

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203313Orig1s000**

**203314Orig1s000**

**CLINICAL PHARMACOLOGY AND  
BIOPHARMACEUTICS REVIEW(S)**

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**OFFICE OF CLINICAL PHARMACOLOGY MEMO**

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|--------------------------|-----------------------------------------------------------------|
| NDA: 203313              | Submission Date(s): 03/26/2015                                  |
| Brand Name               | Ryzodeg®                                                        |
| Generic Name             | Insulin degludec/ Insulin aspart                                |
| Reviewer                 | Ritesh Jain, Ph.D.                                              |
| Team Leader (Acting)     | Manoj Khurana, Ph.D.                                            |
| OCP Division             | Clinical Pharmacology 2                                         |
| OND Division             | Metabolic and Endocrinology Products                            |
| Sponsor                  | Novo Nordisk                                                    |
| Submission Type          | NDA 505(b)(1); Class 2 Resubmission                             |
| Formulation; Strength(s) | 100 Units of insulin degludec/insulin aspart<br>per mL (U-100)  |
| Indication               | To improve glycemic control in adults with diabetes<br>mellitus |

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## **1. Executive Summary**

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This is class 2 resubmission of the NDA 203313 for Insulin degludec/insulin aspart 70/30 pre-mix (100 units/mL) by Novo Nordisk (the sponsor) in response to the complete response that was issued on 02/13/2012 to address its cardiovascular risk. In this re-submission, there is no new clinical pharmacology information for agency's review. Since the label was not discussed in the first review cycle, this memo captures the relevant labeling recommendations negotiated with the sponsor from a Clinical Pharmacology perspective up to the time of finalization of this review. For complete details on the Clinical Pharmacology information for this NDA refer to the original Clinical Pharmacology review by Dr. Ritesh Jain in DARRTs dated 06/15/2012.

## **2. Detailed Labeling Recommendations**

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### **Labeling recommendations are listed by relevant sections of the label:**

Labeling statements that were proposed by the sponsor are shown in the **red font** and the suggested labeling to be included is shown in **blue font**. Rationale for the recommended changes is summarized under reviewer's comments.

### **Section 7 DRUG INTERACTIONS**

**Proposed Labeling**

(b) (4)

**Final Recommended Labeling**

**Table 5: Clinically Significant Drug Interactions with RYZODEG 70/30**

| <b><u>Drugs That May Increase the Risk of Hypoglycemia</u></b>                                       |                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i><u>Drugs:</u></i>                                                                                 | <u>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors</u>          |
| <i><u>Intervention:</u></i>                                                                          | <u>Dose reductions and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.</u>                                                                                                                                                                                                               |
| <b><u>Drugs That May Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30</u></b>             |                                                                                                                                                                                                                                                                                                                                                            |
| <i><u>Drugs:</u></i>                                                                                 | <u>Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</u> |
| <i><u>Intervention:</u></i>                                                                          | <u>Dose increases and increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.</u>                                                                                                                                                                                                                |
| <b><u>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of RYZODEG 70/30</u></b> |                                                                                                                                                                                                                                                                                                                                                            |
| <i><u>Drugs:</u></i>                                                                                 | <u>Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.</u>                                                                                                                                                                                                         |
| <i><u>Intervention:</u></i>                                                                          | <u>Dose adjustment and increased frequency of glucose monitoring</u>                                                                                                                                                                                                                                                                                       |

|                                                                                |                                                                                                                                   |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|
|                                                                                | <a href="#">may be required when RYZODEG 70/30 is co-administered with these drugs.</a>                                           |
| <b><a href="#">Drugs That May Blunt Signs and Symptoms of Hypoglycemia</a></b> |                                                                                                                                   |
| <i><a href="#">Drugs:</a></i>                                                  | <a href="#">beta-blockers, clonidine, guanethidine, and reserpine</a>                                                             |
| <i><a href="#">Intervention:</a></i>                                           | <a href="#">Increased frequency of glucose monitoring may be required when RYZODEG 70/30 is co-administered with these drugs.</a> |

*Reviewer's Comment: The information was converted into table format with recommendations on interventions, consistent with current practice.*

## Section 12.1 Mechanism of Action

### Proposed Labeling

(b) (4)

### **Final Recommended Labeling**

[The primary activity of insulin, including RYZODEG 70/30, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. The insulin degludec component in RYZODEG 70/30 forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of RYZODEG 70/30 is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin. Insulin aspart monomers are released rapidly into the circulation.](#)

## Section 12.2 Pharmacodynamics

### **Proposed Labeling**

**Final Recommended Labeling**

The pharmacodynamic profile of RYZODEG 70/30 reflects the action profile of rapid-acting insulin aspart and long-acting insulin degludec. The pharmacodynamic profile for RYZODEG 70/30 given as single dose subcutaneous injections of 0.8 U/kg dose in a euglycemic clamp study in patients with type 1 diabetes, is shown in Figure 3. The mean maximum glucose lowering effect ( $GIR_{max}$ ) of a 0.8 U/kg dose of RYZODEG 70/30 was 6.9 mg/kg/min, which was observed at a median  $t_{GIRmax}$  of 2.3 hours post-dose .

In patients with type 1 diabetes mellitus and type 2 diabetes mellitus, RYZODEG 70/30 has an onset of action that rapidly follows injection. Basal insulin degludec in RYZODEG 70/30 provides a glucose lowering effect over 24 hours upon once-daily administration. The duration of action of a single-dose of RYZODEG 70/30 (b) (4) 24 hours (Figure 3) due to the presence of the basal component, insulin degludec.

The total and maximum glucose-lowering effect of RYZODEG 70/30 increases linearly with increasing doses from 0.4U/kg-0.8U/kg in patients with type 1 diabetes mellitus and type 2 diabetes mellitus. (b) (4) However, the magnitude of the glucose-lowering effect at steady state is reduced in type 2 diabetic subjects in comparison to type 1 diabetic subjects given the same unit/kg RYZODEG 70/30 dose.

***Reviewer's Comment:** Changes to the proposed language in this section are primarily made to only reflect the language that was adequately supported by the studies submitted in the first review cycle and including additional relevant information from these studies to reflect the pharmacodynamic of this premix insulin.*

**Section 12.3 Pharmacokinetics****Proposed Labeling**

(b) (4)

(b) (4)

(b) (4)

Distribution (b) (4)

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has low binding to plasma proteins, <10%, similar to regular human insulin. (b) (4)

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady state is approximately 25 hours independent of dose. Degradation of insulin degludec is similar to that of human insulin. All metabolites formed are inactive

**Final Recommended Labeling**

Absorption

The concentration-time profile following a single subcutaneous dose of 0.4, 0.6, and 0.8 U/kg RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus showed increased exposure with increasing dose for both components of RYZODEG 70/30 (insulin degludec and insulin aspart).

Insulin aspart showed dose proportional increase in maximum concentration ( $C_{max}$ ) and slightly more than dose proportional increase in overall exposure  $AUC_{0-12h}$  following single

subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus.

Insulin degludec showed dose proportional increase in  $C_{max}$  and  $AUC_{0-120h}$  following single subcutaneous administration of RYZODEG 70/30 in patients with type 1 diabetes mellitus and type 2 diabetes mellitus .

The (b) (4) for the (b) (4) (insulin aspart) (b) (4) 14 minutes (b) (4) injection with a peak concentration after 72 minutes. Steady state serum concentrations of the basal component (insulin degludec) of RYZODEG 70/30 (b) (4) reached after 3-4 days of dose administrations [see *Dosage and Administration (2.2)*].

#### *Distribution*

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. Insulin aspart has low binding to plasma proteins, <10%, similar to regular human insulin.

#### *Elimination*

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life of the basal component (insulin degludec) at steady state is approximately 25 hours independent of dose. Degradation of insulin degludec is similar to that of human insulin. All metabolites formed are inactive.

***Reviewer's Comment:** Changes to the proposed language in this section are primarily made to only reflect the language that was adequately supported by the studies submitted in the first review cycle and including additional relevant information from these studies*

### **Specific Populations Section Under Section 12.3**

#### **Proposed Labeling**

As with other insulin preparations, Ryzodeg should always be titrated according to individual requirements.

(b) (4)

#### **Geriatrics-**

Pharmacokinetic and pharmacodynamic responses of (b) (4) were investigated in 13 younger adult (18–35 years) and 15 geriatric ( $\geq 65$  years) subjects with T1DM following two single s.c. dose administrations of 0.5 U/kg: one of (b) (4) and one of NovoLog Mix 70/30. The total

exposure of insulin aspart in (b) (4) (based on AUCIAsp,0-12h,SD) tended to be higher in geriatric subjects than in younger adult subjects. The total exposure of insulin degludec in (b) (4) (based on AUCIDeg,0-120h,SD) and the pharmacodynamic response to (b) (4) (based on AUCGIR (b) (4)) was similar in younger adult and geriatric subjects with T1DM

**Gender-**

The effect of gender on the pharmacokinetics of the separate components of (b) (4) insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec or insulin aspart between female and male subjects.

**Obesity-**

The effect of BMI on the pharmacokinetics of the separate components of (b) (4) insulin degludec and insulin aspart, was examined in (b) (4) cross trial analyses of the pharmacokinetic and pharmacodynamic studies. (b) (4)

(b) (4)  
(b) (4)  
(b) (4)  
For insulin aspart, there was no relationship between BMI and exposure in subjects with T1DM or T2DM.

**Race and ethnicity-**

The effect of race and ethnic origin on the pharmacokinetics of Ryzodeg has not been studied. The basal component of Ryzodeg, insulin degludec, has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

(b) (4)

**Pregnancy-**

(b) (4)

**Renal impairment-**

(b) (4)

### Hepatic impairment-

### **Final Recommended Labeling**

As with other insulin preparations, RYZODEG 70/30 should always be titrated according to individual requirements.

#### *Geriatrics-*

Pharmacokinetic and pharmacodynamic responses of RYZODEG 70/30 were investigated in 13 younger adult (18–35 years) and 15 geriatric ( $\geq 65$  years) subjects with T1DM following two single s.c. dose administrations of 0.5 U/kg: one of RYZODEG 70/30 and one of NovoLog Mix 70/30. The total exposure of insulin aspart in RYZODEG 70/30 (based on  $AUC_{IAsp,0-12h,SD}$ ) tended to be higher in geriatric subjects than in younger adult subjects. The total exposure of insulin degludec in RYZODEG 70/30 (based on  $AUC_{IDeg,0-120h,SD}$ ) and the pharmacodynamic response to RYZODEG 70/30 (based on  $AUC_{GIR,0-24h}$ ) was similar in younger adult and geriatric subjects with T1DM, albeit higher between subjects variability among the geriatric subjects.

#### *Gender-*

The effect of gender on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec or insulin aspart between female and male subjects.

#### *Obesity-*

The effect of BMI on the pharmacokinetics of the separate components of RYZODEG 70/30, insulin degludec and insulin aspart, was examined in across trial analyses of the pharmacokinetic and pharmacodynamic studies. (b) (4)



#### *Race and Ethnicity-*

The effect of race and ethnic origin on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

#### *Pregnancy-*

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of RYZODEG 70/30 has not been studied [see *Use in Specific Populations (8.1)*].

#### *Renal Impairment-*

The effect of renal impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4 U/kg) of insulin degludec. Renal function was defined using creatinine clearance (Cl<sub>cr</sub>) as follows: ≥90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total (AUC<sub>IDeg,0-120h,SD</sub>) and peak exposure of insulin degludec were on average about 10-25% and 13-27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of insulin degludec (CL/F<sub>IDeg,SD</sub>) in subjects with ESRD.

A single subcutaneous dose of 0.08 U/kg NovoLog (insulin aspart, the rapid-acting component of RYZODEG 70/30) was administered in a study to subjects with either normal, mild, moderate

or severe (but not requiring hemodialysis) renal impairment. In this study, there was no apparent effect of creatinine clearance values on AUC and Cmax of insulin aspart.

*Hepatic Impairment-*

The effect of hepatic impairment on the pharmacokinetics of RYZODEG 70/30 has not been studied. The basal component of RYZODEG 70/30, insulin degludec, has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4U/kg) of insulin degludec. No differences in the pharmacokinetics of insulin degludec were identified between healthy subjects and subjects with hepatic impairment [see *Use in Specific Populations (8.7)*].

A single subcutaneous dose of 0.06 U/kg insulin aspart, the rapid-acting component of RYZODEG 70/30, was administered in an open-label, single-dose study of 24 subjects (N=6/group) with different degrees of hepatic impairment (mild, moderate, and severe). In this study, there was no correlation between the degree of hepatic failure and any insulin aspart pharmacokinetic parameter.

***Reviewer's Comment:*** *Some of the changes that were made in this section such as language on renal impairment study using the cutoff values recommended in current labeling guidance, half-life values of degludec were made to keep the label consistent with Tresiba (NDA 203314). Please refer to labeling review of Tresiba by Dr. Manoj Khurana for further details*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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RITESH JAIN  
09/24/2015

MANOJ KHURANA  
09/24/2015

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**OFFICE OF CLINICAL PHARMACOLOGY MEMO**

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|-------------------------------------|----------------------------------------------------------------------------------------|
| <b>NDA:</b> 203314                  | Submission Date(s): 03/26/2015                                                         |
| <b>Brand Name</b>                   | Tresiba®                                                                               |
| <b>Generic Name</b>                 | Insulin degludec                                                                       |
| <b>Reviewer</b>                     | Manoj Khurana, Ph.D.                                                                   |
| <b>Team Leader (Acting)</b>         | Jayabharathi Vaidyanathan, Ph.D.                                                       |
| <b>OCP Division</b>                 | Clinical Pharmacology 2                                                                |
| <b>OND Division</b>                 | Metabolic and Endocrinology Products                                                   |
| <b>Sponsor</b>                      | Novo Nordisk                                                                           |
| <b>Submission Type</b>              | NDA 505(b)(1); Class 2 Resubmission                                                    |
| <b>Formulation;<br/>Strength(s)</b> | Insulin degludec solution for subcutaneous injection;<br>100 units/mL and 200 units/mL |
| <b>Indication</b>                   | To improve glycemic control in adults with diabetes mellitus                           |

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## **1. Executive Summary**

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This is class 2 resubmission of the NDA 203314 for Insulin degludec (100 units/mL and 200 units/mL) by Novo Nordisk (the sponsor) in response to the complete response that was issued on 02/13/2012 to address its cardiovascular risk. In this re-submission, there is no new clinical pharmacology information for agency's review. Since the label was not discussed in the first review cycle, this memo captures the relevant labeling recommendations negotiated with the sponsor from a Clinical Pharmacology perspective up to the time of finalization of this review. For complete details on the Clinical Pharmacology information for this NDA refer to the original Clinical Pharmacology review by Dr. Manoj Khurana in DARRTs dated 06/15/2012 and Addendum to the Review in DAARTS dated 06/27/2012.

## **2. Detailed Labeling Recommendations**

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### **Labeling recommendations are listed by relevant sections of the label:**

Labeling statements that were proposed by the sponsor are shown in the **red font** and the suggested labeling to be included is shown in **blue underlined font**. Strikeout ~~the~~ text indicates key portions of the label that were either deemed unacceptable and/or replaced with relevant information. Rationale for the recommended changes is summarized under reviewer's comments.

**Section INDICATIONS AND USAGE and throughout the label:**

**Proposed Labeling**

Tresiba is (b) (4) long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1).

