L)	89,092 (16)	83,327 (15)	88,944 (23)	79,846 (19)
$C_{max,SD}$ (pmol/L)	3099 (13)	2796 (18)	2394 (54)	2350 (31)
$t_{max,SD}$ a) (h)	13.5 (11.0-16.0)	14.5 (11.0-17.0)	13.0 (8.0-19.0)	13.5 (8.0-24.0)
$t_{1/2,SD}$ b) (h)	15.9 (34)	15.8 (21)	17.8 (30)	17.3 (32)
MRT_{SD} (h)	27.1 (15)	27.4 (17)	34.5 (29)	32.1 (21)
CL/F_{SD} (mL/h/kg)	26.8 (16)	28.6 (13)	26.2 (28)	29.2 (20)

Geometric mean (CV%)
$AUC_{0\text{-}120h,SD}$: area under the serum concentration-time curve from 0 to 120 hours, $C_{max,SD}$: maximum serum concentration
$t_{max,SD}$: time to maximum serum concentration
$t_{1/2,SD}$: elimination half-life, MRT_{SD}: mean residence time, CL/F_{SD}: apparent body clearance
a) Median (Min.-Max.)
b) Harmonic mean (CV%)

The results of comparison of pharmacokinetic parameters between subjects with hepatic impairment and healthy adult subjects were as shown in Table 26.

Table 26. Comparison of pharmacokinetic parameters between subjects with hepatic impairment and healthy adult subjects

Parameter	Mild hepatic impairment (n = 6)	Moderate hepatic impairment (n = 6)	Severe hepatic impairment (n = 6)
$AUC_{0\text{-}120h,SD}$ (pmol·h/L) [90% CI]	0.95 [0.77, 1.16]	1.00 [0.82, 1.22]	0.92 [0.74, 1.14]
$C_{max,SD}$ (pmol/L) [90% CI]	0.90 [0.67, 1.20]	0.77 [0.58, 1.03]	0.75 [0.55, 1.02]

Estimated geometric mean ratio (subjects with hepatic impairment/healthy adult subjects) with its 90% CI

Regarding safety, no adverse events were reported. No confirmed hypoglycaemia,[31] nocturnal confirmed hypoglycaemia,[32] or severe hypoglycaemia[33] was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically

[45] Key inclusion criteria: hepatic impairment was classified as mild (Child-Pugh Grade A [Score 5-6]), moderate (Child-Pugh Grade B [Score 7-9]), or severe (Child-Pugh Grade C [Score 10-15]); stable symptoms; BMI ≥18.5 and ≤40.0 kg/m^2; and ≥18 and ≤75 years of age. Subjects with concurrent diabetes mellitus were allowed to be included in the trial.

significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(4).2) Pharmacokinetic trial in subjects with renal impairment (5.3.3.3.2, Trial 1990 [November 2009 to May 2010], Reference data)

An open-label, parallel-group, comparative trial in foreign healthy adult subjects and foreign subjects with renal impairment[46] (Target sample size of 30) was conducted to evaluate the pharmacokinetics and safety of IDeg.

A single dose of 0.4 U/kg of IDeg was to be subcutaneously administered in the thigh and two doses were subcutaneously administered[47] to subjects with end-stage renal disease requiring dialysis, one before and one after hemodialysis, to evaluate the pharmacokinetics of IDeg during hemodialysis and in the period between hemodialysis sessions. Six subjects were assigned to each group.

All of 32 treated subjects were included in the safety analysis and 30 subjects excluding 2 healthy adult subjects who failed to meet the inclusion criteria were included in the pharmacokinetic analysis.

Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg were as shown in Table 27.

Table 27. Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg

Parameter	Healthy adult (n = 6)	Mild renal impairment (n = 6)	Moderate renal impairment (n = 6)	Severe renal impairment (n = 6)	End-stage renal disease (n = 6)
$AUC_{0\text{-}120h,SD}$ (pmol·h/L)	107,332 (26)	124,403 (47)	116,153 (33)	125,945 (28)	112,065 (20)[c)]
$C_{max,SD}$ (pmol/L)	3085 (28)	3502 (30)	3237 (39)	3918 (28)	3172 (37)
$t_{max,SD}$[a)] (h)	15.5 (12.0-19.0)	13.5 (12.0-24.0)	12.5 (10.0-17.0)	11.0 (10.0-14.0)	17.0 (10.0-19.0)
$t_{1/2,SD}$[b)] (h)	18.9 (22)	14.8 (29)	16.4 (25)	14.8 (27)	13.3 (155)
MRT_{SD} (h)	34.2 (12)	30.8 (23)	31.5 (15)	28.5 (21)	38.3 (108)
CL/F_{SD} (mL/h/kg)	22.0 (32)	19.1 (31)	20.5 (39)	18.9 (24)	21.3 (19)

Geometric mean (CV%)
$AUC_{0\text{-}120h,SD}$: area under the serum concentration-time curve from 0 to 120 hours, $C_{max,SD}$: maximum serum concentration
$t_{max,SD}$: time to maximum serum concentration
$t_{1/2,SD}$: elimination half-life, MRT_{SD}: mean residence time, CL/F_{SD}: apparent body clearance
a) Median (Min.-Max.)
b) Harmonic mean (CV%)
c) $AUC_{0\text{-}\infty,SD}$: area under the serum concentration-time curve extrapolated to infinity

The results of comparison of pharmacokinetic parameters between subjects with renal impairment and healthy adult subjects were as shown in Table 28.

[46] The degree of renal impairment was classified according to creatinine clearance (CL_{CR}) (mL/min) estimated using the Cockcroft-Gault formula (men, [(140 − age) × body weight (kg)]/[72 × serum creatinine (mg/dL)]; women, [(140 − age) × body weight (kg) × 0.85]/[72 × serum creatinine (mg/dL)]) (normal, CL_{CR} >80 mL/min; mild, CL_{CR} ≥50 and ≤80 mL/min; moderate, CL_{CR} ≥30 and <50 mL/min; severe, CL_{CR} <30 mL/min); BMI ≤40.0 kg/m^2; and ≥18 and ≤85 years of age. Subjects with concurrent diabetes mellitus were allowed to be included in the trial.

[47] One dose of IDeg was administered immediately after the completion of hemodialysis to evaluate the pharmacokinetics of IDeg in the period between hemodialysis sessions, and another dose of IDeg was administered about 13 hours prior to hemodialysis to evaluate the pharmacokinetics of IDeg during hemodialysis. Dialysis time was 4 hours per session and dialysate was sampled four times.

Table 28. Comparison of pharmacokinetic parameters between subjects with renal impairment and healthy adult subjects

Parameter	Mild renal impairment (n = 6)	Moderate renal impairment (n = 6)	Severe renal impairment (n = 6)	End-stage renal disease (n = 6)
$AUC_{0\text{-}120h,SD}$ (pmol·h/L) [90% CI]	1.12 [0.77, 1.63]	1.12 [0.78, 1.60]	1.20 [0.83, 1.74]	—a)
$C_{max,SD}$ (pmol/L) [90% CI]	1.14 [0.81, 1.61]	1.06 [0.76,1.49]	1.23 [0.87,1.73]	1.05 [0.75,1.46]

Estimated geometric mean ratio (subjects with renal impairment/healthy adult subjects) with its 90% CI
－: not applicable
a) $AUC_{0\text{-}\infty,SD}$ was 1.02 [0.74, 1.40].

Unchanged insulin degludec in dialysate samples collected during a 4-hour dialysis session was below the detection limit.

Regarding safety, adverse events occurred in 3 of the 32 subjects, which included injection site reaction (1 subject with moderate renal impairment), nausea (1 subject with mild renal impairment), and vomiting (1 subject with mild renal impairment and 1 subject with end-stage renal disease), and these events were all mild in severity, but the vomiting occurring in 1 subject with end-stage renal disease was classified as moderate in severity. The injection site reaction was classified as an adverse drug reaction. While 1 episode of confirmed hypoglycaemia[31] and 1 episode of nocturnal confirmed hypoglycaemia[32] occurred in 1 subject (during or after dialysis in the end-stage renal disease group), no severe hypoglycaemia[33] was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

4.(ii).A.(4).(5) Pharmacodynamic trial

Trial investigating hypoglycemic response (5.3.4.2.4, Trial 3538 [October 2009 to March 2010] Reference data)

A randomized, double-blind, two-period, crossover trial in foreign patients with type 1 diabetes mellitus[48] (Target sample size of 26) was conducted to compare the counter-regulatory responses during hypoglycaemia induced by IDeg or IGlar.

IDeg or IGlar was to be subcutaneously administered once daily for 5 days. Subjects were to receive a dose that was 80% of their individual daily basal insulin requirement for 4 days and a dose that was 3 times their individual daily basal insulin requirement for 1 day. After the last dose, a glucose clamp was used to maintain euglycemia (100 mg/dL of plasma glucose). Plasma glucose was then allowed to decline to 63 mg/dL (maintained for 30 minutes) and thereafter to a nadir of 45 mg/dL (maintained for 15 minutes). After nadir, plasma glucose was raised to 70 mg/dL and maintained at this level for 120 minutes, then raised to 100 mg/dL. A 13- to 21-day washout period was included between treatments.

[48] Key inclusion criteria: treated with insulin therapy for ≥12 months (total daily insulin <1.2 U/kg/day); HbA1c ≥6.7% and ≤10.0 %; BMI ≥18.0 and ≤28.0 kg/m^2; fasting C-peptide <0.3 nmol/L; and patients with type 1 diabetes mellitus aged ≥18 and ≤65 years.

All of 28 treated subjects were included in the safety and pharmacodynamic analyses. Two subjects were withdrawn from the trial due to adverse events.

With respect to plasma glucose levels during a period of hypoglycaemia, the estimated geometric mean ratio (IDeg/IGlar) of the rate of decline in plasma glucose level from 100 mg/dL to a nadir of 45 mg/dL with its 95% CI was 0.84 [0.72, 0.99]. The estimated geometric mean ratio of the rate of decline in plasma glucose level from 80 mg/dL to a nadir of 45 mg/dL was 1.02 [0.89, 1.18]. The estimated geometric mean ratio of plasma glucose at nadir (IDeg/IGlar) with its 95% CI was 1.03 [0.99, 1.08]. While the estimated geometric mean ratio of GIR required to maintain euglycemia (100 mg/dL) during the 30 minutes right before hypoglycaemia induction (IDeg/IGlar) with its 95% confidence interval was 0.55 [0.41, 0.74], the estimated geometric mean ratios of GIR at 63 mg/dL and at plasma glucose nadir were 0.62 [0.37, 1.06] and 0.43 [0.15, 1.22], respectively. As to hypoglycemic symptoms, the least square mean difference in the baseline-adjusted hypoglycemic symptom score[49] at plasma glucose nadir ($HSS_{PG,nadir}$) (IDeg minus IGlar) was 0.17 [-1.71, 2.05] and an increased awareness towards hypoglycaemia was observed at <72 mg/dL, i.e. 74% with IDeg and 68% with IGlar at nadir. As to counter-regulatory hormones, the ratio of the slope of the rise curve (IDeg/IGlar) was estimated and the estimated geometric mean ratio with its 95% CI was 1.07 [1.01, 1.14] for adrenaline, 1.35 [1.19, 1.54] for growth hormone, and 1.03 [1.00, 1.06] for cortisol.

Regarding safety, adverse events occurred in 18 of the 28 subjects (12 subjects after administration of IDeg, 13 subjects after administration of IGlar). Adverse events reported by at least 2 subjects were headache only (11 subjects [7 subjects after administration of IDeg and 8 subjects after administration of IGlar]) and the events were all mild in severity and their causal relationship to trial drug was denied. A serious adverse event of moderate anaphylactic reaction occurred in 1 subject after administration of IDeg, which was classified as an adverse drug reaction and led to trial discontinuation. No injection site reaction was reported. While confirmed hypoglycaemia[31] occurred in 8 subjects (17 episodes) after administration of IDeg and 7 subjects (15 episodes) after administration of IGlar and nocturnal confirmed hypoglycaemia[32] occurred in 4 subjects (5 episodes) after administration of IDeg and 2 subjects (3 episodes) after administration of IGlar, no severe hypoglycaemia[33] was reported. No deaths occurred and there were no clinically significant changes in laboratory tests, vital signs, or ECG.

[49] Based on the Edinburgh Hypoglycaemia Scale, 11 hypoglycaemic symptoms (autonomic [sweating, palpitations, shaking, hunger], neuroglycopenic [confusion, drowsiness, odd behaviour, speech difficulty, incoordination], and general malaise [headache, nausea]) were scored for each subject (from 1 to 7) and a total score was calculated by multiplying the average score of the 11 symptoms by 11.

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

Pharmacokinetic and pharmacodynamic similarities between Japanese and foreign patients with type 1 or type 2 diabetes mellitus

PMDA asked the applicant to explain pharmacokinetic and pharmacodynamic similarities between Japanese and foreign patients with type 1 or type 2 diabetes mellitus.

The applicant responded as follows:

Pharmacokinetic parameters following multiple-dose administration of 0.4 U/kg of IDeg were similar between Japanese patients with type 1 diabetes mellitus in Trial 1996 and foreign patients with type 1 diabetes mellitus in Trial 1993 (Table 29).

Table 29. Comparison of pharmacokinetic parameters following multiple-dose administration of 0.4 U/kg of IDeg between Japanese and foreign patients with type 1 diabetes mellitus

Parameter	Japanese patients with type 1 diabetes mellitus (n = 21)	Foreign patients with type 1 diabetes mellitus (n = 21)[a)]
$AUC_{\tau,SS}$ (pmol·h/L)	81,270 (28)	82,612 (28)
$C_{max,SS}$ (pmol/L)	4311 (27)	4363 (25)
$t_{max,SS}$[b)] (h)	8.0 (5.0-12.0)	9.0 (7.0-16.0)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state
$C_{max,SS}$: maximum steady-state serum concentration
$t_{max,SS}$: time to maximum blood concentration at steady state
a) Parameters during clamp periods are presented to be compared with those in Trial 1996.
b) Median (Min.-Max.)

The mean steady-state 24-hour insulin degludec serum concentration-time profiles in Japanese and foreign patients with type 1 diabetes mellitus were as shown in Figure 1.

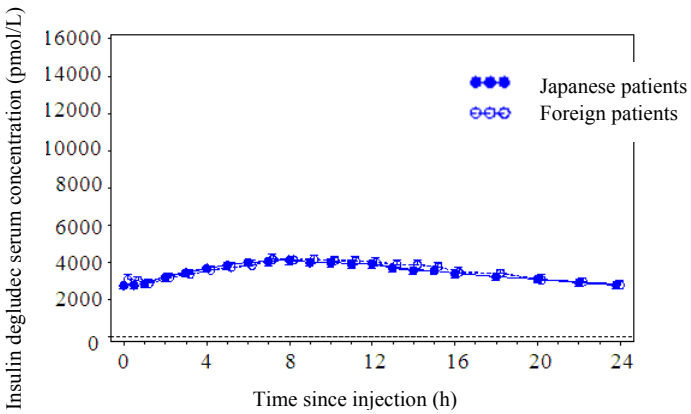

Figure 1. Mean steady-state 24-hour insulin degludec serum concentration-time profiles in Japanese and foreign patients with type 1 diabetes mellitus

Although the estimated half-life ($t_{1/2,SS}$, harmonic mean) was about 18 hours in Japanese patients with type 1 diabetes mellitus and about 25 hours in foreign patients with type 1 diabetes mellitus, this difference is considered attributable to a difference in the serum concentration-time profile beyond 48 hours post-dose and the insulin degludec serum concentration up to 48 hours after the last dose was similar between Japan and overseas (Table 30).

Table 30. Comparison of insulin degludec serum concentrations at 30, 36, and 48 hours after the last dose between Japanese and foreign patients with type 1 diabetes mellitus

Timepoint	Japanese patients with type 1 diabetes mellitus (n = 21)	Foreign patients with type 1 diabetes mellitus (n = 21)
30 hours after the last dose	2136 (48)	2171 (43)
36 hours after the last dose	1674 (49)	1745 (47)
48 hours after the last dose	1054 (55)	1136 (63)

Unit: pmol/L, Geometric mean (CV%)

The distribution of and fluctuation in the exposure of insulin degludec over the dosing interval at steady state were similar between Japanese and foreign patients with type 1 diabetes mellitus (Table 31).

Table 31. Comparison of distribution of and fluctuation in the exposure of insulin degludec over the dosing interval at steady state between Japanese and foreign patients with type 1 diabetes mellitus

Parameter	Japanese patients with type 1 diabetes mellitus (n = 21)	Foreign patients with type 1 diabetes mellitus (n = 21)[a)]
$AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$	0.53 (5.8)	0.53 (3.3)
$AUCF\%_{\tau,SS}$	11.6 (47)	12.5 (39)

Geometric mean (CV%)
$AUC_{0\text{-}12h,SS}$: area under the serum concentration-time curve from 0 to 12 hours after dosing
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state
$AUCF\%_{\tau,SS}$: relative fluctuation in the area under the concentration-time curve
a) Parameters during clamp periods are presented to be compared with those in Trial 1996.

Pharmacodynamic parameters following multiple-dose administration of 0.4 U/kg of IDeg were similar between Japanese and foreign patients with type 1 diabetes mellitus (Table 32).

Table 32. Comparison of pharmacodynamic parameters following multiple-dose administration of 0.4 U/kg of IDeg between Japanese and foreign patients with type 1 diabetes mellitus

Parameter	Japanese patients with type 1 diabetes mellitus (n = 21)	Foreign patients with type 1 diabetes mellitus (n = 21)
$AUC_{GIR,\tau,SS}$ (mg/kg)	1446 (55)	1948 (54)
$GIR_{max,SS}$ (mg/kg/min)	1.7 (43)	2.0 (49)
$tGIR_{max,SS}$[a)] (h)	10.6 (0.0-26.0)	11.6 (4.8-42.0)

Geometric mean (CV%)
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state, $GIR_{max,SS}$: maximum GIR at steady state
$tGIR_{max,SS}$: time to maximum GIR at steady state
a) Median (Min.-Max.)

In both Japanese and foreign patients, the pharmacodynamic profile of insulin degludec was flat and stable (Figure 2), the glucose-lowering effect was consistent and evenly distributed across a 24-hour dosing interval, and the distribution and fluctuation of the pharmacodynamic profile of insulin degludec over the dosing interval at steady state were similar between Japanese and foreign patients with type 1 diabetes mellitus (Table 33).

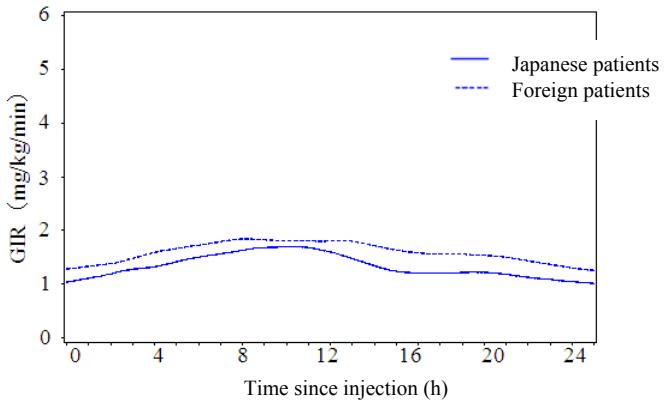

Figure 2. Steady-state pharmacodynamic profiles in Japanese and foreign patients with type 1 diabetes mellitus

Table 33. Comparison of distribution and fluctuation of pharmacodynamic profile of insulin degludec over the dosing interval at steady state between Japanese and foreign patients with type 1 diabetes mellitus

Parameter	Japanese patients with type 1 diabetes mellitus (n = 21)	Foreign patients with type 1 diabetes mellitus (n = 21)
$AUC_{GIR,0\text{-}12h,SS}/AUC_{GIR,\tau,SS}$	0.48 (30)	0.45 (27)
$AUCF\%_{GIR,\tau,SS}$	0.28 (46)	0.25 (76)

Geometric mean (CV%)
$AUC_{GIR,0\text{-}12h,SS}$: area under the GIR curve from 0 to 12 hours after dosing
$AUC_{GIR,\tau,SS}$: area under the GIR curve during a dosing interval at steady state
$AUCF\%_{GIR,\tau,SS}$: relative fluctuation in the area under the GIR curve

Based on the above, the pharmacokinetics and pharmacodynamics of insulin degludec are considered to be similar between Japanese and foreign patients with type 1 diabetes mellitus.

In patients with type 2 diabetes mellitus, based on the results of a PPK analysis of data from Trial 3586, the dose-normalized AUCs at steady state within the Asian region (Japan, Korea, Hong Kong, Malaysia, Taiwan, Thailand) were similar [see "4.(ii).A.(3).7) PPK analysis of data from phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586)"]. Among foreign patients, pharmacokinetic parameters were similar between patients with type 1 diabetes mellitus (Trial 1993) and patients with type 2 diabetes mellitus (Trial 1987) (Table 34) and the steady-state half-life ($t_{1/2,SS}$, harmonic mean) was approximately 25 hours. The distribution of the pharmacokinetic profile of insulin degludec over the dosing interval ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$) was 0.52 to 0.54 in both foreign patients with type 1 diabetes mellitus and foreign patients with type 2 diabetes mellitus.

Table 34. Comparison of pharmacokinetic parameters between foreign patients with type 1 diabetes mellitus and foreign patients with type 2 diabetes mellitus

Parameter	Dose (U/kg)	Foreign patients with type 1 diabetes mellitus[a)]	Foreign patients with type 2 diabetes mellitus
$AUC_{\tau,SS}$ (pmol·h/L)	0.4	82,501 [72,996; 93,242] (n = 21)	91,937 [84,630; 99,874] (n = 22)
	0.6	131,195 [116,082; 148,277] (n = 21)	129,371 [120,208; 139,233] (n = 37)
	0.8	158,968 [141,058; 179,153] (n = 22)	176,167 [161,994; 191,580] (n = 21)
$C_{max,SS}$ (pmol/L)	0.4	4357 [3884; 4888] (n = 21)	4643 [4238; 5086] (n = 22)
	0.6	6842 [6099; 7676] (n = 21)	6528 [6040; 7056] (n = 37)
	0.8	8435 [7539; 9437] (n = 22)	9018 [8220; 9893] (n = 21)

Least square mean [95% CI]
$AUC_{\tau,SS}$: area under the serum concentration-time curve during a dosing interval at steady state
$C_{max,SS}$: maximum steady-state serum concentration
a) Parameters during clamp periods are presented to be compared with those in Trial 1987.

In conclusion, the pharmacokinetics of insulin degludec were similar between Japanese patients with type 1 diabetes mellitus and foreign patients with type 1 diabetes mellitus, between foreign patients with type 1 diabetes mellitus and foreign patients with type 2 diabetes mellitus, and among patients with type 2 diabetes mellitus in the Asian countries including Japan. Thus, the pharmacokinetics of insulin degludec is considered to be similar between Japan and overseas.

PMDA considers as follows:
Although pharmacokinetic and pharmacodynamic similarities between Japanese and foreign patients with type 2 diabetes mellitus have not been assessed based on comparison of the data from Japanese and foreign clinical trials, pharmacokinetic and pharmacodynamic similarities between Japanese and foreign patients with type 1 diabetes mellitus have been demonstrated by the data from Japanese and foreign clinical trials and a PPK analysis of data from Trial 3586 revealed no differences in the steady-state pharmacokinetics among the participating countries. Therefore, although the similarities between Japanese and foreign patients with type 2 diabetes mellitus were explained indirectly, there should be no major differences in the pharmacokinetics and pharmacodynamics of insulin degludec between Japanese and foreign patients with type 1 or type 2 diabetes mellitus.

PMDA accepted the applicant's response.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from 3 phase I trials (1788, 1790, 1996), 1 phase II trial (3569), 2 phase III trials (3585, 3586), and 1 long-term treatment trial (3725) as the extension to Trial 3585, were submitted. As the reference data, the results from a total of 40 foreign trials (22 clinical pharmacology trials, 2 phase II trials, 9 phase III trials, 2 other trials, 5 ongoing trials) were submitted. HbA1c results are reported in NGSP units except for Trials 1996 and 3569.

4.(iii).A.(1) Phase I trials

4.(iii).A.(1).1) Single-dose trial in Japanese healthy adult subjects (5.3.4.1.1, Trial 1788 [December 2006 to March 2007])

A randomized, placebo-controlled, double-blind, parallel-group, comparative trial in Japanese healthy adult male subjects living in Europe (Target sample size of 32) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of single subcutaneous administration of IDeg (Formulation B) and IDegAsp [for pharmacokinetic data, see "4.(ii).A.(2).1) Single-dose trial"].

A single dose of 0.3, 0.6, or 1.2 U/kg of Formulation B, 0.9 U/kg of a coformulation of IAsp (50%) and insulin degludec (50%) (IDegAsp50), or placebo was to be subcutaneously administered in the abdomen. Eight subjects (6 subjects receiving active treatment, 2 subjects receiving placebo) were assigned to each group.

All of 32 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.

Regarding safety, adverse events occurred in 3 of the 32 subjects (haematoma of left thigh in 1 subject in the IDeg 1.2 U/kg group, tooth disorder in 1 subject in the IDegAsp50 group, tinnitus in 1 subject in the placebo group), but a causal relationship to trial drug was denied for all events. No injection site reaction or hypoglycemic symptom was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant findings in vital signs, ECG, laboratory tests, or physical examination.

4.(iii).A.(1).2) Multiple-dose trial in Japanese healthy adult subjects (5.3.4.1.2, Trial 1790 [December 2007 to February 2008])

A randomized, placebo-controlled, double-blind, parallel-group, comparative trial in Japanese healthy adult male subjects (Target sample size of 32, 8 subjects per group) was conducted to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple subcutaneous doses of IDeg (Formulation D and Formulation E) and IDegAsp [for pharmacokinetic data, see "4.(ii).A.(2).2) Multiple-dose trial"].

Formulation D, Formulation E, IDegAsp containing IAsp (30%) and insulin degludec (70%) (IDegAsp30), or IDegAsp containing IAsp (45%) and insulin degludec (55%) (IDegAsp45) at a dose of 0.1 U/kg or placebo was to be subcutaneously administered in the abdomen once daily for 6 days. Eight subjects (6 subjects receiving active treatment, 2 subjects receiving placebo) were assigned to each group.

All of 32 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses.

Regarding safety, 1 of the 32 subjects had an adverse event (syncope vasovagal in the IDegAsp30 group), but the event was mild in severity and its causal relationship to trial drug was denied. As to local tolerance at the injection site, 4 subjects had injection site reactions (1 subject in the Formulation D group, 2 subjects in the Formulation E group, 1 subject in the placebo group), but the reactions did

not meet the adverse event criteria.[50] No hypoglycemic symptoms were reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant findings in vital signs, ECG, laboratory tests, or physical examination.

4.(iii).A.(1).3) Multiple-dose trial in Japanese patients with type 1 diabetes mellitus (5.3.4.2.1, Trial 1996 [June to October 2010])

A randomized, double-blind, IDet-controlled, two-period, crossover trial in Japanese patients with type 1 diabetes mellitus [51] (Target sample size of 20) was conducted to evaluate the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple subcutaneous doses of IDeg [for pharmacokinetic data, see "4.(ii).A.(3).1) Multiple-dose trial in Japanese patients with type 1 diabetes mellitus"].

IDeg or IDet at a dose of 0.4 U/kg was to be subcutaneously administered in the thigh once daily for 6 days. A 7- to 21-day washout period was included between treatments.

All of 22 treated subjects were included in the safety, pharmacokinetic, and pharmacodynamic analyses. One subject was withdrawn from the trial after receiving 6 doses of IDet followed by 4 doses of IDeg (consent withdrawal).

Regarding safety, adverse events occurred in 4 of the 22 subjects (3 subjects after administration of IDeg [vomiting, oedema peripheral, and tendon rupture; 1 subject each], 1 subject after administration of IDet [nasopharyngitis]), but all events were mild in severity and their causal relationship to trial drug was denied. While confirmed hypoglycaemia[31] occurred in 13 subjects (93 episodes) after administration of IDeg and 15 subjects (76 episodes) after administration of IDet and nocturnal confirmed hypoglycaemia[32] occurred in 6 subjects (16 episodes) after administration of IDeg and 7 subjects (12 episodes) after administration of IDet, no severe hypoglycaemia[33] was reported. No injection site reaction was reported. No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant findings in vital signs, ECG, laboratory tests, or physical examination.

[50] Each injection site reaction was scored on a 6-point scale (0 = no reaction, 0.5 = barely perceptible erythema, 1 = slight erythema [with or without slight edema], 2 = moderate erythema and edema [with or without papules], 3 = severe erythema, edema, and induration [with or without papules], 4 = serious erythema [with edema, vesicle, or blister]) and an injection site reaction with a score of ≥2 was classified as an adverse event.

[51] Key inclusion criteria: treated with insulin therapy for ≥12 months (basal insulin ≥0.3 U/kg/day); HbA1c (JDS) at screening ≤10.0%; BMI ≥18.0 and ≤28.0 kg/m^2; fasting C-peptide <0.3 nmol/L; and patients with type 1 diabetes mellitus aged ≥20 and ≤65 years.

4.(iii).A.(2) Phase II trial

Exploratory trial in patients with type 1 diabetes mellitus (5.3.5.1.1, Trial 3569 [January to May 2009])

A randomized, open-label, IDet-controlled, parallel-group, comparative trial in Japanese patients with type 1 diabetes mellitus on a basal-bolus regimen with IAsp[52] (Target sample size of 60, 30 subjects per group) was conducted to evaluate the safety of subcutaneous administration of IDeg (Formulation E).

Formulation E or IDet as basal insulin (once daily at bedtime) and IAsp as bolus insulin (three times daily immediately before meals) were to be subcutaneously administered for 6 weeks. The starting dose of basal insulin (Formulation E or IDet) was the same as the subject's basal insulin dose immediately prior to the start of study treatment and then doses were adjusted based on self-measured plasma glucose (SMPG) values before breakfast, before lunch, before the evening meal, and at bedtime from the two days prior to site visits and telephone contacts, according to a titration algorithm (Table 35).

Table 35. Titration algorithm

Pre-breakfast SMPG[a)] (mg/dL)	Basal insulin dose adjustment
<80	Decrease by ≥1 U
≥80 and <110	No adjustment
≥110 and <130	Increase by 1 U
≥130 and <160	Increase by 2 U
≥160	Increase by 3 U

a) Mean pre-breakfast SMPG of 2 days

All of 65 treated subjects (33 subjects in the Formulation E group, 32 subjects in the IDet group) were included in the Safety Analysis Set and the Full Analysis Set (FAS), and FAS was used for efficacy analysis.

According to efficacy analysis, the change in fasting plasma glucose (FPG) from baseline to the end of treatment (Week 6) (least square mean ± SE) was as shown in Table 36.

Table 36. Change in FPG from baseline to the end of treatment (Week 6) (Trial 3569, FAS)

Treatment group	Baseline	Week 6 (LOCF)	Change (LOCF)	Least square mean change[a)]	Treatment difference [95% CI][a)]
Formulation E (n = 33)	181.8 (66.2)	146.7 (60.2)	-35.1 (77.5)	-15.9 ± 12.6	3.1 [-25.7, 31.9]
IDet (n = 32)	141.8 (54.3)	135.7 (49.0)	-6.1 (68.5)	-19.0 ± 13.8	

Unit: mg/dL, Mean (SD), Least square mean ± SE

a) Calculated using an analysis of variance (ANOVA) model with treatment and pre-trial basal insulin (insulin glargine, NPH insulin) as fixed factors and baseline FPG as a covariate.

[52] Key inclusion criteria: treated with a basal-bolus regimen consisting of a long-acting insulin analog (excluding IDet) or an intermediate-acting human insulin preparation (basal insulin) and IAsp (bolus insulin) for ≥12 weeks prior to screening (3 weeks prior to the start of trial drug administration [± 7 days]); total daily insulin ≤100 U/day; HbA1c (JDS) at screening <10.0%; and patients with type 1 diabetes mellitus aged ≥20 years.

Regarding safety, the incidence of adverse events[53] was 33.3% (11 of 33 subjects) in the Formulation E group and 28.1% (9 of 32 subjects) in the IDet group and adverse events reported by at least 2 subjects in either treatment group were nasopharyngitis (15.2% [5 of 33 subjects] in the IDeg group) and upper respiratory inflammation (6.3% [2 of 32 subjects] in the IDet group). Most of the events were mild in severity. One subject in the IDet group had moderate events (hepatitis alcoholic/oedema peripheral), but no severe events were reported. Palpitation reported by 1 subject (Formulation E group) only was classified as an adverse drug reaction.

The occurrence of hypoglycaemia was as shown in Table 37 and no severe hypoglycaemia was reported.

Table 37. Occurrence of hypoglycaemia (Safety Analysis Set)

		Formulation E (n = 33)			IDet (n = 32)		
		Incidence % (No. of subjects with episodes)	Total number of episodes	Number of episodes/patient-year	Incidence % (No. of subjects with episodes)	Total number of episodes	Number of episodes/patient-year
Hypoglycaemia	Overall	90.9 (30)	315	74.56	78.1 (25)	365	88.88
	Severe hypoglycaemia[b)]	0.0 (0)	0	0.00	0.0 (0)	0	0.00
	Minor hypoglycaemia[c)]	90.9 (30)	266	62.97	78.1 (25)	332	80.84
	Hypoglycaemic symptoms[d)]	36.4 (12)	49	11.60	31.3 (10)	33	8.04
Nocturnal hypoglycaemia[a)]	Overall	36.4 (12)	25	5.92	53.1 (17)	74	18.02
	Severe hypoglycaemia[b)]	0.0 (0)	0	0.00	0.0 (0)	0	0.00
	Minor hypoglycaemia[c)]	36.4 (12)	21	4.97	46.9 (15)	65	15.83
	Hypoglycaemic symptoms[d)]	12.1 (4)	4	0.95	18.8 (6)	9	2.19

a) Hypoglycaemia occurring between 23:00 p.m. and 5:59 a.m.
b) Hypoglycaemia requiring the assistance of another person for treatment
c) Subjects were able to treat themselves and had a SMPG <56 mg/dL.
d) Subjects were able to treat themselves and had a SMPG ≥56 mg/dL.

