Review Report

July 10, 2015
Pharmaceuticals and Medical Devices Agency

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

[Brand name]	(a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination) (JAN*)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	October 31, 2014
[Dosage form/Strength]	(a) Solution for injection: One pre-filled pen (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination). (b) Solution for injection: One cartridge (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).
[Application classification]	Prescription drug (6) Drug with a new dosage
[Items warranting special mention]	None
[Reviewing office]	Office of New Drug I

**Japanese Accepted Name (modified INN)*

Review Results

July 10, 2015

[Brand name] (a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name] Insulin Degludec (Genetical Recombination)
[Applicant] Novo Nordisk Pharma Ltd.
[Date of application] October 31, 2014
[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) has concluded that the efficacy of the product in pediatric patients with diabetes mellitus who require insulin has been demonstrated and its safety is acceptable in view of its observed benefits.

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

[Indication]
Diabetes mellitus where treatment with insulin is required

(No changes)

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

Usually in pediatric population, Insulin Degludec is administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 0.5 to 1.5 units/kg/day. However, a higher dose than stated above may be used as needed.

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

Usually in pediatric population, Insulin Degludec is administered subcutaneously once daily, using a specific insulin pen device. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition. Insulin Degludec may be used in combination with other insulin products and typically,

the total insulin maintenance dose is 0.5 to 1.5 units/kg/day. However, a higher dose than stated above may be used as needed.

(Words underlined are additions; words underscored with a wavy line are changes.)

[Condition for approval]
The applicant is required to develop and appropriately implement a risk management plan.

Review Report (1)

June 3, 2015

I. Product Submitted for Registration

[Brand name]	(a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)
[Applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	October 31, 2014
[Dosage form/Strength]	(a) Solution for injection: One pre-filled pen (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination). (b) Solution for injection: One cartridge (3 mL) contains 300 units of Insulin Degludec (Genetical Recombination).

[Proposed indication]

Diabetes mellitus where treatment with insulin is required

(No changes)

[Proposed dosage and administration]

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

For pediatric population, the starting dose of Insulin Degludec in insulin-naïve patients should be determined on an individual basis, and the usual dosage of Insulin Degludec in patients transferring from other insulin products is 0.1 to 0.6 units/kg administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's symptoms and test results. Typically, the total insulin maintenance dose is 0.5 to 1.6 units/kg/day. However, a higher dose than stated above may be used as needed.

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

For pediatric population, the starting dose of Insulin Degludec in insulin-naïve patients should be determined on an individual basis, and the usual dosage of Insulin Degludec in patients transferring from other insulin products is 0.1 to 0.6 units/kg administered subcutaneously once daily. It should be injected at the same time

every day. The dose should be adjusted according to the patient's symptoms and test results. Typically, the total insulin maintenance dose is 0.5 to 1.6 units/kg/day. However, a higher dose than stated above may be used as needed.

(Words underlined are additions.)

II. Summary of the Submitted Data and Outline of the Review

The submitted data and the review thereof by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The current application is for a new dosage. Therefore data relating to quality have not been submitted. No new non-clinical data have been submitted since the non-clinical aspects of the current application can be assessed based on the data submitted in the initial application.

1. Origin or history of discovery, use in foreign countries, and other information

Tresiba FlexTouch or Tresiba Penfill is a solution for injection containing Insulin Degludec (Genetical Recombination) ("insulin degludec"), a long-acting insulin analog, as an active ingredient (hereinafter, the drug product is referred to as "IDeg"). Tresiba FlexTouch and Tresiba Penfill were approved for the indication of "diabetes mellitus where treatment with insulin is required" in September 2012. In Japan, the following long-acting insulin analogs have been approved: Insulin Glargine (Genetical Recombination) approved in October 2003, and Insulin Detemir (Genetical Recombination) approved in October 2007.

Type 1 diabetes mellitus is one of the most common chronic diseases in children and adolescents. An estimated 497,100 patients under 15 years were living with type 1 diabetes worldwide in 2013. Some 79,100 patients under 15 years are estimated to develop type 1 diabetes mellitus annually worldwide.[1] In the Japanese pediatric population, the annual incidence of type 1 diabetes mellitus is estimated to be 1.5 to 2.5 patients per 100,000 people, and the prevalence is estimated to be 1 patient per 10,000 people.[2] According to the research report on diabetes for Research Project on Treatment of Chronic Intractable Diseases in Children, 5088 of 6258 pediatric patients living with diabetes mellitus had type 1 diabetes in 2011.[3]

In pediatric patients as in adults, one of the goals of treating diabetes mellitus is normalizing glycemic control and preventing the development and progression of diabetic complications. For insulin treatment in pediatric patients with type 1 diabetes mellitus, multiple daily insulin injections (2-5 injections/day) or continuous subcutaneous insulin infusion (CSII) have been used according to the patient's situation such as age, diabetes mellitus duration, pubertal status, body weight, diet, activities at school, and glycemic control.[4]

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1 *IDF Diabetes Atlas, 6th ed*., International Diabetes Federation, Brussels, 2013.

2 Urakami T. *Journal of the Japan Pediatric Society*. 2013; 1839-50, Kuzuya T, et al. *Diabetes*. 1992; 35: 173-94.

3 Sugihara S. Research on registration, analysis, and information provision for diabetes mellitus. 2012 Report.

4 Ragnar H, et al. *Pediatric Diabetes*. 2009; 10(12): 1-210, Urakami T. *Journal of the Japan Pediatric Society*. 2013; 1839-50, Urakami T. *Diagnosis and Treatment*. 2013; 101: 1803-7.

Currently in Japan, no insulin product has separate dosage regimen for adults and pediatric patients. Many pediatric patients use approved insulin products by adjusting the insulin dose according to their symptoms and test results. Insulin Glargine (Genetical Recombination), Insulin Detemir (Genetical Recombination), and CSII have mainly been used as basal insulin.[5]

The applicant claims that a global phase III trial etc. have demonstrated the efficacy and safety of IDeg in pediatric patients with diabetes mellitus, and has filed a supplemental marketing application for IDeg.

IDeg is licensed for use in adult patients with diabetes mellitus in at least 58 countries as of April 2015. The drug was approved in the EU for the treatment of pediatric patients with diabetes mellitus in January 2015.

2. Clinical data

In this section, trial numbers are abbreviated (e.g. Trial NN1250-3561 is Trial 3561 and Trial NN1250-1995 is Trial 1995).

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

2.(i).A Summary of the submitted data

Human serum concentrations of insulin degludec and Insulin Detemir (Genetical Recombination) (IDet) were determined by an enzyme-linked immunosorbent assay (ELISA method). The lower limit of quantification was 20 pmol/L (insulin degludec) and 25 pmol/L (IDet). Human serum concentrations of Insulin Glargine (Genetical Recombination) (IGlar) were determined by a luminescent oxygen channelling immunoassay (LOCI method). The lower limit of quantification was 8 or 20 pmol/L. Serum anti-insulin degludec antibodies were detected by a radioimmunoassay (RIA method).

2.(ii) Summary of clinical pharmacology studies

2.(ii).A Summary of the submitted data

The applicant submitted evaluation data (the results from a global clinical trial in patients with type 1 diabetes mellitus [Trial 3561] and a population pharmacokinetic [PPK] analysis) and reference data (the results from a single-dose trial in non-Japanese patients with type 1 diabetes mellitus [Trial 1995]). Data from Trial 1995 had already been submitted in the initial application.

2.(ii).A.(1) Global clinical trial in patients with type 1 diabetes mellitus (5.3.5.1-1, Trial 3561 [January 2012 to February 2013])

A randomized, open-label, IDet-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of IDeg in Japanese and non-Japanese patients with type 1 diabetes mellitus, aged between 1 and less than 18 years (target number of subjects, 346) [for trial design and efficacy and safety, see "2.(iii).A Global clinical trial in patients with type 1 diabetes mellitus"].

[5] Kikuchi T, et al. *Diabetes*. 2014; 57(Suppl 1): S369.

Steady-state drug concentrations following subcutaneous administration of IDeg or IDet are shown in Table 1.

Table 1. Steady-state drug concentrations following subcutaneous administration of IDeg or IDet

Treatment	Week 2	Week 12	Week 26
IDeg	4540 ± 3999 (n = 171)	4148 ± 3727 (n = 164)	4106 ± 3457 (n = 170)
IDet	3972 ± 6722 (n = 171)	5430 ± 9068 (n = 163)	6377 ± 10931 (n = 164)

Unit: pmol/L, Mean ± standard deviation (SD)

2.(ii).A.(2) Single-dose trial in non-Japanese patients with type 1 diabetes mellitus (5.3.3.3-4, Trial 1995 [December 2009 to May 2010], Reference data)

A randomized, double-blind, IGlar-controlled, two-period, crossover trial was conducted to investigate the pharmacokinetics and safety of a single dose of IDeg in non-Japanese patients with type 1 diabetes mellitus[6] (target number of subjects, 36).

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

Of 38 treated subjects, 37 subjects (12 children [6-11 years], 13 adolescents [12-17 years], 12 adults [18-65 years]) were included in the pharmacokinetic analysis. Excluded was 1 child who withdrew from the trial because of difficulty in collecting blood after the first dose.

Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg or IGlar by age group are shown in Table 2.

Table 2. Pharmacokinetic parameters following a single subcutaneous dose of 0.4 U/kg of IDeg or IGlar by age group

	Parameter	Children (n = 12)	Adolescents (n = 13)	Adults (n = 12)
IDeg	$AUC_{inf,SD}$ (pmol·h/L)	145891 (73)	130713 (30)	98594 (21)
	$C_{max,SD}$ (pmol/L)	3350 (51)	3422 (33)	2792 (17)
	$t_{max,SD}$ (h) [a)]	11.0 (4.0-17.8)	14.8 (9.0-21.1)	13.0 (9.0-21.0)
IGlar	$AUC_{inf,SD}$ (pmol·h/L)	3834 (32)	3255 (34) [b)]	3017 (58)
	$C_{max,SD}$ (pmol/L)	80 (38)	72 (35)	80 (38)
	$t_{max,SD}$ (h) [a)]	14.0 (4.0-36.0)	15.0 (4.0-24.0)	12.0 (4.0-20.9)

Geometric mean (coefficient of variation [CV] %)
$AUC_{inf,SD}$: area under the serum concentration-time curve extrapolated to infinity, $C_{max,SD}$: maximum serum concentration, $t_{max,SD}$: time to maximum serum concentration
a) Median (Min.-Max.)
b) n = 9

The estimated geometric mean ratios of $AUC_{inf,SD}$ (95% confidence intervals [CI]) and $C_{max,SD}$ (95% CI) of IDeg were as follows: $AUC_{inf,SD}$ (children/adults), 1.48 (0.98, 2.24); $C_{max,SD}$ (children/adults), 1.20 (0.90, 1.60); $AUC_{inf,SD}$ (adolescents/adults), 1.33 (1.08, 1.64); $C_{max,SD}$ (adolescents/adults), 1.23 (1.00, 1.51). The estimated geometric mean ratios of $AUC_{inf,SD}$ (95% CI) and $C_{max,SD}$ (95% CI) of IGlar were as follows: $AUC_{inf,SD}$ (children/adults), 1.27 (0.90, 1.79); $C_{max,SD}$ (children/adults), 1.00 (0.73, 1.37); $AUC_{inf,SD}$ (adolescents/adults), 1.08 (0.77, 1.52); $C_{max,SD}$ (adolescents/adults), 0.90 (0.66, 1.22).

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

2.(ii).A.(3) Population pharmacokinetic analysis (5.3.5.4-1)

Using 894 insulin degludec serum concentrations obtained from a global clinical trial in patients with type 1 diabetes mellitus (infants, children, adolescents) (Trial 3561) and a single-dose trial in non-Japanese patients with type 1 diabetes mellitus (children, adolescents, adults) (Trial 1995), a PPK analysis was performed using non-linear mixed effect modeling (software, NONMEM [version 7.1.2]). The base model was a one-compartment model with first-order absorption through a single transit compartment. The PPK analysis included data from 205 subjects (112 male subjects, 93 female subjects). Their mean age (Min.-Max.) was 11.2 (1.5-57.0) years, mean body weight was 42.0 (11.2-102.0) kg, mean BMI was 19.3 (12.9-34.5) kg/m^2, and mean BMI Z-score was 0.55 (-2.97-3.51).

The covariates investigated on clearance (CL/F) were body weight, age group (infants [1-5 years], children [6-11 years], adolescents [12-17 years], adults [18-65 years]), BMI z-score,[7] gender, and race. For volume of distribution (V/F), the effect of body weight was investigated. Of the covariates screened, body weight and race were found to have significant effects on clearance; body weight was found to have a significant effect on volume of distribution. These investigated covariates were included into the base model to yield a full model. The final model was developed using backward elimination. As a result, body weight as a significant covariate on clearance and volume of distribution was included into the final model. The estimated values of the non-proportionality index for the effects of body weight on clearance and volume of distribution in the final model [95% CI] were 0.98 [0.82, 1.14] and 1.01 [0.49, 1.52], respectively, suggesting linear increases. Age group was not found to be a significant covariate on clearance, suggesting that there are no major differences among infants (1-5 years), children (6-11 years), adolescents (12-17 years), and adults (18-65 years) in the pharmacokinetics of IDeg administered according to body weight.

2.(ii).B Outline of the review by PMDA

Pharmacokinetics in pediatric population

The applicant's explanation:

A single-dose trial in non-Japanese patients (children, adolescents, adults) with type 1 diabetes mellitus (Trial 1995) compared the pharmacokinetics of a single dose of IDeg between adults and children or adolescents. As a result, IDeg exposure (AUC_{infSD}) was greater in children and adolescents compared with adult subjects (Table 2). According to the US Food and Drug Administration (FDA) draft guidance,[8] developmental changes in skin, muscle, and fat, including changes in water content and degree of vascularization, and plasma protein binding and tissue binding changes arising from changes in body composition with growth and development can affect absorption and distribution in the pediatric population. Thus, the differences in IDeg exposure may have been related to these factors. The effect of age on insulin exposure has been reported with NPH insulin as well; it has been discussed that the clearance of insulin or differences in circulating growth hormone concentrations among the age groups may have contributed to the trend towards greater insulin exposure ($AUC_{0\text{-}24\ h}$) in children and adolescents with type 1 diabetes mellitus than in adult patients.[9] Using the insulin degludec serum

[7] BMI category as a covariate: BMI z-score, <-1; ≥-1 and ≤1; and >1

[8] FDA Guidance for Industry General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products, 2014

[9] Danne T, et al. *Diabetes Care*. 2003; 26(11): 3087-92.

concentration data from Trials 1995 and 3561, a PPK analysis was performed to estimate the steady-state pharmacokinetics of IDeg in a typical subject based on the median body weight in four different age groups (infants [1-5 years], children [6-11 years], adolescents [12-17 years], adults [18-65 years]). The results suggested that there were no major pharmacokinetic differences among the age groups (Figure 1). In a pharmacokinetic/pharmacodynamic (PK/PD) analysis of the relationship between steady-state IDeg exposure ($AUC_{0\text{-}24\ h,ss}$) and pre-breakfast blood glucose values, age group was not a significant covariate.

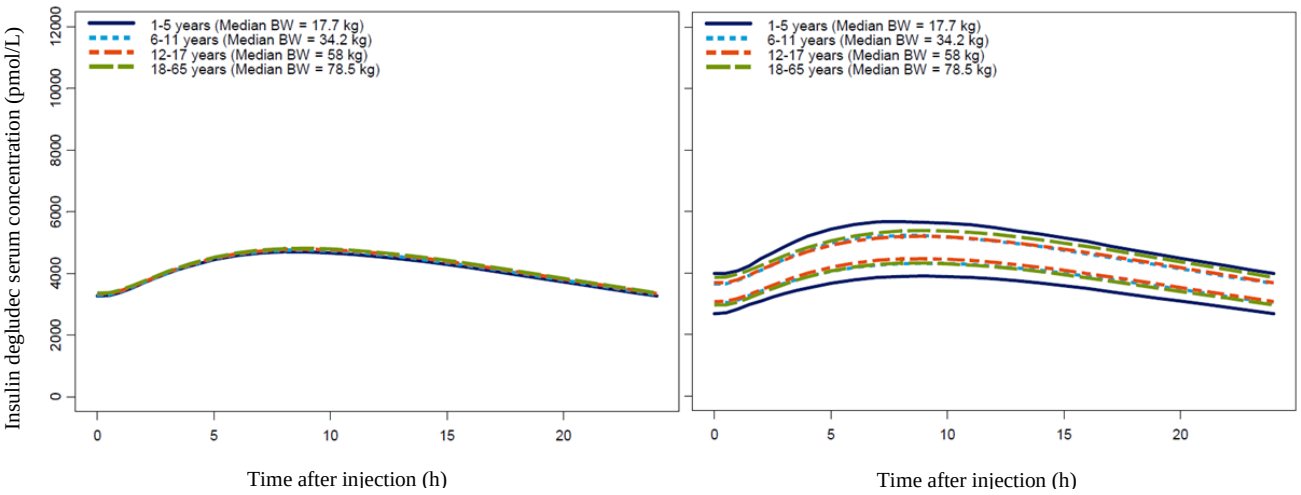

Figure 1. Insulin degludec serum concentration-time profiles over a 24-hour dosing interval at steady-state following once-daily dosing of 0.4 U/kg of IDeg
(Median insulin degludec serum concentrations [left figure] and their 95% CIs [right figure] based on PPK analysis)

In Trial 1991 in adult patients with type 1 diabetes mellitus (the results of the trial were submitted in the initial application),[10] the steady-state pharmacodynamic effect of IDeg was stable over the 24-hour period. The intra-subject variability in the area under the glucose infusion rate curve (AUC_{GIR}) was low.[11]

As described above, although IDeg exposure tended to be greater in children and adolescents compared with adults in Trial 1995, age group was not a significant covariate on clearance in the PPK analysis, suggesting that there are no major differences among the age groups (infants, children, adolescents, adults) in the pharmacokinetics of IDeg administered according to body weight. The results of the PK/PD analysis also suggested that age group has no significant effect. Therefore, the intra-subject variability should be low also in infants, children, and adolescents as in adult patients, and there should be no clinical safety concern in pediatric population from a pharmacokinetic standpoint.

The pharmacokinetics of IDeg were compared between the Japanese and non-Japanese populations to analyze the similarity of the two populations, using dose (U/kg)-adjusted insulin degludec serum concentration data at Weeks 2, 12, and 26 from Trial 3561. Insulin degludec serum concentrations in Japanese subjects were within

[10] A phase I trial investigating the pharmacodynamic intra-subject day-to-day variability of IDeg after multiple-dose administration of IDeg in non-Japanese patients with type 1 diabetes mellitus

[11] Heise T, et al. *Diabetes Obes Metab.* 2012; 14(9): 859-64.

the variation range of the data from non-Japanese subjects in each age group (infants [1-5 years], 1 Japanese subject and 25 non-Japanese subjects; children [6-11 years], 9 Japanese subjects and 74 non-Japanese subjects; adolescents (12-17 years), 12 Japanese subjects and 48 non-Japanese subjects) and in all age groups combined (=the overall population [22 Japanese subjects, 147 non-Japanese subjects]). Thus, no major differences were observed in Insulin degludec serum concentrations between the Japanese and non-Japanese populations. The results from Trial 1996[12] (Japanese subjects) and Trial 1993[13] (non-Japanese subjects) in adult patients with type 1 diabetes mellitus (the results of both trials were submitted in the initial application) demonstrated that Japanese and non-Japanese adult patients with type 1 diabetes mellitus had similar pharmacokinetic and pharmacodynamic profiles of IDeg, and that IDeg had a flat and long profile in both patient populations.

Therefore, there should be no major differences in the pharmacokinetics of IDeg between adult and pediatric populations in Japan or overseas.

PMDA considers that there is no particular problem with the applicant's explanation (The results of Trial 1995 and the PPK analysis etc. suggested that there are no major differences in the pharmacokinetics of IDeg between adult and pediatric populations. The results from Trial 3561 etc. indicated that there are no major differences between adult and pediatric populations in Japan or overseas).

