Report on the Deliberation Results

December 3, 2012
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	(a) Ryzodeg FlexTouch
	(b) Ryzodeg Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)/Insulin Aspart (Genetical Recombination) (JAN*)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	March 9, 2012

[Results of deliberation]
In the meeting held on November 30, 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 and its re-examination period should be until September 27, 2020 so that it is in line with the re-examination period for an approved product containing Insulin Degludec (Genetical Recombination), one of the active ingredients of the product. The drug substance and the drug product are both classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

Review Report

November 13, 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) Ryzodeg FlexTouch (b) Ryzodeg Penfill (The proposed Japanese brand names have been modified.)
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)/Insulin Aspart (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	March 9, 2012
[Dosage form/Strength]	(a) Solution for injection: One pre-filled pen (3 mL) contains 210 units of Insulin Degludec (Genetical Recombination) and 90 units of Insulin Aspart (Genetical Recombination). (b) Solution for injection: One cartridge (3 mL) contains 210 units of Insulin Degludec (Genetical Recombination) and 90 units of Insulin Aspart (Genetical Recombination).
[Application classification]	Prescription drug (2) New prescription combination product
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

Review Results

November 13, 2012

[Brand name] (a) Ryzodeg FlexTouch, (b) Ryzodeg Penfill
(The proposed Japanese brand names have been modified.)
[Non-proprietary name] Insulin Degludec (Genetical Recombination)/Insulin Aspart (Genetical Recombination)
[Applicant] Novo Nordisk Pharma Ltd.
[Date of application] March 9, 2012
[Items warranting special mention] None

[Results of review]
Based on the submitted data, the significance of the product (a co-formulation of insulin degludec and insulin aspart) has been shown, its efficacy in patients with diabetes mellitus who require insulin has been demonstrated, and its safety is acceptable in view of its observed benefits. It is necessary to further investigate the safety of the product, e.g. the occurrence of hypoglycaemia, injection site reactions, and allergic reactions and antibody development, as well as its safety and efficacy in elderly patients, patients with renal impairment, and patients with hepatic impairment 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) Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the rapid-acting insulin aspart and the long-acting insulin degludec (molar ratio 3:7).
The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily. In a once-daily regimen, it should be given immediately before the main meal, at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

(b) Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the rapid-acting insulin aspart and the long-acting insulin degludec (molar ratio 3:7).
The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily, using a specific insulin pen device. In a once-daily regimen, it should be given immediately before the main meal, at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

Review Report (1)

October 10, 2012

I. Product Submitted for Registration

[Brand name] (a) Ryzodeg FlexTouch
(b) Ryzodeg Penfill

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

[Name of applicant] Novo Nordisk Pharma Ltd.

[Date of application] March 9, 2012

[Dosage form/Strength] (a) Solution for injection: One pre-filled pen (3 mL) contains 210 units of Insulin Degludec (Genetical Recombination) and 90 units of Insulin Aspart (Genetical Recombination).
(b) Solution for injection: One cartridge (3 mL) contains 210 units of Insulin Degludec (Genetical Recombination) and 90 units of Insulin Aspart (Genetical Recombination).

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

[Proposed dosage and administration]

(a) Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the ultra-long-acting insulin degludec and the rapid-acting insulin aspart (molar ratio 7:3).

The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily. In a once-daily regimen, it should be given immediately before the main meal (the largest meal of the day), usually at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

(b) Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the ultra-long-acting insulin degludec and the rapid-acting insulin aspart (molar ratio 7:3).

The usual initial adult dosage is at 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily, using a specific insulin pen device. In a once-daily regimen, it should be given immediately before the main meal (the largest meal of the day), usually at the same time every day. In a twice-daily regimen, it should be given immediately before

breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual 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 an 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 7:3 molar ratio of Insulin Degludec (Genetical Recombination) (hereinafter, "insulin degludec"), a long-acting insulin analogue, and Insulin Aspart (Genetical Recombination) (hereinafter, "insulin aspart"), a rapid-acting insulin analogue (hereinafter the propose product is referred to as "IDegAsp").

One of the active ingredients, insulin degludec, was approved in September 2012 in Japan and is under regulatory review in [redacted] countries including the US and European countries as of October 2012. Once injected into the subcutaneous tissue, the insulin degludec di-hexamers form soluble and stable multi-hexamers, leading to a depot from which insulin degludec monomers are slowly and continuously absorbed into the blood circulation. This mechanism underlies the long duration of action of insulin degludec. Furthermore, binding to albumin both in the subcutaneous space and in the circulation via the fatty acid side-chain contributes to a lesser degree to the protraction mechanism.

Another active ingredient, insulin aspart, was approved in October 2001 and has been used in clinical practice for ≥10 years in Japan. Inhibiting dimer formation allows for the rapid-action of insulin aspart. Once injected into the subcutaneous tissue, the IAsp hexamers immediately form monomers, which are rapidly absorbed into the capillaries.

In insulin therapy for patients with diabetes mellitus, insulin products are selected according to the patient's state of diabetes, glycaemic control, and life style. In patients who have difficulty with frequent administration or those for whom intensified insulin therapy is not required, premixed insulin or long-acting insulin, etc. is used. In Japan, as a premixed insulin analogue containing the rapid-acting component at the same ratio as IDegAsp, biphasic NovoRapid 30 Mix containing intermediate-acting protamine-crystallized and rapid-acting soluble insulin aspart at a ratio of 7:3 was approved in August 2003. In addition, biphasic Humalog Mix 25 containing intermediate-acting protamine-crystallized and rapid-acting soluble insulin lispro (genetical recombination) at a ratio of 75:25 was approved in March 2003. Both products have been used in clinical practice since market launch. As long-acting insulin

analogues, insulin glargine (genetical recombination) and insulin detemir (genetical recombination) were approved in Japan and as rapid-acting insulin analogues, insulin lispro (genetical recombination) and insulin glulisine (genetical recombination) were approved in Japan. These products have been used in clinical practice since market launch.

Based on the claim that the efficacy and safety of IDegAsp have been confirmed, the applicant has filed a new drug application for IDegAsp. As of October 2012, IDegAsp is being reviewed by regulatory agencies in [redacted] countries including the US and European countries.

2. Data relating to quality

2.A *Summary of the submitted data*

2.A.(1) Drug substance

The drug substances, i.e., insulin degludec and insulin aspart, are identical to the ones used in the approved products (manufactured by Novo Nordisk), Tresiba FlexTouch/Penfill (hereinafter referred to as "Tresiba") and NovoRapid 30 Mix FlexPen/Penfill, NovoRapid 50 Mix FlexPen/Penfill, NovoRapid 70 Mix FlexPen/Penfill, and NovoRapid FlexPen/InnoLet/Penfill/100 U/mL (hereinafter collectively referred to as "NovoRapid"), respectively.

2.A.(2) Drug product

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

The drug product is a clear, colourless solution intended for subcutaneous injection, containing insulin degludec in a concentration of 420 nmol/ml and insulin aspart in a concentration of 180 nmol/ml. It contains isotonic agent (concentrated glycerol), stabilising agents (zinc acetate, sodium chloride), preservatives (phenol and metacresol), and solvent (water for injections). 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 disc made of [redacted] rubber and synthetic [redacted] rubber and the opposite end is closed by a plunger made of [redacted] rubber. 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).

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

The drug product manufacturing process consists of formulation, sterile filtration, filling, inspection, testing, storage, assembly, labelling, packaging, inspection, and storage. Formulation, sterile filtration, and filing 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 release 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, insulin aspart content,), description, pH, identity (insulin degludec, insulin aspart, metacresol, and phenol [RP-HPLC]), purity (impurities,[1] related substances,[1] impurities,[1] insulin aspart, insulin aspart, and insulin aspart impurities [RP-HPLC], high molecular weight proteins [gel permeation chromatography]), metacresol and phenol (RP-HPLC), bacterial endotoxins, sterility, foreign insoluble matter, insoluble particulate matter, dose accuracy[2] (weighing), and assay (insulin degludec and insulin aspart [RP-HPLC], [ ]).

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

Primary stability studies on the drug product are as shown in Table 1.

Table 1. Overview of primary stability studies on drug product

Stability study	Number of batches	Storage condition	Storage forms	Test periods
Long term	3	5 ± 3°C	Primary packaging (3 ml Penfill cartridge) and carton	36 months
	3			months[a)]
Accelerated	3	25 ± 2°C		6 months
	3			6 months
Photostability	1	25 ± 2°C, an overall illumination of approximately lux hours and an integrated near ultraviolet energy of Wh/m^2	Primary packaging (3 ml Penfill cartridge) and secondary packaging (PDS290 pre-filled pen, blister pack, and carton)	-
	1			-

a) The stability study is ongoing.

At the long term conditions (5 ± 3°C/ambient humidity/dark place, 36 months and months), a trend in high molecular weight proteins, impurities, impurities, related substances, insulin aspart, insulin aspart, and insulin aspart impurities was seen, but there were no changes for other attributes tested.

At the accelerated conditions (25 ± 2°C/ambient humidity, 6 months), in high molecular weight proteins, impurities, related substances, and impurities, and

[1] Impurities or related substances of insulin degludec
[2] Only for Ryzodeg FlexTouch

[redacted] in [redacted] insulin aspart, [redacted] insulin aspart, and insulin aspart [redacted] impurities were seen, but there were no changes for other attributes tested.

In the photostability study (25 ± 2°C, an overall illumination of approximately [redacted] lux hours and an integrated near ultraviolet energy of [redacted] Wh/m^2), the product in primary packaging was not sufficiently stable when exposed to light, compared with when protected from light.

Based on the above results, a shelf life of 30 months has been proposed for the drug product when stored in sealed containers at 2-8°C, without freezing and protected from light. The long term stability study on the proposed drug product will be continued for up to [redacted] months.

2.A.(3) Reference materials

The reference materials for insulin degludec and insulin aspart are the same as those for the approved products, Tresiba and NovoRapid (manufactured by Novo Nordisk), respectively.

2.B *Outline of the review by PMDA*

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

Formation of assemblies of each active ingredient of IDegAsp

PMDA asked the applicant to explain whether insulin degludec is present as di-hexamers and insulin aspart is present as hexamers also in the formulation of IDegAsp and how the formation of the assemblies is assured.

The applicant responded as follows:

In the case of insulin degludec, the presence of zinc and phenol promotes the self-association into non-covalent di-hexamers, while insulin aspart has the ability to bind zinc ions and self-associate into non-covalent hexamers. In the presence of zinc and phenol, the approved products (Tresiba and NovoRapid) have been shown to have the ability to form non-covalent di-hexamers and hexamers, respectively. It has been confirmed by [redacted] chromatography that the formulation of IDegAsp also consists of approximately 70% of non-covalent insulin degludec di-hexamers and approximately 30% of insulin aspart hexamers. The optimal concentrations of [redacted] for the insulin degludec solution and insulin aspart solution in the formulation of IDegAsp are the same as those for the approved products, and the concentrations of [redacted] and [redacted] in the formulation of IDegAsp are controlled by the specifications. The stability batches stored up to [redacted] months at 5°C were tested for the concentrations of [redacted] and [redacted] and the [redacted] patterns of insulin degludec and insulin aspart. As a result, no changes were observed. Furthermore, the batches manufactured in [redacted] concentrations and stored at [redacted] condition at [redacted]°C for [redacted] month showed insulin degludec [redacted] and insulin aspart [redacted] in a ratio of

approximately 70% and approximately 30%, and the di-hexamers and the hexamers were stable. Based on the above, the [redacted] of insulin degludec [redacted] and insulin aspart [redacted] can be assured adequately by control of the concentrations of [redacted] and [redacted] and there is no need to include a test for identification of these in the drug product specifications.

PMDA accepted the response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

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

As primary pharmacodynamic studies with insulin degludec (IDeg) and insulin aspart (IAsp), an *in vitro* study for additive effect of IDeg and IAsp and *in vivo* studies for the efficacy of co-formulation (IDegAsp) with constant mix-ratios of IDeg to IAsp were conducted. In addition, the results from studies with IDeg, which had been evaluated for the new drug application for Tresiba, were submitted.

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

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

Additive effect of IDeg and IAsp (4.2.1.1.18)

Cell suspension of primary rat adipocytes prepared from epididymal fat pad was incubated in the buffer containing ^{3}H-labelled glucose and IDeg (8 concentrations) and IAsp (8 concentrations), set-up in a complete factorial design comprising all 64 combinations, in the presence of 0.5% or 1.0% human serum albumin (HSA) for 2 hours. Lipids were extracted after incubation and the incorporation of ^{3}H-labelled glucose was determined. As a result,[3] relative potency [95% confidence interval (CI)] of IDeg vs. IAsp was 1.38% [1.22, 1.56] in the presence of 0.5% HSA and 0.79% [0.70, 0.88] in the presence of 1.0% HSA. The interaction parameter σ [95% CI] was 0.06 [-0.01, 0.22] in the presence of 0.5% HSA and -0.03 [-0.15, 0.09] in the presence of 1.0% HSA, indicating that the effects of IDeg and IAsp are additive.

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

(a) Euglycaemic clamp studies using IDegAsp formulations with different mix-ratios in pigs (4.2.1.1.19)

Female pigs (n = 6), fasted overnight, received a single subcutaneous injection of IDegAsp[4] (120 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, or separate single subcutaneous injections of IDeg (84 nmol/pig) containing [redacted]/IDeg hexamer and IAsp (36 nmol/pig) containing [redacted]/IAsp hexamer.

[3] A mathematical model based on four-parameter logistic method developed by the applicant.
[redacted]

[4] Formulation containing [redacted] nmol/mL IDeg and [redacted] nmol/mL IAsp

Female pigs (n = 6), fasted overnight, received a single subcutaneous injection of IDegAsp[5] (360 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, or IAsp (54 nmol/pig) containing [redacted]/IAsp hexamer.

Female pigs (n = 8), fasted overnight, received a single subcutaneous injection of IDegAsp[7] (288 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, at different pH.[6]

Female pigs (n = 8), fasted overnight, received a single subcutaneous injection of IDegAsp[9] (389 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, at different pH.[8]

Female pigs (n = 4), fasted overnight, received a single subcutaneous injection of protamine-crystallized insulin aspart ([redacted] nmol/mL, a dose of 216 nmol/pig) with a mix-ratio equal to 7:3 of fraction of IAsp crystallized with protamine vs. fraction of soluble rapid-acting IAsp, or IDegAsp[4] (216 nmol/pig) with a mix-ratio equal to [redacted] ([redacted]), containing [redacted]/IDeg hexamer.

On the day of experiment, 20% glucose solution was intravenously infused at a variable rate to maintain euglycaemia for 24 hours, plasma glucose was measured at regular intervals (from 60 minutes pre-dose to 24 hours post-dose), and glucose infusion rate (GIR) was calculated. Moreover, plasma concentrations of IDeg and IAsp were measured by enzyme-linked immunosorbent assay (ELISA). As a result, at a mix-ratio of IDeg/IAsp equal to [redacted], the pharmacokinetic profiles of IAsp and IDeg were not altered when compared to those of IDeg and IAsp obtained with separate injections of IDeg formulation and IAsp formulation. However, at a mix-ratio of IDeg/IAsp equal to [redacted], the peak of plasma IAsp concentration was lower than that of separate injection of IAsp formulation alone. When the GIR was compared,[10] the profiles of IDegAsp with a mix-ratio equal to [redacted] were slower when compared to those of IDegAsp with a mix-ratio equal to [redacted]. In addition, when the GIR profiles of NovoMix 30 and IDegAsp with a mix-ratio equal to [redacted] were compared, there was a sharper peak and longer duration of action after injection of IDegAsp than NovoMix 30.

[5] Formulation containing [redacted] nmol/mL IDeg and [redacted] nmol/mL IAsp
[7] Formulation containing [redacted] nmol/mL IDeg and [redacted] nmol/mL IAsp
[6] Using eight pigs, 3 formulations of 4 formulations of pH[redacted] containing [redacted] (5 pigs), pH[redacted] containing [redacted] (6 pigs), pH[redacted] containing [redacted] (6 pigs), and pH[redacted] containing [redacted] (6 pigs) were administered in a random manner.
[9] Formulation containing [redacted] nmol/mL IDeg and [redacted] nmol/mL IAsp
[8] Using eight pigs, 2 formulations of 4 formulations of pH [redacted] containing [redacted] (4 pigs), pH[redacted] containing [redacted] (4 pigs), pH[redacted] containing [redacted] (4 pigs), and pH[redacted] containing [redacted] (4 pigs) were administered in a random manner.
[10] Combined data obtained in the experiments using formulations with different pH value

(b) Euglycaemic clamp studies using IDegAsp formulations consisting of different [redacted] concentrations in pigs (4.2.1.1.20)

Female pigs (n = 8), fasted overnight, received a single subcutaneous injection of IDegAsp[9] (486 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, or IDegAsp[9] (486 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, or separate single subcutaneous injections of IDeg (432 nmol/pig) formulation containing [redacted]/IDeg hexamer and IAsp (54 nmol/pig) formulation containing [redacted]/IAsp hexamer. GIR was calculated as shown in the above section and plasma concentrations of IDeg and IAsp were measured. As a result, for the IDegAsp [redacted], there was no interference with the pharmacokinetic profile of either insulin component after injection of IDegAsp even with a mix-ratio equal to [redacted], but lowered IAsp peak and heightened IDeg peak in the plasma occurred for the IDegAsp formulation with a mix-ratio equal to [redacted], containing [redacted]. With regards to GIR, compared to separate injections of IDeg formulation and IAsp formulation, GIR profiles after the peak were higher for IDegAsp with [redacted] and even higher for IDegAsp with [redacted].

(c) Euglycaemic clamp studies comparing the injection of IDegAsp formulation to separate injections of IDeg formulation and IAsp formulation in pigs (4.2.1.1.21)

Female pigs (n = 8), fasted overnight, received a single subcutaneous injection of IDegAsp[11] (216 nmol/pig) with a mix-ratio equal to [redacted], containing [redacted]/IDeg hexamer, or separate single subcutaneous injections of IDeg formulation ([redacted] nmol/mL, a dose of 108 nmol/pig) containing [redacted]/IDeg hexamer and IAsp formulation ([redacted] nmol/mL, a dose of 108 nmol/pig) containing [redacted]/IAsp hexamer as well as IDeg formulation ([redacted] nmol/mL, a dose of 108 nmol/pig) containing [redacted]/IDeg hexamer and IAsp formulation ([redacted] nmol/mL, a dose of 108 nmol/pig) containing [redacted]/IAsp hexamer. GIR was calculated as shown in the above section and plasma concentrations of IDeg and IAsp were measured. As a result, the pharmacokinetic profiles and GIR profiles for IDegAsp formulation with [redacted] were not different from those after separate injection of [redacted] or [redacted] nmol/mL of IDeg formulation or IAsp formulation.

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

3.(i).B.(1) Relationship between [redacted] concentration and formation of assemblies

PMDA asked the applicant to present any study confirming that IDeg is di-hexameric in pharmaceutical formulation, becoming multi-hexameric after injection and that IAsp is present as hexamers in pharmaceutical formulation and dissociates into monomers after injection, and then explain the relationship between [redacted] concentration and the formation of assemblies in IDegAsp.

[11] Formulation containing [redacted] nmol/mL IDeg and [redacted] nmol/mL IAsp

The applicant responded as follows:
When IDegAsp (IDeg:IAsp = [redacted]) was analysed by size exclusion chromatography under conditions mimicking the pharmaceutical formulation (in the presence of phenol and [redacted]), IDeg eluted as di-hexamers and IAsp eluted as hexamers in the presence of [redacted] mmol/L of phenol. When size exclusion chromatography was performed in the absence of phenol ([redacted][12]), i.e. under physiological conditions mimicking the subcutaneous tissue, IDeg eluted as large multi-hexamers while IAsp eluted as monomers.

Furthermore, when the pharmacokinetic (PK) profiles after injection of IDegAsp with a mix-ratio equal to approximately [redacted], containing [redacted]/IDeg hexamer, were compared to those after separate injections of IDeg formulation and IAsp formulation, the PK profiles of IDeg and IAsp were not altered. These results suggest that there is little mixed hexamer formation of IDeg and IAsp (hetero-hexamer) in the presence of [redacted] enabling IDeg multi-hexamer formation in the subcutis. In contrast, after injection of IDegAsp with a higher IDeg ratio (IDeg:IAsp = [redacted]), the [redacted]/IDeg hexamer led to an alteration in the IAsp peak concentration, while the PK and pharmacodynamic profiles of IDegAsp with [redacted]/IDeg hexamer were similar to those obtained by separate injections of IDeg formulation and IAsp formulation. These results suggested that the [redacted]/IDeg hexamer formulation did not contain [redacted] sufficient to prevent the formation of hetero-hexamers while the [redacted] concentration of [redacted]/IDeg hexamer formulation was sufficient to prevent the formation of hetero-hexamers.

Based on the above study results, clinical trials were conducted using co-formulations containing at least [redacted] per IDeg hexamer.

PMDA accepted the response.

3.(i).B.(2) Mitogenicity
PMDA asked the applicant to explain the possibility that the combination of IDeg and IAsp exerts synergistic mitogenic effects.

The applicant responded as follows:
In the study on the lipogenic response as a metabolic effect in adipocytes (4.2.1.1.18) it has been suggested that the effects of IDeg and IAsp are additive and not synergistic. Since the effects of IDeg and IAsp are mediated by activation of insulin receptors, it would be expected that the results obtained from adipocytes can be extrapolated to all other insulin target cells. Thus, the mitogenic effects of the combination of IDeg and IAsp are also likely to be additive and not synergistic. Furthermore, compared with human insulin, neither IDeg nor IAsp has been demonstrated to have a higher IGF-1 receptor binding

[12] [redacted] ([redacted] mmol/L), [redacted] ([redacted] mmol/L), trishydroxymethylaminomethane ([redacted] mmol/L) (pH[redacted])

affinity compared to insulin receptor binding. Therefore, there is no evidence suggesting the possibility that the combination of IDeg and IAsp exerts synergistic mitogenic effects.

PMDA has accepted 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*

The pharmacokinetics of IDegAsp were studied following subcutaneous administration to rats and pigs. In addition, the results from studies with IDeg, which had been evaluated for NDA for Tresiba, were submitted. IDeg concentrations in serum or plasma and IAsp concentrations in plasma were quantified by ELISA. The lower limit of quantification (LLOQ) for IDeg was 320 and 63.5 pmol/L in rat serum and plasma, respectively, whereas LLOQ for IAsp was 10 pmol/L in rat plasma. Radioactivity in biological samples was determined by liquid scintillation counting 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 (4.2.3.2.5, 4.2.3.2.11)

The pharmacokinetic parameters of IDeg and IAsp following single subcutaneous administration of IDegAsp, which contains IDeg and IAsp at a 7:3 ratio, to male and female rats were as shown in Table 2.

Table 2. IDeg and IAsp PK parameters following single subcutaneous administration of IDegAsp to male/female rats

Study No.		208289[a)]			208337[b)]		
Dose of IDegAsp (nmol/kg/day)		36	107	214	36	71	107
N (M/F)		10/10	10/10	10/10	14/14	14/14	14/14
IDeg	Dose as IDeg (nmol/kg/day)	25	75	150	25	50	75
	t_{max} (h)	1 1	3 3	3 3	3 1	3 3	3 3
	C_{max} (nmol/L)	56.8 59.0	136 133	260 349	53.9 64.3	137 107	192 190
	AUC_{0-24h} (nmol·h/L)	274 253[c)]	956 766	1820 1780	317 256[c)]	581 545	1140 964
	$t_{1/2}$ (h)	3.5 –	3.0 3.0	3.5 3.3	3.5 –	3.3 3.0	3.2 2.9
IAsp	Dose as IAsp (nmol/kg/day)	11	32	64	11	21	32
	t_{max} (h)	1 1	1 1	1 1	0.5 0.5	0.5 0.5	0.5 0.5
	C_{max} (nmol/L)	0.979 0.342	6.25 1.68	16.1 23.4	3.29 3.65	13.6 15.6	18.8 21.1
	AUC_{0-24h} (nmol·h/L)	2.33 1.99	6.68 2.38	15.9 21.6	2.07[d)] 1.74[e)]	10.6 8.75[e)]	18.2[d)] 19.1[d)]
	$t_{1/2}$ (h)	– –	– –	– –	0.40 –	0.24 –	0.26 0.28

Upper: male, Lower: female, -: not reported

t_{max}: time to maximum concentration, C_{max}: maximum concentration, AUC_{0-24h}: area under the concentration-time curve from time 0 to 24 h, $t_{1/2}$: half-life

a) Data from Day 1 of 4-week subcutaneous repeat-dose toxicity study (4.2.3.2.5). Parameters were derived from 5-point sampling scheme (2 animals/timepoint). Though another formulation of IDegAsp (IDeg:IAsp = [redacted]) was also investigated in the study, only the data from IDegAsp (IDeg:IAsp = 70:30), which is identical to the to-be-marketed formulation, are shown here.

b) Data from Day 1 of 13-week subcutaneous repeat-dose toxicity study (4.2.3.2.11). Parameters were derived from 7-point sampling scheme (2 animals/timepoint).

c) AUC_{0-9h}

d) AUC_{0-3h}

e) AUC_{0-1h}

The accumulation factors following repeated dosing (AUC_{0-24h} of last dosing day/AUC_{0-24h} of 1st dosing day) were 1.0 to 1.4 for IDeg and 0.4 to 4.3 for IAsp in a rat 4-week subcutaneous repeat-dose toxicity study (4.2.3.2.5) and 0.87 to 1.6 for IDeg and 1.1 to 1.4[13] for IAsp in a rat 13-week subcutaneous repeat-dose toxicity study (4.2.3.2.11).

3.(iii) Summary of toxicology studies

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

A repeat-dose toxicity study, a study of effects on embryo-foetal development, local tolerance studies, and a repeat-dose toxicity study with forced-degraded drug products were conducted using IDegAsp. No additional toxicity study with IDeg or IAsp was conducted and the results from studies with IDeg, which had been evaluated for NDA for Tresiba, were submitted.

[13] Calculated as [AUC_{0-1h} of last dosing day]/[AUC_{0-1h} of 1st dosing day]

3.(iii).A.(1) Rat 13-week repeated subcutaneous administration toxicity study (4.2.3.2.11)

Male and female rats (Wistar, n = 10/sex/group) were dosed subcutaneously with 0 (vehicle[15]), 36 (IDeg 25 and IAsp 11), 71 (IDeg 50 and IAsp 21), or 107 (IDeg 75 and IAsp 32) nmol/kg/day IDegAsp (IDeg:IAsp = 7:3)[14] or 75 nmol/kg/day neutral protamin Hagedorn (NPH) insulin for 13 weeks. In the 0 (vehicle) and 107 nmol/kg/day IDegAsp groups and 75 nmol/kg/day NPH insulin group (n = 10/sex/group), 13-week subcutaneous administration was followed by a 4-week recovery period. Out of 14 male and 14 female animals in the satellite group dosed with 71 nmol/kg/day IDegAsp for toxicokinetic measurements, one female was dead due to hypoglycaemia. Clinical signs of hypoglycaemia were seen in the 71 and 107 nmol/kg/day IDegAsp groups and NPH insulin group. Changes in hematological parameters of females of the 107 nmol/kg/day IDegAsp group, changes in clinical chemistry parameters in the IDegAsp groups, changes in urinalysis parameters in the 71 and 107 nmol/kg/day IDegAsp groups, and decreased liver weight of females of the 71 and 107 nmol/kg/day IDegAsp groups were seen at the end of dosing period. All changes were considered related to pharmacological effects of insulin. Decreased body weight gain of males in the 107 nmol/kg/day IDegAsp group was seen at the end of recovery period, but other findings were reversible. Consequently, a no observed adverse effect level (NOAEL) of 107 nmol/kg/day was established. The exposures (AUC) of IDeg and IAsp in the 107 nmol/kg/day IDegAsp group were 1210 and 24.3 nmol·h/L, respectively, which were 15- and 25-fold higher than the human exposures at the clinical dose, respectively.[16]

3.(iii).A.(2) Study of effects on embryo-foetal development in rats (4.2.3.5.2.4)

Pregnant rats (Wistar, n = 20/group) were dosed subcutaneously with 0 (vehicle[15]), 29 (IDeg 20 and IAsp 9), 114 (IDeg 80 and IAsp 34), or 179 (IDeg 125 and IAsp 54) nmol/kg/day IDegAsp[14] or 80 nmol/kg/day NPH insulin from gestation days 6 to 17. In the maternal animals, increased body weight gain and food consumption were seen in the 179 nmol/kg/day IDegAsp group but IDegAsp had no effect on reproductive performance (number of corpora lutea, number of implantations, embryonic loss, etc.). In the foetuses, decreased foetal weight in the 114 and 179 nmol/kg/day IDegAsp groups and NPH insulin group and a higher incidence compared to the vehicle control group of short/bent/thickened humerus and bent scapula in the 179 nmol/kg/day IDegAsp group were seen. All of these findings were small in magnitude and within the background control data and were not considered related to IDegAsp. Consequently, a NOAEL of 179 nmol/kg/day was established for maternal general toxicity and reproductive performance and embryo-foetal development. The exposures (AUC) of IDeg and IAsp in the 179 nmol/kg/day IDegAsp

[15] [redacted] mg/mL [redacted], [redacted] mg/mL [redacted], [redacted] mg/mL [redacted], [redacted] mg/mL [redacted] (pH=[redacted])

[14] The to-be-marketed drug product containing 420 nmol/mL IDeg and 180 nmol/mL IAsp

[16] IDeg $AUC_{0\text{-}24h}$ after multiple doses of IDeg in a Japanese phase I trial (Trial 1996) and IAsp AUC after a single dose of IDegAsp in a Japanese phase I trial (Trial 1983) were dose-normalized and the human exposures at 3.48 nmol/kg/day (0.58 U/kg/day), i.e. the mean clinical dose used by the Japanese sub-population in a IDegAsp multinational phase III trial in type 2 DM (Trial 3597), were calculated.

group were 1300 and 47.4 nmol·h/L,[17] respectively, which were 16- and 49-fold higher than the human exposures at the clinical dose, respectively.[16]

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

The local reaction after subcutaneous administration of IDeg[18] 600 or 1200 nmol/mL formulation, IDegAsp[14] 600 nmol/mL formulation, vehicle for IDeg,[19] or vehicle for IDegAsp[15] was studied in minipigs by comparing histopathologically with NPH insulin and physiological saline. The local reaction 2 days after IDeg or IDegAsp administration was comparable to that of vehicle controls and less pronounced than that of NPH insulin. At 5 days after injection, it was comparable to that of physiological saline or NPH insulin. There was no difference between the 600 nmol/mL and 1200 nmol/mL formulations of IDeg. The local reaction after administration of the early development drug product of IDeg or IDegAsp was also studied in pigs in a similar way. The local reaction after administration of IDeg or IDegAsp was comparable to that of vehicle control or physiological saline control and less pronounced than that of NPH insulin.

The local reaction after intramuscular, intravenous, or intra-arterial administration of IDeg[18] 600 or 1200 nmol/mL formulation, IDegAsp[14] 600 nmol/mL formulation, vehicle for IDeg,[19] or vehicle for IDegAsp[15] was studied in rabbits by comparing histopathologically with NPH insulin and its vehicle. The changes observed after intramuscular, intravenous, or intra-arterial administration of IDeg or IDegAsp were similar to those of vehicle control or NPH insulin.

Based on the above, the applicant considered that local irritations of IDeg and IDegAsp are unlikely to be more of a concern than NPH insulin in clinical use.

3.(iii).A.(4) Immunogenicity

Anti-IDeg antibodies and anti-IAsp antibodies were measured in a repeat-dose toxicity study in rats. As a result, the applicant considered that the development of anti-IDeg antibodies and anti-IAsp antibodies has little effect on the exposure and blood glucose lowering effect of IDeg and IAsp.

3.(iii).A.(5) 4-week repeat-dose study in rats with drug products subjected to forced degradation (4.2.3.7.6.1)

A rat 4-week subcutaneous repeat-dose study was conducted with the drug products subjected to forced degradation at 37°C for 5 months (IDeg) or 3 months (IDegAsp) after production. There was no difference in the findings between the forced-degraded and non-degraded drug products.

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[17] The exposures in the IDeg 125 nmol/kg/day and IAsp 53.6 nmol/kg/day group on gestation day 17 in a preliminary embryo-foetal development study of IDegAsp in rats (4.2.3.5.2.3).

[18] The to-be-marketed drug product of IDeg (Formulation M).

[19] [redacted] mg/mL [redacted], [redacted] mg/mL [redacted], [redacted] mg/mL [redacted] (pH=[redacted]).

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

In the IDegAsp studies including a repeat-dose toxicity study, a study of effects on embryo-foetal development, local tolerance studies, and a repeat-dose toxicity study with forced-degraded drug products, after administration of IDegAsp, there were no toxicity findings other than those anticipated from data on the existing insulin products. Therefore, PMDA has concluded that there is no specific concern about IDegAsp toxicity.

4. Clinical data

In this section, the trial identification numbers are abbreviated, e.g. Trial NN5401-1778 and Trial NN1250-3585 are Trial 1778 and Trial 3585, respectively.

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

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

Table 3 shows the details of the formulations used in the main clinical trials during the development of the combination product (IDegAsp) containing a fixed ratio of insulin degludec (genetical recombination) (hereinafter, "IDeg") and insulin aspart (genetical recombination) (hereinafter, "IAsp"). IDegAsp (F) (unless otherwise specified, "IDegAsp" refers to as IDegAsp (F)) was selected as the proposed commercial formulation.

Table 3 also shows the details of the formulations used in the main clinical trials during the development of IDeg. IDeg (M) (unless otherwise specified, "IDeg" refers to as IDeg (M)) was selected as the proposed commercial formulation.

IDeg and IAsp concentrations in human serum were determined by ELISA, and the lower limit of quantification for IDeg in human serum was 20 pmol/L or 32 pmol/L, and the lower limit of quantification for IAsp in human serum was 10 pmol/L. Anti-IDeg antibodies and anti-IAsp antibodies in serum were detected by radioimmunoassay (RIA).

Table 3. Formulations used in the main clinical trials

	Type of formulation	Concentration for each pre-combined formulation (nmol/mL)		Actual concentration in formulation (nmol/mL)		Development Phase (Trial ID)	
		IDeg	IAsp	IDeg	IAsp	Japanese Subjects	Non-Japanese Subjects
IDegAsp	IDegAsp 50 (A) [a)]	1200	600	600	300	Phase I (Trial 1788)	—
	IDegAsp 45 (B) [b)]	600	600	330	270	Phase I (Trial 1790)	Phase I (Trial 1959)
	IDegAsp 40 (C) [a)]	900	600	540	240	-	Phase I (Trial 1959)
	IDegAsp 55 (C) [a)]	900	600	405	330	-	Phase I (Trial 1959)
	IDegAsp 30 (B) [a)]	600	600	420	180	Phase I (Trial 1790) Phase II (Trial 3570)	Phase I (Trials 1959, 1980)
	IDegAsp (F) [c)] (proposed commercial formulation)	600	600	420 (70 U/mL)	180 (30 U/mL)	Phase I (Trial 1983) Phase III (Trial 3896)	Phase I (Trials 1978, 1980, 1981, 1982, 3539, 3857)
						Phase III (Trial 3597)	
IDeg	IDeg (B) [d)]	-	-	1200	-	Phase I (Trial 1788)	-
	IDeg (D) [e)]	-	-	900	-	Phase I (Trial 1790)	-
	IDeg (E) [e)]	-	-	600 (100 U/mL)	-	Phase I (Trial 1790) Phase II (Trial 3569)	Phase I (Trial 1988)
	IDeg (M) [f)] (proposed commercial formulation)	-	-	600 (100 U/mL)	-	Phase I (Trial 1996)	Phase I (Trials 1987, 1988, 1989, 1990, 1991, 1992, 1993, 1994, 1995, 3538)
		-	-			Phase III (Trials 3585/3725, 3586)	

-: Not applicable
a) IDegAsp formulation of [redacted]/IDeg hexamer, containing sodium chloride
b) IDegAsp formulation of [redacted]/IDeg hexamer, containing sodium chloride
c) IDegAsp (F) of [redacted]/IDeg hexamer, containing sodium chloride. This is the proposed commercial formulation. The drug substance (IDeg) production strain *(S.cerevisiae*) was changed from IDegAsp 30 (B) and the drug substance production capacity was improved.
d) IDeg formulation of [redacted]/IDeg hexamer, containing sodium chloride
e) IDeg formulation of [redacted]/IDeg hexamer
f) IDeg (M) of [redacted]/IDeg hexamer. This is the proposed commercial formulation. The drug substance production strain *(S.cerevisiae*) was changed from IDeg (E) and the drug substance production capacity was improved.

As the reference data on biopharmaceutics, the results from 5 foreign trials including Trial 1980 were submitted. The results from the main clinical trial are described below.

Bioequivalence trial

Trial 1980[20] (5.3.1.2.1) was conducted to test for bioequivalence between IDegAsp 30 (B) and IDegAsp (F), the two formulations derived from different drug substance (IDeg) production strains. Pharmacokinetic analysis showed that the estimated geometric mean ratios (IDegAsp (F)/IDegAsp 30 (B)) with their 90% confidence intervals for the $AUC_{0\text{-}12h,SD}$ and $C_{max,SD}$ of IAsp were 0.96 [0.93, 0.99] and 1.01 [0.94, 1.09], respectively, and the estimated geometric mean ratios (IDegAsp (F)/IDegAsp 30 (B)) with their 90% confidence intervals for the $AUC_{0\text{-}120h,SD}$ and $C_{max,SD}$ of IDeg were 1.02 [0.99, 1.06] and 1.00 [0.94, 1.06], respectively, meeting 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).

[20] A randomized, double-blind, two-period, crossover trial in healthy male and female adult non-Japanese subjects. A single subcutaneous dose of 0.5 U/kg of IDegAsp 30 (B) or IDegAsp (F) was to be administered.

4.(ii) Summary of clinical pharmacology studies

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

As the evaluation data, the following results were submitted.

・Single-dose trial with IDegAsp and IDeg in healthy adult Japanese subjects (Trial 1788) and multiple-dose trial with IDegAsp and IDeg in healthy adult Japanese subjects (Trial 1790)

・Single-dose trial with IDegAsp in Japanese subjects with type 1 diabetes mellitus (T1DM) (Trial 1983)

・Multiple-dose trial with IDeg in Japanese subjects with T1DM (Trial 1996). The trial results have been evaluated for the new drug application for Tresiba.

・Population pharmacokinetics (PPK) analysis of data from a phase III multinational trial with IDeg in subjects with type 2 diabetes mellitus (T2DM) (Trial 3586). The results have been evaluated for the new drug application for Tresiba.

As the reference data, the results from 25 foreign clinical trials were submitted. In addition, the results from studies using human biomaterials were submitted. The results from the main trials are described below. In this section, HbA1c results are reported in National Glycohemoglobin Standardization Program (NGSP) units with the exception of Trials 1983 and 1996.

IDegAsp trials

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

4.(ii).A.(1).1) IDegAsp single-dose trial in Japanese healthy adult subjects (5.3.4.1.1, Trial 1788 [Dec. 2006 to Mar. 2007])

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic properties after a single subcutaneous administration of IDegAsp or IDeg in healthy adult male Japanese subjects living in Europe (target sample size of 32).

A single dose of 0.9 U/kg of IDegAsp 50 (A), a co-formulation of 50% of IDeg (1200 nmol/mL) and 50% of IAsp (600 nmol/mL), 0.3, 0.6, or 1.2 U/kg of IDeg (B), or placebo was subcutaneously administered in the abdomen. Eight subjects were randomized to each treatment arm (active drug, 6 subjects; placebo, 2 subjects).

All 32 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set.

Pharmacokinetic analysis showed that after a single subcutaneous administration of 0.9 U/kg of IDegAsp 50 (A), the $AUC_{0\text{-}\infty,SD}$ of IAsp (geometric mean [coefficient of variation %, CV%]) was 2133 (16)

pmol·h/L, its $C_{max,SD}$ was 848 (11) pmol/L, its $t_{max,SD}$ (median [min-max]) was 1.2 (0.8-1.5) hours, and its $t_{1/2,SD}$ (harmonic mean [CV%]) was 1.3 (33.5) hours.