No deaths, serious adverse events, or adverse events leading to trial discontinuation were reported and there were no clinically significant findings in vital signs or ECG.

4.(iii).A.(3) Phase III trials

4.(iii).A.(3).1) Multinational trial in patients with type 1 diabetes mellitus (5.3.5.1.2, Trial 3585 [February to December 2010])

A randomized, open-label, IDet-controlled, parallel-group, comparative trial in Japanese and foreign[54] patients with type 1 diabetes mellitus[55] on a basal-bolus regimen (Target sample size of 426) was conducted to evaluate the efficacy and safety of IDeg.

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53 Events occurring between the start of trial drug administration and 5 days after the end of administration.

54 Europe (UK, Finland, Italy, Macedonia), India, and Brazil

55 Key inclusion criteria: diabetes duration ≥12 months; BMI ≤35.0 kg/m^2; HbA1c (NGSP) ≤10.0%; treated with a basal-bolus regimen for ≥12 months prior to screening (about 1 week prior to the start of trial drug administration); and patients with type 1 diabetes mellitus aged ≥18 years (≥20 years for Japanese patients).

The trial consisted of a run-in period (about 1 week), a treatment period (26 weeks) in which basal insulin (IDeg or IDet) and bolus insulin (IAsp) are administered, and a follow-up period (1 week) in which subjects are switched from IDeg or IDet to NPH insulin for basal insulin coverage, for insulin antibody measurements. This trial was followed by a 26-week extension trial for long-term treatment [see "4.(iii).A.(3).3) Extension of Trial 3585"]. Region was set as the stratification factor, and subjects were assigned randomly. The randomization ratio was 2:1 (IDeg:IDet).

IDeg or IDet as basal insulin and IAsp as bolus insulin were to be subcutaneously administered for 26 weeks. IDeg or IDet was to be administered in the thigh, upper arm, or abdomen once daily in the evening (from the start of the evening meal until bedtime) and IAsp was to be administered in the abdomen three times daily, immediately before meals. The starting dose of basal insulin (IDeg or IDet) was the same as the subject's basal insulin dose immediately prior to the start of study treatment and then doses were adjusted to reach a target value of 90 mg/dL according to a titration guideline (Table 38), based on pre-breakfast SMPG values from the three days prior to site visits and telephone contacts. In the IDet group, switching from once-daily IDet regimen to twice-daily regimen was allowed when glycemic control is inadequate after ≥8 weeks of dose optimization.[56] When a second dose of IDet was initiated, 4 units were to be administered before breakfast and then doses were adjusted based on pre-dinner SMPG values according to the titration guideline (Table 38). The starting dose of bolus insulin was the same as the subject's bolus insulin dose immediately prior to the start of study treatment and then doses were adjusted to reach a target value of 90 mg/dL according to the titration guideline (Table 38), based on SMPG values before the next meals from the three days prior to site visits and telephone contacts.

Table 38. Titration guideline[a)] (Trial 3585)

Basal insulin		Bolus insulin	
Pre-breakfast SMPG[b)] (mg/dL)	Dose adjustment	Pre-meal SMPG[c)] (mg/dL)	Dose adjustment
<56	Decrease by 4 U	<90	No adjustment
≥56 and <70	Decrease by 2 U	≥90 and <144	Increase by 2 U
≥70 and <90	No adjustment	≥144 and <180	Increase by 3 U
≥90 and <180	Increase by 2 U	≥180	Increase by 4
≥180 and <270	Increase by 4 U	—	—
≥270	Increase by 6 U	—	—

a) In initial insulin titration, changes in the bolus insulin dose could be considered once the basal insulin dose had been optimized, unless the investigator found it necessary to adjust the bolus insulin dose first.
b) When IDet was administered twice daily, the insulin dose before breakfast was adjusted based on pre-dinner SMPG value.
c) Doses were adjusted based on mean SMPG values before the next meals from 3 days and the dose of IAsp before the evening meal was adjusted based on SMPG value at bedtime.

For antibody measurements, at ≥24 hours after the last dose of basal insulin (IDeg or IDet), NPH insulin (the dose of NPH insulin was 80% of the basal insulin dose at the end of treatment) was to be

[56] If all of the following three criteria were met: (a) no adequate improvement in glycemic control (a worsening of HbA1c in the case of baseline HbA1c <8.0% or a <0.5% improvement in HbA1c in the case of baseline HbA1c ≥8.0% and ≤10.0%) (b) pre-dinner SMPG value (mean) >108 mg/dL (c) no treatable intercurrent cause for the hyperglycemia diagnosed.

subcutaneously administered twice daily in divided doses (before breakfast and from before the evening meal until bedtime) for 1 week after the end of trial drug administration (IAsp was continued).

Of 456 randomized subjects (303 subjects in the IDeg group [including 124 Japanese subjects], 153 subjects in the IDet group [including 62 Japanese subjects]), 455 subjects (302 subjects in the IDeg group [including 124 Japanese subjects], 153 subjects in the IDet group [including 62 Japanese subjects]) were included in the FAS, and 1 subject who was withdrawn from the trial due to failure to meet the inclusion criteria (IDeg group) was excluded. A total of 453 treated subjects (301 subjects in the IDeg group [including 124 Japanese subjects], 152 subjects in the IDet group [including 61 Japanese subjects]) were included in the Safety Analysis Set and 2 subjects who did not receive trial drug (1 subject each in the IDeg and IDet groups) were excluded. The FAS was used for efficacy analysis. Two hundred eighty-three subjects in the IDeg group (including 121 Japanese subjects) and 138 subjects in the IDet group (including 56 Japanese subjects) completed 26-week treatment with trial drug. There were 35 withdrawals from the trial (20 subjects in the IDeg group [including 3 Japanese subjects], 15 subjects in the IDet group [including 6 Japanese subjects]) and the reasons for withdrawal included adverse events in 4 subjects (3 subjects in the IDeg group [including 1 Japanese subject], 1 subject in the IDet group), ineffective therapy in 2 subjects (IDet group), non-compliance with the protocol in 7 subjects (3 subjects in the IDeg group, 4 subjects in the IDet group [including 3 Japanese subjects]), withdrawal criteria met in 9 subjects (6 subjects in the IDeg group [including 1 Japanese subject], 3 subjects in the IDet group [including 1 Japanese subject]), and others in 13 subjects (8 subjects in the IDeg group [including 1 Japanese subject], 5 subjects in the IDet group [including 2 Japanese subjects]).

Regarding efficacy, the change in HbA1c from baseline (at the start of trial drug administration) to Week 26 (least square mean ± SE) in the FAS in the entire trial population, the primary endpoint, was -0.71 ± 0.06% in the IDeg group and -0.61 ± 0.07% in the IDet group and the treatment difference with its 95% CI was -0.09% [-0.23, 0.05]. Since the upper limit of the CI was less than the predefined non-inferiority margin (0.4%), the non-inferiority of IDeg to IDet was demonstrated (Table 39). The treatment difference with its 95% CI in the Japanese subgroup was -0.09% [-0.29, 0.10].

Table 39. HbA1c change from baseline to Week 26
(Trial 3585 [26 weeks of treatment], FAS)

	Treatment group	Baseline	Week 26 (LOCF)	Change (LOCF)	Least square mean change[a)]	Treatment difference [95% CI][a)]
Entire trial population	IDeg (n = 302)	7.98 (0.98)	7.25 (0.99)	-0.73 (0.88)	-0.71 ± 0.06	-0.09 [-0.23, 0.05]
	IDet (n = 153)	7.99 (0.88)	7.35 (0.91)	-0.65 (0.86)	-0.61 ± 0.07	
Japanese subgroup	IDeg (n = 124)	7.93 (0.92)	6.94 (0.73)	-0.99 (0.72)	-1.03 ± 0.06	-0.09 [-0.29, 0.10]
	IDet (n = 62)	8.20 (0.86)	7.18 (0.83)	-1.02 (0.77)	-0.94 ± 0.08	

Unit: %, Mean (SD), Least square mean ± SE

a) Calculated by an ANOVA with treatment, anti-diabetic therapy at screening (basal insulin once daily or twice daily), sex, and region (Europe, Japan, India, Brazil; Not included in the analysis of the Japanese subgroup) as fixed factors and age and baseline HbA1c as covariates.

The change in HbA1c over time from baseline to Week 26 in the Japanese subgroup or in the entire trial population was as shown in Figure 3.

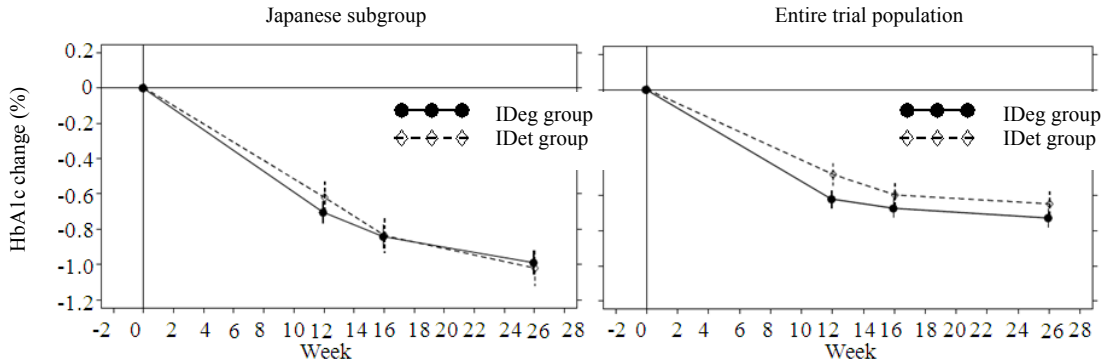

Figure 3. Change in HbA1c over time from baseline to Week 26
(Trial 3585, Japanese subgroup and entire trial population, LOCF) (mean ± SE)

The results of analyses of the main secondary endpoints from baseline to Week 26 in the entire trial population and the Japanese subgroup were as shown in Table 40 and Table 41, respectively.

Table 40. Results of analyses of main secondary endpoints
(Trial 3585 [26 weeks of treatment] Entire trial population;
Upper five items, FAS; Lower four items, Safety Analysis Set)

Endpoint		IDeg	IDet
FPG (mg/dL)	Baseline	178.2 ± 71.9 (n = 301)	170.8 ± 72.4 (n = 148)
	Change (LOCF)	-46.8 ± 87.8 (n = 301)	-11.3 ± 80.9 (n = 148)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment (%) (LOCF)		41.1 (124/302 subjects)	37.3 (57/153 subjects)
Proportion of subjects achieving HbA1c ≤6.5% at the end of treatment (%) (LOCF)		24.2 (73/302 subjects)	21.6 (33/153 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without confirmed hypoglycaemia[a)] (%) (LOCF)		6.2 (18/292 subjects)	6.9 (10/145 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without severe hypoglycaemia[b)] (%) (LOCF)		39.7 (116/292 subjects)	36.6 (53/145 subjects)
Body weight (kg)	Baseline	66.5 ± 14.9 (n = 301)	66.7 ± 13.5 (n = 152)
	Change (LOCF)	1.5 ± 2.7 (n = 301)	0.4 ± 2.4 (n = 152)
Basal insulin dose (U/day)	Baseline (Week 1)	22 ± 12 (n = 298)	22 ± 12 (n = 149)
	Week 26 (LOCF)	25 ± 16 (n = 301)	29 ± 20 (n = 152)
Bolus insulin dose (U/day)	Baseline (Week 1)	28 ± 15 (n = 298)	30 ± 15 (n = 149)
	Week 26 (LOCF)	36 ± 26 (n = 301)	41 ± 25 (n = 152)
Total insulin dose (U/day)	Baseline (Week 1)	50 ± 22 (n = 298)	52 ± 23 (n = 149)
	Week 26 (LOCF)	61 ± 36 (n = 301)	69 ± 38 (n = 152)

Mean ± SD
a) Confirmed hypoglycaemia: "severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"
b) Severe hypoglycaemia: hypoglycaemia requiring the assistance of another person for treatment

Table 41. Results of analyses of main secondary endpoints
(Trial 3585 [26 weeks of treatment] Japanese subgroup;
Upper five items, FAS; Lower four items, Safety Analysis Set)

Endpoint		IDeg	IDet
FPG (mg/dL)	Baseline	175.5 ± 65.9 (n = 124)	171.3 ± 56.8 (n = 61)
	Change (LOCF)	-54.6 ± 74.0 (n = 124)	-14.0 ± 73.7 (n = 61)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment (%) (LOCF)		53.2 (66/124 subjects)	46.8 (29/62 subjects)
Proportion of subjects achieving HbA1c ≤6.5% at the end of treatment (%) (LOCF)		28.2 (35/124 subjects)	25.8 (16/62 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without confirmed hypoglycaemia[a)] (%) (LOCF)		2.4 (3/123 subjects)	6.7 (4/60 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without severe hypoglycaemia[b)] (%) (LOCF)		52.8 (65/123 subjects)	46.7 (28/60 subjects)
Body weight (kg)	Baseline	59.1 ± 10.2 (n = 124)	60.7 ± 10.6 (n = 61)
	Change (LOCF)	1.2 ± 2.4 (n = 124)	0.2 ± 2.3 (n = 61)
Basal insulin dose (U/day)	Baseline (Week 1)	15 ± 7 (n = 124)	16 ± 8 (n = 61)
	Week 26 (LOCF)	16 ± 9 (n = 124)	21 ± 15 (n = 61)
Bolus insulin dose (U/day)	Baseline (Week 1)	26 ± 13 (n = 124)	29 ± 12 (n = 61)
	Week 26 (LOCF)	28 ± 14 (n = 124)	34 ± 15 (n = 61)
Total insulin dose (U/day)	Baseline (Week 1)	41 ± 18 (n = 124)	45 ± 18 (n = 61)
	Week 26 (LOCF)	45 ± 21 (n = 124)	56 ± 27 (n = 61)

Mean ± SD
a) Confirmed hypoglycaemia: "severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"
b) Severe hypoglycaemia: hypoglycaemia requiring the assistance of another person for treatment

Regarding safety, in the entire trial population, the incidence of adverse events[57] was 72.8% (219 of 301 subjects) in the IDeg group and 73.7% (112 of 152 subjects) in the IDet group and the incidence of adverse drug reactions was 21.9% (66 of 301 subjects) in the IDeg group and 19.1% (29 of 152 subjects) in the IDet group. In the Japanese subgroup, the incidence of adverse events was 83.1% (103 of 124 subjects) in the IDeg group and 86.9% (53 of 61 subjects) in the IDet group and the incidence of adverse drug reactions was 20.2% (25 of 124 subjects) in the IDeg group and 8.2% (5 of 61 subjects) in the IDet group. Adverse events occurring in ≥3% of subjects in either treatment group and adverse drug reactions in the entire trial population and in the Japanese subgroup were as shown in Table 42 and Table 43, respectively.

[57] Events occurring between the start of trial drug administration and 7 days after the end of administration.

Table 42. Adverse events and/or adverse drug reactions occurring in ≥3% of subjects in either treatment group (Trial 3585 [26 weeks of treatment] Entire trial population; Safety Analysis Set)

Event	IDeg (n = 301)		IDet (n = 152)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	72.8 (219)	21.9 (66)	73.7 (112)	19.1 (29)
Nasopharyngitis	19.6 (59)	0.0 (0)	22.4 (34)	0.0 (0)
Upper respiratory tract infection	7.3 (22)	0.0 (0)	7.2 (11)	0.0 (0)
Gastroenteritis	4.7 (14)	0.3 (1)	3.9 (6)	0.0 (0)
Bronchitis	1.7 (5)	0.0 (0)	3.3 (5)	0.0 (0)
Diarrhoea	5.0 (15)	0.3 (1)	4.6 (7)	0.0 (0)
Abdominal pain upper	3.3 (10)	0.3 (1)	3.3 (5)	0.7 (1)
Vomiting	4.7 (14)	0.3 (1)	0.7 (1)	0.0 (0)
Nausea	3.3 (10)	0.7 (2)	2.0 (3)	0.7 (1)
Headache	12.0 (36)	2.0 (6)	6.6 (10)	0.7 (1)
Hypoglycaemia	6.3 (19)	6.0 (18)	9.9 (15)	8.6 (13)
Hypoglycaemic unconsciousness	4.0 (12)	3.3 (10)	2.6 (4)	1.3 (2)
Back pain	4.7 (14)	0.0 (0)	2.0 (3)	0.0 (0)
Arthralgia	3.7 (11)	0.7 (2)	0.7 (1)	0.0 (0)
Pyrexia	4.3 (13)	0.3 (1)	3.9 (6)	0.0 (0)
Wrong drug administered	3.3 (10)	0.7 (2)	1.3 (2)	0.0 (0)
Cough	4.3 (13)	0.3 (1)	5.3 (8)	0.0 (0)
Diabetic retinopathy	3.3 (10)	1.3 (4)	2.6 (4)	0.7 (1)

Incidence % (no. of subjects with events), MedDRA/J (ver.13.1)

Table 43. Adverse events and/or adverse drug reactions occurring in ≥3% of subjects in either treatment group (Trial 3585 [26 weeks of treatment] Japanese subgroup; Safety Analysis Set)

Event	IDeg (n = 124)		IDet (n = 61)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	83.1 (103)	20.2 (25)	86.9 (53)	8.2 (5)
Nasopharyngitis	30.6 (38)	0.0 (0)	34.4 (21)	0.0 (0)
Upper respiratory tract infection	6.5 (8)	0.0 (0)	3.3 (2)	0.0 (0)
Bronchitis	3.2 (4)	0.0 (0)	8.2 (5)	0.0 (0)
Gastroenteritis	3.2 (4)	0.0 (0)	4.9 (3)	0.0 (0)
Rhinitis	4.0 (5)	0.0 (0)	1.6 (1)	0.0 (0)
Abdominal pain upper	4.8 (6)	0.0 (0)	6.6 (4)	0.0 (0)
Diarrhoea	5.6 (7)	0.8 (1)	0.0 (0)	0.0 (0)
Abdominal discomfort	4.0 (5)	0.0 (0)	1.6 (1)	0.0 (0)
Gastritis	3.2 (4)	0.0 (0)	1.6 (1)	0.0 (0)
Nausea	2.4 (3)	0.0 (0)	3.3 (2)	0.0 (0)
Gingivitis	0.0 (0)	0.0 (0)	3.3 (2)	0.0 (0)
Back pain	6.5 (8)	0.0 (0)	1.6 (1)	0.0 (0)
Musculoskeletal stiffness	4.8 (6)	0.0 (0)	1.6 (1)	0.0 (0)
Arthralgia	4.0 (5)	0.8 (1)	0.0 (0)	0.0 (0)
Arthropod sting	3.2 (4)	0.0 (0)	1.6 (1)	0.0 (0)
Wrong drug administered	3.2 (4)	0.0 (0)	1.6 (1)	0.0 (0)
Headache	6.5 (8)	0.0 (0)	3.3 (2)	0.0 (0)
Hypoaesthesia	1.6 (2)	0.0 (0)	3.3 (2)	0.0 (0)
Eczema	2.4 (3)	0.8 (1)	3.3 (2)	0.0 (0)
Dermatitis	0.0 (0)	0.0 (0)	3.3 (2)	0.0 (0)
Diabetic retinopathy	4.0 (5)	1.6 (2)	6.6 (4)	1.6 (1)
Weight increased	5.6 (7)	4.8 (6)	0.0 (0)	0.0 (0)
Hyperglycaemia	0.0 (0)	0.0 (0)	3.3 (2)	1.6 (1)

Incidence % (no. of subjects with events), MedDRA/J (ver.13.1)

No deaths were reported. In the entire trial population, the incidence of serious adverse events was 7.6% (23 of 301 subjects) (33 events) in the IDeg group and 5.3% (8 of 152 subjects) (13 events) in the IDet group and serious adverse events reported by at least 2 subjects were hypoglycaemia (2.3% [7

of 301 subjects] [10 events] in the IDeg group, 3.3% [5 of 152 subjects] [7 events] in the IDet group), hypoglycaemic unconsciousness (1.3% [4 of 301 subjects] [4 events] in the IDeg group, 2.0% [3 of 152 subjects] [3 events] in the IDet group), and hypoglycaemic coma (1.0% [3 of 301 subjects] [3 events] in the IDeg group). Of which, 8 events of hypoglycaemia reported by 7 subjects in the IDeg group and 6 events of hypoglycaemia reported by 4 subjects in the IDet group, 3 events of hypoglycaemic unconsciousness reported by 3 subjects in the IDeg group and 1 event of hypoglycaemic unconsciousness reported by 1 subject in the IDet group, and 3 events of hypoglycaemic coma reported by 3 subjects were classified as adverse drug reactions. In the Japanese subgroup, the incidence of serious adverse events was 9.7% in the IDeg group (12 of 124 subjects; hypoglycaemic unconsciousness in 2 subjects, hypoglycaemic coma in 2 subjects, hypoglycaemia, hypoglycaemic coma/heat stroke, upper abdominal pain, hyperthyroidism, pyelonephritis/ketosis, fractured ischium/rib fracture, lumbar spinal stenosis, cellulitis/oral abscess) and 1.6% in the IDet group (1 of 61 subjects; hyperglycaemia/dehydration), of which the events reported by 5 subjects in the IDeg group (hypoglycaemic coma in 3 subjects, hypoglycaemic unconsciousness, hypoglycaemia) and the events reported by 1 subject in the IDet group (hyperglycaemia/dehydration) were classified as adverse drug reactions. Adverse events leading to trial discontinuation occurred in 3 subjects in the IDeg group (fractured ischium/rib fracture [a Japanese subject], hypoglycaemia/pyrexia, hypoglycaemic unconsciousness) and 1 subject in the IDet group (hypoglycaemia), of which hypoglycaemia/pyrexia and hypoglycaemic unconsciousness in the IDeg group and hypoglycaemia in the IDet group were classified as adverse drug reactions.

The occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population was as shown in Table 44 and the estimated rate ratios (IDeg/IDet) for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia with their 95% CIs[58] were 0.98 [0.80, 1.20] and 0.66 [0.49, 0.88], respectively, in the entire trial population and 0.94 [0.70, 1.25] and 0.48 [0.31, 0.75], respectively, in the Japanese subgroup.

[58] The number of episodes was analyzed using a negative binomial regression model with a log link function and log of treatment-emergent period as offset. The model included treatment, anti-diabetic therapy at screening, sex, and region (not included in the analysis of the Japanese subgroup) as fixed factors and age as a covariate.

Table 44. Occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population (Trial 3585 [26 weeks of treatment] Safety Analysis Set)

Endpoint	Japanese subgroup		Entire trial population	
	IDeg (n = 124)	IDet (n = 61)	IDeg (n = 301)	IDet (n = 152)
Confirmed hypoglycaemia[a)]	98.4 (122)	98.4 (60)	93.0 (280)	91.4 (139)
	3666 [5994]	1759 [5916]	6673 [4583]	3295 [4569]
Nocturnal confirmed hypoglycaemia[a)b)]	59.7 (74)	72.1 (44)	58.5 (176)	58.6 (89)
	318 [520]	281 [945]	603 [414]	428 [593]
Severe hypoglycaemia[c)]	6.5 (8)	0.0 (0)	10.6 (32)	10.5 (16)
	9 [15]	0 [0]	45 [31]	28 [39]
Severe nocturnal hypoglycaemia[b)c)]	0.8 (1)	0.0 (0)	4.0 (12]	3.3 (5)
	1 [2]	0 [0]	13 [9]	6 [8]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]
a) Confirmed hypoglycaemia: "severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"
b) Nocturnal hypoglycaemia: hypoglycaemia occurring between 0:01 a.m. and 5:59 a.m.
c) Severe hypoglycaemia: hypoglycaemia requiring the assistance of another person for treatment

There were no clinically significant findings in vital signs, ECG, or the ocular fundus.

4.(iii).A.(3).2) Multinational trial in patients with type 2 diabetes mellitus (5.3.5.1.3, Trial 3586 [February to December 2010])

A randomized, open-label, IGlar-controlled, parallel-group, comparative trial in insulin-naïve Japanese and Asian[59] patients with type 2 diabetes mellitus[60] (Target sample size of 426) was conducted to evaluate the efficacy and safety of IDeg when used concominantly with oral anti-diabetic drugs [for pharmacokinetic data, see "4.(ii).A.(3).7) PPK analysis of data from phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586)"].

The trial consisted of a run-in period (about 1 week), a treatment period (26 weeks) in which IDeg or IGlar was administered, and a follow-up period (1 week) in which subjects were switched from IDeg or IGlar to NPH insulin for insulin antibody measurements. Region was set as the stratification factor, and subjects were assigned randomly. The randomization ratio was 2:1 (IDeg:IGlar).

IDeg or IGlar was to be subcutaneously administered for 26 weeks. IDeg was to be administered in the thigh, upper arm, or abdomen once daily in the evening (from the start of the evening meal until bedtime) and IGlar was to be administered according to the local labeling. Insulin doses were adjusted to reach a target value of 90 mg/dL according to a titration guideline (Table 45), based on pre-breakfast SMPG values (mean) from the three days prior to site visits and telephone contacts. The recommended starting dose was 10 U/day, but the dose was allowed to be adjusted at the discretion of the investigator. Previous oral anti-diabetic therapy was to be continued unless dose reduction was

[59] Korea, Malaysia, Taiwan, Thailand, and Hong Kong

[60] Key inclusion criteria: diabetes duration ≥6 months; BMI ≤35.0 kg/m^2; HbA1c (NGSP) ≥7.0% and ≤10.0%; treated with an insulin secretagogue (an SU or a rapid-acting insulin secretagogue) ± metformin ± an α-glucosidase inhibitor or a DPP-4 inhibitor at stable dosages for ≥3 months prior to screening (about 1 week prior to the start of trial drug administration); and patients with type 2 diabetes mellitus aged ≥18 years (≥20 years for Japanese patients).

required from a safety point of view, except for dipeptidyl peptidase-4 (DPP-4) inhibitors, which were discontinued at the start of trial drug administration.

Table 45. Titration guideline (Trial 3586)

Pre-breakfast SMPG (mg/dL)	Basal insulin dose adjustment
<56	Decrease by 4 U
≥56 and <70	Decrease by 2 U
≥70 and <90	No adjustment
≥90 and <126	Increase by 2 U
≥126 and <144	Increase by 4 U
≥144 and <162	Increase by 6 U
≥162	Increase by 8 U

For antibody measurements, NPH insulin (the dose of NPH insulin was 80% of the basal insulin dose at the end of treatment) was to be subcutaneously administered twice daily in divided doses (before breakfast and from before the evening meal until bedtime) for 1 week after the end of trial drug administration, i.e. 24 hours after the last dose of IDeg or IGlar.

All of 435 randomized subjects (289 subjects in the IDeg group [including 89 Japanese subjects], 146 subjects in the IGlar group [including 44 Japanese subjects]) were included in the FAS. A total of 430 treated subjects (284 subjects in the IDeg group [including 88 Japanese subjects], 146 subjects in the IGlar group [including 44 Japanese subjects]) were included in the Safety Analysis Set and 5 subjects who did not receive trial drug (IDeg group) were excluded. The FAS was used for efficacy analysis. Two hundred fifty-eight subjects in the IDeg group (including 84 Japanese subjects) and 136 subjects in the IGlar group (including 44 Japanese subjects) completed 26-week treatment with trial drug. There were 41 withdrawals from the trial (31 subjects in the IDeg group [including 5 Japanese subjects], 10 subjects in the IGlar group). The reasons for withdrawal included adverse events in 5 subjects (2 subjects in the IDeg group [including 1 Japanese subject), 3 subjects in the IGlar group), ineffective therapy in 1 subject (IDeg group [a Japanese subject]), non-compliance with the protocol in 5 subjects (3 subjects in the IDeg group, 2 subjects in the IGlar group), withdrawal criteria met in 15 subjects (13 subjects in the IDeg group [including 1 Japanese subject], 2 subjects in the IGlar group), and others in 15 subjects (12 subjects in the IDeg group [including 2 Japanese subjects], 3 subjects in the IGlar group).

The change in HbA1c from baseline (at the start of trial drug administration) to Week 26 (least square mean ± SE) in the FAS in the entire trial population, the primary efficacy endpoint, was -1.42 ± 0.06% in the IDeg group and -1.52 ± 0.07% in the IGlar group and the treatment difference with its 95% CI was 0.11% [-0.03, 0.24]. Since the upper limit of the CI was less than the pre-defined non-inferiority margin (0.4%), the non-inferiority of IDeg to IGlar was demonstrated (Table 46). The treatment difference with its 95% CI in the Japanese subgroup was 0.11% [-0.09, 0.31].

Table 46. HbA1c change from baseline to Week 26 (Trial 3586, FAS)

Treatment group		Baseline	Week 26 (LOCF)	Change (LOCF)	Least square mean change[a)]	Treatment difference [95% CI][a)]
Entire trial population	IDeg (n = 289)	8.45 (0.79)	7.21 (0.70)	-1.24 (0.87)	-1.42 ± 0.06	0.11 [-0.03, 0.24]
	IGlar (n = 146)	8.46 (0.76)	7.10 (0.80)	-1.35 (0.87)	-1.52 ± 0.07	
Japanese subgroup	IDeg (n = 89)	8.56 (0.75)	7.10 (0.58)	-1.46 (0.83)	-1.52 ± 0.06	0.11 [-0.09, 0.31]
	IGlar (n = 44)	8.44 (0.69)	6.96 (0.58)	-1.48 (0.68)	-1.63 ± 0.09	

Unit: %, Mean (SD), Least square mean ± SE

a) Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening (oral anti-diabetic monotherapy or combination therapy), sex, and region (Japan or others; Excluded from the analysis of the Japanese subgroup) as fixed factors and age and baseline HbA1c as covariates.

The change in HbA1c over time from baseline to Week 26 in the Japanese subgroup or in the entire trial population was as shown in Figure 4.

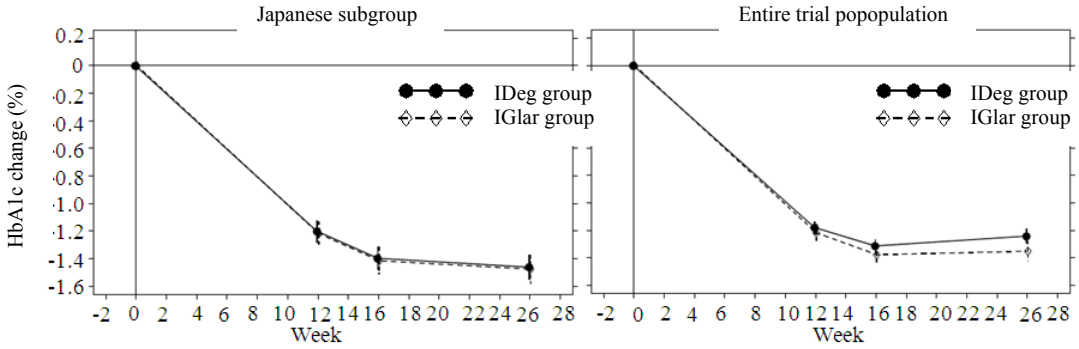

Figure 4. Change in HbA1c over time from baseline to Week 26
(Trial 3586, Japanese subgroup and entire trial population, LOCF) (mean ± SE)

The results of analyses of the main secondary endpoints from baseline to Week 26 in the entire trial population and Japanese subgroup were as shown in Table 47 and Table 48, respectively.