2.(iii) Summary of clinical efficacy and safety

2.(iii).A Summary of the submitted data

The applicant submitted evaluation data, namely the results from a phase III trial in Japanese and non-Japanese patients with type 1 diabetes mellitus (Trial 3561). HbA1c results are reported in NGSP units.

Global clinical trial in patients with type 1 diabetes mellitus (5.3.5.1-1, Trial 3561 [January 2012 to July 2013])

A randomized, open-label, IDet-controlled, parallel-group trial was conducted to evaluate the efficacy and safety of IDeg in a basal-bolus regimen in Japanese and non-Japanese[14] patients with type 1 diabetes mellitus[15] aged between 1 and less than 18 years who had been receiving insulin treatment (target number of subjects, 346).

The trial consisted of a run-in period (approximately 1 week), a main period (26 weeks), an extension period (26 weeks), and a follow-up period (1 week). The patients received basal insulin (IDeg or IDet) and bolus insulin (Insulin Aspart [Genetical Recombination] [IAsp]) during the main and extension periods. During the follow-up period, the patients were transferred from IDeg or IDet to intermediate-acting (NPH) insulin for the

[12] A phase I trial investigating the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg in Japanese patients with type 1 diabetes mellitus

[13] A phase I trial investigating the pharmacodynamics, pharmacokinetics, safety, and tolerability of multiple doses of IDeg in non-Japanese patients with type 1 diabetes mellitus

[14] Europe (UK, Bulgaria, Finland, Italy, France, the Netherlands, Macedonia, Germany), US, Russia, South Africa

[15] Key inclusion criteria: patients with type 1 diabetes mellitus aged between 1 and less than 18 years who had been receiving insulin treatment for at least 3 months with a total daily dose of ≤2.0 U/kg, without concomitant oral anti-diabetic drugs and with HbA1c (NGSP) of ≤11.0% at screening (approximately 1 week prior to the start of trial drug administration).

assay for insulin antibody measurement.

Subjects were randomized in a 1:1 ratio to receive either IDeg or IDet. Randomization was stratified according to age group (infants [1-5 years], children [6-11 years], adolescents [12-17 years]).

As basal insulin, IDeg once daily (OD) (at the same time of the day every day) or IDet OD or twice daily (BID) (according to local labeling; BID at "breakfast and dinner" or "breakfast and bedtime") was subcutaneously administered in the thigh, upper arm, or abdomen. Subjects in both treatment groups, according to local labeling, subcutaneously received IAsp as bolus insulin twice to four times daily immediately before meals. The basal (IDeg or IDet) and bolus insulin doses at initiation were determined based on the subject's total daily insulin dose immediately prior to the start of trial treatment, to achieve a daily basal:bolus ratio of between 50:50 and 30:70. Then, basal insulin titration was performed once weekly according to the insulin titration guideline (Table 3) and based on the lowest self-measured blood glucose (SMBG) value on the three days prior to visit/phone contact, to achieve a target of 90 to 145 mg/dL. For subjects receiving IDet OD whose pre-breakfast SMBG had reached target but whose pre-dinner SMBG was >145 mg/dL, transfer from IDet OD to BID was considered based on the investigator's judgment. When a subject has been transferred from IDet OD to BID, he/she commenced an additional pre-breakfast dose of IDet at 2 to 4 U, and thereafter underwent morning dose titration based on pre-dinner SMBG. Titration of bolus insulin was performed once weekly according to the insulin titration guideline (Table 4) and based on the lowest pre-meal or bedtime SMBG value on the three days prior to visit/phone contact. If, at the start of the trial, the investigator considered that titration of bolus insulin could be performed by use of insulin/carbohydrate ratios and plasma glucose correction factors, bolus insulin dose was adjusted multiple times daily based on the meal carbohydrate content and pre-prandial plasma glucose value.

Table 3. Basal insulin titration guideline [a)]

Pre-breakfast or pre-dinner SMBG (mg/dL)	Current daily dose		
	<5 U	≥5 U and ≤15 U	>15 U
<90	Decrease by 0.5 U	Decrease by 1 U	Decrease by 2 U
90-145	No adjustment	No adjustment	No adjustment
146-180	Increase by 0.5 U	Increase by 1 U	Increase by 2 U
181-270	Increase by 1 U	Increase by 2 U	Increase by 4 U
>270	Increase by 1.5 U	Increase by 3 U	Increase by 6 U

a) IDeg or IDet OD (before dinner or at bedtime) titration was based on the lowest pre-breakfast SMBG value on the 3 days prior to visit/phone contact. If using IDet BID, morning dose titration was based on the lowest pre-dinner SMBG value on the 3 days prior to visit/phone contact.

Table 4. Bolus insulin titration guideline [a)]

Pre-meal or bedtime SMBG [a)] (mg/dL)	Current bolus dose	
	≤5 U	>5 U
<90	Decrease by 1 U	Decrease by 2 U
90-145	No adjustment	No adjustment
146-180	Increase by 0.5 U	Increase by 1 U
181-270	Increase by 1 U	Increase by 2 U
>270	Increase by 1.5 U	Increase by 3 U

a) Pre-breakfast IAsp was adjusted according to the lowest SMBG pre-lunch, pre-lunch IAsp was adjusted according to the lowest SMBG before dinner, and pre-dinner IAsp was adjusted according to the lowest SMBG at bedtime.

For the assay for antibody measurement, NPH insulin (the dose of NPH insulin was 80% of the basal insulin

dose at the end of treatment) was subcutaneously administered twice daily in divided doses (before breakfast and between dinner and bedtime) for 1 week from 24 hours after the last dose of basal insulin (IDeg or IDet) (IAsp was continued).

All of 350 randomized subjects (174 subjects [including 23 Japanese subjects] in the IDeg group, 176 subjects [including 32 Japanese subjects] in the IDet group) were included in the Full Analysis Set (FAS). The FAS was used for efficacy analysis. Of these subjects, 349 treated subjects (174 subjects [including 23 Japanese subjects] in the IDeg group, 175 subjects [including 32 Japanese subjects] in the IDet group) were included in the Safety Analysis Set. Excluded was 1 subject who received no dose of trial drug (IDet group). There were 15 subjects (4 subjects in the IDeg group, 11 subjects [including 2 Japanese subjects] in the IDet group) withdrawn from the trial before the end of the main period. The reasons for withdrawals were adverse events (2 subjects) (IDet group), withdrawal criteria met (11 subjects) (4 subjects in the IDeg group, 7 subjects [including 2 Japanese subjects] in the IDet group), and others (2 subjects)[16] (IDet group). There were 7 subjects withdrawn from the trial during the extension period (1 subject in the IDeg group, 6 subjects (including 1 Japanese subject) in the IDet group) and the reasons for withdrawals were adverse events (1 subject) (IDet group) and withdrawal criteria met (6 subjects) (1 subject in the IDeg group, 5 subjects [including 1 Japanese subject] in the IDet group). Of 335 subjects who completed the main period (at 26 weeks from the start of trial drug administration) (170 subjects [including 23 Japanese subjects] in the IDeg group, 165 subjects [including 30 Japanese subjects] in the IDet group), 280 subjects (152 subjects [including 22 Japanese subjects] in the IDeg group, 128 subjects [including 21 Japanese subjects] in the IDet group) continued treatment in the extension period. Excluded were 55 subjects (18 subjects [including 1 Japanese subject] in the IDeg group, 37 subjects [including 9 Japanese subjects] in the IDet group). Two hundred seventy-three subjects (151 subjects [including 22 Japanese subjects] in the IDeg group, 122 subjects [including 20 Japanese subjects] in the IDet group) completed the extension period (at 52 weeks from the start of trial drug administration).

The primary efficacy endpoint was change in HbA1c from baseline (at the start of trial drug administration) to Week 26 of treatment (least-square mean ± standard error [SE]). In the FAS, the results were -0.15% ± 0.09% in the IDeg group and -0.30% ± 0.08% in the IDet group, with a treatment difference [95% CI] of 0.15% [-0.03%, 0.32%]. The upper limit of the confidence interval was less than 0.4%[17] (the pre-defined non-inferiority margin), showing the non-inferiority of IDeg to IDet (Table 5). The treatment difference [95% CI] in the Japanese subgroup was -0.16% [-0.62%, 0.31%].

16 Including 1 subject who received no dose of trial drug.

17 A non-inferiority margin was chosen based on FDA guidance (FDA Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention, 2008).

Table 5. Change in HbA1c from baseline to Week 26 of treatment (Trial 3561 [26 weeks of treatment], FAS)

	Treatment group	Baseline	Week 26 (LOCF)	Change (LOCF)	Least-square mean change [a)]	Treatment difference [95% CI] [a)]
Entire trial population	IDeg (n = 174)	8.2 (1.1)	8.0 (1.1)	-0.20 (0.95)	-0.15 ± 0.09	0.15 [-0.03, 0.32]
	IDet (n = 176)	8.0 (1.1)	7.7 (1.0)	-0.31 (0.89)	-0.30 ± 0.08	
Japanese subgroup	IDeg (n = 23)	8.0 (0.8)	7.6 (0.9)	-0.34 (1.04)	-0.23 ± 0.21	-0.16 [-0.62, 0.31]
	IDet (n = 32)	7.6 (1.1)	7.6 (1.0)	0.01 (0.81)	-0.07 ± 0.17	

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

a) An analysis of variance (ANOVA) with treatment, sex, region (Europe [including Russia], US, Japan, South Africa; Not included in the analysis of the Japanese subgroup), and age group (≥1 years and <6 years, ≥6 years and <12 years, ≥12 years and <18 years) as fixed factors and baseline HbA1c as a covariate.

Figure 2 shows changes in HbA1c from baseline to Week 52 in the entire trial population and the Japanese subgroup.

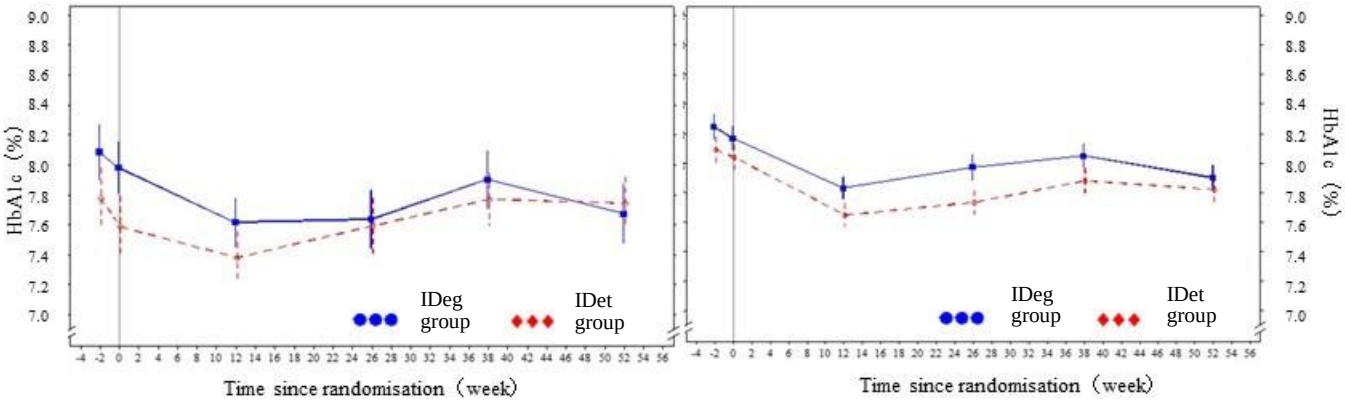

Figure 2. Changes in HbA1c from baseline to Week 52
(Trial 3561, Japanese subgroup [left figure] and entire trial population [right figure], FAS)
(Mean ± SE, LOCF)

The results of analyses of the main secondary endpoints in the entire trial population and the Japanese subgroup are shown in Table 6.

Table 6. Results of analyses of main secondary endpoints (Trial 3561; Upper two items, FAS; Lower four items, Safety Analysis Set)

Endpoint		Entire trial population		Japanese subgroup	
		IDeg	IDet	IDeg	IDet
Fasting plasma glucose (mg/dL)	No. of subjects	n = 157	n = 160	n = 22	n = 31
	Baseline	162.1 ± 94.4	151.0 ± 87.7	117.6 ± 78.1	118.1 ± 66.2
	Change (Week 26)	-12.1 ± 108.0	9.0 ± 150.8	6.2 ± 98.2	43.5 ± 79.9
	Change (Week 52)	-23.2 ± 117.7	19.8 ± 148.5	-4.7 ± 76.4	48.4 ± 102.9
Pre-breakfast SMBG value for dose titration (mg/dL)	No. of subjects	n = 173	n = 176	n = 23	n = 32
	Baseline	169.6 ± 64.8	162.6 ± 60.1	154.6 ± 69.5	132.7 ± 48.8
	Change (Week 26)	-10.1 ± 78.4	10.2 ± 69.9	-4.1 ± 56.4	32.9 ± 66.3
	Change (Week 52)	-12.7 ± 80.1	6.5 ± 77.4	0.9 ± 82.3	24.9 ± 64.5
Body weight (kg)	No. of subjects	n = 174	n = 175	n = 23	n = 32
	Baseline	38.0 ± 18.7	38.0 ± 18.8	41.1 ± 20.0	40.4 ± 16.2
	Change (Week 26)	2.1 ± 2.3	1.4 ± 2.2	1.4 ± 2.1	0.6 ± 2.2
	Change (Week 52)	4.0 ± 3.5	2.6 ± 3.3	3.9 ± 3.1	2.0 ± 3.1
Daily basal insulin dose (Upper row: U) (Lower row: U/kg)	Baseline[a)]	15 ± 11 (n = 173)	16 ± 12 (n = 174)	18 ± 10 (n = 23)	19 ± 13 (n = 32)
		0.37 ± 0.17	0.40 ± 0.20	0.44 ± 0.13	0.46 ± 0.22
	Week 26	16 ± 12 (n = 174)	22 ± 18 (n = 175)	19 ± 12 (n = 23)	24 ± 15 (n = 32)
		0.37 ± 0.16	0.51 ± 0.27	0.42 ± 0.14	0.56 ± 0.27
	Week 52	17 ± 12 (n = 174)	24 ± 20 (n = 175)	19 ± 12 (n = 23)	24 ± 15 (n = 32)
		0.38 ± 0.14	0.55 ± 0.29	0.41 ± 0.12	0.56 ± 0.26
Daily bolus insulin dose (Upper row: U) (Lower row: U/kg)	Baseline[a)]	20 ± 16 (n = 174)	20 ± 13 (n=174)	31 ± 24 (n = 23)	28 ± 16 (n = 32)
		0.50 ± 0.21	0.52 ± 0.20	0.73 ± 0.24	0.71 ± 0.25
	Week 26	23 ± 16 (n = 174)	22 ± 15 (n = 175)	35 ± 23 (n = 23)	31 ± 16 (n = 32)
		0.56 ± 0.23	0.57 ± 0.21	0.80 ± 0.27	0.75 ± 0.22
	Week 52	24 ± 16 (n = 174)	24 ± 16 (n = 175)	36 ± 22 (n = 23)	33 ± 17 (n = 32)
		0.55 ± 0.22	0.58 ± 0.21	0.79 ± 0.27	0.77 ± 0.22
Total daily insulin dose (Upper row: U) (Lower row: U/kg)	Baseline[a)]	35 ± 24 (n = 174)	36 ± 23 (n = 174)	50 ± 32 (n = 23)	47 ± 25 (n = 32)
		0.87 ± 0.30	0.93 ± 0.32	1.16 ± 0.27	1.18 ± 0.31
	Week 26	39 ± 25 (n = 174)	44 ± 30 (n = 175)	53 ± 34 (n = 23)	54 ± 24 (n = 32)
		0.92 ± 0.32	1.07 ± 0.36	1.21 ± 0.34	1.31 ± 0.30
	Week 52	41 ± 26 (n = 174)	48 ± 33 (n = 175)	55 ± 32 (n = 23)	57 ± 28 (n = 32)
		0.93 ± 0.30	1.13 ± 0.39	1.19 ± 0.33	1.33 ± 0.34

Mean ± SD, LOCF
a) Week 1

In the entire trial population, the incidences of adverse events[18] and adverse drug reactions (i.e., adverse events for which a causal relationship to trial drug could not be denied) were 92.5% (161 of 174 subjects) and 27.0% (47 of 174 subjects), respectively, in the IDeg group; and 89.7% (157 of 175 subjects) and 26.9% (47 of 175 subjects), respectively, in the IDet group. In the Japanese subgroup, the incidences of adverse events and adverse drug reactions were 95.7% (22 of 23 subjects) and 39.1% (9 of 23 subjects), respectively, in the IDeg group and 93.8% (30 of 32 subjects) and 34.4% (11 of 32 subjects), respectively, in the IDet group. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group are shown in the tables below (Table 7, the entire trial population; Table 8, the Japanese subgroup).

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

Table 7. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trial 3561 [52 weeks of treatment] Entire trial population, Safety Analysis Set)

Event term	IDeg (n = 174)		IDet (n = 175)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	161 (92.5)	47 (27.0)	157 (89.7)	47 (26.9)
Nasopharyngitis	72 (41.4)	0 (0.0)	67 (38.3)	0 (0.0)
Headache	46 (26.4)	2 (1.1)	51 (29.1)	1 (0.6)
Upper respiratory tract infection	34 (19.5)	0 (0.0)	24 (13.7)	0 (0.0)
Cough	31 (17.8)	1 (0.6)	29 (16.6)	0 (0.0)
Blood ketone body increased	31 (17.8)	7 (4.0)	46 (26.3)	24 (13.7)
Pyrexia	30 (17.2)	1 (0.6)	28 (16.0)	0 (0.0)
Oropharyngeal pain	29 (16.7)	0 (0.0)	34 (19.4)	0 (0.0)
Abdominal pain upper	28 (16.1)	2 (1.1)	17 (9.7)	2 (1.1)
Hypoglycaemia	28 (16.1)	21 (12.1)	19 (10.9)	13 (7.4)
Vomiting	26 (14.9)	1 (0.6)	23 (13.1)	0 (0.0)
Diarrhoea	22 (12.6)	2 (1.1)	17 (9.7)	0 (0.0)
Gastroenteritis	16 (9.2)	0 (0.0)	23 (13.1)	0 (0.0)
Influenza	16 (9.2)	0 (0.0)	18 (10.3)	0 (0.0)
Nausea	13 (7.5)	0 (0.0)	9 (5.1)	0 (0.0)
Nasal congestion	13 (7.5)	0 (0.0)	7 (4.0)	0 (0.0)
Rhinitis	12 (6.9)	0 (0.0)	14 (8.0)	0 (0.0)
Abdominal pain	12 (6.9)	0 (0.0)	8 (4.6)	1 (0.6)
Pain in extremity	11 (6.3)	0 (0.0)	5 (2.9)	0 (0.0)
Gastroenteritis viral	10 (5.7)	1 (0.6)	10 (5.7)	0 (0.0)
Ear pain	10 (5.7)	1 (0.6)	5 (2.9)	0 (0.0)
Ear infection	9 (5.2)	0 (0.0)	11 (6.3)	0 (0.0)
Bronchitis	9 (5.2)	0 (0.0)	8 (4.6)	0 (0.0)
Sinusitis	9 (5.2)	0 (0.0)	6 (3.4)	0 (0.0)
Wrong drug administered	9 (5.2)	3 (1.7)	6 (3.4)	3 (1.7)
Pharyngitis	6 (3.4)	0 (0.0)	10 (5.7)	0 (0.0)
Viral infection	6 (3.4)	0 (0.0)	10 (5.7)	0 (0.0)

No. of subjects with events (incidence %), MedDRA/J (ver.16.0)

Table 8. Adverse events and/or adverse drug reactions occurring in ≥5% of subjects in either treatment group (Trial 3561 [52 weeks of treatment] Japanese subgroup, Safety Analysis Set)