**Final Labeling**

TRESIBA is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus (1).

*Reviewer's Comment: In concurrence with the review team, the qualitative description is (b) (4) "long-acting" consistent with the once-daily use of Insulin Degludec throughout the label.*

**Section 7 DRUG INTERACTIONS**

**Proposed Labeling**



**Final Recommended Labeling**

**Table 5: Clinically Significant Drug Interactions with TRESIBA**

| <b><u>Drugs That May Increase the Risk of Hypoglycemia</u></b> |                                                                                                                                                                                                                                                                                                                                                   |
|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <i><u>Drugs:</u></i>                                           | <u>Antidiabetic agents, ACE inhibitors, angiotensin II receptor blocking agents, disopyramide, fibrates, fluoxetine, monoamine oxidase inhibitors, pentoxifylline, pramlintide, propoxyphene, salicylates, somatostatin analogs (e.g., octreotide), and sulfonamide antibiotics, GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors</u> |
| <i><u>Intervention:</u></i>                                    | <u>Dose reductions and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these</u>                                                                                                                                                                                                                   |

|                                                                                                |                                                                                                                                                                                                                                                                                                                                                            |
|------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                                                | <u>drugs.</u>                                                                                                                                                                                                                                                                                                                                              |
| <b><u>Drugs That May Decrease the Blood Glucose Lowering Effect of TRESIBA</u></b>             |                                                                                                                                                                                                                                                                                                                                                            |
| <u>Drugs:</u>                                                                                  | <u>Atypical antipsychotics (e.g., olanzapine and clozapine), corticosteroids, danazol, diuretics, estrogens, glucagon, isoniazid, niacin, oral contraceptives, phenothiazines, progestogens (e.g., in oral contraceptives), protease inhibitors, somatropin, sympathomimetic agents (e.g., albuterol, epinephrine, terbutaline), and thyroid hormones.</u> |
| <u>Intervention:</u>                                                                           | <u>Dose increases and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.</u>                                                                                                                                                                                                                      |
| <b><u>Drugs That May Increase or Decrease the Blood Glucose Lowering Effect of TRESIBA</u></b> |                                                                                                                                                                                                                                                                                                                                                            |
| <u>Drugs:</u>                                                                                  | <u>Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.</u>                                                                                                                                                                                                         |
| <u>Intervention:</u>                                                                           | <u>Dose adjustment and increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.</u>                                                                                                                                                                                                                     |
| <b><u>Drugs That May Blunt Signs and Symptoms of Hypoglycemia</u></b>                          |                                                                                                                                                                                                                                                                                                                                                            |
| <u>Drugs:</u>                                                                                  | <u>beta-blockers, clonidine, guanethidine, and reserpine</u>                                                                                                                                                                                                                                                                                               |
| <u>Intervention:</u>                                                                           | <u>Increased frequency of glucose monitoring may be required when TRESIBA is co-administered with these drugs.</u>                                                                                                                                                                                                                                         |

*Reviewer's Comment: The information was converted into table format with recommendations on interventions, consistent with current practice.*

## Section 12.1 Mechanism of Action

### **Proposed Labeling**

The primary activity of (b) (4) is the regulation of glucose metabolism. (b) (4)

(b) (4)

(b) (4)

**Final Recommended Labeling**

The primary activity of insulin, including TRESIBA, is regulation of glucose metabolism. Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis, and enhances protein synthesis. TRESIBA forms multi-hexamers when injected into the subcutaneous tissue resulting in a subcutaneous insulin degludec depot. The protracted time action profile of TRESIBA is predominantly due to delayed absorption of insulin degludec from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin.

**Section 12.2 Pharmacodynamics**

**Proposed Labeling**



(b) (4)



**Final Recommended Labeling**

The glucose-lowering effect of TRESIBA after 8 days of once-daily dosing was measured in a euglycemic glucose clamp study enrolling 21 patients with type 1 diabetes. Figure 2 shows the pharmacodynamic effect of TRESIBA over time following 8 once-daily subcutaneous injections of 0.4 U/kg of TRESIBA in patients with type 1 diabetes.

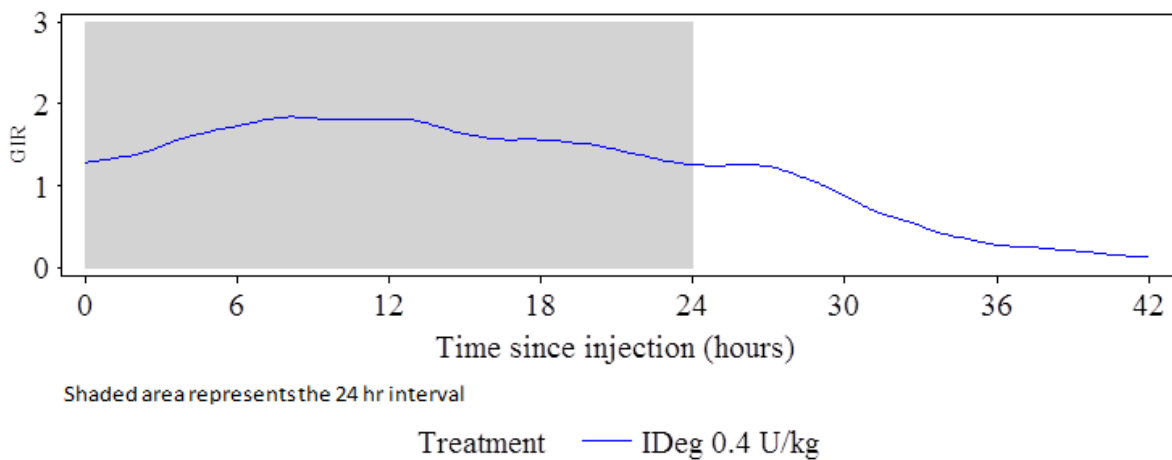


**Figure 2: Mean GIR profile for 0.4 U/kg dose of TRESIBA (steady state) in patients with Type 1 diabetes mellitus**

The mean maximum glucose lowering effect ( $GIR_{max}$ ) of a 0.4 U/kg dose of TRESIBA was 2.0 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect of TRESIBA lasted at least 42 hours after the last of 8 once-daily injections.

In patients with type 1 diabetes mellitus, the steady-state, within subjects, day-to-day variability in total glucose lowering effect was 20% with TRESIBA (within-subject coefficient of variation for  $AUCGIR_{\tau,SS}$ ).

The total glucose-lowering effect of TRESIBA over 24 hours measured in a euglycemic clamp study after 8 days of once-daily administration in patients with type 1 diabetes increases approximately in proportion to the dose for doses between 0.4 U/kg to 0.8 U/kg.

The total glucose-lowering effect of 0.4 U/kg of TRESIBA U-100 and 0.4 U/kg of TRESIBA U-200, administered at the same dose, and assessed over 24 hours in a euglycemic clamp study after 8 days of once-daily injection was comparable.

***Reviewer's Comment:** Pharmacodynamic section describes the TRESIBA specific information, at clinically relevant dose and population, which is the primary intent of the product label. The PD effect till 24 hours is highlighted to emphasize the effect over the once-daily use and effect beyond 24 hours after multiple daily dosing may be important to know in certain clinical situations (e.g. switching to a different insulin etc.).*

### **Section 12.3 Pharmacokinetics**

#### **Proposed Labeling**

(b) (4)



**Distribution** (b) (4)

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. The results of the *in vitro* protein binding studies demonstrate that there is no clinically relevant interaction between insulin degludec and other protein bound drugs.

**Final Recommended Labeling**

Absorption

In patients with type 1 diabetes, after 8 days of once daily subcutaneous dosing with 0.4 U/kg of TRESIBA, maximum degludec concentrations of 4472 pmol/L were attained at a median of 9 hours (t<sub>max</sub>). After the first dose of TRESIBA, median onset of appearance was around one hour.

Total insulin degludec concentration (i.e., exposure) increased in a dose proportional manner after subcutaneous administration of 0.4 U/kg to 0.8 U/kg TRESIBA. Total and maximum insulin degludec exposure at steady state are comparable between TRESIBA U-100 and TRESIBA U-200 when each is administered at the same U/kg dose.

Insulin degludec concentration reach steady state levels after 3-4 days of TRESIBA administration [see Dosage and Administration (2.2)].

Distribution

The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. The results of the *in vitro* protein binding studies demonstrate that there is no clinically relevant interaction between insulin degludec and other protein bound drugs.

Elimination

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. On average, the half-life at steady state is approximately 25 hours independent of dose. Degradation of TRESIBA is similar to that of insulin human; all metabolites formed are inactive. The mean apparent clearance of insulin degludec is 0.03 L/kg (2.1 L/h in 70 kg individual) after single subcutaneous dose of 0.4 U/kg.

**Reviewer's Comment:** *Changes to the proposed language in this section are primarily made to only reflect the language that was* (b) (4)

*. The* (b) (4)  
*was also updated according to the observations from PK/PD studies.*

## Specific Populations Section Under Section 12.3

### Proposed Labeling

As with other insulin preparations, Tresiba should always be titrated according to individual requirements.

(b) (4)

#### Geriatrics-

Pharmacokinetic and pharmacodynamic response of Tresiba (b) (4) in 13 younger adult (18–35 years) and 14 geriatric ( $\geq 65$  years) subjects with T1DM following two 6 day periods of once-daily subcutaneous dosing with (0.4 U/kg) of Tresiba or insulin glargine. The pharmacokinetic and pharmacodynamic properties of Tresiba at steady state were similar in younger adult and geriatric subjects. (b) (4)

#### Gender-

The effect of gender on the pharmacokinetics of Tresiba was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

#### Obesity-

The effect of BMI on the pharmacokinetics of Tresiba was examined in a (b) (4) cross-trial analysis of (b) (4) pharmacokinetic and pharmacodynamic studies. (b) (4)

#### Race and ethnicity-

Tresiba has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

(b) (4)

### Pregnancy-

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of Tresiba has not been studied [see Use in Specific Populations (8.1)].

### Renal impairment-

Tresiba (b) (4) pharmacokinetic study in 32 subjects (b) (4)/group) with normal or impaired renal function/end-stage renal disease following administration of a single dose (0.4U/kg) of Tresiba. Renal function was defined using creatinine clearance (Cl<sub>cr</sub>) as follows:

(b) (4)  
Hemodialysis did not affect clearance of Tresiba (CL/F<sub>IDeg,SD</sub>) in subjects with ESRD (b) (4)

### Hepatic impairment-

Tresiba has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single dose (0.4U/kg) of Tresiba. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No (b) (4) differences in the pharmacokinetics of Tresiba were identified between healthy subjects and subjects with hepatic impairment (b) (4)

### **Final Recommended Labeling**

As with other insulin preparations, TRESIBA should always be titrated according to individual requirements.

### *Geriatrics-*

Pharmacokinetic and pharmacodynamic response of TRESIBA in 13 younger adult (18–35 years) and 14 geriatric (≥65 years) subjects with type 1 diabetes following two 6 day periods of once-daily subcutaneous dosing with 0.4 U/kg dose of TRESIBA or insulin glargine. On average, the pharmacokinetic and pharmacodynamic properties of TRESIBA at steady state were similar in younger adult and geriatric subjects, albeit with greater between subjects variability among the geriatric subjects.

### *Gender-*

The effect of gender on the pharmacokinetics of TRESIBA was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically relevant differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

### *Obesity-*

The effect of BMI on the pharmacokinetics of TRESIBA was examined in (b) (4) cross-trial analysis of the pharmacokinetic and pharmacodynamic studies. (b) (4)

#### *Race and Ethnicity-*

TRESIBA has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated.

#### *Pregnancy-*

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of TRESIBA has not been studied [see *Use in Specific Populations (8.1)*].

#### *Renal Impairment-*

TRESIBA pharmacokinetics was studied in 32 subjects (n=4-8/group) with normal or impaired renal function/end-stage renal disease following administration of a single subcutaneous dose (0.4U/kg) of TRESIBA. Renal function was defined using creatinine clearance (Cl<sub>cr</sub>) as follows: ≥90 mL/min (normal), 60-89 mL/min (mild), 30-59 mL/min (moderate) and <30 mL/min (severe). Subjects requiring dialysis were classified as having end-stage renal disease (ESRD). Total (AUC<sub>0-120h,SD</sub>) and peak exposure of TRESIBA were on average about 10-25% and 13-27% higher, respectively in subjects with mild to severe renal impairment except subjects with ESRD who showed similar exposure as compared to subjects with normal renal function. No systematic trend was noted for this increase in exposure across different renal impairment subgroups. Hemodialysis did not affect clearance of TRESIBA (CL/F<sub>0-120h,SD</sub>) in subjects with ESRD [see *Use in Specific Populations (8.6)*].

#### *Hepatic Impairment-*

TRESIBA has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a single subcutaneous dose (0.4U/kg) of TRESIBA. Hepatic function was defined using Child-Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment). No differences in the pharmacokinetics of TRESIBA were identified between healthy subjects and subjects with hepatic impairment [see *Use in Specific Populations (8.7)*].

**Reviewer's Comment:** Major changes that were made in this section were to make the label consistent with the current guidance. The language for the (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
09/24/2015

JAYABHARATHI VAIDYANATHAN  
09/24/2015

## CLINICAL PHARMACOLOGY ADDENDUM TO ORIGINAL REVIEW

|                                            |                                                                                                                  |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| NDA: 203314                                | Submission Date(s): 09/29/2011                                                                                   |
| Brand Name                                 | Tresiba®                                                                                                         |
| Generic Name                               | Insulin Degludec (NN1250)                                                                                        |
| Clinical Pharmacology Reviewer             | Manoj Khurana, Ph.D.                                                                                             |
| Clinical Pharmacology Team Leader (Acting) | Jayabharathi Vaidyanathan, Ph.D.                                                                                 |
| OCP Division                               | Clinical Pharmacology-2                                                                                          |
| OND division                               | Metabolic and Endocrine Products                                                                                 |
| Sponsor                                    | Novo-Nordisk                                                                                                     |
| Submission Type; Code                      | NDA 505(b)(1); Standard                                                                                          |
| Formulation; Strength(s)                   | Solution for Subcutaneous (SC) Injection                                                                         |
| Proposed Indication                        | An ultra-long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus |

|            |                                                                                                     |            |
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**1 Executive Summary**

*See Clinical Pharmacology review of the original NDA in DARRTS dated 6/15/12.*

**2 Question-Based Review (QBR)**

*See Clinical Pharmacology review of the original NDA in DARRTS dated 6/15/12.*

**3 Labeling Comments**

*See Clinical Pharmacology review of the original NDA in DARRTS dated 6/15/12.*

25 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

## 4.2 Individual Study Reviews

### 4.2.1 Injection Site Variation in Healthy Subjects (Trial ID: NN1250-1992)

**Rationale:** The commonly used injection sites for insulin products include abdomen, thigh, and deltoid area in arm. The variation in thickness of skin and regional blood flows among these sites could affect insulin PK by affecting the rate and extent of absorption with or without changes in pharmacodynamic effect profile. While injection sites are not restricted in the Phase 3 evaluation, this Phase 1 PK/PD evaluation provides supportive information and confidence over the use of either of the sites in clinical evaluation.

The study synopsis is as follows:

#### **Title of Trial**

A Trial Comparing the Pharmacokinetic and Pharmacodynamic Properties of NN1250<sup>1</sup> after Different Routes of Administration in Healthy Subjects **Objectives**

#### **Primary Objective:**

- To compare the systemic extent of absorption of insulin degludec (IDeg) (based on AUC<sub>IDeg,0-120h,SD</sub>) between injection in the thigh, the abdomen and the deltoid area following single-dose subcutaneous administration of IDeg in healthy subjects.