Table 47. Results of analyses of main secondary endpoints
(Trial 3586 [26 weeks of treatment] Entire trial population;
Upper four items, FAS; Lower two items, Safety Analysis Set)

Endpoint		IDeg (n = 289)	IGlar (n = 146)
FPG (mg/dL)	Baseline	152.0 ± 37.4 (n = 288)	155.5 ± 34.8 (n = 145)
	Change (LOCF)	-52.0 ± 44.7 (n = 288)	-53.5 ± 41.1 (n = 145)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment (%) (LOCF)		40.8 (118/289 subjects)	48.6 (71/146 subjects)
Proportion of subjects achieving HbA1c ≤6.5% at the end of treatment (%) (LOCF)		18.0 (52/289 subjects)	24.7 (36/146 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without confirmed hypoglycaemia (%) (LOCF)		29.1 (78/268 subjects)	31.5 (45/143 subjects)
Body weight (kg)	Baseline	64.9 ± 11.3 (n = 284)	67.4 ± 11.6 (n = 146)
	Change (LOCF)	1.3 ± 2.2 (n = 284)	1.4 ± 2.2 (n = 146)
Insulin dose (U/day)	Baseline (Week 1)	9 ± 2 (n = 280)	9 ± 2 (n = 145)
	Week 26 (LOCF)	19 ± 13 (n = 282)	24 ± 17 (n = 146)

Mean ± SD

Table 48. Results of analyses of main secondary endpoints
(Trial 3586 [26 weeks of treatment] Japanese subgroup;
Upper four items, FAS; Lower two items, Safety Analysis Set)

Endpoint		IDeg (n = 89)	IGlar (n = 44)
FPG (mg/dL)	Baseline	164.1 ± 37.9 (n = 88)	169.7 ± 31.3 (n = 44)
	Change (LOCF)	-67.0 ± 42.8 (n = 88)	-67.5 ± 35.3 (n = 44)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment (%) (LOCF)		42.7 (38/89 subjects)	56.8 (25/44 subjects)
Proportion of subjects achieving HbA1c ≤6.5% at the end of treatment (%) (LOCF)		18.0 (16/89 subjects)	27.3 (12/44 subjects)
Proportion of subjects achieving HbA1c <7.0% at the end of treatment without confirmed hypoglycaemia (%)		30.6 (26/85 subjects)	34.1 (15/44 subjects)
Body weight (kg)	Baseline	62.8 ± 11.3 (n = 88)	66.5 ± 12.1 (n = 44)
	Change (LOCF)	1.5 ± 2.2 (n = 88)	1.6 ± 2.2 (n = 44)
Insulin dose (U/day)	Baseline (Week 1)	7 ± 2 (n = 88)	7 ± 2 (n = 44)
	Week 26 (LOCF)	17 ± 13 (n = 88)	23 ± 12 (n = 44)

Mean ± SD

Regarding safety, in the entire trial population, the incidence of adverse events[57] was 58.8% (167 of 284 subjects) in the IDeg group and 65.1% (95 of 146 subjects) in the IGlar group and the incidence of adverse drug reactions was 8.1% (23 of 284 subjects) in the IDeg group and 5.5% (8 of 146 subjects) in the IGlar group. In the Japanese subgroup, the incidence of adverse events was 71.6% (63 of 88 subjects) in the IDeg group and 65.9% (29 of 44 subjects) in the IGlar group and the incidence of adverse drug reactions was 14.8% (13 of 88 subjects) in the IDeg group and 9.1% (4 of 44 subjects) in the IGlar group. Adverse events and/or adverse drug reactions occurring in ≥3% of subjects in either treatment group in the entire trial population and Japanese subgroup were as shown in Table 49 and Table 50, respectively.

Table 49. Adverse events and/or adverse drug reactions occurring in ≥3% of subjects in either treatment group
(Trial 3586 [26 weeks of treatment] Entire trial population; Safety Analysis Set)

Event	IDeg (n = 284)		IGlar (n = 146)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	58.8 (167)	8.1 (23)	65.1 (95)	5.5 (8)
Nasopharyngitis	9.2 (26)	0.0 (0)	13.7 (20)	0.0 (0)
Upper respiratory tract infection	7.7 (22)	0.0 (0)	11.0 (16)	0.0 (0)
Constipation	3.2 (9)	0.4 (1)	1.4 (2)	0.7 (1)
Diarrhoea	2.1 (6)	0.0 (0)	3.4 (5)	0.0 (0)
Dizziness	1.8 (5)	0.0 (0)	3.4 (5)	0.7 (1)
Diabetic retinopathy	5.3 (15)	1.8 (5)	4.1 (6)	1.4 (2)
Hypertension	2.1 (6)	0.0 (0)	3.4 (5)	0.0 (0)

Incidence % (no. of subjects with events), MedDRA/J (ver.13.1)

Table 50. Adverse events and/or adverse drug reactions occurring in ≥3% of subjects in either treatment group (Trial 3586 [26 weeks of treatment] Japanese subgroup; Safety Analysis Set)

Event	IDeg (n = 88)		IGlar (n = 44)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	71.6 (63)	14.8 (13)	65.9 (29)	9.1 (4)
Nasopharyngitis	20.5 (18)	0.0 (0)	27.3 (12)	0.0 (0)
Upper respiratory tract infection	3.4 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Pharyngitis	3.4 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Cystitis	3.4 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Constipation	3.4 (3)	1.1 (1)	2.3 (1)	2.3 (1)
Back pain	2.3 (2)	0.0 (0)	6.8 (3)	0.0 (0)
Muscle spasms	3.4 (3)	0.0 (0)	4.5 (2)	0.0 (0)
Headache	1.1 (1)	0.0 (0)	4.5 (2)	0.0 (0)
Dry eye	0.0 (0)	0.0 (0)	4.5 (2)	0.0 (0)
Injection site haematoma	2.3 (2)	0.0 (0)	4.5 (2)	0.0 (0)
Dermatitis contact	0.0 (0)	0.0 (0)	4.5 (2)	0.0 (0)
Arthropod sting	0.0 (0)	0.0 (0)	4.5 (2)	0.0 (0)
Diabetic retinopathy	8.0 (7)	3.4 (3)	9.1 (4)	4.5 (2)
Contusion	4.5 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Weight increased	4.5 (4)	4.5 (4)	2.3 (1)	2.3 (1)

Incidence % (no. of subjects with events), MedDRA/J (ver.13.1)

One death occurred in the IDeg group (drowning). This was a 69-year-old Japanese male subject, and the subject was on an SU (gliclazide 80 mg/day) etc. as an anti-diabetic drug. The subject was enrolled into the trial and found dead drowning in a river 34 days after the start of trial drug administration. Based on the post-mortem findings, it was reported that multiple trauma, presumably from falling off a cliff, was indirectly related to the subject's death. On the day of death, the subject had SMPG values of 62 mg/dL at 6:27 and 88 mg/dL at 13:51. This event was classified as an adverse drug reaction. The incidence of serious adverse events (including the fatal case) was 2.8% in the IDeg group (8 of 284 subjects; cataract operation complication, rib fracture/pneumothorax [a Japanese subject], unstable angina, coronary artery occlusion, large intestine carcinoma [a Japanese subject], drowning [a Japanese subject], diverticulitis, cerebrovascular accident, ureteric calculus removal [a Japanese subject]) and 5.5% in the IGlar group (8 of 146 subjects; muscle strain, road traffic accident, congestive cardiac failure, coronary artery disease, breast cancer, endometrial cancer, colonic polyp, hypoglycaemia). The event of hypoglycaemia observed in the IGlar group was classified as an adverse drug reaction and led to trial discontinuation. Adverse events leading to trial discontinuation occurred in 2 subjects in the IDeg group (drowning [a Japanese subject], diarrhoea) and 3 subjects in the IGlar group (hypoglycaemia, endometrial cancer, breast cancer).

The occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population was as shown in Table 51 and the estimated rate ratios (IDeg/IGlar) for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia with their 95% CIs[58] were 0.82 [0.60, 1.11] and 0.62 [0.38, 1.04], respectively, in the entire trial population and 0.87 [0.51, 1.48] and 0.50 [0.19, 1.32], respectively, in the Japanese subgroup. Although one subject in the IGlar group (a non-Japanese subject) had severe hypoglycaemia, no severe nocturnal hypoglycaemia was reported.

Table 51. Occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population (Trial 3586, Safety Analysis Set)

Endpoint	Japanese subgroup		Entire trial population	
	IDeg (n = 88)	IGlar (n = 44)	IDeg (n = 284)	IGlar (n = 146)
Confirmed hypoglycaemia[a)]	53.4 (47)	61.4 (27)	50.0 (142)	53.4 (78)
	151 [355]	98 [447]	397 [298]	260 [370]
Nocturnal confirmed hypoglycaemia[a)b)]	17.0 (15)	22.7 (10)	20.4 (58)	24.0 (35)
	25 [59]	28 [128]	104 [78]	87 [124]
Severe hypoglycaemia[c)]	0.0 (0)	0.0 (0)	0.0 (0)	0.7 (1)
	0 [0]	0 [0]	0 [0]	1 [1]

Upper row: incidence % (no. of subjects with episodes)
Lower row: total number of episodes [no. of episodes/100 patient-years]
a) Confirmed hypoglycaemia: "severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"
b) Nocturnal hypoglycaemia: hypoglycaemia occurring between 0:01 a.m. and 5:59 a.m.
c) Severe hypoglycaemia: hypoglycaemia requiring the assistance of another person for treatment

There were no clinically significant findings in vital signs, ECG, or the ocular fundus.

4.(iii).A.(3).3) Extension of Trial 3585 (5.3.5.1.4, Trial 3725 [September 2010 to June 2011])

A 26-week, IDet-controlled, open-label, extension trial in subjects who completed Trial 3585 (the duration of treatment with IDeg or IDet was up to 52 weeks in Trial 3585 with the extension) was conducted to evaluate the long-term safety and efficacy of IDeg.

The same trial drug at the same dose and dosing schedule as in Trial 3585 was resumed and IDeg (once daily) or IDet (once or twice daily) as basal insulin and IAsp as bolus insulin were to be subcutaneously administered for 26 weeks. IDeg or IDet was to be administered in the thigh, upper arm, or abdomen in the evening (from the start of the evening meal until bedtime) and IAsp was to be administered in the abdomen three times daily, immediately before meals. Insulin doses were to be adjusted according to the same titration guideline as in Trial 3585 (Table 38). For antibody measurements, NPH insulin (the dose of NPH insulin was 80% of the basal insulin dose at the end of treatment) was to be subcutaneously administered twice daily in divided doses (before breakfast and from before the evening meal until bedtime) for 1 week after the last dose of trial drug (Week 52) (IAsp was continued).

In Trial 3585, of 456 randomized subjects (303 subjects in the IDeg group [including 124 Japanese subjects], 153 subjects in the IDet group [including 62 Japanese subjects]), 455 subjects (302 subjects in the IDeg group [including 124 Japanese subjects], 153 subjects in the IDet group [including 62 Japanese subjects]) were included in the FAS and 1 subject who was withdrawn from the trial due to failure to meet the inclusion criteria (IDeg group) was excluded. A total of 453 treated subjects (301 subjects in the IDeg group [including 124 Japanese subjects], 152 subjects in the IDet group [including 61 Japanese subjects]) were included in the Safety Analysis Set and 2 subjects who did not receive trial drug (1 subject each in the IDeg and IDet groups) were excluded. The FAS was used for efficacy analysis. Of 421 subjects who completed Trial 3585 (283 subjects in the IDeg group [including 121 Japanese subjects], 138 subjects in the IDet group [including 56 Japanese subjects]), 370 subjects (248

subjects in the IDeg group [including 114 Japanese subjects], 122 subjects in the IDet group [including 53 Japanese subjects]) entered the extension trial, and 51 subjects (35 subjects in the IDeg group [including 7 Japanese subjects], 16 subjects in the IDet group [including 3 Japanese subjects]) were excluded. A total of 357 subjects (242 subjects in the IDeg group [including 112 Japanese subjects], 115 subjects in the IDet group [including 51 Japanese subjects]) completed 52-week treatment with trial drug. There were 13 withdrawals from the extension trial (6 subjects in the IDeg group [including 2 Japanese subjects], 7 subjects in the IDet group [including 2 Japanese subjects]) and the reasons for withdrawal included adverse events in 2 subjects (1 subject each in the IDeg and IDet groups [both Japanese subjects]), non-compliance with the protocol in 2 subjects (2 subjects in the IDet group), withdrawal criteria met in 4 subjects (2 subjects in the IDeg group [including 1 Japanese subject], 2 subjects in the IDet group [including 1 Japanese subject]), and others in 5 subjects (3 subjects in the IDeg group, 2 subjects in the IDet group).

No primary efficacy endpoint was specified, and the change in HbA1c from baseline (at the start of trial drug administration in Trial 3585) to Week 52 in the FAS (least square mean ± SE[61]) was -0.48 ± 0.06% in the IDeg group and -0.47 ± 0.08% in the IDet group. In the Japanese subgroup, the change in HbA1c from baseline to Week 52 (least square mean ± SE) was -0.68 ± 0.07% in the IDeg group and -0.65 ± 0.10% in the IDet group. The change in HbA1c over time from baseline to the end of treatment with trial drug in Trials 3585 and 3725 (Trials 3585/3725, 52 weeks of treatment) in the Japanese subgroup or in the entire trial population was as shown in Figure 5.

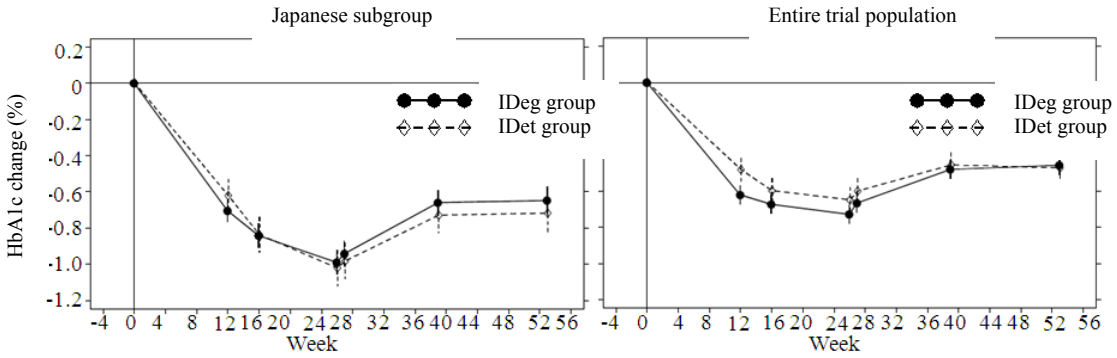

Figure 5. Change in HbA1c over time from baseline to Week 52
(Trials 3585/3725, Japanese subgroup and entire trial population, LOCF) (Mean ± SE)

Regarding safety, adverse events occurring from the start of trial drug administration in Study 3585 (Week 0) through Week 52 were analyzed. As a result, in the entire trial population, the incidence of adverse events[57] was 82.4% (248 of 301 subjects) in the IDeg group and 77.6% (118 of 152 subjects) in the IDet group and the incidence of adverse drug reactions was 25.9% (78 of 301 subjects) in the IDeg group and 25.0% (38 of 152 subjects) in the IDet group. In the Japanese subgroup, the incidence of adverse events was 92.7% (115 of 124 subjects) in the IDeg group and 91.8% (56 of 61 subjects) in

[61] Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening, sex, and region (Europe, Japan, India, Brazil; Not included in the analysis of the Japanese subgroup) as fixed factors and age and baseline HbA1c as covariates.

the IDet group and the incidence of adverse drug reactions was 23.4% (29 of 124 subjects) in the IDeg group and 19.7% (12 of 61 subjects) in the IDet group. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group in the entire trial population and Japanese subgroup were as shown in Table 52 and Table 53, respectively.

Table 52. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trials 3585/3725 (52 weeks of treatment) Entire trial population; Safety Analysis Set)

Event	IDeg (n = 301)		IDet (n = 152)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	82.4 (248)	25.9 (78)	77.6 (118)	25.0 (38)
Nasopharyngitis	31.2 (94)	0.0 (0)	32.2 (49)	0.0 (0)
Upper respiratory tract infection	11.3 (34)	0.0 (0)	11.2 (17)	0.0 (0)
Gastroenteritis	7.3 (22)	0.3 (1)	6.6 (10)	0.0 (0)
Influenza	4.7 (14)	0.0 (0)	5.9 (9)	0.7 (1)
Diarrhoea	6.6 (20)	0.3 (1)	5.9 (9)	0.0 (0)
Back pain	7.3 (22)	0.0 (0)	3.3 (5)	0.0 (0)
Headache	14.0 (42)	2.0 (6)	7.9 (12)	0.7 (1)
Hypoglycaemia	7.6 (23)	7.0 (21)	10.5 (16)	9.2 (14)
Hypoglycaemic unconsciousness	6.0 (18)	5.0 (15)	3.9 (6)	2.6 (4)
Pyrexia	5.3 (16)	0.3 (1)	5.9 (9)	0.0 (0)
Cough	7.0 (21)	0.3 (1)	5.3 (8)	0.0 (0)
Diabetic retinopathy	6.6 (20)	2.7 (8)	4.6 (7)	2.0 (3)

Incidence % (no. of subjects with events), MedDRA/J (ver.14.0)

Table 53. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trials 3585/3725 (52 weeks of treatment) Japanese subgroup; Safety Analysis Set)

Event	IDeg (n = 124)		IDet (n = 61)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	92.7 (115)	23.4 (29)	91.8 (56)	19.7 (12)
Nasopharyngitis	46.0 (57)	0.0 (0)	49.2 (30)	0.0 (0)
Upper respiratory tract infection	12.9 (16)	0.0 (0)	4.9 (3)	0.0 (0)
Bronchitis	3.2 (4)	0.0 (0)	8.2 (5)	0.0 (0)
Gastroenteritis	7.3 (9)	0.0 (0)	6.6 (4)	0.0 (0)
Abdominal pain upper	6.5 (8)	0.0 (0)	6.6 (4)	0.0 (0)
Diarrhoea	6.5 (8)	0.8 (1)	0.0 (0)	0.0 (0)
Abdominal discomfort	7.3 (9)	0.0 (0)	1.6 (1)	0.0 (0)
Back pain	9.7 (12)	0.0 (0)	3.3 (2)	0.0 (0)
Musculoskeletal stiffness	7.3 (9)	0.0 (0)	3.3 (2)	0.0 (0)
Headache	8.1 (10)	0.0 (0)	3.3 (2)	0.0 (0)
Diabetic retinopathy	11.3 (14)	4.8 (6)	11.5 (7)	4.9 (3)
Eczema	3.2 (4)	0.8 (1)	8.2 (5)	0.0 (0)
Weight increased	5.6 (7)	4.8 (6)	6.6 (4)	4.9 (3)

Incidence % (no. of subjects with events), MedDRA/J (ver.14.0)

No deaths were reported. In the entire trial population, the incidence of serious adverse events from the start of trial drug administration (Week 0) through Week 52 was 12.0% (36 of 301 subjects) (54 events) in the IDeg group and 7.2% (11 of 152 subjects) (23 events) in the IDet group. Serious adverse events reported by at least 2 subjects were hypoglycaemia (4.0% [12 of 301 subjects] [16 events] in the IDeg group, 3.3% [5 of 152 subjects] [8 events] in the IDet group), hypoglycaemic unconsciousness (3.0% [9 of 301 subjects] [9 events] in the IDeg group, 3.3% [5 of 152 subjects] [6 events] in the IDet group), hypoglycaemic coma (1.3% [4 of 301 subjects] [4 events] in the IDeg group, 0.7% [1 of 152 subjects] [1 event] in the IDet group), diabetic ketoacidosis (0.7% [2 of 301

subjects] [2 events] in the IDeg group, 0.7% [1 of 152 subjects] [1 event] in the IDet group), gastroenteritis (1.3% [2 of 152 subjects] [2 events] in the IDet group), and hyperthyroidism (0.3% [1 of 301 subjects] [1 event] in the IDeg group, 0.7% [1 of 152 subjects] [1 event] in the IDet group). Of these events, 12 events of hypoglycaemia reported by 11 subjects in the IDeg group and 6 events of hypoglycaemia reported by 4 subjects in the IDet group, 7 events of hypoglycaemic unconsciousness reported by 7 subjects in the IDeg group and 3 events of hypoglycaemic unconsciousness reported by 3 subjects in the IDet group, all events of hypoglycaemic coma, and the event of diabetic ketoacidosis in the IDet group were classified as adverse drug reactions. In the Japanese subgroup, the incidence of serious adverse events was 14.5% in the IDeg group (18 of 124 subjects; hypoglycaemic unconsciousness in 3 subjects, hypoglycaemia in 3 subjects, hypoglycaemic coma/heat stroke, upper abdominal pain, hyperthyroidism, pyelonephritis/ketosis, fractured ischium/rib fracture, lumbar spinal stenosis, cellulitis/oral abscess, muscle spasms/radius fracture/fall, hypoglycaemic unconsciousness/back pain, diabetic ketoacidosis, hypoglycaemic coma/contusion/hypoglycaemic unconsciousness, hypoglycaemic coma) and 6.6% in the IDet group (4 of 61 subjects; hyperglycaemia/dehydration/diabetic ketoacidosis, hypoglycaemic coma/hypoglycaemic unconsciousness, hypoglycaemic unconsciousness, gastroenteritis). Serious adverse events reported by at least 2 subjects were hypoglycaemic unconsciousness (4.0% [5 of 124 subjects] [5 events] in the IDeg group, 3.3% [2 of 61 subjects] [3 events] in the IDet group), hypoglycaemia (2.4% [3 of 124 subjects] [3 events] in the IDeg group), and hypoglycaemic coma (2.4% [3 of 124 subjects] [3 events] in the IDeg group, 1.6% [1 of 61 subjects] [1 event] in the IDet group). Of which, 9 events reported by 8 subjects in the IDeg group (hypoglycaemic unconsciousness [2 subjects, 2 events], hypoglycaemic coma [2 subjects, 2 events], hypoglycaemia [2 subjects, 2 events], hypoglycaemic coma/hypoglycaemic unconsciousness, muscle spasms) and 6 events reported by 3 subjects in the IDet group (hyperglycaemia/dehydration/diabetic ketoacidosis, hypoglycaemic coma/hypoglycaemic unconsciousness, hypoglycaemic unconsciousness) were classified as adverse drug reactions. Adverse events leading to discontinuation of the extension trial occurred in 1 subject in the IDeg group (aspartate aminotransferase increased/alanine aminotransferase increased [a Japanese subject]) and 1 subject in the IDet group (diabetic ketoacidosis [a Japanese subject]), which were all classified as adverse drug reactions.

The occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population was as shown in Table 54.

Table 54. Occurrence of hypoglycaemia in the Japanese subgroup or in the entire trial population (Trials 3585/3725 [52 weeks of treatment] Safety Analysis Set)

Endpoint	Japanese subgroup		Entire trial population	
	IDeg (n = 124)	IDet (n = 61)	IDeg (n = 301)	IDet (n = 152)
Confirmed hypoglycaemia[a)]	98.4 (122)	98.4 (60)	94.7 (285)	92.8 (141)
	5992 [5002]	2997 [5307]	10,326 [3778]	5269 [3926]
Nocturnal confirmed hypoglycaemia[a)b)]	74.2 (92)	77.0 (47)	68.1 (205)	64.5 (98)
	508 [424]	426 [754]	924 [338]	646 [481]
Severe hypoglycaemia[c)]	9.7 (12)	3.3 (2)	14.0 (42)	11.8 (18)
	14 [12]	4 [7]	63 [23]	37 [28]
Severe nocturnal hypoglycaemia[b)c)]	1.6 (2)	0.0 (0)	5.3 (16)	3.9 (6)
	2 [2]	0 [0]	18 [7]	7 [5]

Upper row: incidence % (no. of subjects with episodes)
Lower row: total number of episodes [no. of episodes/100 patient-years]
a) Confirmed hypoglycaemia: "severe hypoglycaemia" and "hypoglycaemia with plasma glucose <56 mg/dL, regardless of symptoms"
b) Nocturnal hypoglycaemia: hypoglycaemia occurring between 0:01 a.m. and 5:59 a.m.
c) Severe hypoglycaemia: hypoglycaemia requiring the assistance of another person for treatment

There were no clinically significant findings in vital signs, ECG, or fundoscopy.

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

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

PMDA asked the applicant to explain the clinical positioning of IDeg in insulin therapy.

The applicant responded as follows:

Long-acting insulin analogs that are currently used in Japan, i.e., IDet and IGlar, have advantages of a longer duration of action and fewer hypoglycemic episodes compared with intermediate-acting NPH insulin. However, treatment with a long-acting insulin analog administered once daily may not be sufficient to provide the daily basal insulin requirement, necessitating twice-daily administration. Thus, a long-acting insulin analog that can cover the basal insulin needs with a once-daily schedule is necessary. In Japan, a fear of hypoglycaemia, non-compliance with insulin therapy and other reasons lead to many patients on insulin therapy not being able to achieve their therapeutic goals, which is considered a problem. In addition, while treatment with a long-acting insulin analog is associated with fewer hypoglycemic episodes, nocturnal hypoglycaemia remains a concern. Since IDeg has a longer duration of action compared with current long-acting insulin analogs, once-daily IDeg can meet the basal insulin requirements of more patients and improve patient adherence to insulin therapy. Foreign clinical trial data suggest that IDeg has a long and flat action profile. Thus, if a scheduled dose is missed, IDeg can be taken as soon as the patient remembers. Concerning the choice between IDet that has already been marketed by the applicant and IDeg, IDet has clinical advantages, which are different from IDeg: IDet causes less weight gain compared with IDeg; IDet has been used since 2007 in Japan and its efficacy and safety in children have been established; and there is a report that IDet has been shown to be safe to use in pregnant women (Mathiesen ER, et al., *Diabetes Metab Res Rev*, 2011;27: 543-51). Thus, physicians will choose between IDeg and IDet, according to the individual patient's condition.

PMDA considers as follows:
The efficacy of IDeg administered once daily has been demonstrated in clinical trials in patients with type 1 or type 2 diabetes mellitus [see "4.(iii).B.(3) Efficacy"] and its safety is acceptable [see "4.(iii).B.(4) Safety"]. Therefore, IDeg can be chosen as a new long-acting basal insulin analog.

4.(iii).B.(2) Interpretation of multinational trial results

For interpretation of the results from the two multinational studies, i.e., Trial 3585 in patients with type 1 diabetes mellitus and Trial 3586 in patients with type 2 diabetes mellitus, PMDA conducted the following reviews based on the guideline "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and the ICH-E5 guideline.

4.(iii).B.(2).1) Trial 3585 in patients with type 1 diabetes mellitus

(a) Intrinsic and extrinsic ethnic factors

PMDA asked the applicant to explain the influence of intrinsic and extrinsic ethnic differences on the evaluation of the efficacy and safety of IDeg.

The applicant responded as follows:
The pathogenesis of type 1 diabetes mellitus is characterized by the destruction of pancreatic β-cells, and therefore, insulin therapy is required for survival. In this regard, there should be no differences between Japanese and non-Japanese patients. In the treatment of the disease, insulin doses are adjusted according to the individual patient's condition. Also from this standpoint, there should be no differences between Japanese and non-Japanese patients.

Since the pharmacokinetic and pharmacodynamic results from Trial 1996 (Japanese subjects) and Trial 1993 (foreign subjects) demonstrated a flat and long action profile of IDeg in both Japanese and foreign patients with type 1 diabetes mellitus, there should be no pharmacokinetic or pharmacodynamic differences affecting efficacy and safety evaluation.

The baseline characteristics of the Japanese subgroup and entire trial population in Trial 3585 were as shown in Table 55. There were no major differences in intrinsic ethnic factors between the Japanese subgroup and entire trial population except for a lower proportion of male subjects, a lower body weight, and a higher proportion of the elderly in the Japanese subgroup compared with the entire trial population. Since there were no major differences in BMI between the Japanese subgroup and entire trial population, the differences in body weight should not affect evaluation. As to extrinsic ethnic factors, although the daily insulin dose at baseline (U/day) was lower in the Japanese subgroup than in the entire trial population, the differences in the daily insulin dose at baseline (U/day) should not affect evaluation, as there were no major differences in the daily insulin dose per body weight (U/kg/day) between the Japanese subgroup and entire trial population.

Table 55. Baseline characteristics (Trial 3585, FAS)

		Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 62)	IDeg (n = 302)	IDet (n = 153)
Intrinsic ethnic factors					
Age group	≤ 65 years	83.9 (104)	87.1 (54)	91.7 (277)	92.2 (141)
	> 65 years	16.1 (20)	12.9 (8)	8.3 (25)	7.8 (12)
Gender	Males	37.9 (47)	51.6 (32)	49.7 (150)	56.2 (86)
	Females	62.1 (77)	48.4 (30)	50.3 (152)	43.8 (67)
Body weight (kg)		59.1 ± 10.2	60.8 ± 10.5	66.5 ± 14.9	66.7 ± 13.4
BMI (kg/m^2)		22.7 ± 2.9	22.9 ± 3.3	24.0 ± 3.5	23.7 ± 3.4
Diabetes duration (years)		12.5 ± 9.6	12.9 ± 8.6	13.7 ± 10.6	14.4 ± 9.7
HbA1c (%)		7.9 ± 0.9	8.2 ± 0.9	8.0 ± 1.0	8.0 ± 0.9
FPG (mg/dL)		175.5 ± 65.9	171.3 ± 56.8	178.2 ± 71.9	170.8 ± 72.4
Extrinsic ethnic factors					
Daily insulin dose (Upper row: U/day) (Lower row: U/kg/day)	Basal	15 ± 7	16 ± 8 (n = 61)	22 ± 12 (n = 298)	22 ± 12 (n = 149)
		0.25 ± 0.10	0.26 ± 0.10 (n = 61)	0.33 ± 0.16 (n = 298)	0.32 ± 0.16 (n = 149)
	Bolus	26 ± 13	29 ± 12 (n = 61)	28 ± 15 (n = 298)	30 ± 15 (n = 149)
		0.44 ± 0.20	0.47 ± 0.16 (n = 61)	0.42 ± 0.21 (n = 298)	0.46 ± 0.22 (n = 149)
	Total	41 ± 18	45 ± 18 (n = 61)	50 ± 22 (n = 298)	52 ± 23 (n = 149)
		0.69 ± 0.24	0.72 ± 0.22 (n = 61)	0.75 ± 0.28 (n = 298)	0.78 ± 0.31 (n = 149)
Basal insulin injection frequency	Once/day	70.2 (87)	79.0 (49)	65.2 (197)	75.8 (116)
	Twice or more/day[a)]	29.8 (37)	21.0 (13)	34.8 (105)	24.2 (37)
Basal insulin type	IGlar	50.8 (63)	59.7 (37)	46.4 (140)	52.9 (81)
	IDet	41.1 (51)	37.1 (23)	37.1 (112)	34.6 (53)
	NPH	8.1 (10)	3.2 (2)	16.6 (50)	12.4 (19)

Mean ± SD, % (n)

a) In the entire trial population, 9 subjects in the IDeg group and 4 subjects in the IDet group treated with thrice-daily basal insulin. All subjects in the Japanese subgroup treated with twice-daily basal insulin.

The influence of the observed ethnic differences between the Japanese subgroup and entire trial population (age and gender) on efficacy and safety evaluation was assessed. Regarding efficacy, there were no major differences in the treatment difference in HbA1c change between the subgroups (men vs. women and ≤65 years vs. >65 years) in the Japanese subgroup or in the entire trial population (Table 56). As to safety, in both the Japanese subgroup and entire trial population, the occurrence of adverse events tended to differ between male and female subjects in the IDeg group while no major differences between male and female subjects were observed in the IDet group, and the occurrence of adverse events tended to differ between the age groups in the IDet group while no major differences between the age groups were observed in the IDeg group (Table 57).

Table 56. Comparison of HbA1c change by age and gender
(Trial 3585, FAS)

		Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 62)	IDeg (n = 302)	IDet (n = 153)
Age group	≤65 years	-1.01 ± 0.7 (n = 104)	-1.03 ± 0.8 (n = 54)	-0.73 ± 0.9 (n = 277)	-0.64 ± 0.9 (n = 141)
	>65 years	-0.88 ± 0.8 (n = 20)	-0.99 ± 1.0 (n = 8)	-0.68 ± 0.8 (n = 25)	-0.78 ± 0.9 (n = 12)
Gender	Males	-1.06 ± 0.8 (n = 47)	-0.94 ± 0.7 (n = 32)	-0.72 ± 1.0 (n = 150)	-0.58 ± 0.8 (n = 86)
	Females	-0.95 ± 0.7 (n = 77)	-1.10 ± 0.8 (n = 30)	-0.74 ± 0.8 (n=152)	-0.73 ± 0.9 (n = 67)

Mean ± SD (%), LOCF

Table 57. Comparison of occurrence of adverse events by age and gender
(Trial 3585, Safety Analysis Set)

		Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 61)	IDeg (n = 301)	IDet (n = 152)
Age group	≤65 years	81.7 (85)	90.6 (48)	72.5 (200)	75.0 (105)
		271 [529.3]	100 [388.2]	730 [546.5]	326 [492.9]
	>65 years	90.0 (18)	62.5 (5)	76.0 (19)	58.3 (7)
		58 [582.2]	16 [402.5]	64 [532.1]	23 [384.6]
Gender	Males	78.7 (37)	90.3 (28)	64.4 (96)	70.6 (60)
		83 [356.9]	61 [397.4]	322 [453.1]	161 [395.1]
	Females	85.7 (66)	83.3 (25)	80.9 (123)	77.6 (52)
		246 [649.0]	55 [382.4]	472 [633.3]	188 [599.3]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]

In conclusion, although there were intrinsic and extrinsic ethnic differences between the Japanese subgroup and entire trial population, it should have no clinically meaningful influence on efficacy and safety evaluation.

PMDA considers as follows:
The pharmacokinetic and pharmacodynamic profiles of insulin degludec are similar between Japanese and foreign patients [see "4.(ii).B. Pharmacokinetic and pharmacodynamic similarities between Japanese and foreign patients with type 1 or type 2 diabetes mellitus"]. Also, patients with type 1 diabetes mellitus in Japan and overseas are treated in the same manner and the doses of insulin preparations including IDeg are adjusted according to the individual patient's condition. Although there were differences between the Japanese subgroup and entire trial population in Trial 3585 for age and gender as intrinsic ethnic factors and the insulin dose at baseline (U/day) as an extrinsic ethnic factor, these differences have no relevant influence on efficacy and safety evaluation.

(b) Efficacy in Japanese subgroup and entire trial population
PMDA asked the applicant to explain the consistency of efficacy results between the Japanese subgroup and entire trial population.

The applicant responded as follows:
There were no major differences between the Japanese subgroup and entire trial population or non-Japanese subgroup for the difference in HbA1c change between the IDeg and IDet groups (Table 58), which is the primary endpoint. The difference in FPG change from baseline to Week 26 between the IDeg and IDet groups (IDeg minus IDet) with its 95% CI was different, i.e. -39.36 [-56.04, -22.68] mg/dL in the Japanese subgroup and -29.84 [-42.64, -17.05] mg/dL in the entire trial population, but were similar for the fact that FPG was reduced from baseline in both the Japanese subgroup and entire trial population (Table 40 and Table 41). Both the basal and bolus insulin doses at baseline were lower in the Japanese subgroup than in the entire trial population, but there was no major difference in the difference between the IDeg and IDet groups in the Japanese subgroup or in the entire trial population (Table 59).