Event term	IDeg (n = 23)		IDet (n = 32)	
	Adverse event	Adverse drug reaction	Adverse event	Adverse drug reaction
Any event	22 (95.7)	9 (39.1)	30 (93.8)	11 (34.4)
Nasopharyngitis	17 (73.9)	0 (0.0)	17 (53.1)	0 (0.0)
Blood ketone body increased	5 (21.7)	4 (17.4)	11 (34.4)	8 (25.0)
Vomiting	4 (17.4)	1 (4.3)	1 (3.1)	0 (0.0)
Headache	4 (17.4)	0 (0.0)	2 (6.3)	0 (0.0)
Influenza	3 (13.0)	0 (0.0)	4 (12.5)	0 (0.0)
Eczema	3 (13.0)	1 (4.3)	3 (9.4)	0 (0.0)
Hypoglycaemia	3 (13.0)	3 (13.0)	4 (12.5)	3 (9.4)
Gastroenteritis	2 (8.7)	0 (0.0)	9 (28.1)	0 (0.0)
Sinusitis	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Tonsillitis	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	2 (8.7)	0 (0.0)	2 (6.3)	1 (3.1)
Stomatitis	2 (8.7)	0 (0.0)	1 (3.1)	0 (0.0)
Rash	2 (8.7)	2 (8.7)	0 (0.0)	0 (0.0)
Hypersensitivity	2 (8.7)	0 (0.0)	0 (0.0)	0 (0.0)
Dental caries	1 (4.3)	0 (0.0)	2 (6.3)	0 (0.0)
Diarrhoea	1 (4.3)	1 (4.3)	2 (6.3)	0 (0.0)
Nausea	1 (4.3)	0 (0.0)	2 (6.3)	0 (0.0)
Dry skin	1 (4.3)	0 (0.0)	2 (6.3)	0 (0.0)
Urticaria	1 (4.3)	1 (4.3)	2 (6.3)	0 (0.0)
Upper respiratory tract inflammation	1 (4.3)	0 (0.0)	3 (9.4)	0 (0.0)
Pyrexia	0 (0.0)	0 (0.0)	4 (12.5)	0 (0.0)
Head injury	0 (0.0)	0 (0.0)	2 (6.3)	0 (0.0)

No. of subjects with events (incidence %), MedDRA/J (ver.16.0)

No deaths were reported. In the entire trial population, the incidences of serious adverse events from the start of trial drug administration (Week 0) through Week 52 were 10.3% (18 of 174 subjects) in the IDeg group and 9.1% (16 of 175 subjects) in the IDet group. Serious adverse events reported by at least 2 subjects were hypoglycaemia (5 subjects [7 events] in the IDeg group, 2 subjects [2 events] in the IDet group), hypoglycaemic seizure (1 subject [1 event] in the IDeg group, 3 subjects [4 events] in the IDet group), blood ketone body increased (1 subject [1 event] in the IDeg group, 2 subjects [4 events] in the IDet group), gastroenteritis (1 subject [1 event] in the IDeg group, 2 subjects [2 events] in the IDet group), appendicitis (1 subject [1 event] in the IDeg group, 2 subjects [2 events] in the IDet group), hypoglycaemic unconsciousness (1 subject [1 event] in the IDeg group, 1 subject [1 event] in the IDet group), ketosis (1 subject [1 event] in the IDeg group, 1 subject [1 event] in the IDet group), and gastroenteritis viral (2 subjects [2 events] in the IDet group). Serious adverse events classified as adverse drug reactions were hypoglycaemia (3 subjects [3 events] in the IDeg group, 1 subject [1 event] in the IDet group), hypoglycaemic seizure (1 subject [1 event] in the IDeg group, 2 subjects [3 events] in the IDet group), hypoglycaemic unconsciousness (1 subject [1 event] in the IDeg group, 1 subject [1 event] in the IDet group), headache (1 subject [1 event] in the IDeg group), accidental overdose (1 subject [1 event] in the IDeg group), and wrong drug administered (1 subject [1 event] in the IDeg group). In the Japanese subgroup, serious adverse events were reported by 1 subject (1 event) (hypoglycaemia) in the IDeg group and 1 subject (1 event) (pharyngitis) in the IDet group, of which hypoglycaemia reported by 1 subject in the IDeg group was classified as an adverse drug reaction.

In the entire trial population, adverse events leading to trial discontinuation occurred in 3 subjects (3 events) (incorrect dose administered, anxiety disorder, hypoglycaemic seizure) in the IDet group (all non-Japanese subjects). All of these events except for anxiety disorder were classified as adverse drug reactions.

The occurrence of hypoglycaemia in the entire trial population or in the Japanese subgroup is shown in Table 9.

Table 9. Hypoglycaemia in the entire trial population and the Japanese subgroup
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

Endpoint	Entire trial population		Japanese subgroup	
	IDeg (n = 174)	IDet (n = 175)	IDeg (n = 23)	IDet (n = 32)
Confirmed hypoglycaemia [a)]	171 (98.3)	168 (96.0)	23 (100.0)	32 (100.0)
	9317 [5771]	7967 [5405]	1587 [7072]	1735 [6782]
Nocturnal confirmed hypoglycaemia [a) b)]	133 (76.4)	125 (71.4)	22 (95.7)	27 (84.4)
	973 [603]	1120 [760]	239 [1065]	286 [1118]
Severe hypoglycaemia [c)]	31 (17.8)	24 (13.7)	4 (17.4)	5 (15.6)
	82 [51]	48 [33]	4 [18]	8 [31]
Severe nocturnal hypoglycaemia [b) c)]	10 (5.7)	9 (5.1)	0 (0.0)	0 (0.0)
	18 [11]	10 [7]	0 [0]	0 [0]

Upper row, No. of subjects with episodes (incidence %); Lower row, total number of episodes [no. of episodes/100 patient-years]
a) Confirmed hypoglycaemia: "a severe hypoglycaemic episode" or "an episode where plasma glucose was <56 mg/dL, with or without the presence of hypoglycaemic symptoms"
b) Nocturnal hypoglycaemia: hypoglycaemic episodes occurring between 11:00 p.m. and 7:00 a.m.
c) Severe hypoglycaemia: as defined by ISPAD (e.g., when the child has altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma with or without convulsions and may require parenteral therapy [glucagon or intravenous glucose])

There were no clinically relevant differences in vital signs, physical findings, or laboratory values between the treatment groups during the trial period.

2.(iii).B Outline of the review by PMDA

2.(iii).B.(1) Clinical positioning of IDeg

PMDA asked the applicant to explain the clinical positioning of IDeg in insulin therapy for pediatric patients with diabetes mellitus.

The applicant's response:

Since IDeg has a longer duration of action compared with current long-acting insulin analogs, once-daily IDeg can meet the basal insulin requirements of more patients. While treatment with a long-acting insulin analog is associated with fewer hypoglycaemic episodes, nocturnal hypoglycaemia remains a concern. The prevention of nocturnal hypoglycaemia is especially important in pediatric patients, because they have lower awareness of the signs and symptoms of hypoglycaemia and difficulty explaining their symptoms verbally. IDeg may reduce the risk of nocturnal hypoglycaemia due to its flatter pharmacodynamic profile compared with current long-acting insulin analogs.

IDet, currently marketed by the applicant, has some clinical advantages over IDeg: IDet causes less weight gain compared with IDeg; IDet has been used for a longer period of time than IDeg in Japan; and IDet has been used in the Japanese pediatric population.[19] Thus, physicians will choose between IDeg and IDet, according to the individual patient's condition.

PMDA's view:

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

2.(iii).B.(2) Efficacy

For interpretation of the results from a global clinical trial, namely Trial 3561 in patients with type 1 diabetes mellitus, PMDA conducted the following reviews based on the guideline "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010 dated September 28, 2007) and the ICH-E5 guideline.

2.(iii).B.(2).1) Efficacy in Japanese subgroup and entire trial population in Trial 3561

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

The applicant's response:

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

[19] Thalange N, et al. *Diabet Med*. 2013; 30: 216–25.

patients.

There are no differences in the pharmacokinetic and pharmacodynamic profiles of IDeg between Japanese and non-Japanese patients [see "2.(ii).B Outline of the review by PMDA"].

The baseline characteristics of the Japanese subgroup and entire trial population in Trial 3561 are shown in Table 10. There were some differences in intrinsic ethnic factors: Compared with the entire trial population, the Japanese subgroup had a lower proportion of male subjects, longer duration of diabetes mellitus, a lower percentage of infant subjects (1-5 years), a higher percentage of adolescent subjects (12-17 years), and lower mean HbA1c and lower fasting plasma glucose (FPG). The longer duration of diabetes mellitus in the Japanese subgroup than in the entire trial population is considered attributable to fewer infants and more adolescents in the Japanese subgroup than in the entire trial population.

As for extrinsic ethnic factors, the bolus insulin dose (U/kg) was higher in the Japanese subgroup than in the entire trial population. This may be related to a higher carbohydrate ratio of the meal taken by the Japanese subgroup, because the basal to total daily insulin dose ratio is lower in Japanese patients than in non-Japanese patients (a higher bolus insulin proportion in Japanese patients).[20] In Trial 3561, the basal to total daily insulin dose (U/kg) ratios at baseline were 0.38 in the IDeg group and 0.39 in the IDet group in the Japanese subgroup and 0.42 in the IDeg group and 0.44 in the IDet group in the entire trial population. These values were similar to the results from Trial 3585 in adult patients with type 1 diabetes mellitus[21] (0.37 in the IDeg group and 0.35 in the IDet group in the Japanese subgroup and 0.44 in the IDeg group and 0.41 in the IDet group in the entire trial population). (The results of Trial 3585 were submitted in the initial application.)

[20] Hashimoto T, et al. *J Diabetes Investig*. 2012; 3(3): 276-82.

[21] A global, IDet-controlled, phase III trial evaluating the efficacy and safety of IDeg in Japanese and non-Japanese patients with type 1 diabetes mellitus on a basal-bolus regimen

Table 10. Baseline characteristics (Trial 3561, FAS)

		Entire trial population		Japanese subgroup	
		IDeg (n = 174)	IDet (n = 176)	IDeg (n = 23)	IDet (n = 32)
Intrinsic ethnic factors					
Age group	Infants (1-5 years)	43 (24.7)	42 (23.9)	1 (4.3)	4 (12.5)
	Children (6-11 years)	70 (40.2)	68 (38.6)	10 (43.5)	12 (37.5)
	Adolescents (12-17 years)	61 (35.1)	66 (37.5)	12 (52.2)	16 (50.0)
Age (years)		10.0 ± 4.4	10.0 ± 4.4	11.9 ± 4.0	11.8 ± 4.3
Gender	Males	96 (55.2)	98 (55.7)	9 (39.1)	16 (50.0)
	Females	78 (44.8)	78 (44.3)	14 (60.9)	16 (50.0)
Height (m)		1.37 ± 0.25	1.38 ± 0.25	1.40 ± 0.20	1.41 ± 0.22
Body weight (kg)		38.0 ± 18.7	37.8 ± 18.9	41.1 ± 20.0	40.4 ± 16.2
BMI (kg/m^2)		18.7 ± 3.6	18.5 ± 3.6	19.6 ± 4.4	19.2 ± 3.5
Diabetes duration (years)		3.9 ± 3.6	4.0 ± 3.4	6.1 ± 4.1	5.4 ± 3.9
HbA1c (%)		8.2 ± 1.1	8.0 ± 1.1	8.0 ± 0.8	7.6 ± 1.1
Fasting plasma glucose (mg/dL)		162.1 ± 94.4[c]	151.0 ± 87.7[d]	117.6 ± 78.1[e]	118.1 ± 66.2[f]
Extrinsic ethnic factors					
Daily insulin dose [a] (Upper row: U) (Lower row: U/kg)	Basal	15 ± 11[g]	16 ± 12[h]	18 ± 10	19 ± 13
		0.37 ± 0.17	0.41 ± 0.20	0.44 ± 0.13	0.46 ± 0.22
	Bolus	20 ± 16	20 ± 13[h]	31 ± 24	28 ± 16
		0.50 ± 0.21	0.52 ± 0.20	0.73 ± 0.24	0.71 ± 0.25
	Total	35 ± 24	36 ± 23[h]	50 ± 32	47 ± 25
		0.87 ± 0.30	0.93 ± 0.32	1.16 ± 0.27	1.18 ± 0.31
Insulin regimen	Basal-Bolus	169 (97.1)	166 (94.3)	23 (100.0)	32 (100.0)
	Others[b]	5 (2.9)	10 (5.7)	0 (0.0)	0 (0.0)
Basal insulin type	IDet	85 (48.9)	83 (47.2)	9 (39.1)	13 (40.6)
	IGlar	71 (40.8)	76 (43.2)	14 (60.9)	19 (59.4)
	NPH	13 (7.5)	9 (5.1)	0 (0.0)	0 (0.0)

Mean ± SD, n (%)
a) Safety Analysis Set. Baseline is Week 1 for daily insulin doses.
b) basal insulin alone, bolus insulin alone, premix insulin alone, premix insulin combined with either basal or bolus insulin, insulin pump
c) n = 157, d) n = 160, e) n = 22, f) n = 31, g) n = 173, h) n = 174

As for the consistency of results between the Japanese subgroup and entire trial population, the IDeg group tended to have a greater reduction in HbA1c after 26 weeks of treatment (the primary endpoint for Trial 3561) in the Japanese subgroup than in the entire trial population (Table 5). However, the change in HbA1c after 52 weeks of treatment in the IDeg group (mean ± SD) was similar in the Japanese subgroup and entire trial population (entire trial population, -0.27 ± 1.07%; Japanese subgroup, -0.31 ± 0.99%).

The influence of the observed ethnic differences between the Japanese subgroup and entire trial population (age group and gender distribution, baseline HbA1c, baseline fasting plasma glucose, baseline bolus insulin dose) on efficacy (HbA1c change) was assessed. The results are shown in Table 11.

Age group

In the entire trial population, there were no major differences in HbA1c change between the treatment groups across all age groups. In the Japanese subgroup, while HbA1c change was similar in both treatment groups in adolescents, HbA1c change was greater in the IDeg group than in the IDet group in children (6-11 years), which is considered attributable to higher baseline HbA1c in the IDeg group, and HbA1c after 52 weeks of treatment was similar in both treatment groups (7.6% in the IDeg group, 7.7% in the IDet group). Analysis of infants was difficult because of the small number of Japanese (1 subject in the IDeg group, 4 subjects in the IDet group), but HbA1c was reduced in the IDeg group, and there was no efficacy concern.

Gender

In the entire trial population, there were no major differences in HbA1c change between the treatment groups in either male or female subjects. In the Japanese subgroup, there were no major differences in HbA1c change between the treatment groups in males, and HbA1c change was greater in the IDeg group than in the IDet group in females. The change in HbA1c after 52 weeks of treatment (mean ± SD) was greater in the IDeg group than in the IDet group in both male and female subjects (male subjects, -0.17 ± 0.8% in the IDeg group [n = 9] and 0.24 ± 0.9% in the IDet group [n = 16]; female subjects, -0.40 ± 1.1% in the IDeg group [n = 14] and 0.07 ± 0.8% in the IDet group [n = 16]). In both the entire trial population and Japanese subgroup, HbA1c change never got worse in the IDeg group than in the IDet group in both male and female subjects.

Baseline HbA1c

In the entire trial population, HbA1c change was similar in both treatment groups in both subjects with baseline HbA1c <7.5% or ≥7.5%. In the Japanese subgroup, there were no major differences in HbA1c change between the treatment groups in subjects with baseline HbA1c ≥7.5%. Since only 3 Japanese subjects in the IDeg group had baseline HbA1c <7.5%, analysis was difficult. The influence of differences in fasting plasma glucose on the evaluation of the results can be assessed by examining the influence of differences in baseline HbA1c (a measure of glycemic control).

Baseline bolus insulin dose

In the entire trial population, there were no major differences in HbA1c change between the treatment groups in either subjects with baseline bolus insulin dose <0.5 U/kg or ≥0.5 U/kg. In the Japanese subgroup, there were no major differences in HbA1c change between the treatment groups in subjects with baseline bolus insulin dose ≥0.5 U/kg. HbA1c change was greater in the IDeg group than in the IDet group in subjects with baseline bolus insulin dose <0.5 U/kg. Though this is considered attributable to higher baseline HbA1c in the IDeg group, as the number of subjects with baseline bolus insulin dose <0.5 U/kg was small, the findings should be interpreted with caution. Given that a treat-to-target approach was used in this trial and that basal and bolus insulin doses were adjusted using titration algorithms throughout the trial period, differences in baseline bolus insulin dose should have no influence on efficacy evaluation.

Table 11. Change in HbA1c (Week 26) according to ethnic factors that differed between the entire trial population and the Japanese subgroup (Trial 3561, FAS)

			Entire trial population		Japanese subgroup	
			IDeg	IDet	IDeg	IDet
Age group	Infants (1-5 years)	No. of subjects	n = 43	n = 42	n = 1	n = 4
		Baseline	8.13 ± 1.2	8.01 ± 1.3	9.00	7.73 ± 1.2
		Change	-0.20 ± 0.9	-0.22 ± 1.1	-1.30	0.05 ± 0.8
	Children (6-11 years)	No. of subjects	n = 70	n = 68	n = 10	n = 12
		Baseline	8.12 ± 1.0	8.07 ± 1.0	8.10 ± 0.7	7.50 ± 1.1
		Change	-0.30 ± 0.9	-0.42 ± 0.8	-0.66 ± 0.6	0.03 ± 0.6
	Adolescents (12-17 years)	No. of subjects	n = 61	n = 66	n = 12	n = 16
		Baseline	8.25 ± 1.1	8.03 ± 1.1	7.80 ± 0.9	7.62 ± 1.2
		Change	-0.08 ± 1.0	-0.24 ± 0.9	-0.00 ± 1.3	-0.02 ± 1.0
Gender	Males	No. of subjects	n = 96	n = 98	n = 9	n = 16
		Baseline	8.15 ± 1.2	7.93 ± 1.1	8.07 ± 0.8	7.08 ± 1.0
		Change	-0.23 ± 0.9	-0.28 ± 1.0	-0.01 ± 1.0	0.17 ± 0.9
	Females	No. of subjects	n = 78	n = 78	n = 14	n = 16
		Baseline	8.19 ± 1.0	8.18 ± 1.0	7.93 ± 0.9	8.10 ± 1.0
		Change	-0.16 ± 1.0	-0.33 ± 0.8	-0.56 ± 1.1	-0.16 ± 0.7
Baseline HbA1c	<7.5%	No. of subjects	n = 42	n = 50	n = 3	n = 16
		Baseline	6.79 ± 0.5	6.75 ± 0.5	6.40 ± 0.6	6.66 ± 0.4
		Change	0.22 ± 0.84	0.17 ± 0.79	0.73 ± 0.76	0.28 ± 0.8
	≥7.5%	No. of subjects	n = 132	n = 126	n = 20	n = 16
		Baseline	8.61 ± 0.8	8.55 ± 0.8	8.22 ± 0.6	8.51 ± 0.8
		Change	-0.33 ± 0.94	-0.49 ± 0.86	-0.51 ± 1.00	-0.26 ± 0.75
Baseline bolus insulin dose [a)]	<0.5 U/kg	No. of subjects	n = 95	n = 89	n = 5	n = 5
		Baseline	8.13 ± 1.2	7.92 ± 1.2	8.54 ± 1.0	7.48 ± 1.7
		Change	-0.12 ± 0.9	-0.21 ± 0.9	-0.14 ± 1.4	0.88 ± 0.4
	≥0.5 U/kg	No. of subjects	n = 79	n = 85	n = 18	n = 27
		Baseline	8.22 ± 0.9	8.12 ± 1.0	7.83 ± 0.7	7.61 ± 1.0
		Change	-0.29 ± 1.0	-0.41 ± 0.8	-0.40 ± 1.0	-0.16 ± 0.8

Mean ± SD (%), LOCF
a) Week 1

As described above, some ethnic differences between the Japanese subgroup and entire trial population were observed, but those differences should have no impact on the outcomes. Therefore, it is considered there are no differences in efficacy between the entire trial population and Japanese subgroup.