The pharmacokinetic parameters of IDeg after a single subcutaneous administaration of 0.9 U/kg of IDegAsp 50 (A) or 0.3, 0.6, or 1.2 U/kg of IDeg (B) are shown in Table 4.

Table 4. Pharmacokinetic parameters of IDeg after single subcutaneous administaration of IDegAsp or IDeg

Parameter	IDegAsp 50 (A)	IDeg (B)		
	0.9 U/kg (n = 6)	0.3 U/kg (n = 6)	0.6 U/kg (n = 6)	1.2 U/kg (n = 6)
$AUC_{0-\infty, SD}$ (pmol·h/L)	133,420 (12)	74,667 (11)	134,935 (14)	248,735 (13)
$C_{max, SD}$ (pmol/L)	4427 (17)	2058 (31)	4279 (24)	6860 (33)
$t_{max, SD}$ [a] (h)	13.0 (10.0-20.0)	17.0 (10.0-36.0)	13.0 (10.0-18.0)	15.0 (8.0-20.0)
$t_{½, SD}$ [b] (h)	11.0 (23.5)	15.9 (30.7)	13.5 (18.3)	12.9 (26.0)

Geometric mean (CV%)
$AUC_{0-\infty, SD}$: area under the serum concentration-time curve from zero extrapolated to infinity, $C_{max, SD}$: maximum observed serum concentration, $t_{max, SD}$; time to maximum observed serum concentration, $t_{½, SD}$: elimination half-life
a) Median (min – max)
b) Harmonic mean (CV%)

The estimated geometric mean ratios between 0.6 U/kg of IDeg (B) and IDeg component of 0.9 U/kg of IDegAsp 50(A) (IDeg (B)/IDegAsp 50 (A)) with their 95% confidence intervals for $AUC_{0-\infty,SD}$ and $C_{max,SD}$ were 1.01 [0.88, 1.16] and 0.97 [0.71, 1.31], respectively.

The pharmacodynamic parameters after a single subcutaneous administration of placebo, 0.9 U/kg of IDegAsp 50(A), or 0.3, 0.6, or 1.2 U/kg of IDeg (B) are shown in Table 5.

Table 5. Pharmacodynamic parameters after single subcutaneous administration of placebo, IDegAsp, or IDeg

Parameter	Placebo (n = 8)	IDegAsp 50 (A)	IDeg (B)		
		0.9 U/kg (n = 6)	0.3 U/kg (n = 6)	0.6 U/kg (n = 6)	1.2 U/kg (n = 6)
$AUC_{GIR,0-24h,SD}$ (mg/kg)	954 (26)	5524 (26)	1241 (46)	2853 (31)	5002 (32)
$GIR_{max,SD}$ (mg/kg/min)	1.5 (30)	9.0 (30)	1.6 (35)	3.1 (24)	5.8 (19)
$tGIR_{max,SD}$ [a] (h)	13.1 (5.7-24.0)	2.5 (1.9-3.0)	10.1 (3.8-24.0)	16.5 (10.5-20.3)	12.0 (6.0-24.0)
$AUC_{GIR,12-24h}/AUC_{GIR,0-24h}$ [b]	0.59 (0.14)	0.33 (0.09)	0.54 (0.21)	0.65 (0.05)	0.66 (0.09)

Geometric mean (CV%)
$AUC_{GIR,0-24h,SD}$: area under the GIR curve from 0 to 24 hours, $GIR_{max,SD}$: maximum GIR, $tGIR_{max,SD}$: time to $GIR_{max,SD}$
$AUC_{GIR,12-24h}/AUC_{GIR,0-24h}$: ratio between the areas under the GIR curve from 12 to 24 hours and from 0 to 24 hours
a) Median (min – max)
b) Arithmetic mean (SD)

Regarding safety, adverse events were reported by 3 out of 32 subjects (1.2 U/kg of IDeg (B), left thigh haematoma in 1 subject; IDegAsp 50 (A), tooth disorder in 1 subject; placebo, tinnitus in 1 subject), all of which were mild in severity except for left thigh haematoma (moderate) and a causal relationship to trial product was denied for all events. No hypoglycaemic symptoms or injection site reactions were reported. No deaths, severe adverse events (SAEs), or adverse events (AEs) leading to withdrawal were reported.

No clinically significant changes in vital signs, ECG, laboratory parameters, or physical examination were observed.

4.(ii).A.(1).2) IDegAsp multiple-dose trial in Japanese healthy adult subjects (5.3.4.1.2, Trial 1790 [Dec. 2007 to Feb. 2008])

A randomized, double-blind, placebo-controlled, parallel-group trial was conducted to investigate the safety, tolerability, and pharmacokinetic and pharmacodynamic properties after multiple subcutaneous doses of IDegAsp or IDeg in healthy adult male Japanese subjects (target sample size of 32).

IDegAsp 30 (B) [a co-formulation of 70% IDeg (600 nmol/mL) and 30% IAsp (600 nmol/mL)], IDegAsp 45 (B) [a co-formulation of 55% IDeg (600 nmol/mL) and 45% IAsp (600 nmol/mL)], IDeg (D), or IDeg (E) at a dose of 0.1 U/kg or placebo was subcutaneously administered once daily in the abdomen for 6 days. Eight subjects were randomized to each treatment arm (active drug, 6 subjects; placebo, 2 subjects).

All 32 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set.

The pharmacokinetic parameters of IAsp after 6 days of once-daily subcutaneous administration of 0.1 U/kg of IDegAsp 30 (B) or IDegAsp 45 (B) are shown in Table 6.

Table 6. Pharmacokinetic parameters of IAsp after 6 days of once-daily subcutaneous administration of 0.1 U/kg of IDegAsp

Parameter	Day	IDegAsp	
		IDegAsp 30 (B) (n = 6)	IDegAsp 45 (B) (n = 6)
$AUC_{0-\infty}$ (pmol·h/L)	Day 1	130 (73.2)	273 (38.5)
	Day 6	141 (39.0)	263 (44.7)
AUC_{0-6h} (pmol·h/L)	Day 1	106 (86.1)	255 (39.5)
	Day 6	130 (38.3)	245 (41.9)
C_{max} (pmol/L)	Day 1	80.1 (47.9)	148 (21.0)
	Day 6	116 (35.7)	186 (31.8)
t_{max} [a)] (h)	Day 1	0.67 (0.5-0.8)	0.59 (0.5-1.0)
	Day 6	0.50 (0.5-0.7)	0.67 (0.5-0.8)
$t_{½}$ [b)] (h)	Day 1	1.02 (50.4)	0.89 (34.8)
	Day 6	0.61 (56.6)	0.82 (65.5)

Geometric mean (CV%), -: Not applicable

$AUC_{0-\infty}$: area under the serum concentration-time curve from zero extrapolated to infinity, AUC_{0-6h}: area under the serum concentration-time curve from 0 to 6 hours, C_{max}: maximum observed serum concentration, t_{max}: time to maximum observed serum concentration, $t_{½}$: elimination half-life

a) Median (min – max)

b) Harmonic mean (CV%)

The pharmacokinetic parameters of IDeg after 6 days of once-daily subcutaneous administration of 0.1 U/kg of IDegAsp 30 (B), IDegAsp 45 (B), IDeg (D), or IDeg (E) are shown in Table 7.

Table 7. Pharmacokinetic parameters of IDeg after 6 days of once-daily subcutaneous administration of 0.1 U/kg of IDegAsp or IDeg

Parameter	Day	IDegAsp		IDeg	
		IDegAsp 30 (B) (n = 6)	IDegAsp 45 (B) (n = 6)	IDeg (D) (n = 6)	IDeg (E) (n = 6)
$AUC_{0-\infty}$ (pmol·h/L)	-	10,366 (18.6)	8681 (23.8)	16,419 (19.1)	18,959 (21.9)
AUC_{0-24h} (pmol·h/L)	Day 1	7948 (43.6)	7367 (13.9)	11,797 (19.2)	12,885 (8.1)
	Day 6	9365 (15.6)	7753 (18.8)	13,738 (17.1)	16,009 (13.0)
C_{max} (pmol/L)	Day 1	603 (37.9)	564 (16.0)	891 (25.7)	932 (23.4)
	Day 6	742 (8.4)	636 (19.9)	1030 (13.1)	1180 (9.7)
t_{max} [a)] (h)	Day 1	8.0 (4.0-12.0)	8.0 (4.0-10.0)	8.0 (8.0-10.0)	8.0 (8.0-18.0)
	Day 6	8.0 (4.0-8.0)	4.0 (4.0-10.0)	8.0 (4.0-8.0)	8.0 (4.0-8.0)
$t_{½}$ [b)] (h)	Day 1	-	-	-	-
	Day 6	6.6 (13.5)	6.6 (31.5)	10.1 (31.2)	9.1 (58.0)

Geometric mean (CV%), -: Not applicable

$AUC_{0-\infty}$: area under the serum concentration-time curve from zero extrapolated to infinity, AUC_{0-24h}: area under the serum concentration-time curve from 0 to 24 hours, C_{max}: maximum observed serum concentration, t_{max}: time to maximum observed serum concentration, $t_{½}$: elimination half-life

a) Median (min – max)

b) Harmonic mean (CV%)

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

Regarding safety, an adverse event was reported by 1 out of 32 subjects (IDegAsp 30 (B), syncope vasovagal), which was mild in severity, and its causal relationship to trial product was denied. No hypoglycaemic symptoms were reported. Injection site reactions were reported by 4 subjects (1 subject in the IDeg (D) group, 2 subjects in the IDeg (E) group, 1 subject in the placebo group), but none met the criteria for an adverse event.[21] No deaths, SAEs, or AEs leading to withdrawal were reported. No clinically significant changes in vital signs, ECG, laboratory parameters, or physical examination were observed.

4.(ii).A.(2) Trials in diabetic patients

4.(ii).A.(2).1) Single-dose trial with IDegAsp in Japanese subjects with T1DM (5.3.4.2.1, Trial 1983 [Jan. 2010 to Apr. 2010])

A randomized, double-blind,[23] two-period crossover trial was conducted to investigate the pharmacodynamic and pharmacokinetic properties, safety, and tolerability after a single subcutaneous dose of IDegAsp compared to a biphasic premixed product containing intermediate-acting protamine-

[21] Injection site reactions were scored on a 6-point scale (0: no reaction, 0.5: hardly perceptible erythema, 1: mild [slight erythema with or without slight edema], 2: moderate [moderate erythema, edema, with or without papules], 3: intense [marked erythema, edema, induration, with or without papules], 4: severe [intense erythema with edema, vesicles, or blisters]), and a score of ≥2 was considered as an adverse event.

[22] Key inclusion criteria: subjects with T1DM, treated with insulin (>0.2 U/kg/day) for ≥12 months, aged 20-65 (both inclusive), HbA1c (JDS) ≤10.0%, and BMI 18.0-28.0 kg/m^2 (both inclusive)

[23] Cartridges containing the trial product were blinded to subjects, investigators, and study coordinators. The trial products were administered by another medical professional not involved in assessment for the trial.

crystallized IAsp and rapid-acting soluble IAsp at a molar ratio of 70:30 (NovoRapid 30 Mix; hereinafter "BIAsp 30") in Japanese subjects with T1DM[22] (Target sample size of 20).

A single dose of 0.5 U/kg of IDegAsp or BIAsp 30 was subcutaneously administered in the thigh. A 13- to 21-day washout period was included between treatments.

All 21 exposed subjects were included in the pharmacokinetic and pharmacodynamic analysis set and the safety analysis set. One subject was withdrawn from the trial due to an adverse event.

The pharmacokinetic parameters[24] of IAsp after a single subcutaneous administration of 0.5 U/kg of IDegAsp or BIAsp 30 are shown in Table 8.

Table 8. Pharmacokinetic parameters of IAsp after single subcutaneous dose of 0.5 U/kg of IDegAsp or BIAsp 30

Parameter	IDegAsp 0.5 U/kg (n = 21)	BIAsp 30 0.5 U/kg (n = 21)
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	813 (53)	2246 (71)
$C_{max,SD}$ (pmol/L)	280 (49)	415 (46)
$t_{max,SD}$ [a)] (h)	1.2 (0.5-2.8)	1.5 (0.7-2.5)
Onset of appearance$_{,SD}$ (min)	10 (46)	7 (54)

Geometric mean (CV%)

$AUC_{0\text{-}12h,\ SD}$: area under the serum concentration-time curve from 0 to 12 hours, $C_{max,\ SD}$: maximum observed serum concentration, $t_{max,\ SD}$: time to maximum observed serum concentration, Onset of appearance$_{,SD}$: time from trial product administration until the first time serum IAsp concentration is above 30 pmol/L

a) Median (min – max)

Concerning the pharmacokinetic parameters of IDeg after a single subcutaneous dose of 0.5 U/kg of IDegAsp, $AUC_{0\text{-}120h,SD}$ (geometric mean [CV%]) was 66,178 (45) pmol·h/L, $C_{max,SD}$ was 2068 (36) pmol/L, $t_{max,SD}$ (median [min-max]) was 12 (6-24) hours, and $t_{1/2,SD}$ (harmonic mean [CV%]) was 11 (62) hours.

The pharmacodynamic parameters after a single subcutaneous administration of 0.5 U/kg of IDegAsp or BIAsp 30 are shown in Table 9.

[24] The basal component in BIAsp 30 is protamine-crystallized IAsp, which contributes to an increase in IAsp concentration from 4 to 5 hours after dosing. Therefore, the applicant explains that it is not possible to make a direct comparison between the pharmacokinetics of IAsp in IDegAsp and BIAsp 30.

Table 9. Pharmacodynamic parameters after single subcutaneous administration of 0.5 U/kg of IDegAsp or BIAsp 30

Parameter	IDegAsp 0.5 U/kg (n = 21)	BIAsp 30 0.5 U/kg (n = 21)
$AUC_{GIR,0-24h,SD}$ (mg/kg)	1170 (52)	1856 (47)
$GIR_{max,SD}$ (mg/kg/min)	3.0 (32)	4.5 (38)
$tGIR_{max,SD}$ [a)] (h)	2.3 (1.1-4.1)	3.3 (1.5-6.3)
Onset of $action_{,SD}$ (min)	31 (49)	30 (31)

Geometric mean (CV%)

$AUC_{GIR,0-24h,SD}$: area under the GIR curve from 0 to 24 hours, $GIR_{max,SD}$: maximum GIR, $tGIR_{max,SD}$: time to maximum GIR, Onset of $action_{,SD}$: time from trial product administration until the blood glucose concentration decreases at least 5 mg/dL from baseline

a) Median (min – max)

Regarding safety, adverse events were reported by 1 out of 21 subjects (after administration of BIAsp 30, Basedow's disease/abdominal pain upper/vomiting), all of which were mild in severity and their causal relationship to trial product was denied. No severe hypoglycaemia[25] was reported. Fifty-four confirmed hypoglycaemic[26] episodes were reported by 16 subjects after administration of IDegAsp and 53 confirmed hypoglycaemic episodes by 18 subjects after administration of BIAsp 30. Fourteen nocturnal confirmed hypoglycaemic episodes[27] were reported by 7 subjects after administration of IDegAsp and 8 nocturnal confirmed hypoglycaemic episodes by 6 subjects after administration of BIAsp 30. No injection site reactions were reported. No deaths or SAEs were reported. No clinically significant changes in vital signs, ECG, laboratory parameters, or physical examination were observed.

4.(ii).A.(2).2) Trial comparing IDegAsp with IDeg alone or IAsp alone given in identical doses in non-Japanese subjects with T1DM (5.3.4.2.6, Trial 3857 [Jul. 2010 to Nov. 2010], Reference data)

A randomized, open-label, three-period crossover trial was conducted to investigate the single-dose pharmacokinetic and pharmacodynamic properties between IDegAsp relative to both IDeg alone and IAsp alone, when given as single doses at the same total dose level, in non-Japanese subjects with T1DM[28] (Target sample size of 24).

A single dose of 0.5 U/kg of IDegAsp, IDeg (M) alone, or IAsp alone was subcutaneously administered in the abdomen. A 7- to 21-day washout period was included between treatments.

All 27 exposed subjects were included in the pharmacokinetic and pharmacodynamic analysis set and the safety analysis set.

[25] Hypoglycaemic episodes requiring assistance of another person

[26] Severe hypoglycaemia as well as episodes with plasma glucose of ≤ 56 mg/dL with or without symptoms

[27] Hypoglycaemic episodes (severe hypoglycaemia as well as episodes with plasma glucose of ≤ 56 mg/dL with or without symptoms) occurring between 00:00 and 05:59 (both inclusive)

[28] Key inclusion criteria: subjects with T1DM, treated with insulin (<1.2 U/kg/day) for ≥12 months, aged 18-65 (both inclusive), HbA1c ≤ 10.0%, BMI 18.0-28.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

The pharmacokinetic parameters of IAsp after a single subcutaneous administration of 0.5 U/kg of IDegAsp are shown in Table 10.

Table 10. Pharmacokinetic parameters of IAsp after single subcutaneous administration of 0.5 U/kg of IDegAsp

Parameter	IDegAsp 0.5 U/kg (n = 27)
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	833 (33)
$C_{max,SD}$ (pmol/L)	252 (30)
$t_{max,SD}$ [a)] (h)	1.3 (0.5-2.8)

Geometric mean (CV%)
$AUC_{0\text{-}12h,SD}$: area under the serum concentration-time curve from 0 to 12 hours, $C_{max,SD}$: maximum observed serum concentration,
$t_{max,SD}$: time to maximum observed serum concentration
a) Median (min – max)

Concerning the pharmacokinetic parameters of IDeg after a single subcutaneous administration of 0.5 U/kg of IDegAsp, $AUC_{0\text{-}120h,SD}$ (geometric mean [CV%]) was 114,809 (24) pmol·h/L, $C_{max,SD}$ was 3286 (25) pmol/L, $t_{max,SD}$ (median [min-max]) was 12 (8-24) hours, and $t_{1/2,SD}$ (harmonic mean [CV%]) was 18 (31) hours.

The estimated geometric mean ratios of IDegAsp to IAsp alone (IDegAsp/IAsp alone) and of IDegAsp to IDeg alone (IDegAsp/IDeg alone) with their 95% confidence intervals for the pharmacokinetic parameters of IAsp and IDeg are shown in Table 11 and Table 12, respectively.

Table 11. Pharmacokinetic parameters of IAsp after administration of IDegAsp versus IAsp alone

Parameter	Ratio (IDegAsp/IAsp alone)
$AUC_{0\text{-}2h,SD}$ (pmol·h/L)	0.19 [0.17, 0.21]
$AUC_{0\text{-}6h,SD}$ (pmol·h/L)	0.22 [0.20, 0.23]
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	0.23 [0.21, 0.24]
$C_{max,SD}$ (pmol/L)	0.19 [0.16, 0.22]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{0\text{-}th,SD}$: area under the serum concentration-time curve from 0 to t hours, $C_{max,SD}$: maximum observed serum concentration

Table 12. Pharmacokinetic parameters of IDeg after administration of IDegAsp versus IDeg alone

Parameter	Ratio (IDegAsp/IDeg alone)
$AUC_{0\text{-}24h,SD}$ (pmol·h/L)	0.74 [0.69, 0.80]
$AUC_{0\text{-}120h,SD}$ (pmol·h/L)	0.71 [0.68, 0.74]
$C_{max,SD}$ (pmol/L)	0.75 [0.69, 0.82]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{0\text{-}th,SD}$: area under the serum concentration-time curve from 0 to t hours, $C_{max,SD}$: maximum observed serum concentration

Based on $AUC_{0\text{-}12h,SD}$, the relative bioavailability (BA) of IDegAsp compared to IAsp alone with its 90% confidence interval (adjusted for dose) was 0.75 [0.72, 0.79]. Based on $AUC_{0\text{-}120h,SD}$, the relative BA of IDegAsp compared to IDeg alone with its 90% confidence interval (adjusted for dose) was 1.01 [0.98, 1.05].

For the pharmacodynamic parameters after a single subcutaneous dose of IDegAsp and IAsp alone or IDeg alone, the estimated geometric mean ratios of IDegAsp to IAsp alone (IDegAsp/IAsp alone) and of IDegAsp to IDeg alone (IDegAsp/IDeg alone) with their 95% confidence intervals are shown in Table 13.

Table 13. Pharmacodynamic parameters after administration of IDegAsp versus IAsp alone or IDeg alone

Period	Parameter	Ratio (IDegAsp/IAsp alone)	Ratio (IDegAsp/IDeg alone)
Early (0-6 hours post-dose)	$AUC_{GIR,0\text{-}2h,SD}$ (mg/kg)	0.37 [0.16, 0.87]	746.9 [315.5, 1768]
	$AUC_{GIR,0\text{-}6h,SD}$ (mg/kg)	0.42 [0.16, 1.11]	40.7 [15.3, 109]
Late (6-24 hours post-dose)	$AUC_{GIR,6\text{-}24h,SD}$ (mg/kg)	3.88 [1.99, 7.55]	－
	$AUC_{GIR,12\text{-}24h,SD}$ (mg/kg)	5787 [991, 33,792]	－
Others	$AUC_{GIR,0\text{-}12h,SD}$ (mg/kg)	0.54 [0.46, 0.64]	－
	$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	0.69 [0.56, 0.86]	1.57 [1.26, 1.95]
	$GIR_{max,SD}$ (mg/kg/min)	0.44 [0.36, 0.52]	2.78 [2.30, 3.35]

Estimated geometric mean ratio with its 95% confidence interval, －: not calculated
$AUC_{GIR,\ t1\text{-}t2h,SD}$: area under the GIR curve from t_1 to t_2 hours, $GIR_{max,\ SD}$: maximum GIR

Regarding safety, adverse events were reported by 5 out of 27 subjects (1 subject after administration of IDegAsp, 5 subjects after administration of IDeg alone). Adverse events reported by at least 2 subjects were nasopharyngitis (3 subjects after administration of IDeg alone) and headache (2 subjects after administration of IDegAsp, 1 subject after administration of IDeg alone), all of which were mild or moderate in severity. Since a causal relationship to trial product could not be denied for the headaches reported by 2 subjects (both moderate), they were classified as adverse drug reactions. No severe hypoglycaemic episodes[25]were reported. Four confirmed hypoglycaemic episodes[26] were reported by 4 subjects after administration of IDegAsp and 5 confirmed hypoglycaemic episodes by 4 subjects after administration of IDeg alone. Three nocturnal confirmed hypoglycaemic episodes[27] were reported by 3 subjects after administration of IDegAsp and 2 nocturnal confirmed hypoglycaemic episodes by 2 subjects after administration of IDeg alone. No injection site reactions were reported. No deaths, SAEs, or AEs leading to withdrawal were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

4.(ii).A.(2).3) Trial comparing IDegAsp and simultaneous separate injections of IDeg and IAsp products in non-Japanese subjects with T1DM (5.3.4.2.3, Trial 1959 [Apr. 2008 to Aug. 2008], Reference data)

A randomized, double-blind,[23] incomplete block, four-period crossover trial was conducted to compare the single-dose pharmacokinetic and pharmacodynamic properties of IDegAsp with corresponding separate simultaneous injections of the IDeg and IAsp products in non-Japanese subjects with T1DM[29] (Target

[29] Key inclusion criteria: subjects with T1DM, treated with insulin (≤1.2 U/kg/day) for ≥12 months, aged 18-65 (both inclusive), HbA1c ≤10.0%, BMI 18.0-27.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

sample size of 53). The dose levels of the separate simultaneous injections of the IDeg and IAsp products were chosen to mimic the fractions of respective components in IDegAsp.

Four of the 9 treatments as shown in Table 14 (IDegAsp, simultaneous separate injections of the IDeg and IAsp products, BIAsp 30) were administered as a single subcutaneous dose in the abdomen. A 7- to 15-day washout period was included between treatments.

Table 14. Treatments with trial product

IDegAsp	IDegAsp 30 (B) 0.92 U/kg (IDeg 0.64 U/kg + IAsp 0.28 U/kg)
	IDegAsp 40 (C) 0.92 U/kg (IDeg 0.64 U/kg + IAsp 0.28 U/kg)
	IDegAsp 45 (B) 0.92 U/kg (IDeg 0.51 U/kg + IAsp 0.41 U/kg)
	IDegAsp 55 (C) 0.92 U/kg (IDeg 0.51 U/kg + IAsp 0.41 U/kg)
Simultaneous separate injections of IDeg and IAsp products	IDeg (E) 0.64 U/kg + IAsp 0.28 U/kg[a)]
	IDeg (D) 0.63 U/kg + IAsp 0.28 U/kg[b)]
	IDeg (E) 0.51 U/kg + IAsp 0.41 U/kg[c)]
	IDeg (D) 0.51 U/kg + IAsp 0.41 U/kg[d)]
BIAsp 30	BIAsp 30 0.64 U/kg

IDegAsp 30 (B): contains 70% IDeg (600 nmol/mL) and 30% IAsp (600 nmol/mL) [v/v]
IDegAsp 40 (C): contains 60% IDeg (900 nmol/mL) and 40% IAsp (600 nmol/mL) [v/v]
IDegAsp 45 (B): contains 55% IDeg (600 nmol/mL) and 45% IAsp (600 nmol/mL) [v/v]
IDegAsp 55 (C): contains 45% IDeg (900 nmol/mL) and 55% IAsp (600 nmol/mL) [v/v]
a) Simultaneous separate injections of IDeg (E) and IAsp products, equivalent to a dose of IDegAsp 30 (B)
b) Simultaneous separate injections of IDeg (D) and IAsp products, equivalent to a dose of IDegAsp 40 (C)
c) Simultaneous separate injections of IDeg (E) and IAsp products, equivalent to a dose of IDegAsp 45 (B)
d) Simultaneous separate injections of IDeg (D) and IAsp products, equivalent to a dose of IDegAsp 55 (C)

All 55 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set. Two subjects were withdrawn from the trial due to technical problems of the glucose clamp apparatus and because they met the withdrawal criteria.

For the pharmacokinetic parameters of IAsp and IDeg, the estimated geometric mean ratios between IDegAsp and simultaneous separate administration of the IDeg and IAsp products (IDegAsp/IDeg + IAsp) with their 95% confidence intervals are shown in Table 15 and Table 16, respectively.

Table 15. Pharmacokinetic parameters of IAsp after dosing of IDegAsp versus simultaneous separate dosing of IDeg and IAsp products

Parameter	Trial Products	Ratio (IDegAsp/IDeg+IAsp)
$AUC_{0\text{-}2h,SD}$ (pmol·h/L)	IDegAsp 30 (B)/IDeg + IAsp	0.68 [0.61, 0.75]
	IDegAsp 40 (C)/IDeg + IAsp	0.71 [0.64, 0.78]
	IDegAsp 45 (B)/IDeg + IAsp	0.68 [0.60, 0.76]
	IDegAsp 55 (C)/IDeg + IAsp	0.67 [0.60, 0.74]
$C_{max,SD}$ (pmol/L)	IDegAsp 30 (B)/IDeg + IAsp	0.72 [0.64, 0.79]
	IDegAsp 40 (C)/IDeg + IAsp	0.73 [0.67, 0.80]
	IDegAsp 45 (B)/IDeg + IAsp	0.69 [0.62, 0.78]
	IDegAsp 55 (C)/IDeg + IAsp	0.70 [0.63, 0.77]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{0\text{-}2h,SD}$: area under the serum concentration-time curve from 0 to 2 hours, $C_{max,\ SD}$: maximum observed serum concentration

Table 16. Pharmacokinetic parameters of IDeg after dosing of IDegAsp versus simultaneous separate dosing of IDeg and IAsp products

Parameter	Trial Products	Ratio (IDegAsp/Deg+IAsp)
$AUC_{0\text{-}\infty,SD}$ (pmol·h/L)	IDegAsp 30 (B)/IDeg + IAsp	1.05 [0.95, 1.16]
	IDegAsp 40 (C)/IDeg + IAsp	1.01 [0.93, 1.10]
	IDegAsp 45 (B)/IDeg + IAsp	1.04 [0.94, 1.16]
	(IDegAsp 55 (C)/IDeg + IAsp	1.07 [0.98, 1.18]
$C_{max,SD}$ (pmol/L)	IDegAsp 30 (B)/IDeg + IAsp	1.03 [0.93, 1.14]
	IDegAsp 40 (C)/IDeg + IAsp	1.05 [0.96, 1.15]
	IDegAsp 45 (B)/IDeg + IAsp	0.96 [0.86, 1.07]
	IDegAsp 55 (C)/IDeg + IAsp	1.13 [1.03, 1.24]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{0\text{-}\infty,SD}$: area under the serum concentration-time curve from 0 extrapolated to infinity, $C_{max,\ SD}$: maximum observed serum concentration

For the pharmacodynamic parameters, the estimated geometric mean ratios of IDegAsp to simultaneous separate administration of IDeg and IAsp products (IDegAsp/IDeg+IAsp) with their 95% confidence intervals are shown in Table 17.

Table 17. Pharmacodynamic parameters after dosing of IDegAsp versus simultaneous separate dosing of IDeg and IAsp products

Parameter	Trial Products	Ratio (IDegAsp/IDeg+IAsp)
$AUC_{GIR,0\text{-}6h,SD}$ (mg/kg)	IDegAsp 30 (B)/IDeg + IAsp	0.97 [0.88, 1.06]
	IDegAsp 40 (C)/IDeg + IAsp	1.00 [0.92, 1.09]
	IDegAsp 45 (B)/IDeg + IAsp	0.98 [0.88, 1.08]
	IDegAsp 55 (C)/IDeg + IAsp	1.02 [0.93, 1.11]
$AUC_{\ GIR,0\text{-}24h,SD}$ (mg/kg)	IDegAsp 30 (B)/IDeg + IAsp	1.04 [0.94, 1.14]
	IDegAsp 40 (C)/IDeg + IAsp	1.12 [1.03, 1.22]
	IDegAsp 45 (B)/IDeg + IAsp	1.08 [0.97, 1.19]
	IDegAsp 55 (C)/IDeg + IAsp	1.12 [1.02, 1.23]
$GIR_{max,SD}$ (mg/kg/min)	IDegAsp 30 (B)/IDeg + IAsp	0.94 [0.86, 1.03]
	IDegAsp 40 (C)/IDeg + IAsp	0.95 [0.87, 1.03]
	IDegAsp 45 (B)/IDeg + IAsp	0.93 [0.84, 1.03]
	IDegAsp 55 (C)/IDeg + IAsp	0.96 [0.88, 1.05]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{GIR,\ 0\text{-}th,SD}$: area under the GIR curve from 0 to t hours, $GIR_{max,\ SD}$: maximum GIR

Regarding safety, the occurrence of adverse events and hypoglycaemic episodes are shown in Table 18. Adverse events reported by at least 3 subjects were headache, all of which were mild or moderate in severity. One SAE (hypoglycaemic unconsciousness [severe]) was reported by 1 subject after administration of IDegAsp 55 (C). However, since the onset of this event was 7 days after dosing, its causal relationship to trial product was denied. No injection site reactions were reported. No deaths or AEs leading to withdrawal were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

Table 18. Adverse events, adverse drug reactions, and hypoglycaemia

Treatment	Adverse event (adverse drug reaction) (no. of subjects)		Hypoglycaemia (no. of episodes)		
	Overall	Headache[a)]	Minor[b)]	Symptoms only[c)]	Major[d)]
Overall	20 (9)	12 (9)	190	2	1
IDegAsp 30 (B)	3 (1)	3 (1)	20	0	0
IDegAsp 40 (C)	8 (6)	6 (6)	38	1	0
IDegAsp 45 (B)	4 (3)	3 (3)	25	0	0
IDegAsp 55 (C)	4 (1)	2 (1)	25	1	1
IDeg (E) 0.64 U/kg + IAsp 0.28 U/kg	5 (2)	2 (1)	16	0	0
IDeg (D) 0.63 U/kg + IAsp 0.28 U/kg	6 (2)	6 (2)	26	0	0
IDeg (E) 0.51 U/kg + IAsp 0.41 U/kg	1 (0)	0 (0)	10	0	0
IDeg (D) 0.51 U/kg + IAsp 0.41 U/kg	4 (0)	2 (0)	20	0	0
BIAsp 30	2 (0)	1 (0)	10	0	0

a) Adverse events reported by at least 3 subjects
b) Hypoglycaemic episodes not requiring assistance of another person where plasma glucose <56 mg/dL was recorded
c) Symptoms that are considered to be related to hypoglycaemia but not confirmed by a plasma glucose measurement
d) Hypoglycaemic episodes requiring assistance of another person

4.(ii).A.(2).4) Single-dose trial with IDegAsp in non-Japanese subjects with T1DM (5.3.4.2.4, Trial 3539 [Sep. 2009 to Dec. 2009], Reference data)

A randomized, double-blind,[23] incomplete block, four-period crossover trial was conducted to investigate the dose-response relationship of pharmacodynamic and pharmacokinetic parameters after a single dose of IDegAsp in non-Japanese subjects with T1DM[30] (Target sample size of 30).

For 4 out of 6 treatments (0.4, 0.6, and 0.8 U/kg of IDegAsp and 0.4, 0.6, and 0.8 U/kg of BIAsp 30), two dose levels each of IDegAsp and BIAsp 30 were selected, and a total of 4 injections were administered in the abdomen as a single subcutaneous dose. A 13- to 21-day washout period was included between treatments.

All 33 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set. Two subjects withdrew their consents and were withdrawn from the trial.

[30] Key inclusion criteria: subjects with T1DM treated with insulin (<1.2 U/kg/day) for ≥12 months, aged 18-65 (both inclusive), HbA1c ≤10.0%, BMI 18.0-28.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

The pharmacokinetic parameters[24] of IAsp and IDeg after a single subcutaneous administration of IDegAsp or BIAsp 30 are shown in Table 19 and Table 20.

Table 19. Pharmacokinetic parameters of IAsp after a single subcutaneous administration of IDegAsp or BIAsp 30

Parameter	IDegAsp			BIAsp 30		
	0.4 U/kg (n = 21)	0.6 U/kg (n = 20)	0.8 U/kg (n = 20)	0.4 U/kg (n = 22)	0.6 U/kg (n = 20)	0.8 U/kg (n = 21)
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	669 (35)	1105 (32)	1444 (31)	1587 (35)	2338 (37)	3063 (29)
$C_{max,SD}$ (pmol/L)	257 (29)	351 (28)	481 (30)	342 (27)	497 (28)	663 (32)
$t_{max,SD}$ [a)] (h)	1.2 (0.5-2.0)	1.4 (0.9-2.8)	1.4 (0.7-2.0)	1.4 (0.7-2.8)	1.5 (0.5-2.8)	1.4 (0.9-2.0)
Onset of appearance,SD (min)	14 (32)	17 (34)	15 (30)	12 (34)	11 (43)	8 (52)

Geometric mean (CV%)

$AUC_{0\text{-}12h,SD}$: area under the serum concentration-time curve from 0 to 12 hours, $C_{max,SD}$: maximum observed serum concentration, $t_{max,SD}$: time to maximum observed serum concentration, Onset of appearance,SD: time from trial product administration until the first time serum IAsp concentration is above 30 pmol/L

a) Median (min – max)

Table 20. Pharmacokinetic parameters of IDeg after a single subcutaneous administration of IDegAsp

Parameter	0.4 U/kg (n = 21)	0.6 U/kg (n = 20)	0.8 U/kg (n = 20)
$AUC_{0\text{-}\infty,SD}$ (pmol·h/L)	65,441 (34)	96,748 (25)	120,584 (22)
$AUC_{0\text{-}24h,SD}$ (pmol·h/L)	33,532 (24)	44,921 (21)	56,126 (18)
$C_{max,SD}$ (pmol/L)	2053 (25)	2721 (22)	3373 (19)
$t_{max,SD}$ [a)] (h)	11.0 (6.0-7.0)	13.0 (8.0-20.0)	12.5 (8.0-19.0)
$t_{1/2,SD}$ [b)] (h)	16.2 (26)	18.0 (32)	18.3 (16)

Geometric mean (CV%)

$AUC_{0\text{-}\infty,SD}$; area under the serum concentration-time curve from zero extrapolated to infinity, $AUC_{0\text{-}24h,SD}$: area under the serum concentration-time curve from 0 to 24 hours, $C_{max,SD}$: maximum observed serum concentration, $t_{max,SD}$: time to maximum observed serum concentration, $t_{½,SD}$: elimination half-life

a) Median (min – max)

b) Harmonic mean (CV%)

The pharmacodynamic parameters after a single subcutaneous administration of IDegAsp or BIAsp 30 are shown in Table 21.

Table 21. Pharmacodynamic parameters after a single subcutaneous administration of IDegAsp or BIAsp 30

Parameter	IDegAsp			BIAsp 30		
	0.4 U/kg (n = 21)	0.6 U/kg (n = 20)	0.8 U/kg (n = 20)	0.4 U/kg (n = 22)	0.6 U/kg (n = 20)	0.8 U/kg (n = 21)
$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	1681 (34)	2700 (42)	3603 (25)	2321 (39)	3234 (38)	3955 (30)
$GIR_{max,SD}$ (mg/kg/min)	3.8 (32)	6.0 (3.8)	6.9 (32)	5.9 (31)	7.5 (39)	8.8 (26)
$tGIR_{max,SD}$ [a)] (h)	2.3 (1.5-3.7)	2.1 (1.5-3.7)	2.3 (1.9-4.9)	2.6 (1.2-5.0)	2.8 (1.4-4.9)	2.3 (1.8-5.0)
Onset of action,SD (min)	32 (45)	24 (63)	24 (52)	24 (51)	28 (41)	24 (47)

Geometric mean (CV%)

$AUC_{GIR,0\text{-}24h,SD}$: area under the GIR curve from 0 to 24 hours, $GIR_{max,SD}$: maximum GIR, $tGIR_{max,SD}$: time to maximum GIR, Onset of action,SD: time from trial product administration until the blood glucose concentration decreases at least 5 mg/dL from baseline

a) Median (min – max)

Regarding safety, adverse events were reported by 15 out of 33 subjects (7 subjects after administration of IDegAsp, 10 subjects after administration of BIAsp 30). Adverse events reported by at least 3 subjects were nasopharyngitis (6 subjects [3 subjects after administration of 0.4 U/kg of IDegAsp, 1 subject after administration of 0.8 U/kg of IDegAsp, 1 subject after administration of 0.4 U/kg of BIAsp 30, 1 subject after administration of 0.6 U/kg of BIAsp 30, 1 subject after administration of 0.8 U/kg of BIAsp 30]) and headache (4 subjects [1 subject after administration of 0.6 U/kg of IDegAsp, 2 subjects after administration of 0.8 U/kg of IDegAsp, 1 subject after administration of 0.4 U/kg of BIAsp 30, 1 subject after administration of 0.6 U/kg of BIAsp 30, 1 subject after administration of 0.8 U/kg of BIAsp 30]). All these events were mild or moderate in severity, but 1 headache reported by 1 subject after administration of 0.8 U/kg of IDegAsp, 1 headache reported by 1 subject after administration of 0.6 U/kg of BIAsp 30, and 1 headache reported by 1 subject after administration of 0.8 U/kg of BIAsp 30 (all of which were moderate in severity and reported by the same subject) were classified as adverse drug reactions. One severe hypoglycaemic episode[25] was reported by 1 subject after administration of 0.4 U/kg of IDegAsp. Sixteen confirmed hypoglycaemic episodes[26] were reported by 13 subjects after administration of 0.4 U/kg of IDegAsp, 9 episodes by 5 subjects after administration of 0.6 U/kg of IDegAsp, and 11 episodes by 8 subjects after administration of 0.8 U/kg of IDegAsp, while 5 confirmed hypoglycaemic episodes were reported by 5 subjects after administration of 0.4 U/kg of BIAsp 30, 7 episodes by 7 subjects after administration of 0.6 U/kg of BIAsp 30, and 11 episodes by 8 subjects after administration of 0.8 U/kg of BIAsp 30. Seven nocturnal confirmed hypoglycaemic episodes[27] were reported by 7 subjects after administration of 0.4 U/kg of IDegAsp, 4 episodes by 3 subjects after administration of 0.6 U/kg of IDegAsp, and 4 episodes by 4 subjects after administration of 0.8 U/kg of IDegAsp, while 2 nocturnal confirmed hypoglycaemic episodes were reported by 2 subjects after administration of 0.6 U/kg of BIAsp 30 and 6 episodes by 6 subjects after administration of 0.8 U/kg of BIAsp 30. No injection site reactions were reported. No deaths, SAEs, or AEs leading to withdrawal were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

4.(ii).A.(2).5) Single-dose trial with IDegAsp in non-Japanese subjects with T2DM (5.3.4.2.14, Trial 1978 [May 2010 to Nov. 2010], Reference data)

A randomized, double-blind,[23] incomplete block, four-period crossover trial was conducted to investigate the pharmacodynamic and pharmacokinetic properties, safety, and tolerability of a single dose of IDegAsp in non-Japanese subjects with T2DM[31] (Target sample size of 36).