In conclusion, there should be no major differences in the trend in the efficacy results between the Japanese subgroup and entire trial population.

Table 58. Comparison of HbA1c change from baseline to Week 26
(Trial 3585, FAS)

	Japanese subgroup		Non-Japanese subgroup[a)]		Entire trial population	
	IDeg (n = 124)	IDet (n = 62)	IDeg (n = 178)	IDet (n = 91)	IDeg (n = 302)	IDet (n = 153)
Baseline	7.93 (0.9)	8.20 (0.9)	8.01 (1.0)	7.85 (0.9)	7.98 (0.98)	7.99 (0.88)
Week 26[b)]	6.99 ± 0.06	7.08 ± 0.08	7.35 ± 0.08	7.47 ± 0.10	7.28 ± 0.06	7.37 ± 0.07
HbA1c change[b)]	-1.03 ± 0.06	-0.94 ± 0.08	-0.61 ± 0.08	-0.49 ± 0.10	-0.71 ± 0.06	-0.61 ± 0.07
Treatment difference (IDeg minus IDet) [95% CI][b)]	-0.09 [-0.29, 0.10]		-0.12 [-0.33, 0.09]		-0.09 [-0.23, 0.05]	

Unit: %, Mean (SD), Least square mean ± SE, LOCF

a) As the Basic Principles on Global Clinical Trials state that a global trial should be designed so that consistency can be obtained between results from the entire population and the Japanese population, this review report basically presents the results from the Japanese subgroup and entire trial population accordingly, but the results from the non-Japanese subgroup are also included for the primary endpoint of HbA1c change, for reference.

b) Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening (basal insulin once daily or twice daily), sex, and region (Europe, Japan, India, Brazil; Not included in the analysis of the Japanese subgroup) as fixed factors and age and baseline HbA1c as covariates.

Table 59. Comparison of insulin dose
(Study 3585, FAS)

	Timepoint	Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 62)	IDeg (n = 302)	IDet (n = 153)
Basal insulin dose	Baseline (Week 1)	15 ± 7	16 ± 8 (n = 61)	22 ± 12 (n = 298)	22 ± 12 (n = 149)
		0.25 ± 0.10	0.26 ± 0.10	0.33 ± 0.16	0.32 ± 0.16
	Week 26[a)]	16 ± 9	21 ± 15 (n = 61)	25 ± 16 (n = 301)	29 ± 20 (n = 152)
		0.26 ± 0.12	0.33 ± 0.20	0.36 ± 0.19	0.41 ± 0.25
Bolus insulin dose	Baseline (Week 1)	26 ± 13	29 ± 12 (n = 61)	28 ± 15 (n = 298)	30 ± 15 (n = 149)
		0.44 ± 0.20	0.47 ± 0.16	0.42 ± 0.21	0.46 ± 0.22
	Week 26[a)]	28 ± 14	34 ± 15 (n = 61)	36 ± 26 (n = 301)	41 ± 25 (n = 152)
		0.47 ± 0.20	0.55 ± 0.20	0.54 ± 0.40	0.63 ± 0.38
Total insulin dose	Baseline (Week 1)	41 ± 18	45 ± 18 (n = 61)	50 ± 22 (n = 298)	52 ± 23 (n = 149)
		0.69 ± 0.24	0.72 ± 0.22	0.75±0.28	0.78 ± 0.31
	Week 26[a)]	45 ± 21	56 ± 27 (n = 61)	61 ± 36 (n = 301)	69 ± 38 (n = 152)
		0.72 ± 0.27	0.89 ± 0.33	0.89 ± 0.52	1.03 ± 0.52

Mean ± SD (No. of subjects included in the analysis set), Upper row: U/day, Lower row: U/kg/day

a) Missing data were imputed by LOCF.

PMDA considers as follows:

The non-inferiority of IDeg to IDet was demonstrated in terms of the HbA1c change in the entire trial population as the primary endpoint. There were no major differences between the Japanese subgroup and entire trial population for the difference in HbA1c change between the IDeg and IDet groups and furthermore, there were also no major differences between the Japanese and non-Japanese subgroups. There were differences in the secondary efficacy endpoint of FPG change and the insulin dose at baseline (U/day) etc. between the Japanese subgroup and entire trial population, which were not clinically relevant. Thus, there was no clear discrepancy in efficacy between the Japanese subgroup and entire trial population. It may be interpreted that the efficacy results were consistent between the Japanese subgroup and entire trial population.

(c) Safety in Japanese subgroup and entire trial population

PMDA asked the applicant to explain safety in the Japanese subgroup and entire trial population.

The applicant responded as follows:

The occurrence of adverse events was analyzed by severity and causality. As a result, there were no clear differences between the Japanese subgroup and entire trial population (Table 60).

Table 60. Occurrence of adverse events in the Japanese subgroup or in the entire trial population (Trial 3585 [26 weeks of treatment] Safety Analysis Set)

		Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 61)	IDeg (n = 301)	IDet (n = 152)
Overall adverse events		83.1 (103)	86.9 (53)	72.8 (219)	73.7 (112)
		329 [538]	116 [390]	794 [545]	349 [484]
Serious adverse events		9.7 (12)	1.6 (1)	7.6 (23)	5.3 (8)
		16 [26]	2 [7]	33 [23]	13 [18]
Severity	Mild	80.6 (100)	86.9 (53)	67.8 (204)	68.4 (104)
		311 [508]	113 [380]	667 [458]	287 [398]
	Moderate	5.6 (7)	1.6 (1)	15.6 (47)	14.5 (22)
		8 [13]	1 [3]	82 [56]	30 [42]
	Severe	5.6 (7)	1.6 (1)	10.0 (30)	10.5 (16)
		10 [16]	2 [7]	45 [31]	32 [44]
Causality	Related	8.1 (10)	1.6 (1)	9.6 (29)	10.5 (16)
		10 [16]	1 [3]	32 [22]	22 [31]
	Possibly related	13.7 (17)	6.6 (4)	15.3 (46)	10.5 (16)
		20 [33]	8 [27]	72 [49]	24 [33]
	Unrelated	80.6 (100)	85.2 (52)	68.1 (205)	71.1 (108)
		298 [487]	105 [353]	670 [460]	295 [409]
	Unknown	0.8 (1)	3.3 (2)	6.0 (18)	4.6 (7)
		1 [2]	2 [7]	20 [14]	8 [11]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]

In order to detect any adverse event (System Organ Class) particularly more frequently reported in the Japanese subgroup than in the entire trial population, adverse events with an incidence of ≥5% in either treatment group in the Japanese subgroup or in the entire trial population and a ≥20% higher incidence rate (patient-time rate) in the Japanese subgroup than in the entire trial population were identified. These events include “eye disorders” (Japanese subgroup, 20 events/100 patient-years in the IDeg group and 24 events/100 patient-years in the IDet group; entire trial population, 18 events/100 patient-years in the IDeg group and 11 events/100 patient-years in the IDet group), “skin and subcutaneous tissue disorders” (Japanese subgroup, 18 events/100 patient-years in the IDeg group and 37 events/100 patient-years in the IDet group; entire trial population, 16 events/100 patient-years in the IDeg group and 25 events/100 patient-years in the IDet group), and “investigations” (Japanese subgroup, 23 events/100 patient-years in the IDeg group and 7 events/100 patient-years in the IDet group; entire trial population, 16 events/100 patient-years in the IDeg group and 11 events/100 patient-years in the IDet group). However, in the Japanese subgroup, the number of each of these preferred term events in the SOCs that were reported in the IDeg group was as small as less than three, except for diabetic retinopathy (Japanese subgroup, 6 events in the IDeg group and 4 events in the IDet group; entire trial population, 11 events in the IDeg group and 4 events in the IDet group), weight increased (Japanese subgroup, 7 events in the IDeg group and 0 events in the IDet group; entire trial population, 9 events in the IDeg group and 1 event in the IDet group), eczema (Japanese subgroup, 3 events in the IDeg group and 2 events in the IDet group; entire trial population, 4 events in the IDeg group and 2 events in the IDet group), and pruritus (Japanese subgroup, 3 events in the IDeg group and 2 events in the IDet group; entire trial population, 3 events in the IDeg group and 4 events in the

IDet group), and these differences are not considered clinically relevant. The events of eczema, pruritus, diabetic retinopathy, and weight increased were reported mostly by the Japanese subgroup. The rate of diabetic retinopathy was 9.8 events/100 patient-years in the IDeg group and 13.5 events/100 patient-years in the IDet group in the Japanese subgroup and 7.6 events/100 patient-years in the IDeg group and 5.5 events/100 patient-years in the IDet group in the entire trial population and the treatment differences are not considered clinically relevant. The events of weight increased were also reported mostly by the Japanese subgroup and the weight increase from baseline to the end of treatment in Japanese subjects with an adverse event of weight increased (7 subjects in the IDeg group) was 3.5 to 7.4 kg. Also in the entire trial population, there were 72 subjects with a comparable weight increase (+3.5 kg or more) (60 subjects in the IDeg group, 12 subjects in the IDet group), but most of these cases were not reported as adverse events. Thus, this seems associated with the fact that Japanese patients have low tolerance to weight gain, and hence these differences are not considered clinically relevant. The differences in the events of eczema and pruritus are not considered clinically relevant since among those events reported by Japanese subjects, only 1 case of mild eczema in the IDeg group was classified as an adverse drug reaction. As to hypoglycaemia, there were no major differences in the incidence of confirmed hypoglycaemia in either treatment group between the Japanese subgroup and entire trial population. There were no major differences in the incidence of nocturnal confirmed hypoglycaemia in the IDeg group between the Japanese subgroup and entire trial population. The incidence rate of confirmed hypoglycaemia in either treatment group was higher in the Japanese subgroup than in the entire trial population while there were no major differences in the incidence rate of confirmed hypoglycaemia between the treatment groups in the Japanese subgroup or in the entire trial population (Table 44). The incidence rate of nocturnal confirmed hypoglycaemia was slightly different between the Japanese subgroup and entire trial population, but the incidence rate of nocturnal confirmed hypoglycaemia was higher in the IDet group than in the IDeg group in both the Japanese subgroup and entire trial population. Although the incidence rate of severe hypoglycaemia was higher in the IDeg group than in the IDet group in the Japanese subgroup, there were no differences between the IDeg and IDet groups in the entire trial population. The incidence rate of severe hypoglycaemia in either treatment group was lower in the Japanese subgroup than in the entire trial population. The occurrence of severe hypoglycaemia by time of onset was analyzed. As a result, in both the Japanese subgroup and entire trial population, the number of episodes of severe hypoglycaemia was high in the titration period (Week 0-15) (Japanese subgroup, 15.7 episodes/100 patient-years in the IDeg group and 0 episodes in the IDet group; entire trial population, 32.8 episodes/100 patient-years in the IDeg group and 50.6 episodes/100 patient-years in the IDet group) and low in the maintenance period (Week 16 to the end of trial) (Japanese subgroup, 9.8 episodes/100 patient-years in the IDeg group and 10.6 episodes/100 patient-years in the IDet group; entire trial population, 18.2 episodes/100 patient-years in the IDeg group and 15.8 episodes/100 patient-years in the IDet group).

In conclusion, there should be no clinically relevant differences in safety in Trial 3585 between the Japanese subgroup and entire trial population.

PMDA considers as follows:
Although the occurrence of some adverse events (diabetic retinopathy, severe hypoglycaemia, etc.) was different between the Japanese subgroup and entire trial population, there were no clear differences in the trend of occurrence of adverse events between the IDeg and IDet groups in the entire trial population and there were no clinically relevant differences in safety between the Japanese subgroup and entire trial population. Therefore, it may be interpreted from the results of this trial that there were no safety concerns for Japanese patients.

(d) Long-term efficacy and safety
PMDA considers as follows:
Based on 52-week data from Trial 3585 with the extension (Trial 3725), there were no major differences in HbA1c change over time between the IDeg and IDet groups (Figure 5). Also as to safety, there were no major differences in the occurrence of adverse events or hypoglycaemia between IDeg and a comparator, IDet (Table 52, Table 53, Table 54). Thus, the long-term efficacy and safety of IDeg have been demonstrated.

Based on the above (a) to (d), PMDA considers that there is no major problem with the generalization of the results from the entire population in Trials 3585/3725 to Japanese patients with type 1 diabetes mellitus.

4.(iii).B.(2).2) Trial 3586 in patients with type 2 diabetes mellitus
(a) Intrinsic and extrinsic ethnic factors
PMDA asked the applicant to explain the influence of intrinsic and extrinsic ethnic differences on the evaluation of the efficacy and safety of IDeg.

The applicant responded as follows:
Impaired insulin secretion and insulin resistance play a major role in the pathogenesis of type 2 diabetes mellitus and Asian patients with type 2 diabetes mellitus are considered to have more severely impaired insulin secretion and lower insulin resistance than Caucasian patients with type 2 diabetes mellitus. According to DIABCARE-ASIA 2003[62] (Mohamed M on Behalf of the Diabcare-Asia 2003 Study Group, *Curr Med Research and Opinion*, 2008;24: 507-14) and clinical trials of IDeg conducted to date etc., the age, diabetes duration, BMI, and HbA1c of patients with type 2 diabetes mellitus were similar among Asian countries. The diagnostic criteria for diabetes mellitus

[62] A study conducted by Novo Nordisk and local diabetes societies etc. in the Asian region (China, Indonesia, Korea, Malaysia, the Philippines, Singapore, Taiwan, Thailand, Vietnam) in order to collect information on diabetic patients managed by specialists.

are based on the international or local guidelines, e.g. the guidelines from the Japan Diabetes Society, the American Diabetes Association, and the World Health Organization, and there should be no major differences among these guidelines.

Concerning the pharmacokinetic profile of insulin degludec, a PPK analysis of data from Trial 3586 showed that the total exposure to insulin degludec (AUC) at steady state was similar among the different Asian ethnic groups [see "4.(ii).A.(3).7) PPK analysis of data from phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586)"]. Thus, there should be no pharmacokinetic differences affecting efficacy and safety evaluation.

The baseline characteristics of the Japanese subgroup and entire trial population in Trial 3586 were as shown in Table 61. There were no major differences in intrinsic ethnic factors between the Japanese subgroup and entire trial population except for a higher baseline FPG, a higher proportion of male subjects, and a higher proportion of the elderly in the Japanese subgroup compared with the entire trial population. Since there were no differences in baseline HbA1c and this trial was conducted using a treat-to-target design (doses were adjusted based on plasma glucose values), the differences in baseline FPG should have no significant impact on efficacy evaluation. As to extrinsic ethnic factors, the proportion of subjects treated with 1 oral anti-diabetic drug at screening and the proportion of subjects not treated with an SU at screening were higher in the Japanese subgroup than in the entire trial population.

Table 61. Baseline characteristics
(Trial 3586, FAS)

		Japanese subgroup		Entire trial population	
		IDeg (n = 89)	IGlar (n = 44)	IDeg (n = 289)	IGlar (n = 146)
Intrinsic ethnic factors					
Age group	≤65 years	58.4 (52)	63.6 (28)	71.3 (206)	73.3 (107)
	>65 years	41.6 (37)	36.4 (16)	28.7 (83)	26.7 (39)
Gender	Males	67.4 (60)	54.5 (24)	54.7 (158)	51.4 (75)
	Females	32.6 (29)	45.5 (20)	45.3 (131)	48.6 (71)
Body weight (kg)		62.8 ± 11.2	66.5 ± 12.1	64.9 ± 11.5	67.4 ± 11.6
BMI (kg/m^2)		23.5 ± 3.2	25.4 ± 3.2	24.6 ± 3.4	25.8 ± 3.7
Diabetes duration (years)		12.8 ± 6.7	11.9 ± 7.3	11.8 ± 6.5	11.1 ± 6.5
HbA1c (%)		8.6 ± 0.7	8.4 ± 0.7	8.4 ± 0.8	8.5 ± 0.8
FPG (mg/dL)		164.1 ± 37.9	169.7 ± 31.3	152.0 ± 37.4	155.5 ± 34.8
Extrinsic ethnic factors					
Oral anti-diabetic therapy at screening	1 oral anti-diabetic drug	24.7 (22)	22.7 (10)	12.5 (36)	11.6 (17)
	≥2 oral anti-diabetic drugs	75.3 (67)	77.3 (34)	87.5 (253)	88.4 (129)
	SU	75.3 (67)	84.1 (37)	88.2 (255)	90.4 (132)
	No SU	24.7 (22)	15.9 (7)	11.8 (34)	9.6 (14)

Mean ± SD, % (n)

The influence of the observed ethnic differences between the Japanese subgroup and entire trial population (gender, age, oral anti-diabetic therapy at screening) on efficacy and safety evaluation was assessed (Table 62). Regarding efficacy, when data were evaluated for the impact of age, HbA1c

change from baseline was smaller at >65 years of age compared with ≤65 years of age in both the IDeg and IGlar groups in the Japanese subgroup, but a similar trend was observed in the entire trial population as well. There were no major differences between the age groups in the Japanese subgroup or in the entire trial population for the difference in HbA1c change between the IDeg and IGlar groups. Also as to gender, there were no major differences between male and female subjects in the Japanese subgroup or in the entire trial population for the difference in HbA1c change between the IDeg and IGlar groups. As to oral anti-diabetic therapy at screening, although HbA1c change was greater in the subgroup of "1 oral anti-diabetic drug" than in the subgroup of "≥2 oral anti-diabetic drugs" in both treatment groups in the entire trial population, there were no major differences between the subgroups for the difference in HbA1c change between the IDeg and IGlar groups. On the other hand, in the Japanese subgroup, a largely similar trend as in the entire trial population was observed, but HbA1c change in the IGlar group was similar between the subgroup of "1 oral anti-diabetic drug" and the subgroup of "≥2 oral anti-diabetic drugs," which is considered due to the limited number of subjects previously treated with "1 oral anti-diabetic drug" in the IGlar group (10 subjects) and lower baseline HbA1c in subjects previously treated with "1 oral anti-diabetic drug" compared with those previously treated with "≥2 oral anti-diabetic drugs" in the IGlar group ("1 oral anti-diabetic drug," 8.16%; "≥2 oral anti-diabetic drugs," 8.52%). As to the impact of an SU at screening, there were no major differences in HbA1c change between the subgroup of "SU" and the subgroup of "no SU" in either treatment group in the Japanese subgroup or in the entire trial population.

Table 62. Comparison of HbA1c change by age and gender
(Trial 3586, FAS)

Factor		Japanese subgroup		Entire trial population	
		IDeg (n = 89)	IGlar (n = 44)	IDeg (n = 289)	IGlar (n = 146)
Age group	≤65 years	-1.64 ± 0.8 (n = 52)	-1.60 ± 0.7 (n = 28)	-1.32 ± 0.9 (n = 206)	-1.38 ± 0.9 (n = 107)
	>65 years	-1.21 ± 0.8 (n = 37)	-1.26 ± 0.6 (n = 16)	-1.06 ± 0.8 (n = 83)	-1.28 ± 0.9 (n = 39)
Gender	Males	-1.52 ± 0.9 (n = 60)	-1.53 ± 0.8 (n = 24)	-1.25 ± 0.9 (n = 158)	-1.43 ± 0.9 (n = 75)
	Females	-1.34 ± 0.6 (n = 29)	-1.41 ± 0.5 (n = 20)	-1.24 ± 0.8 (n = 131)	-1.27 ± 0.8 (n = 71)
Oral anti-diabetic therapy at screening	1 oral anti-diabetic drug	-1.85 ± 0.8 (n = 22)	-1.48 ± 0.5 (n = 10)	-1.68 ± 1.0 (n = 36)	-1.67 ± 0.8 (n = 17)
	≥2 oral anti-diabetic drugs	-1.33 ± 0.8 (n = 67)	-1.48 ± 0.7 (n = 34)	-1.18 ± 0.8 (n = 253)	-1.31 ± 0.9 (n = 129)
	SU	-1.48 ± 0.9 (n = 67)	-1.46 ± 0.7 (n = 37)	-1.22 ± 0.9 (n = 255)	-1.33 ± 0.9 (n = 132)
	No SU	-1.42 ± 0.7 (n = 22)	-1.54 ± 0.8 (n = 7)	-1.44 ± 0.8 (n = 34)	-1.60 ± 0.8 (n = 14)

Unit: %, Mean ± SD

Regarding safety, there were no major differences in the occurrence of adverse events between the subgroups (age, oral anti-diabetic therapy [SU or no SU]) in the Japanese subgroup or in the entire trial population (Table 63). On the other hand, as to gender, the incidence of adverse events tended to be higher in female subjects than in male subjects in the IGlar group in the Japanese subgroup, but no major differences were observed in the IDeg group. In the entire trial population, there were no major differences in the occurrence of adverse events according to gender in either treatment group. As to oral anti-diabetic therapy (1 oral anti-diabetic drug, ≥2 oral anti-diabetic drugs), although the occurrence of adverse events tended to vary between the subgroups, there were no major differences in

such trend between the Japanese subgroup and entire trial population. However, due to the small number of subjects in the subgroup of "1 oral anti-diabetic drug," the results should be interpreted carefully.

Table 63. Comparison of occurrence of adverse events by age and gender
(Trial 3586, Safety Analysis Set)

		Japanese subgroup		Entire trial population	
		IDeg (n = 88)	IGlar (n = 44)	IDeg (n = 284)	IGlar (n = 146)
Age group	≤65 years	76.5 (39)	64.3 (18)	59.2 (119)	62.6 (67)
		77 [311.3]	41 [293.7]	284 [299.4]	148 [287.4]
	>65 years	64.9 (24)	68.8 (11)	57.8 (48)	71.8 (28)
		65 [366.1]	19 [238.3]	107 [277.5]	56 [298.3]
Gender	Males	67.8 (40)	50.0 (12)	56.8 (88)	62.7 (47)
		86 [303.8]	25 [208.8]	190 [262.8]	95 [261.9]
	Females	79.3 (23)	85.0 (17)	61.2 (79)	67.6 (48)
		56 [394.7]	35 [351.4]	201 [329.0]	109 [320.5]
Oral anti-diabetic therapy at screening	1 oral anti-diabetic drug	95.5 (21)	50.0 (5)	74.3 (26)	58.8 (10)
		47 [428.7]	8 [160.1]	55 [315.4]	21 [258.4]
	≥2 oral anti-diabetic drugs	63.6 (42)	70.6 (24)	56.6 (141)	65.9 (85)
		95 [301.3]	52 [307.0]	336 [289.7]	183 [294.4]
	SU	69.7 (46)	67.6 (25)	58.6 (147)	65.2 (86)
		111 [351.8]	54 [292.7]	356 [304.3]	175 [276.4]
	No SU	77.3 (17)	57.1 (4)	60.6 (20)	64.3 (9)
		31 [283.4]	6 [172.2]	35 [213.0]	29 [416.4]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]

In conclusion, there were intrinsic and extrinsic ethnic differences between the Japanese subgroup and entire trial population, but the differences should have no clinically meaningful influence on the evaluation of the efficacy and safety of IDeg.

PMDA considers as follows:

The results of the PPK analysis of data from Trial 3586 confirmed that the pharmacokinetic profile of insulin degludec is similar among the Asian ethnic groups [see "4.(ii).A.(3).7) PPK analysis of data from phase III multinational trial in patients with type 2 diabetes mellitus (Trial 3586)"]. As to ethnic factors, although there were differences in previous oral anti-diabetic therapy as an extrinsic ethnic factor between the Japanese subgroup and entire trial population, these differences have no relevant influence on efficacy and safety evaluation. Unlike the data from foreign trials, no data from Japanese subjects treated with IDeg plus >750 mg/day of metformin were obtained. Thus, it is necessary to collect information via post-marketing surveillance.

(b) Efficacy in Japanese subgroup and entire trial population

PMDA asked the applicant to explain the consistency of efficacy results between the Japanese subgroup and entire trial population.

The applicant responded as follows:

There were no major differences between the Japanese subgroup and entire trial population or non-Japanese subgroup for the difference in HbA1c change between the IDeg and IGlar groups as the

primary endpoint (Table 64). The difference in FPG change from baseline to Week 26 between the IDeg and IGlar groups (IDeg minus IGlar) with its 95% CI was slightly different, i.e. -5.30 [-14.28, 3.68] mg/dL in the Japanese subgroup and -1.57 [-7.31, 4.18] mg/dL in the entire trial population, but FPG had been reduced from the beginning of treatment in both the Japanese subgroup and entire trial population (Table 47 and Table 48). There were no major differences in insulin dose in either treatment group between the Japanese subgroup and entire trial population (Table 65).

In conclusion, there should be no major differences in the trend in the efficacy results between the Japanese subgroup and entire trial population.

Table 64. Comparison of HbA1c change from baseline to Week 26
(Trial 3586, FAS)

	Japanese subgroup		Non-Japanese subgroup[a)]		Entire trial population	
	IDeg (n = 89)	IGlar (n = 44)	IDeg (n = 200)	IGlar (n = 102)	IDeg (n = 289)	IGlar (n = 146)
Baseline	8.56 (0.75)	8.44 (0.69)	8.40 (0.8)	8.47 (0.8)	8.45 (0.79)	8.46 (0.76)
HbA1c at Week 26[b)]	7.00 ± 0.06	6.89 ± 0.09	7.08 ± 0.09	6.97 ± 0.10	7.04 ± 0.06	6.93 ± 0.07
HbA1c change (estimate)[b)]	-1.52 ± 0.06	-1.63 ± 0.09	-1.34 ± 0.09	-1.45 ± 0.10	-1.42 ± 0.06	-1.52 ± 0.07
Treatment difference (IDeg minus IGlar) [95% CI][b)]	0.11 [-0.09, 0.31]		0.11 [-0.06, 0.29]		0.11 [-0.03, 0.24]	

Unit: %, Mean (SD), Least square mean ± SE, LOCF

a) As the Basic Principles on Global Clinical Trials state that a global trial should be designed so that consistency can be obtained between results from the entire population and the Japanese population, this review report basically presents the results from the Japanese subgroup and entire trial population accordingly, but the results from the non-Japanese subgroup are also included for the primary endpoint of HbA1c change, for reference.

b) Calculated by an ANOVA with treatment, anti-diabetic therapy at screening (oral anti-diabetic monotherapy or combination therapy), sex, and region (Japan or others; Excluded from the analyses of the Japanese subgroup and non-Japanese subgroup) as fixed factors and age and baseline HbA1c as covariates.

Table 65. Comparison of insulin dose
(Trial 3586, FAS)

	Timepoint	Japanese subgroup		Entire trial population	
		IDeg (n = 89)	IGlar (n = 44)	IDeg (n = 289)	IGlar (n = 146)
Basal insulin dose	Baseline (Week 1)	7 ± 2 (n = 88)	7 ± 2	9 ± 2 (n = 280)	9 ± 2 (n = 145)
		0.11 ± 0.04	0.11 ± 0.04	0.14 ± 0.04	0.14 ± 0.04
	Week 26[a)]	17 ± 13 (n = 88)	23 ± 12	19 ± 13 (n = 282)	24 ± 17 (n = 146)
		0.26 ± 0.18	0.34 ± 0.15	0.28 ± 0.17	0.35 ± 0.23

Mean ± SD (no. of subjects included in the analysis set), Upper row: U/day, Lower row: U/kg/day

a) Missing data were imputed by LOCF.

PMDA considers as follows:

The non-inferiority of IDeg to IGlar was demonstrated in terms of the primary endpoint of HbA1c change in the entire trial population. There were no major differences between the Japanese subgroup and entire trial population for the difference in HbA1c change between the IDeg and IGlar groups and furthermore, there were also no major differences between the Japanese subgroup and non-Japanese subgroup. Also for the secondary efficacy endpoint, there were no major differences between the Japanese subgroup and entire trial population. Thus, there was no clear discrepancy in efficacy between the Japanese subgroup and entire trial population. It may be interpreted that the efficacy results were consistent.

(c) Safety in Japanese subgroup and entire trial population

PMDA asked the applicant to explain safety in the Japanese subgroup and entire trial population.

The applicant responded as follows:

The occurrence of adverse events was analyzed by severity and causality. As a result, there were no clear differences between the Japanese subgroup and entire trial population (Table 66).

Table 66. Occurrence of adverse events in the Japanese subgroup or in the entire trial population (Trial 3586, Safety Analysis Set)

		Japanese subgroup		Entire trial population	
		IDeg (n = 88)	IGlar (n = 44)	IDeg (n = 284)	IGlar (n = 146)
Overall adverse events		71.6 (63)	65.9 (29)	58.8 (167)	65.1 (95)
		142 [334]	60 [274]	391 [293]	204 [290]
Serious adverse events		4.5 (4)	0.0 (0)	2.8 (8)	5.5 (8)
		5 [12]	0 [0]	10 [7]	8 [11]
Severity	Mild	67.0 (59)	65.9 (29)	55.3 (157)	60.3 (88)
		134 [315]	59 [269]	346 [259]	183 [260]
	Moderate	5.7 (5)	2.3 (1)	10.6 (30)	10.3 (15)
		6 [14]	1 [5]	41 [31]	17 [24]
	Severe	2.3 (2)	0.0 (0)	1.1 (3)	2.7 (4)
		2 [5]	0 [0]	4 [3]	4 [6]
Causality	Related	5.7 (5)	2.3 (1)	2.5 (7)	1.4 (2)
		5 [12]	2 [9]	10 [7]	3 [4]
	Possibly related	9.1 (8)	6.8 (3)	5.6 (16)	4.8 (7)
		14 [33]	3 [14]	23 [17]	7 [10]
	Unrelated	65.9 (58)	65.9 (29)	55.6 (158)	63.7 (93)
		123 [289]	55 [251]	353 [265]	191 [272]
	Unknown	0.0 (0)	0.0 (0)	1.8 (5)	2.1 (3)
		0 [0]	0 [0]	5 [4]	3 [4]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]

In order to detect any adverse event (System Organ Class) particularly more frequently reported in the Japanese subgroup than in the entire trial population, adverse events with an incidence of ≥5% in either treatment group in the Japanese subgroup or in the entire trial population and a ≥20% higher incidence rate in the Japanese subgroup than in the entire trial population were identified. These events include “eye disorders” (Japanese subgroup, 31 events/100 patient-years in the IDeg group and 41 events/100 patient-years in the IGlar group; entire trial population, 19 events/100 patient-years in the IDeg group and 21 events/100 patient-years in the IGlar group), “skin and subcutaneous tissue disorders” (Japanese subgroup, 24 events/100 patient-years in the IDeg group and 23 events/100 patient-years in the IGlar group; entire trial population, 14 events/100 patient-years in the IDeg group and 17 events/100 patient-years in the IGlar group), “investigations” (Japanese subgroup, 12 events/100 patient-years in the IDeg group and 5 events/100 patient-years in the IGlar group; entire trial population, 4 events/100 patient-years in the IDeg group and 3 events/100 patient-years in the IGlar group), and “injury, poisoning and procedural complications” (Japanese subgroup, 24 events/100 patient-years in the IDeg group and 9 events/100 patient-years in the IGlar group; entire trial population, 13 events/100 patient-years in the IDeg group and 10 events/100 patient-years in the IGlar group). However, the number of each of the preferred term events in these SOCs in the IDeg group in the Japanese subgroup was small, not more than three, except for diabetic retinopathy (Japanese subgroup, 7 events in the IDeg group and 4 events in the IGlar group; entire trial population, 16 events in the IDeg group and 6 events in the IGlar group), weight increased (4 events in the IDeg group and 1 event in the IGlar group in the Japanese subgroup), and contusion (5 events in the IDeg group in the

Japanese subgroup) and these differences are not considered clinically relevant. The incidence rate of diabetic retinopathy was 16 events/100 patient-years in the IDeg group and 18 events/100 patient-years in the IGlar group in the Japanese subgroup and 12 events/100 patient-years in the IDeg group and 9 events/100 patient-years in the IGlar group in the entire trial population and the treatment differences are not considered clinically relevant. Although weight increased was reported only in the Japanese subgroup, the weight increase from baseline to the end of treatment in Japanese subjects with an adverse event of weight increased (5 subjects in the IDeg group) was 1.9 to 8.0 kg. Also in the entire trial population, there were 72 subjects with a comparable weight increase (+3.5 kg or more) (48 subjects in the IDeg group, 24 subjects in the IGlar group) and a comparable weight increase occurred also in the non-Japanese subgroup, but most of these cases were not reported as adverse events. The adverse events of contusion were all non-serious and the causal relationship of the events to trial drug was denied. As to the occurrence of hypoglycaemia, the incidence rate of confirmed hypoglycaemia in either treatment group was higher in the Japanese subgroup than in the entire trial population, but the rate of confirmed hypoglycaemia was higher in the IGlar group than in the IDeg group in both the Japanese subgroup and entire trial population (Table 51). The incidence rate of nocturnal confirmed hypoglycaemia tended to be lower in the Japanese subgroup than in the entire trial population, but the rate of nocturnal confirmed hypoglycaemia was higher in the IGlar group than in the IDeg group in both the Japanese subgroup and entire trial population. Only 1 severe hypoglycemic episode was reported (IGlar group, a non-Japanese subject).

In conclusion, there should be no clinically relevant differences in safety in Trial 3586 between the Japanese subgroup and entire trial population.

PMDA considers as follows:
Although the numbers of some adverse events (diabetic retinopathy, etc.) were higher in the Japanese subgroup than in the entire trial population, these differences in the occurrence of adverse events are not of particular relevance. Since there were no clear differences in the trend of occurrence of adverse events between the IDeg and IGlar groups in the entire trial population and there were no clinically relevant differences in safety between the Japanese subgroup and entire trial population, it may be interpreted from the results of this trial that there were no safety concerns for Japanese patients.