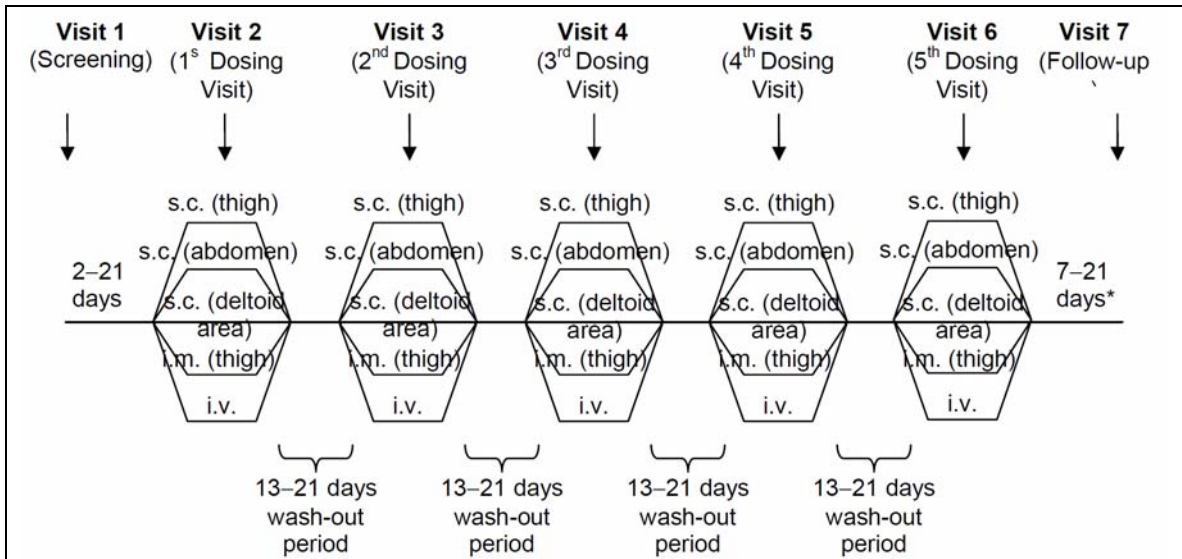
#### **Secondary Objectives:**

- To characterize the pharmacokinetic and pharmacodynamic profiles following single-dose subcutaneous administration of IDeg injected in the thigh, the abdomen and the deltoid area.
- To compare the systemic extent of absorption of IDeg (based on AUC<sub>IDeg,0-120h,SD</sub>) following single-dose subcutaneous and intramuscular administration of IDeg in the thigh.
- To characterize the pharmacokinetic and pharmacodynamic profiles following single-dose intramuscular administration of IDeg in the thigh.
- To estimate the absolute bioavailability of IDeg when IDeg was administered as a single-dose subcutaneously in the thigh, the abdomen and the deltoid area and intramuscularly in the thigh.
- To evaluate the short-term safety and tolerability of IDeg when administered subcutaneously in the thigh, the abdomen and the deltoid area, intramuscularly in the thigh and intravenously.

#### **Methodology**

This was a randomised, single-centre, open-label, five-period cross-over trial in healthy subjects investigating the pharmacokinetic and pharmacodynamic properties of IDeg after different routes of administration. Each subject was randomly allocated to five single doses on five separate dosing visits, administered subcutaneously (s.c.) in the thigh, the abdomen and the deltoid area, intramuscularly (i.m.) in the thigh and intravenously (i.v.), respectively. The trial consisted of 7 visits: a Screening Visit (Visit 1) followed by 5 dosing visits (Visits 2-6) and a Follow-Up Visit (Visit 7). Each dosing visit included a euglycaemic clamp procedure after trial product administration (24-hour clamp in case of s.c. or i.m. dosing and 12-hour clamp in case of i.v. dosing, respectively). Each subject stayed in-house for 48 hours after s.c. and i.m. dosing and returned to the clinic with 24-hour intervals to have blood samples taken for pharmacokinetic assessments at 72, 96 and 120 hours after administration of trial product. Subjects stayed in-house for 30 hours post i.v. dosing. Dosing visits were separated by 1321 days with 721 days (in case of s.c. or i.m. dosing) or 421 days (in case of i.v. dosing) between the last dosing visit and the Follow-Up Visit. The total planned duration of the trial for the individual subject was between 59 and 127 days.

**Study Design:** The study design is presented in the figure below:



\* 4-21 days follow-up period if dosing on Visit 6 was intravenous (i.v.)

**Diagnosis and Main Criteria for Inclusion**

Healthy male or female subjects aged 18-55 years (both inclusive) with body mass index of 18.0-27.0 kg/m<sup>2</sup> both inclusive).

Key exclusion criteria included donation of blood or plasma in the past month or more than 500 mL within 3 months prior to screening, use of prescription drugs within 3 weeks prior to screening, use of non-prescription drugs including over-the-counter medication, non-routine vitamins and herbal products within 3 weeks prior to screening and smoking.

**Test Product, Dose and Mode of Administration, Batch Number**

Insulin degludec in 3 mL (b) (4) cartridges (100 U/mL) was administered at the dose level of 0.4 U/kg body weight (BW) for s.c. or i.m. dosing and 0.04 U/kg BW for i.v. dosing, respectively. For administration of the small i.v. dose, IDeg was diluted 20 times to a concentration of 5 U/mL. Batch no. XCQ0001.

**Duration of Treatment**

Five (5) single injections of IDeg administered on five separate dosing visits (s.c. in the thigh, the abdomen and the deltoid area, i.m. in the thigh, i.v.).

**Reference Therapy, Dose and Mode of Administration, Batch Number**

Not applicable as there were no control groups in this trial.

**Criteria for Evaluation – Efficacy**

**Pharmacokinetic variable**

- Serum IDeg concentration after s.c., i.m. and i.v. administration

**Pharmacodynamic variables**

- Glucose infusion rate (GIR)
- Serum C-peptide concentrations

**Criteria for Evaluation – Safety**

- Adverse events
- Laboratory safety variables
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Hypoglycaemic episodes
- Local tolerability at the injection site

**Statistical Methods**

The pharmacokinetic and pharmacodynamic analyses were based on the Full Analysis Set, which

included all randomized subjects. The safety analyses were based on the Safety Analysis Set, including all subjects, who received at least one dose of the investigational product or its comparator.

#### ***Statistical Analysis of Primary Endpoint***

The primary endpoint was  $AUC_{IDeg,0-120h,SD}$ , area under the serum IDeg concentration-time curve from 0 to 120 hours after single dose (only for s.c. administration).

$AUC_{IDeg,0-120h,SD}$  was derived as the area under the IDeg concentration time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 120 hours. Missing values were imputed using linear interpolation. If not possible to interpolate and all values after  $t_z$  were below LLOQ, where  $t_z$  was the time point of the last quantifiable observation,  $AUC_{0-t_z}$  was used instead. If there were missing observations after  $t_z$ , extrapolation was done if the terminal slope could be determined from the profile in question with reasonable precision. The decision to extrapolate or not was taken during the blinded data review.

The  $AUC_{IDeg,0-t,SD}$  was let to be equal to  $AUC_{IDeg,0-120h,SD}$  for s.c. and i.m. administration and equal to  $AUC_{IDeg,0-30h,SD}$  for i.v. administration. The log-transformed  $AUC_{IDeg,0-t,SD}$ , was then analysed using an Analysis of Variance (ANOVA) method with treatment (s.c. [thigh]/s.c. [abdomen]/s.c. [deltoid area]/i.m./i.v.) and treatment period (period 1/period 2/period 3/period 4/period 5) as fixed factors and subject as a random effect. In order to account for

potential heteroscedasticity, the error-term depended on the treatment. Treatment ratios and 95% confidence intervals (CIs) between the three s.c. treatments were derived.

#### ***Statistical Analysis of Secondary Pharmacokinetic Endpoints***

The secondary pharmacokinetic endpoints derived from the individual IDeg concentration-time curves after administration of single dose of IDeg included:

- $AUC_{IDeg,SD}$  in the time periods 0-120 hours (only for i.m. administration), 0-30hours (only for i.v. administration), 0-24 hours (only for s.c. and i.m. administration), 0-12 hours (only for i.v. administration) and 0-inf after single dose
- Maximum observed serum IDeg concentration ( $C_{max,IDeg,SD}$ ) after single dose (only for s.c. and i m. administration)
- Back-extrapolated initial serum IDeg concentration ( $C_0,IDeg,SD$ ) after single dose (only for i.v. administration)
- Time to  $C_{max,IDeg,SD}$  ( $t_{max,IDeg,SD}$ ) after single dose (only for s.c. and i m. administration)
- Onset of appearance  $IDeg,SD$ , time from trial product administration until the first time serum IDeg concentration > 100 pmol/L after single dose using linear interpolation (only for s.c. and i.m. administration)
- Terminal half-life for IDeg ( $t_{1/2,IDeg,SD}$ ) after single dose
- Mean residence time for IDeg ( $MRT_{IDeg,SD}$ ) after single dose
- Mean absorption time for IDeg ( $MAT_{IDeg,SD}$ ) after single dose (only for s.c. and i.m. administration)
- Apparent serum clearance of IDeg ( $CL/F_{IDeg,SD}$ ) after single-dose extravascular administration (only for s.c. and i.m. administration)
- Serum clearance of IDeg ( $CL_{IDeg,SD}$ ) after single dose (only for i.v. administration)
- Apparent volume of distribution of IDeg ( $V_z/F_{IDeg,SD}$ ) after extravascular administration estimated during the terminal phase after single dose (only for s.c. and i.m. administration)
- Volume of distribution of IDeg ( $V_z,IDeg,SD$ ), estimated during the terminal phase after single dose (only for i.v. administration)

To compare the systemic extent of absorption of IDeg following single-dose s.c. and i.m. administration of IDeg in the thigh,  $AUC_{IDeg,0-120h,SD}$  for i.m. administration was analysed using the same approach as for the primary endpoint.  $AUC_{IDeg,0-120h,SD}$  was compared between s.c. and i.m. administration in

the thigh. The treatment ratio and 95% CI were estimated.

$C_{max, IDeg, SD}$  was analyzed using the same approach as for the primary endpoint; however, only s.c. and i.m. treatments were included in the model. Treatment ratios and 95% CIs between the three s.c. treatments as well as between s.c. and i.m. administrations in the thigh were presented.

In order to estimate the absolute bioavailability of IDeg when IDeg was administered as a single-dose s.c. in the thigh, the abdomen and the deltoid area and i.m. in the thigh,  $AUC_{IDeg, 0-\infty, SD}$  was analyzed using the same approach as for the primary endpoint. The dose-adjusted treatment ratios and 95% CIs between s.c./i.m. administrations and i.v. administration were estimated and presented as the absolute bioavailability. All other secondary pharmacokinetic endpoints were summarized by route of administration using descriptive statistics.

#### ***Statistical Analysis of Secondary Pharmacodynamic Endpoints***

The secondary pharmacodynamic endpoints included area under the glucose infusion rate (GIR) curve after single dose of IDeg ( $AUC_{GIR, SD}$ ) for the time periods 0-24 hours (only for s.c. and i.m. administration) and 0-12 hours (only for i.v. administration), maximum GIR after single dose ( $GIR_{max, SD}$ ) and time to  $GIR_{max, SD}$  ( $t_{GIR_{max, SD}}$ ) after single dose.

In order to evaluate the pharmacodynamic profiles following single-dose s.c., i.m. and i.v. administration of IDeg, all the pharmacodynamic endpoints were summarised by route of administration using descriptive statistics.

#### ***Statistical Analyses of Safety Endpoints***

The safety endpoints included adverse events, laboratory safety variables, physical examination, vital signs, electrocardiogram, hypoglycaemic episodes and local tolerability at the injection site.

An adverse event was defined as treatment-emergent if onset occurred after first trial product administration and no later than 7 days after last trial product administration. A hypoglycaemic episode was defined as treatment-emergent if the onset of the episode was on or after first trial product administration and no later than 7 days after the last trial product administration. All safety endpoints were listed and summarised using descriptive statistics.

#### **Demography of Trial Population**

Of the 20 randomised and exposed subjects, 17 (85%) were men and 3 (15%) were women. The majority of the subjects were white. The subjects' mean age was 37.4 years and mean body mass index was 24.1  $kg/m^2$ .

#### **Efficacy Results and Conclusions**

##### ***IDeg after Single Dose – s.c. Administration***

##### ***Pharmacokinetic Endpoints***

- The primary endpoint,  $AUC_{IDeg, 0-120h, SD}$ , was statistically significantly higher by 67% following s.c. administration in the abdomen or the deltoid than in the thigh, with no difference between abdomen and deltoid.
- The maximum serum concentration ( $C_{max, IDeg, SD}$ ) was statistically significantly higher by 2327% following s.c. administration in the abdomen and the deltoid than in the thigh, with no difference between abdomen and deltoid.

|                                                       | Mean ratio | 95% CI       |
|-------------------------------------------------------|------------|--------------|
| <b><math>AUC_{IDeg, 0-120h, SD}</math> (pmol*h/L)</b> |            |              |
| s.c. abdomen/thigh                                    | 1.07       | [1.03; 1.11] |
| s.c. deltoid/thigh                                    | 1.06       | [1.01; 1.10] |
| s.c. abdomen/deltoid                                  | 1.01       | [0.96; 1.06] |

**C<sub>max</sub>,IDeg,SD (pmol/L)**

|                      |      |               |
|----------------------|------|---------------|
| s.c. abdomen/thigh   | 1.23 | [1.07; 1.42]  |
| s.c. deltoid/thigh   | 1.27 | [1.08; 1.49]  |
| s.c. abdomen/deltoid | 0.97 | [[0.84; 1.12] |

The endpoints are log-transformed and analysed using an ANOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.

ANOVA: analysis of variance, AUC: area under the curve, C<sub>max</sub>: maximum observed concentration, CI: confidence interval, IDeg: insulin degludec, i.m.: intramuscular, s.c.: subcutaneous, SD: single dose

- The overall shape of the pharmacokinetic profiles was similar for the three s.c. injection sites, with the mean serum IDeg concentration-time profile over the first 3040 hours being higher following s.c. administration in the abdomen and the deltoid than in the thigh. Serum IDeg concentrations were detectable for the majority of subjects until the end of observation period (i.e., up to 120 hours) for all three s.c. injection sites.
- The secondary pharmacokinetic endpoints supported the results of the analyses of AUC<sub>IDeg,0-120h,SD</sub> and C<sub>max,IDeg,SD</sub>.

**Pharmacodynamic Endpoints**

- Based on descriptive statistics, the glucose-lowering effect, as measured by the geometric means for AUC<sub>GIR,0-24h,SD</sub> and GIR<sub>max,SD</sub>, was in the same range following s.c. administration in the thigh, abdomen and deltoid.
- The overall shape of the GIR profiles was similar irrespective of whether IDeg was administered s.c. in the thigh, the abdomen or the deltoid. The duration of glucose-lowering effect extended beyond 24 hours for all subjects following s.c. administration in all three injection sites.

**IDeg after Single Dose – i.m. versus s.c. Administration****Pharmacokinetic Endpoints**

Total exposure as measured by AUC<sub>IDeg,0-120h,SD</sub> was statistically significantly higher by 7% following i.m. administration than s.c. administration in the thigh.