For 4 out of 6 treatments (0.4, 0.6, and 0.8 U/kg of IDegAsp and 0.4, 0.6, and 0.8 U/kg of BIAsp 30), two dose levels each of IDegAsp and BIAsp 30 were selected, and a total of 4 injections were administered in the abdomen as a single subcutaneous dose. A 13- to 21-day washout period was included between treatments.

[31] Key inclusion criteria: subjects with T2DM treated with insulin (total daily insulin <1.2 U/kg/day) for ≥3 months, aged 18-70 (both inclusive), HbA1c ≤10.0%, BMI ≤35.0 kg/m^2, and fasting C-peptide <1.0 nmol/L

All 39 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set. Three subjects were withdrawn from the trial due to non-compliance with the protocol (1 subject) and consent withdrawal (2 subjects).

The pharmacokinetic parameters[24] of IAsp after a single subcutaneous administration of IDegAsp or BIAsp 30 and the pharmacokinetic parameters of IDeg after a single subcutaneous administration of IDegAsp are shown in Table 22 and Table 23, respectively.

Table 22. Pharmacokinetic parameters of IAsp after a single subcutaneous administration of IDegAsp or BIAsp 30

Parameter	IDegAsp			BIAsp 30		
	0.4 U/kg (n = 24)	0.6 U/kg (n = 25)	0.8 U/kg (n = 25)	0.4 U/kg (n = 24)	0.6 U/kg (n = 24)	0.8 U/kg (n = 24)
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	712 (47)	1141 (45)	1628 (20)	1669 (46)	2209 (48)	3041 (23)
$C_{max,SD}$ (pmol/L)	193 (42)	285 (41)	377 (30)	294 (45)	392 (45)	534 (31)
$t_{max,SD}$[a] (h)	1.3 (0.8-3.0)	1.7 (0.8-2.8)	1.7 (0.8-3.0)	2.2 (0.8-3.0)	2.3 (1.2-4.0)	2.1 (1.0-4.0)
Onset of $appearance_{,SD}$ (min)	18 (42)	21 (34)	16 (50)	15 (46)	15 (48)	11(51)

Geometric mean (CV%)

$AUC_{0\text{-}12h,\ SD}$: area under the serum concentration-time curve from 0 to 12 hours, $C_{max,\ SD}$: maximum observed serum concentration, $t_{max,\ SD}$: time to maximum observed serum concentration, Onset of $appearance_{,SD}$: time from trial product administration until the first time serum IAsp concentration is above 30 pmol/L

a) Median (min – max)

Table 23. Pharmacokinetic parameters of IDeg after a single subcutaneous administration of IDegAsp

Parameter	0.4 U/kg (n = 24)	0.6 U/kg (n = 25)	0.8 U/kg (n = 25)
$AUC_{0\text{-}\infty,SD}$ (pmol·h/L)	69,799 (23)	99,128 (20)	138,934 (20)
$AUC_{0\text{-}24h,SD}$ (pmol·h/L)	27,938 (29)	37,860 (33)	45,552 (27)
$C_{max,SD}$ (pmol/L)	1722 (31)	2403 (34)	2854 (25)
$t_{max,SD}$[a] (h)	13.0 (8.0-20.0)	15.0 (11.0-36.0)	15.0 (11.0-20.0)
$t_{1/2,SD}$[b] (h)	16.8 (51)	17.7 (32)	21.8 (36)

Geometric mean (CV%)

$AUC_{0\text{-}\infty,\ SD}$: area under the serum concentration-time curve from zero extrapolated to infinity, $AUC_{0\text{-}24h,\ SD}$: area under the serum concentration-time curve from 0 to 24 hours, $C_{max,\ SD}$: maximum observed serum concentration, $t_{max,\ SD}$: time to maximum observed serum concentration, $t_{½,\ SD}$: elimination half-life

a) Median (min – max)

b) Harmonic mean (CV%)

The pharmacodynamic parameters after a single subcutaneous administration of IDegAsp or BIAsp 30 are shown in Table 24.

Table 24. Pharmacodynamic parameters after a single subcutaneous administration of IDegAsp or BIAsp 30

Parameter	IDegAsp			BIAsp 30		
	0.4 U/kg (n = 23)	0.6 U/kg (n = 24)	0.8 U/kg (n = 25)	0.4 U/kg (n = 23)	0.6 U/kg (n = 23)	0.8 U/kg (n = 24)
$AUC_{GIR,0-24h,SD}$ (mg/kg)	423 (74)	1082 (53)	1318 (53)	956 (60)	1775 (39)	2191 (44)
$GIR_{max,SD}$ (mg/kg/min)	1.4 (55)	2.6 (43)	2.9 (57)	2.4 (55)	4.0 (39)	4.4 (43)
$tGIR_{max,SD}$ [a)] (h)	2.8 (0.3-5.3)	3.3 (1.9-5.0)	3.3 (1.5-26)	3.3 (1.9-5.3)	3.3 (1.9-6.1)	3.5 (1.9-5.3)
Onset of $action_{,SD}$ (min)	64 (67)	66 (34)	52 (55)	58 (46)	47 (43)	34 (49)

Geometric mean (CV%)

$AUC_{GIR,0-24h,SD}$: area under the GIR curve from 0 to 24 hours, $GIR_{max,SD}$: maximum GIR, $tGIR_{max,SD}$: time to maximum GIR, Onset of $action_{,SD}$: time from trial product administration until the blood glucose concentration decreases at least 5 mg/dL from baseline

a) Median (min – max)

Regarding safety, adverse events were reported by 20 out of 39 subjects (14 out of 39 subjects after administration of IDegAsp, 11 out of 37 subjects after administration of BIAsp 30). Adverse events reported by at least 3 subjects were headache only (10 subjects [5 subjects after administration of 0.6 U/kg of IDegAsp, 2 subjects after administration of 0.8 U/kg of IDegAsp, 3 subjects after administration of 0.4 U/kg of BIAsp 30, 1 subject after administration of 0.6 U/kg of BIAsp 30, 3 subjects after administration of 0.8 U/kg of BIAsp 30]). All these events were mild or moderate in severity and their causal relationship to trial product was denied. No severe hypoglycaemic episodes[25] were reported. One confirmed hypoglycaemic episode[26] was reported by 1 subject after administration of 0.4 U/kg of IDegAsp. One nocturnal confirmed hypoglycaemic episode[32] was reported by 1 subject after administration of 0.4 U/kg of IDegAsp. No injection site reactions were reported. No deaths, SAEs, or AEs leading to withdrawal were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

4.(ii).A.(2).6) Single-dose trial with IDegAsp in non-Japanese subjects with T1DM (younger adult and geriatric subjects) (5.3.3.3.1, Trial 1981 [Aug. 2010 to Nov. 2010], Reference data)

A randomized, double-blind,[23] two-period crossover trial was conducted to investigate the pharmacodynamic and pharmacokinetic properties, safety, and tolerability of a single dose of IDegAsp in non-Japanese younger adult and geriatric subjects with T1DM[33] (target sample size of 24 [12 younger adult subjects and 12 geriatric subjects]).

A single dose of 0.5 U/kg of IDegAsp or BIAsp 30 was subcutaneously administered in the thigh. A 7- to 21-day washout period was included between treatments.

[32] Hypoglycaemic episodes (severe hypoglycaemia as well as episodes with plasma glucose of <56 mg/dL with or without symptoms) occurring between 00:01 and 05:59 (both inclusive)

[33] Key inclusion criteria: geriatric (≥65 years) or younger adult (18-35 years) subjects with T1DM treated with insulin (basal insulin ≥0.2 U/kg/day, total daily insulin <1.2 U/kg/day) for ≥12 months, HbA1c ≤10.0%, BMI 18.0-28.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

All 28 exposed subjects (13 younger adult subjects, 15 geriatric subjects) were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set.

Pharmacokinetic analysis[34] showed that the estimated geometric mean ratios of geriatrics to younger adults (geriatrics/younger adults) with their 95% confidence intervals for the $AUC_{0\text{-}12h,\ SD}$ and $C_{max,SD}$ of IAsp were 1.27 [0.97, 1.65] and 1.39 [0.98, 1.96], respectively, while the estimated geometric mean ratios of geriatrics to younger adults (geriatrics/younger adults) with their 95% confidence intervals for the $AUC_{0\text{-}120h,\ SD}$ and $C_{max,SD}$ of IDeg were 1.12 [0.89, 1.40] and 1.24 [0.97, 1.59], respectively.

As for IAsp, $t_{max,SD}$ (median [min-max]) was 1.3 (0.7-3.0) and 1.2 (0.7-2.3) hours in younger adult and geriatric subjects, respectively, and onset of $appearance_{,SD}$, i.e. time from trial product administration until the first time serum IAsp concentration is above 30 pmol/L, was 13 (35) and 13 (46) minutes, respectively. The $t_{max,SD}$ of IDeg was 14 (7-18) and 13 (9-18) hours, respectively.

The pharmacodynamic parameters after a single subcutaneous administration of IDegAsp in younger adult and geriatric subjects are shown in Table 25.

Table 25. Pharmacodynamic parameters after a single subcutaneous administration of IDegAsp in younger adult and geriatric subjects

Parameter	Younger Adults (n = 13)	Geriatrics (n = 15)
$AUC_{GIR,0\text{-}6h,SD}$ (mg/kg)	1001 (25)	909 (45)
$AUC_{GIR,\ 0\text{-}24h,SD}$ (mg/kg)	1786 (28)	1794 (62)
$GIR_{max,SD}$ (mg/kg/min)	4.4 (30)	3.9 (53)
$tGIR_{max,SD}$ [a)] (h)	2.3 (1.5-4.1)	2.8 (1.9-4.5)
Onset of $action_{,SD}$ (min)	20 (66)	23 (55)

Geometric mean (CV%)

$AUC_{GIR,0\text{-}6h,\ SD}$: area under the GIR curve from 0 to 6 hours, $AUC_{GIR,0\text{-}24h,\ SD}$: area under the GIR curve from 0 to 24 hours, $GIR_{max,\ SD}$: maximum GIR, $tGIR_{max,\ SD}$: time to maximum GIR, Onset of $action_{,SD}$: time from trial product administration until the blood glucose concentration decreases at least 5 mg/dL from baseline

[a)] Median (min-max)

The estimated geometric mean ratio of geriatrics to younger adults (geriatrics/ younger adults) with its 95% confidence interval for $AUC_{GIR,0\text{-}24h,SD}$ was 1.01 [0.69, 1.47].

Regarding safety, adverse events were reported by 9 out of 28 subjects (5 subjects after administration of IDegAsp, 4 subjects after administration of BIAsp 30). Adverse events reported by at least 2 subjects were headache (6 subjects [2 younger adult subjects after administration of IDegAsp, 1 geriatric subject after administration of IDegAsp, 2 younger adult subjects after administration of BIAsp 30, 1 geriatric subject after administration of BIAsp 30]) and nasopharyngitis (2 subjects [1 younger adult subject after administration of IDegAsp, 1 younger adult subject after administration of BIAsp 30]). All these events were mild in severity and their causal relationship to trial product was denied. No severe hypoglycaemic

[34] Calculated excluding 1 subject with outliers for serum IAsp and IDeg concentrations

episodes[25] were reported. Thirty-four confirmed hypoglycaemic episodes[26] were reported by 17 subjects after administration of IDegAsp (15 episodes by 8 younger adult subjects, 19 episodes by 9 geriatric subjects) while 21 confirmed hypoglycaemic episodes were reported by 11 subjects after administration of BIAsp 30 (5 episodes by 5 younger adult subjects, 16 episodes by 6 geriatric subjects). Four nocturnal confirmed hypoglycaemic episodes[32] were reported by 4 subjects after administration of IDegAsp (1 episode by 1 younger adult subject, 3 episodes by 3 geriatric subjects) while 2 nocturnal confirmed hypoglycaemic episodes were reported by 2 subjects after administration of BIAsp 30 (1 episode by 1 younger adult subject, 1 episode by 1 geriatric subject). No injection site reactions were reported. No deaths or SAEs were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

4.(ii).A.(2).7) Single-dose trial with IDegAsp in non-Japanese subjects with T1DM (children, adolescents, adults) (5.3.3.3.2, Trial 1982 [Jun. 2010 to Nov. 2010], Reference data)

An open-label, parallel-group trial was conducted to investigate the pharmacokinetic and pharmacodynamic properties, safety, and tolerability of a single dose of IDegAsp in non-Japanese children, adolescents, and adults with T1DM[35] (target sample size of 36).

A single dose of 0.5 U/kg of IDegAsp was subcutaneously administered in the abdomen.

All 38 exposed subjects (12 children, 13 adolescents, 13 adults) were included in the pharmacokinetic and pharmacodynamic analysis set and safety analysis set.

Pharmacokinetic analysis showed that the estimated geometric mean ratios between children and adults (children/adults) with their 95% confidence intervals for the $AUC_{0\text{-}12h,\ SD}$ and $C_{max,SD}$ of IAsp were 1.69 [1.02, 2.80] and 1.66 [1.10, 2.51], respectively, while those between adolescents and adults (adolescents/adults) were 1.14 [0.76, 1.69] and 1.16 [0.84, 1.61], respectively. The estimated geometric mean ratios of children to adults (children/adults) with their 95% confidence intervals for the $AUC_{0\text{-}\infty,\ SD}$ and $C_{max,SD}$ of IDeg were 1.42 [0.94, 2.16] and 1.38 [1.09, 1.76], respectively, while those of adolescents to adults (adolescents/adults) were 1.23 [0.96, 1.58] and 1.16 [0.95, 1.42], respectively.

As for IAsp, $t_{max,SD}$ (median [min-max]) was 1.3 (0.8-2.0), 1.2 (0.7-1.8), and 1.0 (0.5-2.0) hours in children, adolescents, and adults, respectively, and onset of appearance$_{,SD}$ was 8 (50), 13 (34), and 12 (41) minutes, respectively. The $t_{max,SD}$ of IDeg was 9.9 (8.9-18.1), 11.0 (8.9-13.2), and 9.0 (7.1-18.0) hours, respectively.

The pharmacodynamic parameters after a single subcutaneous administration of IDegAsp in children, adolescents, and adults are shown in Table 26.

[35] Key inclusion criteria: subjects with T1DM treated with insulin (total daily insulin 0.6-1.2 U/kg/day) for ≥12 months, HbA1c ≤10.0%, and BMI for children (6-11 years) and adolescents (12-17 years) between the 3rd and 97th BMI percentile and BMI for adults (18-65 years) ≤30.0 kg/m^2

Table 26. Pharmacodynamic parameters after a single subcutaneous administration of IDegAsp

Parameter	Children (n = 12)	Adolescents (n = 13)	Adults (n = 13)
$AUC_{PG\ baseline,0\text{-}6h,std,meal,SD}$ [a)] (mg·min/dL)	33,625 (22453)	31,102 (15,335)	29,102 (22,038)
Delta $PG_{max,meal,SD}$ (mg/dL)	221.6 (22)	191.0 (25)	167.6 (35)
$PG_{max,meal,SD}$ (mg/dL)	340.6 (15)	317.2 (16)	290.1 (20)

Geometric mean (CV%)

$AUC_{PG\ baseline,0\text{-}6h,std,meal,SD}$: area under the plasma glucose concentration curve above baseline from 0 to 6 hours following trial product administration and standard meal ingestion,

Delta $PG_{max,meal,SD}$: difference between maximum plasma glucose concentration following trial product administration and standard meal ingestion and baseline value, $PG_{max,meal,SD}$: maximum plasma glucose concentration following trial product administration and standard meal ingestion

[a)] Mean (SD)

Regarding safety, adverse events were reported by 10 out of 38 subjects. Adverse events reported by at least 2 subjects were nasopharyngitis (4 subjects [1 child, 1 adolescent, 2 adults]) and headache (2 subjects [2 adults]) and a causal relationship to trial product was denied for all events. One SAE was reported by 1 child (nasopharyngitis, moderate) and classified as an adverse drug reaction. No severe hypoglycaemic episodes[25] were reported. Forty-four confirmed hypoglycaemic episodes[26] were reported by 19 subjects (20 episodes by 6 children, 6 episodes by 5 adolescents, 18 episodes by 8 adults). Seven nocturnal confirmed hypoglycaemic episodes[27] were reported by 7 subjects (3 episodes by 3 children, 4 episodes by 4 adults). One injection site reaction was reported by 1 adult (injection site haematoma, mild). No deaths or AEs leading to withdrawal were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

IDeg trials

4.(ii).A.(1) Multiple-dose trial with IDeg in Japanese subjects with T1DM (5.3.4.2.2, Trial 1996 [Jun. 2010 to Oct. 2010])

A randomized, double-blind,[23] two-period crossover trial was conducted to investigate the pharmacodynamic and pharmacokinetic properties, safety, and tolerability of multiple subcutaneous doses of IDeg compared to insulin detemir (IDet) in Japanese subjects with T1DM[36] (target sample size of 20).

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

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

[36] Key inclusion criteria: subjects with T1DM treated with insulin (basal insulin ≥0.3 U/kg/day) for ≥12 months, aged 20-65 (both inclusive), HbA1c (JDS) ≤10.0%, BMI 18.0-28.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

The pharmacokinetic parameters after 6 days of once-daily subcutaneous administration of 0.4 U/kg of IDeg (IDeg (M): the proposed commercial formulation) or IDet are shown in Table 27.

Table 27. Pharmacokinetic parameters after 6 days of once-daily subcutaneous administration of 0.4 U/kg of IDeg or IDet

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)
$t_{½,SS}$ [b)] (h)	18.3 (34.3)	6.3 (44.7)

Geometric mean (CV%)
$AUC_{\tau,SS}$: area under the serum concentration-time curve during one dosing interval at steady state, $C_{max,SS}$: maximum observed serum concentration at steady state, $t_{max,SS}$: time to maximum observed serum concentration at steady state, $t_{½,SS}$: 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 ratios of the exposure from 0 to 12 hours after dosing ($AUC_{0–12h,SS}$) to the exposure during one dosing interval (24 hours) ($AUC_{\tau,SS}$) for IDeg and IDet ($AUC_{0–12h,SS}/AUC_{\tau,SS}$) (CV%) were 0.53 (5.8) and 0.65 (12.5), respectively.

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

The pharmacodynamic parameters after 6 days of once-daily subcutaneous administration of 0.4 U/kg of IDeg or IDet are shown in Table 28.

Table 28. Pharmacodynamic parameters after 6 days of once-daily subcutaneous administration of 0.4 U/kg of IDeg or IDet

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 one 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 ($AUC_{GIR,0–12h,SS}$) to glucose-lowering effect during one dosing interval (24 hours) ($AUC_{GIR,\tau,SS}$) for IDeg and IDet ($AUC_{GIR,0–12h,SS}/AUC_{GIR,\tau,SS}$) (CV%) were 0.48 (29.9) and 0.66 (27.7), respectively.

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

As to the duration of action,[37] blood glucose did not exceed 8.3 mmol/L (150 mg/dL) within the 26-hour clamp period for any subjects dosed with IDeg.

Regarding safety, adverse events were reported by 4 out of 22 subjects (3 subjects after administration of IDeg [vomiting by 1 subject, oedema peripheral by 1 subject, tendon rupture by 1 subject], 1 subject after administration of IDet [nasopharyngitis]). All these events were mild in severity and their causal relationship to trial product was denied. No severe hypoglycaemic episodes[25] were reported. Ninety-three confirmed hypoglycaemic episodes[26] were reported by 13 subjects after administration of IDeg and 76 confirmed hypoglycaemic episodes by 15 subjects after administration of IDet while 16 nocturnal confirmed hypoglycaemic episodes[27] were reported by 6 subjects after administration of IDeg and 12 nocturnal confirmed hypoglycaemic episodes by 7 subjects after administration of IDet. No injection site reactions were reported. No deaths, SAEs, or AEs leading to withdrawal were reported. No clinically significant changes in vital signs, ECG, laboratory parameters, or physical examination were observed.

4.(ii).A.(2) Multiple-dose trial with IDeg in non-Japanese subjects with T1DM (5.3.4.2.8, Trial 1993 [May 2010 to Aug. 2010], Reference data)

A randomized, double-blind,[23] incomplete block, two-period crossover trial was conducted to investigate the pharmacodynamic and pharmacokinetic properties, safety, and tolerability of multiple doses of IDeg in non-Japanese subjects with T1DM[38] (target sample size of 60).

One of 3 dose levels (0.4, 0.6, or 0.8 U/kg) of IDeg or insulin glargine (IGlar) was subcutaneously administered in the thigh once daily for 8 days in one of the two dosing sequences (IDeg was administered first and then IGlar or vice versa). A 7- to 21-day washout period was included between treatments.

All 66 exposed subjects were included in the safety analysis set and the pharmacokinetic and pharmacodynamic analysis set. Two subjects were withdrawn from the trial due to SAEs (intraspinal abscess, gastrointestinal haemorrhage).

The pharmacokinetic parameters after 8 days of once-daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar are shown in Table 29.

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

[38] Key inclusion criteria: subjects with T1DM treated with insulin (<1.2 U/kg/day) for ≥12 months, aged 18-65 (both inclusive), HbA1c ≤10.0%, BMI 18.0-28.0 kg/m^2 (both inclusive), and fasting C-peptide <0.3 nmol/L

Table 29. Pharmacokinetic parameters after 8 days of once-daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar (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)
$t_{½,SS}$ [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 one dosing interval at steady state, $C_{max,SS}$: maximum observed serum concentration, $t_{max,SS}$: time to maximum observed serum concentration, $t_{½,SS}$: elimination half-life

a) Median (min – max)

b) Harmonic mean (CV%), Clamp periods (Not calculated for no clamp)

The pharmacodynamic parameters after 8 days of once-daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar are shown in Table 30.

Table 30. Pharmacodynamic parameters after 8 days of once-daily subcutaneous administration of 0.4, 0.6, or 0.8 U/kg of IDeg or IGlar

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 one 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)

As to the duration of action of IDeg,[37] no subject had a blood glucose level exceeding 8.3 mmol/L (150 mg/dL) within the 42-hour clamp period at the 0.6 and 0.8 U/kg dose levels, but 3 subjects[39] did at the 0.4 U/kg dose level.

Regarding safety, adverse events were reported by 15 out of 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, 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 of 0.6 U/kg of IGlar, 1 subject after administration of 0.8 U/kg of IGlar]). All of these events were mild or moderate in severity. All these events except for phlebitis after administration of 0.6 U/kg of IGlar were considered as adverse drug reactions. SAEs were reported by 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).

[39] In the 3 subjects whose 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.

Both SAEs led to withdrawal, but their causal relationship to trial product was denied. Severe hypoglycaemia[25] was reported by 1 subject after administration of 0.4 U/kg of IGlar. Eighty-two confirmed hypoglycaemic episodes[26] were reported by 40 subjects after administration of IDeg (0.4, 0.6, and 0.8 U/kg) (24 episodes by 13 subjects, 26 episodes by 13 subjects, and 32 episodes by 14 subjects, respectively) and 102 confirmed hypoglycaemic episodes by 40 subjects after administration of IGlar (16 episodes by 7 subjects, 41 episodes by 15 subjects, and 45 episodes by 18 subjects, respectively) while 17 nocturnal confirmed hypoglycaemic episodes[32] were reported by 13 subjects after administration of IDeg (6 episodes by 5 subjects, 5 episodes by 3 subjects, and 6 episodes by 5 subjects, respectively) and 25 nocturnal confirmed hypoglycaemic episodes by 16 subjects after administration of IGlar (2 episodes by 2 subjects, 11 episodes by 8 subjects, and 12 episodes by 6 subjects, respectively). No injection site reactions were reported. No deaths were reported. No clinically significant changes in laboratory parameters, vital signs, or ECG were observed.

4.(ii).A.(3) PPK analysis of data from IDeg phase III multinational trial in subjects with T2DM (Trial 3586)

Using the plasma IDeg concentration data (690 sampling points), a PPK analysis was performed using a non-linear mixed-effects modelling approach (software, NONMEM7.1.2). The base model was a one-compartment model. The analysis set consisted of 259 subjects (119 males and 140 females [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 (min-max) was 65.3 kg (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 (age, body weight, BMI, country, sex) on CL/F was investigated using a step-wise method, and 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 of 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 (each Asian country/Japan) are as shown in Table 31.

Table 31. CL/F and dose-normalized AUC ratios
(T2DM subjects in each Asian country/T2DM subjects in Japan)

	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% confidence interval

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

4.(ii).B.(1) Similarity in pharmacokinetic and pharmacodynamic properties between Japanese and non-Japanese populations with T1DM or T2DM

PMDA asked the applicant to explain the similarity in pharmacokinetic and pharmacodynamic properties between Japanese and non-Japanese populations with T1DM or T2DM.

The applicant responded as follows:

The pharmacokinetic parameters of IAsp after a single subcutaneous administration of 0.5 U/kg of IDegAsp were similar between Japanese (Trial 1983) and non-Japanese subjects (Trial 3857) with T1DM (Table 32).

Table 32. Comparison of pharmacokinetic parameters of IAsp after single subcutaneous administration of 0.5 U/kg of IDegAsp between Japanese and non-Japanese subjects with T1DM

Parameter	Japanese subjects with T1DM (n = 21)	Non-Japanese subjects with T1DM (n = 27)
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	813 (53)	833 (33)
$C_{max,SD}$ (pmol/L)	280 (49)	252 (30)
$t_{max,SD}$ [a)] (h)	1.2 (0.5-2.8)	1.3 (0.5-2.8)

Geometric mean (CV%)

$AUC_{0\text{-}12h,SD}$: area under the serum concentration-time curve from zero to 12 hours, $C_{max,SD}$: maximum observed serum concentration, $t_{max,SD}$: time to maximum observed serum concentration

a) Median (min – max)

The mean 12-hour IAsp serum concentration-time profiles after a single-dose administration of IDegAsp in Japanese and non-Japanese subjects with T1DM are shown in Figure 1. The onset of appearance for IAsp after a single-dose administration of IDegAsp was 10 minutes and 14 to 17 minutes (geometric mean) in Japanese and non-Japanese subjects, respectively. The half-life ($t_{1/2}$) of IAsp after a single-dose administration of IDegAsp was similar between Japanese and non-Japanese subjects, i.e. 1.3 hours and 1.2 to 1.4 hours (harmonic mean), respectively.

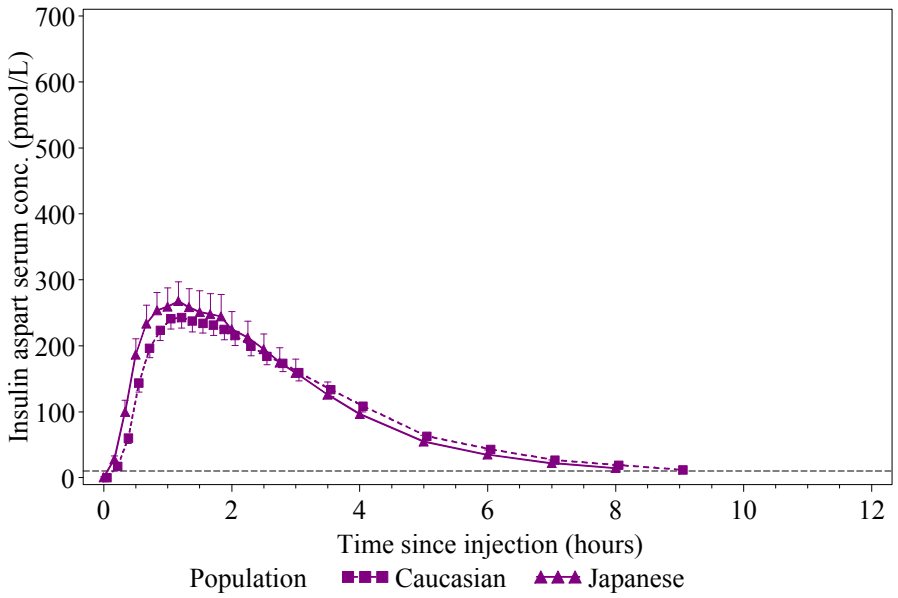

Figure 1. Mean 12-Hour IAsp serum concentration-time profiles after single dose of IDegAsp in Japanese and non-Japanese subjects with T1DM

Based on the above results, it is considered that the pharmacokinetic properties of IAsp in IDegAsp are similar between Japanese and non-Japanese populations with T1DM.

Concerning the similarity in the pharmacokinetic properties of IDeg, the pharmacokinetic profile of IDeg was not affected by co-formulation with IAsp in Trial 3857. The application contains the single-dose pharmacokinetic data of IDeg after administration of IDegAsp in patients. Since the half-life of IDeg is long, the steady-state pharmacokinetics of IDeg were determined. The mean steady-state 24-hour IDeg serum concentration-time profiles after multiple-dose administration of IDeg were similar between Japanese (Trial 1996) and non-Japanese subjects (Trial 1993) with T1DM, as shown in Figure 2.

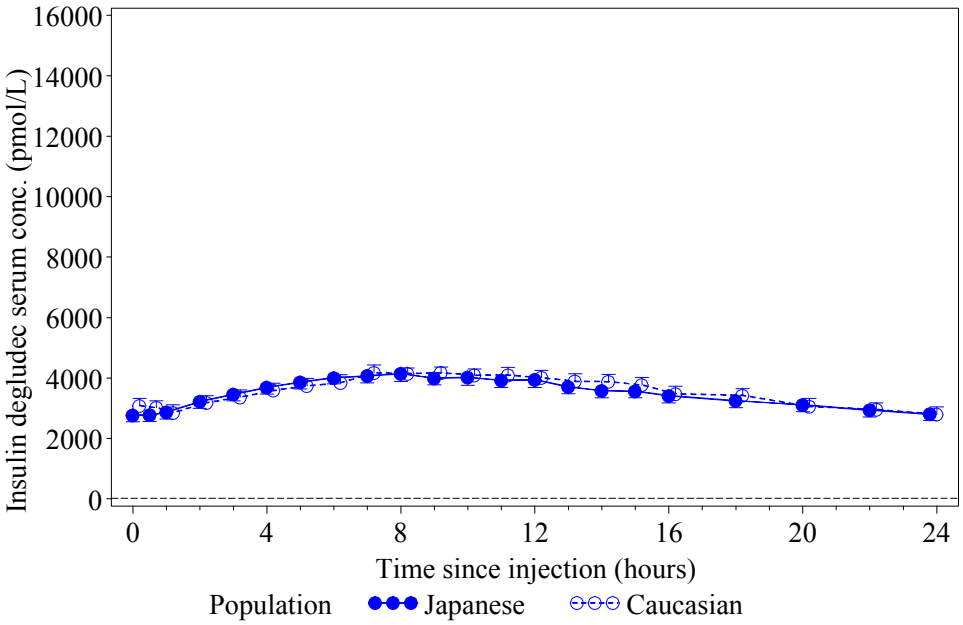

Figure 2. Mean steady-state 24-hour IDeg serum concentration-time profiles after multiple-dose administration of IDeg in Japanese and non-Japanese subjects with T1DM

The distribution of IDeg exposure during one dosing interval at steady state ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$[40]) after multiple-dose administration of IDeg was similar between Japanese and non-Japanese subjects with T1DM, i.e. 0.53 in both Japanese and non-Japanese subjects with T1DM.

Concerning the pharmacokinetic profile of twice-daily IDegAsp, it is considered that IAsp does not accumulate because IAsp has a rapid onset of action and is eliminated by approximately 8 hours after administration. Since IDeg has a long duration of action and the time to reach the steady state depends on its half-life, it is expected that IDeg steady state is reached after 2 to 3 days of twice-daily dosing with IDegAsp, as observed with multiple-dose administration of IDeg alone. Thus, at steady state, the exposure of the IDeg component in IDegAsp will reach the same level as long as the same total daily dose is given.

As to pharmacodynamic properties, the shape of the mean GIR profiles after a single dose of IDegAsp was similar between Japanese (Trial 1983) and non-Japanese subjects (Trial 3857) with T1DM. The time to the maximum glucose infusion rate ($tGIR_{max,SD}$, median [min–max]) was similar between Japanese and non-Japanese subjects, i.e. 2.3 (1.1-4.1) and 2.9 (1.8-5.0) hours, respectively. Furthermore, the geometric mean onset of $action_{,SD}$ (the time from trial product administration until the blood glucose concentration decreases at least 5 mg/dL from baseline) was also similar between Japanese and non-Japanese subjects,

[40] Parameters during clamp periods were used in order to compare between data in Trial 1996 and Trial 1993 under the same conditions.

i.e. 31 minutes at 0.5 U/kg in Japanese subjects (Trial 1983) and 32, 24, and 24 minutes at 0.4, 0.6, and 0.8 U/kg, respectively, in non-Japanese subjects (Trial 3539).

Based on the above results, the applicant considers that pharmacokinetic and pharmacodynamic properties are similar between Japanese and non-Japanese populations with T1DM.

The pharmacokinetic parameters of IAsp after a single-dose administration of IDegAsp were similar between non-Japanese subjects with T1DM (Trial 3539) and T2DM (Trial 1978), as shown in Table 33.

Table 33. Comparison of pharmacokinetic parameters of IAsp after single-dose administration of IDegAsp in non-Japanese subjects with T1DM and T2DM

Parameter	Dose (U/kg)	Non-Japanese subjects with T1DM	Non-Japanese subjects with T2DM
$AUC_{0\text{-}12h,SD}$ (pmol·h/L)	0.4	678 [610, 754] (n = 21)	712 [641, 792] (n = 24)
	0.6	1069 [961, 1189] (n = 20)	1136 [1023, 1261] (n = 25)
	0.8	1445 [1300, 1607] (n = 20)	1607 [1449, 1782] (n = 25)
$C_{max,SD}$ (pmol/L)	0.4	259 [232, 289] (n = 21)	192 [170, 217] (n = 24)
	0.6	346 [309, 386] (n = 20)	288 [255, 325] (n = 25)
	0.8	479 [429, 535] (n = 20)	377 [335, 425] (n = 25)

LS mean [95% CI]

$AUC_{0\text{-}12h,SD}$: area under the serum concentration-time curve from zero to 12 hours, $C_{max,SD}$: maximum observed serum concentration

The pharmacokinetic parameters after multiple-dose administration of IDeg were similar between non-Japanese subjects with T1DM (Trial 1993) and T2DM (Trial 1987[41]), as shown in Table 34. The distribution of IDeg exposure during the dosing interval at steady state ($AUC_{0\text{-}12h,SS}/AUC_{\tau,SS}$) was similar between non-Japanese subjects with T1DM and T2DM, i.e. 0.52 to 0.54 in both subjects with T1DM and T2DM.

Table 34. Comparison of pharmacokinetic parameters after multiple-dose administration of IDeg in non-Japanese subjects with T1DM and T2DM

Parameter	Dose (U/kg)	Non-Japanese subjects with T1DM [a)]	Non-Japanese subjects with T2DM
$AUC_{\tau,SS}$ (pmol·h/L)	0.4	82501 [72996, 93242] (n = 21)	91937 [4630, 99874] (n = 22)
	0.6	131195 [116082, 148277] (n = 21)	129371 [120208, 139233] (n = 37)
	0.8	158968 [141058, 179153] (n = 22)	176167 [161994, 191580] (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)

LS means [95% CI]

$AUC_{\tau,SS}$: area under the serum concentration-time curve during one dosing interval at steady state, $C_{max,SS}$: maximum observed serum concentration at steady state

a) Parameters during clamp periods are presented in order to compare between data in Trial 1993 and Trial 1987.

Furthermore, based on the results of a PPK analysis of data from Trial 3586 in subjects with T2DM, the dose-normalized AUC at steady state after multiple-dose administration of IDeg was similar within the

[41] A randomized, double-blind, incomplete block, two-period, crossover trial investigating the pharmacodynamic and pharmacokinetic properties and safety of multiple doses of IDeg in non-Japanese subjects with T2DM. Two of four treatments, 0.4, 0.6, and 0.8 U/kg of IDeg (100 U/mL) and 0.6 U/kg of IDeg (200 U/mL) were subcutaneously administered in the thigh once daily for 6 days in a randomly assigned sequence.

Asian region [see “IDeg trials 4.(ii).A.(3) PPK analysis of data from IDeg phase III multinational trial in subjects with T2DM (Trial 3586)”].

As to pharmacodynamic properties, the shape of the mean GIR profiles after a single dose of IDegAsp was similar between non-Japanese subjects with T1DM (Trial 3539) and T2DM (Trial 1978). $tGIR_{max,SD}$ (median [min–max]) was also similar between non-Japanese subjects with T1DM and T2DM, i.e. 2.3 (1.5-3.7) hours at 0.4 U/kg, 2.1 (1.5-3.7) hours at 0.6 U/kg, and 2.3 (1.9-4.9) hours at 0.8 U/kg in subjects with T1DM and 2.8 (0.3-5.3) hours at 0.4 U/kg, 3.3 (1.9-5.0) hours at 0.6 U/kg, and 3.3 (1.5-26.0) hours at 0.8 U/kg in subjects with T2DM.

Based on the above, the pharmacokinetic and pharmacodynamic properties of IDegAsp were similar between Japanese and non-Japanese subjects with T1DM, between non-Japanese subjects with T1DM and T2DM, and among subjects with T2DM within the Asian region including Japan. It is therefore considered that the pharmacokinetic and pharmacodynamic properties of IDegAsp are similar between Japanese and non-Japanese populations.

PMDA considers as follows:
The similarity in the pharmacokinetic properties of IAsp after administration of IDegAsp and the similarity in the pharmacodynamic properties of IDegAsp between Japanese subjects with T1DM and non-Japanese subjects with T1DM have been demonstrated. In addition, the similarity in the pharmacokinetic properties of IAsp after administration of IDegAsp and the similarity in the pharmacodynamic properties of IDegAsp between non-Japanese subjects with T1DM and those with T2DM have been demonstrated. Although the pharmacokinetic properties of IDeg after administration of IDegAsp have not been compared between Japan and overseas, Trial 3857 and Trial 1959 have suggested that the pharmacokinetic properties of IDeg are not affected by co-formulation with IAsp. Furthermore, the pharmacokinetic and pharmacodynamic properties after administration of IDeg have been shown to be similar between Japanese and non-Japanese subjects with T1DM and between non-Japanese subjects with T1DM and those with T2DM. A PPK analysis of data from Trial 3586 has revealed no differences in the pharmacokinetic properties of IDeg at steady state among the participating countries. Based on the above, there should be no major differences in the pharmacokinetic and pharmacodynamic properties of IDegAsp between Japanese and non-Japanese populations with T1DM or T2DM although the similarity in subjects with T2DM between Japan and overseas was indirectly explained.

PMDA accepted the applicant’s response.

4.(ii).B.(2) Comparison of pharmacokinetic and pharmacodynamic profiles between IDegAsp and IAsp alone

It was suggested that the pharmacokinetic profile of IAsp is affected by co-formulation with IDeg. PMDA asked the applicant to explain its impact.