PMDA's view:

As for ethnic factors, it is inferred that the pharmacokinetic and pharmacodynamic profiles of insulin degludec are similar in Japanese and non-Japanese patients [see "2.(ii).B Outline of the review by PMDA"]. In and out of Japan, patients with type 1 diabetes mellitus are treated in the same manner, and the doses of insulin preparations including IDeg are adjusted according to the individual patient's condition. In Trial 3561, IDeg was shown to be non-inferior to IDet in HbA1c change (the primary endpoint) in the entire trial population, and treatment difference (IDeg vs. IDet) in HbA1c change did not differ significantly between the Japanese subgroup and entire trial population. Some ethnic differences between the Japanese subgroup and entire trial population were observed, which are not clinically relevant. These findings show no clear discrepancy in efficacy between the Japanese subgroup and entire trial population, demonstrating consistency in efficacy between the Japanese subgroup and entire trial population.

2.(iii).B.(2).2) Efficacy by age group

The applicant's explanation:

The percentages of subjects in the 3 age groups (infants [1-5 years], children [6-11 years], adolescents [12-17 years]) were 24.7% (43 of 174 subjects), 40.2% (70 of 174 subjects), and 35.1% (61 of 174 subjects), respectively, in the IDeg group and 23.9% (42 of 176 subjects), 38.6% (68 of 176 subjects), and 37.5% (66 of

176 subjects), respectively, in the IDet group; no major differences between the treatment groups were observed. HbA1c from baseline to Week 52 by age group is shown in Figure 3. In the IDeg group, infants and children showed similar changes in HbA1c over time, with an HbA1c of 7.8% at Week 52 in both age groups. This percentage was near the target HbA1c (7.5%) recommended by the International Society for Pediatric and Adolescent Diabetes (ISPAD). In the IDeg group, HbA1c in adolescents decreased from baseline to Week 12, as in the other age groups, but increased from Week 12 to Week 26, and thereafter stabilized at a level slightly below the baseline. In infants and children in the IDet group, HbA1c decreased from baseline to Week 12 and then increased slightly. In adolescents in the IDet group, HbA1c decreased from baseline to Week 12, increased from Week 12 to Week 38, and decreased from Week 38 to Week 52.

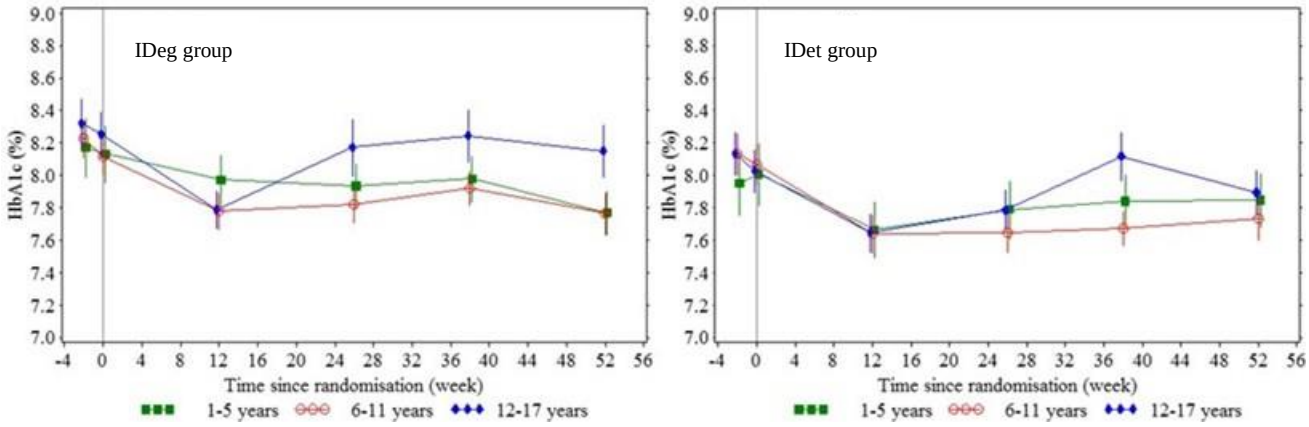

Figure 3. Changes in HbA1c (%) from baseline to Week 52 by age group
(Trial 3561, IDeg group (left figure) and IDet group (right figure), FAS) (Mean ± SE, LOCF)

As for the efficacy of IDeg by age group, PMDA asked the applicant to explain the reason for the increase in HbA1c at Week 26 in adolescents in the IDeg group.

The applicant's response:
In adolescents, baseline HbA1c (mean ± SD) was similar in both treatment groups (IDeg, 8.3 ± 1.1%; IDet, 8.0 ± 1.1%); the change in HbA1c from baseline to Week 26 was -0.08 ± 1.05% (n = 61) in the IDeg group and -0.24 ± 0.91% (n = 66) in the IDet group; the change in HbA1c from baseline to Week 52 was similar in both treatment groups (IDeg, -0.10 ± 1.09% [n = 61]; IDet, -0.14 ± 0.87% [n = 66]).

In adolescents, FPG (mean ± SD) at baseline was slightly higher in the IDeg group than in the IDet group: 153.5 ± 105.1 mg/dL in the IDeg group and 145.1 ± 82.5 mg/dL in the IDet group. FPG from baseline to Week 52 by age group is shown in Figure 4. The change in FPG from baseline to Week 26 was -18.2 ± 111.3 mg/dL in infants, -12.7 ± 99.7 mg/dL in children, and -7.3 ± 115.9 mg/dL in adolescents. The change in FPG from baseline to Week 52 was -40.9 ± 139.9 mg/dL in infants, -28.2 ± 86.8 mg/dL in children, and -6.1 ± 130.1 mg/dL in adolescents. The IDeg group showed a reduction in FPG across all age groups, but the reduction was smaller in adolescents than in infants and children. In the IDet group, FPG increased from baseline to Week 52 across all age groups; the change in FPG from baseline to Week 26 was 17.9 ± 196.4 mg/dL in infants, 16.9

± 159.4 mg/dL in children, and -4.0 ± 104.9 mg/dL mg/dL in adolescents; the change in FPG from baseline to Week 52 was 36.3 ± 185.3 mg/dL in infants, 8.9 ± 151.9 mg/dL in children, and 20.1 ± 118.5 mg/dL in adolescents.

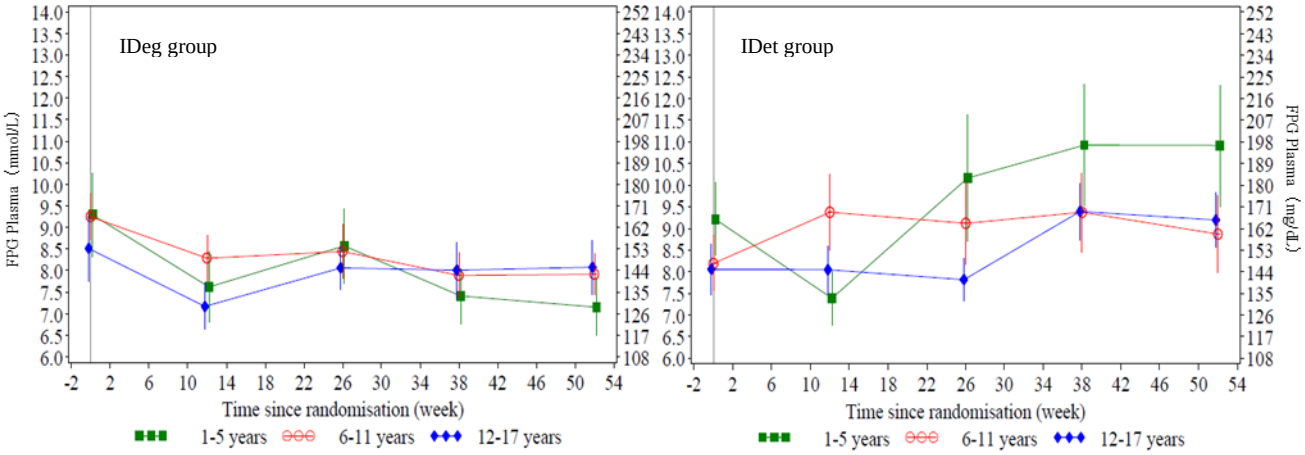

Figure 4. Changes in FPG from baseline to Week 52 by age group
(Trial 3561, IDeg group (left figure) and IDet group (right figure), FAS) (mean ± SE, LOCF)

As described above, efficacy (FPG and HbA1c) was lower in adolescents compared with infants and children in both the IDeg and IDet groups. As it is known that glycemic control in adolescents is challenging due to multiple factors including physiological changes of puberty (increased insulin resistance), and psychosocial factors,[22] it is inferred that the finding was due to irregular lifestyles of adolescents.

PMDA's view:

In Trial 3561, the reduction in HbA1c tended to be smaller in adolescents in the IDeg group, but a similar trend was observed also in the IDet group. Thus, the applicant's explanation (the tendency is attributable to difficult glycemic control in adolescents) is understood. Additionally, the non-inferiority of IDeg to IDet in the overall population was demonstrated for the primary endpoint of HbA1c change. These findings show the efficacy of IDeg in pediatric patients with type 1 diabetes mellitus.

2.(iii).B.(3) Safety

2.(iii).B.(3).1) Safety in Japanese subgroup and entire trial population in Trial 3561

The applicant's explanation:

The occurrence of adverse events in the entire trial population or in the Japanese subgroup is shown in Table 12. In the entire trial population or in the Japanese subgroup, there were no clear differences in the nature or incidence of adverse events or their causality to trial drug between the treatment groups; most of the adverse events in each treatment group were mild or moderate in severity. On the other hand, the incidence rate (or person-time rate) of overall adverse events tended to be lower in the Japanese subgroup than in the entire trial population in both treatment groups.

[22] ISPAD Clinical Practice Consensus Guidelines. 2014, Moran A, et al. *J Clin Endocrinol Metab*. 2002; 87: 4817-20.

Table 12.Adverse events occurring in the entire trial population or in the Japanese subgroup
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

		Entire trial population		Japanese subgroup	
		IDeg (n = 174)	IDet (n = 175)	IDeg (n = 23)	IDet (n = 32)
Overall adverse events		161 (92.5)	157 (89.7)	22 (95.7)	30 (93.8)
		1462 [906]	1266 [859]	133 [593]	145 [567]
Serious adverse events		18 (10.3)	16 (9.1)	1 (4.3)	1 (3.1)
		25 [15]	24 [16]	1 [4]	1 [4]
Severity	Mild	159 (91.4)	155 (88.6)	22 (95.7)	30 (93.8)
		1251 [775]	1108 [752]	124 [553]	140 [547]
	Moderate	72 (41.4)	51 (29.1)	7 (30.4)	3 (9.4)
		177 [110]	136 [92]	9 [40]	4 [16]
	Severe	23 (13.2)	12 (6.9)	0 (0.0)	1 (3.1)
		34 [21]	21 [14]	0 [0]	1 [4]
Causality	Related	26 (14.9)	22 (12.6)	6 (26.1)	3 (9.4)
		32 [20]	28 [19]	7 [31]	3 [12]
	Possibly related	30 (17.2)	31 (17.7)	4 (17.4)	9 (28.1)
		80 [50]	57 [39]	12 [53]	14 [55]
	Unrelated	157 (90.2)	156 (89.1)	20 (87.0)	29 (90.6)
		1336 [827]	1175 [797]	114 [508]	128 [500]
	Unknown	13 (7.5)	6 (3.4)	0 (0.0)	0 (0.0)
		14 [9]	6 [4]	0 [0]	0 [0]

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

The occurrence of hypoglycaemia is shown in Table 9. In the Japanese subgroup or in the entire trial population, there were no clear differences between the IDeg and IDet groups for the incidence or incidence rate of confirmed hypoglycaemia.[23] In both treatment groups, the incidence rate of confirmed hypoglycaemia tended to be slightly higher in the Japanese subgroup than in the entire trial population.

The incidence of nocturnal confirmed hypoglycaemia[24] tended to be higher in the IDeg group than in the IDet group in the Japanese subgroup, but was similar in the IDeg and IDet groups in the entire trial population. On the other hand, the incidence rate of nocturnal confirmed hypoglycaemia was similar in the IDeg and IDet groups in the Japanese subgroup, but tended to be lower in the IDeg group than in the IDet group in the entire trial population. In both treatment groups, the incidence rate of nocturnal confirmed hypoglycaemia tended to be higher in the Japanese subgroup than in the entire trial population.

Since the number of episodes of severe hypoglycaemia[25] was low in the Japanese subgroup, it is difficult to discuss the consistency of results between the entire trial population and Japanese subgroup, but the incidence rate of severe hypoglycaemia in the IDeg group tended to be lower in the Japanese subgroup than in the entire trial population. On the other hand, the incidence rate of severe hypoglycaemia in the IDet group was similar in the Japanese subgroup and entire trial population.

Figure 5 shows the number of confirmed hypoglycaemic episodes per subject over time in the entire trial population or in the Japanese subgroup. The number of confirmed hypoglycaemic episodes per subject tended

[23] "A severe hypoglycaemic episode" or "an episode where plasma glucose was <56 mg/dL, with or without the presence of hypoglycaemic symptoms"

[24] "A severe hypoglycaemic episode" or "an episode where plasma glucose was <56 mg/dL, with or without the presence of hypoglycaemic symptoms" occurring between 11:00 p.m. and 7:00 a.m.

[25] As defined by ISPAD. e.g., when the child has altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma with or without convulsions and may require parenteral therapy (glucagon or intravenous glucose).

to be higher in the Japanese subgroup than in the entire trial population throughout the trial period in both the IDeg and IDet groups.

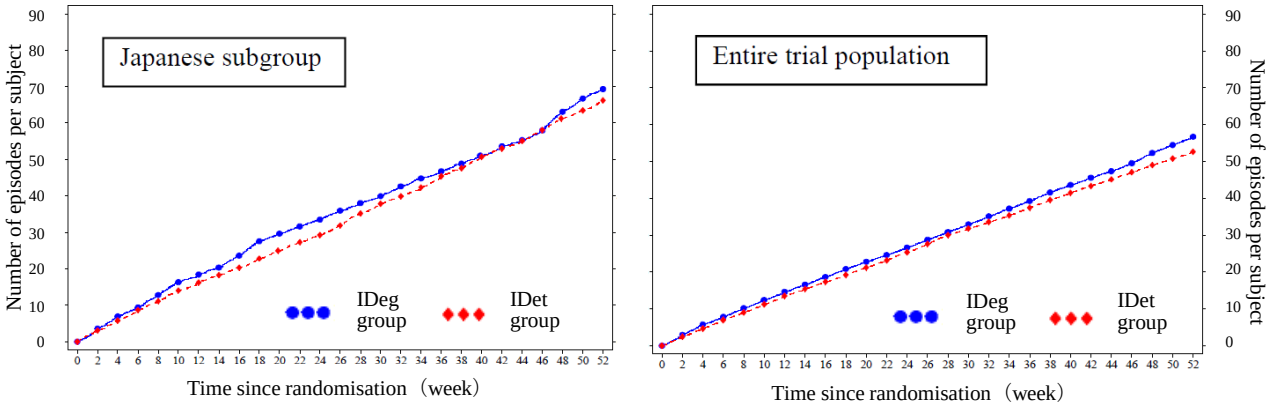

Figure 5. Confirmed hypoglycaemia over time in the Japanese subgroup (left figure) or in the entire trial population (right figure) (Trial 3561, Safety Analysis Set)

Table 13 shows the influence of the observed ethnic differences between the Japanese subgroup and entire trial population (age group and gender distribution, baseline HbA1c, and baseline bolus insulin dose) on safety.

Age group

In the entire trial population and Japanese subgroup, the incidence rate of adverse events was similar in both treatment groups in children and adolescents. In the entire trial population, the incidence rate was higher in the IDeg group than in the IDet group in infants. Although it was difficult to analyze adverse events occurring in the Japanese infants because they were small in number (1 in the IDeg group, 4 in the IDet group), no specific adverse events occurred more frequently, and there was no safety concern in this age group. Based on the above, there were no clinically relevant differences between the treatment groups across all age groups in the entire trial population or in the Japanese subgroup.

Gender

In the entire trial population, the incidence rate of adverse events was similar in both treatment groups in both male and female subjects. In the Japanese subgroup, the incidence rate of adverse events was higher in the IDeg group than in the IDet group in females, while the incidence rate was lower in the IDeg group than in the IDet group in males. No specific adverse events occurred particularly more frequently in the IDeg group than in the IDet group (the number of events in the IDeg group was >5 and the incidence rate was >2-fold higher in the IDeg group than in the IDet group) in female subjects. In male subjects, the following adverse events occurred particularly more frequently in the IDet group than in the IDeg group (the number of events in the IDet group was >5 and the incidence rate was >2-fold higher in the IDet group than in the IDeg group): gastroenteritis (1 event in the IDeg group [11.8 events/100 patient-years], 6 events in the IDet group [48.1 events/100 patient-years]) and blood ketone body increased (2 events in the IDeg group [23.6 events/100 patient-years], 9 events in the IDet group [72.1 events/100 patient-years]). The numbers of these events were low and there were clinically relevant differences between the treatment groups.

Baseline HbA1c

In the entire trial population, the incidence rate of adverse events was similar in both treatment groups in both subjects with baseline HbA1c ≥7.5% or <7.5%. In the Japanese subgroup, the incidence rate of adverse events was similar in both treatment groups in subjects with baseline HbA1c ≥7.5% while the incidence rate was lower in the IDeg group than that in the IDet group in subjects with baseline HbA1c <7.5%. The number of Japanese subjects with baseline HbA1c <7.5% in the IDeg group was small (3 subjects). No specific adverse events occurred more frequently in either treatment group, and there was no safety concern associated with differences in baseline HbA1c. Based on the above, as no clinically relevant differences between the treatment groups were observed in subjects with baseline HbA1c ≥7.5% or <7.5% in the entire trial population or in the Japanese subgroup, differences in baseline HbA1c should have no influence on safety evaluation.

Baseline bolus insulin dose

In the entire trial population, the incidence rate of adverse events was similar in both treatment groups in both subjects with baseline bolus insulin dose <0.5 U/kg or ≥0.5 U/kg. In the Japanese subgroup, the incidence rate of adverse events was lower in the IDeg group than in the IDet group in subjects with baseline bolus insulin dose ≥0.5 U/kg. In subjects with baseline bolus insulin dose ≥0.5 U/kg, the following adverse events occurred particularly more frequently in either treatment group (the number of events was >5 in one treatment group and the incidence rate was >2-fold higher compared with the other treatment group) (preferred terms): blood ketone body increased (4 events [22.9 events/100 patient-years] in the IDeg group, 18 events [85.3 events/100 patient-years] in the IDet group) and gastroenteritis (0 events [0 events/100 patient-years] in the IDeg group, 8 events [37.9 events/100 patient-years] in the IDet group). The number of subjects with baseline bolus insulin dose <0.5 U/kg was too small to draw any conclusions, but no specific adverse events occurred more frequently (no events were reported >4 times, except for nasopharyngitis, in either treatment group) and there was no safety concern. Therefore, differences in baseline bolus insulin dose should have no influence on safety evaluation.