- The maximum serum concentration (C<sub>max,IDeg,SD</sub>) was statistically significantly higher by 58% following i.m. administration than s.c. administration in the thigh.

|                                                | Mean ratio | 95% CI       |
|------------------------------------------------|------------|--------------|
| <b>AUC<sub>IDeg,0-120h,SD</sub> (pmol*h/L)</b> |            |              |
| i m/s.c. thigh                                 | 1.07       | [1.02; 1.13] |
| <b>C<sub>max,IDeg,SD</sub> (pmol/L)</b>        |            |              |
| i m./s.c thigh                                 | 1.58       | [1.36; 1.84] |

The endpoints are log-transformed and analysed using an ANOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.

ANOVA: analysis of variance, AUC: area under the curve, C<sub>max</sub>: maximum observed concentration, CI: confidence interval, IDeg: insulin degludec, i.m.: intramuscular, s.c.: subcutaneous, SD: single dose

- The secondary pharmacokinetic endpoints of i.m. and s.c. administration in the thigh supported the results of the analyses of AUC<sub>IDeg,0-120h,SD</sub> and C<sub>max,IDeg,SD</sub>.
- Following i m. administration, the mean serum IDeg concentration was higher over the first 3035 hours and lower beyond 40 hours compared to s.c. administration. Serum IDeg concentrations were detectable until the end of observation period (i.e., up to 120 hours) for the majority of subjects

following s.c. administration in contrast to i.m. administration (i.e., up to approximately 72 hours).

#### *Pharmacodynamic Endpoints*

- Based on descriptive statistics, the glucose-lowering effect of IDeg as measured by the estimated geometric means for  $AUC_{GIR,0-24h,SD}$  and  $GIR_{max,SD}$ , was higher following i.m. administration in the thigh compared to s.c. administration in the thigh.
- From 3-4 hours after the trial product administration, the mean smoothed GIR profile was higher throughout the 24-hour clamp period following i.m. administration as compared to the s.c. administration in the thigh. Overall, the glucose-lowering effect was in accordance with the corresponding pharmacokinetic profiles, however, the differences were less pronounced in the GIR profiles. The duration of glucose-lowering effect extended beyond 24 hours for all subjects irrespective of the administration route.

#### *IDeg after Single Dose – i.v. versus s.c. and i.m. Administration*

- [REDACTED] (b) (4)

#### **Safety Results and Conclusions**

- A total of 14 adverse events were reported in 8 (40%) out of 20 subjects exposed to IDeg; 4 events in 4 subjects (20%) in the s.c. abdomen treatment group, 4 events in 4 subjects (20%) in the s.c. deltoid treatment group, 4 events in 3 subjects (15.8%) in the i.m. thigh treatment group, 1 event in 1 subject in the s.c. thigh treatment group and 1 event in 1 subject in the i.v. treatment group, respectively. There were no apparent differences in the distribution of adverse events between the 5 treatments. There were no severe adverse events; the majority of events were of mild (10 events) severity; one mild event of headache and one mild event of diarrhoea (both in the same subject) were considered probably related to trial product; the subject recovered. The most common adverse events were headache (6 events in 3 subjects) and nasopharyngitis (3 events in 2 subjects). All other adverse events were only reported once or twice for each administration route or site.
- No serious adverse events or medical events of special interest were reported. No injection site reactions were reported.
- In total, 41 treatment-emergent hypoglycaemic episodes were reported and all were asymptomatic. Only 1 nocturnal episode was reported (following i.m. administration in the thigh). There were no obvious differences in the frequency of hypoglycaemic episodes reported between the three s.c. administration sites and the i.m. administration route.
- There were no clinically significant findings in laboratory parameters, vital signs, physical examination or ECG.

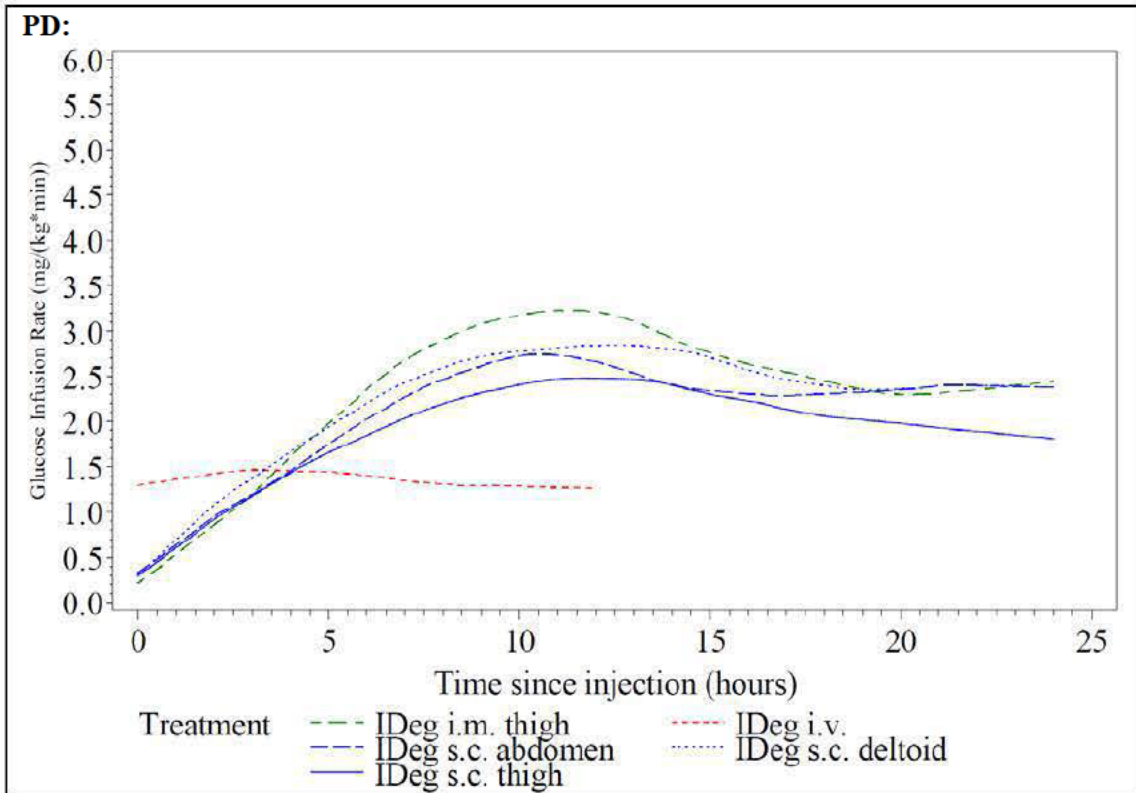
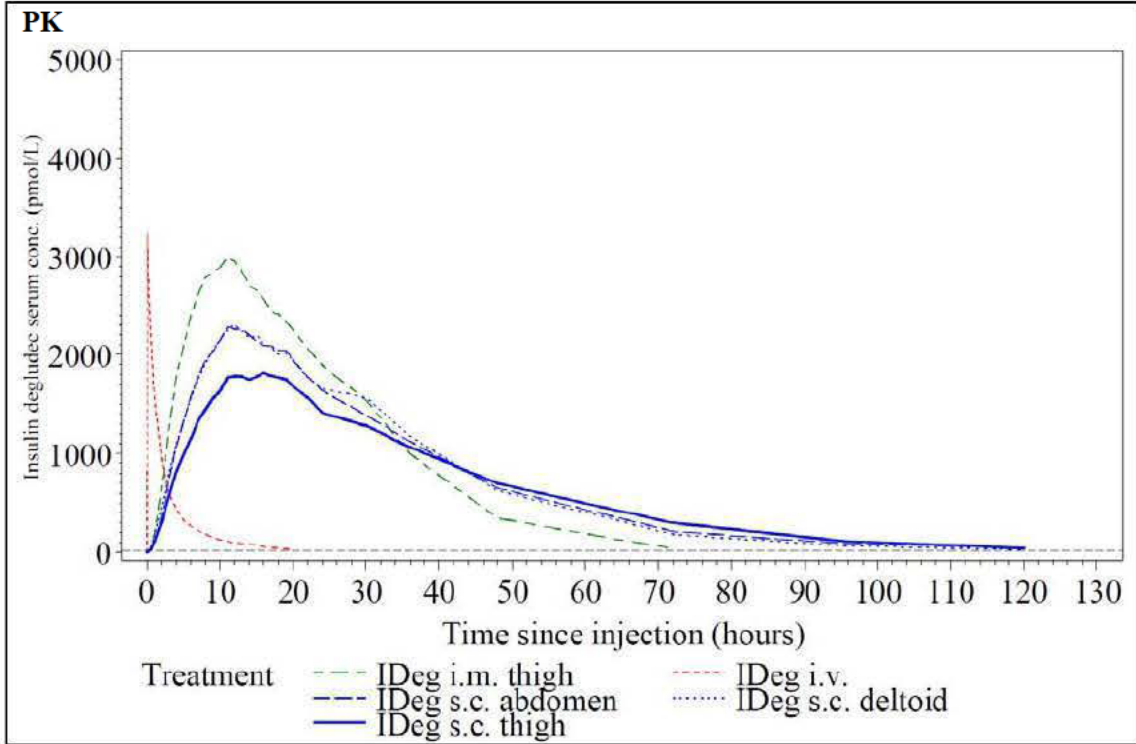
#### **Overall Conclusions**

The conclusions of this randomised, single-centre, open-label, five-period cross-over trial in healthy subjects investigating the comparison of pharmacokinetic and pharmacodynamic properties of IDeg after different routes of administration are:

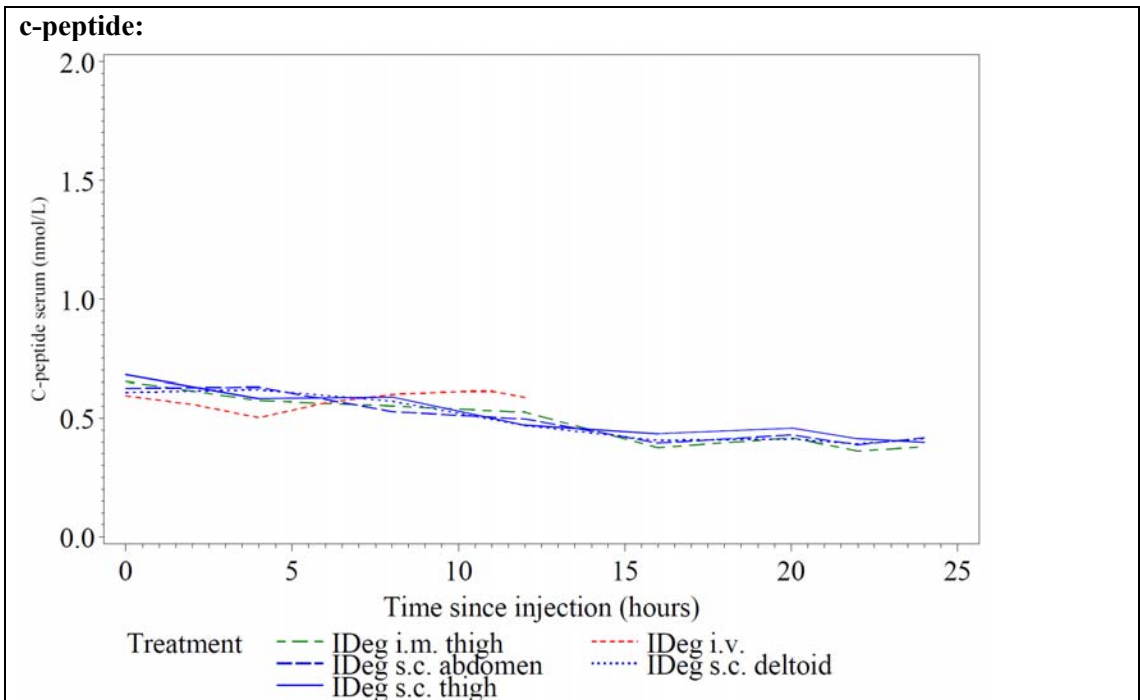
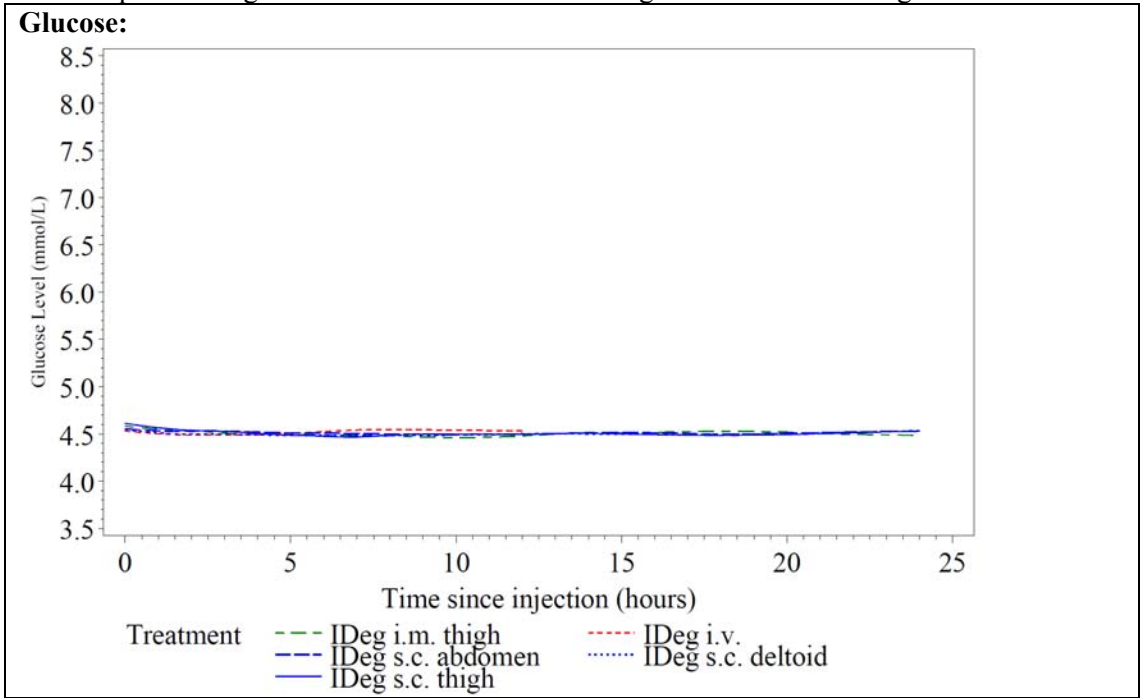
- Total exposure of IDeg ( $AUC_{IDeg,0-120h,SD}$ ) is higher after s.c. administration in the abdomen and the deltoid area compared to s.c. administration in the thigh.
- The glucose-lowering effect of IDeg after s.c. administration is similar in the thigh, the abdomen and the deltoid area.
- Intramuscular administration of IDeg leads to a higher maximum exposure ( $C_{max,IDeg,SD}$ ) and glucose-lowering effect ( $GIR_{max,SD}$ ) compared to s.c. administration.
- IDeg is well tolerated and no safety issues are identified in this trial.

The trial was conducted in accordance with the Declaration of Helsinki (Seoul 2008) and ICH Good Clinical Practice (10 Jun 1996).

**Results:**



The integrity of the euglycemic clamp was evident from the average blood glucose values, which were around the pre-specified target of 4.5 mmol/L. C-peptide levels remained suppressed during the clamp indicating minimal interference from endogenous insulin on IDeg PD effect.