The applicant responded as follows:

The AUC of IAsp was reduced after administration of IDegAsp (co-formulation) compared to IAsp alone. The relative bioavailability (BA) of IDegAsp compared to IAsp was 75% in Trial 3857 and 84% in Trial 1977.[42] Although the mechanism or reason for the relative BA of <100% is unknown, a similar trend has been observed also for currently marketed premixed biphasic insulin products containing soluble and protamine-crystallized insulin aspart (genetical recombination) or insulin lispro (genetical recombination) and it has been reported that the BA of IAsp or insulin lispro decreases with increasing proportion of protamine-crystallized Asp or insulin lispro (Heise T, et al., *Diabetes Technol Ther*, 2008;10(6):479-85, Heise T, et al., *Diabetes Care*, 1998;21(5):800-3). The BA of premixed biphasic insulin aspart was 98%, 94%, and 84% when the molar ratio of protamine-crystallized insulin aspart/soluble insulin aspart was 30:70, 50:50, and 70:30, respectively. The BA of premixed biphasic insulin lispro was 77%, 78%, and 58% when the molar ratio of protamine-crystallized insulin lispro/soluble insulin lispro was 25:75, 50:50, and 75:25, respectively. The impact of <100% relative BA of IDegAsp compared to IAsp alone on the pharmacodynamic properties of IDegAsp was assessed. In Trial 1959, there was no pharmacodynamic difference between the administration of 0.92 U/kg of IDegAsp 30 (B) and simultaneous separate injections of 0.64 U/kg of IDeg (E) and 0.28 U/kg of IAsp (Table 35).

Table 35. Comparison of pharmacodynamic parameters between administration of IDegAsp 30(B) and simultaneous separate injections of IDeg (E) and IAsp

Parameter	Ratio (IDegAsp/IDeg + IAsp)
$AUC_{GIR,0\text{-}6h,SD}$ (mg/kg)	0.97 [0.88, 1.06]
$AUC_{GIR,0\text{-}24h,SD}$ (mg/kg)	1.04 [0.94, 1.14]
$GIR_{max,SD}$ (mg/kg/min)	0.94 [0.86, 1.03]

Estimated geometric mean ratio with its 95% confidence interval

$AUC_{GIR,0\text{-}th,SD}$: area under the GIR curve from 0 to t hours, $GIR_{max,SD}$: maximum GIR

The shape of the mean GIR profiles was similar between administration of IDegAsp 30 (B) and separate simultaneous injections of IDeg (E) and IAsp. $tGIR_{max,SD}$ (median [mix-max]) was similar between administration of IDegAsp 30 (B) and separate simultaneous injections of IAsp and IDeg (E), i.e. 2.6 [2.1-4.0] and 2.2 [1.8-3.5] hours, respectively.

[42] A randomized, open-label, three-period crossover trial comparing the pharmacodynamic and pharmacokinetic properties and safety between IDegAsp and IDeg (M) alone and between IDegAsp and IAsp alone in non-Japanese subjects with T1DM. A single dose of 0.5 U/kg of trial product was administered in the abdomen.

Moreover, the pharmacodynamic parameters reflecting the early glucose-lowering effect of IAsp component in IDegAsp were compared between IDegAsp and IAsp alone in Trial 3857 (Table 36). For this comparison, these parameters were dose-normalized, taking into consideration the fact that IDegAsp contains 30% IAsp and that IDegAsp and IAsp were given in identical doses in Trial 3857. As a result, the early pharmacodynamic effect (dose-normalized glucose-lowering effect) of IAsp component in IDegAsp was not smaller than that of IAsp alone.

Table 36. Comparison of pharmacodynamic parameters between IDegAsp and IAsp (dose-normalized)

Parameter	Ratio (IDegAsp/IAsp)
$AUC_{GIR,0\text{-}2h,SD}$	1.23 [0.52, 2.89]
$GIR_{max,SD}$	1.45 [1.21, 1.75]

Estimated geometric mean ratio with its 95% confidence interval
$AUC_{GIR,0\text{-}2h}$: area under the GIR curve from 0 to 2hours, $GIR_{max,SD}$: maximum GIR

In conclusion, although the reason why the pharmacokinetic profile of IAsp is affected by co-formulation with IDeg remains unknown, there should be no clinically relevant problem as the pharmacodynamic parameters of IAsp are unaffected by co-formulation with IDeg.

PMDA accepted the response.

4.(iii) Summary of clinical efficacy and safety

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

As the evaluation data, the results from the following trials were submitted: three phase I IDegAsp trials (Trials 1788, 1790, and 1983), one phase II IDegAsp trial (Trial 3570), and two phase III IDegAsp trials (Trials 3597 and 3896), one phase I IDeg trial (Trial 1996), and one Phase III trial with IDeg plus IAsp (Trial 3585) and its extension trial (Trial 3725). The IDeg trials had already been evaluated for NDA for Tresiba. As the reference data, the results from a total of 54 foreign trials (27 phase I trials, 5 phase II trials, 22 Phase III trials) were submitted. HbA1c results are reported in NGSP units except for Trials 1983, 1996, and 3570.

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

See "4.(ii) Summary of clinical pharmacology studies" for overviews and safety results of two trials in Japanese healthy adult subjects (Trial 1788, Trial 1790) and two trials in Japanese T1DM patients (IDegAsp, Trial 1983; IDeg, Trial 1996).

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

Exploratory trial in T2DM patients (5.3.5.1.1, Trial 3570 [Jan. 2009 to Jun. 2009])

A randomized, open-label, parallel-group trial was conducted to investigate the safety of IDegAsp 30 (B) compared to BIAsp 30 on a twice-daily regimen in Japanese subjects with T2DM on insulin therapy[43] (target sample size of 60, 30 subjects per group).

The trial consisted of an observation period (3 weeks), a treatment period (6 weeks) in which IDegAsp 30 (B) or BIAsp 30 was administered, and a follow-up period (8-14 days). A dynamic allocation procedure was used to randomize patients. Patients were balanced with respect to the stratification factor of pre-trial insulin treatment ('premixed human insulin,' 'premixed insulin analogue [except BIAsp 30],' or 'long-acting insulin analogue [except insulin glargine]/intermediate-acting insulin'). Patients were randomized in a 1:1 ratio to IDegAsp 30 (B) or BIAsp 30.

IDegAsp 30 (B) or BIAsp 30 was subcutaneously administered in the abdominal region (where possible) twice daily immediately before breakfast and dinner for 6 weeks. The starting daily dose was the same as the subject's total daily insulin dose immediately prior to the start of treatment with trial product. About half the total daily insulin dose was given immediately before breakfast and the other half was given immediately before dinner at the discretion of the investigator. Then, doses were adjusted according to a titration algorithm (Table 37), based on self-measured plasma glucose (SMPG) values.

Table 37. Titration algorithm

Pre-breakfast and pre-dinner SMPG[a] (mg/dL)	Insulin dose adjustment[b]
<80 (or if at least one value measured during the week prior to a site visit/telephone contact is <80)	Decrease by 1 U or more
≥80 and <130	No adjustment
≥130 and <160	Increase by 1 U or more
≥160	Increase by 2 U or more

a) Mean SMPG values from at least two days during the week prior to site visits/telephone contacts

b) Pre-breakfast and pre-dinner insulin doses were adjusted based on the SMPG measured before dinner and breakfast, respectively.

Of the 66 randomized subjects (IDegAsp 30 (B) group, 33 subjects; BIAsp 30 group, 33 subjects), a total of 65 exposed subjects (IDegAsp 30 (B) group, 33 subjects; BIAsp 30 group, 32 subjects), excluding 1 subject (BIAsp 30 group) who received no dose of trial product, were included in the safety analysis set. Of those, 63 subjects (IDegAsp 30 (B) group, 32 subjects; BIAsp 30 group, 31 subjects), excluding 2 subjects withdrawn from the trial (1 subject in each group), were included in the full analysis set (FAS). The FAS was used for efficacy analysis. Two subjects were withdrawn from the trial after receiving trial

[43] Key inclusion criteria: subjects with T2DM, aged ≥20 years, having an HbA1c value (JDS) <10.0% and a BMI <30.0 kg/m^2 at the time of screening, who had been treated with insulin (long-acting insulin analogue [except insulin glargine], intermediate-acting insulin, or premixed insulin/premixed insulin analogue [except BIAsp 30] on a twice-daily regimen) for at least 12 weeks before screening (3 weeks [±7 days] before the start of treatment with trial product) without changing the type and dose regimen of insulin.

product (non-compliance with the protocol in the IDegAsp 30 (B) group, other reasons in the BIAsp 30 group).

Efficacy analysis showed that the change in fasting plasma glucose (FPG) from baseline to end-of-treatment (Week 6) (least squares mean ± standard error[44]) in the FAS was -23.6 ± 5.7 mg/dL in the IDegAsp 30 (B) group and 5.2 ± 6.1 mg/dL in the BIAsp 30 group and the treatment difference (IDegAsp 30 (B) minus BIAsp 30) with its 95% confidence interval was -28.8 [-43.7, -13.8] mg/dL.

Regarding safety, the incidence of adverse events[45] was 30.3% (10 of 33 subjects) in the IDegAsp 30 (B) group and 18.8% (6 of 32 subjects) in the BIAsp 30 group. The adverse events reported by at least 2 subjects in either treatment group were nasopharyngitis (IDegAsp 30 (B) group, 9.1% [3 of 33 subjects]; BIAsp 30 group, 9.4% [3 of 32 subjects]) and supraventricular extrasystoles (IDegAsp 30 (B) group, 6.1% [2 of 33 subjects]). Most of the events were mild in severity and the event reported by 1 subject of the IDegAsp 30 (B) group (thermal burn) was moderate in severity, but there were no severe events. Only the events of supraventricular extrasystoles occurring in 2 subjects of the IDegAsp 30 (B) group were classified as adverse drug reactions. A serious adverse event (thermal burn) was reported in 1 subject of the IDegAsp 30 (B) group, but its causal relationship to trial product was denied. Table 38 shows the occurrence of hypoglycaemia.

Table 38. Hypoglycaemia (Safety analysis set)

		IDegAsp 30 (B) (n = 33)			BIAsp 30 (n = 32)		
		Incidence % (Number of subjects with episodes)	Number of episodes	Incidence rate (number of episodes/PYE)	Incidence % (Number of subjects with episodes)	Number of episodes	Incidence rate (number of episodes/PYE)
Hypoglycaemia	All	57.6 (19)	69	17.10	68.8 (22)	102	25.89
	Major hypoglycaemia[b)]	0.0 (0)	0	0.00	0.0 (0)	0	0.00
	Minor hypoglycaemia[c)]	57.6 (19)	55	13.63	59.4 (19)	86	21.83
	Symptoms only[d)]	15.2 (5)	14	3.47	28.1 (9)	16	4.06
Nocturnal hypoglycaemia[a)]	All	15.2 (5)	5	1.24	12.5 (4)	8	2.03
	Major hypoglycaemia[b)]	0.0 (0)	0	0.00	0.0 (0)	0	0.00
	Minor hypoglycaemia[c)]	12.1 (4)	4	0.99	12.5 (4)	8	2.03
	Symptoms only[d)]	3.0 (1)	1	0.25	0.0 (0)	0	0.00

a) An episode occurring between 23:00 p.m. and 05:59 a.m.
b) An episode requiring assistance of another person
c) An episode where subject was able to treat himself/herself and had a SMPG value <56 mg/dL
d) An episode where subject was able to treat himself/herself and had a SMPG value ≥56 mg/dL

[44] Calculated using an ANOVA model with treatment and pre-trial insulin treatment as fixed effects and baseline FPG as a covariate.
[45] An event occurring on or after the first day of exposure to trial product and no later than 5 days after the last day of trial product administration.

No deaths or adverse events leading to withdrawal were reported and there were no clinically relevant findings in vital signs or ECG.

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

4.(iii).A.(3).1) Multinational trial in subjects with T2DM (5.3.5.1.2, Trial 3597 [Feb. 2010 to Dec. 2010])

A randomized, open-label, parallel-group trial was conducted to investigate the efficacy and safety of IDegAsp BID compared to BIAsp 30 BID in Japanese and Asian subjects[46] with T2DM[47] on insulin therapy (target sample size of 426).

The trial consisted of an observation period (approximately 1 week), a treatment period (26 weeks) in which IDegAsp or BIAsp 30 was administered, and a follow-up period (1 week) for insulin antibody measurements. The subjects were stratified according to previous insulin regimen and metformin treatment at screening. The randomization of the subjects was carried out in a 2:1 ratio (IDegAsp: BIAsp 30).

IDegAsp was subcutaneously administered twice daily immediately before breakfast and the main evening meal in the thigh, upper arm, or abdomen and BIAsp 30 was subcutaneously administered twice daily immediately before breakfast and the main evening meal either in the thigh or abdomen[48] for 26 weeks. The starting daily dose was the same as the subject's total daily insulin dose immediately prior to the start of treatment with trial product and in subjects transferred from a QD regimen, about half the total daily insulin dose was given immediately before breakfast and the other half was given immediately before evening meal at the discretion of the investigator. Then, doses were adjusted according to a titration guideline (Table 39), based on the mean pre-breakfast and pre-dinner SMPG values from the three days prior to site visits and telephone contacts. Subjects previously treated with metformin continued metformin treatment during the trial.

[46] South Korea, Malaysia, Taiwan, and Hong Kong

[47] Key inclusion criteria: T2DM patients aged at least 18 years (aged ≥20 years in Japan and Taiwan), diagnosed ≥6 months, having a BMI value ≤35.0 kg/m^2 and an HbA1c value ≥7.0% and ≤10.0%, who had been treated with OD or BID basal insulin (human insulin or insulin analogue) or OD or BID premixed insulin (human insulin, insulin analogue, or self-mixed insulin [except for Japan]) containing 20% to 40% of the fast- or rapid-acting component, with or without metformin, for at least 3 months prior to screening (1 week before the start of treatment with trial product)

[48] If convenient to subjects, the use of the upper arm (the deltoid region) or the gluteal region for injections was allowed.

Table 39. Titration guideline (Trial 3597)

Pre-breakfast and pre-dinner SMPG (mg/dL)	Insulin dose adjustment[a)]
<56 mg/dL	Decrease by 4 U[b)]
<70 mg/dL	Decrease by 2 U[c)]
<90 mg/dL	No adjustment
<126 mg/dL	Increase by 2 U
<144 mg/dL	Increase by 4 U
<162 mg/dL	Increase by 6 U
≥162 mg/dL	Increase by 8 U

a) Pre-breakfast and pre-dinner insulin doses were adjusted based on the SMPG measured before dinner and breakfast, respectively.
b) For an insulin dose of >45 U, a dose reduction of 10% was recommended.
c) For an insulin dose of >45 U, a dose reduction of 5% was recommended.

For antibody measurements, IDegAsp or BIAsp 30 was switched to premixed biphasic human insulin (a combination of 70% intermediate-acting and 30% short-acting human insulin) at least 24 hours after the last dose of IDegAsp or BIAsp 30. Premixed biphasic human insulin (the dose of premixed biphasic human insulin was 80% of the total daily insulin dose at the end of treatment) was subcutaneously administered twice daily (before breakfast and dinner) in divided doses for 1 week after the end of treatment with trial product.

Of the 424 randomized subjects (IDegAsp group, 282 subjects [118 Japanese subjects]; BIAsp 30 group, 142 subjects [60 Japanese subjects]), 422 subjects (IDegAsp group, 280 subjects [118 Japanese subjects]; BIAsp 30 group, 142 subjects [60 Japanese subjects]), excluding 2 subjects in the IDegAsp group due to screening failure, were included in the FAS. Of these, all 420 subjects exposed (IDegAsp group, 279 subjects [118 Japanese subjects]; BIAsp 30 group, 141 subjects [60 Japanese subjects]), excluding 2 subjects who were not exposed (1 subject in each group), were included in the safety analysis set. Efficacy analyses were based on the FAS.

The number of subjects who completed 26 weeks of treatment were 245 in the IDegAsp group (109 Japanese subjects) and 126 in the BIAsp 30 group (55 Japanese subjects). Fifty-three subjects were withdrawn from the trial (IDegAsp group, 37 subjects [9 Japanese subjects]; BIAsp 30 group, 16 subjects [5 Japanese subjects]). The reasons for withdrawal were as follows: adverse events for 14 subjects (IDegAsp group, 9 subjects [7 Japanese subjects]; BIAsp 30 group, 5 subjects [4 Japanese subjects]), ineffective therapy for 4 subjects (2 subjects in each group), non-compliance with the protocol for 4 subjects (IDegAsp group, 3 subjects; BIAsp 30 group, 1 subject), withdrawal criteria met for 13 subjects (IDegAsp group, 9 subjects; BIAsp 30 group, 4 subjects), and others for 18 subjects (IDegAsp group, 14 subjects [2 Japanese subjects]; BIAsp 30 group, 4 subjects [1 Japanese subject]).

The primary efficacy endpoint of the change in HbA1c (least squares mean ± standard error) from baseline (the start of treatment) to Week 26 in the FAS in the entire trial population was -1.39 ± 0.05%-points in the IDegAsp group and -1.44 ± 0.07%-points in the BIAsp 30 group. The estimated treatment difference with its 95% confidence interval was 0.05%-points [-0.10, 0.20]. The non-inferiority of IDegAsp to BIAsp 30 was confirmed, as the upper limit of the 95% confidence interval for the estimated treatment difference was below or equal to the pre-defined non-inferiority margin (0.4%). The estimated treatment difference with its 95% confidence interval in the Japanese subgroup was -0.13%-points [-0.31, 0.04] (Table 40).

Table 40. Change in HbA1c from baseline to Week 26 (Trial 3597 [26 weeks of treatment] FAS)

	Treatment group	Baseline	Week 26 (LOCF)	Change (LOCF)	LS mean change[a)]	Treatment difference [95% CI][a)]
Entire trial population	IDegAsp (n = 280)	8.45 (0.81)	7.07 (0.81)	-1.38 (0.88)	-1.39 ± 0.05	0.05 [-0.10, 0.20]
	BIAsp 30 (n = 142)	8.44 (0.87)	7.02 (0.80)	-1.42 (0.97)	-1.44 ± 0.07	
Japanese subgroup	IDegAsp (n = 118)	8.34 (0.76)	6.94 (0.60)	-1.40 (0.73)	-1.45 ± 0.06	-0.13 [-0.31, 0.04]
	BIAsp 30 (n = 60)	8.37 (0.76)	7.08 (0.69)	-1.29 (0.80)	-1.32 ± 0.08	

Unit: %, Mean (SD), LS mean ± SE

a) Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening (prior insulin therapy [basal insulin or others] and metformin treatment at screening), sex, and region (Japan or others: not included in the analysis of the Japanese subgroup) as fixed effects and age and baseline HbA1c as covariates.

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

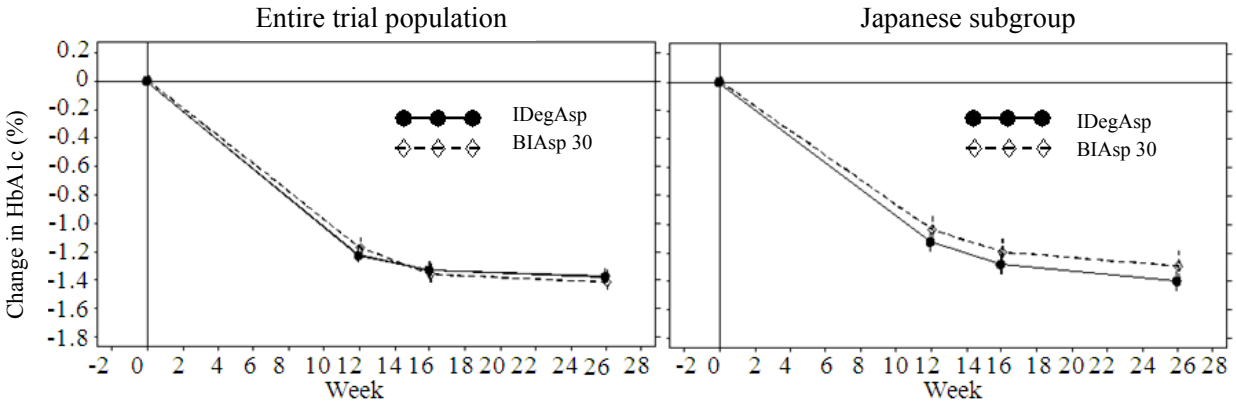

Figure 3. Change in HbA1c over time from baseline to Week 26 (Trial 3597, Entire trial population and Japanese subgroup, LOCF) (Mean ± SE)

The results of analyses of key secondary endpoints from baseline to Week 26 in the entire trial population and Japanese subgroup are shown in Tables 41 and 42, respectively.

Table 41. Results of analyses of key secondary endpoints (Trial 3597 [26 weeks of treatment] Entire trial population; FAS for the first 6 endpoints, safety analysis set for the last 4 endpoints)

Endpoints		IDegAsp (n = 280)	BIAsp 30 (n = 142)
FPG (mg/dL)	Baseline	143.1 ± 45.0 (n = 280)	142.8 ± 45.6 (n = 140)
	Change (LOCF)	-45.9 ± 46.5 (n = 280)	-26.6 ± 47.6 (n = 140)
Postprandial PG increment[a] (mg/dL)	Baseline	70.52 ± 47.21 (n = 273)	69.03 ± 46.88 (n = 141)
	Change (LOCF)	-16.22 ± 43.85 (n = 261)	-18.78 ± 48.79 (n = 133)
Proportion of subjects achieving HbA1c <7.0% at end of treatment (%) (LOCF)		48.2 (n = 135/280)	49.3 (n = 70/142)
Proportion of subjects achieving HbA1c ≤6.5% at end of treatment (%) (LOCF)		28.9 (n = 81/280)	27.5 (n = 39/142)
Proportion of subjects achieving HbA1c <7.0% at end of treatment without confirmed hypoglycaemic episodes[b] (%) (LOCF)		21.9 (n = 56/256)	13.2 (n = 17/129)
Proportion of subjects achieving HbA1c <7.0% at end of treatment without severe hypoglycaemic episodes[c] (%) (LOCF)		52.3 (n = 134/256)	53.5 (n = 69/129)
Body weight (kg)	Baseline	66.0 ± 11.2 (n = 279)	65.9 ± 11.2 (n = 141)
	Change (LOCF)	1.1 ± 2.9 (n = 279)	1.4 ± 3.0 (n = 141)
Pre-breakfast insulin dose (U/day)	Baseline (Week 1)	20 ± 12 (n = 275)	21 ± 13 (n = 140)
	Week 26 (LOCF)	34 ± 25 (n = 276)	38 ± 28 (n = 141)
Pre-dinner insulin dose (U/day)	Baseline (Week 1)	17 ± 10 (n = 275)	16 ± 11 (n = 140)
	Week 26 (LOCF)	21 ± 18 (n = 276)	30 ± 20 (n = 141)
Total insulin dose (U/day)	Baseline (Week 1)	37 ± 21 (n = 275)	37 ± 23 (n = 140)
	Week 26 (LOCF)	55 ± 40 (n = 276)	68 ± 46 (n = 141)

Mean ± SD

a) Postprandial PG increment for each meal was derived from the 9-point SMPG profile (measurements before and 90 minutes after start of breakfast, lunch, and evening meal, measurements at bedtime and at 4:00 a.m., measurement before breakfast the following day) as the difference between PG values 90 minutes after start of meal and before meal.

b) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of <56 mg/dL with or without symptoms

c) Severe hypoglycaemia: an episode requiring assistance of another person

Table 42. Results of analyses of key secondary endpoints (Trial 3597 [26 weeks of treatment] Japanese subgroup; FAS for the first 6 endpoints, safety analysis set for the last 4 endpoints)

Endpoints		IDegAsp (n = 118)	BIAsp 30 (n = 60)
FPG (mg/dL)	Baseline	146.6 ± 41.2 (n = 118)	150.8 ± 45.5 (n = 60)
	Change (LOCF)	-52.4 ± 41.9 (n = 118)	-29.0 ± 50.4 (n = 60)
Postprandial PG increment[a](mg/dL)	Baseline	84.41 ± 47.18 (n = 118)	82.73 ± 42.06 (n = 60)
	Change (LOCF)	-20.46 ± 45.30 (n = 116)	-23.68 ± 49.27 (n = 58)
Proportion of subjects achieving HbA1c <7.0% at end of treatment (%) (LOCF)		52.5 (n = 62/118)	48.3 (n = 29/60)
Proportion of subjects achieving HbA1c ≤6.5% at end of treatment (%) (LOCF)		29.7 (n = 35/118)	23.3 (n = 14/60)
Proportion of subjects achieving HbA1c <7.0% at end of treatment without confirmed hypoglycaemic episodes[b] (%) (LOCF)		21.2 (n = 24/113)	14.0 (n = 8/57)
Proportion of subjects achieving HbA1c <7.0% at end of treatment without severe hypoglycaemic episodes[c] (%) (LOCF)		54.9 (n = 62/113)	50.9 (n = 29/57)
Body weight (kg)	Baseline	64.3 ± 12.2 (n = 118)	63.9 ± 11.4 (n = 60)
	Change (LOCF)	1.3 ± 3.0 (n = 118)	1.4 ± 2.6 (n = 60)
Pre-breakfast insulin dose (U/day)	Baseline (Week 1)	14 ± 9 (n = 117)	13 ± 8 (n = 60)
	Week 26 (LOCF)	21 ± 15 (n = 117)	22 ± 14 (n = 60)
Pre-dinner insulin dose (U/day)	Baseline (Week 1)	13 ± 9 (n = 117)	10 ± 6 (n = 60)
	Week 26 (LOCF)	18 ± 16 (n = 117)	22 ± 13 (n = 60)
Total insulin dose (U/day)	Baseline (Week 1)	27 ± 17 (n = 117)	23 ± 14 (n = 60)
	Week 26 (LOCF)	39 ± 29 (n = 117)	44 ± 26 (n = 60)

Mean ± SD

a) Postprandial PG increment for each meal was derived from the 9-point SMPG profile (measurements before and 90 minutes after start of breakfast, lunch, and evening meal, measurements at bedtime and at 4:00 a.m., measurement before breakfast the following day) as the difference between PG values 90 minutes after start of meal and before meal.

b) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of <56 mg/dL with or without symptoms

c) Severe hypoglycaemia: an episode requiring assistance of another person

Regarding safety, the incidence of adverse events[49] in the entire trial population was 69.5% (194 of 279 subjects) in the IDegAsp group and 73.0% (103 of 141 subjects) in the BIAsp 30 group and the incidence of adverse drug reactions was 10.4% (29 of 279 subjects) in the IDegAsp group and 12.1% (17 of 141 subjects) in the BIAsp 30 group. The incidence of adverse events in the Japanese subgroup was 75.4% (89 of 118 subjects) in the IDegAsp group and 81.7% (49 of 60 subjects) in the BIAsp 30 group and the incidence of adverse drug reactions was 11.0% (13 of 118 subjects) in the IDegAsp group and 16.7% (10 of 60 subjects) in the BIAsp 30 group. Adverse events and/or adverse drug reactions reported in ≥2% of subjects in either treatment group in the entire trial population and the Japanese subgroup are shown in Tables 43 and 44, respectively.

[49] An adverse event that had an onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment

Table 43. Adverse events and/or adverse drug reactions reported in ≥2% of subjects in either treatment group (Trial 3597 [26 weeks of treatment] Entire trial population, safety analysis set)

Event	IDegAsp (n = 279)		BIAsp 30 (n = 141)	
	AE	Adverse drug reaction	AE	Adverse drug reaction
All AEs	69.5 (194)	10.4 (29)	73.0 (103)	12.1 (17)
Nasopharyngitis	18.3 (51)	0.0 (0)	13.5 (19)	0.0 (0)
Upper respiratory tract infection	7.5 (21)	0.4 (1)	8.5 (12)	0.0 (0)
Viral upper respiratory tract infection	0.0 (0)	0.0 (0)	2.1 (3)	0.0 (0)
Diabetic retinopathy	7.2 (20)	2.2 (6)	6.4 (9)	2.8 (4)
Cataract	1.8 (5)	0.0 (0)	2.1 (3)	0.0 (0)
Back pain	3.2 (9)	0.0 (0)	2.8 (4)	0.0 (0)
Arthralgia	2.2 (6)	0.0 (0)	3.5 (5)	0.0 (0)
Constipation	2.2 (6)	0.0 (0)	1.4 (2)	0.0 (0)
Gastritis	1.1 (3)	0.0 (0)	2.8 (4)	0.0 (0)
Diarrhoea	2.2 (6)	0.4 (1)	0.0 (0)	0.0 (0)
Nausea	0.4 (1)	0.0 (0)	2.1 (3)	0.0 (0)
Headache	3.2 (9)	0.7 (2)	2.8 (4)	0.0 (0)
Dizziness	1.8 (5)	0.0 (0)	2.1 (3)	0.0 (0)
Joint sprain	1.4 (4)	0.0 (0)	2.1 (3)	0.0 (0)
Oedema peripheral	1.4 (4)	0.0 (0)	2.8 (4)	0.7 (1)
Cough	2.9 (8)	0.0 (0)	4.3 (6)	0.0 (0)
Eczema	1.8 (5)	0.0 (0)	2.1 (3)	0.0 (0)
Weight increased	2.5 (7)	1.8 (5)	1.4 (2)	1.4 (2)
Hypertension	3.2 (9)	0.0 (0)	2.8 (4)	0.0 (0)

Incidence % (number of subjects with events), MedDRA/J (ver.13.1)

Table 44. Adverse events and/or adverse drug reactions reported in ≥2% of subjects in either treatment group (Trial 3597 [26 weeks of treatment] Japanese subgroup, safety analysis set)

Event	IDegAsp (n = 118)		BIAsp 30 (n = 60)	
	AE	Adverse drug reaction	AE	Adverse drug reaction
All AEs	75.4 (89)	11.0 (13)	81.7 (49)	16.7 (10)
Nasopharyngitis	26.3 (31)	0.0 (0)	25.0 (15)	0.0 (0)
Upper respiratory tract infection	2.5 (3)	0.0 (0)	3.3 (2)	0.0 (0)
Herpes zoster	0.8 (1)	0.0 (0)	3.3 (2)	0.0 (0)
Tinea pedis	0.8 (1)	0.8 (1)	3.3 (2)	0.0 (0)
Diabetic retinopathy	11.9 (14)	3.4 (4)	8.3 (5)	6.7 (4)
Conjunctivitis	2.5 (3)	0.8 (1)	1.7 (1)	0.0 (0)
Dry eye	0.0 (0)	0.0 (0)	3.3 (2)	0.0 (0)
Constipation	2.5 (3)	0.0 (0)	1.7 (1)	0.0 (0)
Back pain	3.4 (4)	0.0 (0)	6.7 (4)	0.0 (0)
Arthralgia	1.7 (2)	0.0 (0)	5.0 (3)	0.0 (0)
Muscle spasms	0.8 (1)	0.0 (0)	3.3 (2)	0.0 (0)
Tenosynovitis	0.0 (0)	0.0 (0)	3.3 (2)	0.0 (0)
Eczema	3.4 (4)	0.0 (0)	5.0 (3)	0.0 (0)
Arthropod sting	0.8 (1)	0.0 (0)	3.3 (2)	0.0 (0)
Heat illness	0.8 (1)	0.0 (0)	3.3 (2)	0.0 (0)
Weight increased	5.9 (7)	4.2 (5)	3.3 (2)	3.3 (2)
Blood pressure increased	0.8 (1)	0.0 (0)	3.3 (2)	0.0 (0)
Headache	3.4 (4)	0.0 (0)	3.3 (2)	0.0 (0)
Hypertension	6.8 (8)	0.0 (0)	5.0 (3)	0.0 (0)
Upper respiratory tract inflammation	2.5 (3)	0.0 (0)	1.7 (1)	0.0 (0)
Vertigo	2.5 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Oedema peripheral	0.8 (1)	0.0 (0)	5.0 (3)	1.7 (1)
Nephrolithiasis	0.0 (0)	0.0 (0)	3.3 (2)	1.7 (1)

Incidence % (number of subjects with events), MedDRA/J (ver.13.1)

One subject in the IDegAsp group died (interstitial lung disease). The subject was an 85-year-old Japanese female patient with T2DM. She was hospitalized due to dyspnea 104 days after the start of treatment with trial product and received steroid pulse therapy, but died 2 days later without receiving any further life support according to family wishes. No autopsy was performed. The subject had concurrent rheumatoid arthritis and had been treated with methotrexate. Since 20% of patients with rheumatoid arthritis have concurrent pleural disease and interstitial lung disease (King TE, *Harrison's Principles of Internal Medicine*, 18th ed., ed. by Longo DL, et al., New York: McGraw-Hill, 2011;2160-70) and it has been reported that methotrexate-induced lung disease, including acute or chronic interstitial pneumonitis, may occur acutely at any time during therapy (Methotrexate Sodium, Summary Basis of Approval, NDA 011719), its causal relationship to trial product was denied. The incidence of serious adverse events (including deaths) in the entire trial population was 8.2% (23 of 279 subjects, 27 events) in the IDegAsp group and 8.5% (12 of 141 subjects, 17 events) in the BIAsp 30 group and the events reported in at least 2 subjects of either treatment group were gastroenteritis (IDegAsp group, 0.7% [2 of 279 subjects, 2 events]), acute myocardial infarction (BIAsp 30 group, 1.4% [2 of 141 subjects, 2 events]), and hypoglycaemic unconsciousness (IDegAsp group, 0.7% [2 of 279 subjects, 2 events]; BIAsp 30 group, 0.7% (1 of 141 subjects, 1 event]). Two events of hypoglycaemic unconsciousness reported in 2 subjects

of the IDegAsp group and 1 hypoglycaemic unconsciousness in 1 subject of the BIAsp 30 group, as well as 2 events of hypoglycaemia in 1 subject of the IDegAsp group, were classified as adverse drug reactions. The incidence of serious adverse events in the Japanese subgroup was 5.9% (7 of 118 subjects [coronary artery stenosis, subcutaneous abscess, cellulitis, breast cancer, emphysema, interstitial lung disease, suicide attempt]) in the IDegAsp group and 5.0% (3 of 60 subjects [acute myocardial infarction, angina pectoris/nephrolithiasis, metastatic gastric cancer]) in the BIAsp 30 group and a causal relationship to trial product was denied for all events. The incidence of adverse events leading to withdrawal in the entire trial population was 3.2% (9 of 279 subjects [suicide attempt (Japanese subject), wrong drug administered in 2 subjects (Japanese subjects), emphysema (Japanese subject), subcutaneous abscess (Japanese subject), interstitial lung disease (Japanese subject, death), breast cancer (Japanese subject), carotid artery occlusion, headache]) in the IDegAsp group and 3.5% (5 of 141 subjects [ischaemic stroke, angina pectoris/nephrolithiasis (Japanese subject), acute myocardial infarction (Japanese subject), metastatic gastric cancer (Japanese subject), depression (Japanese subject)]) in the BIAsp 30 group. Among these events, only the headache in the IDegAsp group was classified as an adverse drug reaction.

The occurrence of hypoglycaemia in the Japanese subgroup and the entire trial population is shown in Table 45. The estimated incidence rate ratios (IDegAsp/BIAsp 30) for confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia with their 95% confidence intervals[50] were 1.00 [0.76, 1.32] and 0.67 [0.43, 1.06], respectively, in the entire trial population and 1.06 [0.69, 1.64] and 0.44 [0.20, 0.99], respectively, in the Japanese subgroup.

Table 45. Hypoglycaemia in the Japanese subgroup and the entire trial population (Trial 3597 [26 weeks of treatment] safety analysis set)

Endpoints	Japanese subgroup		Entire trial population	
	IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 279)	BIAsp 30 (n = 141)
Confirmed hypoglycaemia [a)]	74.6 (88)	68.3 (41)	73.5 (205)	75.9 (107)
	509 [907]	269 [947]	1227 [956]	621 [952]
Nocturnal confirmed hypoglycaemia [a) b)]	17.8 (21)	28.3 (17)	25.1 (70)	31.2 (44)
	43 [77]	46 [162]	143 [111]	101 [155]
Severe hypoglycaemia [c)]	0.0 (0)	0.0 (0)	1.4 (4)	1.4 (2)
	0 [0]	0 [0]	6 [5]	2 [3]
Nocturnal severe hypoglycaemia [b) c)]	0.0 (0)	0.0 (0)	0.4 (1)	0.0 (0)
	0 [0]	0 [0]	1 [1]	0 [0]

Upper column: incidence % (number of subjects with episodes), lower column: number of episodes [rate (number of episodes/100 PYE)]
a) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of less than 56 mg/dL with or without symptoms
b) Nocturnal hypoglycaemia: episodes occurring between 00:01 and 05:59 (both inclusive)
c) Severe hypoglycaemia: an episode requiring assistance of another person

There were no clinically relevant findings in vital signs, ECG, or fundoscopy/fundsphotography.

[50] The number of hypoglycaemic episodes was analysed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment emergent 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 effects and age as a covariate.

4.(iii).A.(3).2) Confirmatory trial in Japanese subjects with T2DM (5.3.5.1.3, Trial 3896 [Jan. 2011 to Sep. 2011])

A randomized, open-label, parallel-group trial was conducted to compare the efficacy and safety of once-daily IDegAsp or once-daily IGlar, with or without oral anti-diabetic drugs (OADs) in insulin-naïve Japanese subjects with T2DM[51] (target sample size of 268).

The trial consisted of an observation period (1 week), a treatment period (26 weeks) in which IDegAsp or IGlar was administered, and a follow-up period (1 week). The subjects were stratified according to prior anti-diabetic treatment ("sulfonylureas [SU] and/or fast-acting insulin secretagogues [glinides]" and "other OADs"). The randomization of the subjects was carried out in a 1:1 ratio (IDegAsp:IGlar).

IDegAsp was subcutaneously administered once daily immediately before the largest meal of the day in the thigh, upper arm, or abdomen for 26 weeks and IGlar was subcutaneously administered once daily before breakfast or at bedtime for 26 weeks according to the Japanese package insert. Insulin doses were adjusted to reach a target of 90 mg/dL, according to a titration guideline (Table 46), based on the mean pre-breakfast SMPG values from the three days prior to site visits and telephone contacts. The recommended starting dose was 10 U/day, but the dose adjustment was allowed at the discretion of the investigator. If subjects were on one or two OADs pre-trial, they were to continue with the OADs at unchanged doses unless a dose reduction was required for safety concerns. If subjects were on >2 OADs pre-trial, they were to continue with the 2 OADs allowed by the investigator and other OADs were to be discontinued at randomization. If SU, dipeptidyl-peptidase-4 (DPP-4) inhibitor, and/or glinide were used as pre-trial treatment, these drugs were to be discontinued at the start of treatment with trial product.

Table 46. Titration guideline (Trial 3896)

Pre-breakfast SMPG (mg/dL)	Insulin dose adjustment
<56	Decrease by 4U[a)]
<70	Decrease by 2U[b)]
<90	No adjustment
<126	Increase by 2U
<144	Increase by 4U
<162	Increase by 6U
≥162	Increase by 8U

a) For an insulin dose of >45 U, a dose reduction of 10% was recommended.
b) For an insulin dose of >45 U, a dose reduction of 5% was recommended.

All of the 296 randomized subjects (IDegAsp group, 147 subjects; IGlar group, 149 subjects) were included in the FAS and safety analysis set. The FAS was used for efficacy analyses. One hundred thirty-seven subjects in the IDegAsp group and 137 subjects in the IGlar group completed 26 weeks of treatment.

[51] Key inclusion criteria: insulin-naïve subjects with T2DM, aged ≥20 years, having diabetes duration ≥6 months, a BMI (kg/m^2) ≤35.0 kg/m^2, and HbA1c 7.0%–10.0% (both inclusive), who had been treated with one or more OAD(s) according to the Japanese product labelling (at recommended doses) for at least 12 weeks before screening (1 week before the start of treatment with trial product).

Twenty-two subjects (IDegAsp group, 10 subjects; IGlar group, 12 subjects) were withdrawn from the trial. The reasons for withdrawal were adverse events for 2 subjects (1 subject in each group), ineffective therapy for 3 subjects (all in the IGlar group), withdrawal criteria met for 2 subjects (1 subject in each group), and other reasons for 15 subjects (IDegAsp group, 8 subjects; IGlar group, 7 subjects).