(d) Long-term efficacy and safety

The duration of treatment was 26 weeks in Trial 3586 of IDeg administered once daily in patients with type 2 diabetes mellitus on oral anti-diabetic drugs. The use of DPP-4 inhibitors was discontinued at the initiation of the trial. Moreover, patients on thiazolidinediones (TZDs) were excluded from the trial. Thus, PMDA asked the applicant to explain the long-term safety and efficacy of IDeg, taking account of these points.

The applicant responded as follows:
In Trials 3585/3725 in patients with type 1 diabetes mellitus, IDeg was administered for 52 weeks. As a result, there were no safety or efficacy problems. Since insulin-naïve patients with type 2 diabetes mellitus on oral anti-diabetic therapy are considered to retain some insulin secretion, the long-term efficacy and safety of IDeg are expected to be at least non-inferior to those observed in patients with type 1 diabetes mellitus from Trials 3585/3725. The efficacy of long-term treatment with once-daily IDeg in combination with oral anti-diabetic drugs in insulin-naïve patients with type 2 diabetes mellitus was evaluated in Foreign Trial 3579.[63] As a result, the change in HbA1c from baseline to Week 52 (mean ± SD, LOCF) in the IDeg group was -1.06 ± 1.01%, which was not substantially different from the change at Week 26 in Trial 3586 (-1.24 ± 0.87%). Also regarding safety, the incidence and number of adverse events in Trial 3579 were 74.7% (572 of 766 subjects) (2688 events) in the IDeg group and 70.8% (182 of 257 subjects) (837 events) in the IGlar group and the incidence rate of adverse events was 403 events/100 patient-years in the IDeg group and 384 events/100 patient-years in the IGlar group. There were no major differences between the treatment groups as in Trials 3585/3725 (459 events/100 patient-years in the IDeg group, 420 events/100 patient-years in the IDet group) and Trial 3586 (293 events/100 patient-years in the IDeg group, 290 events/100 patient-years in the IGlar group). Also as to hypoglycaemia, the incidence rate of confirmed hypoglycaemia in Trial 3579 was 152 episodes/100 patient-years in the IDeg group and 185 episodes/100 patient-years in the IGlar group. There were no major differences between the treatment groups. The incidence rate of nocturnal confirmed hypoglycaemia was 25 episodes/100 patient-years in the IDeg group and 39 episodes/100 patient-years in the IGlar group and the rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group compared with the comparator group, showing a similar trend as in Trials 3585/3725 and Trial 3586.

Based on the results from Trial 3586 in patients with type 2 diabetes mellitus and the long-term treatment trials of IDeg (Trials 3585/3725 and 3579), long-term treatment with once-daily IDeg in combination with oral anti-diabetic drugs should be effective and of no safety concern also in Japanese patients with type 2 diabetes mellitus.

Concerning the safety of IDeg in combination with a DPP-4 inhibitor or TZD, adverse events from IDeg and IDegAsp foreign clinical trials were analyzed. As to the safety of IDeg in combination with a DPP-4 inhibitor,[64] the incidence rate of adverse events among patients treated with concomitant DPP-4 inhibitors (85 patients in the pooled IDeg/IDegAsp group, 78 patients in the pooled comparator group) was lower in the pooled IDeg/IDegAsp group compared with the pooled comparator group (363 events/100 patient-years in the pooled IDeg/IDegAsp group, 503 events/100 patient-years in the

[63] A 52-week, IGlar-controlled, open-label trial of once-daily IDeg in combination with oral anti-diabetic drugs (metformin ± DPP-4 inhibitor) in insulin-naïve patients with type 2 diabetes mellitus.

[64] In Foreign Trials 3579, 3672, 3718, 3724, 3592, and 3593, the concomitant use of DPP-4 inhibitors was permitted.

pooled comparator group). Also when compared with all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group (4171 patients), the incidence rate of adverse events was lower in patients treated with concomitant DPP-4 inhibitors in the pooled IDeg/IDegAsp group (363 events/100 patient-years in patients treated with concomitant DPP-4 inhibitors in the pooled IDeg/IDegAsp group, 406 events/100 patient-years in all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group). The incidence rate of peripheral oedema among patients treated with concomitant DPP-4 inhibitors was higher in the pooled comparator group compared with the pooled IDeg/IDegAsp group (2.6 events/100 patient-years in the pooled IDeg/IDegAsp group, 8.6 events/100 patient-years in the pooled comparator group). The occurrence of hypoglycaemia was analyzed in insulin preparation-controlled trials investigating once-daily IDeg.[65] Although there were no major differences in the incidence rate of confirmed hypoglycaemia among patients treated with concomitant DPP-4 inhibitors (22 patients in the IDeg group, 18 patients in the comparator group) between the IDeg group and the comparator group (163 episodes/100 patient-years in the IDeg group, 171 episodes/100 patient-years in the comparator group), the incidence rate of confirmed hypoglycaemia was higher in subjects treated with concomitant DPP-4 inhibitors compared with those not treated with concomitant DPP-4 inhibitors in either treatment group (118 episodes/100 patient-years in patients not treated with concomitant DPP-4 inhibitors in the IDeg group, 140 episodes/100 patient-years in patients not treated with concomitant DPP-4 inhibitors in the comparator group). There was no severe hypoglycaemia or serious hypoglycaemia reported as an adverse event in patients treated with concomitant DPP-4 inhibitors in either treatment group.

Concerning the safety of IDeg in combination with TZD,[66] the incidence rate of adverse events among patients treated with concomitant TZD (119 patients in the pooled IDeg/IDegAsp group, 63 patients in the pooled comparator group) was higher in the pooled IDeg/IDegAsp group compared with the pooled comparator group (501 events/100 patient-years in the pooled IDeg/IDegAsp group, 370 events/100 patient-years in the pooled comparator group). Also when compared with all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group, the incidence rate of adverse events was higher in patients treated with concomitant TZD in the pooled IDeg/IDegAsp group (501 events/100 patient-years in patients treated with concomitant TZD in the pooled IDeg/IDegAsp group, 406 events/100 patient-years in all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group). Although the incidence rate of adverse events was higher in patients treated with concomitant TZD in the pooled IDeg/IDegAsp group compared with either the pooled comparator group or all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group, when analyzed according to preferred terms, there were no differences in the pattern of occurrence of adverse events. The incidence rate of peripheral oedema among patients treated with concomitant TZD was higher in the

[65] The concomitant use of DPP-4 inhibitors was investigated in Trial 3672 and the concomitant use of TZD was investigated in Trial 3582 and Trial 3668.

[66] The concomitant use of TZD (pioglitazone) was permitted in Foreign Trials 3582, 3580, 3668, NN5401-3592, and NN5401-3593.

pooled comparator group compared with the pooled IDeg/IDegAsp group (5.5 events/100 patient-years in the pooled IDeg/IDegAsp group, 8.4 events/100 patient-years in the pooled comparator group) and also in the pooled comparator group, the event rate was higher in patients treated with concomitant TZD compared with all patients with type 2 diabetes mellitus (8.4 events/100 patient-years in patients treated with concomitant TZD in the pooled comparator group, 4.3 events/100 patient-years in all patients with type 2 diabetes mellitus in the pooled comparator group). Other SOCs of adverse events were similar or fewer in patients treated with concomitant TZD compared with all patients with type 2 diabetes mellitus in both treatment groups. As to the occurrence of hypoglycaemia, the incidence rate of confirmed hypoglycaemia among patients treated with concomitant TZD (76 patients in the pooled IDeg group, 27 patients in the pooled comparator group) was higher in the pooled IDeg group than in the pooled comparator group (1117 episodes/100 patient-years in patients treated with concomitant TZD in the pooled IDeg group, 594 episodes/100 patient-years in patients treated with concomitant TZD in the pooled comparator group) and the inicidence rate of confirmed hypoglycaemia in patients treated with concomitant TZD in the pooled IDeg group was also higher compared with patients not treated with concomitant TZD in the pooled IDeg group (1117 episodes/100 patient-years in patients treated with concomitant TZD in the pooled IDeg group, 919 episodes/100 patient-years in patients not treated with concomitant TZD in the pooled IDeg group). Among patients treated with concomitant TZD, the number of severe hypoglycemic episodes or hypoglycemic episodes classified as serious adverse events was small in both treatment groups (8 episodes in patients treated with concomitant TZD in the pooled IDeg/IDegAsp group, 2 episodes in patients treated with concomitant TZD in the pooled comparator group). However, as the number of patients treated with concomitant TZD in the pooled comparator group was smaller than that in the pooled IDeg group, the results should be interpreted carefully.

In conclusion, concerning the safety of IDeg in combination with a DPP-4 inhibitor, the incidence rate of adverse events was lower in the pooled IDeg/IDegAsp group than in the pooled comparator group and there were no differences in the pattern of occurrence of adverse events between patients treated with concomitant DPP-4 inhibitors and all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group. The number of hypoglycemic episodes was higher in patients treated with concomitant DPP-4 inhibitors compared with those not treated with concomitant DPP-4 inhibitors, but there were no major differences between the pooled IDeg group and the pooled comparator group. Concerning the safety of IDeg in combination with TZD, the incidence rate of adverse events was higher in the pooled IDeg/IDegAsp group compared with the pooled comparator group and the rate of adverse events was also higher in patients treated with concomitant TZD in the pooled IDeg/IDegAsp group compared with all patients with type 2 diabetes mellitus in the pooled IDeg/IDegAsp group. As to individual events, the incidence rate of peripheral oedema among patients treated with concomitant TZD was higher in the pooled comparator group than in the pooled IDeg/IDegAsp group and the event

rate was higher in patients treated with concomitant TZD compared with all patients with type 2 diabetes mellitus.

PMDA considers as follows:
Trial 3586 investigating once-daily IDeg in patients with type 2 diabetes mellitus on oral anti-diabetic drugs including Japanese patients and Trials 3585/3725 in patients with type 1 diabetes mellitus on a basal-bolus regimen including Japanese patients are different in the trial population and treatment regimen. Also, Trial 3579 investigating once-daily IDeg in foreign patients with type 2 diabetes mellitus is different in terms of the patient background, e.g. BMI and concomitant oral anti-diabetic drugs. However, as to the usage of IDeg, doses are adjusted according to the patient's condition also in patients with type 2 diabetes mellitus, as in patients with type 1 diabetes mellitus, and there should be no major differences in insulin therapy for patients with type 2 diabetes mellitus between Japan and overseas. Therefore, though it is necessary to collect information on the long-term safety and efficacy of IDeg in Japanese patients with type 2 diabetes mellitus via post-marketing surveillance, there is no need to conduct an additional long-term treatment trial in Japanese patients with type 2 diabetes mellitus.

Based on the above sections (a) to (d), PMDA considers that there is no major problem with the generalization of the results from the entire population in Trial 3586 to Japanese patients with type 2 diabetes mellitus.

4.(iii).B.(3) Efficacy
The applicant explained about the influence of antibody formation on efficacy as follows:
Anti-insulin antibodies were measured at baseline and Weeks 12, 26, 27, 39, 53, and 54 in Trials 3585/3725 in patients with type 1 diabetes mellitus and at baseline and Weeks 12, 26, and 27 in Trial 3586 in patients with type 2 diabetes mellitus. Concerning anti-insulin antibody titers over time, in Trials 3585/3725, the titer of antibodies cross-reacting with human insulin remained low in the IDeg group throughout the trial period while the titer rose slightly in the IDet group. The titers of IDeg-, IDet-, and IAsp-specific antibodies were low at baseline and remained low throughout the trial period (Table 67).

Table 67. Insulin antibody titers (B/T %) over time
(Trials 3585/3725, Safety Analysis Set)

Endpoint	Timing	Japanese subgroup		Entire trial population	
		IDeg (n = 124)	IDet (n = 61)	IDeg (n = 301)	IDet (n = 152)
Titer of antibodies cross-reacting with human insulin	Baseline	3.0 [0.0, 77.0]	3.0 [0.0, 36.0]	5.0 [0.0, 77.0] (n = 300)	4.0 [0.0, 81.0] (n = 151)
	Week 27	2.0 [0.0, 75.0]	9.5 [0.0, 61.0] (n = 58)	6.0 [0.0, 75.0] (n = 288)	13.5 [0.0, 68.0] (n = 138)
	Week 54	2.0 [0.0, 77.0] (n = 111)	10.0 [0.0, 62.0] (n = 52)	4.0 [0.0, 77.0] (n = 240)	17.5 [0.0, 68.0] (n = 118)
Titer of IDeg- or IDet-specific antibodies	Baseline	0.0 [-1.0, 1.0]	1.0 [0.0, 5.0]	0.0 [-1.0, 10.0] (n = 300)	1.0 [0.0, 14.0] (n = 151)
	Week 27	0.0 [-1.0, 18.0]	2.0 [0.0, 18.0] (n = 58)	0.0 [-1.0, 18.0] (n = 288)	3.0 [0.0, 40.0] (n = 138)
	Week 54	0.0 [-1.0, 10.0] (n = 111)	2.5 [0.0, 13.0] (n = 52)	0.0 [-1.0, 10.0] (n = 240)	3.0 [0.0, 43.0] (n = 118)
Titer of IAsp-specific antibodies	Baseline	0.0 [0.0, 21.0]	0.0 [0.0, 33.0]	0.0 [-1.0, 32.0] (n = 300)	0.0 [0.0, 33.0] (n = 151)
	Week 27	1.0 [0.0, 15.0]	1.0 [0.0, 12.0] (n = 58)	1.0 [0.0, 42.0] (n = 288)	1.0 [0.0, 12.0] (n = 138)
	Week 54	1.0 [0.0, 17.0] (n = 111)	1.0 [0.0, 7.0] (n = 52)	1.0 [0.0, 39.0] (n = 240)	1.0 [0.0, 9.0] (n = 118)
Titer of total insulin antibodies	Baseline	4.5 [0.0, 79.0]	5.0 [0.0, 42.0]	7.0 [0.0, 79.0] (n = 300)	7.0 [0.0, 83.0] (n = 151)
	Week 27	5.0 [0.0, 95.0] (n = 123)	15.0 [3.0, 65.0] (n=57)	7.5 [0.0, 95.0] (n = 286)	18.0 [2.0, 111.0] (n = 135)
	Week 54	4.0 [-1.0, 90.0] (n = 110)	14.0 [3.0, 70.0] (n = 52)	5.0 [-1.0, 90.0] (n = 239)	24.5 [1.0, 113.0] (n = 118)

Median [Min., Max.]

In Trial 3586, the titer of antibodies cross-reacting with human insulin and the titers of IDeg- and IGlar-specific antibodies were low at baseline and throughout the treatment period (Table 68).

Table 68. Insulin antibody titers (B/T %)
(Trial 3586, Safety Analysis Set)

Endpoint	Timing	Japanese subgroup		Entire trial population	
		IDeg (n = 88)	IGlar (n = 44)	IDeg (n = 284)	IGlar (n = 146)
Titer of antibodies cross-reacting with human insulin	Baseline	0.0 [-1.0, 6.0]	0.0 [-1.0, 1.0]	0.0 [-1.0, 17.0]	0.0 [-1.0, 69.0]
	Week 27	0.0 [-1.0, 10.0] (n = 84)	0.0 [0.0, 62.0]	0.0 [-1.0, 22.0] (n = 269)	0.0 [0.0, 70.0] (n = 138)
Titer of IDeg- or IGlar-specific antibodies	Baseline	0.0 [-1.0, 0.0]	-1.0 [-4.0, 0.0]	0.0 [-1.0, 3.0]	-1.0 [-6.0, 0.0]
	Week 27	0.0 [0.0, 0.0] (n = 84)	-1.0 [-2.0, 7.0]	0.0 [0.0, 3.0] (n = 269)	-1.0 [-5.0, 7.0] (n = 138)
Titer of total insulin antibodies	Baseline	0.0 [-1.0, 6.0]	-1.0 [-5.0, 0.0]	0.0 [-1.0, 17.0]	-1.0 [-5.0, 69.0]
	Week 27	0.0 [-1.0, 10.0] (n = 84)	-1.0 [-2.0, 65.0]	0.0 [-1.0, 22.0] (n = 268)	-1.0 [-5.0, 75.0] (n = 138)

Median [Min., Max.]

With respect to the influence of antibody formation on efficacy, the number of subjects with type 1 diabetes mellitus experiencing an increase in the titer of cross-reacting antibodies of ≥10%B/T (percent bound/total radioactivity) (absolute) and an increase in HbA1c of >0.2% (absolute) was as small as 12 subjects (3 subjects in the IDeg group, 9 subjects in the IDet group) in Trials 3585/3725. The number of subjects with type 2 diabetes mellitus experiencing an increase in the titer of cross-reacting antibodies of ≥10%B/T (absolute) and not having a decrease in HbA1c of >0.2% (absolute) was zero in Trial 3586. According to the global pooled data from IDeg confirmatory trials in patients with type 1 diabetes mellitus,[67] 18 subjects in the pooled IDeg group and 8 subjects in the pooled comparator group experienced an increase in the titer of cross-reacting antibodies of ≥10%B/T

[67] Pooled data from three confirmatory trials of IDeg administered in patients with type 1 diabetes mellitus (multinational trial [3585], Trial 3583, Trial 3770) (Safety Analysis Set, 1102 subjects in the pooled IDeg group and 467 subjects in the pooled comparator group)

(absolute) and an increase in HbA1c of >0.2% (absolute). According to the global pooled data from IDeg confirmatory trials in patients with type 2 diabetes mellitus,[68] 4 subjects in the pooled IDeg group and 5 subjects in the pooled comparator group experienced an increase in the titer of cross-reacting antibodies of 10%B/T (absolute) and did not have a decrease in HbA1c of >0.2% (absolute). The total insulin dose increased in 6 subjects in the pooled IDeg group and 7 subjects in the pooled comparator group for type 1 diabetes mellitus and 3 subjects in the pooled IDeg group and 3 subjects in the pooled comparator group for type 2 diabetes mellitus. Correlation coefficients (Spearman correlation coefficients) between HbA1c at the end of treatment and antibodies (IDeg-, IAsp-, IDet-, and IGlar-specific antibodies and antibodies cross-reacting with human insulin) for the IDeg group were 0.10, 0.08, and 0.13 for anti-IDeg antibodies, anti-IAsp antibodies, and antibodies cross-reacting with human insulin, respectively, in Trials 3585/3725 and 0.07 and -0.03 for anti-IDeg antibodies and antibodies cross-reacting with human insulin, respectively, in Trial 3586. Correlation coefficients between insulin dose and antibodies (IDeg-, IAsp-, IDet-, or IGlar-specific antibodies and antibodies cross-reacting with human insulin) were 0.04, -0.01, and 0.24 for anti-IDeg antibodies, anti-IAsp antibodies, and antibodies cross-reacting with human insulin, respectively, in Trials 3585/3725 and 0.02 and 0.17 for anti-IDeg antibodies and antibodies cross-reacting with human insulin, respectively, in Trial 3586. All correlation coefficients were low and there was no clear relationship between the titer of antibodies cross-reacting with human insulin and HbA1c or insulin dose at the end of treatment.

PMDA considers as follows:
The efficacy of IDeg in patients with type 1 or type 2 diabetes mellitus has been demonstrated by the results of Trials 3585 and 3725 (type 1) and Trial 3586 (type 2) [see "4.(iii).B.(2) Interpretation of multinational trial results"]. With respect to the influence of antibody formation on efficacy, clinical trials showed no trend towards marked rises in antibody titers following treatment with IDeg and there was no clear relationship between the level of antibody formation and efficacy. However, as the information on antibody formation following long-term treatment with IDeg is limited, it is necessary to continue to collect information on the relationship between antibody formation and efficacy via post-marketing surveillance [for the relationship between antibody formation and safety, see "4.(iii).B.(4).6) Antibody formation"]. The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(4) Safety

Based on the results of Trials 3585 and 3725 (type 1) and Trial 3586 (type 2), PMDA considers that the safety of IDeg in patients with type 1 or type 2 diabetes mellitus is acceptable. Individual events were analyzed as follows.

[68] Pooled data from four confirmatory trials of IDeg administered in patients with type 2 diabetes mellitus (multinational trial [3586], Trial 3579, Trial 3668, Trial 3672) (Safety Analysis Set, 3173 subjects in the pooled IDeg group and 1802 subjects in the pooled comparator group)

4.(iii).B.(4).1) Hypoglycaemia

The applicant explained as follows:

In Trial 3585 (26 weeks of treatment) in patients with type 1 diabetes mellitus on a basal-bolus regimen, although there were no major differences in the incidence rate of severe hypoglycaemia or confirmed hypoglycaemia between the IDeg and IDet groups, the incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IDet group (Table 44). Trials 3585/3725 (52 weeks of treatment) also showed similar trend as Trial 3585 (Table 54). Concerning hypoglycemic episodes over time, there were no differences in the number of confirmed hypoglycemic episodes per subject between the treatment groups throughout 52 weeks (Figure 6). The number of nocturnal confirmed hypoglycemic episodes per subject was similar up to 4 weeks after the start of treatment, but was lower in the IDeg group than in the IDet group in subsequent weeks (Figure 7).

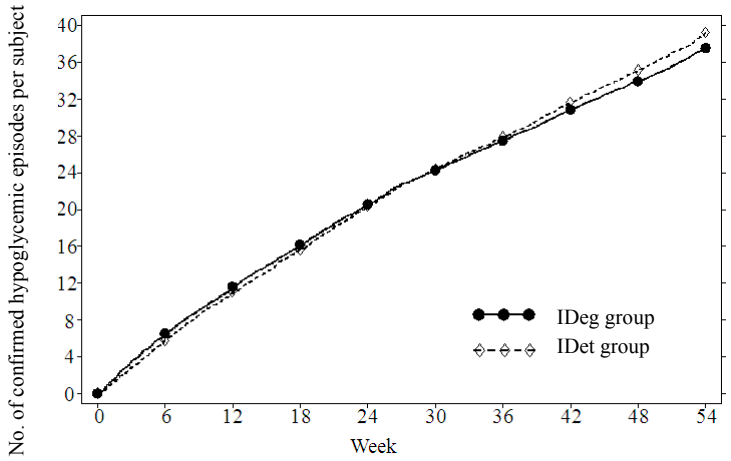

Figure 6. Confirmed hypoglycemic episodes over time (Mean cumulative function)
(Trials 3585/3725, Safety Analysis Set)

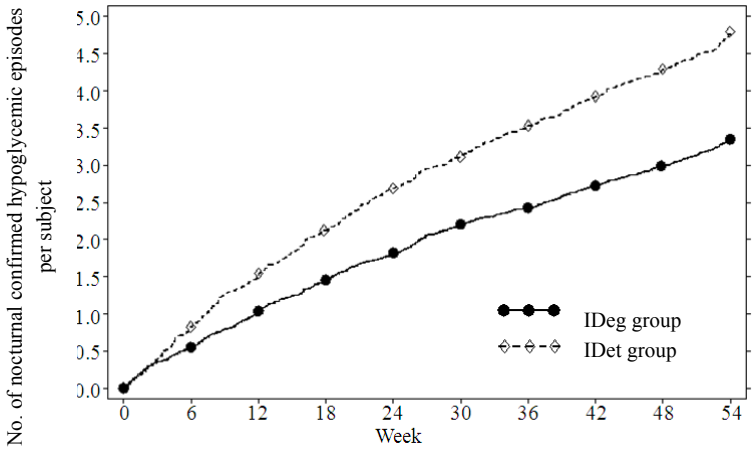

Figure 7. Nocturnal confirmed hypoglycemic episodes over time (Mean cumulative function)
(Trials 3585/3725, Safety Analysis Set)

In Trial 3586 investigating insulin in combination with oral anti-diabetic drugs in patients with type 2 diabetes mellitus (26 weeks of treatment), the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were lower in the IDeg group than in the IGlar group (Table 51). No severe hypoglycaemia was reported in the IDeg group. Furthermore, analyses were conducted for the maintenance period when basal insulin titration was completed and stable glycemic control was achieved (defined as after Week 16). As a result, the estimated incidence rate ratio (IDeg/IGlar) for confirmed hypoglycaemia with its 95% CI was 0.629 [0.420, 0.941] and the incidence rate was lower in the IDeg group than in the IGlar group. The estimated incidence rate ratio (IDeg/IGlar) for nocturnal confirmed hypoglycaemia with its 95% CI was 0.518 [0.268, 1.005].

A meta-analysis of 7 Japanese or foreign IGlar-controlled confirmatory trials of once-daily IDeg[69] was performed. As a result, in the whole pooled population (type 1 diabetes + type 2 diabetes), the incidence rate of confirmed hypoglycaemia was lower in the IDeg group compared with the IGlar group (Table 69). When analyzed by type of diabetes, the pooled type 2 diabetes population showed a similar trend as the whole pooled population, while the point estimate for the incidence rate ratio (IDeg/IGlar) was ≥1 in the pooled type 1 diabetes population. The incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IGlar group in all of the whole pooled population, the pooled type 1 diabetes population, and the pooled type 2 diabetes population.

Table 69. Occurrence of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia
(Meta-analysis of 7 Japanese or foreign confirmatory trials, FAS)

	No. of subjects analyzed in IDeg group	No. of subjects analyzed in IGlar group	Confirmed hypoglycaemia	Nocturnal confirmed hypoglycaemia
			Incidence rate ratio[a)] [95% CI]	Incidence rate ratio[a)] [95% CI]
Whole pooled population	2886	1421	0.91 [0.83, 0.99]	0.74 [0.65, 0.85]
Type 1 diabetes	637	316	1.10 [0.96, 1.26]	0.83 [0.69, 1.00]
Type 2 diabetes	2249	1105	0.83 [0.74, 0.94]	0.68 [0.57, 0.82]
Patients aged ≥65 years	628	282	0.82 [0.66, 1.00]	0.65 [0.46, 0.93]
Insulin-naïve type 2 diabetic patients	1279	631	0.83 [0.70, 0.98]	0.64 [0.48, 0.86]
Maintenance period (after Week 16)				
Whole pooled population	2631	1317	0.84 [0.75, 0.93]	0.68 [0.58, 0.80]
Type 1 diabetes	596	303	1.02 [0.88, 1.19]	0.75 [0.60, 0.94]
Type 2 diabetes	2035	1014	0.75 [0.66, 0.87]	0.62 [0.49, 0.78]

Rate (no. of episodes/100 patient-years) ratio (IDeg/IGlar) with its 95% CI

a) The number of episodes was analyzed using a negative binomial regression model with a log link function and log of treatment-emergent period as offset. The model included trial, treatment, anti-diabetic therapy at screening, sex, and region as fixed factors and age as a covariate.

Since IDeg has a longer duration of action compared with the currently approved basal insulin preparations, PMDA asked the applicant to explain the possibility of prolonged hypoglycaemia.

[69] Phase III multinational trial (3586, type 2), Foreign Trial 3583 (type 1), Foreign Trial 3770 (type 1), Foreign Trial 3582 (type 2), Foreign Trial 3579 (type 2), Foreign Trial 3672 (type 2), and Foreign Trial 3668 (type 2). However, the data from the fixed dosing group only were used for Trial 3770 and Trial 3668. The analysis set included 2899 subjects in the IDeg group and 1431 subjects in the IGlar group.

The applicant responded as follows:

A clinical pharmacology trial (Trial 3538[70]) was conducted to evaluate the response to hypoglycaemia induced by IDeg. As a result, the estimated ratio (IDeg/IGlar) of the time to recovery from hypoglycaemia to a normal plasma glucose level (70 mg/dL) with its 95% CI was 0.75 [0.56; 1.02][71] and the glucose infusion rate required during the entire period of recovery from hypoglycaemia and the maintenance of plasma glucose at 70 mg/dL for 2 hours was lower in the IDeg group than in the IGlar group (the estimated ratio [IDeg/IGlar] with its 95% CI, 0.71 [0.53; 0.93][71]). Furthermore, based on the global pooled data from IDeg confirmatory trials,[72] the course of 281 subjects with severe hypoglycaemia was reviewed. As a result, 11 of the 281 subjects (4 subjects in the IDeg group, 7 subjects in the comparator group) were considered to have possible prolongation or recurrence of hypoglycaemia, but 8 of these 11 subjects (3 subjects in the IDeg group, 5 subjects in the comparator group) received bolus insulin as well, and therefore, the possibility that bolus insulin also caused the recurrence of hypoglycaemia can not be denied.

In conclusion, the response to hypoglycaemia was not particularly different between IGlar and IDeg and a review of severe hypoglycaemia cases reported in confirmatory trials did not suggest the possibility that the recovery from hypoglycaemia is delayed with IDeg compared with the comparator.

PMDA considers as follows:

The results of Trials 3585/3725 and Trial 3586 suggested that there were no particular differences in the occurrence of confirmed hypoglycaemia between the IDeg and comparator groups, the incidence rate of nocturnal confirmed hypoglycaemia tended to be lower in the IDeg group than in the comparator group, and there were no major differences in the response to hypoglycaemia between IDeg and IGlar. However, the incidence of nocturnal confirmed hypoglycaemia was comparable between the IDeg and comparator groups. Also, in the Japanese subgroup of a long-term treatment trial in patients with type 1 diabetes mellitus (Trials 3585/3725), severe hypoglycaemia occurred more frequently in the IDeg group than in the IDet group though in a limited number of subjects with episodes (Table 54). Given these findings, an adequate attention should be paid to the possible occurrence of hypoglycaemia during treatment with IDeg. Taking account of the above, it is necessary to continue to collect information on hypoglycaemia via post-marketing surveillance.

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[70] A double-blind, two-period, crossover trial in foreign patients with type 1 diabetes mellitus in which IDeg or IGlar was administered once daily for 5 days. Subjects received a dose that was 80% of their individual daily basal insulin requirement for the first 4 days and a dose that was 3 times their individual daily basal insulin requirement on the 5th day.

[71] The endpoint was log-transformed and analyzed in a linear mixed model with treatment and period as fixed effects and subject as a random effect.

[72] Pooled data from 11 confirmatory trials with administration of IDeg (multinational trial [3585, type 1], multinational trial [3586, type 2], Trial 3579 [type 2], Trial 3580 [type 2], Trial 3582 [type 2], Trial 3583 [type 1], Trial 3770 [type 1], Trial 3668 [type 2], Trial 3672 [type 2], Trial 3718 [type 2], Trial 3724 [type 2]) (Safety Analysis Set, 4275 subjects in the pooled IDeg group and 2269 subjects in the pooled comparator group).

4.(iii).B.(4).2) Immunogenicity-related adverse events (allergic reactions)

The applicant explained as follows:

Concerning immunogenicity-related adverse events (allergic reactions), in Trials 3585/3725, the incidence of events identified by SMQs (standardized MedDRA queries) "anaphylactic reaction," "angioedema," and "severe cutaneous adverse reactions" was 1.3% (4 of 301 subjects) (5 events) (face oedema, face oedema/urticaria, facial swelling, periorbital oedema) in the IDeg group and 1.3% (2 of 152 subjects) (2 events) (urticaria) in the IDet group, showing that there were no differences between the treatment groups. The 1 event of facial swelling reported by 1 subject in the IDeg group was severe in severity, which was caused by assault and was not considered an immunogenicity-related event. Other events were all mild in severity and the causal relationship of the events to trial drug was denied. Events that were not SMQ preferred terms, but were judged by the investigator to be related to immunogenicity were reported by 2 subjects in the IDeg group (2 events) (eczema, skin sensitisation). Both events were mild in severity, but classified as adverse drug reactions. In Trial 3586, one immunogenicity-related adverse event was reported by 1 subject in the IDeg group (urticaria), which was mild in severity. No immunogenicity-related adverse events were reported in other clinical trials in which Japanese subjects participated.

According to the global pooled data on IDeg and IDegAsp,[73] the incidence of immunogenicity-related adverse events was 0.7% (47 of 6382 subjects) (48 events) in the pooled IDeg/IDegAsp group and 0.4% (16 of 3754 subjects) (17 events) in the pooled comparator group. All events including 2 events reported across all clinical pharmacology trials and 16 events that were not SMQ preferred terms, but were reported by the investigator as immunogenicity-related events were assessed individually. As a result, 7 events in the pooled IDeg/IDegAsp group (urticaria [4], hypersensitivity [2], drug hypersensitivity [1]) and 3 events in the pooled comparator group (generalised pruritus [1], abdominal discomfort [1], pruritus [1]) were classified by the sponsor as adverse drug reactions. According to the global pooled data from IDeg and IDegAsp clinical pharmacology trials,[74] there were only 2 immunogenicity-related adverse events in the pooled IDeg/IDegAsp group (anaphylactic reaction [1], urticaria [1]). The subject with an anaphylactic reaction was a 29-year-old patient with type 1 diabetes mellitus who participated in Foreign Trial 3538. Pruritus and redness occurred in the subject about 1 hour after the first dose of IDeg and were generalized except on the lower limbs about 2 hours after the dose. This event was classified as an adverse drug reaction. Although the event was considered as a serious adverse event and led to trial discontinuation, its severity was moderate. There were no problems with vital signs and the symptoms resolved spontaneously about 4 hours after onset.

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[73] Pooled data from clinical trials with administration of IDeg or IDegAsp, completed by January 31, 2011, including 6 exploratory trials, 17 confirmatory trials, and 2 other trials (Safety Analysis Set, 6382 subjects in the pooled IDeg/IDegAsp group and 3754 subjects in the pooled comparator group).

[74] Pooled data from 31 clinical pharmacology trials with administration of IDeg or IDegAsp (Safety Analysis Set, 1128 subjects in the pooled IDeg/IDegAsp group and 650 subjects in the pooled comparator group).