**Key PK Parameters:**

|                                     | IDeg, s.c.,<br>thigh | IDeg, s.c.,<br>abdomen | IDeg, s.c.,<br>deltoid | IDeg, i.m.,<br>thigh |
|-------------------------------------|----------------------|------------------------|------------------------|----------------------|
| AUC IDeg, 0-120h, SD (pmol*h/L)     |                      |                        |                        |                      |
| N                                   | 19                   | 20                     | 20                     | 19                   |
| Geometric mean (CV)                 | 75853 ( 19)          | 82059 ( 17)            | 81135 ( 20)            | 81521 ( 18)          |
| Min ; Max                           | 48731 ; 102344       | 59729 ; 104438         | 55749 ; 107877         | 51022 ; 110972       |
| AUC IDeg, 0-inf, SD (pmol*h/L)      |                      |                        |                        |                      |
| N                                   | 19                   | 20                     | 20                     | 19                   |
| Geometric mean (CV)                 | 77364 ( 19)          | 83155 ( 17)            | 82733 ( 21)            | 82494 ( 18)          |
| Min ; Max                           | 49291 ; 102849       | 60092 ; 105261         | 56078 ; 114764         | 51286 ; 111443       |
| Cmax IDeg, SD (pmol/L)              |                      |                        |                        |                      |
| N                                   | 19                   | 20                     | 20                     | 19                   |
| Geometric mean (CV)                 | 1945 ( 22)           | 2388 ( 24)             | 2462 ( 25)             | 3067 ( 21)           |
| Min ; Max                           | 1160 ; 2830          | 1710 ; 3820            | 1390 ; 3860            | 2010 ; 4150          |
| tmax IDeg, SD (h)                   |                      |                        |                        |                      |
| N                                   | 19                   | 20                     | 20                     | 19                   |
| Median                              | 15.0                 | 13.0                   | 12.0                   | 11.0                 |
| Min ; Max                           | 11.0 ; 30.0          | 7.0 ; 20.0             | 8.0 ; 20.0             | 7.0 ; 15.0           |
| Onset of appearance, IDeg, SD (min) |                      |                        |                        |                      |
| N                                   | 19                   | 20                     | 20                     | 19                   |
| Median                              | 58                   | 62                     | 48                     | 45                   |
| Min ; Max                           | 41 ; 137             | 32 ; 89                | 22 ; 95                | 26 ; 96              |

AUC: area under the curve, Cmax: maximum observed concentration, CV: coefficient of variation in %, IDeg: insulin degludec, i.m.: intramuscular, N: number of subjects contributing to the analysis, s.c.: subcutaneous, SD: single dose, tmax: time to maximum observed concentration

**Key PD Parameters:**

|                            | IDeg, s.c.,<br>thigh | IDeg, s.c.,<br>abdomen | IDeg, s.c.,<br>deltoid | IDeg, i.m.,<br>thigh |
|----------------------------|----------------------|------------------------|------------------------|----------------------|
| Number of Subjects         | 19                   | 20                     | 20                     | 19                   |
| AUC GIR, 0-24h, SD (mg/kg) |                      |                        |                        |                      |
| N                          | 19                   | 20                     | 20                     | 19                   |
| Geometric mean (CV)        | 2571.5 ( 38.0)       | 2833.0 ( 42.2)         | 2960.1 ( 43.2)         | 3269.0 ( 25.0)       |
| Min ; Max                  | 1109.1 ; 4957.4      | 1480.3 ; 6859.0        | 951.2 ; 6356.7         | 1734.0 ; 4652.4      |
| GIR max, SD (mg/[kg*min])  |                      |                        |                        |                      |
| N                          | 19                   | 20                     | 20                     | 19                   |
| Geometric mean (CV)        | 2.7 ( 32.0)          | 3.0 ( 37.3)            | 3.0 ( 42.2)            | 3.4 ( 23.9)          |
| Min ; Max                  | 1.6 ; 4.8            | 1.8 ; 6.3              | 1.3 ; 6.2              | 1.8 ; 5.0            |
| tGIR max, SD (h)           |                      |                        |                        |                      |
| N                          | 19                   | 20                     | 20                     | 19                   |
| Median                     | 13.2                 | 11.1                   | 12.4                   | 12.4                 |
| Min ; Max                  | 7.5 ; 24.0           | 6.4 ; 24.0             | 7.0 ; 24.0             | 8.8 ; 24.0           |

AUC: area under the curve, CV: coefficient of variation in %, GIR: glucose infusion rate, IDeg: insulin degludec, i.m.: intramuscular, N: number of subjects contributing to the analysis, s.c.: subcutaneous, SD: single dose, tGIR: time to GIR

**Statistical Comparison of Primary PK Parameter:**

|                                 | FAS | N  | Estimate | 95% CI       |
|---------------------------------|-----|----|----------|--------------|
| AUC IDeg, 0-120h, SD (pmol*h/L) |     |    |          |              |
| Least square means              |     |    |          |              |
| IDeg s.c. thigh                 | 20  | 19 | 76679    |              |
| IDeg s.c. abdomen               | 20  | 20 | 82059    |              |
| IDeg s.c. deltoid               | 20  | 20 | 81135    |              |
| Mean ratio                      |     |    |          |              |
| s.c. abdomen/thigh              |     |    | 1.07     | [1.03; 1.11] |
| s.c. deltoid/thigh              |     |    | 1.06     | [1.01; 1.10] |
| s.c. abdomen/deltoid            |     |    | 1.01     | [0.96; 1.06] |
| AUC IDeg, 0-120h, SD (pmol*h/L) |     |    |          |              |
| Least square means              |     |    |          |              |
| IDeg i.m. thigh                 | 20  | 19 | 82301    |              |
| IDeg s.c. thigh                 | 20  | 19 | 76679    |              |
| Mean ratio                      |     |    |          |              |
| thigh i.m./s.c.                 |     |    | 1.07     | [1.02; 1.13] |

The endpoints are log-transformed and analyzed using an ANOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.  
ANOVA: analysis of variance, CI: confidence interval, FAS: full analysis set, IDeg: insulin degludec, i.m.: intramuscular, N: number of subjects contributing to the analysis, s.c.: subcutaneous, SD: single dose

**Statistical Comparison of Secondary PK Parameter:**

|                        | FAS | N  | Estimate | 95% CI       |
|------------------------|-----|----|----------|--------------|
| Cmax IDeg, SD (pmol/L) |     |    |          |              |
| Least square means     |     |    |          |              |
| IDeg s.c. thigh        | 20  | 19 | 1938     |              |
| IDeg s.c. abdomen      | 20  | 20 | 2388     |              |
| IDeg s.c. deltoid      | 20  | 20 | 2462     |              |
| Mean ratio             |     |    |          |              |
| s.c. abdomen/thigh     |     |    | 1.23     | [1.07; 1.42] |
| s.c. deltoid/thigh     |     |    | 1.27     | [1.08; 1.49] |
| s.c. abdomen/deltoid   |     |    | 0.97     | [0.84; 1.12] |
| Cmax IDeg, SD (pmol/L) |     |    |          |              |
| Least square means     |     |    |          |              |
| IDeg i.m. thigh        | 20  | 19 | 3066     |              |
| IDeg s.c. thigh        | 20  | 19 | 1938     |              |
| Mean ratio             |     |    |          |              |
| thigh i.m./s.c.        |     |    | 1.58     | [1.36; 1.84] |

The endpoints are log-transformed and analyzed using an ANOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.  
ANOVA: analysis of variance, CI: confidence interval, FAS: full analysis set, IDeg: insulin degludec, i.m.: intramuscular, N: number of subjects contributing to the analysis, s.c.: subcutaneous, SD: single dose

**Reviewer's Comment:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. Only change reported after database lock was that C<sub>0</sub>,IDeg,SD was used in the calculation of AUCIDeg,0-30h,SD, AUCIDeg,0-12h,SD and AUCIDeg,0-∞,SD during i.v. treatment instead of the observed pre-dose value. This modification enabled a better estimate of the actual AUC, which is reasonable. The analytical method adequately supported the results with accuracy and precision for calibration standards, QC samples, and dilution QC samples within ±9%.

#### 4.2.2 Single Dose BE Study (NN1250-1988) IDeg M versus E in Healthy

**Rationale:** The IDeg formulation used for the Phase 3 studies is identical to the formulation used for the Phase 2 studies, but (b) (4) from different (b) (4) as the manufacturing process has been optimized. The rationale for this trial is to test for bioequivalence between the two formulations IDeg (E) and IDeg (M) (used in Phase 2 and Phase 3, respectively) in a randomized crossover design PK and PD study.

The study synopsis is as follows:

##### Title of Trial

A Trial to Test for Bioequivalence between Two NN1250 Formulations in Healthy Subjects

##### Objectives

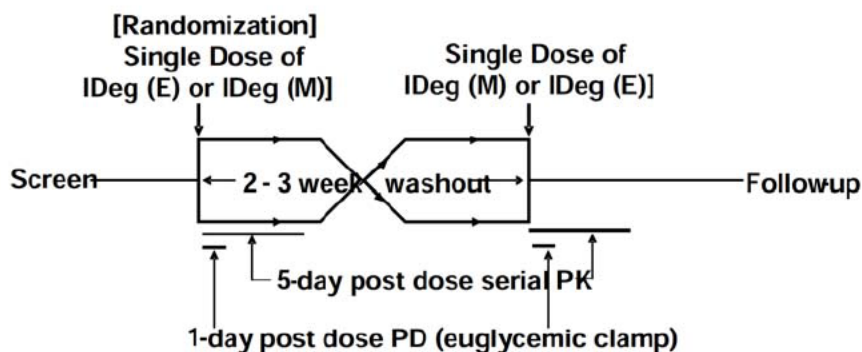
The primary objective of the trial was to test for bioequivalence between two formulations of insulin degludec based on  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$ . The secondary objectives of the trial were to compare the pharmacokinetic and pharmacodynamic profiles of the two insulin degludec formulations, and to evaluate the short-term safety and tolerability of these formulations.

##### Methodology

This was a randomized, single-centre, double-blinded, two-period cross-over trial in healthy subjects. Each subject was randomly allocated to 2 single dose administrations (one for each of the 2 insulin degludec formulations) on 2 separate dosing visits. The trial consisted of 4 visits: a screening visit followed by the 2 dosing visits (separated by a wash-out period of 13-21 days between the 2 dosing events) and a follow-up visit.

At each of the 2 dosing visits, the subjects stayed in-house for the first 48 hours after trial drug administration. The pharmacokinetic profile of insulin degludec was determined for 120 hours, while the pharmacodynamic response was evaluated during a 24-hour euglycemic glucose clamp. Pharmacokinetic samples were collected before trial drug administration and frequently thereafter. During the euglycemic glucose clamp, the blood glucose level was kept constant by a continuous variable intravenous glucose infusion. The glucose infusion rate was continuously monitored. Subjects were discharged from the clinic 48 hours post-dosing and returned at 72, 96 and 120 hours after dosing to have additional blood samples drawn for pharmacokinetic analysis.

**Study Design:** The study design is presented in the figure below:



##### Number of Subjects Planned and Analyzed

A total of 26 subjects were planned to be randomized for the trial. Altogether, 48 subjects were screened, 26 were randomized and 25 completed the trial. Analyses of PK/PD endpoints were based on the Full Analysis Set, which includes all randomized subjects ( $n=26$ ). For IDeg (E) analyses,  $n=25$  as there was 1 subject who did not complete the second clamp [IDeg (E)] in the assigned treatment sequence.

##### Diagnosis and Main Criteria for Inclusion

Healthy men or women 18–55 years of age (inclusive) with BMI 18–27  $kg/m^2$ , and FPG  $\leq 108$  mg/dL (or 6 mmol/L)

**Test Product, Dose and Mode of Administration, Batch Number**

IDeg (E) 100U/mL (Phase 2 formulation), and IDeg (M) 100U/mL (Phase 3 formulation), both subcutaneously administered.

| Trial Product | Concentration | Batch Number | Expiry Date |
|---------------|---------------|--------------|-------------|
| IDeg (E)      | 100U/mL       | XLDP005      | 12/9/2010   |
| IDeg (M)      | 100U/mL       | VCQ0013      | 3/4/2011    |

**Duration of Treatment**

This was a single dose trial - subjects were allocated to 2 single injections of trial product (one of each product) on 2 separate dosing visits. The trial consisted of 4 visits: a screening visit followed by the 2 dosing visits (separated by a wash-out period of 13-21 days between the 2 dosing events) and a follow-up visit.

**Reference Therapy, Dose and Mode of Administration, Batch Number**

IDeg (E) 100U/mL (b) (4) (Phase 2 formulation), 0.4 U/kg, batch number XLDP005, subcutaneously administered.

**Criteria for Evaluation – Efficacy**

- The criteria for evaluation of efficacy were serum concentration of IDeg, glucose infusion rate during euglycemic clamp for 24 hours after dosing, and serum C-peptide concentrations. **Criteria for Evaluation**

**– Safety**

- The criteria for evaluation of safety were physical examination, vital signs (diastolic and systolic blood pressure, pulse, body temperature), electrocardiogram, blood glucose measurements, hypoglycemic episodes, adverse events, and clinical laboratory tests.

**Statistical Methods**

Analyses of PK/PD endpoints were based on the Full Analysis Set, which includes all randomized subjects (n=26). For IDeg (E) analyses, n=25 as there was one subject who did not complete the second clamp [IDeg (E)] in the assigned treatment sequence.

**Primary Endpoints**

The following primary endpoints were derived from individual serum insulin degludec concentration profiles:  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$ . These were analysed using an analysis of variance (ANOVA) approach. Log-transformed values were used to account for heteroscedasticity. The statistical model for each endpoint had treatment, period and sequence effect (treatment by period interaction) as fixed effects, and subject as a random

effect. Bioequivalence between the 2 insulin degludec formulations was to be claimed if the 90% CI was fully within the interval [80%;125%]. Thus, the null hypothesis was that the 2 treatments (insulin degludec formulations) are non-equivalent and the alternative hypothesis was that they are equivalent. Bioequivalence between the 2 insulin degludec formulations was to be claimed if the null hypothesis was rejected for both  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$ .

To determine whether the dose-adjusted primary endpoints fulfil the bioequivalence criteria, the primary analysis was also performed with an adjustment for actual drug content (corrected drug concentrations).

**Secondary Endpoints**

The following secondary pharmacokinetic endpoints were derived from individual insulin degludec concentration-time curves:  $AUC_{IDeg,0-24h,SD}$ ,  $AUC_{IDeg,0-12h,SD}$ ,  $AUC_{IDeg,0-\infty,SD}$ ,  $t_{max,IDeg,SD}$ ,  $t_{1/2,IDeg}$ ,  $MRT_{IDeg}$ ,  $CL/FIDeg$ ,  $V_z/FIDeg$ , onset of appearance<sub>IDeg</sub>,  $\lambda_z,IDeg$ . The following secondary pharmacodynamic endpoints were derived from individual GIR profiles:  $AUC_{GIR,0-12h,SD}$ ,  $AUC_{GIR,0-24h,SD}$ ,  $GIR_{max,SD}$ ,  $t_{GIRmax,SD}$ . All secondary endpoints were compared between the 2 insulin degludec formulations using descriptive statistics except for  $AUC_{IDeg,0-\infty,SD}$ , which was analyzed using the same approach as for the primary endpoint.