The primary efficacy endpoint of the change in HbA1c from baseline (the start of treatment) to Week 26 in the FAS (least squares mean ± standard error) was -1.61 ± 0.08%-points in the IDegAsp group and –1.33 ± 0.08%-points in the IGlar group. The estimated treatment difference with its 95% confidence interval was -0.28%-points [-0.46, -0.10]. The non-inferiority of IDegAsp to IGlar was confirmed, as the upper limit of the 95% confidence interval for the estimated treatment difference was below or equal to the pre-defined non-inferiority margin (0.4%) (Table 47).

Table 47. Change in HbA1c from baseline to Week 26 (Trial 3896 [26 weeks of treatment] FAS)

Treatment group	Baseline	Week 26 (LOCF)	Change (LOCF)	LS mean change[a)]	Treatment difference [95% CI][a)]
IDegAsp (n =147)	8.31 (0.8)	6.96 (0.8)	-1.35 (0.86)	-1.61 ± 0.08	-0.28 [-0.46, -0.10]
IGlar (n = 149)	8.52 (0.8)	7.29 (0.9)	-1.22 (0.98)	-1.33 ± 0.08	

Unit: %, Mean (SD), LS mean ± SE

a) Calculated using an ANOVA model with treatment, anti-diabetic treatment at screening (“SU and/or glinides” and “other OADs”), and sex as fixed effects and age and baseline HbA1c as covariates.

Figure 4 shows the change in HbA1c over time from baseline to Week 26.

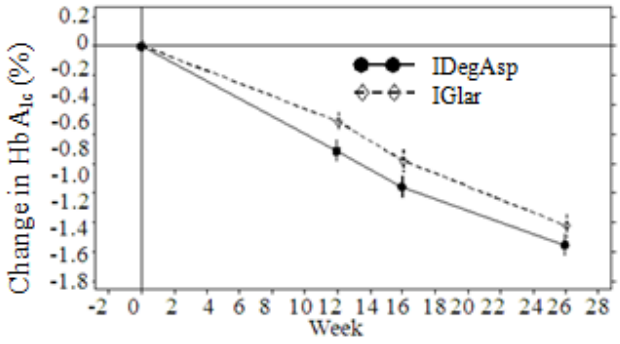

Figure 4. Change in HbA1c over time from baseline to Week 26 (Trial 3896, LOCF) (mean ± standard error)

Table 48 shows the results of analyses of key secondary endpoints from baseline to Week 26.

Table 48. Results of analyses of key secondary endpoints (Trial 3896 [26 weeks of treatment] FAS for the first 6 items, safety analysis set for the last 2 items)

Endpoints		IDegAsp (n = 147)	IGlar (n = 149)
FPG (mg/dL)	Baseline	161.41 ± 29.02 (n = 147)	163.67 ± 33.55 (n = 149)
	Change (LOCF)	-58.52 ± 43.62 (n = 147)	-63.43 ± 42.49 (n = 149)
Postprandial PG increment[a)] (mg/dL)	Baseline	77.03 ± 45.75 (n = 147)	83.79 ± 41.11 (n = 148)
	Change (LOCF)	-6.17 ± 49.15 (n = 147)	3.77 ± 46.49 (n = 148)
Postprandial PG increment at the main evening meal[b)] (mg/dL)	Baseline	79.99 ± 89.34 (n = 146)	85.98 ± 71.86 (n = 148)
	Change (LOCF)	-53.82 ± 108.95 (n = 146)	-0.42 ± 76.46 (n = 148)
Proportion of subjects achieving HbA1c <7.0% at end of treatment (%) (LOCF)		58.5 (n = 86/147)	40.3 (n = 60/149)
Proportion of subjects achieving HbA1c ≤6.5% at end of treatment (%) (LOCF)		33.3 (n = 49/147)	19.5 (n = 29/149)
Proportion of subjects achieving HbA1c <7.0% at end of treatment without confirmed hypoglycaemic episodes[c)] (%) (LOCF)		43.3 (n = 61/141)	25.0 (n = 35/140)
Body weight (kg)	Baseline	66.2 ± 13.4 (n = 147)	66.4 ± 13.3 (n = 149)
	Change (LOCF)	0.7 ± 2.8 (n = 147)	0.7 ± 2.2 (n = 149)
Insulin dose (U/day)	Baseline (Week 1)	8 ± 2 (n = 147)	9 ± 2 (n = 149)
	Week 26 (LOCF)	28 ± 15 (n = 147)	29 ± 16 (n = 149)

Mean ± SD

a) Postprandial PG increment for each meal was derived from the 9-point SMPG profile (measurements before and 90 minutes after start of breakfast, lunch, and evening meal, measurements at bedtime and at 4:00 a.m., measurement before breakfast the following day) as the difference between PG values 90 minutes after start of meal and before meal. Mean postprandial PG increment over all meals was derived as the mean of all available meal increments.

b) Postprandial PG increment at the main evening meal was derived as the difference between PG values 90 minutes after start of the main evening meal and before the main evening meal from the 9-point SMPG profile.

c) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of >56 mg/dL with or without symptoms

Regarding safety, the incidence of adverse events[49] was 70.7% (104 of 147 subjects) in the IDegAsp group and 76.5% (114 of 149 subjects) in the IGlar group and the incidence of adverse drug reactions was 9.5% (14 of 147 subjects) in the IDegAsp group and 18.8% (28 of 149 subjects) in the IGlar group. Table 49 shows adverse events and/or adverse drug reactions reported in ≥2% of subjects in either treatment group.

Table 49. Adverse events and/or adverse drug reactions reported in ≥2% of subjects in either treatment group (Trial 3896 [26 weeks of treatment] safety analysis set)

Event	IDegAsp (n = 147)		IGlar (n = 149)	
	AE	Adverse drug reaction	AE	Adverse drug reaction
All adverse events	70.7 (104)	9.5 (14)	76.5 (114)	18.8 (28)
Nasopharyngitis	22.4 (33)	0.0 (0)	25.5 (38)	0.7 (1)
Bronchitis	4.8 (7)	0.7 (1)	0.7 (1)	0.0 (0)
Pharyngitis	1.4 (2)	0.0 (0)	2.0 (3)	0.0 (0)
Upper respiratory tract infection	2.0 (3)	0.0 (0)	0.7 (1)	0.0 (0)
Otitis media	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Diabetic retinopathy	5.4 (8)	0.7 (1)	6.7 (10)	4.0 (6)
Cataract	3.4 (5)	0.7 (1)	4.7 (7)	0.7 (1)
Conjunctivitis	1.4 (2)	0.0 (0)	2.0 (3)	0.7 (1)
Glaucoma	2.0 (3)	0.0 (0)	0.0 (0)	0.0 (0)
Constipation	1.4 (2)	0.0 (0)	2.7 (4)	0.0 (0)
Nausea	0.7 (1)	0.0 (0)	2.7 (4)	0.0 (0)
Gastritis	2.0 (3)	0.0 (0)	1.3 (2)	0.0 (0)
Dental caries	2.7 (4)	0.0 (0)	0.0 (0)	0.0 (0)
Abdominal pain	0.0 (0)	0.0 (0)	2.0 (3)	0.0 (0)
Back pain	1.4 (2)	0.7 (1)	4.0 (6)	0.0 (0)
Tenosynovitis	2.7 (4)	0.0 (0)	2.0 (3)	0.0 (0)
Myalgia	2.7 (4)	0.0 (0)	1.3 (2)	0.7 (1)
Muscle spasms	2.0 (3)	0.7 (1)	2.0 (3)	0.0 (0)
Arthralgia	2.7 (4)	0.0 (0)	0.7 (1)	0.0 (0)
Spinal osteoarthritis	0.0 (0)	0.0 (0)	2.7 (4)	0.0 (0)
Headache	2.7 (4)	0.7 (1)	3.4 (5)	1.3 (2)
Diabetic neuropathy	0.0 (0)	0.0 (0)	3.4 (5)	1.3 (2)
Dizziness	0.7 (1)	0.7 (1)	2.0 (3)	1.3 (2)
Upper respiratory tract inflammation	2.7 (4)	0.0 (0)	1.3 (2)	0.0 (0)
Rhinitis allergic	0.7 (1)	0.0 (0)	2.7 (4)	0.0 (0)
Eczema	0.7 (1)	0.0 (0)	2.0 (3)	0.0 (0)
Contusion	1.4 (2)	0.0 (0)	2.7 (4)	0.0 (0)
Injection site reaction	0.0 (0)	0.0 (0)	2.0 (3)	1.3 (2)
Renal cyst	0.7 (1)	0.0 (0)	2.0 (3)	0.0 (0)
Blood pressure increased	0.0 (0)	0.0 (0)	2.0 (3)	0.0 (0)
Hypertension	1.4 (2)	0.0 (0)	2.0 (3)	0.7 (1)
Vertigo	0.0 (0)	0.0 (0)	2.0 (3)	0.7 (1)

Incidence % (number of subjects with events), MedDRA/J (ver.14.0)

No deaths were reported. The incidence of serious adverse events was 3.4% (5 of 147 subjects [cerebral infarction, inguinal hernia, pulmonary tuberculosis, cardiac failure, bladder cancer]) in the IDegAsp group and 2.0% (3 of 149 subjects [cerebral infarction, dizziness, osteitis condensans]) in the IGlar group. Among these events, only the cerebral infarction reported in the IGlar group was classified as an adverse drug reaction. Adverse events leading to withdrawal were cardiac failure reported in 1 subject of the IDegAsp group and injection site erythema reported in 1 subject of the IGlar group, and the injection site erythema was classified as an adverse drug reaction. Table 50 shows the occurrence of hypoglycaemia. The estimated rate ratios (IDegAsp/IGlar) for confirmed hypoglycaemia and nocturnal confirmed

hypoglycaemia with their 95% confidence intervals[50] were 0.73 [0.50, 1.08] and 0.75 [0.34, 1.64], respectively. No severe hypoglycaemic episodes were reported.

Table 50. Hypoglycaemia (Trial 3896 [26 weeks of treatment] safety analysis set)

Endpoints	IDegAsp (n = 147)	IGlar (n = 149)
Confirmed hypoglycaemia [a)]	44.2 (65)	44.3 (66)
	134 [191]	190 [271]
Nocturnal confirmed hypoglycaemia[a) b)]	8.2 (12)	16.1 (24)
	27 [39]	37 [53]

Upper column: incidence % (number of subjects with episodes), Lower column: number of episodes [rate (number of episodes/100 PYE)]
a) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of <56 mg/dL with or without symptoms
b) Nocturnal hypoglycaemia: episodes occurring between 00:01 and 05:59 (both inclusive)

There were no clinically relevant findings in vital signs, ECG, or fundoscopy/fundsphotography.

4.(iii).A.(3).3) Multinational trial with IDeg in combination with IAsp in subjects with T1DM and its extension trial (5.3.5.1.22, 5.3.5.1.23, Trial 3585/3725 [Feb. 2010 to Jun. 2011])

A randomized, open-label, parallel-group trial was conducted to investigate the efficacy and safety of IDeg compared with IDet in Japanese and non-Japanese[52] subjects with T1DM[53] on a basal-bolus regimen (target sample size of 426) and its open-label, extension trial (the duration of treatment with IDeg or IDet was up to 52 weeks in Trial 3585 with its extension trial) was conducted to investigate the long-term safety of IDeg.

Trial 3585 consisted of an observation period (approximately 1 week), a treatment period (26 weeks) in which basal insulin (IDeg or IDet) and bolus insulin (IAsp) were administered, and a follow-up period (1 week) for insulin antibody measurements. The subjects were stratified according to region. Randomization of the subjects was carried out in a 2:1 ratio (IDeg:IDet). Trial 3725 included subjects who completed Trial 3585 and consisted of a treatment period (26 weeks), in which the subjects resumed the same trial product as given in Trial 3585, and a follow-up period (1 week) for insulin antibody measurements.

As basal insulin, IDeg or IDet was subcutaneously administered in the thigh, upper arm or abdomen once daily in the evening (from the start of evening meal until bedtime) and as bolus insulin, IAsp was subcutaneously administered in the abdomen thrice daily immediately before each meal for 26 weeks. 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 treatment with trial product and then doses were adjusted to reach a target of 90 mg/dL according to a titration guideline (Table 51), based on pre-breakfast SMPG values from the three days prior to site visits and telephone contacts. In the IDet group, once-daily IDet was allowed to be intensified

[52] Europe (United Kingdom, Finland, Italy, Macedonia), India, and Brazil
[53] Key inclusion criteria: subjects with T1DM aged ≥18 (≥20, for Japanese subjects), having diabetes duration ≥12 months, a BMI ≤35.0 kg/m^2, and HbA1c (NGSP) ≤10.0%, who had been treated with a basal-bolus regimen for ≥12 months before screening (1 week before the start of treatment with trial product).

to twice daily after 8 weeks of dose optimization in case of inadequate glycaemic control.[54] If 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. The starting dose of bolus insulin was the same as the subject's bolus insulin dose immediately prior to the start of treatment with trial product and then doses were adjusted to reach a target of 90 mg/dL, according to the titration guideline (Table 51), based on SMPG values before the next meals from the three days prior to site visits and telephone contacts. In a follow-up period for antibody measurements, NPH insulin was subcutaneously administered from at least 24 hours after the last dose of basal insulin (IDeg or IDet), for 1 week after the end of treatment with trial product (IAsp was continued). The total daily dose of NPH insulin was 80% of the basal insulin dose at the end of treatment and administered twice daily in divided doses (before breakfast and from before the evening meal until bedtime).

Table 51. Titration guideline[a)] (Trial 3585/3725)

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

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, pre-breakfast insulin dose was adjusted based on pre-dinner SMPG value.
c) Doses were adjusted based on mean SMPG values before the next meals from three days and pre-dinner IAsp dose was adjusted based on SMPG value at bedtime.

Of the 456 randomized subjects (303 subjects [124 Japanese subjects] in the IDeg group, 153 subjects [62 Japanese subjects] in the IDet group), 455 subjects (302 subjects [124 Japanese subjects] in the IDeg group, 153 subjects [62 Japanese subjects] in the IDet group), excluding 1 subject (IDeg group) who was withdrawn from the trial due to failure to meet the inclusion criteria, were included in the FAS. Of these, all 453 exposed subjects (301 subjects [124 Japanese subjects] in the IDeg group, 152 subjects [61 Japanese subjects] in the IDet group), excluding 2 subjects (1 subject in each group) who were not exposed, were included in the safety analysis set. The FAS was used for efficacy analyses. Three hundred fifty-seven subjects (242 subjects [112 Japanese subjects] in the IDeg group, 115 subjects [51 Japanese subjects] in the IDet group) completed 52 weeks of treatment.

[54] If all of the following three criteria were met: (a) no adequate improvement in glycaemic control (a worsening of HbA1c for subjects with baseline HbA1c <8.0% or a <0.5% improvement in HbA1c for subjects with baseline HbA1c 8.0%-10.0%) (b) Mean pre-dinner SMPG >108 mg/dL (c) no treatable intercurrent cause for the hyperglycaemia diagnosed.

No primary efficacy endpoint was specified for Trial 3725 and the change in HbA1c from baseline (at the start of treatment in Trial 3585) to Week 52 in the FAS (least squares mean ± standard error[55]) was -0.48 ± 0.06%-points in the IDeg group and -0.47 ± 0.08%-points in the IDet group. Figure 5 shows the change in HbA1c over time from baseline to the end of treatment in Trials 3585 and 3725 (Trial 3585/3725, 52 weeks of treatment) in the entire trial population.

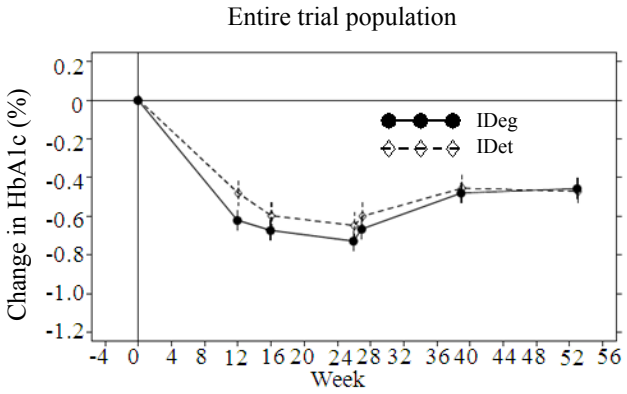

Figure 5. Change in HbA1c over time from baseline to Week 52 (Trial 3585/3725, entire trial population, LOCF) (mean ± standard error)

Regarding safety, the incidence of adverse events[49] reported during the period from the start of treatment in Trial 3585 (Week 0) to Week 52 in the entire trial population was 82.4% (248 of 301 subjects) in the IDeg group and 77.6% (118 of 152 subjects) in the IDet group. 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. Table 52 shows adverse events and/or adverse drug reactions reported in ≥5% of subjects in either treatment group in the entire trial population.

[55] Calculated using an ANOVA model with treatment, anti-diabetic therapy at screening, sex, and region (Europe, Japan, India, Brazil) as fixed effects and age and baseline HbA1c as covariates.

Table 52. Adverse events and/or adverse drug reactions reported in ≥5% of subjects in either treatment group (Trial 3585/3725 [52 weeks of treatment] entire trial population, safety analysis set)

Event	IDeg (n = 301)		IDet (n = 152)	
	AE	Adverse drug reaction	AE	Adverse drug reaction
All AEs	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 % (number of subjects with events), MedDRA/J (ver.14.0)

No deaths were reported. The incidence of serious adverse events reported during the period from the start of treatment (Week 0) to Week 52 in the entire trial population 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. The serious adverse events reported in at least 2 subjects were hypoglycaemia (IDeg group, 4.0% [12 of 301 subjects, 16 events]; IDet group, 3.3% [5 of 152 subjects, 8 events]), hypoglycaemic unconsciousness (IDeg group, 3.0% [9 of 301 subjects, 9 events]; IDet group, 3.3% [5 of 152 subjects, 6 events]), hypoglycaemic coma (IDeg group, 1.3% [4 of 301 subjects, 4 events]; IDet group, 0.7% [1 of 152 subjects, 1 event]), diabetic ketoacidosis (IDeg group, 0.7% [2 of 301 subjects, 2 events]; IDet group, 0.7% [1 of 152 subjects, 1 event]), gastroenteritis (IDet group, 1.3% [2 of 152 subjects, 2 events]), and hyperthyroidism (IDeg group, 0.3% [1 of 301 subjects, 1 event]; IDet group, 0.7% [1 of 152 subjects, 1 event]). Of those, the following events were classified as adverse drug reactions: hypoglycaemia (IDeg group, 12 events in 11 subjects; IDet group, 6 events in 4 subjects), hypoglycaemic unconsciousness (IDeg group, 7 events in 7 subjects; IDet group, 3 events in 3 subjects), hypoglycaemic coma (all events), and diabetic ketoacidosis (all events in the IDet group). In Trial 3585, adverse events leading to withdrawal were reported by 3 subjects in the IDeg group (fractured ischium/rib fracture, hypoglycaemia/fever, hypoglycaemic unconsciousness) and 1 subject in the IDet group (hypoglycaemia). Among these events, hypoglycaemia/fever and hypoglycaemic unconsciousness in the IDeg group and hypoglycaemia in the IDet group were classified as adverse drug reactions. In the extension trial (Trial 3725), adverse events leading to withdrawal were reported by 1 subject in the IDeg group (aspartate aminotransferase increased/alanine aminotransferase increased) and 1 subject in the IDet group (diabetic ketoacidosis), all of which were classified as adverse drug reactions.

Table 53 shows the occurrence of hypoglycaemia in the entire trial population.

Table 53. Hypoglycaemia in the entire trial population
(Trial 3585/3725 [52 weeks of treatment] safety analysis set)

Endpoints	IDeg (n = 301)	IDet (n = 152)
Confirmed hypoglycaemia[a)]	94.7 (285)	92.8 (141)
	10326 [3778]	5269 [3926]
Nocturnal confirmed hypoglycaemia[a) b)]	68.1 (205)	64.5 (98)
	924 [338]	646 [481]
Severe hypoglycaemia[c)]	14.0 (42)	11.8 (18)
	63 [23]	37 [28]
Nocturnal severe hypoglycaemia[b) c)]	5.3 (16)	3.9 (6)
	18 [7]	7 [5]

Upper column: incidence % (number of subjects with episodes), Lower column: number of episodes [rate (number of episodes/100 PYE)]
a) Confirmed hypoglycaemia: episodes of severe hypoglycaemia as well as episodes with plasma glucose of <56 mg/dL with or without symptoms
b) Nocturnal hypoglycaemia: episodes occurring between 00:01 and 05:59 (both inclusive)
c) Severe hypoglycaemia: an episode requiring assistance of another person

There were no clinically relevant findings in vital signs, ECG, or fundoscopy/fundsphotography.

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

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

The applicant explained as follows:

A twice-daily regimen with a premixed insulin product is a commonly used insulin therapy for Japanese patients with T2DM and offers a balance between glycaemic control and the convenience of fewer injections. A once-daily regimen with a premixed insulin product is also used for insulin initiation, similarly to a long-acting insulin analogue (IDet or IGlar). According to the prescription data from IMS (2010) in Japan, approximately 34% of patients who initiated insulin therapy in 2010 started with premixed insulin products, and premixed insulin products were used in 45% of patients on insulin therapy. Intensive insulin therapy including basal-bolus therapy is usually recommended for patients with T1DM and T2DM patients with diminished insulin secretory capacity. Although premixed insulin products are commonly used in Japan as mentioned above, the currently available premixed insulin products have disadvantages to be improved: They are not capable of providing 24-hour basal insulin coverage with once-daily dosing and require resuspension before use. In contrast, IDegAsp (a co-formulation of long-acting insulin and rapid-acting insulin) is considered useful because once-daily administration of IDegAsp can cover both mealtime and 24-hour basal insulin requirements, with no need of resuspension. Furthermore, while the currently available premixed insulin products are labelled only for use before breakfast for once-daily dosing, IDegAsp QD may be dosed immediately before any largest meal of the day, thereby accommodating individual dietary patterns. Also from this point of view, IDegAsp is considered useful.

PMDA asked the applicant to explain the reason for the composition of 30% IAsp and 70% IDeg in IDegAsp.

The applicant responded as follows:
In the earlier stage of the clinical development programme, an alternative formulation of IDegAsp containing 45% IAsp was also investigated, but IDegAsp containing 30% IAsp was associated with a lower incidence rate of hypoglycaemic episodes and a higher proportion of subjects achieving HbA1c targets without hypoglycaemia, compared with IDegAsp containing 45% IAsp, in foreign therapeutic exploratory trials (Trials 1791[56] and 1792[57]). Furthermore, premixed insulin analogue products containing 30%, 50% and 70% soluble IAsp are marketed by the applicant in Japan (NovoRapid 30 Mix, NovoRapid 50 Mix, and NovoRapid 70 Mix, respectively). During the first half of 2012, 30 Mix, 50 Mix, and 70 Mix accounted for 89.1%, 6.5%, and 4.5% of the total prescription volume of NovoRapid Mix, respectively, and the product containing 30% soluble IAsp was predominantly prescribed, supporting the composition of 30% IAsp and 70% IDeg in IDegAsp.

PMDA considers as follows:
Taking into consideration that the efficacy of IDegAsp BID or QD has been demonstrated [see "4.(iii).B.(3) Efficacy"] and its safety is considered acceptable [see "4.(iii).B.(4) Safety"] and taking also account of the utilization of insulin products intended for the same patient population as that for IDegAsp (NovoRapid 30 Mix is most commonly used among the NovoRapid Mix products), IDegAsp can be a new option in insulin therapy. Furthermore, it is expected that once-daily administration of IDegAsp can cover both mealtime and 24-hour basal insulin requirements, with no need of resuspension. The significance of this co-formulation lies in patient's convenience (e.g., fewer injections compared with a rapid-acting [short-acting] insulin product in combination with a long-acting insulin product; and easier handling of the insulin preparation and injection needles) and avoidance of the unfavourable influence of inadequate resuspension on treatment. There should be no problem with this point in light of "handling of prescription combinations" as specified in the "Points to Consider when Applying for Marketing Approval for Drugs" (PFSB/ELD Notification No. 0331009 dated March 31, 2005). PMDA will review the appropriateness of the statement about the timing of injection in the package insert in "4.(iii).B.(6) Dosage and administration."

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

For interpretation of the results from a multinational trial, Trial 3597 in subjects with T2DM, PMDA conducted the following reviews based on the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and the ICH-E5 guideline.

[56] A 16-week open-label trial comparing IDegAsp (IDegAsp 30B) OD, IDegAsp (IDegAsp 45B) OD, and IGlar OD, all in combination with metformin (other OADs were discontinued) in non-Japanese subjects with T2DM inadequately controlled on OAD treatment
[57] A 16-week open-label trial comparing IDegAsp (IDegAsp 30B) BID, IDegAsp (IDegAsp 45B) BID, and BIAsp 30 BID, all in combination with metformin (other OADs were discontinued) in non-Japanese subjects with T2DM inadequately controlled on OAD treatment

4.(iii).B.(2).1) 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 IDegAsp.

The applicant responded as follows:

According to DIABCARE-ASIA 2003[58] (Mohamed M on Behalf of the Diabcare-Asia 2003 Trial Group, *Curr Med Research and Opinion*, 2008;24:507-14) and IDegAsp clinical trials conducted to date, the age, diabetes duration, BMI, and HbA1c of T2DM patients are considered to be similar among Asian countries. The diagnostic criteria for diabetes mellitus are also based on the international or local guidelines and there should be no major differences among the countries/regions that participated in Trial 3597 (Japan, Korea, Malaysia, Taiwan, Hong Kong).

The pharmacokinetics and pharmacodynamics after administration of IDegAsp are little influenced by ethnic factors, suggesting no impact on the efficacy and safety evaluation of IDegAsp.

The baseline characteristics of subjects in Trial 3597 are shown in Table 54. There were no apparent differences in the intrinsic ethnic factors between the Japanese subgroup and entire trial population except that FPG, the percentage of male subjects, and the percentage of subjects aged >65 years were slightly higher in the Japanese subgroup than in the entire trial population. Since there was no difference in baseline HbA1c and this trial was conducted using a treat-to-target design, the applicant considers that the differences in baseline FPG have no significant impact on efficacy and safety. As to extrinsic ethnic factors, the percentage of subjects previously treated without metformin was higher in the Japanese subgroup than in the entire trial population.

[58] 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.

Table 54. Baseline characteristics of subjects (Trial 3597, FAS)

		Japanese subgroup		Entire trial population	
		IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 280)	BIAsp 30 (n = 142)
Intrinsic factors					
Sex	male	61.9 (73)	68.3 (41)	53.9 (151)	55.6 (79)
	female	38.1 (45)	31.7 (19)	46.1 (129)	44.4 (63)
Age (years)	≤65	62.7 (74)	53.3 (32)	71.4 (200)	61.3 (87)
	>65	37.3 (44)	46.7 (28)	28.6 (80)	38.7 (55)
Body weight (kg)		64.3 ± 12.2	63.9 ± 11.4	66.1 ± 11.2	66.0 ± 11.2
BMI (kg/m^2)		24.6 ± 3.3	24.5 ± 3.6	25.4 ± 3.4	25.4 ± 3.7
Duration of diabetes (years)		15.5 ± 8.2	16.8 ± 9.6	16.3 ± 7.9	16.3 ± 8.2
HbA1c (%)		8.3 ± 0.8	8.4 ± 0.8	8.4 ± 0.8	8.4 ± 0.9
FPG (mg/dL)		146.6 ± 41.2	150.8 ± 45.5	143.1 ± 45.0	142.8 ± 45.6
Extrinsic factors					
Metformin treatment	yes	29.7 (35)	31.7 (19)	60.0 (168)	59.9 (85)
	no	70.3 (83)	68.3 (41)	40.0 (112)	40.1 (57)
Transfer from pre-trial insulin	Basal insulin	33.1 (39)	36.7 (22)	29.3 (82)	29.6 (42)
	Premixed insulin[a)]	66.9 (79)	63.3 (38)	70.7 (198)	70.4 (100)

Mean ± SD, Percentage of subjects % (number of subjects)
a) Including self-mixed insulin

The influence of the observed ethnic differences between the Japanese subgroup and entire trial population (sex, age, metformin treatment) on efficacy and safety evaluation was assessed. Regarding efficacy, there were no apparent differences in the treatment difference in HbA1c change between the subgroups (men vs. women, ≤65 years vs. >65 years) in either the Japanese subgroup or entire trial population (Table 55). As for "metformin treatment," the HbA1c reduction was greater in subjects previously treated with metformin than in subjects previously treated without metformin in both treatment groups in both the Japanese subgroup and entire trial population, but the treatment difference in HbA1c change was comparable between the two subgroups.

Table 55. HbA1c changes by age group, sex, and metformin treatment (Trial 3597, FAS)

		Japanese subgroup		Entire trial population	
		IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 280)	BIAsp 30 (n = 142)
Sex	male	-1.44 ± 0.8 (n =73)	-1.34 ± 0.8 (n = 41)	-1.36 ± 0.9 (n = 151)	-1.33 ± 0.9 (n = 79)
	female	-1.33 ± 0.6 (n = 45)	-1.19 ± 0.8 (n = 19)	-1.39 ± 0.9 (n = 129)	-1.52 ± 1.0 (n = 63)
Age (years)	≤65	-1.48 ± 0.8 (n = 74)	-1.31 ± 0.8 (n = 33)	-1.42 ± 0.9 (n = 200)	-1.43 ± 1.0 (n = 88)
	>65	-1.26 ± 0.6 (n = 44)	-1.27 ± 0.8 (n = 27)	-1.28 ± 0.8 (n = 80)	-1.39 ± 1.0 (n = 54)
Metformin treatment	yes	-1.56 ± 0.7 (n = 35)	-1.38 ± 0.9 (n = 19)	-1.46 ± 0.9 (n = 168)	-1.50 ± 1.1 (n = 85)
	no	-1.33 ± 0.7 (n = 83)	-1.25 ± 0.8 (n = 41)	-1.24 ± 0.8 (n = 112)	-1.28 ± 0.8 (n = 57)

Mean ± SD

Regarding safety, the incidence of adverse events tended to be higher in females than in males in both treatment groups of the Japanese subgroup and entire trial population. As for age, the incidence of adverse events in the subgroup aged >65 years in the BIAsp 30 group tended to be lower in the entire trial population than in the Japanese subgroup. However, there were no apparent differences in the incidence rate of adverse events between the two subgroups in either treatment group in both the Japanese subgroup and entire trial population. There were no apparent differences in the incidence of adverse events between the two subgroups (with/without metformin) in both the Japanese subgroup and entire trial population (Table 56).

Table 56. Adverse events by age group, sex, and metformin treatment (Trial 3597, safety analysis set)

		Japanese subgroup		Entire trial population	
		IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 279)	BIAsp 30 (n = 141)
Sex	male	72.6 (53)	78.0 (32)	62.9 (95)	69.2 (54)
		125 [355.1]	64 [324.1]	213 [302.9]	103 [279.4]
	female	80.0 (36)	89.5 (17)	77.3 (99)	77.8 (49)
		91 [434.5]	56 [646.3]	235 [405.0]	153 [539.7]
Age (years)	≤65	73.0 (54)	84.8 (28)	69.3 (138)	81.6 (71)
		126 [348.4]	56 [351.4]	312 [338.4]	171 [415.2]
	>65	79.5 (35)	77.8 (21)	70.0 (56)	59.3 (32)
		90 [450.6]	64 [513.1]	136 [376.1]	85 [353.8]
Metformin treatment	yes	71.4 (25)	84.2 (16)	68.3 (114)	69.4 (59)
		63 [364.3]	33 [368.9]	262 [340.0]	149 [385.7]
	no	77.1 (64)	80.5 (33)	71.4 (80)	78.6 (44)
		153 [393.8]	87 [446.9]	186 [362.5]	107 [402.6]

Upper column: incidence % (number of subjects with events), Lower column: number of events [rate (number of events/100 PYE)]

In conclusion, the applicant considers that there were differences in some of the intrinsic and extrinsic ethnic factors between the Japanese subgroup and entire trial population, which should have no clinically significant impact on efficacy and safety evaluation.

PMDA has concluded, based on the results of analyses of IDegAsp Trial 3597, that the intrinsic and extrinsic ethnic differences have no significant impact on efficacy and safety evaluation and accepted the applicant's response [for similarity in pharmacokinetic and pharmacodynamic properties between Japanese and non-Japanese populations, see "4.(ii).B.(1) Similarity in pharmacokinetic and pharmacodynamic properties between Japanese and non-Japanese populations with T1DM or T2DM"].

4.(iii).B.(2).2) 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 apparent differences between the Japanese subgroup and entire trial population or non-Japanese subgroup for the treatment difference in the primary endpoint of HbA1c change (IDegAsp versus

BIAsp 30) (Table 57).

Table 57. HbA1c changes from baseline to Week 26 (Trial 3597, FAS)

	Japanese subgroup		Non-Japanese subgroup[a)]		Entire trial population	
	IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 162)	BIAsp 30 (n = 82)	IDegAsp (n = 280)	BIAsp 30 (n = 142)
Baseline	8.34 (0.8)	8.37 (0.8)	8.53 (0.8)	8.49 (0.9)	8.45 (0.8)	8.44 (0.9)
Week 26 (LOCF)[b)]	6.89 ± 0.06	7.03 ± 0.08	7.33 ± 0.10	7.18 ± 0.12	7.06 ± 0.05	7.01 ± 0.07
HbA1c change (LOCF)[b)]	-1.45 ± 0.06	-1.32 ± 0.08	-1.19 ± 0.10	-1.34 ± 0.12	-1.39 ± 0.05	-1.44 ± 0.07
Treatment difference (IDegAsp minus BIAsp 30) [95% CI][b)]	-0.13 [-0.31, 0.04]		0.15 [-0.08, 0.38]		0.05 [-0.10, 0.20]	

Unit: %, Mean (SD), LS mean ± SE

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 (pretrial insulin therapy [basal insulin or others] and metformin treatment at screening), sex, and region (Japan or others; not included in the analyses of the Japanese subgroup and non-Japanese subgroup) as fixed effects and age and baseline HbA1c as covariates.

The treatment difference in the change in FPG from baseline to Week 26 (IDegAsp versus BIAsp 30) with its 95% confidence interval was -26.97 [-35.71, -18.22] mg/dL in the Japanese subgroup and -19.15 [−25.69, −12.62] mg/dL in the entire trial population and there was no apparent difference between the Japanese subgroup and entire trial population. As for other endpoints, the proportion of subjects achieving HbA1c <7.0% without confirmed hypoglycaemia was 21.2% in the IDegAsp group and 14.0% in the BIAsp 30 group in the Japanese subgroup and 21.9% in the IDegAsp group and 13.2% in the BIAsp 30 group in the entire trial population and there were no apparent differences between the Japanese subgroup and entire trial population. The total daily insulin dose and the insulin doses at breakfast and evening meal at baseline and Week 26 were all lower in the Japanese subgroup than in the entire trial population in both treatment groups. The total daily insulin dose at Week 26 was lower in the IDegAsp group than in the BIAsp 30 group in both the Japanese subgroup and entire trial population and a similar pattern was observed in both the Japanese subgroup and entire trial population (Table 41 and Table 42).

PMDA considers as follows:

Concerning the change in HbA1c as the primary endpoint, the non-inferiority of IDegAsp to BIAsp 30 was confirmed in the entire trial population. In addition there were no apparent differences in the treatment difference (IDegAsp versus BIAsp 30) in HbA1c change between the Japanese subgroup and entire trial population and between the Japanese and non-Japanese subgroups. As to the secondary endpoints, there were differences in insulin dose between the Japanese subgroup and entire trial population, but the differences were not considered clinically relevant. Therefore, there was no clear discrepancy in efficacy between the Japanese subgroup and entire trial population. Based on the findings, it may be interpreted that the efficacy results were consistent between the Japanese subgroup and entire trial population.

4.(iii).B.(2).3) 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 analysed by severity and causality. As a result, there were no apparent differences between the Japanese subgroup and entire trial population (Table 58).

Table 58. Adverse events in Japanese subgroup and entire trial population (Trial 3597 [26 weeks of treatment] safety analysis set)

		Japanese subgroup		Entire trial population	
		IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 279)	BIAsp 30 (n = 141)
All AEs		75.4 (89)	81.7 (49)	69.5 (194)	73.0 (103)
		216 [385]	120 [422]	448 [349]	256 [393]
SAEs		5.9 (7)	5.0 (3)	8.2 (23)	8.5 (12)
		7 [12]	4 [14]	27 [21]	17 [26]
Severity	mild	72.0 (85)	78.3 (47)	61.3 (171)	66.0 (93)
		204 [363]	111 [391]	371 [289]	213 [327]
	moderate	6.8 (8)	6.7 (4)	15.1 (42)	14.2 (20)
		8 [14]	8 [28]	62 [48]	36 [55]
	severe	3.4 (4)	1.7 (1)	5.0 (14)	3.5 (5)
		4 [7]	1 [4]	15 [12]	7 [11]
Causal relationship	related or possibly related	11.0 (13)	16.7 (10)	10.4 (29)	12.1 (17)
		15 [27]	11 [39]	34 [26]	19 [29]
	unrelated	73.7 (87)	78.3 (47)	66.3 (185)	70.2 (99)
		197 [351]	107 [377]	405 [316]	234 [359]
	unknown	3.4 (4)	3.3 (2)	2.5 (7)	2.1 (3)
		4 [7]	2 [7]	9 [7]	3 [5]

Upper column: incidence % (number of subjects with events), Lower column: number of events [rate (number of events/100 PYE)]

In order to detect any adverse event (System Organ Class) reported particularly more frequently in the Japanese subgroup than in the entire trial population, SOCs 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 include “eye disorders” (57 events/100 person-year equivalents (PYE) in the IDegAsp group and 49 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 35 events/100 PYE in the IDegAsp group and 37 events/100 PYE in the BIAsp 30 group in the entire trial population), “skin and subcutaneous tissue disorders” (23 events/100 PYE in the IDegAsp group and 21 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 16 events/100 PYE in the IDegAsp group and 11 events/100 PYE in the BIAsp 30 group in the entire trial population), “investigations” (16 events/100 PYE in the IDegAsp group and 21 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 12 events/100 PYE in the IDegAsp group and 14 events/100 PYE in the BIAsp 30 group in the entire trial population), “infections and infestations” (93 events/100 PYE in the IDegAsp group and 127 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 83 events/100 PYE in the IDegAsp group and 101 events/100 PYE in the BIAsp 30 group in the entire trial population), “musculoskeletal and connective tissue disorders” (28 events/100 PYE in the IDegAsp group

and 56 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 34 events/100 PYE in the IDegAsp group and 40 events/100 PYE in the BIAsp 30 group in the entire trial population), and "vascular disorders" (16 events/100 PYE in the IDegAsp group and 14 events/100 PYE in the BIAsp 30 group in the Japanese subgroup; 10 events/100 PYE in the IDegAsp group and 8 events/100 PYE in the BIAsp 30 group in the entire trial population). The number of each of the preferred term events in these SOCs in the IDegAsp group in the Japanese subgroup was small, being not more than three, except for diabetic retinopathy, weight increased, nasopharyngitis, back pain, eczema, and hypertension. As to diabetic retinopathy, 14 out of 20 subjects with diabetic retinopathy in the IDegAsp group and 5 out of 9 subjects with diabetic retinopathy in the BIAsp 30 group were Japanese and 4 events reported by 4 subjects in the IDegAsp group and 4 events reported by 4 subjects in the BIAsp 30 group were classified as adverse drug reactions. The incidence rate of diabetic retinopathy was 25 events/100 PYE in the IDegAsp group and 18 events/100 PYE in the BIAsp 30 group in the Japanese subgroup and 16 events/100 PYE in the IDegAsp group and 14 events/100 PYE in the BIAsp 30 group in the entire trial population. Subjects with weight increased (IDegAsp group, 7 subjects; BIAsp 30 group, 2 subjects) were all Japanese and the events reported by 5 subjects in the IDegAsp group and the events reported by 2 subjects in the BIAsp 30 group were classified as adverse drug reactions. The incidence rate of weight increased was 12 events/100 PYE in the IDegAsp group and 7 events/100 PYE in the BIAsp 30 group. The events of nasopharyngitis, back pain, eczema, and hypertension were all non-serious and their causal relationship to trial product was denied.