Table 13. Adverse events according to ethnic factors that differed between the entire trial population and the Japanese subgroup (Trial 3561 [52 weeks of treatment], Safety Analysis Set)

		Entire trial population		Japanese subgroup	
		IDeg (n = 174)	IDet (n = 175)	IDeg (n = 23)	IDet (n = 32)
Age group	Infants (1-5 years)	39/43 (90.7)	35/41 (85.4)	1/1 (100.0)	4/4 (100.0)
		510 [1310.4]	296 [867.5]	26 [2608.9]	27 [903.9]
	Children (6-11 years)	64/70 (91.4)	60/68 (88.2)	10/10 (100.0)	12/12 (100.0)
		532 [802.9]	562 [961.3]	70 [701.1]	77 [807.2]
	Adolescents (12-17 years)	58/61 (95.1)	62/66 (93.9)	11/12 (91.7)	14/16 (87.5)
		420 [746.4]	408 [744.2]	37 [322.8]	41 [314.0]
Gender	Males	86/96 (89.6)	88/98 (89.8)	8/9 (88.9)	16/16 (100.0)
		761 [831.1]	746 [890.5]	44 [518.3]	83 [665.3]
	Females	75/78 (96.2)	69/77 (89.6)	14/14 (100.0)	14/16 (87.5)
		701 [1003.1]	520 [817.1]	89 [637.9]	62 [473.1]
Baseline HbA1c	≥7.5%	123/132 (93.2)	109/125 (87.2)	19/20 (95.0)	14/16 (87.5)
		1164 [947.5]	929 [887.8]	126 [647.6]	68 [585.9]
	<7.5%	38/42 (90.5)	48/50 (96.0)	3/3 (100.0)	16/16 (100.0)
		298 [771.9]	337 [787.9]	7 [234.6]	77 [550.9]
Baseline bolus insulin dose[a)]	<0.5 U/kg	86/95 (90.5)	79/89 (88.8)	5/5 (100.0)	5/5 (100.0)
		813 [929.2]	753 [974.4]	55 [1103.8]	18 [400.9]
	≥0.5 U/kg	75/79 (94.9)	77/85 (90.6)	17/18 (94.4)	25/27 (92.6)
		649 [877.5]	510 [727.4]	78 [446.8]	127 [602.1]

Upper row, no. of subjects with events/no. of evaluable subjects (incidence %); Lower row, total number of events [no. of events/100 patient-years]
a) Week 1

Based on the above, there should be no clinically relevant differences in safety between the Japanese subgroup and the entire trial population in Trial 3561.

2.(iii).B.(3).2) Safety by age group

The applicant's explanation:

The occurrence of adverse events by age group is shown in Table 14. There were no major differences in the incidence of adverse events among the age groups in both treatment groups. There were no major differences in the incidence rate of adverse events between children and adolescents; the incidence rate of adverse events was similar also in both treatment groups. In the IDeg group, the incidence rate of adverse events was higher in infants than in the other age groups. The incidence rate of adverse events in infants was higher in the IDeg group than in the IDet group. The system organ classes of adverse events with highest rates were "infections and infestations," "respiratory disorders," and "gastrointestinal disorders," which are all common in the general pediatric population. The reason for the difference in the incidence rate of adverse events may be that approximately 47% of subjects in the IDet group had already been treated with IDet before the trial. The incidence or incidence rate of adverse drug reactions showed no consistent trend between the treatment groups or among the age groups. The number of serious adverse events occurring in each age group was low; most of the events occurred as a single episode in a single subject. Infection-related events and blood ketone body increased occurred more frequently in infants in both treatment groups.

Adverse events leading to trial discontinuation occurred in only 3 subjects (all non-Japanese subjects) in the IDet group after the first month of treatment: 1 subject aged 13 years (incorrect dose administered), 1 subject aged 11 years (anxiety disorder), and 1 subject aged 5 years (hypoglycaemic seizure). The anxiety disorder was assessed as unrelated to trial drug while the two other events were judged as "related to trial drug" or "possibly related to trial drug."

Table 14. Adverse events by age group (Trial 3561 [52 weeks of treatment], Safety Analysis Set)

	Age group	IDeg		IDet	
Overall adverse events	Overall	161/174 (92.5)	1462 [906]	157/175 (89.7)	1266 [859]
	Infants (1-5 years)	39/43 (90.7)	510 [1310.4]	35/41 (85.4)	296 [867.5]
	Children (6-11 years)	64/70 (91.4)	532 [802.9]	60/68 (88.2)	562 [961.3]
	Adolescents (12-17 years)	58/61 (95.1)	420 [746.4]	62/66 (93.9)	408 [744.2]
Adverse drug reactions	Overall	47/174 (27.0)	112 [69]	47/175 (26.9)	85 [58]
	Infants (1-5 years)	10/43 (23.3)	24 [61.7]	12/41 (29.3)	23 [67.4]
	Children (6-11 years)	22/70 (31.4)	55 [83.0]	20/68 (29.4)	39 [66.7]
	Adolescents (12-17 years)	15/61 (24.6)	33 [58.6]	15/66 (22.7)	23 [42.0]
Serious adverse events	Overall	18/174 (10.3)	25 [15]	16/175 (9.1)	24 [16]
	Infants (1-5 years)	6/43 (14.0)	9 [23]	7/41 (17.1)	13 [38]
	Children (6-11 years)	5/70 (7.1)	8 [12]	6/68 (8.8)	8 [14]
	Adolescents (12-17 years)	7/61 (11.5)	8 [14]	3/66 (4.5)	3 [5]

Left, no. of subjects with events/no. of evaluable subjects (incidence %); Right, total number of events [no. of events/100 patient-years]

According to the IDeg post-marketing data in Japan (March 7, 2012 [the launch date] to December 31, 2014), the events reported by patients aged <18 years had a similar profile to those reported by adult patients. No new concern was identified for patients aged <18 years.

As described above, adverse events tended to occur more frequently in infants than in children and adolescents in Trial 3561. This was probably because these infants had a high incidence of adverse events commonly observed in the general pediatric population (e.g. infections).

PMDA's view on 1) and 2):
Based on the occurrence of adverse events and adverse drug reactions in Trial 3561, there are no clinically relevant differences between the Japanese subgroup and entire trial population. However, regarding safety by age group, as there was a trend towards more adverse events in infants compared with the other age groups and the number of infants studied was small, it is necessary to continue to collect safety information.

PMDA further examined the following events of interest for safety evaluation.

2.(iii).B.(3).3) Hypoglycaemia

The applicant's explanation:
The occurrence of hypoglycaemia in Trial 3561 is shown in Table 9. In the entire trial population, the incidence and incidence rate of confirmed hypoglycaemia at Week 52 were similar in both treatment groups. While the incidence of nocturnal confirmed hypoglycaemia was similar in both treatment groups, the incidence rate of nocturnal confirmed hypoglycaemia was lower in the IDeg group than in the IDet group. The incidence rate of severe hypoglycaemia as defined by the ISPAD (severe hypoglycaemia [ISPAD definition]) was higher in the IDeg group than in the IDet group. Approximately 80% of the severe hypoglycaemic episodes (ISPAD definition) occurred during the daytime in both treatment groups; in most cases, bolus insulin was the last insulin administered before the onset of hypoglycaemic episode. About half of all reported severe hypoglycaemic episodes (ISPAD definition) (42 of 82 episodes) were reported by 11 subjects reporting ≥4 severe hypoglycaemic episodes (ISPAD definition) (8 subjects in the IDeg group [3 infants (1-5 years), 4 children (6-11 years), 1 subject aged 17 years] and 3 subjects in the IDet group [2 children (6-11 years), 1 subject aged 16 years]).

The numbers of confirmed hypoglycaemic episodes, nocturnal confirmed hypoglycaemic episodes, and severe hypoglycaemic episodes (ISPAD definition) per subject over time are shown in Figure 6. The number of hypoglycaemic episodes during the first 4 weeks of treatment was as follows: 999 confirmed hypoglycaemic episodes in the IDeg group and 806 confirmed hypoglycaemic episodes in the IDet group; 141 nocturnal confirmed hypoglycaemic episodes in the IDeg group and 97 nocturnal confirmed hypoglycaemic episodes in the IDet group; and 21 severe hypoglycaemic episodes (ISPAD definition) in the IDeg group and 6 severe hypoglycaemic episodes (ISPAD definition) in the IDet group. The numbers of episodes of confirmed hypoglycaemia, nocturnal confirmed hypoglycaemia, and severe hypoglycaemia (ISPAD definition) tended to be higher in the IDeg group than in the IDet group during the first 4 weeks of treatment. From Week 5 through Week 52, the number of confirmed hypoglycaemia episodes over time was similar in both treatment groups, and the number of nocturnal confirmed hypoglycaemic episodes was lower in the IDeg group than in the IDet group (Figure 6). Patients transferred to a new insulin product or regimen may have an increased risk of hypoglycaemia during the initial weeks of treatment with the new insulin product or regimen. This risk is particularly high in patients who have switched the basal insulin unit-to-unit based on the previous basal insulin dose without dose reduction. There was a trend towards a greater difference between the treatment groups in severe hypoglycaemia (ISPAD definition) after Week 26 (Figure 6). The reason for this difference may be that subjects treated with IDet reporting severe hypoglycaemic more frequently were withdrawn from the trial at Week 26.

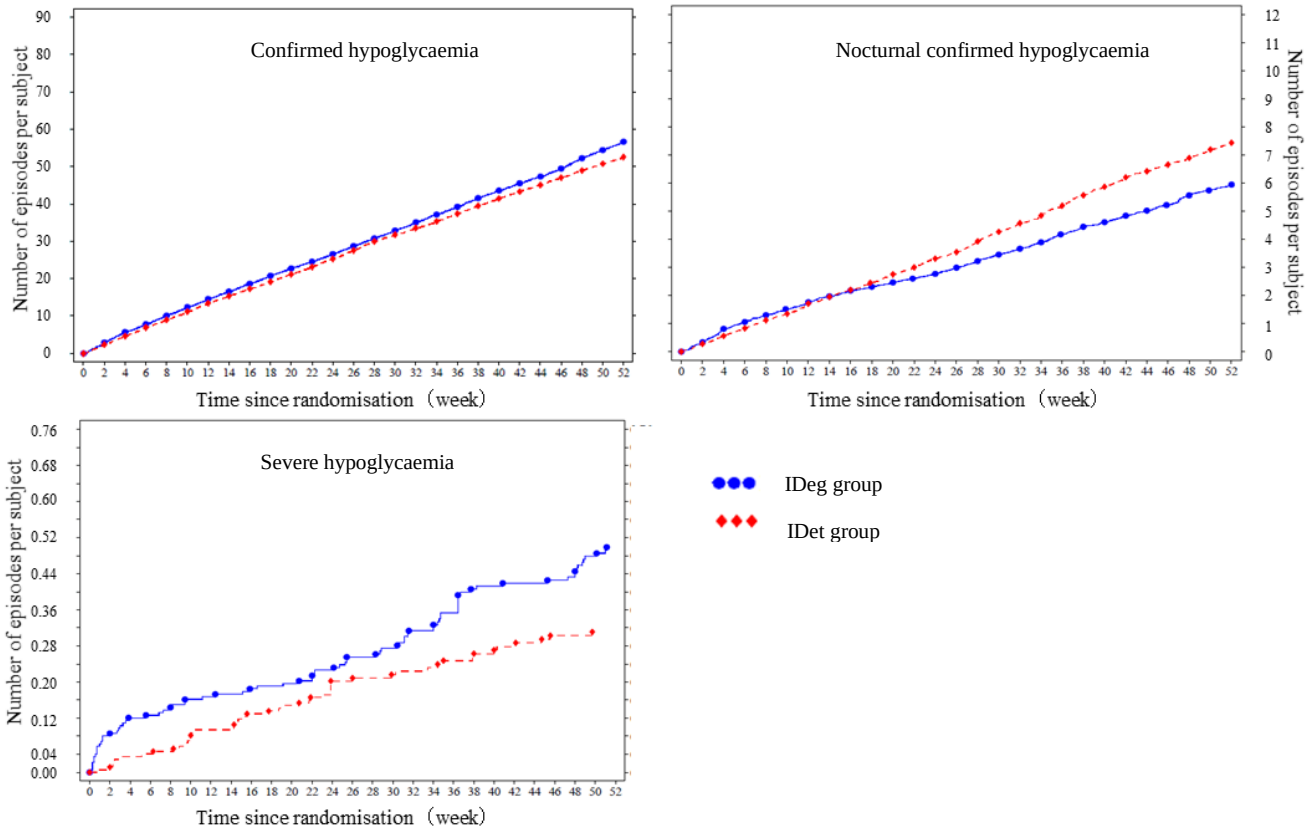

Figure 6. Hypoglycaemia over time (Mean cumulative function) (Trial 3561, Safety Analysis Set)

The estimated ratios of incidence rate (IDeg/IDet) for confirmed hypoglycaemia and nocturnal confirmed

hypoglycaemia during the entire treatment period [95% CI] were 1.11 [0.89, 1.38] and 0.99 [0.72, 1.34], respectively. These ratios during the maintenance period (from Week 16 until Week 52) were 1.05 [0.83, 1.32] and 0.88 [0.63, 1.23], respectively.

The occurrence of treatment-emergent hypoglycaemia by age group is shown in Table 15. There were no major differences in the incidence of confirmed hypoglycaemia among all age groups. There were no major differences in the incidence of confirmed hypoglycaemia between the treatment groups across all age groups. The incidence rate of confirmed hypoglycaemia was higher in children compared with infants and adolescents in both treatment groups. The incidence rate of confirmed hypoglycaemia was similar in both treatment groups in children and adolescents, but was higher in the IDeg group than in the IDet group in infants.

In the IDeg group, the incidence of nocturnal confirmed hypoglycaemia tended to increase with increasing age. In the IDet group, the incidence was lower in infants but similar in children and adolescents. In infants and children, there were no major differences in the incidence between the treatment groups. In adolescents, however, the incidence was higher in the IDeg group than in the IDet group. The incidence rate of nocturnal confirmed hypoglycaemia tended to increase with increasing age in both treatment groups. This may be related to lifestyle changes such as irregular meals and nighttime activities during the adolescent period. The differences in the incidence among the age groups tended to be greater in the IDet group compared with the IDeg group.

The results of severe hypoglycaemia (ISPAD definition) should be interpreted with caution because of the small number of episodes occurring in each age group. The incidence of severe hypoglycaemia tended to be high in children and low in adolescents in both treatment groups. The incidence tended to be higher in the IDeg group than in the IDet group across all age groups. The incidence rate of severe hypoglycaemia tended to be high in children and low in adolescents in the IDeg group. In the IDet group, the incidence rate was similar among the age groups. The differences in the occurrence of severe hypoglycaemia are considered mainly associated with a high incidence rate of severe hypoglycaemia in children in the IDeg group during the extension period. During the extension period after Week 26, a total of 28 severe hypoglycaemic episodes were reported by 11 children in the IDeg group. Of the 28 episodes, 22 occurred in 5 children. In other subgroups defined by age and treatment, only 4 to 6 episodes occurred in 2 to 4 subjects during the extension period.

Table 15. Hypoglycaemia by age group (Trial 3561 [52 weeks of treatment], Safety Analysis Set)

Classification	Age group	IDeg (n = 174)		IDet (n = 175)	
Confirmed hypoglycaemia	Infants (1-5 years)	42/43 (97.7)	2248 [5776]	40/41 (97.6)	1221 [3579]
	Children (6-11 years)	69/70 (98.6)	4304 [6495]	65/68 (95.6)	3999 [6840]
	Adolescents (12-17 years)	60/61 (98.4)	2765 [4913]	63/66 (95.5)	2747 [5011]
	Overall	171/174 (98.3)	9317 [5771]	168/175 (96.0)	7967 [5405]
Nocturnal confirmed hypoglycaemia	Infants (1-5 years)	27/43 (62.8)	169 [434]	24/41 (58.5)	85 [249]
	Children (6-11 years)	52/70 (74.3)	382 [577]	52/68 (76.5)	423 [724]
	Adolescents (12-17 years)	54/61 (88.5)	422 [750]	49/66 (74.2)	612 [1116]
	Overall	133/174 (76.4)	973 [603]	125/175 (71.4)	1120 [760]
Severe hypoglycaemia (ISPAD definition)	Infants (1-5 years)	8/43 (18.6)	19 [49]	6/41 (14.6)	11 [32]
	Children (6-11 years)	14/70 (20.0)	47 [71]	11/68 (16.2)	20 [34]
	Adolescents (12-17 years)	9/61 (14.8)	16 [28]	7/66 (10.6)	17 [31]
	Overall	31/174 (17.8)	82 [51]	24/175 (13.7)	48 [33]
Severe nocturnal hypoglycaemia	Infants (1-5 years)	1/43 (2.3)	3 [8]	2/41 (4.9)	3 [9]
	Children (6-11 years)	7/70 (10.0)	12 [18]	4/68 (5.9)	4 [7]
	Adolescents (12-17 years)	2/61 (3.3)	3 [5]	3/66 (4.5)	3 [5]
	Overall	10/174 (5.7)	18 [11]	9/175 (5.1)	10 [7]

Left, no. of subjects with episodes/no. of evaluable subjects (incidence %); Right, total number of episodes [no. of episodes/100 patient-years]

The ISPAD definition of severe hypoglycaemia is broad and may also include a subjective element (the child has altered mental status and cannot assist in their care). Therefore, all reported episodes of severe hypoglycaemia were reviewed in a blinded manner by an independent, external pediatric endocrinologist, as stipulated pre-trial. The results are shown in Table 16. The incidence rate of severe hypoglycaemia based on external classification was lower than the incidence rate of severe hypoglycaemia (ISPAD definition) in both treatment groups. The incidence rate of severe hypoglycaemic episodes resulting in being “semiconscious or unconscious” or “in coma with or without convulsions” was low in both treatment groups. The majority of the severe episodes (ISPAD definition) were classified as being related to a subjective element: “the child has altered mental status and cannot assist in their care” and the differences between the treatment groups resulted from this classification. The trial had an open-label design and many subjects in the IDet group (47%) were familiar with IDet therapy (including injection of IDet) at the start of the trial, which may have affected reporting of severe hypoglycaemia based on this subjective element.

Table 16. Severe hypoglycaemia based on external classification
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

Classification of hypoglycaemia		Age group	IDeg (n = 174)		IDet (n = 175)	
Severe hypoglycaemia (ISPAD definition)		Infants (1-5 years)	8/43 (18.6)	19 [49]	6/41 (14.6)	11 [32]
		Children (6-11 years)	14/70 (20.0)	47 [71]	11/68 (16.2)	20 [34]
		Adolescents (12-17 years)	9/61 (14.8)	16 [28]	7/66 (10.6)	17 [31]
		Overall	31/174 (17.8)	82 [51]	24/175 (13.7)	48 [33]
Severe hypoglycaemia based on external classification	The child has altered mental status and cannot assist in their care	Infants (1-5 years)	8/43 (18.6)	13 [33]	1/41 (2.4)	1 [3]
		Children (6-11 years)	9/70 (12.9)	25 [38]	6/68 (8.8)	10 [17]
		Adolescents (12-17 years)	4/61 (6.6)	8 [14]	4/66 (6.1)	7 [13]
		Overall	21/174 (12.1)	46 [28]	11/175 (6.3)	18 [12]
	Semiconscious or unconscious	Infants (1-5 years)	0/43 (0.0)	0 [0]	1/41 (2.4)	1 [3]
		Children (6-11 years)	5/70 (7.1)	5 [8]	3/68 (4.4)	3 [5]
		Adolescents (12-17 years)	2/61 (3.3)	2 [4]	2/66 (3.0)	6 [11]
		Overall	7/174 (4.0)	7 [4]	6/175 (3.4)	10 [7]
	In coma with or without convulsions	Infants (1-5 years)	2/43 (4.7)	3 [8]	4/41 (9.8)	7 [21]
		Children (6-11 years)	2/70 (2.9)	3 [5]	2/68 (2.9)	2 [3]
		Adolescents (12-17 years)	2/61 (3.3)	2 [4]	1/66 (1.5)	1 [2]
		Overall	6/174 (3.4)	8 [5]	7/175 (4.0)	10 [7]
Not severe hypoglycaemia		Infants (1-5 years)	0/43 (0.0)	0 [0]	1/41 (2.4)	2 [6]
		Children (6-11 years)	3/70 (4.3)	10 [15]	2/68 (2.9)	3 [5]
		Adolescents (12-17 years)	2/61 (3.3)	3 [5]	2/66 (3.0)	3 [5]
		Overall	5/174 (2.9)	13 [8]	5/175 (2.9)	8 [5]
Unclassifiable		Infants (1-5 years)	1/43 (2.3)	3 [8]	0/41 (0.0)	0 [0]
		Children (6-11 years)	3/70 (4.3)	4 [6]	1/68 (1.5)	2 [3]
		Adolescents (12-17 years)	1/61 (1.6)	1 [2]	0/66 (0.0)	0 [0]
		Overall	5/174 (2.9)	8 [5]	1/175 (0.6)	2 [1]

Left, no. of subjects with episodes/no. of evaluable subjects (incidence %); Right, total number of episodes [no. of episodes/100 patient-years]

According to the IDeg post-marketing data in Japan, 27 adverse drug reactions were reported by 20 patients aged <18 years, including hypoglycaemia (7 subjects, 10 episodes), hypoglycaemic seizure (1 subject, 2 episodes), hypoglycaemic unconsciousness (1 subject, 1 episode), and hypoglycaemic coma (1 subject, 1 episode) as hypoglycaemia-related events. Of these hypoglycaemia-related events, 8 episodes reported by 6 subjects were serious (hypoglycaemia [3 subjects, 4 episodes], hypoglycaemic seizure [1 subject, 2 episodes], hypoglycaemic unconsciousness [1 subject, 1 episode], hypoglycaemic coma [1 subject, 1 episode]).