**Safety Endpoints**

All randomized subjects who received at least one dose of study drug were included in the safety population and analysis.

The following safety endpoints were evaluated using descriptive statistics: adverse events, laboratory safety

variables (biochemistry, hematology, lipid panel, coagulation, urinalysis), physical examination, vital signs, electrocardiogram and hypoglycemic episodes.

#### **Demography of Trial Population**

Of the 26 randomized and exposed subjects, 19 (73%) were male and 7 (27%) were female. A total of 18 were White, 6 were Black or African American, 1 was Asian Indian, and 1 was reported as Other. The subjects' mean age was 36.6 years and mean BMI was 24.0 kg/m<sup>2</sup>. Mean FPG was 4.7 mmol/L.

#### **Efficacy Results**

- IDeg (E) was confirmed to be bioequivalent to IDeg (M) for the primary pharmacokinetic parameters AUC<sub>0-120h</sub> and C<sub>max</sub> because the 90% confidence interval for the mean treatment ratio of IDeg (M)/IDeg (E) was fully contained within the interval [0.8;1.25]. Ratios for IDeg (M)/IDeg(E) were 1.00 [CI90%: 0.94; 1.05] for AUC<sub>0-120h</sub> and 0.97 [CI90%: 0.89;1.05] for C<sub>max</sub>.
- The extent of absorption in terms of AUC<sub>0-inf</sub> was identical for the 2 formulations (treatment ratio IDeg (M)/IDeg (E): 1.00 [0.95;1.05]).
- Adjusting for actual drug content did not change the conclusion.
- No marked differences between the 2 insulin formulations were seen for other secondary pharmacokinetic and pharmacodynamic endpoints.

#### **Safety Results**

- A total of 13 treatment-emergent adverse events were reported for 9 subjects: 5 (20.0%) subjects taking IDeg (E) reported 6 AEs, and 5 (19.2%) subjects taking IDeg (M) reported 7 AEs. All AEs were mild (with 1 exception, which was moderate) and all but 1 were considered unlikely related to study drug (1 report of injection site pain experienced by a subject taking IDeg (M) was considered probably related to treatment).
- The only treatment-emergent adverse event reported by ≥ 5% of subjects was headache (reported for 2 subjects in each group).
- No subject withdrew from the study because of adverse events.
- No serious adverse events (SAEs), medical events of special interest (MESIs) or deaths were reported during the trial.
- No clinically relevant findings on laboratory measurements related to hematology, biochemistry, urinalysis, coagulation, or lipids and glucose metabolism were observed for either treatment group.
- A total of 16 hypoglycemic episodes were reported by 7 subjects using the ADA classification (PG ≤3.9mmol/L). None were symptomatic, no severe hypoglycemic episodes were reported during the study, and no nocturnal hypoglycemic episodes were reported.
- No clinically relevant findings on vital signs, physical examination or ECG were noted for either treatment group.

#### **Conclusions**

- The data confirmed that the 2 formulations of IDeg were bioequivalent, as the rate and extent of absorption were nearly identical (ratios for IDeg (M)/IDeg(E) were 1.00 [CI90%: 0.94; 1.05] for AUC<sub>0-120h</sub> and 0.97 [CI90%: 0.89;1.05] for C<sub>max</sub>). Adjusting for actual drug content did not change the conclusion.
- No marked differences between the 2 insulin formulations were seen for other secondary pharmacokinetic and pharmacodynamic endpoints
- Both IDeg (E) and IDeg (M) were safe and well tolerated.

*The trial was conducted in accordance with the Declaration of Helsinki 59th WMA General Assembly, Seoul, October 2008, and ICH Good Clinical Practice 01-May-1996.*

#### **Reviewer's Comment:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards, QC samples, and dilution QC samples within ±9%.

### 4.2.3 Single Dose BE Study (NN1250-3769) IDeg IM2 versus IM1 in Healthy

**Rationale:** The rationale for this trial was to test for bioequivalence between drug products manufactured (b) (4) before (IM1) and after (IM2) a minor optimization of the manufacturing process.

The study synopsis is as follows:

**Title of Trial**  
A Trial to Test for Bioequivalence between Identical NN1250 (IDeg) Formulations, IM1 and IM2, in Healthy Subjects

**Objectives**

**Primary Objective:**

- To test for bioequivalence between identical formulations of insulin degludec (M) IM1 and IDeg (M) IM2 based on AUC<sub>IDeg,0-120h,SD</sub> and C<sub>max,IDeg,SD</sub>

**Secondary Objectives:**

- To compare the pharmacokinetic and pharmacodynamic profiles of identical formulations IDeg (M) IM1 and IDeg (M) IM2
- To evaluate the short-term safety and tolerability of identical IDeg formulations IDeg (M) IM1 and IDeg (M) IM2

**Study Design:** The study design is presented in the figure below:

**Methodology**

This was a randomized, single-centre, double-blind, two-period cross-over trial in healthy subjects. Each subject was randomly allocated to 2 single-dose administrations (one of each of IDeg [M] IM1 and IDeg [M] IM2) on 2 separate Dosing Visits. Thus, the trial consisted of 4 visits: a Screening Visit (Visit 1) followed by 2 Dosing Visits (Visit 2-3) and a Follow-up visit (Visit 4) with randomization taking place at the first dosing visit. Screening took place 2-21 days before the first dosing visit. The Dosing Visits were separated by wash-out periods lasting 13-21 days, and the Follow-up visit took place 7-21 days after the last dosing visit. Each dosing visit consisted of an initial in-house period (48 hours) following the trial

product administration (Visit 2 and 3). The subject was discharged from the clinic 48 hours after the trial product administration, or later if deemed necessary by the Investigator, and returned at 72, 96 and 120 hours after the trial product administration (Visits 2 and 3) in order to have blood samples taken for pharmacokinetic (PK) analysis and blood glucose analysis. Finally, the subject attended a Follow-up Visit (Visit 4), 7-21 days after last dosing. The planned total duration of the trial for individual subjects was between 23 and 64 days.

**Number of Subjects Planned and Analysed**

In total, 36 subjects were screened, 27 were randomised and 26 exposed to trial product.. All 26 exposed subjects were included in the full analysis set and the safety analysis set

**Diagnosis and Main Criteria for Inclusion**

Healthy male or female subjects aged 18-55 years (both inclusive) with a body mass index 18.0-27.0 kg/m<sup>2</sup> (both inclusive) and fasting plasma glucose ≤ 108 mg/dL (≤ 6.0 mmol/L).

Key exclusion criteria included donation of blood/plasma in the past month or > 500ml within 3 months before screening, use of prescription drugs within 3 weeks before screening, use of nonprescription drugs including over- the-counter medication, non-routine vitamins and herbal products within 3 weeks before screening, and smoking

**Test Product, Dose and Mode of Administration, Batch Number**

Insulin degludec (IDeg [M] IM1 or IDeg [M] IM2) (100 U/mL) in 3 mL (b) (4) cartridges was used to administer insulin at the dose level of 0.4 U/kg body weight as a subcutaneous (s.c.) injection.

| Trial Product                                    | Dose     | Batch Number | Expiry Date |
|--------------------------------------------------|----------|--------------|-------------|
| IDeg (M) IM1 100 U/mL in 3 mL (b) (4) cartridges | 0.4 U/Kg | QCQ0009      | 13 May 2011 |
| IDeg (M) IM2 100 U/mL in 3 mL (b) (4) cartridges | 0.4 U/Kg | QCQ0036      | 28 Oct 2011 |

**Duration of Treatment**

Two single injections of IDeg (M) IM1 or IDeg (M) IM2 administered on 2 separate dosing visits.

**Criteria for Evaluation – Efficacy**

*Pharmacokinetic variables*

- IDeg concentration in serum

*Pharmacodynamic variables*

- Glucose infusion rate
- Serum C-peptide

**Criteria for Evaluation – Safety**

- Adverse events (AEs)
- Laboratory safety variables
- Physical examination
- Vital signs
- Electrocardiogram
- Hypoglycaemic episodes

**Statistical Methods**

The pharmacokinetic and pharmacodynamic analyses were based on the Full Analysis Set (FAS), which included all randomised subjects. The safety analyses were based on the Safety Analysis Set, including all subjects, who received at least one dose of even one investigational product.

**Statistical Analysis of Primary Endpoint**

The primary endpoint was AUC<sub>IDeg,0-120h,SD</sub>, area under the serum IDeg concentration-time curve from 0 to 120 hours after single-dose and C<sub>max,IDeg,SD</sub>, maximum observed serum IDeg concentration after single-dose. AUC<sub>IDeg,0-120h,SD</sub> was calculated as the area under the IDeg-time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 120 hours. Missing values were imputed using linear interpolation. C<sub>max,IDeg,SD</sub> was determined as the maximum of all valid IDeg concentration measurements for each measurement series. In order to

investigate whether IDeg (M) IM1 and IDeg (M) IM2 are bioequivalent, the  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$  were analyzed separately using an analysis of variance (ANOVA) approach. Log transformed values are used in order to account for heteroscedasticity. The statistical model for each endpoint had a treatment, period and treatment by period interaction as fixed effects and subject as a random effect. The model was reduced by removing the effect of treatment by period interaction (equivalent to an effect of the treatment sequence) if the p-value for this effect was larger than 1%. To test equivalence for the primary endpoints, the ratios between the two treatments (IDeg [M] IM1 and IDeg [M] IM2) were estimated and the corresponding 90% confidence interval was constructed. For  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$ , equivalence between IDeg (M) IM1 and IDeg (M) IM2 was claimed if the 90% confidence interval was fully within the interval [80%;125%]. Thus, the null hypothesis was that the two treatments (IDeg [M] IM1 and IDeg [M] IM2) are non-equivalent and the alternative hypothesis was that they are equivalent. Bioequivalence between IDeg (M) IM1 and IDeg (M) IM2 was claimed if the null hypothesis was rejected for both  $AUC_{IDeg,0-120h,SD}$  and  $C_{max,IDeg,SD}$ .

### ***Statistical Analysis of Secondary Endpoints***

#### ***Secondary Pharmacokinetic Endpoints***

The secondary PK endpoints derived from the IDeg concentration-time curves after administration of IDeg included  $AUC_{IDeg,SD}$  in the time periods 0-24 hours and 0- $\infty$  after single-dose, time to  $C_{max,IDeg,SD}$  ( $t_{max,IDeg,SD}$ ), terminal half-life for IDeg ( $t_{1/2,IDeg}$ ), mean residence time for IDeg ( $MRT_{IDeg}$ ), apparent serum clearance of IDeg after s.c. administration ( $CL/F_{IDeg}$ ), apparent volume of distribution of IDeg after s.c. administration, estimated during the terminal phase ( $V_z/F_{IDeg}$ ). All secondary PK endpoints were summarised by treatment and dose level using descriptive statistics.

#### ***Secondary Pharmacodynamic Endpoints***

The secondary pharmacodynamic endpoints included area under the glucose infusion rate (GIR) curve from 0-24 hours after single-dose ( $AUC_{GIR,SD}$ ) as well as maximum glucose infusion rate after single-dose ( $GIR_{max,SD}$ ), and time to  $GIR_{max,SD}$  ( $t_{GIR_{max,SD}}$ ) after single-dose.  $AUC_{GIR,0-24h,SD}$  was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. Maximum glucose infusion rate after single-dose ( $GIR_{max,SD}$ ), and time to  $GIR_{max,SD}$  ( $t_{GIR_{max,SD}}$ ) after single-dose were derived from smoothed GIR curve. All secondary pharmacodynamic endpoints were summarized by treatment and dose level using descriptive statistics.

#### ***Statistical Analysis of Safety Endpoints***

The safety endpoints included AEs, laboratory safety variables, physical examination, vital signs, electrocardiogram and hypoglycemic episodes.

A treatment emergent AE was defined as an AE with onset after first trial product administration and no later than 7 days after the last trial product administration and was assigned to the latest treatment. A hypoglycemic episode was defined as treatment emergent if the onset of the episode was on or after first trial product administration and no later than 7 days after the last trial product administration. All safety endpoints were listed and summarized using descriptive statistics.

#### ***Demography of Trial Population***

Of the 26 exposed subjects, 19 (73%) were male and 7 (27%) were female. The entire test population was White (100%). The subjects' mean age was 38.4 years, and mean BMI was 24 kg/m<sup>2</sup>.

#### ***Efficacy Results and Conclusions***

##### ***Pharmacokinetic***

- IDeg (M) IM2 was confirmed to be bioequivalent to IDeg (M) IM1 for the primary pharmacokinetic parameters  $AUC_{IDeg,0-120h}$  and  $C_{max}$  because the 90% confidence interval for the mean treatment ratio of IDeg (M) IM2/IDeg (M) IM1 was fully contained within the interval [0.8; 1.25]. Ratios for IDeg (M) IM2/IDeg (M) IM1 were 0.99 [CI90% 0.95; 1.03] for  $AUC_{IDeg,0-120h,SD}$  and 0.98 [CI90% 0.92; 1.05] for  $C_{max,IDeg,SD}$ .
- The extent of absorption in terms of  $AUC_{IDeg,0-inf}$  was identical for IDeg (M) IM1 and IDeg (M) IM2.

- Adjusting for drug content did not change the conclusion.
- No marked differences between IDeg (M) IM1 and IDeg (M) IM2 were seen for other secondary pharmacokinetic endpoints.

*Pharmacodynamic*

- The observed shapes of the mean GIR profiles were similar for IDeg (M) IM1 and IDeg (M) IM2.
- No marked differences between IDeg (M) IM1 and IDeg (M) IM2 were seen for other secondary PD endpoints.

**Safety Results and Conclusions**

- A total of 15 treatment-emergent adverse events were reported in 9 (34.6%) of 26 subjects; 8 events in 6 (23.1%) of the subjects when treated with IDeg (M) IM1, and 7 events in 5 (20.0%) of the subjects when treated with IDeg (M) IM2. No severe adverse events were reported.
- There were no serious adverse events and no medical events of special interest. No injection site reactions were reported.
- The number of hypoglycaemic episodes was low and all were asymptomatic.
- There were no clinically significant changes in vital signs, laboratory parameters, physical examination, or ECGs from Screening to Follow-up Visit.
- There were no obvious differences between the two groups for any of the safety assessments.

**Overall Conclusions**

The conclusions for this randomised, single-centre, single-dose, double-blind, two-period, cross-over bioequivalence trial between IDeg (M) IM1 and IDeg (M) IM2 in healthy subjects are:

- The two identical formulations IDeg (M) IM2 and IDeg (M) IM1 are bioequivalent.
- IDeg (M) IM2 and IDeg (M) IM1 are well tolerated, and no safety issues are identified in this trial.

*The trial was conducted in accordance with the Declaration of Helsinki(2008) and ICH Good Clinical Practice(1996)*

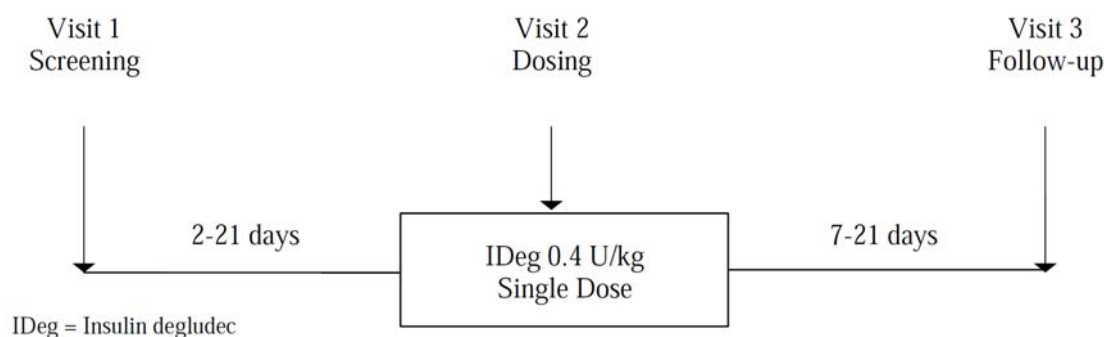
**Reviewer's Comment:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 7\%$ .