As for hypoglycaemia, there were no apparent differences in the incidence or incidence rate of confirmed hypoglycaemia between the Japanese subgroup and entire trial population in either treatment group (Table 45). The incidence rate of nocturnal confirmed hypoglycaemia was higher in the BIAsp 30 group than in the IDegAsp group in both the Japanese subgroup and entire trial population. Severe hypoglycaemia was reported in the entire trial population (6 episodes reported by 4 subjects in the IDegAsp group, 2 episodes reported by 2 subjects in the BIAsp 30 group) but not in the Japanese subgroup.

In conclusion, there were no clinically relevant differences in safety between the Japanese subgroup and entire trial population.

PMDA considers as follows:
There were no apparent differences in the occurrence of adverse events between the Japanese subgroup and entire trial population. Although the incidence rates of some adverse events were higher in the Japanese subgroup than in the entire trial population, there were not apparent differences in the occurrence between the IDegAsp and BIAsp 30 groups. These differences in safety are not considered clinically relevant. Therefore, it may be interpreted that there were no safety concerns for Japanese patients.

Based on the above 1) to 3), PMDA considers that there is no major problem with the generalization of the results from the entire population in Trial 3597 to Japanese patients with T2DM.

4.(iii).B.(3) Efficacy

The applicant explained as follows:

In Trial 3896 and Trial 3597, the non-inferiority of IDegAsp to the comparator was confirmed. In order to investigate the influence of antibody formation on efficacy, insulin antibodies were measured at baseline and Weeks 12, 26, and 27 in Trial 3597 in which Japanese subjects were included (insulin antibodies were not measured in Trial 3896). In the entire trial population, the titer of antibodies cross-reacting with human insulin remained low throughout the trial period in the IDegAsp group while the titer rose slightly in the BIAsp 30 group (Table 59). The titer of IDeg-specific antibodies remained low throughout the trial period. The titer of IAsp-specific antibodies remained low throughout the trial period in both treatment groups.

Table 59. Insulin antibody titers (%B/T) (Trial 3597, safety analysis set)

Endpoint	Timing	Japanese subgroup		Entire trial population	
		IDegAsp (n = 118)	BIAsp 30 (n = 60)	IDegAsp (n = 279)	BIAsp 30 (n = 141)
Titer of antibodies cross-reacting with human insulin	Baseline	3.0 [0.0-76.0] (n = 118)	2.5 [−1.0-60.0] (n = 60)	4.0 [0.0-76.0] (n = 277)	4.0 [−1.0-80.0] (n = 141)
	Week 27	2.5 [0.0-75.0] (n = 112)	5.0 [0.0-72.0] (n = 55)	3.0 [0.0-77.0] (n = 260)	11.0 [0.0-78.0] (n = 131)
Titer of IDeg-specific antibodies	Baseline	0.0 [−1.0-1.0] (n = 118)	—	0.0 [−1.0-6.0] (n = 276)	—
	Week 27	0.0 [−1.0-2.0] (n=112)	—	0.0 [−1.0-2.0] (n = 260)	—
Titer of IAsp-specific antibodies	Baseline	1.0 [0.0-39.0] (n = 118)	1.0 [0.0-59.0] (n = 60)	1.0 [0.0-40.0] (n = 277)	1.0 [0.0-59.0] (n = 141)
	Week 27	1.0 [−1.0-46.0] (n = 112)	1.0 [0.0-60.0] (n = 55)	1.0 [−1.0-46.0] (n = 260)	1.0 [0.0-60.0] (n = 131)
Titer of total insulin antibodies	Baseline	5.0 [−1.0-83.0] (n = 118)	5.0 [−1.0-66.0] (n = 60)	7.0 [−1.0-83.0] (n = 276)	9.0 [−1.0-88.0] (n = 141)
	Week 27	5.0 [0.0-78.0] (n = 111)	11.0 [0.0-78.0] (n = 55)	6.0 [0.0-81.0] (n = 257)	14.0 [0.0-82.0] (n = 131)

Median [min-max], —: NA

Concerning the influence of antibody formation on efficacy, only 1 subject in the BIAsp 30 group (Japanese) had an increase of ≥10%B/T (percent bound/total radioactivity) in antibodies cross-reacting with human insulin (absolute) and did not have a decrease in HbA1c of >0.2% (absolute) in Trial 3597. According to the global pooled data[59] from IDegAsp confirmatory trials in subjects with T2DM, 2 subjects in the pooled IDegAsp group and 3 subjects in the pooled comparator group experienced an increase of ≥10%B/T in antibodies cross-reacting with human insulin (absolute) and did not have a decrease in

[59] Pooled data from two confirmatory trials in which IDegAsp was administered to subjects with T2DM (Trial 3590, Trial 3597) (safety analysis set excluding subjects without antibody titer data at baseline or end of treatment, 541 subjects in the pooled IDegAsp group, 402 subjects in the pooled comparator group).

HbA1c of >0.2% (absolute). All of these subjects had their dose of IDegAsp or comparator increased during the trial period. One subject in the pooled IDegAsp group (Trial 3590[60]) was withdrawn from the trial at Week 5 due to two events of injection site reaction. In this subject, the titer of antibodies cross-reacting with human insulin increased from 0%B/T (baseline) to 25%B/T. According to the global pooled data[61] from IDegAsp confirmatory trials in subjects with T1DM, 6 subjects in the pooled IDegAsp group and 8 subjects in the pooled comparator group experienced an increase of ≥10%B/T in antibodies cross-reacting with human insulin (absolute) and had an increase in HbA1c of >0.2% (absolute). The total insulin dose was increased during the trial period in 3 of the 6 subjects in the pooled IDegAsp group, and the dose of IDegAsp was increased in 2 of these 3 subjects. In the pooled comparator group, the total insulin dose as well as the comparator dose was increased during the trial period in 6 of the 8 subjects. As described above, insulin antibody formation following administration of IDegAsp was minimal. Thus, the applicant considers that there was no clear relationship between the level of antibody formation and efficacy.

PMDA considers as follows:
The efficacy of IDegAsp in subjects with T2DM has been demonstrated by Trial 3896 (QD) that confirmed the non-inferiority of IDegAsp to IGlar and by Trial 3597 (BID) that confirmed the non-inferiority of IDegAsp to BIAsp 30. Concerning the influence of antibody formation on efficacy, a clinical trial showed no trend towards marked rises in antibody titers following administration of IDegAsp compared with the comparator and there was no clear relationship between the level of antibody formation and efficacy. As the information on antibody formation following long-term treatment with IDegAsp 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"].

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

PMDA considers that the safety of IDegAsp in subjects with T2DM is acceptable based on the results of Trials 3896 and 3597. Individual events and the safety of IDegAsp in subjects with T1DM were evaluated as follows.

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

The applicant explained as follows:
In Trial 3896 where IDegAsp was administered once daily to subjects with T2DM for 26 weeks, the incidence of confirmed hypoglycaemia was similar between the two treatment groups, but the incidence

[60] A 26-week, open-label trial of IDegAsp OD vs. IGlar OD in insulin naïve subjects with T2DM on metformin and ≥1 other OAD. IDegAsp was subcutaneously administered in the abdomen, upper arm, or thigh at breakfast.
[61] Pooled data from two confirmatory trials in which IDegAsp was administered to subjects with T1DM (Trial 3594 and Trial 3645 [extension of Trial 3594]) (safety analysis set excluding subjects without antibody titer data at baseline or end of treatment, 362 subjects in the pooled IDegAsp group, 179 subjects in the pooled comparator group).

rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were lower in the IDegAsp group than in the IGlar group (Table 50). No severe hypoglycaemic episodes were reported. Regarding hypoglycaemic episodes over time, the number of confirmed hypoglycaemic episodes per subject was similar between the two treatment groups until Week 4 and was slightly lower thereafter in the IDegAsp group than in the IGlar group (Figure 6). The number of nocturnal confirmed hypoglycaemic episodes per subject was lower in the IDegAsp group than in the IGlar group until Week 18 but there were no apparent differences between the two treatment groups thereafter (Figure 6).

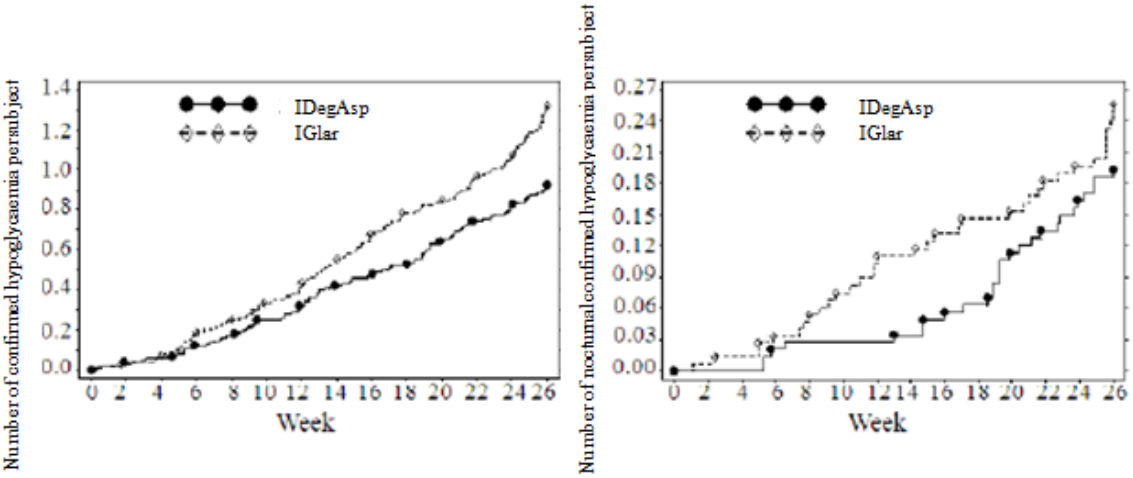

Figure 6. Confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes over time (mean cumulative function) (Trial 3896, safety analysis set)

In Trial 3597 where IDegAsp was administered twice daily to subjects with T2DM for 26 weeks, there were no marked differences in the incidence or incidence rate of confirmed hypoglycaemia between the two treatment groups. There were no marked differences in the incidence of nocturnal confirmed hypoglycaemia between the two treatment groups, but the incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDegAsp group than in the BIAsp 30 group (Table 45). Six episodes of severe hypoglycaemia were reported by 4 subjects in the IDegAsp group and 2 episodes were reported by 2 subjects in the BIAsp 30 group. One episode of nocturnal severe hypoglycaemia was reported by 1 subject in the IDegAsp group. Regarding hypoglycaemic episodes over time, the number of confirmed hypoglycaemic episodes per subject was similar between the two treatment groups throughout the trial period (Figure 7). The number of nocturnal confirmed hypoglycaemic episodes per subject was similar between the two treatment groups in the early phase of treatment but lower in the IDegAsp group than in the BIAsp 30 group at or after Week 12 (Figure 7).

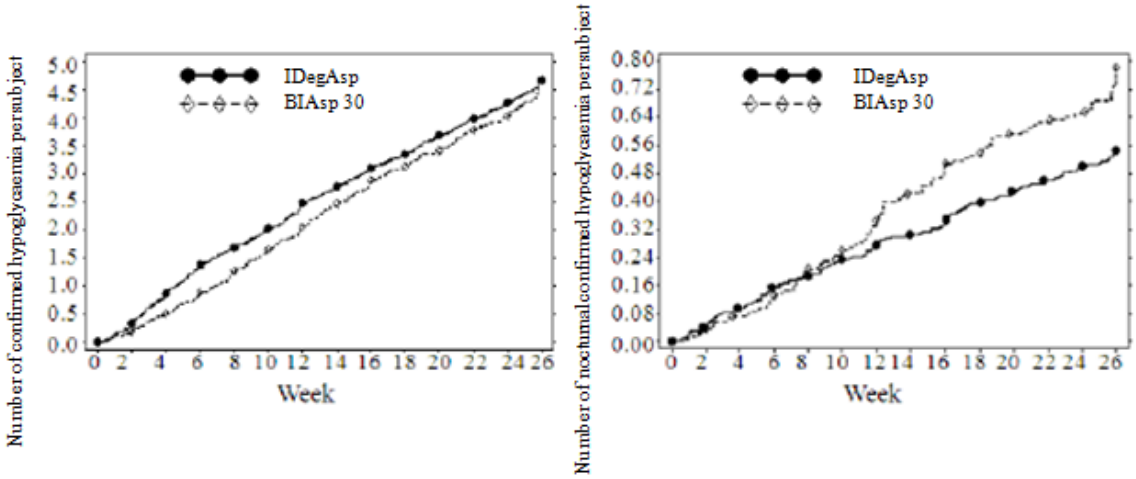

Figure 7. Confirmed hypoglycaemic episodes and nocturnal confirmed hypoglycaemic episodes over time (mean cumulative function) (Trial 3597, safety analysis set)

In Trials 3594/3645[62] in non-Japanese subjects with T1DM (once-daily administration, 52 weeks of treatment), the incidence rate of confirmed hypoglycaemia was 3183 episodes/100 PYE in the IDegAsp group and 3673 episodes/100 PYE in the IDet group, showing no marked difference between the two treatment groups. The incidence rate of nocturnal confirmed hypoglycaemia was 309 episodes/100 PYE in the IDegAsp group and 541 episodes/100 PYE in the IDet group, being lower in the IDegAsp group than in the IDet group. The incidence rates of severe hypoglycaemia and nocturnal severe hypoglycaemia were 27 episodes/100 PYE and 5 episodes/100 PYE, respectively, in the IDegAsp group and 45 episodes/100 PYE and 19 episodes/100 PYE, respectively, in the IDet group, being lower in the IDegAsp group than in the IDet group. The incidences of severe hypoglycaemia and nocturnal severe hypoglycaemia were 13.3% (48 of 362 subjects) and 3.6% (13 of 362 subjects), respectively, in the IDegAsp group and 18.3% (33 of 180 subjects) and 7.8% (14 of 180 subjects), respectively, in the IDet group, being lower in the IDegAsp group than in the IDet group. In Trial 3593[63] in non-Japanese subjects with T2DM (once-daily administration, 26 weeks of treatment), the incidence rate of confirmed hypoglycaemia was 431 episodes/100 PYE in the IDegAsp group and 320 episodes/100 PYE in the IGlar group, being higher in the IDegAsp group than in the IGlar group. The incidence rate of nocturnal confirmed hypoglycaemia was 82 episodes/100 PYE in the IDegAsp group and 101 episodes/100 PYE in the IGlar group, being lower in

[62] A 26-week, open-label trial (Trial 3594) of IDegAsp OD + IAsp (for the remaining meals) vs. IDet OD + IAsp (meal-time) in non-Japanese subjects with T1DM on a basal-bolus insulin regimen or other mixed insulin regimen, followed by a 26-week extension trial (Trial 3645). IDegAsp was to be injected subcutaneously in the abdomen, upper arm, or thigh with any main meal of the day and injection time was allowed to be moved to another meal as needed. In the IDet group, IDet was to be initially dosed once daily and if the predefined criteria were met, a second dose of IDet could be added.

[63] A 26-week, open-label trial of IDegAsp OD vs. IGlar OD, both in combination with metformin ± pioglitazone ± DPP-4 inhibitors in non-Japanese subjects with T2DM on basal insulin (IDet, IGlar, or NPH insulin) OD and metformin ± other OADs. Basal insulin was switched to IDegAsp or IGlar. IDegAsp was to be injected subcutaneously in the abdomen, upper arm, or thigh with evening meal or the largest meal.

the IDegAsp group than in the IGlar group. No severe hypoglycaemia was reported in the IDegAsp group, but 4 episodes were reported by 3 subjects in the IGlar group (the incidence rate of severe hypoglycaemia was 4 episodes/100 PYE).

Based on the above, the incidence rate of nocturnal hypoglycaemia tended to be lower with IDegAsp than with the comparator in subjects with T1DM, insulin-naïve subjects with T2DM, and previously insulin-treated subjects with T2DM.

PMDA considers as follows:
According to the results of the above-mentioned clinical trials including Japanese subjects and global pooled data, there were no marked differences in the occurrence of confirmed hypoglycaemia or severe hypoglycaemia between the IDegAsp group and the comparator group and the incidence rate of nocturnal confirmed hypoglycaemia tended to be lower in the IDegAsp group than in the comparator group. However, since close attention needs to be paid to the occurrence of hypoglycaemia during treatment with IDegAsp, it is necessary to continue to collect information on hypoglycaemia via post-marketing surveillance.

4.(iii).B.(4).2) Immunogenicity-related adverse events (allergic reactions)
The applicant explained as follows:
Concerning immunogenicity-related adverse events (allergic reactions) identified by Standardised MedDRA Queries (SMQs) "anaphylactic reaction," "angioedema," and "severe cutaneous adverse reaction," 1 subject in the IGlar group experienced 1 event of urticaria in Trial 3896, but its causal relationship to trial product was denied. Two adverse events reported by 2 subjects in the IDegAsp group (feeling hot, palmar erythema) were not captured by the SMQ searches, but were judged as immunogenicity-related events by the investigator. These events were classified as adverse drug reactions. In Trial 3597, 1 immunogenicity-related adverse event (face edema) was reported by 1 subject in the BIAsp 30 group, but its causal relationship to trial product was denied. All the immunogenicity-related adverse events were mild in severity. In other clinical trials including Japanese subjects, no immunogenicity-related adverse events were reported after administration of IDegAsp.

According to the global pooled data[64] from IDeg and IDegAsp confirmatory trials, the incidence of immunogenicity-related adverse events was 0.9% (54 of 5782 subjects, 56 events) in the pooled IDeg/IDegAsp group and 0.7% (25 of 3455 subjects, 27 events) in the pooled comparator group. The incidence rate of immunogenicity-related adverse events was 1.1 events/100 PYE in both treatment groups.

[64] Pooled data from 24 IDeg and IDegAsp therapeutic confirmatory trials with a cut-off date of Oct 6, 2011 (IDeg, Trial 3585 and its extension trial [Trial 3725], Trial 3586, Trial 3579 and its extension trial [Trial 3643, interim data], Trial 3580, Trial 3582 and its extension trial [Trial 3667], Trial 3583 and its extension trial (Trial 3644, interim data), Trial 3668, Trial 3672, Trial 3718, Trial 3724, Trial 3770 and its extension trial; IDegAsp, Trial 3597, Trial 3590 and its extension trial (Trial 3726), Trial 3592, Trial 3593, Trial 3594 and its extension trial (Trial 3645), Trial 3896) (safety analysis set, 5782 subjects in the pooled IDeg/IDegAsp group, 3455 subjects in the pooled comparator group)

The most commonly reported immunogenicity-related adverse event was urticaria in both treatment groups, but the incidence rate of urticaria was low (0.6 events/100 PYE in the pooled IDeg/IDegAsp group, 0.7 events/100 PYE in the pooled comparator group). According to the global pooled data[65] from clinical pharmacology trials with IDeg, IDegAsp, or IDegAsp formulation (other than the commercial formulation), only 2 immunogenicity-related adverse events (anaphylactic reaction, urticaria, 1 each) were reported (both in the pooled IDeg/IDegAsp + IDegAsp formulation [other than the commercial formulation] group). A 29-year-old subject with T1DM experienced an anaphylactic reaction in a foreign trial (Trial 3538). Pruritus and redness occurred in the subject about 1 hour after the first dose of IDeg and they were generalized except on the lower limbs about 2 hours after the dose. This event was considered as a serious adverse drug reaction and led to withdrawal from the trial. The event was moderate in severity, there were no problems with vital signs, and the symptoms resolved spontaneously about 4 hours after onset.

In conclusion, according to therapeutic confirmatory trials including Japanese subjects and the global pooled data, the number of immunogenicity-related adverse events (allergic reactions) was low and there were no apparent differences in the occurrence of immunogenicity-related adverse events between the pooled IDeg/IDegAsp + IDegAsp formulation (other than the commercial formulation) group and the pooled comparator group. A caution about allergic reactions will be included in the package insert and 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 low and there were no marked differences compared with the comparators. 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 Trial 3896 (once-daily administration), no injection site reactions were reported in the IDegAsp group while in the IGlar group, the incidence of injection site reactions was 3.4% (5 of 149 subjects, 6 events) and the incidence rate of injection site reactions was 9 events/100 PYE. One injection site reaction reported by 1 subject in the IGlar group (injection site erythema, mild) led to withdrawal from the trial and was classified as an adverse drug reaction. In Trial 3597 (twice-daily administration), the incidence of injection site reactions was 1.4% (4 of 279 subjects, 4 events) in the IDegAsp group and 1.4% (2 of 141

[65] Pooled data from 31 clinical pharmacology trials with IDeg, IDegAsp, or IDegAsp formulation (other than the commercial formulation) (safety analysis set, 1128 subjects in the pooled IDeg/IDegAsp+IDegAsp formulation group, 650 subjects in the pooled comparator group)

subjects, 2 events) in the BIAsp 30 group. The incidence rate of injection site reactions was 3 events/100 PYE in both the IDegAsp group and the BIAsp 30 group. Among those, 3 events in the IDegAsp group and 1 event in the BIAsp 30 group were classified as adverse drug reactions. All injection site reactions reported in Trial 3896 and Trial 3597 were non-serious. In Trial 3896, one lipodystrophy-related event (lipohypertrophy, mild) was reported by one subject in the IGlar group, but its causal relationship to trial product was denied. No lipodystrophy-related events were reported in Trial 3597.

According to the global pooled data[66] from therapeutic confirmatory trials with IDegAsp, the incidence of injection site reactions was 2.0% (27 of 1360 subjects) in the pooled IDegAsp group and 2.2% (23 of 1037 subjects) in the pooled comparator group. The incidence rate of injection site reactions was lower in the pooled IDegAsp group (5.1 events/100 PYE) than in the pooled comparator group (10.0 events/100 PYE). Most of the events were mild in severity and only 1 event reported in the pooled comparator group was severe in severity and no serious events were reported. The incidence of lipodystrophy-related events was 0.1% (2 of 1360 subjects) in the pooled IDegAsp group and 0.9% (9 of 1037 subjects) in the pooled comparator group. The incidence rate of lipodystrophy-related events was 0.3 events/100 PYE in the pooled IDegAsp group and 2.2 events/100 PYE in the pooled comparator group. Lipodystrophy-related events were uncommon in both treatment groups and there were no severe or serious events.

In conclusion, either the therapeutic confirmatory trials including Japanese subjects or the global pooled data showed no differences in the occurrence of injection site reactions between IDegAsp and the comparators and different trends for IDegAsp and the comparators have not been suggested. A caution about injection site reactions will be included in the package insert and the occurrence of injection site reactions (as a priority item) will be identified via post-marketing surveillance.

PMDA considers as follows:
The incidence of injection site reactions after administration of IDegAsp was low and there were no marked differences compared with the comparators in Japanese and foreign clinical trials. Since an injection site reaction is one of significant events in treatment with insulin, 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:
Events identified by the SOC “neoplasms benign, malignant and unspecified (incl cysts and polyps)” and by the SMQ “neoplasms” and events judged by the investigator to be related to neoplasms in confirmatory

[66] Pooled data from 6 therapeutic confirmatory trials with IDegAsp (multinational trial [Trial 3597, T2DM], Trial 3590 [T2DM], Trial 3592 [T2DM], Trial 3593 [T2DM], Trial 3594 [T1DM] and its extension trial [Trial 3645]) (safety analysis set, 1360 subjects in the pooled IDegAsp group, 1037 subjects in the pooled comparator group)

trials were reviewed by an external independent consultant in a blinded manner for classification into three categories: malignant, benign, and unclassifiable. In Trial 3896, 14 events of neoplasms were reported (IDegAsp group, 9 events; IGlar group, 5 events). As a result of a review of these events by an external consultant, none were classified as malignant neoplasms, 12 events (IDegAsp group, 7 events; IGlar group, 5 events) were classified as benign neoplasms, and 2 events (both in the IDegAsp group) were assessed as unclassifiable. None of the events were classified as adverse drug reactions. One of the events classified as benign neoplasms was later confirmed to be "pulmonary tuberculosis." One event assessed as unclassifiable (bladder cancer) in the IDegAsp group was considered as a serious adverse event. In Trial 3597, 16 events of neoplasms were reported (IDegAsp group, 9 events; BIAsp 30 group, 7 events). As a result of a review of these events by an external consultant, 2 events (IDegAsp group, 1 event [breast cancer]; BIAsp 30 group, 1 event [metastatic gastric cancer]) were classified as malignant neoplasms, 11 events (IDegAsp group, 6 events; BIAsp 30 group, 5 events) as benign neoplasms, and 3 events (IDegAsp group, 2 events; BIAsp 30 group, 1 event) were assessed as unclassifiable. The two events classified as malignant neoplasms (IDegAsp group, breast cancer; BIAsp 30 group, metastatic gastric cancer) were considered as serious adverse events. A causal relationship to trial product was denied for all the events of neoplasms, except for 1 event classified as benign neoplasm (colonic polyp) reported in the BIAsp 30 group.

According to the global pooled data[64] from therapeutic confirmatory trials with IDeg/IDegAsp, a total of 323 events of neoplasms were reported. As a result of a review of these events by an external consultant, 67 events (pooled IDeg/IDegAsp group, 48 events; pooled comparator group, 19 events) were classified as malignant neoplasms, 215 events (pooled IDeg/IDegAsp group, 153 events; pooled comparator group, 62 events) as benign neoplasms, and 41 events (pooled IDeg/IDegAsp group, 30 events; pooled comparator group, 11 events) as unclassifiable. The incidence of malignant neoplasms was 0.8% (44 of 5782 subjects) in the pooled IDeg/IDegAsp group and 0.5% (19 of 3455 subjects) in the pooled comparator group and the incidence rate of malignant neoplasms was 0.9 events/100 PYE in the pooled IDeg/IDegAsp group and 0.7 events/100 PYE in the pooled comparator group, showing no apparent differences between the treatment groups. As for the time of onset of malignant neoplasms, of the 48 events in the pooled IDeg/IDegAsp group, 16 events (33.3%) were reported within 3 months after the start of trial treatment, 4 events (8.3%) were reported after 3 to 6 months of treatment, 8 events (16.7%) were reported after 6 to 9 months of treatment, and 17 events (41.7%) were reported ≥9 months after the start of trial treatment. Of the 19 events in the pooled comparator group, 5 events (26.3%) were reported within 3 months after the start of trial treatment, 8 events (42.1%) were reported after 3 to 6 months of treatment, 2 events (10.5%) were reported after 6 to 9 months of treatment, and 4 events (21.1%) were reported ≥9 months after the start of trial treatment. Based on the global pooled data, the most frequently reported types of malignancies involved the skin, gastrointestinal tract, breast, thyroid, and bladder. Skin malignant neoplasms (pooled IDeg/IDegAsp group, 14 events; pooled comparator group, 3 events) and gastrointestinal malignant neoplasms (pooled IDeg/IDegAsp group, 11 events; pooled comparator group,

4 events) were reported more frequently in the pooled IDeg/IDegAsp group, whereas breast malignant neoplasms (pooled IDeg/IDegAsp group, 2 events; pooled comparator group, 3 events) and thyroid malignant neoplasms (pooled IDeg/IDegAsp group, 1 event; pooled comparator group, 3 events) were reported more frequently in the pooled comparator group. There was no difference between the treatment groups for bladder malignant neoplasms (pooled IDeg/IDegAsp group, 3 events; pooled comparator group, 2 events). There was no apparent difference in the incidence rate of benign neoplasms between the pooled IDeg/IDegAsp group (3.0 events/100 PYE) and the pooled comparator group (2.4 events/100 PYE). The incidence rate of unclassifiable neoplasms was low in both the pooled IDeg/IDegAsp group (0.6 events/100 PYE) and the pooled comparator group (0.4 events/100 PYE).

In conclusion, according to the global pooled data, overall, there were no differences in the frequency of neoplasms between the pooled IDeg/IDegAsp group and the pooled comparator group. The observed differences in the numbers of some types of malignancies between the treatment groups are considered incidental since the incidences of each type of malignancies were low. For the occurrence of neoplasms following treatment with IDegAsp during the post-marketing period, as in the case of the currently approved insulin preparations including IDeg, pharmacovigilance activities such as Periodic Safety Update Reports and literature search will be conducted. The cases of neoplasms from clinical investigations and spontaneous reporting will be followed up and assessed.

PMDA considers as follows:
There was no trend towards a particularly higher risk of neoplasms with IDegAsp and IDeg compared with the comparators in clinical trials. 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, since the number of Japanese subjects on long-term treatment with IDegAsp studied was limited, it is necessary to continue to collect information on the development of neoplasms via post-marketing surveillance.

4.(iii).B.(4).5) Cardiovascular risk
The applicant explained as follows:
As for the cardiovascular risk of IDegAsp, the incidence of adverse events in the SOC "cardiac disorders" in Trial 3896 was 2.7% (4 of 147 subjects, 4 events) in the IDegAsp group and 5.4% (8 of 149 subjects, 9 events) in the IGlar group. The incidence of events in the SOC "vascular disorders" was 2.0% (3 of 147 subjects, 3 events) in the IDegAsp group and 2.7% (4 of 149 subjects, 4 events) in the IGlar group. Only the 4 events reported in the IGlar group (supraventricular extrasystoles, splinter hemorrhages, sinus bradycardia, hypertension) were classified as adverse drug reactions. One event reported by 1 subject of the IDegAsp group (cardiac failure) was considered as a serious adverse event. In Trial 3597, the incidence of adverse events in the SOC "cardiac disorders" was 1.8% (5 of 279 subjects, 5 events) in the IDegAsp group and 4.3% (6 of 141 subjects, 10 events) in the BIAsp 30 group. The incidence of events in

the SOC "vascular disorders" was 4.3% (12 of 279 subjects, 13 events) in the IDegAsp group and 3.5% (5 of 141 subjects, 5 events) in the BIAsp 30 group. A causal relationship to trial product was denied for all the adverse events in the SOCs "cardiac disorders" and "vascular disorders." Two events in 2 subjects of the IDegAsp group (coronary artery stenosis, cardiac failure) and 4 events in 4 subjects of the BIAsp 30 group (acute myocardial infarction in 2 subjects, acute coronary syndrome in 1 subject, angina pectoris in 1 subject) were considered as serious adverse events. Cardiovascular events sent to an external event adjudication committee[67] were 4 events in 4 subjects (IDegAsp group, 3 events in 3 subjects [cerebral infarction in 2 subjects, cardiac failure in 1 subject]; IGlar group, 1 event in 1 subject [cerebral infarction]) in Trial 3896 and 13 events in 12 subjects (IDegAsp group, 5 events in 5 subjects [carotid artery occlusion in 1 subject, cerebral infarction in 1 subject, chest pain in 1 subject, cardiac failure in 1 subject, coronary artery stenosis in 1 subject]; BIAsp 30 group, 8 events in 7 subjects [acute myocardial infarction in 2 subjects, angina pectoris in 1 subject, ischemic cerebral stroke in 1 subject, acute coronary syndrome in 1 subject, lacunar infarction in 1 subject, abnormal electrocardiogram in 1 subject, dysarthria in 1 subject) in Trial 3597. Of these, 2 events in 2 subjects of the IDegAsp group and 1 event in 1 subject of the IGlar group in Trial 3896 (all cerebral infarction) and 1 event in 1 subject of the IDegAsp group (carotid artery occlusion) and 5 events in 5 subjects of the BIAsp 30 group (acute myocardial infarction in 2 subjects, angina pectoris in 1 subject, ischemic cerebral stroke in 1 subject, acute coronary syndrome in 1 subject) in Trial 3597 were adjudicated as major adverse cardiovascular events (MACE).

In Trials 3597 and 3896, lipid parameters (total cholesterol, triglycerides, LDL cholesterol, HDL cholesterol) were normal throughout the trial period in most subjects. 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 (Trial 3896, 0%-4.8% in the IDegAsp group and 0%-6.7% in the IGlar group; Trial 3597, 0%-5.0% in the IDegAsp group and 0%-5.7% in the BIAsp 30 group) and there were no clinically meaningful differences between the treatment groups. Lipid-related adverse events in the SOC "investigations" occurred in 1 subject of the IGlar group (1 event, lipids abnormal) in Trial 3896 and 1 subject of the IDegAsp group (1 event, blood cholesterol increased) in Trial 3597. Both events were mild in severity and their causal relationship to trial product was denied.

There were no clinically relevant differences in ECG, blood pressure, or pulse rate findings at Week 26 between the IDegAsp and comparator groups in Trial 3896 and Trial 3597. Vital sign-related adverse events in the SOC "investigations" occurred in 3 subjects of the IGlar group (3 events) in Trial 3896 and 2 subjects of the IDegAsp group (2 events) and 2 subjects of the BIAsp 30 group (2 events) in Trial 3597 (all blood pressure increased). All events were mild in severity except for 1 event reported by 1 subject in the BIAsp 30 group (moderate) and a causal relationship to trial product was denied. ECG-related adverse

[67] Events identified by SMQ search (other ischaemic heart disease, ischaemic cerebrovascular conditions, myocardial infarction, haemorrhagic 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.

events in the SOCs “investigations” and “cardiac disorders” occurred in 4 subjects of the IDegAsp group (4 events) (2 events of ventricular extrasystoles in 2 subjects, 1 event of electrocardiogram T wave amplitude decreased in 1 subject, 1 event of ventricular arrhythmia in 1 subject) and 4 subjects of the IGlar group (4 events) (atrial fibrillation, sinus bradycardia, supraventricular extrasystoles, ventricular extrasystoles) in Trial 3896 and 1 subject of the IDegAsp group (1 event) (sinus bradycardia) and 3 subjects of the BIAsp 30 group (5 events) (1 event of myocardial ischaemia in 1 subject, 1 event of myocardial ischaemia/2 events of sinus bradycardia in 1 subject, 1 event of electrocardiogram abnormal in 1 subject) in Trial 3597. All of the ECG-related adverse events reported in Trial 3896 and Trial 3597 were mild in severity except for 1 event reported by 1 subject in the IGlar group in Trial 3896 (atrial fibrillation, moderate) and a causal relationship to trial product was denied except for 2 events in 2 subjects of the IGlar group in Trial 3896 (sinus bradycardia, supraventricular extrasystoles) and 1 event in 1 subject of the BIAsp 30 group in Trial 3597 (electrocardiogram abnormal). As for body weight, the mean body weight gain (mean ± SD) from baseline to the end of treatment in Trial 3896 was 0.7 ± 2.8 kg (n = 147) in the IDegAsp group and 0.7 ± 2.2 kg (n = 149) in the IGlar group, showing no apparent difference between the two treatment groups. The mean body weight gain (mean ± SD) from baseline to the end of treatment in Trial 3597 was 1.1 ± 2.9 kg (n = 279) in the IDegAsp group and 1.4 ± 3.0 kg (n = 141) in the BIAsp 30 group, showing no apparent difference between the two treatment groups. Adverse events related to body weight in the SOCs “investigations” and “metabolism and nutrition disorders” occurred in 1 subject of the IDegAsp group (1 event) and 2 subjects of the IGlar group (2 events) in Trial 3896 and 8 subjects of the IDegAsp group (8 events) and 2 subjects of the BIAsp 30 group (2 events) in Trial 3597. All of these events reported in Trial 3896 and Trial 3597 were mild in severity and classified as adverse drug reactions except for 3 events reported by 3 subjects in the IDegAsp group in Trial 3597.

In conclusion, the therapeutic confirmatory trials including Japanese subjects suggested no apparent differences in the cardiovascular risk between IDegAsp and the comparators.

According to the global pooled data[68] from therapeutic confirmatory trials with IDeg/IDegAsp, the incidence of adverse events in the SOC “cardiac disorders” was 4.3% (273 of 6374 subjects) in the pooled IDeg/IDegAsp group and 3.6% (125 of 3455 subjects) in the pooled comparator group and the incidence rate of adverse events in the SOC “cardiac disorders” was 6.7 events/100 PYE in the pooled IDeg/IDegAsp group and 6.9 events/100 PYE in the pooled comparator group, showing no marked differences between the two treatment groups. The incidence of adverse events in the SOC “vascular disorders” was 5.4% (346 of 6374 subjects) in the pooled IDeg/IDegAsp group and 4.5% (157 of 3455

[68] Pooled data from 26 therapeutic confirmatory trials with administration of IDeg or IDegAsp, completed by May 1, 2012 (IDeg, Trial 3585 and its extension trial [Trial 3725], Trial 3586, Trial 3579 and its extension trial [Trial 3643], Trial 3580, Trial 3582 and its extension trial [Trial 3667], Trial 3583 and its extension trial [Trial 3644], Trial 3668, Trial 3672, Trial 3718, Trial 3724, Trial 3770 and its extension trial, Trial 3846, Trial 3923; IDegAsp, Trial 3597, Trial 3590 and its extension trial [Trial 3726], Trial 3592, Trial 3593, Trial 3594 and its extension trial [Trial 3645], Trial 3896) (safety analysis set, 6374 subjects in the pooled IDeg/IDegAsp group and 3455 subjects in the pooled comparator group).

subjects) in the pooled comparator group and the incidence rate of adverse events in the SOC "vascular disorders" was 7.6 events/100 PYE in the pooled IDeg/IDegAsp group and 6.8 events/100 PYE in the pooled comparator group, showing no marked differences between the two treatment groups. The incidence of events adjudicated as MACE by the independent Event Adjudication Committee was 1.5% (98 of 6374 subjects, 105 events) in the pooled IDeg/IDegAsp group and 1.1% (37 of 3455 subjects, 39 events) in the pooled comparator group. The incidence rate of MACE was 1.9 events/100 PYE in the pooled IDeg/IDegAsp group and 1.5 events/100 PYE in the pooled comparator group, showing no marked differences between the two treatment groups. Most of the events adjudicated as MACE were considered as serious adverse events. Furthermore, an MACE meta-analysis based on the global pooled data[69] from therapeutic confirmatory trials with IDeg/IDegAsp was performed. Of 9850 subjects included in the meta-analysis (pooled IDeg/IDegAsp group, 6389 subjects; pooled comparator group, 3461 subjects), 141 subjects[70] had at least 1 MACE (pooled IDeg/IDegAsp group, 102 subjects; pooled comparator group, 39 subjects). The incidence rate of MACE was 1.89 events/100 PYE in the pooled IDeg/IDegAsp group and 1.52 events/100 PYE in the pooled comparator group. The hazard ratio of the pooled IDeg/IDegAsp group to the pooled comparator group with its 95% confidence interval was 1.29 [0.881, 1.888].

In conclusion, the analysis did not suggest that IDeg/IDegAsp is associated with an apparent increased cardiovascular risk.

PMDA considers as follows:
In the therapeutic confirmatory trials including Japanese subjects, no apparent differences in the occurrence of cardiovascular adverse events were observed between the IDeg/IDegAsp group and the comparator group and there were no significant changes in vital signs, ECG, or lipid parameters. In addition, the meta-analysis based on the global pooled data did not suggest any apparent increased cardiovascular risk in the pooled IDeg/IDegAsp group. Therefore, there is no major problem with the applicant's response. However, since the number of subjects included in clinical trials was limited, it is necessary to continue to collect information on cardiovascular risk via post-marketing surveillance.