In conclusion, according to the analysis of the confirmatory trials in which Japanese subjects participated and the global pooled data, immunogenicity-related adverse events (allergic reactions) were uncommon and there were no clear differences in the occurrence of immunogenicity-related adverse events between the pooled IDeg/IDegAsp group and the pooled comparator group. A caution about allergic reactions will be included in the package insert. In addition, immunogenicity-related adverse events (allergic reactions) will be listed as a priority item for safety evaluation via post-marketing surveillance and the results will be provided to the medical practice as needed.

PMDA considers as follows:
The number of immunogenicity-related adverse events (allergic reactions) was small and no major differences between the IDeg and comparator groups were observed in Japan or overseas. Nevertheless, it is necessary to provide a caution in the package insert and continue to collect information on the occurrence of anaphylactic reactions and allergic reactions via post-marketing surveillance.

4.(iii).B.(4).3) Injection site reactions
The applicant explained as follows:
In Trials 3585/3725 in patients with type 1 diabetes mellitus, the incidence of injection site reactions was 4.7% (14 of 301 subjects) (14 events) in the IDeg group and 2.6% (4 of 152 subjects) (4 events) in the IDet group and the incidence rate of injection site reactions was 5 events/100 patient-years in the IDeg group and 3 events/100 patient-years in the IDet group. In Trial 3586 in patients with type 2 diabetes mellitus, the incidence of injection site reactions was 1.8% (5 of 284 subjects) (6 events) in the IDeg group and 2.1% (3 of 146 subjects) (3 events) in the IGlar group and the incidence rate of injection site reactions was 4 events/100 patient-years in both the IDeg and IGlar groups. In both trials, the incidence of injection site reactions in each treatment group was low and there were no major differences in the incidence rate of injection site reactions. There were no major differences in the nature of injection site reactions between the treatment groups and no serious adverse events were reported. In Trials 3585/3725, there were 1 lipodystrophy-related event in the IDeg group (lipohypertrophy, moderate) and 2 lipodystrophy-related events in the IDet group (injection site hypertrophy, mild), of which lipohypertrophy occurring in the IDeg group was classified as an adverse drug reaction. No lipodystrophy-related events were reported in Trial 3586.

According to the global pooled data from IDeg confirmatory trials,[75] the incidence of injection site reactions was 3.8% (136 of 3589 subjects) in the pooled IDeg group and 3.7% (59 of 1578 subjects) in the pooled comparator group and the incidence rate of injection site reactions was 7.6 events/100 patient-years in the pooled IDeg group and 8.4 events/100 patient-years in the pooled comparator group. There were no major differences between the treatment groups. Although many of the events were classified as adverse drug reactions, most of the events were mild or moderate in severity. There were only 2 severe events in the pooled comparator group and no serious adverse events were reported. The incidence of lipodystrophy-related events was 0.3% (13 of 4275 subjects) in the pooled IDeg group and 0.3% (6 of 2269 subjects) in the pooled comparator group and the incidence rate of lipodystrophy-related events was low for both treatment groups, i.e. 0.5 events/100 patient-years in the pooled IDeg group and 0.4 events/100 patient-years in the pooled comparator group. There were no severe events or serious adverse events.

In conclusion, according to the analysis of the confirmatory trials in which Japanese subjects participated and the global pooled data, the occurrences of injection site reactions between the IDeg and comparator groups were comparable, which suggested that there may be no difference between IDeg and the comparator for this adverse event. However, a caution about injection site reactions will be included in the package insert and the occurrence of injection site reactions will be identified as a priority item via post-marketing surveillance.

PMDA considers as follows:
The incidence of injection site reactions in the IDeg group was low and there were no major differences between the IDeg and comparator groups in Japanese and foreign clinical trials. Since an injection site reaction is one of significant events associated with insulin therapy, it is necessary to provide a caution in the package insert and continue to collect information on the occurrence of injection site reactions via post-marketing surveillance.

4.(iii).B.(4).4) Neoplasms

The applicant explained as follows:
Concerning the risk of neoplasms associated with IDeg, there were no findings suggesting increased mitogenicity with insulin degludec compared with human insulin in non-clinical studies conducted to assess the mitogenic potential and carcinogenic risk of insulin degludec. In clinical trials, events identified by the SOC “neoplasms benign, malignant and unspecified (incl cysts and polyps)” and SMQ “neoplasms” and events judged by the investigator to be related to neoplasms in confirmatory trials were reviewed by an external independent consultant in a blinded manner for classification into

[75] Pooled data from 8 confirmatory trials with administration of IDeg (IDeg, multinational trial [3585, type 1], multinational trial [3586, type 2], Trial 3579 [type 2], Trial 3582 [type 2], Trial 3583 [type 1], Trial 3668 [type 2], Trial 3672 [type 2], Trial 3770 [type 1]) (Safety Analysis Set, 3589 subjects in the pooled IDeg group and 1578 subjects in the pooled comparator group). Trial 3718 and Trial 3724 of three-times-weekly IDeg and Trial 3580 using a DPP-4 inhibitor as a comparator were excluded.

three categories: malignant, benign, and unclassifiable. In Trials 3585/3725, 19 events of neoplasms (16 events in the IDeg group, 3 events in the IDet group) were reported. As a result of a review of these events by an external consultant, none were classified as malignant neoplasms, 16 events (13 events in the IDeg group [including 9 events reported from Trial 3585], 3 events in the IDet group) were classified as benign neoplasms, and 3 events (IDeg group only) were assessed as unclassifiable. All events were non-serious and the causal relationship of the events to trial drug was denied. In Trial 3586, 13 events of neoplasms (10 events in the IDeg group, 3 events in the IGlar group) were reported. Of these, 1 event in the IDeg group (large intestine carcinoma) and 3 events in the IGlar group (breast cancer, endometrial cancer, colonic polyp) were considered as serious adverse events. As a result of a review by an external consultant, 3 events (1 event in the IDeg group [large intestine carcinoma], 2 events in the IGlar group [breast cancer, endometrial cancer]) were classified as malignant neoplasms and 10 events (9 events in the IDeg group, 1 event in the IGlar group) were classified as benign neoplasms. A causal relationship to trial drug was denied for all events, except for the 1 event in the IDeg group classified as a benign neoplasm (pancreatic cyst).

According to the global pooled data from IDeg and IDegAsp confirmatory trials[14] (a total of 8941 subjects, 5635 subjects in the pooled IDeg/IDegAsp group and 3306 subjects in the pooled comparator group), 211 events of neoplasms were reported. As a result of a review of these events by an external consultant, 46 events (31 events in the pooled IDeg/IDegAsp group, 15 events in the pooled comparator group) were classified as malignant neoplasms, 140 events (98 events in the pooled IDeg/IDegAsp group, 42 events in the pooled comparator group) were classified as benign neoplasms, and 25 events (20 events in the pooled IDeg/IDegAsp group, 5 events in the pooled comparator group) were assessed as unclassifiable. The incidence of malignant neoplasms was 0.5% (30 of 5635 subjects) in the pooled IDeg/IDegAsp group and 0.5% (15 of 3306 subjects) in the pooled comparator group and the incidence rate of malignant neoplasms was similar between the treatment groups, i.e., 0.9 events/100 patient-years in the pooled IDeg/IDegAsp group and 0.8 events/100 patient-years in the pooled comparator group. As to the time of onset, of the 31 events in the pooled IDeg/IDegAsp group, 16 events (52%) were reported within 3 months after the start of study treatment, 4 events (13%) were reported 3 to 6 months after the start of study treatment, 7 events (23%) were reported 6 to 9 months after the start of study treatment, and 4 events (13%) were reported ≥9 months after the start of study treatment. Of the 15 events in the pooled comparator group, 5 events (33%) were reported within 3 months and 8 events (53%) were reported within 6 months after the start of study treatment. Based on the global pooled data, the most frequently reported types of malignancies involved the skin, gastrointestinal tract, breast, thyroid, and bladder. Skin (11 events in the pooled IDeg/IDegAsp group, 2 events in the pooled comparator group) and gastrointestinal (8 events in the pooled IDeg/IDegAsp group, 3 events in the pooled comparator group) malignant neoplasms were reported more frequently in the pooled IDeg/IDegAsp group whereas breast (2 events in the pooled IDeg/IDegAsp group, 3 events in the pooled comparator group), thyroid (1 event in the pooled IDeg/IDegAsp group, 3 events

in the pooled comparator group), and bladder (1 event in the pooled IDeg/IDegAsp group, 2 events in the pooled comparator group) malignant neoplasms were reported more frequently in the pooled comparator group. The incidence rate of benign neoplasms was 2.7 events/100 patient-years in the pooled IDeg/IDegAsp group and 2.2 events/100 patient-years in the pooled comparator group. There were no major differences between the treatment groups. The incidence rate of unclassifiable neoplasms was low for both treatment groups, i.e., 0.6 events/100 patient-years in the pooled IDeg/IDegAsp group and 0.3 events/100 patient-years in the pooled comparator group.

In conclusion, according to the global pooled data, there were no differences in the overall incidence rate of neoplasms between the pooled IDeg/IDegAsp group and the pooled comparator group. The observed differences in the numbers of the various types of malignant neoplasms between the treatment groups are considered coincidental since the incidences of each type of malignancies were low. Since the time from the start of study treatment to diagnosis was short, it is considered that a relationship between IDeg or IDegAsp and the development of neoplasms has not been suggested. For the occurrence of neoplasms following treatment with IDeg during the post-marketing period, like the currently approved insulin preparations, pharmacovigilance activities such as Periodic Safety Update Reports and literature search will be conducted and the cases of neoplasms from clinical investigations and spontaneous reporting will be followed-up and assessed.

PMDA considers as follows:
Since the results of the non-clinical and clinical studies did not indicate a clearly increased risk of neoplasms with IDeg compared with the comparators, there is no particular problem with the applicant's view that similar actions as those for the currently approved insulin preparations will be taken for the occurrence of neoplasms during the post-marketing period. However, it is necessary to continue to collect information on the development of neoplasms via post-marketing surveillance as well.

4.(iii).B.(4).5) Cardiovascular risk

PMDA asked the applicant to explain the cardiovascular risk of IDeg, including adverse events and changes in lipid parameters, ECG, and vital signs (blood pressure, pulse rate, body weight), etc.

The applicant responded as follows:
In Trials 3585/3725 in patients with type 1 diabetes mellitus, the incidence of events in the SOC "cardiac disorders" was 2.3% (7 of 301 subjects) (7 events) in the IDeg group and 2.0% (3 of 152 subjects) (3 events) in the IDet group and the incidence of events in the SOC "vascular disorders" was 2.7% (8 of 301 subjects) (9 events) in the IDeg group and 2.0% (3 of 152 subjects) (3 events) in the IDet group. None of these events were considered as serious adverse events and only 2 events in the IDet group (hypertension, bradycardia) were classified as adverse drug reactions. In Trial 3586 in

patients with type 2 diabetes mellitus, the incidence of events in the SOC "cardiac disorders" was 1.4% (4 of 284 subjects) (5 events) in the IDeg group and 2.7% (4 of 146 subjects) (8 events) in the IGlar group and the incidence of events in the SOC "vascular disorders" was 2.8% (8 of 284 subjects) (8 events) in the IDeg group and 3.4% (5 of 146 subjects) (5 events) in the IGlar group. Of these, 2 events in the IDeg group (unstable angina, coronary artery occlusion) and 2 events in the IGlar group (congestive cardiac failure, coronary artery disease) were considered as serious adverse events and only 1 event in the IDeg group (bundle branch block right) was classified as an adverse drug reaction. Cardiovascular events[76] sent to an external event adjudication committee were 1 event in the IDeg group (cerebral infarction) in Trials 3585/3725 and 5 events (3 events in the IDeg group: coronary artery occlusion, cerebrovascular accident, carotid artery stenosis; 2 events in the IGlar group: coronary artery disease, congestive cardiac failure) in Trial 3586. One event in the IDeg group (cerebral infarction) in Trials 3585/3725 and 2 events in the IDeg group (coronary artery occlusion, cerebrovascular accident) in Trial 3586 were adjudicated as major adverse cardiovascular events (MACE), but a causal relationship to trial drug was denied for all of these events.

Lipid parameters (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol) were normal throughout the trial period in most subjects in Trials 3585/3725 and Trial 3586 and the proportion of subjects with changes from normal to high or low in lipid values during the trial period was also low in both treatment groups (Trials 3585/3725, 0% to 7.3% in the IDeg group, 0% to 7.9% in the IDet group; Trial 3586, 0% to 6.3% in the IDeg group, 0% to 6.8% in the IGlar group) and there were no clinically meaningful differences between the treatment groups. Lipid-related adverse events in the SOC "investigations" occurred in 4 subjects (6 events) (3 subjects [3 events] in the IDeg group, 1 subject [3 events] in the IDet group) in Trials 3585/3725 and 1 subject (1 event) in the IDeg group in Trial 3586, but a causal relationship to trial drug was denied for all events. There were no clinically relevant differences in ECG, blood pressure or pulse rate findings between the IDeg and comparator groups at Week 52 in Trials 3585/3725 and at Week 26 in Trial 3586. In Trials 3585/3725, the mean increase in body weight from baseline to the end of treatment (mean ± SD) was 1.9 ± 3.3 kg in the IDeg group (n = 301) and 0.8 ± 2.8 kg in the IDet group (n = 152) and the increase in body weight was greater in the IDeg group than in the IDet group, which was considered attributable to IDet's property of preventing weight gain. In Trial 3586, the mean increase in body weight from baseline to the end of treatment (mean ± SD) was 1.3 ± 2.2 kg in the IDeg group (n = 284) and 1.4 ± 2.2 kg in the IGlar group (n = 146) and there were no major differences between the treatment groups. Among adverse events in the SOCs "investigations" and "metabolism and nutrition disorders," "weight increased" was an event related to body weight and its incidence was 3.3% (10 of 301 subjects) (10 events) in the IDeg group and 3.3% (5 of 152 subjects) (5 events) in the IDet group in Trials 3585/3725 and 1.4% (4

[76] Events identified by SMQ search (other ischemic heart disease, ischemic cerebrovascular conditions, myocardial infarction, hemorrhagic cerebrovascular conditions) and medical events of special interest (MESI: events suspected to be related to acute coronary syndrome (ACS), stroke, or cardiovascular death) were sent to an external event adjudication committee for blinded adjudication.

of 284 subjects) (4 events) in the IDeg group and 0.7% (1 of 146 subjects) (1 event) in the IGlar group in Trial 3586.

In conclusion, the confirmatory trials in which Japanese subjects participated indicated no major differences in cardiovascular risk between IDeg and comparators.

According to the global pooled data from IDeg and IDegAsp confirmatory trials,[14] the incidence of adverse events in the SOC "cardiac disorders" was 3.3% (184 of 5635 subjects) in the pooled IDeg/IDegAsp group and 2.8% (93 of 3306 subjects) in the pooled comparator group and the incidence rate of adverse events in the SOC "cardiac disorders" was 6.4 events/100 patient-years in the pooled IDeg/IDegAsp group and 6.9 events/100 patient-years in the pooled comparator group. There were no major differences between the treatment groups. The incidence of adverse events in the SOC "vascular disorders" was 4.6% (258 of 5635 subjects) in the pooled IDeg/IDegAsp group and 3.8% (124 of 3306 subjects) in the pooled comparator group and the incidence rate of adverse events in the SOC "vascular disorders" was 8.2 events/100 patient-years in the pooled IDeg/IDegAsp group and 7.1 events/100 patient-years in the pooled comparator group. There were no major differences between the treatment groups. Also for the incidence rate of cardiovascular events sent to the external event adjudication committee, there were no major differences between the treatment groups, i.e., 4.0 events/100 patient-years in the pooled IDeg/IDegAsp group and 3.9 events/100 patient-years in the pooled comparator group. MACE was reported by 81 subjects (84 events) and the incidence of MACE was 1.0% (54 of 5635 subjects) (56 events) in the pooled IDeg/IDegAsp group and 0.8% (27 of 3306 subjects) (28 events) in the pooled comparator group. Most of the events adjudicated as MACE were considered as serious adverse events and 14 events (8 events in the IDeg group, 1 event in the IDegAsp group, 5 events in the comparator [IGlar] group) were fatal. Two events in the IDegAsp group (haemorrhagic stroke, death) and 2 events in the comparator group (myocardial infarction [with a fatal outcome], sudden death) were classified as adverse drug reactions. Furthermore, a meta-analysis of the global pooled data on IDeg and IDegAsp was performed. Of 8918 subjects analyzed (5621 subjects in the pooled IDeg/IDegAsp group, 3297 subjects in the pooled comparator group), 80 subjects experienced events adjudicated as MACE (53 subjects in the pooled IDeg/IDegAsp group, 27 subjects in the pooled comparator group). The incidence rate of MACE was 1.48 events/100 patient-years in the pooled IDeg/IDegAsp group and 1.44 events/100 patient-years in the pooled comparator group. The hazard ratio for IDeg+IDegAsp vs. comparators with its 95% CI was 1.10 [0.68; 1.77].

In conclusion, no major differences in cardiovascular risk between IDeg/IDegAsp and comparators were suggested.

PMDA considers as follows:

In a confirmatory trial in which Japanese subjects participated, the IDeg group tended to show slightly more weight gain than the IDet group, but there were no significant changes in vital signs, ECG, or lipid parameters. A meta-analysis of the global pooled data showed no trend towards a clearly increased cardiovascular risk associated with IDeg or IDeg/IDegAsp compared with comparators. Thus, the applicant's response is largely acceptable. However, due to the limited number of patients included in clinical trials, it is necessary to continue to collect information on cardiovascular risk via post-marketing surveillance etc.

4.(iii).B.(4).6) Antibody formation

The applicant explained as follows:

Clinical trials in which Japanese subjects participated showed no trend towards marked rises in antibody titers following treatment with IDeg (Table 67 and Table 68). In order to assess the relationship between antibody formation and safety, the relationship between a rise in antibody titer and the occurrence of immunogenicity-related adverse events, injection site reactions, or hypoglycaemia was investigated. A rise in antibody titer was defined as an increase in the level of antibodies cross-reacting with human insulin of ≥10% B/T (absolute) or an increase in the level of insulin-specific antibodies of ≥5% B/T at the end of trial (1 week after the end of trial drug administration). The proportion of subjects with a rise in antibody titer was 7.6% (23 of 301 subjects) in the IDeg group and 42.1% (64 of 152 subjects) in the IDet group in Trials 3585/3725 in patients with type 1 diabetes mellitus and 1.1% (3 of 284 subjects) in the IDeg group and 10.3% (15 of 146 subjects) in the IGlar group in Trial 3586 in patients with type 2 diabetes mellitus. Among the subjects with a rise in antibody titer, no immunogenicity-related adverse events were reported in either trial and only 4 subjects (3 subjects in the IDeg group, 1 subject in the IDet group) in Trials 3585/3725 and 1 subject (the IGlar group) in Trial 3586 had injection site reactions and all of the events were mild in severity and treatment was continued. As to hypoglycaemia in Trials 3585/3725, the incidence of confirmed hypoglycaemia was 100.0% (23 of 23 subjects) in the IDeg group and 92.2% (59 of 64 subjects) in the IDet group among the subjects with a rise in antibody titer and 94.2% (261 of 277 subjects) in the IDeg group and 93.1% (81 of 87 subjects) in the IDet group among the subjects without a rise in antibody titer, which indicated no relationship between a rise in antibody titer and the incidence of confirmed hypoglycaemia in either treatment group. The incidence of nocturnal confirmed hypoglycaemia was 73.9% (17 of 23 subjects) in the IDeg group and 62.5% (40 of 64 subjects) in the IDet group among the subjects with a rise in antibody titer and 67.9% (188 of 277 subjects) in the IDeg group and 66.7% (58 of 87 subjects) in the IDet group among the subjects without a rise in antibody titer, which indicated no relationship between a rise in antibody titer and the incidence of nocturnal confirmed hypoglycaemia in either treatment group. The incidence rate of confirmed hypoglycaemia was 5679.5 episodes/100 patient-years in the IDeg group and 3540.6 episodes/100 patient-years in the IDet group among the subjects with a rise in antibody titer and

3630.2 episodes/100 patient-years in the IDeg group and 4297.8 episodes/100 patient-years in the IDet group among the subjects without a rise in antibody titer, which indicated a trend towards a higher rate of confirmed hypoglycaemia among the subjects with a rise in antibody titer in the IDeg group. However, as the number of subjects with a rise in antibody titer in the IDeg group was small, the results should be interpreted with care. The incidence rate of nocturnal confirmed hypoglycaemia was 440.7 episodes/100 patient-years in the IDeg group and 412.9 episodes/100 patient-years in the IDet group among the subjects with a rise in antibody titer and 330.4 episodes/100 patient-years in the IDeg group and 546.3 episodes/100 patient-years in the IDet group among the subjects without a rise in antibody titer and the incidence rate of nocturnal confirmed hypoglycaemia was similar between the treatment groups among the subjects with a rise in antibody titer. Among the subjects with a rise in antibody titer in Trials 3585/3725, the incidence of severe hypoglycaemia was 8.7% (2 of 23 subjects) in the IDeg group and 17.2% (11 of 64 subjects) in the IDet group. Since the number of subjects with severe hypoglycaemia was small, it was difficult to investigate the relationship between a rise in antibody titer and the occurrence of severe hypoglycaemia. In Trial 3586, as the number of sjubjects (3 subjects) with a rise in antibody titer in the IDeg group was small, it was difficult to investigate the relationship of the event with a rise in antibody titer. According to the global pooled data from IDeg confirmatory trials in patients with type 1 diabetes mellitus,[67] among the subjects with a rise in antibody titer, the incidence of severe hypoglycaemia was 11.2% (20 of 178 subjects) in the pooled IDeg group and 14.0% (14 of 100 subjects) in the pooled comparator group and the incidence rate ofsevere hypoglycaemia was 26.1 episodes/100 patient-years in the pooled IDeg group and 47.5 episodes/100 patient-years in the pooled comparator group. Both values were lower in the pooled IDeg group than in the pooled comparator group. The incidence of severe nocturnal hypoglycaemia was 4.5% (8 of 178 subjects) in the pooled IDeg group and 5.0% (5 of 100 subjects) in the pooled comparator group and the incidence rate of severe nocturnal hypoglycaemia was 6.7 episodes/100 patient-years in the pooled IDeg group and 14.6 episodes/100 patient-years in the pooled comparator group. Both values were lower in the pooled IDeg group than in the pooled comparator group. According to the global pooled data from IDeg confirmatory trials in patients with type 2 diabetes mellitus,[68] there was no subject with a rise in antibody titer who experienced severe hypoglycaemia.

In conclusion, the immunogenic response to treatment with IDeg is low and therefore there is no influence of antibody formation on the safety of IDeg.

PMDA considers as follows:
The clinical trials showed no trend towards marked rises in antibody titers following treatment with IDeg and there was no clear relationship between the level of antibody formation and safety. However, as the information on antibody formation following long-term treatment with IDeg in Japan is limited, it is necessary to continue to collect information on antibody formation via post-marketing surveillance.

4.(iii).B.(5) Indication

Since Japanese patients with type 2 diabetes mellitus on a basal-bolus regimen have not been studied, PMDA asked the applicant to explain the efficacy and safety of IDeg in basal-bolus therapy in Japanese patients with type 2 diabetes mellitus.

The applicant responded as follows:

Type 1 diabetes mellitus is characterized by the functional absence of insulin resulting from the destruction of pancreatic β-cells, which should be similar between Japanese and Caucasian patients. On the other hand, type 2 diabetes mellitus is characterized by reduced insulin secretion and increased insulin resistance. Japanese patients with type 2 diabetes mellitus have more severely impaired insulin secretion and lower insulin resistance than Caucasian patients with type 2 diabetes mellitus. Japanese type 2 diabetic patients with a long duration of diabetes and severely impaired insulin secretion are classified as insulin-dependent type 2 diabetic patients, whose conditions are similar to those of type 1 diabetic patients. Basal-bolus therapy has widely been used for treating them. Therefore, the efficacy and safety of IDeg in Japanese patients with type 2 diabetes mellitus requiring basal-bolus therapy have not been studied, but can be explained with the efficacy and safety results from Trial 3585 in type 1 diabetic patients on basal-bolus therapy, in which Japanese patients participated. According to the efficacy and safety results from Trial 3582[77] with basal-bolus therapy in foreign patients with type 2 diabetes mellitus, there were no relevant findings with IDeg compared with the comparator (IGlar) (Table 70).

Therefore, in conclusion, the efficacy and safety of IDeg in basal-bolus therapy in patients with type 2 diabetes mellitus can be predicted from the results of Trial 3585 and its efficacy and safety can be confirmed also in Foreign Trial 3582.

Table 70. Efficacy and safety results from Trial 3582 with basal-bolus therapy in patients with type 2 diabetes mellitus

	IDeg (n = 744)		IGlar (n = 248)	
Baseline HbA1c	8.3 ± 0.8		8.4 ± 0.9	
HbA1c change (%)	-1.17 ± 1.03		-1.29 ± 0.98	
Baseline FPG (mg/dL)	165.7 ± 54.9		165.8 ± 58.3	
FPG change (mg/dL)	-44.0 ± 63.5		-38.6 ± 65.3	
Adverse events	81.0 (610) 2937	438	79.3 (199) 987	431
Serious adverse events	14.9 (112) 140	21	15.9 (40) 46	20
Confirmed hypoglycaemia	80.9 (609) 7437	1109	82.1 (206) 3120	1363
Nocturnal confirmed hypoglycaemia	39.6 (298) 930	139	47.4 (119) 422	184
Severe hypoglycaemia	4.5 (34) 41	6	4.4 (11) 12	5

Mean ± SD, LOCF

Left: incidence % (no. of subjects with events) total number of events, Right: no. of events/100 patient-years

[77] A 52-week, IGlar-controlled, open-label, parallel-group, comparative trial using insulin aspart as bolus insulin in foreign patients with type 2 diabetes mellitus treated with insulin ± metformin ± pioglitazone.

PMDA considers as follows:
Based on the results from Trials 3585/3725 in patients with type 1 diabetes mellitus and the results from Trial 3586 in patients with type 2 diabetes mellitus on oral anti-diabetic therapy, there is no particular problem with the proposed indication of "diabetes mellitus where treatment with insulin is required," which is the same as that for the currently approved insulin preparations. The applicant's explanation that the conditions of Japanese patients with type 2 diabetes mellitus on a basal-bolus regimen are often similar to those of type 1 diabetic patients can be understood. Also, though in a different population, the results of Trial 3582 with basal-bolus therapy in foreign type 2 diabetic patients with high insulin resistance also showed no relevant differences between IDeg and the comparator. Thus, concerning the safety and efficacy of IDeg in basal-bolus therapy in Japanese patients with type 2 diabetes mellitus, the information may be collected via post-marketing surveillance. The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(6) Dosage and administration

4.(iii).B.(6).1) Dose of IDeg when switching from other basal insulin products

PMDA asked the applicant to explain the dose of IDeg when switching from other basal insulin products to the drug product.

The applicant responded as follows:
In a foreign exploratory trial in foreign patients with type 1 diabetes mellitus (Trial 1835[78]), subjects previously treated with once-daily basal insulin were switched to once-daily trial drug on a unit-to-unit basis, and those previously treated with twice-daily basal insulin reduced their daily basal insulin dose by 20% when switching to once-daily trial drug. As a result, many of the subjects in the IDeg group were those previously treated with twice-daily basal insulin and the mean daily basal insulin dose decreased from screening (29 units) to Week 1 (25 units), but increased to the pre-trial dose (29 units) within several weeks of treatment and then remained unchanged.

In an exploratory trial in Japanese patients with type 1 diabetes mellitus (Trial 3569), subjects were switched from once-daily basal insulin on a unit-to-unit basis. As a result, during a 6-week treatment period, the daily basal insulin dose increased by a mean of 2.3 units in the IDeg group, whereas in the IDet group, the daily basal insulin dose was stable. With respect to the incidence rate of hypoglycaemia for 4 weeks after switching, the incidence rate of hypoglycaemia during the first week of treatment was lower in the IDeg group than in the IDet group (49 episodes/patient-year in the IDeg group, 85 episodes/patient-year in the IDet group), but the incidence rate of hypoglycaemia during the

[78] A 16-week, IGlar-controlled, open-label trial of once-daily IDeg in a basal-bolus regimen with IAsp (as bolus insulin) in foreign patients with type 1 diabetes mellitus.

entire period was similar between the treatment groups (75 episodes/patient-year in the IDeg group, 89 episodes/patient-year in the IDet group).

Based on the above results, in Trial 3585 in patients with type 1 diabetes mellitus including Japanese patients, the applicant recommended that subjects should be switched to trial drug on a unit-to-unit basis, regardless of prior basal insulin injection frequency. The mean daily basal insulin doses at screening (23.1 units in the IDeg group, 22.4 units in the IDet group) and at baseline (1 week after the start of trial drug administration) (22.3 units in the IDeg group, 21.6 units in the IDet group) indicated no major changes from the daily basal insulin dose before switching in either treatment group.

The glycemic control status during the early phase of treatment was as follows: The pre-breakfast SMPG values at Weeks 1, 2, and 4 (mean ± SD) by prior basal insulin injection frequency were 143.2 ± 54.0 (n = 196), 134.6 ± 45.1 (n = 196), and 126.8 ± 44.6 (n = 194) mg/dL, respectively, in the IDeg group previously treated with once-daily basal insulin; 143.6 ± 51.4 (n = 115), 137.4 ± 49.5 (n = 115), and 129.4 ± 44.6 (n = 113) mg/dL, respectively, in the IDet group previously treated with once-daily basal insulin; 132.4 ± 53.6 (n = 105), 117.8 ± 45.0 (n = 105), and 132.2 ± 52.9 (n = 104) mg/dL, respectively, in the IDeg group previously treated with twice-daily basal insulin; and 136.5 ± 54.0 (n = 37), 119.6 ± 35.6 (n = 37), and 142.0 ± 66.0 (n = 35) mg/dL, respectively, in the IDet group previously treated with twice-daily basal insulin. Among the subjects previously treated with once-daily basal insulin, the SMPG value at Week 4 tended to be low in both treatment groups. The SMPG value decreased from Week 1 to Week 2 and then increased slightly at Week 4 in both treatment groups among the subjects previously treated with twice-daily basal insulin.

Regarding safety, the occurrence of hypoglycaemia by prior basal insulin injection frequency during the early phase of treatment was as shown in Table 71. Among the subjects previously treated with once-daily basal insulin, the incidence rate of confirmed hypoglycaemia was higher in the IDeg group than in the IDet group during the first 4 weeks of treatment, but there were no major differences during the remaining period. In both treatment groups, there was a tendency to increase from Week 1 to Week 2 and then decrease from Week 2 to Week 4. The incidence rate of nocturnal confirmed hypoglycaemia was generally lower in the IDeg group than in the IDet group during the first 4 weeks of treatment. On the other hand, among the subjects previously treated with twice-daily basal insulin, the incidence rate of confirmed hypoglycaemia was higher from Week 1 to Week 2 and lower in Week 4 in the IDeg group compared with the IDet group. The incidence rate of nocturnal confirmed hypoglycaemia was higher in Week 1 and lower in Weeks 2 and 4 in the IDeg group compared with the IDet group. The incidence rate of nocturnal confirmed hypoglycaemia was higher during the first 4 weeks of treatment compared with the remaining period in both treatment groups. The number of severe hypoglycemic episodes was small in either regimen.

Table 71. Occurrence of hypoglycaemia by prior basal insulin injection frequency during the early phase of treatment (Trial 3585 [26 weeks of treatment], Safety Analysis Set)

		Previously treated with once-daily basal insulin				Previously treated with twice-daily basal insulin			
		IDeg (n = 196)		IDet (n = 115)		IDeg (n = 105)		IDet (n = 37)	
Confirmed hypoglycaemia	Entire period	90.3 (177) 4001	4221.6	88.7 (102) 2092	3817.8	98.1 (103) 2672	5256.9	100.0 (37) 1203	6944.8
	Week 1	43.9 (86) 177	4712.0	40.0 (46) 84	3811.3	59.0 (62) 172	8547.3	59.5 (22) 45	6346.0
	Week 2	46.4 (91) 199	5321.0	42.6 (49) 101	4582.6	67.6 (71) 173	8597.0	62.2 (23) 56	7897.3
	Week 4	46.4 (90) 192	5164.1	37.7 (43) 85	3890.5	53.8 (56) 118	5920.3	61.1 (22) 52	7689.5
Nocturnal confirmed hypoglycaemia	Entire period	49.5 (97) 304	320.8	55.7 (64) 272	496.4	75.2 (79) 299	588.3	67.6 (25) 156	900.6
	Week 1	5.6 (11) 14	372.7	8.7 (10) 15	680.6	17.1 (18) 29	1441.1	13.5 (5) 5	705.1
	Week 2	8.2 (16) 18	481.3	7.0 (8) 11	499.1	16.2 (17) 23	1143.0	18.9 (7) 9	1269.2
	Week 4	3.6 (7) 7	188.3	8.8 (10) 12	549.2	7.7 (8) 10	501.7	19.4 (7) 11	1626.6
Severe hypoglycaemia	Entire period	11.2 (22) 31	32.7	8.7 (10) 15	27.4	9.5 (10) 14	27.5	16.2 (6) 13	75.0
	Week 1	0.0 (0) 0	0	0.0 (0) 0	0	0.0 (0) 0	0	2.7 (1) 1	141.0
	Week 2	0.0 (0) 0	0	1.7 (2) 2	90.7	1.9 (2) 2	99.4	2.7 (1) 1	141.0
	Week 4	1.0 (2) 2	53.8	0.0 (0) 0	0	1.0 (1) 1	50.2	0.0 (0) 0	0

Left: incidence % (no. of subjects with episodes) total number of episodes, Right: no. of episodes/100 patient-years

Based on the above, an improvement in SMPG values was associated with an increase in confirmed hypoglycemic episodes from Week 1 to Week 2 in both treatment groups among the subjects previously treated with once-daily basal insulin, whereas there was no consistent association between SMPG values and confirmed hypoglycaemia during the early phase of treatment among the subjects previously treated with twice-daily basal insulin. Up to Week 2, the incidence rate of confirmed hypoglycaemia was higher in the subjects previously treated with twice-daily basal insulin compared with those previously treated with once-daily basal insulin. The incidence rate of nocturnal confirmed hypoglycaemia was higher during the first 4 weeks of treatment compared with the entire period in both treatment groups.