#### 4.2.4 Intrinsic Factor PK Study in Hepatic Impairment (Non-diabetic) (NN1250-1989)

**Rationale:** The rationale for this trial was to provide information as to whether the pharmacokinetics of a single dose of 0.4 U/kg of IDeg administered to subjects with impaired hepatic function is altered to such an extent compared to subjects with normal hepatic function that the dose should be adjusted.

**Study Design:** The study design is presented in the figure below:



Child-Pugh Criteria for Assessment of Impaired Liver Function:

|                                  | Points Scored for Observed Findings |           |                     |
|----------------------------------|-------------------------------------|-----------|---------------------|
|                                  | 1                                   | 2         | 3                   |
| Encephalopathy <sup>a</sup>      | none                                | 1 or 2    | 3 or 4 <sup>#</sup> |
| Ascites                          | absent                              | slight    | moderate            |
| Serum bilirubin (μmol/L)         | < 34.2                              | 34.2-51.3 | >51.3               |
| Or Serum bilirubin (mg/dL)       | <2                                  | 2-3       | >3                  |
| Serum albumin (g/L)              | > 35                                | 28-35     | <28                 |
| Or Serum albumin (g/dL)          | >3.5                                | 2.8-3.5   | <2.8                |
| Prothrombin time (sec prolonged) | <4                                  | 4-6       | >6                  |

<sup>a</sup>Grade 0: normal consciousness, personality, neurological examination, electro encephalogram

<sup>a</sup>Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves

<sup>a</sup>Grade 2: lethargic, time-disoriented, inappropriate, asterixis, ataxia, slow triphasic waves

<sup>a</sup>Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves

<sup>a</sup>Grade 4: unrousable coma, no personality/behaviour, decerebrate, slow 2-3 cps delta activity

<sup>#</sup>Subjects with encephalopathy grade 3 and 4 were excluded

#### Conversion from Points to Groups of Different Degrees of Hepatic Impairment:

- Child-Pugh Grade A, mild hepatic impairment: 5-6 points
- Child-Pugh Grade B, moderate hepatic impairment: 7-9 points
- Child-Pugh Grade C, severe hepatic impairment: 10-15 points

#### Allocation to Hepatic Function Groups by the Severity of Liver Disease

- Group 1 Healthy volunteers
- Group 2 Child Pugh grade A
- Group 3 Child Pugh grade B
- Group 4 Child Pugh grade C

The study synopsis is as follows:

**Title of Trial**

A Trial Investigating the Pharmacokinetic and Safety Profiles of NN1250 in Subjects with Mild, Moderate and Severe Degrees of Hepatic Impairment and in Subjects with Normal Hepatic Function

**Objectives****Primary Objective**

- To investigate the pharmacokinetic (PK) exposure of insulin degludec (IDeg) after a single dose of insulin degludec (IDeg) in subjects with mild, moderate and severe degrees of hepatic impairment and in subjects with normal hepatic function

**Secondary Objectives**

- To characterize the PK profile of IDeg after a single dose of IDeg in subjects with mild, moderate and severe degrees of hepatic impairment and in subjects with normal hepatic function
- To characterize the safety profile after a single dose of IDeg in subjects with mild, moderate and severe degrees of hepatic impairment and in subjects with normal hepatic function

**Methodology**

This was a single centre, single dose, open label, parallel group trial investigating the pharmacokinetics and safety profile of IDeg in subjects with various degrees of hepatic impairment and in subjects with normal hepatic function. The trial consisted of 3 visits: a screening visit (Visit 1) followed by a single dosing visit (Visit 2) and a follow up visit (Visit 3) within 7 to 21 days after dosing. Subjects were allocated to 1 of the 4 hepatic function groups depending on extent of hepatic impairment (normal hepatic function or hepatic impairment classified as Child-Pugh grade A, B or C). On the dosing day, each subject received a single 0.4 U/kg s.c. dose of IDeg. Subjects were admitted to the clinic the day before dosing (in the evening before 20:00 hours), and stayed in-house for the first 48 hours after trial drug administration, or longer if deemed necessary by the Investigator. A baseline urine sample was collected prior to trial product administration, and fractionated urine collection was performed to determine IDeg concentration/excretion after trial product administration at pre-defined intervals (0-8 h, 8-16 h and 16-24 h). Subjects returned to the clinic at 72, 96 and 120 hours after trial drug administration in order to have blood samples taken for serum IDeg and blood glucose analysis.

**Number of Subjects Planned and Analyzed**

A total of 6 subjects in each of the 4 hepatic function groups were planned to complete the trial. A total of 34 subjects were screened, 24 subjects were exposed to trial product (6 in each group). All 24 subjects completed the trial and were included in the full analysis set and safety analysis set.

**Diagnosis and Main Criteria for Inclusion**

Male or female subjects with normal hepatic function (6 subjects), and male or female subjects with stable hepatic impairment classified as Child-Pugh grade A, B or C (6 subjects per group) as assessed by the investigator. Subjects with hepatic impairment were permitted to have diabetes mellitus. Age between 18 and 75 years (both inclusive) and Body Mass Index between 18.5 and 40.0 kg/m<sup>2</sup> (both inclusive).

**Test Product, Dose and Mode of Administration, Batch Number**

IDeg (100 U/mL), 3 mL (b) (4) cartridges (batch number VCQ0013 and expiry date (b) (4)) administered s.c. as a single dose of 0.4 U/kg into a lifted skin fold on the anterior surface of the thigh.

**Duration of Treatment**

Subjects received 1 single dose of IDeg. The total duration of the trial was 10 to 43 days for the individual subject.

**Criteria for Evaluation – Efficacy**

PK assessments in the present trial included:

- IDeg in serum
- IDeg in urine

**Criteria for Evaluation – Safety**

- Adverse events (AEs)
- Physical examination
- Vital signs
- ECG
- Hypoglycaemic episodes
- adverse events describing injection site reactions
- Clinical laboratory tests

**Statistical Methods**

The pharmacokinetic analyses were based on the Full Analysis Set, which included all exposed subjects. The safety analyses were based on the Safety Analysis Set, which included all subjects exposed to the investigational product.

#### ***Statistical Analysis of the Primary Pharmacokinetic Endpoint***

The primary endpoint was derived from the individual serum IDeg concentration-time curves after single dose:

- $AUC_{IDeg,0-120h,SD}$ , area under the serum IDeg concentration-time curve from 0 to 120 h after single dose  
 $AUC_{IDeg,0-120h,SD}$  was calculated as the area under the insulin concentration time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 120 hours.

The log transformed values of  $AUC_{IDeg,0-120h,SD}$  were analyzed in a linear normal model with hepatic function group and gender as categorical explanatory variables and age and  $\log(\text{weight})$  as continuous explanatory variables. Estimated mean ratios for each of the 3 groups with impaired hepatic function compared to the group with normal hepatic function were estimated together with two-sided 90% confidence intervals. The hypothesis of a monotonous trend in  $\log(AUC_{IDeg,0-120h,SD})$  with increasing impaired hepatic function was tested.

In addition, Spearman's rank-order correlation coefficient between  $AUC_{IDeg,0-120h,SD}$  and serum albumin concentration at Visit 2, Day 1 was calculated.

#### ***Statistical Analysis of the Secondary Pharmacokinetic Endpoints***

All the secondary PK endpoints were derived from the individual serum IDeg concentration-time curves after single dose.

- The log-transformed values of maximum serum IDeg concentration ( $C_{max,IDeg,SD}$ ), terminal half-life for IDeg based on 0-120 h ( $t_{1/2,IDeg,SD}$ ), mean residence time for IDeg ( $MRT_{IDeg,SD}$ ), apparent clearance of IDeg from 0-120 h ( $CL/F_{IDeg,SD}$ ) and apparent volume of distribution of IDeg estimated during the terminal phase ( $V_z/F_{IDeg,SD}$ ) were analysed using the same model as the primary endpoint. However, no formal testing of a monotonous trend was performed. Spearman's rank-order correlation coefficient was calculated for  $C_{max,IDeg,SD}$  versus serum albumin and  $CL/F_{IDeg,SD}$  versus serum albumin.
- Time to maximum observed serum IDeg ( $t_{max,IDeg,SD}$ ) were analysed by use of non-parametric methods for independent samples using the Hodges-Lehmann estimator.
- Area under the serum IDeg concentration-time curve from 0 to infinity ( $AUC_{IDeg,0-\infty,SD}$ ),
- Time from trial product administration until the first time serum IDeg concentration > 100 pmol/L (onset of appearance) $_{IDeg,SD}$

#### ***Assessment of Safety Endpoints***

The safety endpoints included adverse events, laboratory safety variables, physical examination, vital signs, electrocardiogram, hypoglycemic episodes and injection site reactions.

All safety endpoints were listed and summarized using descriptive statistics.

#### ***Demography of Trial Population***

All enrolled subjects were white and were in the range between 23 and 62 years of age across the 4 hepatic function groups. The age across the 4 hepatic function groups was well balanced, although the subjects in the group of severe hepatic function were generally older than the subjects in the other 3 hepatic function groups. In total 8 male and 16 female subjects were included across the 4 hepatic function groups. The overall inclusion of male and female subjects was balanced with 2 males and 4 females per hepatic function group. The weight of subjects in the groups of moderate and severe hepatic function was higher than in the other 2 hepatic function groups.

#### ***Efficacy Results and Conclusions***

- Exposure to IDeg as measured by  $AUC_{IDeg,0-120h,SD}$  was not affected by degree of hepatic impairment. Although  $AUC_{IDeg,0-120h,SD}$  appeared to decrease with increasing degree of hepatic impairment, the statistical test of a trend was not significant (monotonous trend p-value: 0.11)
- No statistically significant differences were found between subjects with normal versus impaired hepatic function for  $C_{max,IDeg,SD}$ ,  $CL/F_{IDeg,SD}$  and  $t_{max,IDeg,SD}$ .

|                                   | N | Mean ratio                  | 90% CI       |
|-----------------------------------|---|-----------------------------|--------------|
| <b>AUC<sub>IDeg, 0-120h</sub></b> |   |                             |              |
| Mild <sup>a</sup> /Normal         | 6 | 0.99                        | [0.83; 1.19] |
| Moderate <sup>b</sup> /Normal     | 6 | 0.92                        | [0.76; 1.11] |
| Severe <sup>c</sup> /Normal       | 6 | 0.82                        | [0.66; 1.01] |
| <b>C<sub>max IDeg</sub></b>       |   |                             |              |
| Mild <sup>a</sup> /Normal         | 6 | 0.90                        | [0.67; 1.22] |
| Moderate <sup>b</sup> /Normal     | 6 | 0.76                        | [0.56; 1.04] |
| Severe <sup>c</sup> /Normal       | 6 | 0.74                        | [0.52; 1.04] |
| <b>CL/F<sub>IDeg</sub></b>        |   |                             |              |
| Mild <sup>a</sup> /Normal         | 6 | 1.00                        | [0.84; 1.20] |
| Moderate <sup>b</sup> /Normal     | 6 | 1.06                        | [0.88; 1.28] |
| Severe <sup>c</sup> /Normal       | 6 | 1.20                        | [0.97; 1.47] |
|                                   | N | Hodges-Lehmann estimate (h) | 90% CI       |
| <b>t<sub>max IDeg</sub></b>       |   |                             |              |
| Mild <sup>a</sup> /Normal         | 6 | 1.0                         | [-3.0; 4.0]  |
| Moderate <sup>b</sup> /Normal     | 6 | -0.5                        | [-5.0; 4.0]  |
| Severe <sup>c</sup> /Normal       | 6 | -0.5                        | [-4.0; 4.0]  |

- Negligible concentrations of intact IDeg were recovered in the urine, suggesting minimal renal clearance of IDeg.
- Renal clearance (CLR<sub>IDeg,SD</sub>) could not be calculated due to too few observations above LLOQ.

**Safety Results and Conclusions**

- No adverse events were reported
- No medical events of special interest were reported
- A total of 12 treatment emergent hypoglycemic episodes (ADA classification – PG ≤3.9mmol/L [70 mg/DL]) were reported 8 subjects – none of which were categorized as severe:
  - 2 episodes occurred in 2 subjects with normal hepatic function; 3 in 2 subjects with mild hepatic impairment; in 3 subjects with moderate impairment; and 1 in 1 subject with severe impairment.
  - 1 nocturnal episode was reported by a subject with normal hepatic function
- There were no clinically significant findings in laboratory parameters, vital signs, physical examination, or ECG.

**Overall Conclusions**

The conclusions from this single-centre, single dose, open-label, parallel-group trial investigating the pharmacokinetic properties and safety profile of IDeg in subjects with normal hepatic function and subjects with varying degrees of hepatic impairment are:

- Total exposure (AUC<sub>IDeg,0-120h,SD</sub>) of IDeg is similar in subjects with normal and impaired hepatic function.
- The pharmacokinetic properties of IDeg are similar in subjects with normal and impaired hepatic function.
- IDeg is well-tolerate in subjects with normal and impaired hepatic function and no safety issues are identified in this trial.

*The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (2008).*

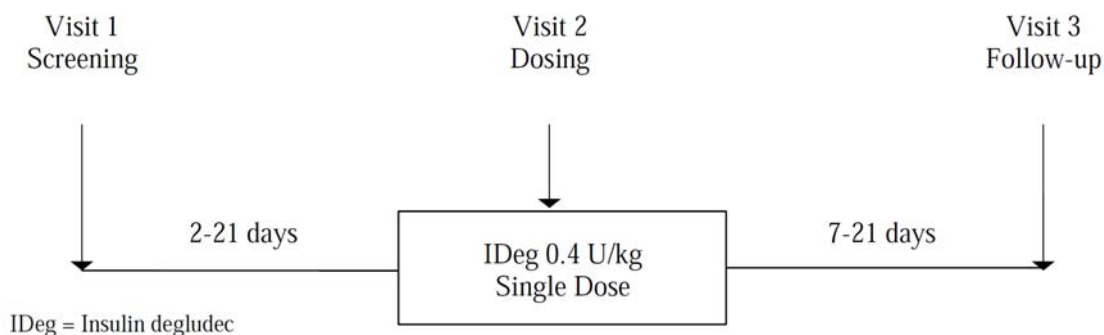
**Reviewer’s Comment:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within ±4%.

#### 4.2.5 Intrinsic Factor PK Study in Renal Impairment (Non diabetic) (NN1250-1990)

**Rationale:** The rationale for this trial was to provide information as to whether the pharmacokinetics of a single dose of 0.4 U/kg of IDeg administered to subjects with impaired renal function is altered to such an extent compared to subjects with normal renal function that the dose should be adjusted.