4.(iii).B.(4).6) Antibody formation

Insulin antibody development after administration of IDegAsp was evaluated in Trial 3597 including Japanese subjects, and the results showed no trend towards marked rises in antibody titers following treatment with IDegAsp (Table 59). "A rise in antibody titer" was defined as an increase of ≥10%B/T (absolute) in antibodies cross-reacting with human insulin or an increase of ≥5%B/T in insulin-specific antibodies (anti-IDeg antibodies or anti-IAsp antibodies) at the end of the trial (1 week after the end of trial treatment: Week 27). The proportion of subjects with a rise in antibody titer was 7.2% (20 of 279

[69] Pooled data from 26 therapeutic confirmatory trials with administration of IDeg or IDegAsp, completed by May 1, 2012 (FAS, 6389 subjects in the pooled IDeg/IDegAsp group and 3461 subjects in the pooled comparator group).
[70] Including non-TEAEs reported in 5 subjects of the pooled IDeg/IDegAsp group and 2 subjects of the pooled comparator group

subjects) in the IDegAsp group and 22.0% (31 of 141 subjects) in the BIAsp 30 group. According to the global pooled data[71] from therapeutic confirmatory trials with IDegAsp, in the overall population (T1DM + T2DM), the proportion of subjects with a rise in antibody titer was 9.5% (86 of 903 subjects) in the pooled IDegAsp group and 26.2% (152 of 581 subjects) in the pooled comparator group. Among subjects with T1DM, the proportion of subjects with a rise in antibody titer was 13.0% (47 of 362 subjects) in the pooled IDegAsp group and 55.9% (100 of 179 subjects) in the pooled comparator group. Among subjects with T2DM, the proportion of subjects with a rise in antibody titer was 7.2% (39 of 541 subjects) in the pooled IDegAsp group and 12.9% (52 of 402 subjects) in the pooled comparator group.

Concerning the influence of antibody formation on the safety of IDegAsp, the relationship between a rise in antibody titer and the occurrence of injection site reactions, immunogenicity-related adverse events (allergic reactions), and hypoglycaemia in therapeutic confirmatory trials with IDegAsp was investigated. Among subjects with a rise in antibody titer in Trial 3597, 1 subject in the BIAsp 30 group had 1 injection site reaction (injection site erythema) and 1 subject in the BIAsp 30 group had 1 immunogenicity-related adverse event (an allergic reaction: face oedema). Both events were mild in severity and non-serious and their causal relationship to trial product was denied. In Trial 3597, the number of subjects with severe hypoglycaemia was low (IDegAsp group, 1.4% [4 of 279 subjects, 6 episodes]; BIAsp 30 group, 1.4% [2 of 141 subjects, 2 episodes]). Among 20 subjects with a rise in antibody titer in the IDegAsp group, 1 subject had 2 episodes of severe hypoglycaemia and among 31 subjects with a rise in antibody titer in the BIAsp 30 group, 1 subject had 1 episode of severe hypoglycaemia.

According to the global pooled data from therapeutic confirmatory trials with IDegAsp, among subjects with a rise in antibody titer, the incidence of injection site reactions was 2.3% (2 of 86 subjects, 3 events) in the pooled IDegAsp group and 5.9% (9 of 152 subjects, 37 events) in the pooled comparator group and the incidence rate of injection site reactions was lower in the pooled IDegAsp group (5.3 events/100 PYE) than in the pooled comparator group (31.2 events/100 PYE). Among subjects without a rise in antibody titer, the incidence of injection site reactions was 2.3% (19 of 817 subjects, 25 events) in the pooled IDegAsp group and 2.1% (9 of 429 subjects, 11 events) in the pooled comparator group and the incidence rate of injection site reactions was comparable between the treatment groups (5.1 events/100 PYE in the pooled IDegAsp group, 5.2 events/100 PYE in the pooled comparator group). The incidence rate of injection site reactions was higher in subjects with a rise in antibody titer than in subjects without a rise in antibody titer in the pooled comparator group, whereas the incidence rate of injection site reactions was comparable between subjects with and without a rise in antibody titer in the pooled IDegAsp group. The number of immunogenicity-related adverse events (allergic reactions) was low and only 2 events were reported by 2 subjects in the pooled comparator group (1.7 events/100 PYE) among subjects with a rise in

[71] Pooled data from 4 therapeutic confirmatory trials in which IDegAsp was administered (Trial 3590, Trial 3594 and its extension trial [Trial 3645], Trial 3597) (safety analysis set excluding subjects in whom antibody titers were measured at baseline or the end of treatment: 903 subjects in the pooled IDegAsp group and 581 subjects in the pooled comparator group)

antibody titer. Also among subjects without a rise in antibody titer, the number of immunogenicity-related adverse events was low, i.e. 4 events reported by 4 subjects in the pooled IDegAsp group (0.8 events/100 PYE) and 1 event reported by 1 subject in the pooled comparator group (0.5 events/100 PYE).

As for hypoglycaemia, according to the global pooled data[61] from therapeutic confirmatory trials with IDegAsp in subjects with T1DM, among subjects with a rise in antibody titer, the incidence and incidence rate of confirmed hypoglycaemia were 97.9% (46 of 47 subjects) and 3087.5 episodes/100 PYE, respectively, in the pooled IDegAsp group and 97.0% (97 of 100 subjects) and 3878.7 episodes/100 PYE, respectively, in the pooled comparator group. Among subjects without a rise in antibody titer, the incidence and incidence rate of confirmed hypoglycaemia were 94.6% (298 of 315 subjects) and 3197.1 episodes/100 PYE, respectively, in the pooled IDegAsp group and 89.9% (71 of 79 subjects) and 3346.8 episodes/100 PYE, respectively, in the pooled comparator group. Thus, a relationship between a rise in antibody titer and the occurrence of confirmed hypoglycaemia was not suggested in either treatment group. Among subjects with a rise in antibody titer, the incidence and incidence rate of severe hypoglycaemia were 8.5% (4 of 47 subjects) and 15.8 episodes/100 PYE, respectively, in the pooled IDegAsp group and 20.0% (20 of 100 subjects) and 45.3 episodes/100 PYE, respectively, in the pooled comparator group. Among subjects without a rise in antibody titer, the incidence and incidence rate of severe hypoglycaemia were 14.0% (44 of 315 subjects) and 28.2 episodes/100 PYE, respectively, in the pooled IDegAsp group and 16.5% (13 of 79 subjects) and 44.4 episodes/100 PYE, respectively, in the pooled comparator group and the incidence rate of severe hypoglycaemia tended to be lower in subjects with a rise in antibody titer than in subjects without a rise in antibody titer in the pooled IDegAsp group.

According to the global pooled data[59] from therapeutic confirmatory trials with IDegAsp in subjects with T2DM, among subjects with a rise in antibody titer, the incidence and incidence rate of confirmed hypoglycaemia were 66.7% (26 of 39 subjects) and 554.6 episodes/100 PYE, respectively, in the pooled IDegAsp group and 61.5% (32 of 52 subjects) and 431.4 episodes/100 PYE, respectively, in the pooled comparator group. Among subjects without a rise in antibody titer, the incidence and incidence rate of confirmed hypoglycaemia were 61.8% (310 of 502 subjects) and 712.2 episodes/100 PYE, respectively, in the pooled IDegAsp group and 48.9% (171 of 350 subjects) and 455.9 episodes/100 PYE, respectively, in the pooled comparator group. Thus, a relationship between a rise in antibody titer and the occurrence of confirmed hypoglycaemia was not suggested in either treatment group. Among subjects with a rise in antibody titer, the incidence and incidence rate of severe hypoglycaemia were 2.6% (1 of 39 subjects) and 10.5 episodes/100 PYE, respectively, in the pooled IDegAsp group and 1.9% (1 of 52 subjects) and 3.9 episodes/100 PYE, respectively, in the pooled comparator group. Among subjects without a rise in antibody titer, the incidence and incidence rate of severe hypoglycaemia were 0.8% (4 of 502 subjects) and 2.2 episodes/100 PYE, respectively, in the pooled IDegAsp group and 0.6% (2 of 350 subjects) and 1.2 episodes/100 PYE, respectively, in the pooled comparator group. The number of severe hypoglycaemic episodes was low in both treatment groups, with or without a rise in antibody titer.

In conclusion, the immunogenic response to treatment with IDegAsp is low and there is no influence of antibody formation on the safety of IDegAsp.

PMDA considers as follows:
Clinical trials showed no trend towards marked rises in antibody titers following treatment with IDegAsp and there was no apparent influence of antibody formation on the safety of IDegAsp. However, since the information on antibody development following long-term treatment with IDegAsp in Japanese subjects is limited, it is necessary to continue to collect information on antibody development via post-marketing surveillance.

4.(iii).B.(4).7) Safety in long-term treatment and T1DM patients
The applicant explained as follows:
There are no clinical trials investigating long-term treatment (≥6 months) with IDegAsp in Japanese patients nor clinical trials investigating long-term treatment with IDegAsp in Japanese patients with T1DM. However, the applicant considers it is possible to evaluate the safety of a co-formulation of two active ingredients in long-term treatment and Japanese patients with T1DM on the basis of the safety data of each active ingredient.

The long-term safety of IDeg (the basal component of IDegAsp) and IAsp (the bolus component of IDegAsp) was investigated in Trials 3585/3725 (52 weeks of treatment) of IDeg in combination with IAsp in subjects with T1DM including Japanese subjects. In addition, as to the long-term safety of IAsp (the bolus component of IDegAsp), ≥10 years have passed since the launch of IAsp in Japan and it has been concluded that there are no problems requiring specific action for the safety of IAsp (NovoRapid re-examination report).

Long-term treatment with IDegAsp in T1DM patients was investigated in Trials 3594/3645[62] (once-daily administration, 52 weeks of treatment) in non-Japanese T1DM patients. The incidence and number of adverse events were 73.8% (267 of 362 subjects) and 1210 events, respectively, in the IDegAsp group and 70.6% (127 of 180 subjects) and 643 events, respectively, in the IDet group. The incidence rate of adverse event was 408 events/100 PYE in the IDegAsp group and 442 events/100 PYE in the IDet group, showing no marked difference between the two treatment groups. As for the occurrence of hypoglycaemia, the incidence rate of confirmed hypoglycaemia was 3183 episodes/100 PYE in the IDegAsp group and 3673 episodes/100 PYE in the IDet group, showing no marked difference between the two treatment groups. The incidence rate of nocturnal confirmed hypoglycaemia was 309 episodes/100 PYE in the IDegAsp group and 541 episodes/100 PYE in the IDet group, being lower in the IDegAsp group than in the IDet group.

Based on the above, the applicant considers that there were no findings raising concern about the long-term safety of IDegAsp in diabetic patients including T1DM patients.

PMDA considers as follows:
No safety concerns were raised in Trials 3585/3725 of IDeg in combination with IAsp (the active ingredients of IDegAsp) and there is no particular problem with the applicant's view that there were no findings raising concern about the long-term safety of IDegAsp in diabetic patients including T1DM patients. In addition, foreign trials 3594/3465 showed no apparent differences in safety between IDegAsp and IDet (a comparator). However, since long-term treatment with IDegAsp was investigated in the limited number of Japanese subjects and was not investigated in Japanese subjects with T1DM, it is necessary to collect information on the safety of IDegAsp in these patients via post-marketing surveillance.

4.(iii).B.(5) Indication
PMDA considers as follows:
There is no problem with the proposed indication of "diabetes mellitus where treatment with insulin is required," since the efficacy of twice-daily and once-daily administration of IDegAsp has been demonstrated [see "4.(iii).B.(3) Efficacy"] and the safety of IDegAsp is acceptable [see "4.(iii).B.(4) Safety"].

4.(iii).B.(6) Dosage and administration
4.(iii).B.(6).1) Safety in the initial phase after switching from other insulin products
PMDA asked the applicant to explain the dose and safety of IDegAsp in the initial phase after switching from other insulin products.

The applicant responded as follows:

(a) Switching to IDegAsp (twice-daily administration) in subjects with T2DM
In Trial 3597, transfer from previous insulin treatments to trial product on a unit-to-unit basis was recommended, irrespective of type of previous insulin treatment. In the IDegAsp group, the mean total daily insulin dose was 26.9 units at screening and 26.2 units at baseline (Week 1) in subjects previously treated with basal insulin and 42.8 units at screening and 41.5 units at baseline (Week 1) in subjects previously treated with premixed insulin. In either case, the mean total daily insulin dose in the initial phase after switching was not apparently different from that before the switch and subjects were transferred to trial product on a unit-to-unit basis.

Glycaemic control in the initial phase after switching to IDegAsp was analysed by type of previous insulin treatment and prior insulin injection frequency. When an analysis was performed by type of previous insulin treatment, there were no apparent differences in pre-breakfast and pre-dinner SMPG profiles in the

IDegAsp group between subjects previously treated with basal insulin and subjects previously treated with premixed insulin (Table 60). When analysed by prior insulin injection frequency, the number of subjects previously treated with once-daily premixed insulin was only 4 (2 subjects in the IDegAsp group, 2 subjects in the BIAsp 30 group). Therefore, only subjects previously treated with basal insulin were included in the analysis. The pre-breakfast SMPG profiles in the IDegAsp group were similar between subjects previously treated with basal insulin QD and subjects previously treated with basal insulin BID. The pre-dinner SMPG profiles were higher in subjects previously treated with basal insulin QD than in subjects previously treated with basal insulin BID in the IDegAsp group, but there was not apparent difference between the trends observed in the IDegAsp group and the BIAsp 30 group (Table 61).

Table 60. SMPG profiles in the initial phase after switching to IDegAsp or BIAsp 30 BID by type of previous insulin treatment (Trial 3597, FAS)

SMPG	Week	Previously treated with basal insulin		Previously treated with premixed insulin[a)]	
		IDegAsp (n = 82)	BIAsp 30 (n = 42)	IDegAsp (n = 195)	BIAsp 30 (n = 98)
Pre-breakfast SMPG (mg/dL)	Week 1	137.6 ± 44.8 (n = 80)	154.2 ± 32.0 (n = 41)	126.1 ± 40.4 (n = 192)	159.1 ± 45.1 (n = 97)
	Week 2	120.0 ± 37.0 (n = 80)	144.5 ± 38.4 (n = 41)	114.1 ± 31.3 (n = 190)	143.3 ± 42.2 (n = 95)
	Week 4	110.8 ± 33.9 (n = 79)	128.3 ± 22.1 (n = 39)	108.0 ± 31.2 (n = 189)	130.1 ± 31.6 (n = 95)
Pre-dinner SMPG (mg/dL)	Week 1	184.9 ± 61.0 (n = 80)	176.5 ± 64.4 (n = 41)	183.6 ± 63.6 (n = 191)	198.6 ± 59.0 (n = 97)
	Week 2	170.1 ± 66.8 (n = 80)	157.4 ± 54.4 (n = 41)	161.5 ± 51.9 (n = 189)	174.5 ± 50.9 (n = 95)
	Week 4	148.1 ± 48.4 (n = 79)	147.4 ± 48.1 (n = 39)	149.9 ± 47.2 (n = 189)	162.0 ± 49.4 (n = 95)

Mean ± SD (number of subjects included in the analysis)

a) Only 2 subjects in each treatment group were previously treated with premixed insulin QD and other subjects were all previously treated with premixed insulin BID.

Table 61. SMPG profiles in the initial phase after switching to IDegAsp or BIAsp 30 BID by prior basal insulin injection frequency (Trial 3597, FAS)

SMPG	Week	Previously treated with basal insulin QD		Previously treated with basal insulin BID	
		IDegAsp (n = 58)	BIAsp 30 (n = 29)	IDegAsp (n = 24)	BIAsp 30 (n = 13)
Pre-breakfast SMPG (mg/dL)	Week 1	139.7 ± 44.0 (n = 56)	159.2 ± 29.0 (n = 29)	132.8 ± 47.2 (n = 24)	142.0 ± 36.8 (n = 12)
	Week 2	119.4 ± 36.7 (n = 56)	140.8 ± 33.6 (n = 28)	121.6 ± 38.4 (n = 24)	152.5 ± 47.7 (n = 13)
	Week 4	110.2 ± 33.7 (n = 56)	128.7 ± 19.8 (n = 28)	112.4 ± 35.2 (n = 23)	127.4 ± 28.2 (n = 11)
Pre-dinner SMPG (mg/dL)	Week 1	190.5 ± 62.9 (n = 56)	183.6 ± 67.0 (n = 29)	171.8 ± 55.4 (n = 24)	159.3 ± 56.7 (n = 12)
	Week 2	179.8 ± 69.6 (n = 56)	165.8 ± 56.0 (n = 28)	147.3 ± 54.6 (n = 24)	139.5 ± 47.9 (n = 13)
	Week 4	155.0 ± 49.7 (n = 56)	156.5 ± 47.1 (n = 28)	131.3 ± 41.4 (n = 23)	124.4 ± 44.4 (n = 11)

Mean ± SD (number of subjects included in the analysis)

Table 62 shows the occurrence of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia in the initial phase after switching by type of previous insulin treatment. The incidence and incidence rate of confirmed hypoglycaemia in the IDegAsp group increased from Week 1 to Week 4 in subjects previously treated with basal insulin but were comparable at Weeks 1, 2, and 4 in subjects previously treated with premixed insulin. In the BIAsp 30 group, the incidence and number of confirmed hypoglycaemia were low, irrespective of type of previous insulin treatment. Due to the low incidence and incidence rate of nocturnal confirmed hypoglycaemia, the assessment was difficult, but there was no trend towards apparent differences in the pattern of occurrence of nocturnal confirmed hypoglycaemia according to the type of previous insulin treatment in either treatment group. Due to the low number of hypoglycaemic episodes, it was difficult to assess the occurrence of hypoglycaemia in the initial phase after switching by prior basal

insulin injection frequency, but the number of confirmed hypoglycaemic episodes in the IDegAsp group was highest at Week 4, regardless of prior basal insulin injection frequency (Table 63). There was no relationship between the occurrence of nocturnal confirmed hypoglycaemia and prior basal insulin injection frequency.

Table 62. Hypoglycaemic episodes in the initial phase after switching to IDegAsp or BIAsp 30 BID by type of previous insulin treatment[a)] (Trial 3597 [26 weeks of treatment] safety analysis set)

		Previously treated with basal insulin				Previously treated with premixed insulin			
		IDegAsp (n = 81)		BIAsp 30 (n = 42)		IDegAsp (n = 195)		BIAsp 30 (n = 97)	
Confirmed hypoglycaemia	Entire trial period	72.8 (59) 261	707.3	71.4 (30) 123	646.8	73.8 (144) 959	1055.3	78.4 (76) 492	1085.1
	Week 1	4.9 (4) 4	257.7	11.9 (5) 8	993.9	12.3 (24) 33	886.9	6.2 (6) 6	322.8
	Week 2	12.3 (10) 13	837.4	9.5 (4) 6	758.3	10.9 (21) 40	1083.0	8.2 (8) 9	488.4
	Week 4	20.0 (16) 27	1780.1	2.6 (1) 1	133.8	11.6 (22) 36	993.9	13.7 (13) 19	1043.6
Nocturnal confirmed hypoglycaemia	Entire trial period	18.5 (15) 30	81.3	21.4 (9) 20	105.2	27.7 (54) 112	123.2	36.1 (35) 81	178.6
	Week 1	0.0 (0) 0	0	2.4 (1) 1	124.2	3.1 (6) 7	188.1	1.0 (1) 1	53.8
	Week 2	0.0 (0) 0	0	2.4 (1) 3	379.2	1.0 (2) 4	108.3	0.0 (0) 0	0
	Week 4	1.3 (1) 1	65.9	0.0 (0) 0	0	1.1 (2) 2	55.2	2.1 (2) 2	109.8

Left column: incidence [%] (number of subjects with episodes), number of episodes; Right column: incidence rate [number of episodes/100 PYE]

a) One severe hypoglycaemic episode occurring during the first 4 weeks of the trial was reported in each treatment group (both episodes occurred at Week 2 in subjects previously treated with premixed insulin).

Table 63. Hypoglycaemic episodes in the initial phase after switching to IDegAsp or BIAsp 30 BID by prior basal insulin injection frequency (Trial 3597 [26 weeks of treatment] safety analysis set)

		once daily				twice daily			
		IDegAsp (n = 57)		BIAsp 30 (n = 29)		IDegAsp (n = 24)		BIAsp 30 (n = 13)	
Confirmed hypoglycaemia	Entire trial period	71.9 (41) 185	726.0	69.0 (20) 69	507.0	75.0 (18) 76	665.5	76.9 (10) 54	998.7
	Week 1	1.8 (1) 1	91.5	0.0 (0) 0	0	12.5 (3) 3	652.2	38.5 (5) 8	3211.0
	Week 2	12.3 (7) 8	732.3	3.4 (1) 3	553.4	12.5 (3) 5	1087.1	23.1 (3) 3	1204.1
	Week 4	21.4 (12) 16	1490.8	3.6 (1) 1	186.4	16.7 (4) 11	2480.1	0.0 (0) 0	0
Nocturnal confirmed hypoglycaemia	Entire trial period	17.5 (10) 24	94.2	17.2 (5) 11	80.8	20.8 (5) 6	52.5	30.8 (4) 9	166.4
	Week 1	0.0 (0) 0	0	0.0 (0) 0	0	0.0 (0) 0	0	7.7 (1) 1	401.4
	Week 2	0.0 (0) 0	0	3.4 (1) 3	553.4	0.0 (0) 0	0	0.0 (0) 0	0
	Week 4	1.8 (1) 1	93.2	0.0 (0) 0	0	0.0 (0) 0	0	0.0 (0) 0	0

Left column: incidence [%] (number of subjects with episodes), number of episodes; Right column: incidence rate [number of episodes/100 PYE]

(b) Switching to IDegAsp (once-daily administration) in subjects with T2DM

In a foreign trial (Trial 3593[63]), switching from basal insulin QD to IDegAsp QD was investigated. In the IDegAsp group, the mean daily insulin dose was 30.5 units at screening and 27.8 units at baseline (Week 1) and the mean daily insulin dose in the initial phase after switching was not apparently different from that before the switch and subjects were transferred to trial product on a unit-to-unit basis. As to the occurrence of hypoglycaemia in the initial phase after switching, the proportions of subjects with confirmed hypoglycaemia at Weeks 1, 2, and 4 were 2.6%, 4.0% and 4.5%, respectively, in the IDegAsp group and 3.4%, 1.7% and 3.5%, respectively, in the IGlar group, being <5% in both treatment groups.

The incidence rates of confirmed hypoglycaemia (number of episodes/100 PYE) at Weeks 1, 2, and 4 were 160.3, 232.8, and 283.3, respectively, in the IDegAsp group and 269.9, 113.4, and 277.6, respectively, in the IGlar group. Taking the low number of hypoglycaemic episodes into consideration, there were no apparent differences among Weeks 1, 2, and 4 in either treatment group and the incidence rates of confirmed hypoglycaemia were lower during the initial phase compared with the entire trial period (IDegAsp group, 431.4; IGlar group, 320.1). In addition, there were no apparent differences between the two treatment groups at any of the initial weeks. The proportions of subjects with nocturnal confirmed hypoglycaemia at Weeks 1, 2 and 4 were low in both treatment groups (0%, 0.4%, and 0.9%, respectively, in the IDegAsp group; 0.9%, 0.4%, and 1.8%, respectively, in the IGlar group). The incidence rates (number of episodes/100 PYE) of nocturnal confirmed hypoglycaemia at Weeks 1, 2, and 4 were 0, 23.3, and 47.2, respectively, in the IDegAsp group and 90.0, 22.7, and 92.5, respectively, in the IGlar group, being lower than the incidence rates in the entire period (82.3 in the IDegAsp group, 100.5 in the IGlar group). No episodes of severe hypoglycaemia were reported at Week 1, 2, or 4 in either treatment group.

(c) Switching to IDegAsp (once-daily administration) plus bolus insulin (twice-daily administration) in subjects with T1DM

Switching from basal-bolus insulin regimen or other mixed insulin regimen in subjects with T1DM was investigated in a foreign trial (Trial 3594[62]). In subjects switching from a basal-bolus regimen (~90%), a unit-to-unit conversion of the basal insulin component was used for the transfer to IDegAsp and IAsp was administered at the remaining meals (two meals). In subjects switching from pre-mixed insulin, 70% of their pretrial total daily insulin dose was administered as IDegAsp QD, and 30% of their pre-trial total daily insulin dose was given as IAsp (divided into two injections) at the remaining meals (the dose of IAsp was 15% of their pre-trial total daily insulin dose). As a result, the total daily insulin dose in each subject at screening was almost identical to that at baseline (Week 1). At Week 26, 61% of all subjects' total insulin dose was given as IDegAsp and 39% was given as IAsp. Table 64 shows the occurrence of hypoglycaemia in the initial phase after switching. In subjects previously treated with a basal-bolus regimen, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia in the IDegAsp group at Weeks 1, 2, and 4 were numerically higher than those in the entire trial period, but were not apparently different from those in the entire trial period in the IDet group. The numbers of severe hypoglycaemic episodes at Weeks 1, 2, and 4 were low in both treatment groups. In subjects previously treated with pre-mixed insulin, there were no apparent differences in the incidence rate of confirmed hypoglycaemia in the IDegAsp group among Weeks 1, 2, and 4 and the entire period. The numbers of nocturnal confirmed hypoglycaemia and severe hypoglycaemia at Weeks 1, 2, and 4 were low in both treatment groups.

Table 64. Hypoglycaemic episodes in the initial phase after switching from basal-bolus regimen or mixed insulin to IDegAsp or IDet QD in subjects with T1DM by type of previous insulin treatment (Trial 3594 [26 weeks of treatment] safety analysis set)

		Previously treated with basal-bolus regimen				Previously treated with mixed insulin			
		IDegAsp (n = 332)		IDet (n = 160)		IDegAsp (n = 30)		IDet (n = 20)	
Confirmed hypoglycaemia	Entire trial period	94.6 (314) 6119	3951.4	94.4 (151) 3288	4389.9	90.0 (27) 515	3553.8	85.0 (17) 432	4804.8
	Week 1	47.9 (159) 326	5150.2	41.9 (67) 119	3898.2	36.7 (11) 24	4174.3	30.0 (6) 14	3787.8
	Week 2	45.8 (151) 316	4996.5	44.0 (70) 115	3794.4	33.3 (10) 20	3580.9	26.3 (5) 10	2746.2
	Week 4	47.9 (156) 310	4974.8	42.7 (67) 130	4320.5	37.9 (11) 22	3958.4	47.4 (9) 19	5217.9
Nocturnal confirmed hypoglycaemia	Entire trial period	53.0 (176) 602	388.7	71.3 (114) 446	595.5	53.3 (16) 27	186.3	55.0 (11) 34	378.2
	Week 1	8.7 (29) 34	537.1	10.0 (16) 18	589.6	6.7 (2) 2	347.9	0.0 (0) 0	0
	Week 2	8.8 (29) 31	490.2	7.5 (12) 14	461.9	0.0 (0) 0	0	5.3 (1) 1	274.6
	Week 4	7.4 (24) 31	497.5	10.8 (17) 19	631.5	3.4 (1) 1	179.9	5.3 (1) 1	274.6
Severe hypoglycaemia	Entire trial period	9.9 (33) 54	34.9	12.5 (20) 33	44.1	6.7 (2) 2	13.8	10.0 (2) 2	22.2
	Week 1	1.5 (5) 5	79.0	0.6 (1) 2	65.5	0.0 (0) 0	0	5.0 (1) 1	270.6
	Week 2	0.3 (1) 1	15.8	0.0 (0) 0	0	3.3 (1) 1	179.0	0.0 (0) 0	0
	Week 4	0.9 (3) 3	48.1	0.0 (0) 0	0	0.0 (0) 0	0	5.3 (1) 1	274.6

Left column: incidence [%] (number of subjects with episodes), number of episodes; Right column: incidence rate [number of episodes/100 PYE]

Based on the above results (a) to (c), the applicant considers as follows:
The results from Trial 3597 including Japanese subjects with T2DM showed that there were no apparent differences in glycaemic control or the occurrence of hypoglycaemia during the initial phase after switching to IDegAsp BID, irrespective of type of previous insulin treatment, supporting that subjects can transfer to IDegAsp BID on a unit-to-unit basis (at the same total daily insulin dose as the previous one of the subject). Based on the results of foreign trials (Trial 3593 and Trials 3594/3645), there were no safety concerns about switching from basal insulin QD to IDegAsp QD in subjects with T2DM and about switching from a basal-bolus regimen or mixed insulin to IDegAsp QD plus IAsp at the remaining meals in subjects with T1DM, respectively.

Since it should be noted that when switching from any insulin regimen, insulin dose is determined by individual needs, taking account of factors such as diet and exercise, a caution about transfer from other insulin products will be included in the package insert. In Trial 3594, there were no safety concerns about switching to IDegAsp QD plus bolus insulin at the remaining meals in subjects with T1DM. However, the starting dose of IDegAsp should be 50% to 60% of the total daily insulin requirements since the percentages of basal insulin (IDeg) and bolus insulin (IAsp) were 36% and 64%, respectively, at Week 26 in the Japanese subgroup in a multinational phase III trial (Trial 3585) including Japanese T1DM subjects treated with IDeg. On the other hand, switching from a basal-bolus regimen to IDegAsp BID or IDegAsp BID plus IAsp QD (at the remaining meal) is not recommended since no relevant clinical trials have been conducted.

PMDA considers as follows:
There were no apparent changes in insulin dose after switching from other insulin products to IDegAsp and there were no relevant safety concerns compared with the comparators in Japanese and foreign clinical trials with IDegAsp. There is no major problem with the applicant's view that it is necessary to caution that when switching from other insulin products to IDegAsp, insulin dose should be determined by individual needs. It is appropriate that switching to IDegAsp BID in patients on a basal-bolus regimen is not recommended. On the other hand, the recommended starting dose of IDegAsp in patients on a basal-bolus regimen was inferred from the results of Trial 3585 including Japanese subjects with T1DM who were treated with IDeg plus IAsp, not based on the data from a clinical trial with IDegAsp plus IAsp in Japanese subjects. Therefore, there is no sufficient information which determines whether patients can transfer, without problems, to IDegAsp at the dose suggested by the applicant. Based on the above, it is necessary to continue to collect information on safety when switching to IDegAsp via post-marketing surveillance. The above conclusion, including the appropriateness of caution statement, will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(6).2) Timing of injection
PMDA asked the applicant to provide a justification for the timing of administration, i.e. IDegAsp may be dosed immediately before the main meal (breakfast, lunch, or dinner).

The applicant responded as follows:
Various dosing times of once-daily IDegAsp were investigated in Trial 3896 in Japanese subjects with T2DM and foreign trials (Trials 3594/3645[62] [T1DM] and Trial 3593[63] [T2DM]). In Trial 3896 and Trial 3593 in subjects with T2DM, IDegAsp was to be administered once daily immediately before the largest meal of the day, at the same time throughout the trial. Meanwhile, in Trials 3594/3645 in subjects with T1DM, injection time was allowed to be moved to another main meal as needed.

In Trial 3896, IDegAsp was dosed before breakfast, lunch, and dinner in 15.1% (22 of 146 subjects), 4.1% (6 of 146 subjects), and 80.8% (118 of 146 subjects) of subjects, respectively.[72] As to the efficacy by dosing time, the change in HbA1c from baseline to Week 26 (mean ± SD) was -1.68 ± 1.0% for dosing before breakfast, -0.85 ± 0.7% for dosing before lunch, and -1.33 ± 0.8% for dosing before dinner. Though dosing before lunch was investigated in a limited number of subjects, good glycaemic control was obtained, regardless of dosing time. As to the occurrence of hypoglycaemia by dosing time, the incidence rate of confirmed hypoglycaemia was higher for dosing before breakfast or lunch compared with dosing before dinner. However, the incidence rate of confirmed hypoglycaemia for dosing before breakfast was

[72] Dosing time was recorded at Week 1, but one subject in the IDegAsp group was withdrawn from the trial before Week 1 and data on dosing time for this subject is missing.

lower in the IDegAsp group than in the IGlar group (Table 65). The incidence rate of nocturnal confirmed hypoglycaemia was low in both treatment groups, regardless of dosing time.

Table 65. Hypoglycaemic episodes by dosing time
(Trial 3896 [26 weeks of treatment], safety analysis set)

	IDegAsp[a] (n = 147)			IGlar[b] (n = 149)	
	Breakfast (n = 22)	Lunch (n = 6)	Dinner (n = 118)	Breakfast (n = 49)	Bedtime (n = 99)
Confirmed hypoglycaemia	59.1 (13)	83.3 (5)	39.8 (47)	44.9 (22)	43.4 (43)
	29 [278.0]	6 [233.9]	99 [173.6]	74 [316.2]	115 [248.5]
Nocturnal confirmed hypoglycaemia	4.5 (1)	0.0 (0)	9.3 (11)	10.2 (5)	18.2 (18)
	4 [38.3]	0 [0.0]	23 [40.3]	6 [25.6]	30 [64.8]

Upper column: incidence % (number of subjects with episodes), Lower column: number of episodes [incidence rate (number of episodes/100 PYE)]

a) One subject in the IDegAsp group was withdrawn from the trial before baseline visit and data on dosing time for this subject is missing.

b) Dosing at dinner in 1 subject in the IGlar group. The subject had one confirmed hypoglycaemic episode and one nocturnal confirmed hypoglycaemic episode.

In a foreign trial (Trial 3593), at baseline, IDegAsp was dosed before breakfast, lunch, dinner, and other meal or unknown time in 10.0% (23 of 230 subjects), 17.8% (41 of 230 subjects), 64.3% (148 of 230 subjects), and 7.8% (18 of 230 subjects) of subjects, respectively. The mean change in HbA1c (mean ± SD) from baseline to Week 26 was -0.97 ± 1.1% for dosing before breakfast, -1.09 ± 0.9% for dosing before lunch, and -0.97 ± 1.0% for dosing before dinner, showing no apparent differences among different dosing times. As to the occurrence of hypoglycaemia by dosing time, the incidence rate of confirmed hypoglycaemia was 540 episodes/100 PYE for dosing before breakfast, 406 episodes/100 PYE for dosing before lunch, and 431 episodes/100 PYE for dosing before dinner, showing no apparent differences among different dosing times. As the incidence rates of nocturnal confirmed hypoglycaemia were low (9.5 episodes/100 PYE for dosing before breakfast, 10.3 episodes/100 PYE for dosing before lunch, 111.6 episodes/100 PYE for dosing before dinner), it was difficult to assess the influence of dosing time.

In foreign trials (Trials 3594/3645) where the injection time was allowed to be moved to another main meal as needed, 61% of subjects did not change the injection time, while 14%, 14%, 3%, and 8% of subjects changed the injection time once, twice, thrice and four times or more, respectively, during the trial period. During the trial period, IDegAsp was dosed predominantly at breakfast, lunch, dinner, and unknown time in 14.4% (52 of 362 subjects), 18.8% (68 of 362 subjects), 66.3% (240 of 362 subjects), and 0.6% (2 of 362 subjects) of subjects, respectively. The mean change in HbA1c (mean ± SD) from baseline to Week 26 was -0.83 ± 0.8% for dosing before breakfast, -0.48 ± 0.7% for dosing before lunch, and -0.79 ± 0.9% for dosing before dinner. The incidence rate of confirmed hypoglycaemia at Week 26 was 3994 episodes/100 PYE for dosing before breakfast, 4233 episodes/100 PYE for dosing before lunch, and 3813 episodes/100 PYE for dosing before dinner, showing no apparent differences among different dosing times. On the other hand, the incidence rate of nocturnal confirmed hypoglycaemia at Week 26 was 378 episodes/100 PYE for dosing at breakfast, 585 episodes/100 PYE for dosing before lunch, and

310 episodes/100 PYE for dosing before dinner and the incidence rate of nocturnal confirmed hypoglycaemia was lower for dosing before dinner.

Based on the above, in a QD regimen, there was no apparent relationship between the dosing time of IDegAsp and the incidence rate of confirmed hypoglycaemia or nocturnal confirmed hypoglycaemia, either when IDegAsp was dosed immediately before the same meal every day (Trial 3896 and Trial 3593) or when the injection time was allowed to be moved to another main meal as needed (Trials 3594/3645). Therefore, IDegAsp QD may be administered immediately before the largest meal of the day (breakfast, lunch, or dinner) and based on the results of a Japanese trial, Trial 3896, IDegAsp should usually be administered at the same meal every day. However, as the duration of action of the basal component of IDegAsp exceeds 24 hours, the time of administration can be changed as long as IDegAsp is dosed immediately before a large meal while basal insulin coverage is being provided.

In a BID regimen, based on the results of Trial 3597 including Japanese subjects, IDegAsp should be administered immediately before breakfast and dinner.

PMDA asked the applicant to explain whether or not it is appropriate that "if a dose of IDegAsp is forgotten or a scheduled dose cannot be taken, the patient can take the missed dose with the next meal of that day," taking into consideration that the IAsp dose cannot be adjusted with IDegAsp and the next meal of that day may not be a main meal.

The applicant responded as follows:
The time of administration can be changed as long as IDegAsp is administered immediately before a large meal, since IDeg, one of the active ingredients of IDegAsp, has pharmacokinetic profiles e.g., a long duration of action. In a QD regimen, for example, if patients forget their dose at breakfast or lunch, they can take the missed dose immediately before the next large meal of that day. On the other hand, if patients forget their dose at dinner, they should resume the usual dosing schedule on the following day, since they will not have a large meal on that day and the basal component of IDegAsp has a long duration of action, and patients should not take an extra dose to make up for a missed dose. In a BID regimen (before breakfast and dinner), if patients forget their dose at breakfast, they can take the missed dose before lunch (which is considered as a large meal) and thereafter resume the usual dosing schedule. On the other hand, if patients forget their dose at dinner, they should take a dose before breakfast as usual on the following day and should not take an extra dose to make up for a missed dose.

PMDA considers as follows:
As there were no apparent differences in glycaemic control or the occurrence of hypoglycaemia among different dosing times in clinical trials, there is no major problem with the applicant's view, i.e. in a QD regimen, IDegAsp may be administered immediately before the largest meal of the day (breakfast, lunch,

or dinner), and it should be administered at the same meal every day. On the other hand, as to changing the time of administration, since the dose of IAsp cannot be adjusted with IDegAsp, postprandial hypoglycaemia may develop if injection time is moved from the largest meal of the day to another less large meal. In both QD and BID regimens, if patients forget a dose of IDegAsp at dinner, they should not take an extra dose to make up for a missed dose, but this is not the case for missed doses at breakfast or lunch. In this regard, since the action for missed doses is complicated, patients may take a wrong action. Furthermore, changing the timing of administration was not investigated in patients with T2DM and the injection time was allowed to be moved to another meal only in Trials 3594/3645 in non-Japanese subjects with T1DM. As the percentage of subjects who changed the injection time and the frequency of changing the injection time during the 52-week trial period were low, the safety profile in the case of changing the timing of administration has not fully been investigated. Therefore, it is important to advise that IDegAsp should be administered at the same meal every day. 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 patients

The applicant explained as follows:

Table 66 shows the occurrence of adverse events and hypoglycaemia by baseline age in therapeutic confirmatory trials including Japanese subjects. In Trial 3896, there was no apparent difference in the incidence rate of adverse events between subjects aged ≤65 years and subjects aged >65 years in either treatment group. In Trial 3597, there was no apparent difference in the incidence rate of adverse events between subjects aged ≤65 years and subjects aged >65 years in either treatment group. Among subjects aged ≤65 years, the incidence rate of adverse events tended to be lower in the IDegAsp group than in the BIAsp 30 group, whereas among subjects aged >65 years, there was no apparent difference between the two treatment groups. As for hypoglycaemia, in Trial 3896, there was no apparent difference in the incidence rate of confirmed hypoglycaemia between subjects aged ≤65 years and subjects aged >65 years in either treatment group. The incidence rate of confirmed hypoglycaemia was lower in the IDegAsp group than in the IGlar group in both subgroups. The number of nocturnal confirmed hypoglycaemia was low and it was difficult to investigate its relationship with age. In Trial 3597, the incidence rate of confirmed hypoglycaemia tended to be higher in subjects aged >65 years than in subjects aged ≤65 years in both treatment groups, but there was no apparent difference between the two treatment groups in either subgroup. The incidence rate of nocturnal confirmed hypoglycaemia tended to be higher in subjects aged >65 years than in subjects aged ≤65 years in the IDegAsp group but there was no apparent difference in the BIAsp 30 group. The incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDegAsp group than in the BIAsp 30 group among subjects aged ≤65 years and there was no apparent difference between the two treatment groups among subjects aged >65 years. No severe hypoglycaemia was reported in Trial 3896 and only 8 episodes were reported by 6 subjects in Trial 3597 (IDegAsp group, 6 episodes in 4 subjects; BIAsp 30 group, 2 episodes in 2 subjects). Thus, it was difficult to investigate its relationship

with age. In both trials, the number of subjects aged >75 years and the number of hypoglycaemic episodes reported in subjects aged >75 years were low, making it difficult to investigate the potential impact of age.