The pre-breakfast SMPG values at Weeks 1, 2, and 4 (mean ± SD) by basal insulin type used before the trial were 150.4 ± 57.4 (n = 139), 135.1 ± 46.5 (n = 139), and 129.3 ± 48.9 (n = 138) mg/dL, respectively, in the IDeg group previously treated with IGlar; 142.1 ± 52.1 (n = 80), 140.7 ± 45.7 (n = 80), and 134.8 ± 50.5 (n = 77) mg/dL, respectively, in the IDet group previously treated with IGlar; 125.1 ± 46.0 (n = 112), 124.3 ± 43.1 (n = 112), and 125.3 ± 41.1 (n = 111) mg/dL, respectively, in the IDeg group previously treated with IDet; 144.8 ± 40.8 (n = 53), 124.6 ± 46.3 (n = 53), and 130.3 ± 48.2 (n = 52) mg/dL, respectively, in the IDet group previously treated with IDet; 141.3 ± 54.5 (n = 50), 120.9 ± 47.9 (n = 50), and 134.9 ± 57.5 (n = 49) mg/dL, respectively, in the IDeg group previously treated with NPH; and 133.0 ± 76.3 (n = 19), 124.6 ± 51.3 (n = 19), and 128.3 ± 58.8 (n = 19) mg/dL, respectively, in the IDet group previously treated with NPH. Regardless of basal insulin type used before the trial, the SMPG value tended to be lower at Week 4 than at Week 1 in both treatment groups.

The occurrence of hypoglycaemia by basal insulin type used before the trial during the early phase of treatment was as shown in Table 72. Among the subjects previously treated with basal insulin IDet,

the incidence and the incidence rate of confirmed hypoglycaemia were higher in the IDeg group than in the IDet group. Nocturnal confirmed hypoglycaemia occurred more frequently in the IDeg group compared with the IDet group in Week 1, but there were no clear differences between the treatment groups in Week 2. This is considered due to the fact that in the IDet group, patients and investigators were already familiar with the use of IDet as they remained on the same basal insulin. Among the subjects previously treated with basal insulin IGlar or NPH, there were no clear differences in the occurrence of hypoglycaemia between the treatment groups. The number of severe hypoglycemic episodes was small in all regimens.

Table 72. Occurrence of hypoglycaemia by basal insulin type used before the trial during the early phase of treatment (Trial 3585 [26 weeks of treatment], Safety Analysis Set)

		Previously treated with IGlar				Previously treated with IDet			
		IDeg (n = 139)		IDet (n = 80)		IDeg (n = 112)		IDet (n = 53)	
Confirmed hypoglycaemia	Entire period	90.6 (126) 3303	4922.4	91.3 (73) 1688	4536.1	93.8 (105) 2363	4376.0	88.7 (47) 1126	4340.1
	Week 1	50.4 (70) 147	5518.2	50.0 (40) 77	5022.2	50.0 (56) 145	6755.3	34.0 (18) 29	2855.1
	Week 2	49.6 (69) 154	5780.9	43.8 (35) 76	4957.0	57.1 (64) 158	7360.9	47.2 (25) 48	4725.6
	Week 4	51.4 (71) 156	5898.4	42.3 (33) 73	4883.4	45.9 (51) 106	4982.8	43.4 (23) 43	4291.2
Nocturnal confirmed hypoglycaemia	Entire period	50.4 (70) 261	389.0	60.0 (48) 281	755.1	62.5 (70) 237	438.9	62.3 (33) 126	485.7
	Week 1	8.6 (12) 15	563.1	12.5 (10) 15	978.3	8.9 (10) 18	838.6	5.7 (3) 3	295.4
	Week 2	7.9 (11) 13	488.0	8.8 (7) 11	717.5	12.5 (14) 20	931.8	15.1 (8) 9	886.1
	Week 4	4.3 (6) 6	226.9	12.8 (10) 15	1103.4	6.3 (7) 9	423.1	11.3 (6) 7	698.6
Severe hypoglycaemia	Entire period	11.5 (16) 25	37.3	7.5 (6) 9	24.2	7.1 (8) 10	18.5	3.8 (2) 2	7.7
	Week 1	0.0 (0) 0	0	0.0 (0) 0	0	0.0 (0) 0	0	1.9 (1) 1	98.5
	Week 2	0.0 (0) 0	0	0.0 (0) 0	0	1.8 (2) 2	93.2	0.0 (0) 0	0
	Week 4	1.4 (2) 2	75.6	2.5 (2) 2	130.4	0.9 (1) 1	47.0	0.0 (0) 0	0

		Previously treated with NPH			
		IDeg (n = 50)		IDet (n = 19)	
Confirmed hypoglycaemia	Entire period	98.0 (49) 1007	4110.0	100.0 (19) 481	5367.7
	Week 1	44.0 (22) 57	5948.4	52.6 (10) 23	6316.4
	Week 2	58.0 (29) 60	6370.6	63.2 (12) 33	9062.6
	Week 4	49.0 (24) 48	5111.4	47.4 (9) 21	5767.1
Nocturnal confirmed hypoglycaemia	Entire period	72.0 (36) 105	428.6	42.1 (8) 21	234.3
	Week 1	14.0 (7) 10	1043.6	10.5 (2) 2	549.2
	Week 2	16.0 (8) 8	849.4	0.0 (0) 0	0
	Week 4	4.1 (2) 2	213.0	5.3 (1) 1	274.6
Severe hypoglycaemia	Entire period	16.0 (8) 10	40.8	42.1 (8) 17	189.7
	Week 1	0.0 (0) 0	0	0.0 (0) 0	0
	Week 2	0.0 (0) 0	0	5.3 (1) 1	274.6
	Week 4	0.0 (0) 0	0	0.0 (0) 0	0

Left: incidence % (no. of subjects with episodes) total number of episodes, Right: no. of episodes/100 patient-years

In conclusion, according to the results of Trial 3585, the number of severe hypoglycemic episodes was small during the early phase of treatment in patients with type 1 diabetes mellitus on a basal-bolus regimen after switching from once-daily basal insulin to once-daily IDeg on a unit-to-unit basis, and there were no major differences in the occurrence of hypoglycaemia between the treatment groups. Thus, there should be no particular problem with the safety of IDeg when switching from once-daily basal insulin therapy. However, as the numbers of confirmed hypoglycemic episodes and nocturnal confirmed hypoglycemic episodes during the early phase of treatment tended to be higher in patients

switched from twice-daily basal insulin to once-daily IDeg, the dose of IDeg needs to be determined according to the patient's condition and a precaution statement will be included in the package insert.

PMDA considers as follows:
Concerning glycemic control and the occurrence of hypoglycaemia by prior basal insulin injection frequency during the early phase of treatment in Trial 3585, fluctuation of glycemic control occurred, and the incidence and number of hypoglycemic episodes increased during the early phase of treatment among the subjects previously treated with twice-daily basal insulin compared with those previously treated with once-daily basal insulin. Since the number of severe hypoglycemic episodes was small in both treatment groups, there should be no major safety concern in patients switched to IDeg on a unit-to-unit basis. However, as the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia during the early phase of treatment tended to be higher in patients switched from twice-daily basal insulin to once-daily IDeg, it is necessary to collect information on the safety of IDeg when switching from other basal insulin products via post-marketing surveillance. The above conclusion, including the appropriateness of a precaution statement etc., will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(6).2) Timing of injection
The applicant explained as follows:
In a multiple-dose trial in foreign patients with type 1 diabetes mellitus (Trial 1993), IDeg produced an extended, flat blood concentration profile at steady state and had a duration of action extending beyond 42 hours. Also in a multiple-dose trial in Japanese patients with type 1 diabetes mellitus (Trial 1996), IDeg produced an extended, flat blood concentration profile at steady state and had a duration of action extending beyond 26 hours.

Since IDeg has a longer duration of action and a longer and flatter profile compared with the current long-acting insulin analogs, two foreign trials (Trial 3770 in patients with type 1 diabetes mellitus[79] and Trial 3668 in patients with type 2 diabetes mellitus[80]) were used to determine whether a missed scheduled dose can be taken as soon as the patient remembers. In these trials, once-daily IDeg (flexible dosing), once-daily IDeg (fixed dosing), and once-daily IGlar were compared. In the IDeg flexible dosing groups, IDeg was injected in the morning (from waking-up until breakfast) on Mondays, Wednesdays, and Fridays and in the evening (from the start of the evening meal until bedtime) on Tuesdays, Thursdays, Saturdays, and Sundays. This meant that IDeg was administered

[79] A 26-week, open-label, parallel-group, comparative trial of IDeg in a flexible doing regimen vs. IGlar or IDeg given once daily in the evening in a basal-bolus regimen with IAsp as bolus insulin in foreign patients with type 1 diabetes mellitus. Then subjects treated with IDeg were transferred to a free-flexible regimen of IDeg (IDeg could be administered once daily at any time of the day but with an 8-40 hours interval between injections) in the 26-week extension.

[80] A 26-week, open-label, parallel-group, comparative trial of IDeg in a flexible dosing regimen vs. IGlar or IDeg given once daily in the evening, with or without oral anti-diabetic therapy (metformin ± SU ± pioglitazone ± rapid-acting insulin secretagogue), in foreign patients with type 2 diabetes mellitus

with alternating narrow (8-12 hours) and wide (36-40 hours) dosing intervals, with the exception of a 24-hour dosing interval between Saturdays and Sundays. In the IDeg fixed dosing groups, IDeg was given at the same time each day (with the evening meal). In the once-daily IGlar groups, IGlar was given once daily according to the local labeling. In Trial 3770 in patients with type 1 diabetes mellitus, the primary efficacy endpoint of the change in HbA1c from baseline (at the start of trial drug administration) to Week 26 (least square mean[81] ± SE) was -0.40 ± 0.05% in the IDeg flexible dosing group, -0.41 ± 0.05% in the IDeg fixed dosing group, and -0.57 ± 0.05% in the once-daily IGlar group. In Trial 3668 in patients with type 2 diabetes mellitus, the change in HbA1c from baseline to Week 26 was -1.17 ± 0.08% in the IDeg flexible dosing group, -1.03 ± 0.08% in the IDeg fixed dosing group, and -1.21 ± 0.08% in the once-daily IGlar group. Regarding safety, the occurrence of hypoglycaemia in the trials investigating a flexible dosing regimen of IDeg (Trials 3770 and 3668) was as shown in Table 73.

Table 73. Occurrence of hypoglycaemia in trials investigating a flexible dosing regimen of IDeg (Safety Analysis Set)

	Trial 3770 (Patients with type 1 diabetes mellitus)			Trial 3668 (Patients with type 2 diabetes mellitus)		
	IDeg flexible dosing group[a)] (n = 164)	IDeg fixed dosing group (n = 165)	Once-daily IGlar group (n = 161)	IDeg flexible dosing group[a)] (n = 230)	IDeg fixed dosing group (n = 226)	Once-daily IGlar group (n = 229)
Entire period						
Confirmed hypoglycaemia	93.9 (154)	99.4 (164)	96.9 (156)	50.9 (117)	43.8 (99)	49.3 (113)
	5988 [8237.7]	6724 [8825.1]	6263 [7973.4]	388 [364.3]	378 [362.6]	368 [348.4]
Nocturnal confirmed hypoglycaemia	67.7 (111)	73.3 (121)	72.7 (117)	13.5 (31)	10.6 (24)	21.4 (49)
	453 [623.2]	732 [960.7]	782 [995.6]	67 [62.9]	58 [55.6]	79 [74.8]
Severe hypoglycaemia	10.4 (17)	12.7 (21)	9.9 (16)	0.4 (1)	0.9 (2)	0.9 (2)
	25 [34.4]	28 [36.7]	37 [47.1]	2 [1.9]	2 [1.9]	2 [1.9]
Mondays/Wednesdays/Fridays						
Confirmed hypoglycaemia	92.1 (151)	96.4 (159)	92.5 (149)	41.3 (95)	31.0 (70)	31.9 (73)
	3248 [10428.4]	2815 [8622.0]	2657 [7895.1]	220 [482.1]	167 [373.7]	146 [322.6]
Nocturnal confirmed hypoglycaemia	45.7 (75)	57.0 (94)	54.0 (87)	7.4 (17)	7.5 (17)	12.2 (28)
	170 [545.8]	349 [1068.9]	366 [1087.5]	29 [63.6]	31 [69.4]	37 [81.7]
Severe hypoglycaemia	7.3 (12)	6.1 (10)	5.6 (9)	0.0 (0)	0.4 (1)	0.4 (1)
	16 [51.4]	11 [33.7]	15 [44.6]	0 [0.0]	1 [2.2]	1 [2.2]
Tuesdays/Thursdays/Saturdays						
Confirmed hypoglycaemia	88.4 (145)	97.0 (160)	94.4 (152)	30.4 (70)	31.4 (71)	31.4 (72)
	2045 [6563.0]	2990 [9152.7]	2722 [8082.4]	126 [275.9]	149 [333.5]	156 [344.5]
Nocturnal confirmed hypoglycaemia	55.5 (91)	52.7 (87)	59.0 (95)	8.3 (19)	5.8 (13)	10.5 (24)
	242 [776.6]	312 [955.1]	334 [991.7]	31 [67.9]	21 [47.0]	31 [68.5]
Severe hypoglycaemia	3.7 (6)	5.5 (9)	6.8 (11)	0.0 (0)	0.4 (1)	0.0 (0)
	7 [22.5]	11 [33.7]	17 [50.5]	0 [0.0]	1 [2.2]	0 [0.0]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]
a) IDeg was injected in the morning (from rising until breakfast) on Mondays, Wednesdays, and Fridays and in the evening (from the start of the evening meal until bedtime) on Tuesdays, Thursdays, Saturdays, and Sundays. This meant that IDeg was administered with alternating narrow (8-12 hours) and wide (36-40 hours) dosing intervals, with the exception of a 24-hour dosing interval between Saturdays and Sundays.

In Trial 3770 in patients with type 1 diabetes mellitus, on Mondays/Wednesdays/Fridays (when IDeg was administered with a narrow dosing interval in the IDeg flexible dosing group), the incidence rate of confirmed hypoglycaemia tended to be higher in the IDeg flexible dosing group compared with the IDeg fixed dosing group and the once-daily IGlar group, whereas the incidence rate of nocturnal

[81] Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening, sex, and region as fixed factors and age and baseline HbA1c as covariates.

confirmed hypoglycaemia was not affected by the dosing interval. Although the number of severe hypoglycemic episodes was small, there was no clear trend within the week. In Trial 3668 in patients with type 2 diabetes mellitus, the incidence rate of severe hypoglycaemia was low in the IDeg flexible dosing group and there was no clear trend within the week in the occurrence of confirmed hypoglycaemia, nocturnal confirmed hypoglycaemia, or severe hypoglycaemia.

Based on the above, there were no particular differences in the efficacy and safety results between the IDeg flexible dosing group and the IDeg fixed dosing group and IDeg may be administered at differing times from day to day without significantly affecting efficacy and safety.

In Trials 3770 and 3668, IDeg was dosed once daily even in the flexible dosing groups and IDeg was administered 8 to 12 hours after the last injected dose only when an evening dose was followed by a morning dose, but not when a morning dose was followed by an evening dose. In Trial 3770, on Mondays/Wednesdays/Fridays (when IDeg was administered 8 to 12 hours after the last injected dose in the IDeg flexible dosing group), the incidence rate of confirmed hypoglycaemia was higher with IDeg flexible dosing compared with the comparator or IDeg given once daily at a fixed time. PMDA asked the applicant to explain the expected use of IDeg in clinical practice and the possibility of increased nocturnal confirmed hypoglycaemia with twice-daily dosing.

The applicant responded as follows:
In the case where the patient takes IDeg once daily in the evening, if a dose is missed, IDeg might be taken in the morning of the next day, resulting in twice-daily dosing of IDeg on that day (the missed dose in the morning and the next scheduled dose in the evening), and then it is predicted that the patient will resume his/her usual once-daily (evening) dosing schedule. In Trials 3770 and 3668, the incidence rate of nocturnal confirmed hypoglycaemia with IDeg was similar to or lower than that with once-daily IGlar throughout the week. In Trial 3770, the incidence rate of confirmed hypoglycaemia tended to be higher with a narrow dosing interval on Mondays/Wednesdays/Fridays compared with a wide dosing interval on Tuesdays/Thursdays/Saturdays, but there were no differences in the incidence of hypoglycaemia between the IDeg flexible dosing group and the once-daily IGlar group. In Trial 3668, the incidence rate of confirmed hypoglycaemia was generally low and differed slightly from day to day. The incidence rate of nocturnal confirmed hypoglycaemia was also generally low and there was no clear pattern. The incidence rate of severe hypoglycaemia was low on any day of the week in patients with type 2 diabetes mellitus and the incidence rate of severe hypoglycaemia was similar between IDeg and the comparator in patients with type 1 diabetes mellitus.

Taking account of the flat and stable pharmacokinetic profile of IDeg with a low day-to-day variability at steady state, occasional twice-daily dosing of IDeg will not result in increased nocturnal hypoglycaemia.

PMDA considers as follows:

PMDA understands the applicant's view that providing information on how to manage missed scheduled doses, in light of the characteristics of IDeg, is of significance. However, as the incidence rate of confirmed hypoglycaemia tended to increase with a narrow dosing interval in both type 1 and type 2 diabetic patients, IDeg should be injected at a consistent time each day as much as possible. Thus, the finding that IDeg can be dosed flexibly at any time of the day should not be informed in an exaggerated manner. Since Trials 3770 and 3668 investigated IDeg dosing at alternating narrow and wide dosing intervals, it is necessary to provide the following information: a morning dose followed by an evening dose 8 to 12 hours later or multiple injections at a narrow dosing interval has not been studied. The above conclusion will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(7) Special populations

4.(iii).B.(7).1) Elderly

The applicant explained as follows:

The occurrence of adverse events by age group at baseline in confirmatory trials in which Japanese subjects participated was as shown in Table 74. In Trials 3585/3725, there were no major differences in the incidence rate of adverse events between the treatment groups in subjects ≤65 years of age or >65 years of age. There were no major differences in the incidence rate of serious adverse events between the treatment groups in subjects ≤65 years of age and the number of serious adverse events was small in both treatment groups in subjects >65 years of age. Due to the small number of subjects aged >75 years in both treatment groups, it was difficult to investigate the relationship of the adverse events to safety. In Trial 3586, there were no major differences in the incidence rate of adverse events between the treatment groups in subjects ≤65 years of age or >65 years of age. Due to the small number of serious adverse events in both treatment groups, it was difficult to investigate the effect of age. No serious adverse events were reported by subjects aged >75 years.

Table 74. Occurrence of adverse events by age group at baseline
(Confirmatory trials in which Japanese subjects participated, Safety Analysis Set)

Trials 3585/3725	IDeg (n = 301)			IDet (n = 152)		
	≤65years (n = 276)	>65 years (n = 25)	>75 years[a)] (n = 3)	≤65 years (n = 140)	>65 years (n = 12)	>75 years[a)] (n = 2)
Overall adverse events	82.2 (227)	84.0 (21)	33.3 (1)	77.1 (108)	83.3 (10)	100.0 (2)
	1156 [462.0]	99 [428.4]	7 [229.5]	516 [420.1]	48 [422.4]	19 [1130.3]
Serious adverse events	10.5 (29)	28.0 (7)	33.3 (1)	7.1 (10)	8.3 (1)	50.0 (1)
	44 [17.6]	10 [43.3]	1 [32.8]	20 [16.3]	3 [26.4]	3 [178.5]
Trial 3586	IDeg (n = 284)			IGlar (n = 146)		
	≤65 years (n = 201)	>65 years (n = 83)	>75 years[a)] (n = 9)	≤65 years (n = 107)	>65 years (n = 39)	>75 years[a)] (n = 6)
Overall adverse events	59.2 (119)	57.8 (48)	66.7 (6)	62.6 (67)	71.8 (28)	83.3 (5)
	284 [299.4]	107 [277.5]	11 [244.8]	148 [287.4]	56 [298.3]	10 [334.8]
Serious adverse events	2.0 (4)	4.8 (4)	0.0 (0)	5.6 (6)	5.1 (2)	0.0 (0)
	4 [4.2]	6 [15.6]	0 [0]	6 [11.6]	2 [10.7]	0 [0]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]
a) A subgroup of the age group >65 years

The occurrence of hypoglycaemia by age group at baseline was as shown in Table 75. In Trials 3585/3725, there were no major differences in the incidence rate of confirmed hypoglycaemia between the treatment groups in subjects ≤65 years of age or >65 years of age and the incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IDet group in both subjects ≤65 years of age and those >65 years of age. There were no clear differences in the incidence rate of severe hypoglycaemia between the treatment groups in subjects ≤65 years of age or >65 years of age. Among subjects >75 years of age, only 3 subjects experienced confirmed hypoglycaemia and severe hypoglycaemia was not reported. In Trial 3586, there were no major differences in the incidence rate of confirmed hypoglycaemia between the treatment groups in subjects ≤65 years of age and the incidence rate of confirmed hypoglycaemia was lower in the IDeg group than in the IGlar group in subjects >65 years of age. The incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IGlar group in both subjects ≤65 years of age and those >65 years of age. Due to the small numbers of confirmed hypoglycemic episodes and nocturnal confirmed hypoglycemic episodes in subjects >75 years of age, it was difficult to investigate the effect of age.

Table 75. Occurrence of hypoglycaemia by age group at baseline
(Confirmatory trials in which Japanese subjects participated, Safety Analysis Set)

Trials 3585/3725	IDeg (n = 301)			IDet (n = 152)		
	≤65 years (n = 276)	>65 years (n = 25)	>75 years[a] (n = 3)	≤65 years (n = 140)	>65 years (n = 12)	>75 years[a] (n = 2)
Confirmed hypoglycaemia	95.3 (263)	88.0 (22)	33.3 (1)	92.9 (130)	91.7 (11)	100.0 (2)
	9272 [3705.3]	1054 [4561.3]	19 [623.0]	4760 [3875.2]	509 [4478.7]	47 [2795.9]
Nocturnal confirmed hypoglycaemia	69.6 (192)	52.0 (13)	0.0 (0)	65.0 (91)	58.3 (7)	50.0 (1)
	860 [343.7]	64 [277.0]	0 [0]	589 [479.5]	57 [501.5]	1 [59.5]
Severe hypoglycaemia	13.4 (37)	20.0 (5)	0.0 (0)	12.9 (18)	0.0 (0)	0.0 (0)
	58 [23.2]	5 [21.6]	0 [0]	37 [30.1]	0 [0]	0 [0]
Severe nocturnal hypoglycaemia	5.8 (16)	0.0 (0)	0.0 (0)	4.3 (6)	0.0 (0)	0.0 (0)
	18 [7.2]	0 [0]	0 [0]	7 [5.7]	0 [0]	0 [0]
Trial 3586[b]	IDeg (n = 284)			IGlar (n = 146)		
	≤65 years (n = 201)	>65 years (n = 83)	>75 years[a] (n = 9)	≤65 years (n = 107)	>65 years (n = 39)	>75 years[a] (n = 6)
Confirmed hypoglycaemia	53.7 (108)	41.0 (34)	55.6 (5)	48.6 (52)	66.7 (26)	66.7 (4)
	285 [300.4]	112 [290.5]	20 [445.2]	176 [341.7]	84 [447.4]	22 [736.5]
Nocturnal confirmed hypoglycaemia	21.4 (43)	18.1 (15)	22.2 (2)	22.4 (24)	28.2 (11)	33.3 (2)
	72 [75.9]	32 [83.0]	8 [178.1]	67 [130.1]	20 [106.5]	7 [234.3]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]
a) A subgroup of the age group >65 years
b) In Trial 3586, severe hypoglycaemia occurred in 1 subject in the IGlar group only.

According to the global pooled data from IDeg confirmatory trials,[72] the occurrence of adverse events by age group at baseline was as shown in Table 76. In patients with type 1 diabetes mellitus, albeit that the number of subjects aged >75 years was small, there were no major differences in the incidence rate of adverse events between the treatment groups in subjects ≤65 years of age, the incidence rate of adverse events was higher in the pooled IDeg group than in the pooled comparator group in subjects >65 years of age, and the incidence rate of adverse events was lower in the pooled IDeg group than in the pooled comparator group in subjects >75 years of age. The incidence rate of serious adverse events was low in both age groups with no major differences between the treatment groups, and there were also no clear differences in the nature of events. In patients with type 2 diabetes mellitus, there were

no major differences in the incidence rate of adverse events or serious adverse events between the treatment groups in either age group.

Table 76. Occurrence of adverse events by age group at baseline
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)			Pooled comparator group (n = 467)		
	≤65 years (n = 1025)	>65 years (n = 77)	>75 years[a)] (n = 9)	≤65 years (n = 438)	>65 years (n = 29)	>75 years[a)] (n = 5)
Overall adverse events	77.0 (789)	81.8 (63)	66.7 (6)	76.5 (335)	72.4 (21)	100.0 (5)
	3126 [461.2]	304 [621.3]	18 [392.3]	1302 [471.7]	84 [444.1]	25 [626.3]
Serious adverse events	7.6 (78)	13.0 (10)	11.1 (1)	7.3 (32)	3.4 (1)	20.0 (1)
	102 [15.0]	11 [22.5]	1 [21.8]	42 [15.2]	2 [10.6]	2 [50.1]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 3173)			Pooled comparator group (n = 1802)		
	≤65 years (n = 2395)	>65 years (n = 778)	>75 years[a)] (n = 94)	≤65 years (n = 1396)	>65 years (n = 406)	>75 years[a)] (n = 60)
Overall adverse events	67.2 (1610)	71.5 (556)	80.9 (76)	65.0 (908)	65.5 (266)	63.3 (38)
	6478 [412.0]	2198 [415.6]	241 [387.0]	3243 [405.1]	974 [399.8]	136 [379.4]
Serious adverse events	6.9 (166)	10.7 (83)	9.6 (9)	5.6 (78)	8.9 (36)	5.0 (3)
	203 [12.9]	111 [21.0]	12 [19.3]	91 [11.4]	46 [18.9]	3 [8.4]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]
a) A subgroup of the age group >65 years

According to the global pooled data from IDeg confirmatory trials,[75] the occurrence of hypoglycaemia by age group at baseline was as shown in Table 77. In patients with type 1 diabetes mellitus, the incidence rate of confirmed hypoglycaemia tended to be lower in subjects ≤65 years of age than in subjects >65 years of age in both treatment groups. There were no major differences in the incidence rate of severe hypogycemia between the treatment groups in either age group and no severe hypoglycaemia was reported by subjects aged >75 years. Also in patients with type 2 diabetes mellitus, a similar trend as in patients with type 1 diabetes mellitus was observed for confirmed hypoglycaemia. There were no major differences in the incidence rate of severe hypoglycaemia between the treatment groups in subjects ≤65 years of age while the incidence rate of severe hypoglycaemia tended to be lower in the pooled IDeg group than in the pooled comparator group in subjects >65 years of age. Due to the small number of events in subjects >75 years of age, a comparison could not be performed.

Table 77. Occurrence of hypoglycaemia by age group at baseline
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)			Pooled comparator group (n = 467)		
	≤65 years (n = 1025)	>65 years (n = 77)	>75 years[a] (n = 9)	≤65 years (n = 438)	>65 years (n = 29)	>75 years[a] (n = 5)
Confirmed hypoglycaemia	95.2 (976)	94.8 (73)	77.8 (7)	94.7 (415)	93.1 (27)	100 (5)
	35,008 [5164.4]	2766 [5653.2]	237 [5164.9]	14,354 [5200.4]	1000 [5287.3]	165 [4133.5]
Nocturnal confirmed hypoglycaemia	68.9 (706)	55.8 (43)	44.4 (4)	68.3 (299)	72.4 (21)	40.0 (2)
	3442 [507.8]	251 [513.0]	33 [719.2]	1892 [685.5]	163 [861.8]	47 [1177.4]
Severe hypoglycaemia	11.7 (120)	10.4 (8)	0.0 (0)	10.5 (46)	6.9 (2)	0.0 (0)
	180 [26.6]	8 [16.4]	0 [0]	85 [30.8]	3 [15.9]	0 [0]
Severe nocturnal hypoglycaemia	3.9 (40)	0.0 (0)	0.0 (0)	2.7 (12)	4.2 (1)	3.4 (1)
	46 [6.8]	0 [0]	0 [0]	21 [7.6]	1 [6.7]	1 [5.3]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 2487)			Pooled comparator group (n = 1111)		
	≤65 years (n = 1863)	>65 years (n = 624)	>75 years[a] (n = 70)	≤65 years (n = 854)	>65 years (n = 257)	>75 years[a] (n = 33)
Confirmed hypoglycaemia	54.3 (1011)	60.4 (377)	60.0 (42)	50.4 (430)	60.7 (156)	60.6 (20)
	6912 [520.2]	2831 [616.7]	248 [468.5]	3081 [555.1]	1222 [700.3]	243 [1027.7]
Nocturnal confirmed hypoglycaemia	21.4 (399)	21.2 (132)	22.9 (16)	23.0 (196)	25.7 (66)	30.3 (10)
	1004 [75.6]	343 [74.7]	43 [81.2]	542 [97.6]	160 [91.7]	29 [122.7]
Severe hypoglycaemia	1.2 (22)	2.7 (17)	1.4 (1)	0.9 (8)	4.3 (11)	3.0 (1)
	28 [2.1]	19 [4.1]	2 [3.8]	8 [1.4]	12 [6.9]	1 [4.2]
Severe nocturnal hypoglycaemia	0.4 (8)	0.6 (4)	0.0 (0)	0.2 (2)	0.8 (2)	0.0 (0)
	12 [0.9]	5 [1.1]	0 [0]	2 [0.4]	2 [1.1]	0 [0]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]
a) A subgroup of the age group >65 years

In conclusion, according to the clinical trial data, there were no clinically relevant differences by age group. However, since hypoglycaemia is likely to occur in elderly patients due to the reduced physiological function, a draft package insert recommends that the product should be administered with care, such as by paying special attention to the dosage and performing tests periodically, and information will be collected via post-marketing surveillance.

PMDA considers as follows:

Although there is no particular problem with the applicant's response that there were no clinically relevant differences by age group, the number of elderly subjects included in clinical trials was limited and especially the number of patients ≥75 years of age studied was small. Therefore, it is necessary to continue to collect information on safety in elderly patients via post-marketing surveillance.

4.(iii).B.(7).2) Patients with renal impairment

The applicant explained as follows:

Regarding safety by renal function, the occurrence of adverse events by renal function in confirmatory trials in which Japanese subjects participated was as shown in Table 78. In Trials 3585/3725 and Trial 3586, there was no consistent relationship between the degree of renal impairment and the incidence rate of adverse events in either treatment group. The number of subjects with moderate impairment was small in both Trials 3585/3725 and Trial 3586 and there was no subject with severe impairment.

Table 78. Occurrence of adverse events by baseline renal function[a)]
(Confirmatory trials in which Japanese subjects participated, Safety Analysis Set)

Trials 3585/3725	IDeg (n = 301)			IDet (n = 152)		
	Normal (n = 239)	Mild impairment (n = 50)	Moderate impairment (n = 9)	Normal (n = 123)	Mild impairment (n = 22)	Moderate impairment (n = 3)
Overall adverse events	82.0 (196)	88.0 (44)	88.9 (8)	78.9 (97)	68.2 (15)	100.0 (3)
	1017 [473.4]	197 [420.4]	41 [449.3]	469 [436.8]	71 [347.0]	9 [412.5]
Serious adverse events	10.5 (25)	16.0 (8)	33.3 (3)	6.5 (8)	4.5 (1)	33.3 (1)
	36 [16.8]	13 [27.7]	5 [54.8]	15 [14.0]	3 [14.7]	3 [137.5]
Trial 3586	IDeg (n = 284)			IGlar (n = 146)		
	Normal (n = 154)	Mild impairment (n = 111)	Moderate impairment (n = 19)	Normal (n = 92)	Mild impairment (n = 45)	Moderate impairment (n = 9)
Overall adverse events	56.5 (87)	62.2 (69)	57.9 (11)	66.3 (61)	62.2 (28)	66.7 (6)
	205 [284.2]	154 [295.0]	32 [352.6]	144 [327.3]	51 [231.4]	9 [212.1]
Serious adverse events	2.6 (4)	3.6 (4)	0.0 (0)	6.5 (6)	4.4 (2)	0.0 (0)
	5 [6.9]	5 [9.6]	0 [0]	6 [13.6]	2 [9.1]	0 [0]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]
a) The degree of renal impairment was classified according to creatinine clearance (CL_{CR}) calculated using the Cockcroft-Gault formula as follows: normal (CL_{CR} >80 mL/min), mild (CL_{CR} ≥50 and ≤80 mL/min), moderate (CL_{CR} ≥30 and <50 mL/min), and severe (CL_{CR} <30 mL/min).