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

The applicant's response:

Since IDeg has a flat and stable action profile, the risk of fluctuations in blood glucose is lower and theoretically, blood glucose levels are not markedly lowered in the patients treated with IDeg. These patients are expected to recover from hypoglycaemia faster after the onset. In a clinical pharmacology trial that investigated the time to recovery from hypoglycaemia and the counter-regulatory response to controlled hypoglycaemia in adult patients (Trial 3538[26]), the response to hypoglycaemia (counter-regulatory hormone response) was similar, at least between IGlar and IDeg. As the population pharmacokinetic analysis indicated that there are no pharmacokinetic differences between adults vs. infants, children, or adolescents, the response to hypoglycaemia (counter-regulatory hormone response) should be similar between IGlar and IDeg also in pediatric population.

[26] A double-blind, two-period, crossover trial in which IDeg and IGlar were administered once daily for 5 days to non-Japanese patients with type 1 diabetes mellitus. Subjects received a dose that was 80% of their individual daily basal insulin requirement for 4 days and a dose that was 3 times their individual daily basal insulin requirement for 1 day.

All reported episodes of severe hypoglycaemia in Trial 3561 (IDeg group, 31 subjects, 82 episodes; IDet group, 24 subjects, 48 episodes) were reviewed to assess the approximate duration and recurrence of hypoglycaemic episodes. As a result, recovery from severe hypoglycaemia within 1 hour was confirmed in most cases. Delayed recovery (time to recovery >1 hour) was observed in the remaining cases. No factors other than the trial drug could clearly explain the delay for 7 severe hypoglycaemic episodes (4 episodes in the IDeg group, 3 episodes in the IDet group), and its occurrence seemed similar in both treatment groups.

The results above show that the time to recovery from hypoglycaemia are similar for IDeg and the current insulin products, and that IDeg is not associated with the risk of prolonged hypoglycaemia.

PMDA's view:
In Trial 3561, there was a trend towards differences in the occurrence of hypoglycaemia among the age groups. The applicant explained that this was related to differences in lifestyle, handling of hypoglycaemia, etc. among the age groups, which is understood. Therefore, the safety of IDeg is acceptable, on condition that appropriate cautions are provided. As the number of subjects studied was small for some of age groups, it is necessary to continue to collect information on the occurrence of hypoglycaemia via post-marketing surveillance.

2.(iii).B.(3).4) Injection site reactions
The applicant's explanation:
The occurrences of injection site reaction-related events[27] and lipodystrophy-related events[28] in Trial 3561 are shown in Table 17. The incidence and incidence rate of injection site reaction-related events were higher in the IDeg group than in the IDet group. Except for 5 moderate events reported by 3 subjects (IDeg group, 2 subjects, 3 events [injection site bruising, vessel puncture site bruise, vessel puncture site swelling]; IDet group, 1 subject, 2 events [injection site mass]), all events were mild in severity. There were no serious adverse events or events leading to treatment discontinuation. The following events were classified as adverse drug reactions: 12 events reported by 8 subjects in the IDeg group (injection site reaction [5 events]; injection site pain [3 events]; injection site erythema, injection site bruising, injection site haemorrhage, and injection site rash, 1 event each) and 6 events reported by 5 subjects in the IDet group (injection site reaction [2 events]; injection site mass [2 events]; injection site erythema and injection site swelling, 1 event each).

Both the incidence and incidence rate of lipodystrophy-related events were low in both treatment groups. Except for 3 moderate events reported by 2 subjects (IDeg group, 1 subject, 1 event [lipohypertrophy]; IDet group, 1 subject, 2 events [lipodystrophy acquired]), all events were mild in severity. There were no serious events or events leading to treatment discontinuation. Three events reported by 3 subjects (lipohypertrophy) in the IDeg group and 3 events reported by 2 subjects (lipodystrophy acquired [2 events], lipohypertrophy [1 event]) in the IDet group were classified as adverse drug reactions.

[27] Preferred terms under the MedDRA High Level Terms (HLTs) of "administration site reactions", "application and instillation site reactions", "infusion site reactions", and "injection site reactions"

[28] Preferred terms under the MedDRA High Level Term (HLT) of "lipodystrophies"

In the IDeg group, the incidence rate of injection site reaction-related events was higher in infants than in children and adolescent. In all age groups, the incidence rate of injection site reaction-related events was higher in the IDeg group than in the IDet group. A higher incidence rate in infants is probably due to 8 injection site reactions reported by 2 infants in the IDeg group. The incidence rate of injection site reaction-related events was higher in the IDeg group than in the IDet group also in children and adolescents, but the difference between the treatment groups was smaller in children and adolescents than in infants.

The incidence rate of lipodystrophy-related events was similar in both treatment groups in infants, but higher in the IDet group than in the IDeg group in children and adolescents.

Table 17. Injection site reaction- and lipodystrophy-related events by age group
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

Age group	Injection site reactions		Lipodystrophies	
	IDeg (n = 174)	IDet (n = 175)	IDeg (n = 174)	IDet (n = 175)
Overall	18 (10.3)	6 (3.4)	5 (2.9)	5 (2.9)
	28 [17.3]	7 [4.7]	5 [3.1]	7 [4.7]
Infants (1-5 years)	6 (14.0)	1 (2.4)	1 (2.3)	1 (2.4)
	13 [33]	1 [3]	1 [3]	1 [3]
Children (6-11 years)	6 (8.6)	2 (2.9)	3 (4.3)	2 (2.9)
	7 [11]	2 [3]	3 [5]	4 [7]
Adolescents (12-17 years)	6 (9.8)	3 (4.5)	1 (1.6)	2 (3.0)
	8 [14]	4 [7]	1 [2]	2 [4]

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

According to the IDeg post-marketing data in Japan, 27 adverse drug reactions were reported by 20 patients aged <18 years. These adverse drug reactions included injection site reaction-related events: injection site pain (2 subjects, 2 events), injection site induration (1 subject, 1 event), and injection site erythema (1 subject, 1 event). These injection site reaction-related events were all non-serious.

As described above, injection site reaction-related events were reported more frequently in the IDeg group than in the IDet group in Trial 3561. Injection site reactions are listed in the precautions section of the current package insert.

PMDA's view:
The clinical trial showed a trend towards more frequent injection site reactions in the IDeg group than in the IDet group. As injection site reactions are one of the significant events in insulin treatment, it is necessary to continue to collect information on the occurrence of injection site reactions via post-marketing surveillance.

2.(iii).B.(3).5) Immunogenicity-related adverse events (allergic reactions)

The applicant's explanation:

In Trial 3561, the incidences of immunogenicity-related adverse events (allergic reactions)[29] were 13.2% (23 of 174 subjects) in the IDeg group and 10.9% (19 of 175 subjects) in the IDet group. The incidence rates of immunogenicity-related adverse events (allergic reactions) were 21.7 events/100 patient-years in the IDeg group and 17.6 events/100 patient-years in the IDet group. No major differences between the treatment groups were observed. Five adverse drug reactions were reported by 2 subjects (rash [2 events]; eczema, urticaria, and injection site rash, 1 event each) in the IDeg group. No adverse drug reactions were reported in the IDet group. There were no severe events, serious adverse events, or adverse events leading to treatment discontinuation.

As for the occurrence by age group, the incidence and incidence rate of immunogenicity-related adverse events (allergic reactions) were 20.9% (9 of 43 subjects) and 41.1 events/100 patient-years, respectively, in infants in the IDeg group; 7.3% (3 of 41 subjects) and 20.5 events/100 patient-years, respectively, in infants in the IDet group; 15.7% (11 of 70 subjects) and 22.6 events/100 patient-years, respectively, in children in the IDeg group; 8.8% (6 of 68 subjects) and 12.0 events/100 patient-years, respectively, in children in the IDet group; 4.9% (3 of 61 subjects) and 7.1 events/100 patient-years, respectively, in adolescents in the IDeg group; and 15.2% (10 of 66 subjects) and 21.9 events/100 patient-years, respectively, in adolescents in the IDet group. There was no consistent trend among the age groups or between the treatment groups. Across all age groups, most events were those in the system organ class of "skin and subcutaneous tissue disorders."

The IDeg post-marketing data in Japan[30] showed that, among serious adverse drug reactions, those related to allergic reactions, injection site reactions, or immunogenicity-related events were 3 events reported by adult patients (urticaria, anti-insulin antibody positive, and anti-insulin antibody increased, 1 event each), but no such events occurred in patients aged <18 years.

Based on the above, there was no particular safety concern associated with the immunogenicity of IDeg, but information will continue to be collected via post-marketing surveillance etc.

PMDA's view:

There were no major differences in the occurrence of immunogenicity-related adverse events (allergic reactions) between the IDeg and comparator groups. It is necessary to continue to collect information on the occurrence of anaphylactic and allergic reactions via post-marketing surveillance.

2.(iii).B.(3).6) Influence of antibody formation

The applicant's explanation on the influence of antibody formation on efficacy:

Anti-insulin antibody titers over time in Trial 3561 (52 weeks) are shown in Table 18. The titer of insulin antibodies cross-reacting between insulin analogs and human insulin decreased with IDeg and increased with

[29] Preferred terms in Standardized MedDRA Queries (SMQs) "anaphylactic reaction (narrow)," "angioedema (narrow)," "anaphylactic/anaphylactoid shock conditions (narrow)," and "hypersensitivity (narrow)"

[30] Estimated cumulative exposure of 87,788 patient-years (including adult patients) as of March 31, 2015

IDet. The titer of insulin antibodies specific to insulin degludec (IDeg) or IDet remained low, but was higher in the IDet group than in the IDeg group. The titer of insulin antibodies specific to IAsp remained low and at a similar level between the IDeg and IDet groups. A similar trend as in the overall population was observed for the three age groups.

Table 18. Anti-insulin antibody titers over time (Trial 3561, Safety Analysis Set)

Age group	Timing	Titer of cross-reacting insulin antibodies		Titer of IDeg- or IDet-specific antibodies		Titer of IAsp-specific antibodies		Titer of total insulin antibodies	
		IDeg (n = 174)	IDet (n = 175)	IDeg (n = 174)	IDet (n = 175)	IDeg (n = 174)	IDet (n = 175)	IDeg (n = 174)	IDet (n = 175)
Overall	Baseline	20.8 [0.0, 83.2] (n = 168)	15.5 [0.2, 76.2] (n = 173)	0.2 [-6.2, 2.1] (n = 167)	2.3 [0.1, 36.9] (n = 166)	0.4 [-0.9, 28.7] (n = 166)	0.5 [-0.9, 15.2] (n = 173)	22.1 [-0.9, 84.5] (n = 171)	18.6 [1.5, 116.0] (n = 175)
	Week 53	15.2 [-0.2, 76.1] (n = 138)	31.6 [0.7, 75.7] (n = 105)	0.0 [-0.9, 7.1] (n = 139)	7.3 [1.1, 45.3] (n = 105)	0.6 [-0.3, 6.9] (n = 138)	0.6 [-0.8, 10.6] (n = 105)	15.2 [-0.8, 76.5] (n = 139)	40.8 [2.5, 108.2] (n = 105)
Infants (1-5 years)	Baseline	31.7 [0.0, 72.0] (n = 43)	27.5 [0.3, 76.2] (n = 41)	0.1 [-6.2, 1.1] (n = 40)	2.7 [0.1, 36.9] (n = 36)	0.4 [-0.8, 28.7] (n = 42)	0.4 [-0.9, 15.2] (n = 40)	32.9 [0.4, 72.3] (n = 43)	28.1 [2.5, 116.0] (n = 41)
	Week 53	18.2 [0.0, 76.1] (n = 33)	43.3 [3.4, 75.7] (n = 21)	0.2 [-0.5, 7.1] (n = 33)	6.7 [1.2, 39.4] (n = 21)	0.7 [-0.3, 6.9] (n = 33)	0.5 [-0.1, 4.6] (n = 21)	19.0 [-0.2, 76.1] (n = 33)	51.1 [11.1, 108.2] (n = 21)
Children (6-11 years)	Baseline	21.8 [0.1, 74.0] (n = 68)	11.2 [0.6, 64.5] (n = 66)	0.3 [-0.7, 2.1] (n = 69)	2.5 [0.8, 26.9] (n = 67)	0.4 [-0.9, 11.2] (n = 66)	0.4 [-0.3, 10.6] (n = 67)	22.4 [0.0, 74.5] (n = 69)	15.6 [1.7, 69.4] (n = 68)
	Week 53	18.8 [-0.2, 65.5] (n = 54)	35.8 [1.1, 69.9] (n = 42)	0.0 [-0.9, 1.4] (n = 54)	7.0 [1.2, 45.3] (n = 42)	0.5 [-0.2, 3.0] (n = 54)	0.6 [-0.8, 10.6] (n = 42)	19.5 [-0.8, 67.5] (n = 54)	44.3 [2.7, 93.7] (n = 42)
Adolescents (12-17 years)	Baseline	13.6 [0.6, 83.2] (n = 57)	13.6 [0.2, 69.3] (n = 66)	0.2 [-0.9, 0.7] (n = 58)	2.0 [1.0, 29.4] (n = 63)	0.5 [-0.5, 6.6] (n = 58)	0.7 [-0.4, 8.5] (n = 66)	13.6 [-0.9, 84.5] (n = 59)	17.5 [1.5, 82.9] (n = 66)
	Week 53	10.4 [0.1, 71.9] (n = 51)	26.3 [0.7, 69.8] (n = 42)	0.0 [-0.5, 2.8] (n = 52)	7.9 [1.1, 31.3] (n = 42)	0.6 [-0.2, 5.8] (n = 51)	1.1 [-0.3, 9.4] (n = 42)	10.2 [0.5, 76.5] (n = 52)	35.0 [2.5, 98.7] (n = 42)

Unit: % (B/T) bound over total radioactivity, Median [Min., Max.]

As for the influence of antibody formation on efficacy, correlation coefficients (Spearman correlation coefficients) between HbA1c at Week 52 and antibody titer at Week 53 in the IDeg group were 0.021 (IDeg-specific antibodies), 0.020 (IAsp-specific antibodies), and -0.040 (antibodies cross-reacting with human insulin). Correlation coefficients between insulin dose at Week 52 and antibody titer at Week 53 were 0.074 (IDeg-specific antibodies), 0.004 (IAsp-specific antibodies), and -0.095 (antibodies cross-reacting with human insulin). All correlation coefficients were low, and there was no clear correlation between insulin antibody titer and HbA1c or insulin dose at the end of treatment.

With respect to the relationship between antibody formation and safety, the relationship between a rise in antibody titer and the occurrence of immunogenicity-related adverse events, injection site reaction-related adverse events, or hypoglycaemia was investigated. A rise in antibody titer was defined as an increase in the level of antibodies cross-reacting with human insulin of ≥10% B/T (absolute) or an increase in the level of insulin-specific antibodies of ≥5% B/T at the end of trial (1 week after the end of trial drug administration). In Trial 3561, the proportions of subjects with a rise in antibody titer were 16.7% (29 of 174 subjects) in the IDeg group and 43.4% (76 of 175 subjects) in the IDet group for antibodies cross-reacting with human insulin; and 1.1% (2 of 174 subjects) in the IDeg group and 37.1% (65 of 175 subjects) in the IDet group for insulin-specific antibodies. In subjects with a rise in the titer of cross-reacting insulin antibodies in the IDeg group, the

incidence rates of immunogenicity-related adverse events, injection site reaction-related adverse events, and confirmed hypoglycaemia were 25, 16, and 6866 events, respectively, per 100 patient-years; no clear differences were observed compared with the results in all subjects in the IDeg group (21.7, 17.3, and 5771 events, respectively, per 100 patient-years). The number of subjects with a rise in specific antibodies in the IDeg group was small; no immunogenicity-related adverse events or injection site reaction-related adverse events occurred in these subjects. In subjects with a rise in insulin-specific antibodies in the IDeg group, the incidence rate of confirmed hypoglycaemia was 3967 episodes per 100 patient-years, which did not exceed the incidence rate in all subjects in the IDeg group (5771 episodes per 100 patient-years).

As shown above, the immunogenic response to treatment with IDeg is low and therefore there is no influence of antibody formation on the efficacy or safety of IDeg.

PMDA's view:
The clinical trial showed no trend towards a marked rise in antibody titer following treatment with IDeg, with no clear relationship between the level of antibody formation and efficacy or safety. However, as only limited data are available on antibody formation following long-term treatment with IDeg in Japan, it is necessary to continue to collect information on antibody formation in pediatric patients as in adults via post-marketing surveillance.

2.(iii).B.(3).7) Cardiovascular risk

The applicant's explanation:
In Trial 3561, there were no clinically relevant changes in lipid parameters or blood pressure in the IDeg group. The mean change in SD score for body weight[31] from baseline to Week 52 of treatment (LOCF) was 0.11 in the IDeg group and -0.06 in the IDet group, showing an increase in weight SD score in the IDeg group and a decrease in the IDet group. The change in weight SD score was similar (increases of 0.10-0.12) across all age groups treated with IDeg throughout the 52-week treatment period. In the IDet group, the weight SD score decreased in infants (1-5 years) and remained unchanged in children and adolescents. The results in the IDet group were consistent with the results from the previous clinical trials that have shown that IDet causes no weight gain or less weight gain compared with other basal insulin products.[32]

Periodic safety update reports[33] (PSURs) have investigated the occurrence of cardiovascular events in adults and children; there has so far been no trend towards a clearly higher cardiovascular risk associated with IDeg compared with other insulin products, but post-marketing information will also be collected.

PMDA's view:

[31] Body weight standardized by age and sex. A child with a weight equal to the mean value for its age and sex has an SD score of 0, while a child with a weight 2 SDs above the mean value for its age and sex has an SD score of +2.

[32] Thalange N, et al. *Diabet Med*. 2013; 30: 216-25, Thalange N, et al. *Pediatric Diabetes*. 2011; 12: 632-41, Robertson KJ, et al. *Diabet Med*. 2007; 24: 27-34, Peterson G. *Diabetes Metab Syndr Obes*. 2009; 2: 31-6, Zachariah S, et al. *Diabetes Care*. 2011; 34(7): 1487-91, Yale JF. *Diabetol Metab Syndr*. 2013; 5: 56.

[33] Data cut-off date of September 30, 2014

The following applicant's explanation is largely acceptable: No relevant changes in vital signs or lipid parameters were observed although there was a trend towards a slight increase in body weight with IDeg compared with IDet; there has so far been no trend towards a clearly high cardiovascular risk associated with IDeg. Close attention should be paid to the upcoming results of clinical studies, post-marketing surveillance etc.

2.(iii).B.(3).8) Neoplasms

The applicant's explanation:

Non-clinical studies showed that as insulin degludec binds to IGF-1 receptors and insulin receptors with a lower affinity than human insulin, the balance between the metabolic and mitogenic effects of insulin degludec is similar to that of human insulin.[34] In Trial 3561, neoplasm-related events[35] were reported by 1 subject in the IDet group (warts/skin papilloma), which were mild in severity and their causal relationship to trial drug was denied.

Periodic safety update reports (PSURs) have investigated the occurrence of neoplasm-related events in adults and children. The frequency of malignant neoplasms presented in the PSURs was similar to the epidemiological data. Thus, there has so far been no safety concern about neoplasms, but post-marketing information will also be collected.

PMDA considers that there is no particular problem with the applicant's explanation (there has so far been no safety concern about neoplasms associated with IDeg, but post-marketing information will also be collected.).