Table 66. Adverse events and hypoglycaemic episodes by baseline age (therapeutic confirmatory trials including Japanese subjects, safety analysis set)

Trial 3896[a)]	IDegAsp (n = 147)			IGlar (n = 149)		
	≤ 65 (n = 98)	> 65 (n = 49)	> 75[c)] (n = 9)	≤ 65 (n = 95)	> 65 (n = 54)	> 75[c)] (n = 9)
All AEs	68.4 (67)	75.5 (37)	66.7 (6)	72.6 (69)	83.3 (45)	66.7 (6)
	151 [327.3]	83 [347.4]	15 [335.3]	159 [356.7]	99 [386.4]	9 [201.8]
SAEs	4.1 (4)	2.0 (1)	0.0 (0)	2.1 (2)	1.9 (1)	0.0 (0)
	4 [8.7]	1 [4.2]	0 [0]	2 [4.5]	1 [3.9]	0 [0]
Confirmed hypoglycaemia	42.9 (42)	46.9 (23)	22.2 (2)	40.0 (38)	51.9 (28)	55.6 (5)
	83 [179.9]	51 [213.5]	2 [44.7]	114 [255.8]	76 [296.7]	13 [291.5]
Nocturnal confirmed hypoglycaemia	6.1 (6)	12.2 (6)	0.0 (0)	14.7 (14)	18.5 (10)	0.0 (0)
	15 [32.5]	12 [50.2]	0 [0]	17 [38.1]	20 [78.1]	0 [0]
Trial 3597[b)]	IDegAsp (n = 279)			BIAsp 30 (n = 141)		
	≤ 65 (n = 199)	> 65 (n = 80)	> 75[c)] (n = 13)	≤ 65 (n = 87)	> 65 (n = 54)	> 75[c)] (n = 8)
All AEs	69.3 (138)	70.0 (56)	100.0 (13)	81.6 (71)	59.3 (32)	50.0 (4)
	312 [338.4]	136 [376.1]	37 [723.5]	171 [415.2]	85 [353.8]	10 [250.9]
SAEs	6.5 (13)	12.5 (10)	38.5 (5)	9.2 (8)	7.4 (4)	0.0 (0)
	17 [18.4]	10 [27.7]	5 [97.8]	11 [26.7]	6 [25.0]	0 [0]
Confirmed hypoglycaemia	71.9 (143)	77.5 (62)	69.2 (9)	78.2 (68)	72.2 (39)	100.0 (8)
	809 [877.5]	418 [1156.1]	33 [645.2]	376 [913.0]	245 [1019.8]	39 [978.3]
Nocturnal confirmed hypoglycaemia	25.6 (51)	23.8 (19)	7.7 (1)	29.9 (26)	33.3 (18)	25.0 (2)
	85 [92.2]	58 [160.4]	1 [19.6]	65 [157.8]	36 [149.8]	4 [100.3]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)]

a) No severe hypoglycamic episodes were reported in Trial 3896.

b) In Trial 3597, 6 severe hypoglycaemic episodes were reported by 4 subjects in the IDegAsp group and 2 severe hypoglycaemic episodes were reported by 2 subjects in the BIAsp group. Only 1 nocturnal severe hypoglycaemic episode was reported by 1 subject in the IDegAsp group.

c) Subgroup of >65

Table 67 shows the occurrence of adverse events and hypoglycaemia by baseline age according to the global pooled data[66] from therapeutic confirmatory trials with IDegAsp. In subjects with T1DM, comparison among the age groups was difficult due to the small number of subjects aged >65 years. In subjects with T2DM, there were no marked differences in the incidence rate of adverse events between subjects aged ≤65 years and subjects aged >65 years in either treatment group. There were no marked differences between the pooled IDegAsp group and the pooled comparator group in either subjects aged ≤65 years or subjects aged >65 years, but the incidence rate was higher in the pooled IDegAsp group than in the pooled comparator group among subjects aged >75 years. The incidence rates of serious adverse events were not apparently different between the pooled IDegAsp group and the pooled comparator group in any age group. As for hypoglycaemia in subjects with T2DM, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were not apparently different between subjects aged ≤65 years and subjects aged >65 years in either treatment group. There were no marked differences in the incidence rate of confirmed hypoglycaemia between the pooled IDegAsp group and the pooled

comparator group in any age group, but the incidence rate of nocturnal confirmed hypoglycaemia was lower in the pooled IDegAsp group than in the pooled comparator group in all age groups. The number of severe hypoglycaemia was low in all age groups and it was difficult to investigate its relationship with age.

Table 67. Adverse events and hypoglycaemic episodes by baseline age (global pooled data from confirmatory trials with IDegAsp, safety analysis set)

T1DM	Pooled IDegAsp group (n = 362)			Pooled comparator group (n = 180)		
	≤ 65 (n = 353)	> 65 (n = 9)	> 75[a] (n = 4)	≤ 65 (n = 166)	> 65 (n = 14)	> 75[a] (n = 2)
All AEs	73.7 (260)	77.8 (7)	75.0 (3)	69.9(116)	78.6 (11)	100.0 (2)
	1180 [406.4]	30 [457.7]	13 [345.8]	554 [411.1]	89 [832.2]	17 [835.7]
SAEs	11.9 (42)	44.4 (4)	75.0 (3)	9.6 (16)	28.6 (4)	100.0 (2)
	67 [23.1]	5 [76.3]	4 [106.4]	23 [17.1]	5 [46.8]	3 [147.5]
Confirmed hypoglycaemia	95.2 (336)	88.9 (8)	100.0 (4)	94.6 (157)	85.7(12)	100.0 (2)
	9279 [3196.1]	171 [2608.9]	90 [2394.2]	4843 [3593.7]	499 [4666.1]	83 [4080.2]
Nocturnal confirmed hypoglycaemia	61.5 (217)	44.4 (4)	25.0 (1)	75.3 (125)	71.4 (10)	100.0 (2)
	911 [313.8]	7 [106.8]	2 [53.2]	740 [549.1]	47 [439.5]	7 [344.1]
Severe hypoglycaemia	12.5 (44)	44.4 (4)	75.0 (3)	15.7 (26)	50.0 (7)	50.0 (1)
	74 [25.5]	5 [76.3]	4 [106.4]	52 [38.6]	13 [121.6]	2 [98.3]
Nocturnal severe hypoglycaemia	3.1 (11)	22.2 (2)	25.0 (1)	6.0 (10)	28.6 (4)	50.0 (1)
	12 [4.1]	2 [30.5]	1 [26.6]	21 [15.6]	7 [65.5]	1 [49.2]
T2DM	Pooled IDegAsp group (n = 998)			Pooled comparator group (n = 857)		
	≤ 65 (n = 742)	> 65 (n = 256)	> 75[a] (n = 32)	≤ 65 (n = 629)	> 65 (n = 228)	> 75[a] (n = 27)
All AEs	62.8 (466)	59.8 (153)	68.8 (22)	60.6 (381)	58.8 (134)	55.6 (15)
	1258 [371.8]	438 [380.8]	82 [611.6]	1124 [385.6]	349 [342.6]	32 [258.6]
SAEs	6.7 (50)	7.4 (19)	18.8 (6)	6.5 (41)	8.3 (19)	11.1 (3)
	55 [16.3]	22 [19.1]	6 [44.8]	50 [17.2]	23 [22.6]	3 [24.2]
Confirmed hypoglycaemia	58.5 (434)	67.2 (172)	75.0 (24)	52.1 (328)	61.4 (140)	70.4 (19)
	2229 [658.8]	942 [819.0]	89 [663.8]	1763 [604.8]	807 [792.1]	75 [606.2]
Nocturnal confirmed hypoglycaemia	18.1 (134)	17.6 (45)	6.3 (2)	22.6 (142)	26.8 (61)	22.2 (6)
	234 [69.2]	93 [80.9]	2 [14.9]	384 [131.7]	131 [128.6]	12 [97.0]
Severe hypoglycaemia	0.9 (7)	2.0 (5)	3.1 (1)	3.0 (19)	1.3 (3)	3.7 (1)
	8 [2.4]	8 [7.0]	2 [14.9]	29 [9.9]	3 [2.9]	1 [8.1]
Nocturnal severe hypoglycaemia	0.1 (1)	0.4 (1)	0.0 (0)	1.3 (8)	0.0 (0)	0.0 (0)
	1 [0.3]	1 [0.9]	0 [0]	9 [3.1]	0 [0]	0 [0]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)]
a) Subgroup of >65

In conclusion, there were no clinically relevant differences by age group. However, since hypoglycaemia is likely to occur in elderly patients due to reduced physiological function, the package insert will advise 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:

There is no particular problem with the applicant's response. However, the number of elderly subjects included in clinical trials was limited and especially, the number of subjects >75 years of age studied was small, and according to the global pooled data, the incidence rate of adverse events tended to be higher in

the pooled IDegAsp group than in the pooled comparator group among T2DM subjects aged >75 years, albeit in small number. Thus, it is necessary to continue to collect information on safety in elderly patients via post-marketing surveillance.

4.(iii).B.(7).2) Renal impairment

The applicant explained as follows:

Regarding safety by renal function, Table 68 shows the occurrence of adverse events and hypoglycaemia by baseline renal function in therapeutic confirmatory trials including Japanese subjects. In Trial 3896 and Trial 3597, 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 renal impairment was low in both Trial 3896 and Trial 3597 and no subjects were categorised as severe renal impairment. As for hypoglycaemia, in Trial 3896, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were higher in subjects with mild renal impairment than in subjects with normal renal function in the IDegAsp group, but this tendency was not seen in the IGlar group. Among subjects with normal renal function, the incidence rates were lower in the IDegAsp group than in the comparator group. In subjects with mild renal impairment, the incidence rates were not apparently different between the two treatment groups. In Trial 3597, the incidence rate of confirmed hypoglycaemia was higher in subjects with mild or moderate renal impairment than in subjects with normal renal function in both treatment groups. There were no marked differences in the incidence rate of nocturnal confirmed hypoglycaemia between subjects with normal renal function and subjects with mild renal impairment in either treatment group. No severe hypoglycaemia was reported in Trial 3896. In Trial 3597, only 6 severe hypoglycaemic episodes were reported by 4 subjects in the IDegAsp group (1 episode in 1 subject with normal renal function, 3 episodes in 2 subjects with mild renal impairment, 2 episodes in 1 subject with moderate renal impairment) and 2 severe hypoglycaemic episodes were reported by 2 subjects in the BIAsp 30 group (1 episode in 1 subject with normal renal function, 1 episode in 1 subject with mild renal impairment). Thus, it was difficult to investigate the potential impact of renal impairment.

Table 68. Adverse events and hypoglycaemic episodes by baseline renal function[a)]
(therapeutic confirmatory trials including Japanese subjects, safety analysis set)

Trial 3896[b)]	IDegAsp (n = 147)			IGlar (n = 149)		
	normal (n = 84)	mild (n = 57)	moderate (n = 6)	normal (n = 82)	mild (n = 66)	moderate (n = 1)
All AEs	72.6 (61)	68.4(39)	66.7 (4)	76.8 (63)	77.3 (51)	0.0 (0)
	147 [379.4]	81 [286.2]	6 [201.1]	148 [390.0]	110 [346.4]	0 [0]
SAEs	4.8 (4)	1.8 (1)	0.0 (0)	1.2 (1)	3.0 (2)	0.0 (0)
	4 [10.3]	1 [3.5]	0 [0]	1 [2.6]	2 [6.3]	0 [0]
Confirmed hypoglycaemia	41.7 (35)	49.1 (28)	33.3 (2)	36.6 (30)	54.5 (36)	0.0 (0)
	51 [131.6]	79 [279.1]	4 [134.0]	98 [258.3]	92 [289.7]	0 [0]
Nocturnal confirmed hypoglycaemia	3.6 (3)	14.0 (8)	16.7 (1)	12.2 (10)	21.2 (14)	0.0 (0)
	4 [10.3]	22 [77.7]	1 [33.5]	11 [29.0]	26 [81.9]	0 [0]
Trial 3597[c)]	IDegAsp (n = 279)			BIAsp 30 (n = 141)		
	normal (n = 154)	mild (n = 106)	moderate (n = 19)	normal (n = 64)	mild (n = 69)	moderate (n = 8)
All AEs	70.8 (109)	67.0 (71)	73.7 (14)	76.6 (49)	69.6 (48)	75.0 (6)
	227 [322.0]	191 [383.3]	30 [374.1]	107 [364.9]	135 [420.9]	14 [367.1]
SAEs	6.5 (10)	8.5 (9)	21.1 (4)	7.8 (5)	8.7 (6)	12.5 (1)
	13 [18.4]	10 [20.1]	4 [49.9]	6 [20.5]	10 [31.2]	1 [26.2]
Confirmed hypoglycaemia	68.2 (105)	79.2 (84)	84.2 (16)	70.3 (45)	79.7 (55)	87.5 (7)
	599 [849.6]	541 [1085.7]	87 [1084.9]	204 [695.7]	375 [1169.3]	42 [1101.3]
Nocturnal confirmed hypoglycaemia	27.9 (43)	20.8 (22)	26.3 (5)	26.6 (17)	33.3 (23)	50.0 (4)
	71 [100.7]	54 [108.4]	18 [224.5]	34 [116.0]	61 [190.2]	6 [157.3]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)]

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) No severe hypoglycaemic episodes were reported in Trial 3896.

c) In Trial 3597, 6 severe hypoglycaemic episodes were reported by 4 subjects in the IDegAsp group and 2 severe hypoglycaemic episodes were reported by 2 subjects in the BIAsp 30 group. Only 1 nocturnal severe hypoglycaemic episode was reported by 1 subject in the IDegAsp group.

Table 69 shows the occurrence of adverse events and hypoglycaemia by baseline renal function according to the global pooled data[66] from therapeutic confirmatory trials with IDegAsp. In subjects with T1DM, the incidence rate of adverse events was higher in subjects with mild renal impairment than in subjects with normal renal function in both treatment groups, although the number of subjects with mild renal impairment was small. Only 1 subject of the pooled IDegAsp group was categorised as moderate renal impairment and analysis could not be performed. No marked differences were observed in the types of serious adverse events according to the degree of renal impairment in either treatment group. In subjects with T2DM, there was no consistent relationship between the degree of renal impairment and the incidence rate of adverse events in either treatment group. Serious adverse events were reported only in subjects with normal renal function and its relationship with renal impairment could not be investigated. As for hypoglycaemia, in subjects with T1DM, the incidence rate of confirmed hypoglycaemia was higher in subjects with mild renal impairment than in subjects with normal renal function in the pooled IDegAsp group while this tendency was not seen in the pooled comparator group. There were no marked differences in the incidence rate of confirmed hypoglycaemia between the treatment groups in either subjects with normal renal function or subjects with mild renal impairment. No marked differences were observed in the incidence rate of nocturnal confirmed hypoglycaemia according to the degree of renal impairment in either treatment group. The incidence rate of severe hypoglycaemia was higher in subjects

with mild renal impairment than in subjects with normal renal function in both treatment groups. In subjects with T2DM, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia in the pooled IDegAsp group generally showed a similar trend as that observed in subjects with T1DM. The number of severe hypoglycaemic episodes was low. Thus, it was difficult to investigate the potential impact of renal impairment.

Table 69. Adverse events and hypoglycaemic episodes by baseline renal function[a)]
(global pooled data from therapeutic confirmatory trials with IDegAsp, safety analysis set)

T1DM	Pooled IDegAsp group (n = 362)			Pooled comparator group (n = 180)		
	normal (n = 342)	mild (n = 19)	moderate (n = 1)	normal (n = 160)	mild (n = 20)	Moderate (n = 0)
All AEs	73.4 (251)	78.9 (15)	100.0 (1)	69.4 (111)	80.0 (16)	–
	1134 [402.4]	72 [511.3]	4 [399.2]	558 [421.3]	85 [653.6]	–
SAEs	11.4 (39)	36.8 (7)	0.0 (0)	8.1 (13)	35.0 (7)	–
	58 [20.6]	14 [99.4]	0 [0]	17 [12.8]	11 [84.6]	–
Confirmed hypoglycaemia	94.7 (324)	100.0 (19)	100.0 (1)	94.4 (151)	90.0 (18)	–
	8825 [3131.7]	599 [4254.0]	26 [2594.7]	4825 [3642.8]	517 [3975.5]	–
Nocturnal confirmed hypoglycaemia	60.5 (207)	68.4 (13)	100.0 (1)	75.6 (121)	70.0 (14)	–
	860 [305.2]	52 [369.3]	6 [598.8]	724 [546.6]	63 [484.4]	–
Severe hypoglycaemia	12.3 (42)	31.6 (6)	0.0 (0)	15.6 (25)	40.0 (8)	–
	70 [24.8]	9 [63.9]	0 [0]	51 [38.5]	14 [107.7]	–
Nocturnal severe hypoglycaemia	2.9 (10)	15.8 (3)	0.0 (0)	6.9 (11)	15.0 (3)	–
	11 [3.9]	3 [21.3]	0 [0]	22 [16.6]	6 [46.1]	–
T2DM	Pooled IDegAsp group (n = 998)			Pooled comparator group (n = 857)		
	normal (n = 764)	mild (n = 213)	moderate (n = 21)	normal (n = 657)	mild (n = 185)	moderate (n = 13)
All AEs	61.8 (472)	61.5 (131)	76.2 (16)	59.8 (393)	61.1 (113)	61.5 (8)
	1266 [363.5]	395 [411.0]	35 [388.2]	1165 [386.3]	288 [337.4]	19 [325.0]
SAEs	6.0 (46)	0.0 (0)	0.0 (0)	6.4 (42)	0.0 (0)	0.0 (0)
	52 [14.9]	0 [0]	0 [0]	49 [16.2]	0 [0]	0 [0]
Confirmed hypoglycaemia	57.7 (441)	69.0 (147)	85.7 (18)	50.8 (334)	67.6 (125)	69.2 (9)
	2238 [642.6]	833 [866.8]	100 [1109.2]	1725 [572.0]	794 [930.3]	51 [872.5]
Nocturnal confirmed hypoglycaemia	17.8 (136)	17.8 (38)	23.8 (5)	22.4 (147)	28.1 (52)	30.8 (4)
	234 [67.2]	75 [78.0]	18 [199.7]	383 [127.0]	126 [147.6]	6 [102.6]
Severe hypoglycaemia	0.8 (6)	2.3 (5)	4.8 (1)	2.6 (17)	2.2 (4)	7.7 (1)
	6 [1.7]	8 [8.3]	2 [22.2]	27 [9.0]	4 [4.7]	1 [17.1]
Nocturnal severe hypoglycaemia	0.0 (0)	0.9 (2)	0.0 (0)	1.1 (7)	0.5 (1)	0.0 (0)
	0 [0]	2 [2.1]	0 [0]	8 [2.7]	1 [1.2]	0 [0]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)], -: NA

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 conclusion, in patients with mild or moderate renal impairment, IDegAsp is not associated with an excessive risk of adverse events, serious adverse events, confirmed hypoglycaemia, or severe hypoglycaemia, as compared with the comparators. As with other insulin products, the package insert for IDegAsp will recommend careful administration in patients with severe renal impairment and advise that glucose-monitoring should be intensified and the dose of IDegAsp should be adjusted on an individual basis.

PMDA considers as follows:
There is no particular problem with the applicant's response. Since the number of patients with moderate renal impairment included in clinical trials was limited and no patients with severe renal impairment were studied, it is necessary to continue to collect information on safety in patients with renal impairment via post-marketing surveillance.

4.(iii).B.(7).3) Hepatic impairment
The applicant explained as follows:
Regarding the safety of IDegAsp in patients with hepatic impairment, when hepatic impairment[73] was defined by serum albumin and bilirubin scored by Child-Pugh classification, there were only 3 subjects with hepatic impairment in Trial 3896 (IDegAsp group, 2 subjects; IGlar group, 1 subject) and 4 subjects with hepatic impairment in Trial 3597 (IDegAsp group, 2 subjects; BIAsp 30 group, 2 subjects). Also according to the global pooled data[66] from therapeutic confirmatory trials with IDegAsp, the number of subjects with hepatic impairment was small (pooled IDegAsp group, 6 subjects; pooled comparator group, 6 subjects) and sufficient information could not be obtained. However, no consistent tendency was observed in the occurrence of individual adverse events or serious adverse events.

Table 70 shows the occurrence of adverse events and hypoglycaemia by baseline hepatic function. In this case, subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as having hepatic impairment. In Trial 3896 and Trial 3597, no apparent differences in the incidence rate of adverse events according to hepatic function were observed in the IDegAsp group. As for hypoglycaemia, in Trial 3896, no apparent differences in the incidence rate of confirmed hypoglycaemia according to hepatic function were observed in the IDegAsp group. In Trial 3597, the incidence rate of confirmed hypoglycaemia was higher in subjects with hepatic impairment than in subjects with normal hepatic function in the IDegAsp group, whereas the rate was lower in subjects with hepatic impairment than in subjects with normal hepatic function in the BIAsp 30 group. Among subjects with hepatic impairment, the incidence rate of confirmed hypoglycaemia was higher in the IDegAsp group than in the BIAsp 30 group, whereas there were no marked differences between the two treatment groups among subjects with normal hepatic function. The potential impact of hepatic impairment on the incidence rate of nocturnal confirmed hypoglycaemia could not be investigated since only a few subjects with hepatic impairment experienced nocturnal confirmed hypoglycaemia (6 subjects in Trial 3896 [IDegAsp group, 4 subjects; IGlar group, 2 subjects], 8 subjects in Trial 3597 [IDegAsp group, 5 subjects; BIAsp 30 group, 3 subjects]). No severe hypoglycaemia was reported in Trial 3896. In Trial 3597, only 6 severe hypoglycaemic episodes were reported by 4 subjects in the IDegAsp group (5 episodes in 3 subjects with

[73] Based on bilirubin score (bilirubin at baseline [μmol/L] <34: a score of 1, bilirubin at baseline 34-50: 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 28-35: a score of 2, albumin at baseline <28: a score of 3), a total score of >2 was defined as having hepatic impairment.

normal hepatic function, 1 episode in 1 subject with hepatic impairment) and 2 severe hypoglycaemic episodes were reported by 2 subjects in the BIAsp 30 group (both subjects had normal hepatic function). Thus, it was difficult to investigate the potential impact of hepatic impairment.

Table 70. Adverse events and hypoglycaemic episodes by baseline hepatic function[a)] (therapeutic confirmatory trials including Japanese subjects, safety analysis set)

Trial 3896[b)]	IDegAsp (n = 147)		IGlar (n = 149)	
	normal (n = 123)	hepatic impairment (n = 24)	normal (n = 128)	hepatic impairment (n = 21)
All AEs	70.7 (87)	70.8 (17)	75.0 (96)	85.7 (18)
	191 [326.6]	43 [372.5]	204 [338.6]	54 [543.3]
SAEs	4.1 (5)	0.0 (0)	1.6 (2)	4.8 (1)
	5 [8.5]	0 [0]	2 [3.3]	1 [10.1]
Confirmed hypoglycaemia	45.5 (56)	37.5(9)	47.7 (61)	23.8 (5)
	114 [194.9]	20 [173.3]	170 [282.1]	20 [201.2]
Nocturnal confirmed hypoglycaemia	6.5 (8)	16.7 (4)	17.2 (22)	9.5 (2)
	19 [32.5]	8 [69.3]	32 [53.1]	5 [50.3]
Trial 3597[c)]	IDegAsp (n = 279)		BIAsp 30 (n = 141)	
	normal (n = 256)	hepatic impairment (n = 23)	normal (n = 126)	hepatic impairment (n = 15)
All AEs	68.8 (176)	78.3 (18)	71.4 (90)	86.7 (13)
	403 [342.4]	45 [422.7]	224 [384.6]	32 [459.6]
SAEs	9.0 (23)	0.0 (0)	8.7 (11)	6.7 (1)
	27 [22.9]	0 [0]	16 [27.5]	1 [14.4]
Confirmed hypoglycaemia	75.0 (192)	56.5 (13)	75.4 (95)	80.0 (12)
	1099 [933.7]	128 [1202.5]	577 [990.6]	44 [632.0]
Nocturnal confirmed hypoglycaemia	25.4 (65)	21.7 (5)	32.5 (41)	20.0 (3)
	129 [109.6]	14 [131.5]	98 [168.3]	3 [43.1]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)]

a) Subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as "having hepatic impairment."

b) No severe hypoglycamic episodes were reported in Trial 3896.

c) In Trial 3597, 6 severe hypoglycaemic episodes were reported by 4 subjects in the IDegAsp group and 2 severe hypoglycaemic episodes were reported by 2 subjects in the BIAsp 30 group. Only 1 nocturnal severe hypoglycaemic episode was reported by1 subject in the IDegAsp group.

Table 71 shows the occurrence of adverse events and hypoglycaemia by baseline hepatic function according to the global pooled data[66] from therapeutic confirmatory trials with IDegAsp. In subjects with T1DM, the incidence rate of adverse events was higher in subjects with hepatic impairment than in subjects with normal hepatic function in the pooled IDegAsp group, whereas no apparent differences in the incidence rate of adverse events according to hepatic function were observed in the pooled comparator group. Among subjects with hepatic impairment, the incidence rate of adverse events was higher in the pooled IDegAsp group than in the pooled comparator group, whereas there were no apparent differences between the treatment groups among subjects with normal hepatic function. In subjects with T2DM, no apparent differences in the incidence rate of adverse events according to hepatic function were observed in the pooled IDegAsp group. As for hypoglycaemia, in subjects with T1DM, there were no clinically relevant differences in the incidence rate of confirmed hypoglycaemia according to hepatic function in the pooled IDegAsp group. In subjects with T2DM, the incidence rate of confirmed hypoglycaemia was lower in subjects with hepatic impairment than in subjects with normal hepatic function in the pooled IDegAsp group. As for nocturnal confirmed hypoglycaemia, in subjects with T1DM, the incidence rate was lower

in subjects with hepatic impairment than in subjects with normal hepatic function in the pooled IDegAsp group. In subjects with T2DM, no differences in the incidence rate of nocturnal confirmed hypoglycaemia according to hepatic function were observed in the pooled IDegAsp group.

Table 71. Adverse events and hypoglycaemic episodes by baseline hepatic function[a)]
(global pooled data from therapeutic confirmatory trials with IDegAsp, safety analysis set)

T1DM	Pooled IDegAsp group (n = 362)		Pooled comparator group (n = 180)	
	normal (n = 334)	hepatic impairment (n = 28)	normal (n = 163)	hepatic impairment (n = 17)
All AEs	73.7 (246)	75.0 (21)	69.3 (113)	82.4 (14)
	1060 [389.1]	150 [614.1]	585 [445.5]	58 [410.0]
SAEs	13.2 (44)	7.1 (2)	11.0 (18)	11.8 (2)
	70 [25.7]	2 [8.2]	26 [19.8]	2 [14.1]
Confirmed hypoglycaemia	94.9 (317)	96.4 (27)	93.9 (153)	94.1 (16)
	8731 [3204.6]	719 [2943.5]	4614 [3513.8]	728 [5146.2]
Nocturnal confirmed hypoglycaemia	60.8 (203)	64.3 (18)	74.2 (121)	82.4 (14)
	855 [313.8]	63 [257.9]	692 [527.0]	95 [671.5]
Severe hypoglycaemia	14.4 (48)	0.0 (0)	19.6 (32)	5.9 (1)
	79 [29.0]	0 [0]	63 [48.0]	2 [14.1]
T2DM	Pooled IDegAsp group (n = 998)		Pooled comparator group (n = 857)	
	normal (n = 840)	hepatic impairment (n = 158)	normal (n = 738)	hepatic impairment (n = 119)
All AEs	61.4 (516)	65.2 (103)	58.5 (432)	69.7 (83)
	1420 [369.8]	276 [397.6]	1195 [354.2]	278 [496.8]
SAEs	7.4 (62)	4.4 (7)	6.8 (50)	8.4 (10)
	67 [17.5]	10 [14.4]	62 [18.4]	11 [19.7]
Confirmed hypoglycaemia	62.9 (528)	49.4 (78)	54.9 (405)	52.9 (63)
	2767 [720.7]	404 [581.9]	2332 [691.1]	238 [425.3]
Nocturnal confirmed hypoglycaemia	18.5 (155)	15.2 (24)	24.8 (183)	16.8 (20)
	276 [71.9]	51 [73.5]	478 [141.7]	37 [66.1]
Severe hypoglycaemia	1.2 (10)	1.3 (2)	2.3 (17)	4.2 (5)
	13 [3.4]	3 [4.3]	23 [6.8]	9 [16.1]

Upper column: incidence % (number of subjects with events/episodes), Lower column: number of events/episodes [incidence rate (number of events/episodes/100 PYE)]

a) Subjects with baseline transaminase levels (either ALAT or ASAT) exceeding the upper limit of normal were defined as "having hepatic impairment."

In conclusion, there were no safety concerns about IDegAsp for subjects with hepatic impairment. However, as the number of subjects with hepatic impairment included in clinical trials was limited, further information will be collected via post-marketing surveillance. The package insert will recommend careful administration in patients with severe hepatic impairment.

PMDA considers as follows:

There is no particular problem with the applicant's response. However, since the incidence rate of confirmed hypoglycaemia in the IDegAsp group in Trial 3597 and the incidence rate of adverse events in the pooled IDegAsp group among subjects with T1DM from the global pooled data tended to be higher in subjects with hepatic impairment than in subjects with normal hepatic function and 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

PMDA asked the applicant to explain a post-marketing surveillance plan (draft version) for IDegAsp.

The applicant responded as follows:

Concerning IAsp, which is one of the active ingredients of IDegAsp, no new safety issues have been reported according to the re-examination results issued as of December 24, 2010. Concerning IDeg, the applicant is planning to conduct a special drug use-results survey on long-term use (a 3-year observation period, a planned sample size of 3000). Concerning IDegAsp, no unexpected safety concerns have been identified according to confirmatory trials with IDegAsp (Trials 3896 and 3597) in which Japanese subjects participated and the global pooled data from confirmatory trials. Based on the above, the applicant is planning to conduct a special drug use-results survey with a 1-year observation period and a planned sample size of 1000 as post-marketing surveillance for IDegAsp in order to collect safety information on the occurrence of hypoglycaemia and allergic reactions etc. as priority items.

PMDA considers as follows:

It is necessary to collect safety information on the occurrence of hypoglycaemia, injection site reactions, allergic reactions, etc. via post-marketing surveillance for IDegAsp. In addition, the safety data in elderly patients, patients with renal impairment, and patients with hepatic impairment should be collected because the numbers of these patients included in clinical trials were limited. Furthermore, since the safety and efficacy of IDegAsp in T1DM patients or the safety and efficacy of long-term treatment with IDegAsp (>6 months) was not investigated in clinical trials with IDegAsp including Japanese subjects, it is necessary to collect the relevant information. The details of post-marketing surveillance will be finalized, taking account of comments from the Expert Discussion.

4.(iii).B.(9) Brand name

The applicant has decided to modify the proposed Japanese brand names for IDegAsp.

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 document.

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 data submitted in the new drug application (5.3.5.1.2, 5.3.5.1.3). As a result, the following findings were identified at some trial sites: non-compliance with the procedures for the tiral product accountability (the wrong trial product was dispensed and administered to a subject). Although the above findings requiring improvement were noted, the relevant cases were handled appropriately. Therefore, 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 documents.

IV. Overall Evaluation

Based on the submitted data, the efficacy of IDegAsp in patients with diabetes mellitus who require insulin has been demonstrated and its safety is acceptable. It is necessary to continue to collect safety information on the occurrence of hypoglycaemia, injection site reactions, anaphylactic reactions, antibody development, etc., as well as safety and efficacy data 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, IDegAsp may be approved.

Review Report (2)

November 12, 2012

I. Product Submitted for Registration

[Brand name]	(a) Ryzodeg FlexTouch, (b) Ryzodeg Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)/Insulin Aspart (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	March 9, 2012

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 the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Interpretation of multinational trial results

Based on the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and the ICH-E5 guideline, PMDA has concluded that there is no major problem with the generalization of the results from the entire population in Trial 3597 to Japanese patients, as a result of reviewing data from Trial 3597 in patients with T2DM (a multinational trial). This conclusion by PMDA was supported by the expert advisors.

(2) Efficacy

PMDA considered as follows:

The efficacy of IDegAsp in subjects with T2DM has been demonstrated by Trial 3896 (QD) that confirmed the non-inferiority of IDegAsp to IGlar and by Trial 3597 (BID) that confirmed the non-inferiority of IDegAsp to BIAsp 30. Since the information on antibody formation following long-term treatment with IDegAsp is limited, it is necessary to continue to collect information on the relationship between antibody formation and efficacy via post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors.

(3) Safety

As a result of reviewing the results of Trial 3896 and Trial 3597 and individual events such as hypoglycaemia, injection site reactions, and antibody development, PMDA has concluded that the safety of IDegAsp is acceptable though it is necessary to collect safety information including the above-mentioned events via post-marketing surveillance. This conclusion by PMDA was supported by the expert advisors.

(4) Dosage and administration

(4).1) Safety in the initial phase after switching from other insulin products

PMDA considered as follows:

There is no major problem with the applicant's view that the following should be advised: it should be noted that when switching from other insulin products to IDegAsp, insulin dose should be determined by individual needs. The applicant does not recommend switching to IDegAsp BID in patients on a basal-bolus regimen, which is also appropriate. On the other hand, the recommended starting dose of IDegAsp (IDegAsp QD plus bolus insulin BID) in patients on a basal-bolus regimen was inferred from the results of Trial 3585 including Japanese subjects with T1DM who were treated with IDeg plus IAsp, and not based on the data from a clinical trial with IDegAsp plus IAsp in Japanese subjects. Therefore, there is no sufficient information regarding this transfer. Based on the above, it is necessary to continue to collect information on safety when switching to IDegAsp via post-marketing surveillance.

The above conclusion by PMDA was supported by the expert advisors.

(4).2) Timing of injection

PMDA considered as follows:

As there were no apparent differences in glycaemic control or the occurrence of hypoglycaemia among different dosing times in clinical trials, there is no major problem with the applicant's view, i.e. in a QD regimen, IDegAsp may be administered immediately before the largest meal of the day, either breakfast, lunch, or dinner, and it should be administered at the same meal every day. On the other hand, as to changing the time of administration, since the dose of IAsp cannot be adjusted with IDegAsp, postprandial hypoglycaemia may develop if injection time is moved from the largest meal of the day to another less large meal. In both QD and BID regimens, if patients forget a dose of IDegAsp at dinner, they should not take an extra dose to make up for a missed dose, but this is not the case for missed doses at breakfast or lunch. In this regard, since the action for missed doses is also complicated, patients may take a wrong action. Furthermore, changing the time of administration was not investigated in patients with T2DM and the injection time was allowed to be moved to another meal only in Trials 3594/3645 in non-Japanese subjects with T1DM. As the percentage of subjects who changed the injection time and the frequency of changing the injection time during the 52-week trial period were low, the safety profile in the case of

changing the timing of administration has not fully been investigated. Therefore, it is important to administer IDegAsp at the same meal (the same dosing time) every day.

The above conclusion by PMDA was supported by the expert advisors.

The following comment was raised by the expert advisors:
As to the timing of administration of IDegAsp QD, IDegAsp should be administered before the main meal because it may be more appropriate to administer IDegAsp "immediately before the meal resulting in the largest postprandial glucose increment" than "immediately before the largest meal."

Based on the above, PMDA instructed the applicant to change the dosage and administration statement and the precautions of dosage and administration statement as shown below, delete information about "the recommended starting dose of IDegAsp in patients on a basal-bolus regimen" in the precautions of dosage and administration section and the statement that "patients can change the time of administration" in the important precautions section, and to collect information on safety and efficacy when switching from other insulin products to IDegAsp via post-marketing surveillance.

The applicant responded accordingly: The dosage and administration statement etc. will be changed as shown below; information about "the recommended starting dose of IDegAsp in patients on a basal-bolus regimen" in the precautions of dosage and administration section and the statement that "patients can change the time of administration" in the important precautions section will be deleted; and information on safety and efficacy when switching from other insulin products to IDegAsp will be collected via post-marketing surveillance. PMDA accepted the response.

(After change)
[Dosage and administration] (for Ryzodeg FlexTouch)
Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the rapid-acting insulin aspart and the long-acting insulin degludec (molar ratio 3:7).
The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily. In a once-daily regimen, it should be given immediately before the main meal, at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

[Precautions of dosage and administration]
(3) In a once-daily regimen, Insulin Degludec/Insulin Aspart may be administered immediately before the main meal (breakfast, lunch, or dinner). It should be administered at the same meal every day.

(5) Post-marketing surveillance

PMDA considered as follows:

Concerning IAsp, which is one of the active ingredients of IDegAsp, no new safety issues have been reported according to the re-examination results. Concerning IDeg, the applicant is planning to conduct a special drug use-results survey on long-term use (a 3-year observation period, a planned sample size of 3000). Therefore, there is no particular problem with the applicant's plan to conduct a special drug use-results survey on long-term use (a 1-year observation period, a planned sample size of 1000) as post-marketing surveillance for IDegAsp. It is necessary to collect safety information on the occurrence of hypoglycaemia, injection site reactions, allergic reactions, etc. via post-marketing surveillance for IDegAsp. It is also necessary to collect the safety data in elderly patients, patients with renal impairment, and patients with hepatic impairment because the numbers of these patients included in clinical trials were limited. Furthermore, since the safety and efficacy of IDegAsp in T1DM patients or the safety and efficacy of long-term treatment with IDegAsp (>6 months) were not investigated in clinical trials with IDegAsp including Japanese subjects, it is necessary to collect the relevant information.

The above conclusion by PMDA was supported by the expert advisors.

Based on the above, PMDA asked the applicant to present a more detailed draft plan for post-marketing surveillance.

The applicant responded as follows:

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 1000) will be conducted. Information on the occurrence of hypoglycaemia, injection site reactions, allergic reactions, etc. will be collected. Also, information on concomitant medications (especially, the data from patients treated with IDegAsp plus >750 mg/day of metformin) will be collected to investigate the relationship between IDegAsp in combination with other anti-diabetic drugs and safety (especially, hypoglycaemia). If judged necessary by healthcare providers, IDeg-specific IgE antibody titers will be measured to investigate its influence on safety and efficacy. Furthermore, information on the safety and efficacy of IDegAsp in Japanese T1DM patients and safety and efficacy when switching from other insulin products to IDegAsp, etc. will also be collected. The safety and efficacy of IDegAsp in elderly patients, those with renal impairment, and those with hepatic impairment will be evaluated by identifying the relevant cases.

PMDA accepted the response.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that IDegAsp may be approved for the following indication and dosage and administration. Its re-examination period should be the period from approval until September 27, 2020 so that it is in line with the re-examination period for an approved product containing Insulin Degludec (Genetical Recombination), one of the active ingredients in IDegAsp. 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]
Ryzodeg FlexTouch
Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the rapid-acting insulin aspart and the long-acting insulin degludec (molar ratio 3:7).
The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily. In a once-daily regimen, it should be given immediately before the main meal, at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

Ryzodeg Penfill
Insulin Degludec/Insulin Aspart is a soluble insulin product consisting of the rapid-acting insulin aspart and the long-acting insulin degludec (molar ratio 3:7).
The usual initial adult dosage is 4 to 20 units of Insulin Degludec/Insulin Aspart administered subcutaneously once or twice daily, using a specific insulin pen device. In a once-daily regimen, it should be given immediately before the main meal, at the same time every day. In a twice-daily regimen, it should be given immediately before breakfast and dinner. The dose should be adjusted according to the patient's symptoms and test findings. The usual maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.