The occurrence of hypoglycaemia by renal function in confirmatory trials in which Japanese subjects participated was as shown in Table 79. In Trials 3585/3725, among subjects with mild impairment, there were no major differences in the incidence rate of confirmed hypoglycaemia between the treatment groups and the incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IDet group. In Trial 3586, among subjects with mild impairment, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were lower in the IDeg group than in the IGlar group. The number of subjects with severe hypoglycaemia was small in both mild and moderate impairment in Trials 3585/3725 and only 1 subject had severe hypoglycaemia in Trial 3586.

Table 79. Occurrence of hypoglycaemia by baseline renal function[a)]
(Confirmatory trials in which Japanese subjects participated, Safety Analysis Set)

Trials 3585/3725	IDeg (n = 301)			IDet (n = 152)		
	Normal (n = 239)	Mild impairment (n = 50)	Moderate impairment (n = 9)	Normal (n = 123)	Mild impairment (n = 22)	Moderate impairment (n = 3)
Confirmed hypoglycaemia	94.6 (226)	96.0 (48)	88.9 (8)	92.7 (114)	95.5 (21)	100.0 (3)
	7713 [3590.4]	2336 [4985.2]	250 [2739.6]	4058 [3779.2]	1052 [5141.8]	124 [5682.7]
Nocturnal confirmed hypoglycaemia	68.2 (163)	68.0 (34)	66.7 (6)	65.0 (80)	72.7 (16)	66.7 (2)
	688 [320.3]	215 [458.8]	19 [208.2]	516 [480.5]	122 [596.3]	8 [366.6]
Severe hypoglycaemia	14.2 (34)	14.0 (7)	11.1 (1)	12.2 (15)	4.5 (1)	0.0 (0)
	54 [25.1]	8 [17.1]	1 [11.0]	32 [29.8]	3 [14.7]	0 [0]
Severe nocturnal hypoglycaemia	6.3 (15)	0.0 (0)	11.1 (1)	4.9 (6)	0.0 (0)	0.0 (0)
	17 [7.9]	0 [0]	1 [11.0]	7 [6.5]	0 [0]	0 [0]
Trial 3586[b)]	IDeg (n = 284)			IGlar (n = 146)		
	Normal (n = 154)	Mild impairment (n = 111)	Moderate impairment (n = 19)	Normal (n = 92)	Mild impairment (n = 45)	Moderate impairment (n = 9)
Confirmed hypoglycaemia	47.4 (73)	55.9 (62)	36.8 (7)	45.7 (42)	66.7 (30)	66.7 (6)
	186 [257.9]	182 [348.6]	29 [319.5]	138 [313.7]	111 [503.6]	11 [259.2]
Nocturnal confirmed hypoglycaemia	18.8 (29)	22.5 (25)	21.1 (4)	21.7 (20)	31.1 (14)	11.1 (1)
	43 [59.6]	52 [99.6]	9 [99.2]	49 [111.4]	35 [158.8]	3 [70.7]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]

a) The degree of renal impairment was classified according to creatinine clearance (CL_{CR}) calculated using the Cockcroft-Gault formula as follows: normal (CL_{CR} >80 mL/min), mild (CL_{CR} ≥50 and ≤80 mL/min), moderate (CL_{CR} ≥30 and <50 mL/min), and severe (CL_{CR} <30 mL/min).
b) In Trial 3586, severe hypoglycaemia occurred in 1 subject in the IGlar group only.

According to the global pooled data from IDeg confirmatory trials,[72] the occurrence of adverse events by renal function was as shown in Table 80. In patients with type 1 diabetes mellitus, the incidence rate of adverse events tended to increase with an increase in the level of renal impairment in the pooled IDeg group, but not in the pooled comparator group. In type 2 diabetes mellitus patients with mild renal impairment, there were no major differences in the incidence rate of adverse events between the treatment groups, and in type 2 diabetes mellitus patients with moderate renal impairment, the incidence rate of adverse events was lower in the pooled IDeg group than in the pooled comparator group There was no consistent relationship between the degree of renal impairment and the incidence rate of adverse events in either treatment group. There was no subject with severe impairment.

Table 80. Occurrence of adverse events by baseline renal function[a)]
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)			Pooled comparator group (n = 467)		
	Normal (n = 966)	Mild impairment (n = 117)	Moderate impairment (n = 14)	Normal (n = 409)	Mild impairment (n = 50)	Moderate impairment (n = 4)
Overall adverse events	77.4 (748)	78.6 (92)	78.6 (11)	77.3 (316)	68.0 (34)	75.0 (3)
	2973 [462.3]	383 [521.2]	71 [970.5]	1259 [483.6]	106 [353.0]	14 [560.1]
Serious adverse events	7.2 (70)	12.0 (14)	21.4 (3)	7.3 (30)	2.0 (1)	25.0 (1)
	86 [13.4]	23 [31.3]	3 [41.0]	40 [15.4]	1 [3.3]	2 [80.0]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 3173)			Pooled comparator group (n = 1802)		
	Normal (n = 2664)	Mild impairment (n = 475)	Moderate impairment (n = 29)	Normal (n = 1570)	Mild impairment (n = 210)	Moderate impairment (n = 20)
Overall adverse events	68.7 (1830)	66.3 (315)	62.1 (18)	65.5 (1029)	60.5 (127)	85.0 (17)
	7614 [424.6]	1002 [343.6]	44 [305.5]	3709 [406.0]	462 [384.9]	45 [437.1]
Serious adverse events	8.0 (212)	7.8 (37)	0.0 (0)	6.2 (98)	6.7 (14)	5.0 (1)
	268 [14.9]	46 [15.8]	0 [0]	117 [12.8]	18 [15.0]	1 [9.7]

Upper row: incidence % (no. of subjects with events), Lower row: total number of events [no. of events/100 patient-years]
a) The degree of renal impairment was classified according to creatinine clearance (CL_{CR}) calculated using the Cockcroft-Gault formula as follows: normal (CL_{CR} >80 mL/min), mild (CL_{CR} ≥50 and ≤80 mL/min), moderate (CL_{CR} ≥30 and <50 mL/min), and severe (CL_{CR} <30 mL/min).

According to the global pooled data from IDeg confirmatory trials,[75] the occurrence of hypoglycaemia by renal function was as shown in Table 81. In patients with type 1 diabetes mellitus, the incidence rate of confirmed hypoglycaemia was higher in subjects with mild impairment compared with those with normal renal function in the pooled IDeg group. This difference was not observed in the pooled comparator group, and was considered due to the fact that the proportion of subjects with renal impairment varied from trial to trial. There were no major differences between the pooled IDeg group and the pooled comparator group in subjects with moderate renal impairment. There were no major differences in the incidence rate of nocturnal confirmed hypoglycaemia regardless of the degree of renal impairment in either treatment group. Although there were no major differences in the incidence rate of severe hypoglycaemia between the pooled IDeg group and the pooled comparator group in subjects with normal renal function, the incidence rate of severe hypoglycaemia was higher in the pooled IDeg group than in the pooled comparator group in subjects with mild or moderate impairment. This difference was considered attributable to the small number of severe hypoglycemic episodes and most of the episodes occurred immediately after bolus insulin injection or after a meal. In patients with type 2 diabetes mellitus, the incidence rate of confirmed hypoglycaemia was higher in subjects with

mild impairment compared with those with normal renal function in both treatment groups. There were no major differences in the incidence rate of nocturnal confirmed hypoglycaemia between the pooled IDeg group and the pooled comparator group in subjects with normal renal function or those with mild renal impairment. The number of severe hypoglycemic episodes was low and similar between the treatment groups in subjects with normal renal function and those with mild renal impairment.

Table 81. Occurrence of hypoglycaemia by baseline renal function[a)]
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)			Pooled comparator group (n = 467)		
	Normal (n = 966)	Mild impairment (n = 117)	Moderate impairment (n = 14)	Normal (n = 409)	Mild impairment (n = 50)	Moderate impairment (n = 4)
Confirmed hypoglycaemia	95.2 (920)	95.7 (112)	92.9 (13)	95.1 (389)	92.0 (46)	100.0 (4)
	32,848 [5107.6]	4633 [6305.3]	235 [3212.3]	13,673 [5251.7]	1570 [5228.8]	79 [3160.4]
Nocturnal confirmed hypoglycaemia	68.4 (661)	64.1 (75)	71.4 (10)	69.4 (284)	68.0 (34)	50.0 (2)
	3171 [493.1]	480 [653.3]	38 [519.4]	1790 [687.5]	257 [855.9]	8 [320.0]
Severe hypoglycaemia	11.3 (109)	13.7 (16)	14.3 (2)	10.5 (43)	6.0 (3)	0.0 (0)
	159 [24.7]	23 [31.3]	4 [54.7]	82 [31.5]	4 [13.3]	0 [0]
Severe nocturnal hypoglycaemia	3.8 (37)	0.9 (1)	14.3 (2)	2.9 (12)	2.0 (1)	0.0 (0)
	42 [6.5]	1 [1.4]	3 [41.0]	21 [8.1]	1 [3.3]	0 [0]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 2487)			Pooled comparator group (n = 1111)		
	Normal (n = 2070)	Mild impairment (n = 390)	Moderate impairment (n = 25)	Normal (n = 948)	Mild impairment (n = 148)	Moderate impairment (n = 13)
Confirmed hypoglycaemia	54.9 (1136)	61.0 (238)	52.0 (13)	51.4 (487)	60.1 (89)	76.9 (10)
	8009 [526.6]	1677 [664.1]	54 [419.8]	3659 [581.5]	615 [660.5]	29 [426.6]
Nocturnal confirmed hypoglycaemia	20.7 (428)	24.1 (94)	32.0 (8)	23.1 (219)	27.0 (40)	23.1 (3)
	1094 [71.9]	236 [93.5]	16 [124.4]	621 [98.7]	76 [81.6]	5 [73.6]
Severe hypoglycaemia	1.5 (31)	2.1 (8)	0.0 (0)	1.6 (15)	2.7 (4)	0.0 (0)
	38 [2.5]	9 [3.6]	0 [0]	16 [2.5]	4 [4.3]	0 [0]
Severe nocturnal hypoglycaemia	0.5 (10)	0.5 (2)	0.0 (0)	0.4 (4)	0.0 (0)	0.0 (0)
	14 [0.9]	3 [1.2]	0 [0]	4 [0.6]	0 [0]	0 [0]

Upper row: incidence % (no. of subjects with episodes), Lower row: total number of episodes [no. of episodes/100 patient-years]
a) The degree of renal impairment was classified according to creatinine clearance (CL_{CR}) calculated using the Cockcroft-Gault formula as follows: normal (CL_{CR} >80 mL/min), mild (CL_{CR} ≥50 and ≤80 mL/min), moderate (CL_{CR} ≥30 and <50 mL/min), and severe (CL_{CR} <30 mL/min).

In a foreign clinical pharmacology trial (Trial 1990), there were no differences in the pharmacokinetic profile of IDeg between subjects with renal impairment and those with normal renal function.

In conclusion, in patients with renal impairment, IDeg is not associated with an excessive risk of adverse events, serious adverse events, confirmed hypoglycaemia, or severe hypoglycaemia, as compared with the comparators. The package insert will recommend careful administration in patients with serious renal impairment.

PMDA considers as follows:
Although there is no particular problem with the applicant's response that there were no clinically relevant differences between IDeg and the comparators in patients with renal impairment, the number of patients with moderate or severe renal impairment investigated was limited and patients with severe

renal impairment have not been included in clinical trials. Therefore, it is necessary to continue to collect information on safety in patients with renal impairment via post-marketing surveillance.

4.(iii).B.(7).3) Patients with hepatic impairment

The applicant explained as follows:

Regarding the safety of IDeg in patients with hepatic impairment, when hepatic impairment[82] was defined by serum albumin and bilirubin scored by Child-Pugh classification, there were only 5 subjects with "hepatic impairment" (IDeg group) in Trials 3585/3725 and 1 subject with "hepatic impairment" in Trial 3586, thus sufficient information could not be obtained. According to the global pooled data from IDeg confirmatory trials,[72] based on serum albumin and bilirubin, 13 patients with type 1 diabetes mellitus had hepatic impairment (11 subjects in the pooled IDeg group, 2 subjects in the pooled comparator group) and 15 patients with type 2 diabetes mellitus had hepatic impairment (9 subjects in the pooled IDeg group, 6 subjects in the pooled comparator group). In the pooled IDeg group, 38 adverse events occurred in 13 of the 20 patients with hepatic impairment. Of the adverse events, 4 (erosive oesophagitis, oesophageal rupture, drowning, hypoglycaemia) were considered as serious adverse events. In the pooled comparator group, 43 adverse events occurred in 7 of the 8 patients with hepatic impairment. Of the adverse events, 1 (urosepsis) was considered as a serious adverse event. Among patients with hepatic impairment, there was no obvious trend in the subjects with adverse events or serious adverse events in the pooled IDeg group or pooled comparator group.

When subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limits of the normal range were defined as having hepatic impairment, there was no consistent relationship between the presence or absence of hepatic impairment and the incidence rate of adverse events or hypoglycaemia in the IDeg group in Trials 3585/3725 or Trial 3586 (Table 82). Also, according to the global pooled data from IDeg confirmatory trials,[72] there were no clinically relevant differences in the occurrence of adverse events or hypoglycaemia, regardless of with or without hepatic impairment, in the pooled IDeg group in patients with type 1 or type 2 diabetes mellitus (Table 83 and Table 84).

[82] Based on bilirubin score (bilirubin at baseline [μmol/L] <34: a score of 1, bilirubin at baseline ≥34 and ≤50: a score of 2, bilirubin at baseline >50: a score of 3) and albumin score (albumin at baseline [g/L] >35: a score of 1, albumin at baseline ≥28 and ≤35: a score of 2, albumin at baseline <28: a score of 3), a total score of >2 was defined as having hepatic impairment.

Table 82. Occurrence of adverse events and hypoglycaemia by baseline hepatic function[a)]
(Confirmatory trials in which Japanese subjects participated, Safety Analysis Set)

Trials 3585/3725	IDeg (n = 301)		IDet (n = 152)	
	Normal (n = 284)	Hepatic impairment (n = 17)	Normal (n = 145)	Hepatic impairment (n = 7)
Overall adverse events	82.7 (235)	76.5 (13)	77.2 (112)	85.7 (6)
	1190 [463.5]	65 [391.3]	527 [411.9]	37 [590.4]
Serious adverse events	12.0 (34)	11.8 (2)	7.6 (11)	0.0 (0)
	49 [19.1]	5 [30.1]	23 [18.0]	0 [0]
Confirmed hypoglycaemia	95.4 (271)	82.4 (14)	92.4 (134)	100.0 (7)
	9804 [3818.8]	522 [3142.1]	5147 [4023.2]	122 [1946.7]
Nocturnal confirmed hypoglycaemia	68.3 (194)	64.7 (11)	64.8 (94)	57.1 (4)
	872 [339.7]	52 [313.0]	625 [488.5]	21 [335.1]
Severe hypoglycaemia	14.1 (40)	11.8 (2)	12.4 (18)	0.0 (0)
	60 [23.4]	3 [18.1]	37 [28.9]	0 [0]
Trial 3586	IDeg (n = 284)		IGlar (n = 146)	
	Normal (n = 233)	Hepatic impairment (n = 51)	Normal (n = 121)	Hepatic impairment (n = 25)
Overall adverse events	59.2 (138)	56.9 (29)	63.6 (77)	72.0 (18)
	316 [290.6]	75 [303.9]	158 [271.1]	46 [383.3]
Serious adverse events	3.4 (8)	0.0 (0)	5.0 (6)	8.0 (2)
	10 [9.2]	0 [0]	6 [10.3]	2 [16.7]
Confirmed hypoglycaemia	51.1 (119)	45.1 (23)	55.4 (67)	44.0 (11)
	340 [312.7]	57 [230.9]	235 [403.2]	25 [208.3]
Nocturnal confirmed hypoglycaemia	20.2 (47)	21.6 (11)	24.0 (29)	24.0 (6)
	89 [81.9]	15 [60.8]	77 [132.1]	10 [83.3]

Upper row: incidence % (no. of subjects with events)
Lower row: total number of events [no. of events/100 patient-years]
a) Subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as "having hepatic impairment."

Table 83. Occurrence of adverse events by baseline hepatic function[a)]
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)		Pooled comparator group (n = 467)	
	Normal (n = 1034)	Hepatic impairment (n = 68)	Normal (n = 440)	Hepatic impairment (n = 27)
Overall adverse events	77.7 (803)	72.1 (49)	76.1 (335)	77.8 (21)
	3270 [478.7]	160 [366.4]	1287 [465.7]	99 [532.6]
Serious adverse events	8.2 (85)	4.4 (3)	7.3 (32)	3.7 (1)
	109 [16.0]	4 [9.2]	43 [15.6]	1 [5.4]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 3173)		Pooled comparator group (n = 1802)	
	Normal (n = 2627)	Hepatic impairment (n = 546)	Normal (n = 1469)	Hepatic impairment (n = 333)
Overall adverse events	67.6 (1777)	71.2 (389)	63.7 (936)	71.5 (238)
	6899 [396.0]	1777 [494.5]	3214 [379.7]	1003 [507.2]
Serious adverse events	7.8 (206)	7.9 (43)	6.5 (95)	5.7 (19)
	265 [15.2]	49 [13.6]	112 [13.2]	25 [12.6]

Upper row: incidence % (no. of subjects with events)
Lower row: total number of events [no. of events/100 patient-years]
a) Subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as "having hepatic impairment."

Table 84. Occurrence of hypoglycaemia by baseline hepatic function[a)]
(Global pooled data from IDeg confirmatory trials, Safety Analysis Set)

Patients with type 1 diabetes mellitus	Pooled IDeg group (n = 1102)		Pooled comparator group (n = 467)	
	Normal (n = 1034)	Hepatic impairment (n = 68)	Normal (n = 440)	Hepatic impairment (n = 27)
Confirmed hypoglycaemia	95.6 (989)	88.2 (60)	94.5 (416)	96.3 (26)
	35,784 [5238.2]	1990 [4557.6]	14,723 [5327.8]	631 [3394.8]
Nocturnal confirmed hypoglycaemia	68.4 (707)	61.8 (42)	68.2 (300)	74.1 (20)
	3505 [513.1]	188 [430.6]	1959 [708.9]	96 [516.5]
Severe hypoglycaemia	11.8 (122)	8.8 (6)	10.5 (46)	7.4 (2)
	182 [26.6]	6 [13.7]	85 [30.8]	3 [16.1]
Patients with type 2 diabetes mellitus	Pooled IDeg group (n = 2487)		Pooled comparator group (n = 1111)	
	Normal (n = 2062)	Hepatic impairment (n = 425)	Normal (n = 906)	Hepatic impairment (n = 205)
Confirmed hypoglycaemia	57.4 (1183)	48.2 (205)	54.6 (495)	44.4 (91)
	8660 [582.9]	1083 [358.5]	3682 [622.4]	621 [450.1]
Nocturnal confirmed hypoglycaemia	22.1 (455)	17.9 (76)	24.6 (223)	19.0 (39)
	1195 [80.4]	152 [50.3]	591 [99.9]	111 [80.5]
Severe hypoglycaemia	1.6 (32)	1.6 (7)	1.9 (17)	1.0 (2)
	40 [2.7]	7 [2.3]	18 [3.0]	2 [1.4]

Upper row: incidence % (no. of subjects with episodes)
Lower row: total number of episodes [no. of episodes/100 patient-years]
a) Subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as "having hepatic impairment."

In a foreign clinical pharmacology trial (Trial 1989), there were no differences in the pharmacokinetic profile of IDeg between subjects with hepatic impairment and those with normal hepatic function.

Based on the above, there were no safety concerns for patients with hepatic impairment. However, as patient enrollment was restricted depending on the degree of hepatic impairment in confirmatory trials, further information will be collected via post-marketing surveillance. The package insert will recommend careful administration in patients with serious hepatic impairment.

PMDA considers as follows:
At present, there is no particular problem with the applicant's response that there were no safety concerns for patients with hepatic impairment. However, as the number of patients with hepatic impairment studied was limited, it is necessary to continue to collect information on safety in patients with hepatic impairment via post-marketing surveillance.

4.(iii).B.(8) Post-marketing surveillance

The applicant plans to conduct a special drug use-results survey on long-term use (a 1-year observation period, a 3-year survey period, a planned sample size of 3000) in order to collect information on the safety and efficacy of IDeg in routine clinical settings. Based on the results of a post-marketing surveillance study of a currently approved long-acting insulin analog, insulin detemir, it is estimated that 15% (450 patients) and 85% (2550 patients) of the patients registered will be patients with type 1 and type 2 diabetes mellitus, respectively, which provides a 95% probability of detecting at least one case of adverse drug reactions with an incidence of 0.67% and 0.12% in patients with type 1 and type 2 diabetes mellitus, respectively. The safety and efficacy of IDeg in elderly patients, patients with renal impairment, and patients with hepatic impairment will be evaluated by

identifying the relevant patients from the survey data. According to the results of post-marketing surveillance studies of currently approved long-acting insulin analogs, insulin glargine and insulin detemir, conducted in Japan, among the above-mentioned special patient groups, patients with hepatic impairment represented the smallest proportion at about 10%. Therefore, with a target number of patients of 3000 for a post-marketing surveillance study of IDeg, ≥100 patients for each special patient group, which is considered necessary for IDeg evaluation by special patient group, can be collected.

PMDA considers as follows:
It is necessary to collect safety information on the occurrence of hypoglycaemia, injection site reactions, anaphylactic reactions, etc. as well as information on the safety of IDeg in elderly patients, patients with renal impairment, and patients with hepatic impairment via post-marketing surveillance, since only a limited number of patients of such cases were included in clinical trials. The details of the post-marketing surveillance study will be finalized, taking account of comments from the Expert Discussion.

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

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

A document compliance review was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted application documents.

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

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the documents data submitted in the new drug application (5.3.5.1.1, 5.3.5.1.2, 5.3.5.1.3, 5.3.5.1.4). As a result, the following findings were found at some trial sites: noncompliance with the procedures for the investigational product accountability (the investigational product was dispensed and administered to persons not enrolled into the clinical trial), protocol deviations (unnecessary blood sampling), and inconsistencies between the source document and the CRF (hypoglycemic episodes were undocumented). Also, the sponsor was found to have failed to appropriately detect some of the above inconsistencies between the source document and the CRF during monitoring visits. Although the above findings requiring improvement were noted, PMDA concluded that the clinical trials as a whole were performed in compliance with GCP and there should be no problem with conducting a regulatory review based on the submitted application douments.

IV. Overall Evaluation

Based on the submitted data, the efficacy of IDeg in patients with diabetes mellitus who require insulin has been demonstrated. Though its safety is acceptable, it is necessary to continue to collect safety information on the occurrence of hypoglycaemia, injection site reactions, and anaphylactic reactions and antibody formation, etc. and information on the safety and efficacy of IDeg in patients with renal impairment, patients with hepatic impairment, and elderly patients via post-marketing surveillance.

If it can be concluded, based on the comments from the Expert Discussion, that there is no particular problem with the review result, the following indication of IDeg may be approved: diabetes mellitus where treatment with insulin is required.

Review Report (2)

August 16, 2012

I. Product Submitted for Registration

[Brand name]	(a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)
[Name of applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	December 22, 2011

II. Content of the Review

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

(1) Interpretation of multinational trial results

(1).1) Trial 3585 in patients with type 1 diabetes mellitus

The following conclusion by PMDA was supported by the expert advisors:

(a) As to ethnic factors, the pharmacokinetic and pharmacodynamic profiles of insulin degludec are similar between Japanese and foreign patients and that the intrinsic and extrinsic ethnic differences have no relevant influence on efficacy and safety evaluation. (b) As to efficacy, the non-inferiority of IDeg to IDet was demonstrated in terms of the primary endpoint of HbA1c change in the entire trial population. There were no major differences between the Japanese subgroup and entire trial population for the difference in HbA1c change between the IDeg and IDet groups and therefore, there were also no major differences between the Japanese and non-Japanese subgroups. Based on the above, there was no clear discrepancy in efficacy between the Japanese subgroup and entire trial population and it may be interpreted that the efficacy results were consistent between the Japanese subgroup and entire trial population. (c) As to safety, although the occurrence of some adverse events (diabetic retinopathy, severe hypoglycaemia, etc.) was different between the Japanese subgroup and entire trial population, there were no clear differences in the trend of occurrence of adverse events between the IDeg and IDet groups in the entire trial population and there were no clinically relevant differences in safety between the Japanese subgroup and entire trial population. Thus, it may be interpreted that there were no safety concerns for Japanese patients. (d) The long-term efficacy and safety of IDeg have been demonstrated by 52-week data from Trial 3585 with the extension (Trial 3725).

Based on the above (a) to (d), there is no major problem with the generalization of the results from the entire population in Trials 3585/3725 to Japanese patients with type 1 diabetes mellitus.

(1).2) Trial 3586 in patients with type 2 diabetes mellitus

The following conclusion by PMDA was supported by the expert advisors:

(a) As to ethnic factors, based on the results of the PPK analysis of data from Trial 3586, the pharmacokinetic profile of insulin degludec is similar among the Asian ethnic groups. In additon, although there were differences in previous oral anti-diabetic therapy as an extrinsic ethnic factor between the Japanese subgroup and entire trial population, these differences have no relevant influence on efficacy and safety evaluation. (b) As to efficacy, the non-inferiority of IDeg to IGlar was demonstrated in terms of HbA1c change in the entire trial population as the primary endpoint. Also, there were no major differences between the Japanese subgroup and entire trial population for the difference in HbA1c change between the IDeg and IGlar groups and furthermore, there were also no major differences between the Japanese and non-Japanese subgroups. Based on the above, there was no clear discrepancy in efficacy between the Japanese subgroup and entire trial population and it may be interpreted that the efficacy results were consistent. (c) As to safety, although the numbers of some adverse events (e.g., diabetic retinopathy) were higher in the Japanese subgroup than in the entire trial population and differences in occurrence were observed, there were no clear differences in the trend of occurrence of adverse events between the IDeg and IGlar groups in the entire trial population and there were no clinically relevant differences in safety between the Japanese subgroup and entire trial population. Thus, it may be interpreted that there were no safety concerns for Japanese patients. (d) Concerning the long-term efficacy and safety of IDeg, as with the use of IDeg in patients with type 1 diabetes mellitus, the dose of IDeg in patients with type 2 diabetes mellitus is intended to be adjusted according to the patient's condition, and there should be no major differences in insulin therapy for patients with type 2 diabetes mellitus between Japan and overseas. Therefore, it is necessary to collect information on the long-term safety and efficacy of IDeg in Japanese patients with type 2 diabetes mellitus via post-marketing surveillance, but there is no need to conduct an additional long-term treatment trial in Japanese patients with type 2 diabetes mellitus.

Based on the above (a) to (d), there is no major problem with the generalization of the results from the entire population in Trial 3586 to Japanese patients with type 2 diabetes mellitus. Unlike overseas, no data from Japanese subjects treated with IDeg plus >750 mg/day of metformin were obtained. Thus, it is necessary to collect information via post-marketing surveillance.

(2) Efficacy

The following conclusion by PMDA was supported by the expert advisors:

The efficacy of IDeg in patients with type 1 or type 2 diabetes mellitus has been demonstrated by the results of Trials 3585 and 3725 (type 1) and Trial 3586 (type 2). With respect to the influence of

antibody formation on efficacy, clinical trials showed no trend towards marked rises in antibody titers following treatment with IDeg and therefore, there was no clear relationship between the level of antibody formation and efficacy. However, as the information on antibody formation following long-term treatment with IDeg is limited, it is necessary to continue to collect information on the relationship between antibody formation and efficacy via post-marketing surveillance.

(3) Safety

The following conclusion by PMDA was supported by the expert advisors:

Based on the results of Trials 3585 and 3725 (type 1) and Trial 3586 (type 2) and the results of a review of individual events (e.g., hypoglycaemia and injection site reactions), the safety of IDeg in patients with type 1 or type 2 diabetes mellitus is acceptable.

(4) Indication

The following conclusion by PMDA was supported by the expert advisors:

Based on the results of Trials 3585/3725 and Trial 3586, there is no particular problem with the proposed indication of "diabetes mellitus where treatment with insulin is required," which is also indicated in currently approved insulin preparations. Although the safety and efficacy of IDeg in basal-bolus therapy in Japanese patients with type 2 diabetes mellitus have not been investigated in a clinical trial, the information may be collected via post-marketing surveillance.

(5) Dosage and administration

(5).1) Dose of IDeg when switching from other basal insulin products

The following conclusion by PMDA was supported by the expert advisors:

Concerning glycemic control and the occurrence of hypoglycaemia by prior basal insulin injection frequency during the early phase of treatment in Trial 3585, fluctuations in glycemic control occurred and the incidence and number of hypoglycemic episodes increased during the early phase of treatment among the subjects previously treated with twice-daily basal insulin compared with those previously treated with once-daily basal insulin. Since the number of severe hypoglycemic episodes was small in both treatment groups, there should be no major safety concern in patients switched to IDeg on a unit-to-unit basis. However, as the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia during the early phase of treatment tended to be higher in patients switched from twice-daily basal insulin to once-daily IDeg, it is necessary to collect information on the safety of IDeg when switching from other basal insulin products via post-marketing surveillance.

(5).2) Timing of injection

The following conclusion by PMDA was supported by the expert advisors:

PMDA understands the applicant's view that providing information on how to manage missed scheduled doses, in light of the characteristics of IDeg, is of significance, but the incidence rate of

confirmed hypoglycaemia tended to increase with a narrow dosing interval in both type 1 and type 2 diabetic patients. Therefore, IDeg should be injected at a consistent time each day as much as possible and the finding that IDeg can be dosed flexibly at any time of the day should not be informed in an exaggerated manner. Trials 3770 and 3668 only investigated IDeg dosing at alternating narrow and wide dosing intervals and it is necessary to provide the following information: a morning dose followed by an evening dose 8 to 12 hours later or multiple injections at a narrow dosing interval has not been studied.

Based on the above, PMDA instructed the applicant to modify the dosage and administration statement and the important precautions statement as shown below and collect information on the safety and efficacy of IDeg when the patient's timing of administration is changed via post-marketing surveillance.

The applicant responded that the dosage and administration statement etc. will be modified as shown below and information on the safety and efficacy of IDeg when the patient's timing of administration is changed will be collected via post-marketing surveillance.

PMDA accepted the response.

(After modification)
[Dosage and administration] (for Tresiba FlexTouch)
The usual initial adult dosage is 4 to 20 units of IDeg administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. IDeg may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, higher doses than the above may be used as needed.

[Important precautions] (The following statement will be added)
Given the characteristics (e.g. duration of action) of IDeg, patients who missed a dose, are advised to take it as soon as they remember, ensuring a minimum of 8 hours between doses, and then resume the usual dosing schedule.

(6) Post-marketing surveillance
The following conclusion by PMDA was supported by the expert advisors:
With respect to the plan of a special drug use-results survey on long-term use intended to collect information on the safety and efficacy of IDeg in routine clinical settings (a 1-year observation period, a 3-year survey period, a planned sample size of 3000), it is necessary to collect the following information: safety information on the occurrence of hypoglycaemia, injection site reactions,

anaphylactic reactions, etc.; the safety of IDeg in elderly patients, patients with renal impairment, and patients with hepatic impairment (due to the limited numbers of these patients included in clinical trials); the safety and efficacy of IDeg in combination with >750 mg/day of metformin; the relationship of antibody formation to efficacy and safety; the safety and efficacy of IDeg in basal-bolus therapy in Japanese patients with type 2 diabetes mellitus; and the safety of IDeg when switching from other basal insulin products.

The expert advisors commented as follows:
IDeg is a drug intended for the long-term treatment and a 3-year observation period is required to assess cardiovascular risk profile as well.

Based on the above, PMDA instructed the applicant to present a more detailed plan (draft) of the post-marketing surveillance study.

The applicant responded as follows:
A special drug use-results survey on long-term use (a 3-year observation period, a 5-year survey period, a planned sample size of 3000) will be conducted and information on the occurrence of hypoglycaemia, injection site reactions, allergic reactions and cardiovascular risk, etc. will be collected for adverse event reporting. Information on concomitant medications (especially, the data from patients treated with IDeg plus >750 mg/day of metformin) will be collected and the relationship between IDeg in combination with other anti-diabetic drugs and safety (especially, hypoglycaemia) will also be investigated. As to cardiovascular risk, patients with cardiovascular events will be followed-up wherever possible and information on body weight, blood pressure, HbA1c, blood lipids, etc. will be obtained. If judged necessary by healthcare providers, IDeg-specific IgE antibody titers will be measured to investigate its influence on safety and efficacy. Furthermore, information will be collected on the safety and efficacy of IDeg in basal-bolus therapy in Japanese patients with type 2 diabetes mellitus and on the safety and efficacy of IDeg when switching from other basal insulin products or when the patient's timing of administration is changed. The safety and efficacy of IDeg in elderly patients, patients with renal impairment, and patients with hepatic impairment will be evaluated by identifying the relevant patients.

PMDA accepted the response.

III. Overall Evaluation

As a result of the above review, PMDA concludes that IDeg may be approved for the following indication and dosage and administration. The re-examination period is 8 years, the drug substance and the drug product are both classified as powerful drugs, and the product is not classified as a biological product or a specified biological product.

[Indication]
Diabetes mellitus where treatment with insulin is required

[Dosage and administration]
(a) The usual initial adult dosage is 4 to 20 units of IDeg administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. IDeg may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.
(b) The usual initial adult dosage is 4 to 20 units of IDeg administered subcutaneously once daily, using a specific insulin pen device. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. IDeg may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.