Based on the above, PMDA considers that the safety of IDeg is acceptable, on condition that appropriate cautions are provided.

2.(iii).B.(4) Dosage and administration

2.(iii).B.(4).1) The method of expressing doses for pediatric population

The applicant's explanation on the appropriateness of doses expressed in units per kg of body weight for pediatric population:

The recommended doses for adult patients are expressed in "units" in the dosage and administration section of the package insert. On the other hand, body weight varies considerably from patient to patient in pediatric population. The range of body weights of patients with type 1 diabetes mellitus who participated in Trial 3561 (1 to <18 years) was wide (Min.-Max., 10.8-102.2 kg; mean, 37.9 kg; median, 34.8 kg). In pediatric population, doses expressed in "units" will result in a wide range of insulin doses. "Units" therefore cannot be used as a dosage guide for pediatric population. In the Guideline for Diabetes in Childhood and Adolescence[36] released by the International Society for Pediatric and Adolescent Diabetes (ISPAD guideline) and the training

[34] Initial application summaries for Tresiba FlexTouch and Tresiba Penfill (approved for marketing as of September 28, 2012)

[35] Preferred terms in the system organ class "neoplasms benign, malignant and unspecified (incl cysts and polyps)" and SMQ "neoplasms"

[36] Global IDF/ISPAD guideline for Diabetes in Childhood and Adolescence. 2011; 63, ISPAD Clinical Practice Consensus Guidelines. 2014; Chapter 9; 126

guidebook for diabetologists published by the Japan Diabetes Society[37] (the Japanese guideline), the recommended insulin doses for children are expressed in units per kg of body weight.

Based on the above, while the recommended doses for adult patients are expressed in "units," the doses for pediatric population should be expressed in "units/kg."

2.(iii).B.(4).2) Dose of IDeg in patients transferring from other insulin treatments

The applicant's explanation:

In Trial 3561, patients who had been receiving insulin treatment (any regimen) were enrolled and transferred from the pre-trial basal insulin to IDeg or IDet at randomization, to achieve a basal:bolus ratio of between 50:50 and 30:70. Most of the subjects were transferred from the pre-trial basal insulin to IDeg or IDet on a unit-to-unit basis. There were no specific dose reduction recommendations. The difference between the mean daily basal insulin dose between screening and baseline was 0.03 U/kg in the IDeg group and 0.02 U/kg in the IDet group; the mean daily dose thus remained fairly constant.

In the IDeg group, insulin doses at Week 1 ranged from 0.02 to 1.04 U/kg (mean, 0.37 U/kg; median, 0.35 U/kg). In most subjects in the IDeg group (88% in the entire trial population, 87% in the Japanese subgroup), insulin doses at Week 1 ranged between 0.1 and 0.6 U/kg. For patients transferring from other insulin medicinal products, the recommended doses of IDeg were thus determined to be 0.1 to 0.6 U/kg. In most subjects in each age group (91% of infants in the entire trial population, 100% of infants in the Japanese subgroup; 90% of children in the entire trial population, 90% of children in the Japanese subgroup; 83% of adolescents in the entire trial population, 83% of adolescents in the Japanese subgroup), insulin doses also ranged between 0.1 and 0.6 U/kg.

Pre-breakfast SMBG values and basal insulin doses during the early phase of treatment are shown in Table 19. With respect to the glycemic control status, pre-breakfast SMBG decreased from baseline to Week 2 and then increased slightly in the IDeg group. The basal insulin dose in the IDeg group decreased slightly with a decrease in mean pre-breakfast SMBG value during the early phase of treatment. As for safety, the incidence rates of severe hypoglycaemia, confirmed hypoglycaemia, and nocturnal confirmed hypoglycaemia tended to be higher in the IDeg group than in the IDet group during the first 4 weeks of treatment (Figure 6). The trend of occurrence of hypoglycaemia by age group was also largely similar to that in the overall population (Table 15, Table 16).

[37] Japan Diabetes Society. Training guidebook for diabetologists 6th edition. Diagnosis and Treatment Inc. Tokyo. 2014; 348

Table 19. Pre-breakfast SMBG values and basal insulin doses during the early phase of treatment
(Trial 3561; pre-breakfast SMBG, FAS; basal insulin dose, Safety Analysis Set)

	Pre-breakfast SMBG (mg/dL)		Basal insulin dose (U/kg)	
	IDeg (n = 174)	IDet (n = 176)	IDeg (n = 174)	IDet (n = 175)
Baseline	169.6 ± 64.8 (n = 173)	162.6 ± 60.1 (n = 176)	—	—
Week 1	150.1 ± 57.1 (n = 171)	171.1 ± 67.6 (n = 172)	0.37 ± 0.17 (n = 173)	0.40 ± 0.20 (n = 174)
Week 2	137.0 ± 52.9 (n = 174)	172.5 ± 58.5 (n = 173)	0.36 ± 0.16 (n = 173)	0.42 ± 0.20 (n = 172)
Week 4	145.9 ± 50.1 (n = 172)	164.7 ± 56.5 (n = 171)	0.35 ± 0.15 (n = 172)	0.44 ± 0.21 (n = 171)

Mean ± SD; —, Not applicable

PMDA asked the applicant to explain the influence of differences in the pre-trial insulin regimen on the efficacy and safety of IDeg and the need for a precautionary statement regarding dosage adjustment at transfer from another insulin product.

The applicant's response:

Tables 20 and 21 show pre-breakfast SMBG values and the occurrence of hypoglycaemia during the early phase of treatment (the first 4 weeks of treatment) in subjects previously treated with a basal-bolus insulin regimen or other insulin regimens. In subjects previously treated with a basal-bolus insulin regimen, pre-breakfast SMBG generally decreased from baseline in the IDeg group, but remained unchanged or increased slightly from baseline in the IDet group. Accordingly, the incidence rates of confirmed hypoglycaemia, nocturnal confirmed hypoglycaemia, and severe hypoglycaemia were higher in the IDeg group than in the IDet group. Severe nocturnal hypoglycaemic episode was difficult to analyze due to very few occurrences. In subjects previously treated with other insulin regimens (i.e., not with a basal-bolus regimen), between-treatment comparison was difficult because of the small number of subjects (5 in the IDeg group, 10 in the IDet group), but no severe hypoglycaemia was reported during the early phase of treatment.

Table 20. Pre-breakfast SMBG values during the early phase of treatment by pre-trial insulin regimen
(Trial 3561 [52 weeks of treatment], FAS)

	Basal-Bolus		Others	
	IDeg (n = 169)	IDet (n = 166)	IDeg (n = 5)	IDet (n = 10)
Baseline	171.4 ± 64.3 (n = 168)	160.8 ± 59.7 (n = 166)	109.4 ± 56.2 (n = 5)	191.8 ± 62.9 (n = 10)
Week 1	151.8 ± 56.9 (n = 166)	171.5 ± 68.6 (n = 162)	94.2 ± 36.2 (n = 5)	165.4 ± 50.3 (n = 10)
Week 4	147.2 ± 49.9 (n = 167)	163.9 ± 54.8 (n = 162)	101.9 ± 36.5 (n = 5)	180.5 ± 84.3 (n = 9)

Mean ± SD

Table 21. Hypoglycaemia occurring during the early phase of treatment by pre-trial insulin regimen (Trial 3561 [52 weeks of treatment], Safety Analysis Set)

		Basal-Bolus		Others	
		IDeg (n = 169)	IDet (n = 165)	IDeg (n = 5)	IDet (n = 10)
Confirmed hypoglycaemia	Entire period	166 (98.2)	159 (96.4)	5 (100.0)	9 (90.0)
		8897 [5686.2]	7687 [5444.4]	420 [8419.6]	280 [4505.3]
	Week 1	95 (56.2)	86 (52.1)	4 (80.0)	5 (50.0)
		221 [6823.4]	204 [6451.2]	16 [16697.1]	9 [4696.1]
	Week 2	97 (57.4)	78 (47.3)	3 (60.0)	4 (40.0)
		267 [8243.6]	198 [6294.1]	7 [7305.0]	5 [2608.9]
	Week 4	99 (58.6)	77 (47.5)	4 (80.0)	2 (20.0)
		234 [7237.0]	184 [5926.5]	7 [7305.0]	3 [1635.4]
Nocturnal confirmed hypoglycaemia	Entire period	129 (76.3)	118 (71.5)	4 (80.0)	7 (70.0)
		899 [574.6]	1042 [738.0]	74 [1483.5]	78 [1255.0]
	Week 1	20 (11.8)	14 (8.5)	1 (20.0)	3 (30.0)
		31 [957.1]	18 [569.2]	2 [2087.1]	4 [2087.1]
	Week 2	19 (11.2)	19 (11.5)	1 (20.0)	0 (0.0)
		24 [741.0]	26 [826.5]	1 [1043.6]	0 [0.0]
	Week 4	32 (18.9)	20 (12.3)	3 (60.0)	1 (10.0)
		42 [1298.9]	25 [805.2]	4 [4174.3]	1 [545.1]
Severe hypoglycaemia	Entire period	31 (18.3)	23 (13.9)	0 (0.0)	1 (10.0)
		82 [52.4]	47 [33.3]	0 [0.0]	1 [16.1]
	Week 1	6 (3.6)	1 (0.6)	0 (0.0)	0 (0.0)
		11 [339.6]	1 [31.6]	0 [0.0]	0 [0.0]
	Week 2	3 (1.8)	1 (0.6)	0 (0.0)	0 (0.0)
		4 [123.5]	1 [31.8]	0 [0.0]	0 [0.0]
	Week 4	3 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
		3 [92.8]	0 [0.0]	0 [0.0]	0 [0.0]

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

Pre-breakfast SMBG values and the occurrence of hypoglycaemia during the early phase of treatment (the first 4 weeks of treatment) by basal insulin type used pre-trial are shown in Table 22 and Table 23, respectively. In subjects previously treated with IGlar, pre-breakfast SMBG decreased from baseline in the IDeg group, but tended to increase from baseline in the IDet group. The incidence rates of confirmed hypoglycaemia and severe hypoglycaemia were higher in the IDeg group than in the IDet group. The incidence rate of nocturnal confirmed hypoglycaemia was similar in both treatment groups. In subjects previously treated with IDet, pre-breakfast SMBG decreased from baseline in the IDeg group, but remained unchanged from baseline in the IDet group. The incidence rates of confirmed hypoglycaemia, nocturnal confirmed hypoglycaemia, and severe hypoglycaemia were higher in the IDeg group than in the IDet group. In subjects previously treated with NPH, analysis of hypoglycaemia had a limitation due to the small number of subjects (13 in the IDeg group, 9 in the IDet group), but no apparent differences between the treatment groups were observed for confirmed hypoglycaemia. Nocturnal confirmed hypoglycaemic episodes was difficult to assess due to very few occurrences. No severe hypoglycaemia was reported. Severe nocturnal hypoglycaemia was difficult to analyze because of the very small number of episodes across all pre-trial basal insulin types.

Table 22. Pre-breakfast SMBG values during the early phase of treatment by pre-trial basal insulin type
(Trial 3561 [52 weeks of treatment], FAS)

	IGlar used pre-trial		IDet used pre-trial		NPH used pre-trial	
	IDeg (n = 71)	IDet (n = 76)	IDeg (n = 85)	IDet (n = 83)	IDeg (n = 13)	IDet (n = 9)
Baseline	163.4 ± 60.6 (n = 70)	160.9 ± 63.2 (n = 76)	174.7 ± 67.0 (n = 85)	164.6 ± 57.6 (n = 83)	192.9 ± 63.4 (n = 13)	137.1 ± 56.0 (n = 9)
Week 1	153.4 ± 54.9 (n = 70)	181.4 ± 71.9 (n = 73)	147.9 ± 60.1 (n = 84)	168.4 ± 66.2 (n = 83)	169.7 ± 43.2 (n = 12)	120.0 ± 34.1 (n = 8)
Week 4	145.1 ± 46.2 (n = 70)	162.5 ± 60.0 (n = 73)	149.9 ± 52.4 (n = 84)	166.6 ± 51.2 (n = 82)	141.4 ± 55.4 (n = 13)	136.7 ± 39.5 (n = 9)

Mean ± SD

Table 23. Hypoglycaemia occurring during the early phase of treatment by pre-trial basal insulin type
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

		IGlar used pre-trial		IDet used pre-trial		NPH used pre-trial	
		IDeg (n = 71)	IDet (n = 75)	IDeg (n = 85)	IDet (n = 83)	IDeg (n = 13)	IDet (n = 9)
Confirmed hypoglycaemia	Entire period	69 (97.2)	71 (94.7)	84 (98.8)	82 (98.8)	13 (100)	8 (88.9)
		3522 [5310.3]	3288 [5032.7]	4593 [5892.1]	4202 [6143.5]	782 [6415.7]	201 [2331.4]
	Week 1	34 (47.9)	30 (40.0)	54 (63.5)	51 (61.4)	7 (53.8)	6 (66.7)
		71 [5217.9]	64 [4452.6]	137 [8410.0]	133 [8361.1]	13 [5217.9]	9 [5217.9]
	Week 2	35 (49.3)	26 (34.7)	55 (64.7)	48 (57.8)	7 (53.8)	4 (44.4)
		88 [6467.2]	65 [4522.1]	163 [10006.0]	125 [7940.2]	16 [6422.0]	8 [4638.1]
	Week 4	35 (49.3)	27 (37.0)	55 (64.7)	44 (53.7)	9 (69.2)	6 (66.7)
		71 [5217.9]	67 [4789.0]	147 [9054.3]	108 [6872.3]	16 [6422.0]	9 [5217.9]
Nocturnal confirmed hypoglycaemia	Entire period	55 (77.5)	52 (69.3)	67 (78.8)	63 (75.9)	7 (53.8)	4 (44.4)
		453 [683.0]	543 [831.1]	369 [473.4]	482 [704.7]	77 [631.7]	19 [220.4]
	Week 1	7 (9.9)	8 (10.7)	12 (14.1)	7 (8.4)	1 (7.7)	0 (0.0)
		10 [734.9]	9 [626.1]	20 [1227.7]	10 [628.7]	1 [401.4]	0 [0.0]
	Week 2	8 (11.3)	7 (9.3)	10 (11.8)	12 (14.5)	1 (7.7)	0 (0.0)
		9 [661.4]	11 [765.3]	14 [859.4]	15 [952.8]	1 [401.4]	0 [0.0]
	Week 4	9 (12.7)	8 (11.0)	22 (25.9)	10 (12.2)	1 (7.7)	2 (22.2)
		11 [808.4]	11 [786.3]	30 [1847.8]	12 [763.6]	1 [401.4]	2 [1159.5]
Severe hypoglycaemia	Entire period	18 (25.4)	8 (10.7)	13 (15.3)	15 (18.1)	0 (0.0)	0 (0.0)
		43 [64.8]	24 [36.7]	39 [50.0]	23 [33.6]	0 [0.0]	0 [0.0]
	Week 1	3 (4.2)	0 (0.0)	3 (3.5)	1 (1.2)	0 (0.0)	0 (0.0)
		6 [440.9]	0 [0.0]	5 [306.9]	1 [62.9]	0 [0.0]	0 [0.0]
	Week 2	2 (2.8)	0 (0.0)	1 (1.2)	1 (1.2)	0 (0.0)	0 (0.0)
		2 [147.0]	0 [0.0]	2 [122.8]	1 [63.5]	0 [0.0]	0 [0.0]
	Week 4	1 (1.4)	0 (0.0)	2 (2.4)	0 (0.0)	0 (0.0)	0 (0.0)
		1 [73.5]	0 [0.0]	2 [123.2]	0 [0.0]	0 [0.0]	0 [0.0]

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

Pre-breakfast SMBG values and the occurrence of hypoglycaemia during the early phase of treatment (the first 4 weeks of treatment) by basal insulin dose (0.1-0.6 U/kg or others [<0.1 U/kg and >0.6 U/kg]) at Week 1 (the first time point recorded post-baseline) are shown in Table 24 and Table 25, respectively.

In subjects with a basal insulin dose of 0.1 to 0.6 U/kg, pre-breakfast SMBG decreased from baseline in the IDeg group, but remained unchanged or slightly increased from baseline in the IDet group. Pre-breakfast SMBG was lower in the IDeg group compared with the IDet group. The incidence rates of confirmed hypoglycaemia, nocturnal confirmed hypoglycaemia, and severe hypoglycaemia were higher in the IDeg group than in the IDet group. In subjects with a basal insulin dose of >0.6 U/kg, baseline pre-breakfast SMBG was slightly higher in the IDeg group than in the IDet group. Subsequently in these subjects, pre-breakfast SMBG decreased from baseline in the IDeg group, but remained unchanged or slightly increased from baseline in the IDet group. The incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were higher during the first 4 weeks of treatment compared with the entire period in both treatment groups; this was particularly notable in the IDeg group. Except for Week 1, the incidence rates of confirmed hypoglycaemia and nocturnal confirmed hypoglycaemia were higher in the IDeg group than in the IDet group. Severe

hypoglycaemia was difficult to analyze because of the very few episodes. The number of subjects with a basal insulin dose of <0.1 U/kg was very small (5 subjects in the IDeg group, 3 subjects in the IDet group), which made it difficult to analyze pre-breakfast SMBG and hypoglycaemia in this population; analysis of severe nocturnal hypoglycaemic episodes was difficult due to very few occurrences.

Table 24. Pre-breakfast SMBG values during the early phase of treatment by basal insulin dose
(Trial 3561 [52 weeks of treatment], FAS)

	Basal insulin dose at the first time point recorded post-baseline			
	0.1-0.6 U/kg		>0.6 U/kg	
	IDeg (n = 153)	IDet (n = 146)	IDeg (n = 15)	IDet (n = 25)
Baseline	165.9 ± 64.1 (n = 152)	162.1 ± 59.1 (n = 146)	208.1 ± 61.7 (n = 15)	169.2 ± 68.0 (n = 25)
Week 1	153.0 ± 58.7 (n = 150)	170.2 ± 67.3 (n = 144)	124.9 ± 37.5 (n = 15)	182.1 ± 67.4 (n = 24)
Week 4	147.3 ± 51.7 (n = 151)	166.5 ± 58.8 (n = 143)	131.3 ± 23.0 (n = 15)	161.2 ± 39.7 (n = 25)

Mean ± SD

Table 25. Hypoglycaemia occurring during the early phase of treatment by basal insulin dose
(Trial 3561 [52 weeks of treatment], Safety Analysis Set)

		Basal insulin dose at the first time point recorded post-baseline			
		0.1-0.6 U/kg		>0.6 U/kg	
		IDeg (n = 153)	IDet (n = 146)	IDeg (n = 15)	IDet (n = 25)
Confirmed hypoglycaemia	Entire period	150 (98.0)	140 (95.9)	15 (100.0)	25 (100.0)
		8400 [5977.6]	6703 [5384.1]	751 [5026.6]	1191 [5986.1]
	Week 1	88 (57.5)	72 (49.3)	8 (53.3)	18 (72.0)
		214 [7298.2]	163 [5825.4]	16 [5565.7]	44 [9183.4]
	Week 2	86 (56.2)	68 (46.6)	12 (80.0)	14 (56.0)
		228 [7775.6]	156 [5575.2]	41 [14262.1]	47 [9809.6]
	Week 4	91 (59.5)	65 (45.1)	9 (60.0)	13 (52.0)
		206 [7038.5]	155 [5633.2]	31 [10783.6]	30 [6261.4]
Nocturnal confirmed hypoglycaemia	Entire period	117 (76.5)	104 (71.2)	14 (93.3)	19 (76.0)
		863 [614.1]	906 [727.7]	107 [716.2]	212 [1065.5]
	Week 1	16 (10.5)	13 (8.9)	4 (26.7)	4 (16.0)
		28 [954.9]	18 [643.3]	4 [1391.4]	4 [834.9]
	Week 2	17 (11.1)	13 (8.9)	3 (20.0)	6 (24.0)
		19 [648.0]	17 [607.6]	6 [2087.1]	9 [1878.4]
	Week 4	28 (18.3)	16 (11.1)	6 (40.0)	5 (20.0)
		37 [1264.2]	19 [690.5]	8 [2782.9]	7 [1461.0]
Severe hypoglycaemia	Entire period	27 (17.6)	18 (12.3)	3 (20.0)	6 (24.0)
		66 [47.0]	39 [31.3]	12 [80.3]	9 [45.2]
	Week 1	6 (3.9)	1 (0.7)	0 (0.0)	0 (0.0)
		11 [375.1]	1 [35.7]	0 [0.0]	0 [0.0]
	Week 2	3 (2.0)	1 (0.7)	0 (0.0)	0 (0.0)
		4 [136.4]	1 [35.7]	0 [0.0]	0 [0.0]
	Week 4	2 (1.3)	0 (0.0)	1 (6.7)	0 (0.0)
		2 [68.3]	0 [0.0]	1 [347.9]	0 [0.0]

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

The trend of occurrence of hypoglycaemia was analyzed by classifying subjects according to “pre-trial insulin treatment” and “basal insulin dose at the first time point recorded post-baseline.” The trend in each age group was generally similar to that in the overall population. During the first 4 weeks of treatment, pre-breakfast blood glucose (self-measured blood glucose) tended to be lower in the IDeg group than in the IDet group, and the incidence rate of hypoglycaemia tended to be higher in the IDeg group than in the IDet group.

The ISPAD guideline does not mention the insulin dose at transfer from one insulin product to another. However, since the doses at transfer were 0.1 to 0.6 U/kg in many subjects in Trial 3561, doses at transfer should be 0.1 to 0.6 U/kg (this information should be provided in the dosage and administration section of the package insert). When transferring a pediatric patient to IDeg, dose reduction should be considered on an individual basis in order to minimize the risk of hypoglycaemia. The precautions for dosage and administration

section of the package insert will thus include the following statements: “For pediatric patients transferring from basal insulin therapy, basal-bolus insulin therapy, continuous subcutaneous insulin infusion (CSII), or premix insulin therapy to IDeg, dose reduction should be considered. Thereafter, dosage in individual patients should be adjusted based on their glycemic response.”

2.(iii).B.(4).3) Maintenance dose

PMDA asked the applicant to explain the rationale for the recommended maintenance dose of 0.5 to 1.6 U/kg.

The applicant’s response:

Insulin resistance increases rapidly from the onset of puberty, but returns to near prepubertal levels by the end of puberty.[38] According to the ISPAD guideline,[39] the recommended total daily insulin dose is <0.5 U/kg during the partial remission phase, 0.7 to 1.0 U/kg for prepubertal children, and 1.0 to 2.0 U/kg during puberty. The 2014 ISPAD guideline recommends 1.2 to 2.0 U/kg during puberty. Higher doses are recommended during puberty compared with the doses in prepubertal children. The Japanese guideline[37] states that “the usual daily insulin dose is 0.7 to 1.0 U/kg/day, which may be increased to 1.2 to 1.5 U/kg/day during puberty,” thus recommending higher doses for patients in puberty than for prepubertal children.

In Trial 3561, the mean total daily insulin dose [5th percentile, 95th percentile] at the end of treatment in the IDeg group was 0.93 [0.55, 1.53] U/kg (median [Min.-Max.], 0.88 [0.24-2.06] U/kg) in the entire trial population and 1.19 [0.87, 1.86] U/kg (median [Min.-Max.], 1.09 [0.86-1.96] U/kg) in the Japanese subgroup. The insulin dose used at the end of the trial was 0.5 to 1.6 U/kg in most subjects (approximately 93% of the entire trial population, 87% of the Japanese subgroup). Six subjects (3%) used insulin >1.6 U/kg (1.61-2.06 U/kg); 5 of the 6 subjects used <2.0 U/kg of insulin. Six subjects (3%) used insulin <0.5 U/kg (0.24-0.49 U/kg); 5 of the 6 subjects used >0.4 U/kg of insulin. At the end of the trial, none of the Japanese subjects were using <0.5 U/kg insulin (total daily dose), and 3 Japanese subjects were using >1.6 U/kg insulin (total daily dose); the maintenance dose in the 3 Japanese subjects ranged from 1.61 to 1.96 U/kg. In most subjects in each age group (91% of infants in the entire trial population, 100% of infants in the Japanese subgroup; 96% of children in the entire trial population, 90% of children in the Japanese subgroup; 92% of adolescents in the entire trial population, 83% of adolescents in the Japanese subgroup), insulin doses also ranged between 0.5 and 1.6 U/kg.

The ISPAD guideline provides information on all available basal insulin products and recommends <0.5 U/kg/day during the partial remission phase, 0.7 to 1.0 U/kg/day for prepubertal children, and 1.2 to 2.0 U/kg/day during puberty. For the Japanese population, however, the recommended maintenance dose of IDeg should be 0.5 to 1.6 U/kg/day, based on the results of Trial 3561 etc. In Trial 3561, a small number of subjects were using insulin doses (total daily dose) outside the recommended range at the end of the trial. In clinical practice, insulin dose is determined based on the individual requirements, taking account of the balance between glycemic control and the risk of hypoglycaemia. Therefore, the following statements have been

38 Moran A, et al. *Diabetes*. 1999; 48(10): 2039-44.

39 Global IDF/ISPAD guideline for Diabetes in Childhood and Adolescence. 2011

included in the dosage and administration section: “The dose should be adjusted according to the patient’s symptoms and test results.” and “However, a higher dose than stated above may be used as needed.”

2.(iii).B.(4).4) Starting dose in insulin-naïve patients

The applicant’s explanation:

The ISPAD guideline states that the total insulin dose including basal and bolus doses at diabetes mellitus onset should be 0.5 to 0.75 U/kg/day, and a separate guideline is available for patients with diabetic ketoacidosis. These guidelines are so detailed that they should not be included in the dosage and administration section. Since insulin treatment is initiated in pediatric patients with various conditions (e.g. patients with diabetic ketoacidosis [acute phase of diabetes mellitus], patients with diabetes mellitus detected during a health examination at school), the dose is determined on an individual basis in clinical practice. There are no clinical trial results involving insulin-naïve pediatric patients, with no data available for the starting dose of insulin. Therefore, the dosage and administration section should not specify the recommended starting dose or dose range, but instead should state that the dose should be determined on an individual basis.

PMDA’s view on 1) to 4):

Method of expressing doses in the dosage and administration section

Expressing doses in units per kg of body weight (units/kg) for pediatric population is acceptable, because body weight of pediatric patients varies considerably, taking account of the statements in the ISPAD guideline, the Japanese guideline, etc.

Dose of IDeg in patients transferring from other insulin treatments

The dose of IDeg in patients transferring from other insulin treatments differs considerably, depending on the previous treatment and the individual patient’s condition, and therefore should be adjusted based on the previous insulin dose. Neither the ISPAD guideline nor the Japanese guideline specifies the dose of IDeg in patients transferring from other insulin treatments. Therefore the dosage and administration section should not indicate the doses of IDeg at transfer from another insulin product in patients enrolled in the clinical trial. The analysis of the occurrence of hypoglycaemia by pre-trial insulin treatment and by basal insulin dose showed that the incidence rate of hypoglycaemia tended to be higher in the IDeg group than in the IDet group during the early phase of treatment across all age groups. There is thus no particular problem with the applicant’s plan to advise healthcare professionals to consider dose reduction when transferring a patient to IDeg, on an individual basis, in order to minimize the risk of hypoglycaemia.

Maintenance dose

In the ISPAD guideline, the recommended total daily insulin dose is <0.5 U/kg during the partial remission phase, 0.7 to 2.0 U/kg in prepubertal children and patients in puberty. In the Japanese guideline, the recommended total daily insulin dose is 0.7 to 1.0 U/kg for general population, or 1.2 to 1.5 U/kg during puberty. The applicant recommends 0.5 to 1.6 U/kg based on the doses used in the majority of subjects in the clinical trial. In the Japanese subgroup of the trial, however, the proportion of subjects treated with IDeg in

this recommended dose range was lower in adolescents than in infants or children. Based on the above, the recommended maintenance dose should be determined, taking also account of the guidelines etc.

Starting dose in insulin-naïve patients

The applicant explained that the dosage and administration section will state that the starting dose in insulin-naïve patients should be determined on an individual basis, because (i) the applicant has not evaluated the starting dose in insulin-naïve patients in any clinical trial, and because (ii) in current clinical practice, the starting dose in an insulin-naïve patient is determined on an individual basis according to the patient's condition. However, while the starting dose is not specified in the Japanese guideline, the ISPAD guideline states that the total daily insulin dose at diabetes mellitus onset should be 0.5 to 0.75 U/kg. Given that the starting dose in insulin-naïve patients has not been evaluated in any clinical trial, PMDA understands that it is difficult to indicate the recommended starting dose. Meanwhile, there is room for discussing whether a starting dose can be recommended, taking account of the guidelines etc.

Based on the above, the dosage and administration statement, including the appropriateness of the precautionary statement, will be determined, taking account of the comments from the Expert Discussion.

2.(iii).B.(5) Post-marketing investigations

The applicant's explanation:

A specified drug use-results survey on long-term use (a total planned sample size of 6000: a 3-year observation period [4000 patients] and a 6-month observation period [2000 patients]) is ongoing to collect information on the safety and efficacy of IDeg in routine clinical settings. Since pediatric patients are included in this survey, the applicants has no plan to conduct additional specified drug use-results survey to evaluate pediatric patients alone. The final enrollment in the survey is expected to be approximately [redacted] pediatric patients for a 6-month observation period (1-5 years, [redacted] patients; 6-11 years, [redacted] patients; 12-17 years, [redacted] patients; 18-19 years, [redacted] patients) and approximately [redacted] pediatric patients for a 3-year observation period (1-5 years, [redacted] patients; 6-11 years, [redacted] patients; 12-17 years, [redacted] patients; 18-19 years, [redacted] patients).

Although PMDA considers that there is no particular problem with the applicant's view (information on the safety and efficacy of IDeg in pediatric patients will be collected via the current post-marketing surveillance study), a final conclusion will be made, taking account of the comments from the Expert Discussion.

III. Results of Compliance Assessment Concerning the Data Submitted in the Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

Document-based compliance inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application. The inspection and assessment revealed no particular problems. PMDA concluded that there should be no problem with conducting

a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection was conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the application (5.3.5.1-1, 5.3.5.1-2). The inspection revealed the clinical trial as a whole was performed in compliance with GCP. PMDA thus concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents. The inspection also revealed protocol deviation at some trial sites, though this issue does not affect the outcome of the overall assessment of the trial. The heads of the trial sites (medical institutions) were notified of the issue as the finding requiring improvement.

<u>Finding requiring improvement</u>

Trial sites

● Protocol deviations (non-compliance with the rules for adverse event reporting)

IV. Overall Evaluation

Based on the submitted data, the efficacy of IDeg in pediatric patients with diabetes mellitus who require insulin has been demonstrated and its safety is acceptable in view of its observed benefits. IDeg have clinical significance as a therapeutic option for pediatric patients with diabetes mellitus. PMDA considers that the dosage and administration statement needs further consideration.

This application may be approved if IDeg is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

July 9, 2015

I. Product Submitted for Registration

[Brand name]	(a) Tresiba FlexTouch, (b) Tresiba Penfill
[Non-proprietary name]	Insulin Degludec (Genetical Recombination)
[Name of applicant]	Novo Nordisk Pharma Ltd.
[Date of application]	October 31, 2014

II. Content of the Review

The comments from the Expert Discussion and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) are outlined in the following sections. The expert advisors for the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy

PMDA's conclusion:

Global clinical Trial 3561 demonstrated the non-inferiority of Tresiba FlexTouch and Tresiba Penfill (IDeg) to Insulin Detemir (Genetical Recombination) (IDet) in the primary endpoint of HbA1c change. The reduction in HbA1c tended to be smaller in adolescents in the IDeg group; a similar trend was observed also in the IDet group. Thus, the applicant's explanation (these adolescents showed a smaller reduction in HbA1c because adolescents in general have difficulty with glycemic control) is understood. Thus, the efficacy of IDeg in pediatric patients with type 1 diabetes mellitus has been demonstrated.

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

(2) Safety

PMDA's conclusion:

Based on the occurrence of adverse events and adverse drug reactions and the examination of individual events such as hypoglycaemia and injection site reactions in Trial 3561, the safety of IDeg is acceptable, on condition that appropriate cautions are provided. As the number of subjects studied was small for some of age groups, it is necessary to continue to collect safety information.

The above conclusions by PMDA were supported by the expert advisors.

(3) Dosage and administration

PMDA's conclusion:

Method of expressing doses in the dosage and administration section

Expressing doses in units per kg of body weight (units/kg) for pediatric population is acceptable, because body weight of pediatric patients varies considerably, taking account of the statements in the Guideline for Diabetes in Childhood and Adolescence released by the International Society for Pediatric and Adolescent Diabetes[36] (ISPAD guideline) and the training guidebook for diabetologists published by the Japan Diabetes Society[37] (the Japanese guideline) etc.

Dose of IDeg in patients transferring from other insulin treatments

The dose of IDeg in patients transferring from other insulin treatments differs considerably, depending on the previous treatment and the individual patient's condition, and therefore should be adjusted based on the previous insulin dose. Neither the ISPAD guideline nor the Japanese guideline specifies the dose of IDeg in patients transferring from other insulin treatments. Therefore the dosage and administration section should not indicate the doses of IDeg at transfer from another insulin product in patients enrolled in the clinical trial. The analysis of the occurrence of hypoglycaemia by pre-trial insulin treatment and by basal insulin dose showed that the incidence rate of hypoglycaemia tended to be higher in the IDeg group than in the IDet group during the early phase of treatment across all age groups. There is thus no particular problem with the applicant's plan to advise healthcare professionals to consider dose reduction when transferring a patient to IDeg, on an individual basis, in order to minimize the risk of hypoglycaemia.

Maintenance dose

In the ISPAD guideline, the recommended total daily insulin dose is <0.5 U/kg during the partial remission phase, 0.7 to 2.0 U/kg in prepubertal children and patients in puberty. In the Japanese guideline, the recommended total daily insulin dose is 0.7 to 1.0 U/kg for general population, or 1.2 to 1.5 U/kg during puberty. The applicant recommends 0.5 to 1.6 U/kg based on the doses used in the majority of subjects in the clinical trial. In the Japanese subgroup of the trial, however, the proportion of subjects treated with IDeg in this recommended dose range was lower in adolescents than in infants or children. Based on the above, the recommended maintenance dose should be determined, taking also account of the guidelines etc.

Starting dose in insulin-naïve patients

The applicant explained that the dosage and administration section will state that the starting dose in insulin-naïve patients should be determined on an individual basis, because (i) the applicant has not evaluated the starting dose in insulin-naïve patients in any clinical trial, and because (ii) in current clinical practice, the starting dose in an insulin-naïve patient is determined on an individual basis according to the patient's condition. However, while the starting dose is not specified in the Japanese guideline, the ISPAD guideline states that the total daily insulin dose at diabetes mellitus onset should be 0.5 to 0.75 U/kg. Given that the starting dose in insulin-naïve patients has not been evaluated in any clinical trial, PMDA understands that it is difficult to indicate the recommended starting dose. Meanwhile, there is room for discussing whether a starting dose can be recommended, taking account of the guidelines etc.

The above conclusions by PMDA were supported by the expert advisors. The expert advisors made the following comments.

- The insulin products currently available in Japan are categorized into either of the 2 groups: (1) Products that have never been evaluated in pediatric clinical studies; or (2) Products that were evaluated in pediatric clinical studies that did not result in the establishment dosage regimen for pediatric population. Therefore in current clinical practice, pediatric patients are treated with insulin based on individual physicians' experiences. Trial 3561 with IDeg has led to establishing its dosage regimen for pediatric population, which is of great clinical significance. Future insulin products to be developed should also be evaluated in pediatric clinical trials, to establish their dosage regimen for pediatric population.
- It is preferable to indicate specific doses expressed in units per kg of body weight for pediatric population.
- As for the maintenance dose, the total daily insulin dose is expected to be up to 1.5 U/kg in most patients as stated in the Japanese guideline. A very few children require >2.0 U/kg, but there is no problem if dosage and administration section states that a higher dose than stated above may be used as needed, as with for adult patients. Therefore, the recommended maintenance dose should be 0.5 to 1.5 U/kg based on the results from the clinical trial and the Japanese guideline.
- In Japan, it is common that slowly progressive type 1 diabetes mellitus is detected and diagnosed by testing urine at school. It is therefore difficult to recommend the starting dose specified in the ISPAD guideline, at the right timing for insulin-naïve patients. Thus, the starting dose in insulin-naïve patients should not be included in the dosage and administration section. The precautions for dosage and administration section should state that the starting dose in insulin-naïve patients should be determined on an individual basis according to the patient's condition.

Based on the above, PMDA concluded that the description under the dosage and administration section should be modified as shown below.

PMDA instructed the applicant to modify the description under the dosage and administration section, and confirmed that appropriate action was taken.

Dosage and administration (Tresiba FlexTouch)

Usually in pediatric population, Insulin Degludec is administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 0.5 to 1.5 units/kg/day. However, a higher dose than stated above may be used as needed.

Precautions for dosage and administration (for pediatric patients only)

- For pediatric patients transferring from basal insulin therapy, basal-bolus insulin therapy, continuous subcutaneous insulin infusion (CSII), or premix insulin therapy to IDeg, the dose of IDeg should be determined based on the previous basal insulin dose, and dose reduction should be considered in order to minimize the risk of hypoglycaemia. Thereafter, dosage in individual patients should be adjusted based on

their glycemic response.

- The starting dose in insulin-naïve pediatric patients should be determined on an individual basis according to the patient's condition.

(4) Draft risk management plan

Taking account of the Review Report (1) "II.2.(iii).B.(5) Post-marketing investigations" and the comments from the expert advisors at the Expert Discussion, PMDA considers that there is no particular problem with the applicant's plan to collect pediatric safety and efficacy information via the ongoing post-marketing surveillance study.

The applicant presented an outline of the draft risk management plan (Tables 26 and 27). PMDA reviewed it and concluded that there is no problem with its content.

Table 26. Safety specification and efficacy concerns of the draft risk management plan

Safety specification		
Important identified risks	Important potential risks	Important missing information
· Hypoglycaemia · Serious allergic reactions · Injection site reactions	· Medication errors (mix-ups between basal and bolus insulin products) · Effect of anti-insulin antibody formation	· Safety in patients aged ≤5 years · Safety in pregnant women or nursing mothers · Safety in patients with renal impairment · Safety in patients with hepatic impairment · Safety in elderly patients · Safety in patients with cardiovascular disease
Efficacy specification		
· Long-term efficacy		

Table 27. Summary of additional pharmacovigilance activities and risk minimization activities in the draft risk management plan

Additional pharmacovigilance activities	Additional risk minimization activities
· Specified drug use-results survey[a)]	· None

a) This is the ongoing specified drug use-results survey. No additional survey will be conducted for this application.

III. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after modifying "Dosage and administration" as shown below, with the following indication and condition for approval. The present application is for a new dosage. The re-examination period for this application is the remainder of the ongoing re-examination period for the initial approval of IDeg (until September 27, 2020).

[Indication]

Diabetes mellitus where treatment with insulin is required

(No changes)

[Dosage and administration]

Tresiba FlexTouch

The usual initial adult dosage is 4 to 20 units of Insulin Degludec administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition.

Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 4 to 80 units/day. However, a higher dose than stated above may be used as needed.

Usually in pediatric population, Insulin Degludec is administered subcutaneously once daily. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 0.5 to 1.5 units/kg/day. However, a higher dose than stated above may be used as needed.

Tresiba Penfill

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

Usually in pediatric population, Insulin Degludec is administered subcutaneously once daily, using a specific insulin pen device. It should be injected at the same time every day. The dose should be adjusted according to the patient's condition. Insulin Degludec may be used in combination with other insulin products and typically, the total insulin maintenance dose is 0.5 to 1.5 units/kg/day. However, a higher dose than stated above may be used as needed.

(Words underlined are additions; words underscored with a wavy line are changes.)

[Condition for approval]

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