**Study Design:** The study design is presented in the figure below:



Groups based on pre-defined creatinine clearance criteria at screening:

- normal renal function
  - mild renal impairment
  - moderate renal impairment
  - severe renal impairment
  - end stage renal disease (ESRD)
- } Non-ESRD

The study synopsis is as follows:

##### **Title of Trial**

A trial investigating the pharmacokinetic and safety profiles of NN1250 (IDeg) in subjects with various degrees of renal impairment and in subjects with normal renal function.

##### **Objectives**

###### **Primary Objective:**

- To investigate the pharmacokinetic (PK) exposure of insulin degludec (IDeg) after a single dose of IDeg in subjects with different degrees of renal impairment and in subjects with normal renal function.

###### **Secondary Objectives:**

- To characterize the PK profile of IDeg after a single dose of IDeg in subjects with different degrees of renal impairment and in subjects with normal renal function.
- To characterize the safety profile after a single dose of IDeg in subjects with different degrees of renal impairment and in subjects with normal renal function.
- To investigate the impact of haemodialysis on the serum clearance of IDeg.

##### **Methodology**

This was a single-centre, single-dose, open-label, parallel-group trial investigating the pharmacokinetics and safety profiles of IDeg in subjects with normal renal function and subjects with different degrees of renal impairment (including subjects with end stage renal disease (ESRD) requiring haemodialysis). Subjects were allocated to 1 of 5 renal function groups (6 subjects in each group - normal renal function, mild, moderate or severe renal impairment, and ESRD) based on creatinine clearance (estimated using the Cockcroft & Gault formula) at screening.

The trial consisted of either three or four visits depending on whether subjects were allocated to the non-ESRD renal

function groups (normal renal function, mild, moderate or severe renal impairment), or to the ESRD group.

For subjects allocated to non-ESRD renal function groups, the trial consisted of 3 visits: a screening visit followed by a dosing visit (2-21 days after screening) and a follow-up visit (7-21 days after dosing). For subjects with ESRD, the trial consisted of 4 visits: a screening visit followed by (2-21 days after), 2 dosing visits separated by 13-21 days (one performed after the end of a haemodialysis session (to evaluate the pharmacokinetics of IDeg outside of haemodialysis; and one 13 hours prior to starting a haemodialysis session to evaluate the pharmacokinetics of IDeg during haemodialysis) and a follow-up visit (7-21 days after the last dose). Standard safety parameters (physical examination, vital signs, electrocardiogram (ECG), laboratory safety variables, and hypoglycemic episodes) were evaluated at screening, at dosing visit(s), and at the follow-up visit. Hematology and biochemistry assessments were performed for all subjects at screening, the 1st dosing and at the follow-up visit.

Subjects received a single 0.4 U/kg dose of IDeg in the thigh at each dosing visit, and were required to stay in-house until 48 hours after administration (or longer if deemed necessary by the investigator). Serum IDeg concentrations were monitored for a period of 120 hours for subjects in the non-ESRD renal function groups, and for approximately 68 hours for subjects with ESRD (as this was the maximum time between two haemodialysis sessions).

#### **Number of Subjects Planned and Analysed**

Fifty-four (54) subjects were planned for screening, with the aim of enrolling 30 subjects to complete the trial (6 subjects each in 5 renal function groups). Non-completers were to be replaced.

A total of 48 subjects were screened, and 32 subjects were exposed to IDeg and completed the trial. Although all 32 subjects were included in the safety analysis set, only 30 were included in the full analysis set for pharmacokinetic evaluation. Two subjects in the normal renal function group were replaced due to non-fulfillment of the inclusion criteria, and were excluded from the pharmacokinetic analyses.

#### **Diagnosis and Main Criteria for Inclusion**

Male and female subjects aged between 18-85 years (both inclusive) meeting the pre-defined creatinine clearance criteria (estimated by the Cockcroft and Gault formula) for any of the renal function groups and body mass index (BMI)

40.0 kg/m<sup>2</sup> were included in the trial.

Key exclusion criteria included:

- any disease or condition which the Investigator felt would interfere with the trial except for conditions associated with renal (Impaired glucose tolerance or diabetes was accepted in subjects with renal impairment)
- normal subjects - use of prescription/non-prescription drugs (including over-the-counter medication, non-routine vitamins and herbal products within 3 weeks prior to dosing of investigational product [use of oral contraceptives, diuretics, non-cardioselective betablockers, topically applied medication (eye-/nose-drops and cremes) and occasional use of metaclopramide, ibuprofen and paracetamol is permitted];
- subjects with renal impairment -any treatment with agents known to alter tubular secretion of creatinine, such as cimetidine, trimethoprim and cibenzoline within 14 days or 5 half-lives prior to first dosing of investigational medicinal product, monoamine oxidase (MAO) inhibitors; thyroid hormones (unless the use of these has been stable during the past 3 months) or growth hormone

#### **Test Product, Dose and Mode of Administration, Batch Number**

IDeg (100 U/mL), 3 mL <sup>(b) (4)</sup> cartridges (batch number VCQ0013 and expiry date 09 December 2010) administered s.c. as a single dose of 0.4 U/kg into a lifted skin fold on the anterior surface of the thigh.

#### **Duration of Treatment**

Subjects with normal renal function or mild, moderate, or severe renal impairment received a single dose of IDeg, while subjects with ESRD received 2 single doses on separate dosing days.

#### **Criteria for Evaluation – Efficacy**

PK assessments in the present trial included:

- IDeg in serum
- IDeg in urine
- IDeg in dialysate

#### **Criteria for Evaluation – Safety**

- Adverse events (AEs)
- Physical examination
- Vital signs
- Electrocardiogram
- Hypoglycemic episodes
- Clinical laboratory tests (hematology, biochemistry and urinalysis)

## Statistical Methods

The pharmacokinetic analyses were based on the full analysis set, which included all exposed subjects who fulfilled the trial inclusion criteria. The safety analyses were based on the Safety Analysis Set, which included all subjects exposed to IDeg.

### Statistical Analysis of the Primary Pharmacokinetic Endpoint

The primary endpoint was derived from the individual serum IDeg concentration-time curves after single dose:

- AUC<sub>IDeg,0-120h,SD</sub> (area under the serum IDeg concentration-time curve from 0 to 120 hours after single-dose) AUC<sub>IDeg,0-120h,SD</sub> was calculated as the area under the insulin concentration time profile using the linear trapezoidal technique based on observed values and actual measurement times between 0 and 120 hours.

The primary analysis of AUC<sub>IDeg,0-120h,SD</sub> was performed in a linear regression model. The log transformed endpoint was used as the dependent variable and the log transformed values of creatinine clearance, estimated by the Cockcroft & Gault formula from data on the screening visit, was the independent variable. Furthermore, the model included gender as categorical explanatory variable and age and log transformed weight, measured at Visit 2, as continuous explanatory variables. Subjects with ESRD were not included in the analysis since any linear relationship between log(AUC) and log(creatinine clearance) could be invalidated due to the ESRD. Furthermore, the maximal time span between haemodialysis sessions for these subjects was 68 hours.

In addition, Spearman's rank-order correlation coefficient between AUC<sub>IDeg,0-120h,SD</sub> and serum albumin concentration at Visit 2, Day 1 was calculated.

### Statistical Analysis of the Secondary Pharmacokinetic Endpoints

#### Non-ESRDrenalfunctiongroups:

The following secondary pharmacokinetic endpoints were derived from the individual serum insulin concentration-time curves after single-dose:

- AUC<sub>IDeg,0-□,SD</sub>, C<sub>max,IDeg,SD</sub>, t<sub>max,IDeg,SD</sub>, t<sub>1/2,IDeg,SD</sub>, MRT<sub>IDeg,SD</sub>, CL/F<sub>IDeg,SD</sub>, V<sub>z/FIDeg,SD</sub>, onset of appearance<sub>IDeg,SD</sub>, and CL<sub>R,IDeg,SD</sub>

| Endpoint                 | N  | Estimated slope | 95% CI          | P-value |
|--------------------------|----|-----------------|-----------------|---------|
| C <sub>max,IDeg,SD</sub> | 24 | -0.227          | [-0.496; 0.043] | 0.09    |
| CL/F <sub>IDeg,SD</sub>  | 24 | 0.247           | [-0.003; 0.496] | 0.05    |
| t <sub>1/2,IDeg,SD</sub> | 24 | 0.121           | [-0.092; 0.335] | 0.25    |
| MRT <sub>IDeg,SD</sub>   | 24 | 0.073           | [-0.063; 0.209] | 0.27    |

The endpoints are log-transformed and analysed using a linear regression ANOVA model with log creatinine clearance at screening, sex, age at baseline and log body weight at baseline as fixed effects.

C<sub>max,IDeg,SD</sub>, t<sub>1/2,IDeg,SD</sub>, MRT<sub>IDeg,SD</sub>, CL/F<sub>IDeg,SD</sub> and V<sub>z/FIDeg,SD</sub>, were analyzed using the same linear regression model as described for the primary analysis of AUC<sub>IDeg,0-120h,SD</sub>. The log transformed values for each of the endpoints were included as the dependent variable. Subjects with ESRD were not included in the analyses.

The analysis of t<sub>max,IDeg,SD</sub> was performed by use of non-parametric methods for independent samples. The difference between the group of subjects with normal renal function and each of the 3 groups of subjects with renal impairment was estimated together with a 95% confidence interval (CI) using the Hodges-Lehmann estimator. Subjects with ESRD were not included in the analyses.

Spearman's rank-order correlation coefficient between both C<sub>max,IDeg,SD</sub> and CL/F<sub>IDeg,SD</sub>, and serum albumin concentrations were also calculated.

#### ESRDgroup:

The subjects with ESRD received two doses of IDeg, one when no dialysis was performed (IDeg was administered immediately after the end of haemodialysis - Visit 2) and one during haemodialysis (IDeg administered approximately 13 hours before haemodialysis - Visit 3)

The following secondary pharmacokinetic endpoints were derived from the individual serum insulin concentration-time curves after single-dose when **no dialysis** was performed:

- AUC<sub>IDeg,0-inf,SD</sub>, AUC<sub>IDeg,0-68h,SD</sub>, AUC<sub>IDeg,13-17h,SD</sub>, C<sub>max,IDeg,SD</sub>, t<sub>max,IDeg,SD</sub>, t<sub>1/2,IDeg,SD</sub>, MRT<sub>IDeg,SD</sub>, CL/F<sub>IDeg,SD</sub>, V<sub>z/FIDeg,SD</sub>, onset of appearance<sub>IDeg,SD</sub>, CL<sub>R,IDeg,SD</sub>

The following secondary pharmacokinetic endpoints were derived from the individual serum insulin concentration-time curves after single-dose **during dialysis**:

- E<sub>IDeg,SD</sub>, Fractional extraction<sub>IDeg,SD</sub> and C<sub>dialysate,IDeg,SD</sub>

The logarithm of CL/FIDeg,SD was analyzed in a mixed model with visit as fixed effect and subject as random effect. From the model the effect of haemodialysis was estimated by the mean ratio between the two visits together with a 95% CI. The estimates for the remaining endpoints were summarized by descriptive statistics.

#### **Assessment of Safety Endpoints**

The safety endpoints included adverse events, laboratory safety variables, physical examination, vital signs, electrocardiogram and hypoglycemic episodes. All safety endpoints were listed and summarized using descriptive statistics.

#### **Demography of Trial Population**

A total of 32 subjects were exposed to the trial product. All enrolled subjects were white and were between 38 and 80 years of age across the 5 renal function groups. None of the subjects with normal renal impairment included in the full analysis set (FAS) had diabetes mellitus - 11 subjects with renal impairment had diabetes mellitus as a concomitant illness (2 of 6 subjects with mild impairment, 5 of 6 subjects with moderate impairment, 1 of 6 with severe impairment, and 3 of 6 with ESRD). As expected creatinine clearance rate decreased with increased renal impairment. Subjects with normal renal function, mild renal impairment or ESRD were generally younger (median age was between 5-12 years younger) than subjects with moderate or severe renal impairment. Sex distribution varied between groups, and was most skewed in the severe renal impairment group where 5 out of 6 subjects were female. Mean body weight/BMI was highest for subjects with moderate renal impairment (31.4 kg/m<sup>2</sup>) and lowest for subjects with severe renal impairment (25.2 kg/m<sup>2</sup>). All three parameters were included as fixed effects in the statistical model for all analyses of the primary and secondary pharmacokinetic endpoints.

#### **Efficacy Results and Conclusions**

##### Non-ESRDsubjects:

- Exposure to IDeg as measured by AUCIDeg,0-120h, SD was not statistically significantly affected by degree of renal impairment as measured by creatinine clearance (estimated slope: -0.254, 95% CI[-0.507; 0.000], P=0.05)
- Degree of renal impairment as measured by creatinine clearance did not have any statistically significant effect on C<sub>max</sub>,IDeg,SD, CL/FIDeg,SD, t<sub>1/2</sub>, IDeg, SD or MRTIDeg, SD

The endpoints are log-transformed and analysed using a linear regression ANOVA model with log creatinine clearance at screening, sex, age at baseline and log body weight at baseline as fixed effects.

- There was no obvious correlation between serum albumin and AUCIDeg,0-120h,SD, C<sub>max</sub>,IDeg,SD, or CL/FIDeg,SD
- Time to maximum IDeg concentration (t<sub>max</sub>IDeg, SD) appeared to decrease with increasing degree of renal impairment. t<sub>max</sub>IDeg,SD occurred statistically significantly later in subjects with normal renal function as compared with subjects with severe impaired renal function.
- Since rate of elimination of IDeg is likely to be limited by absorption, apparent volume of distribution (V<sub>Z</sub>/F) based on the terminal phase (V<sub>Z</sub>) is not considered physiologically meaningful for IDeg.
- Negligible concentrations of intact IDeg were detected in the urine, suggesting minimal renal clearance of IDeg.
- Renal clearance (CL<sub>R</sub>,IDeg,SD) could not be calculated due to too few observations above the lower limit of quantification.

##### ESRDsubjects:

- There was no statistically significant effect of haemodialysis on apparent serum clearance (CL/FIDeg).
- Negligible concentrations of intact IDeg were detected in dialysate, suggesting minimal clearance of IDeg during haemodialysis.

#### **Safety Results and Conclusions**

- A total of 4 adverse events were reported in 3 subjects: There were no severe events. all events were of mild (3 events) or moderate (1 event) severity. 1 mild adverse event (injection site reaction) was considered probably related to IDeg (and the device used to inject IDeg); the subject recovered fully. The most common adverse events were gastrointestinal events (nausea and vomiting) (3 events in 2 subjects).
- No treatment emergent serious adverse events or medical events of special interest were reported
- A total of 31 treatment emergent hypoglycemic episodes (ADA classification) were reported in 10 subjects; the vast majority were asymptomatic. No severe hypoglycemic episodes were reported. 3 documented symptomatic episodes were reported for 2 subjects with moderate or severe renal impairment. 12 nocturnal hypoglycemic episodes were reported (1 documented symptomatic and 11 asymptomatic). Hypoglycemic episodes occurred more frequently in subjects with ESRD as compared with subjects with mild, moderate or severe renal impairment (17 asymptomatic episodes in 4 subjects; 10 of these episodes were nocturnal). No difference in the incidence of hypoglycemic

episodes in relation to whether or not subjects with ESRD underwent haemodialysis was observed. No clinically significant changes in clinical laboratory parameters, vital signs, physical examination or ECG in any of the any renal function groups were reported

- No safety issues were observed in the present trial. IDeg was well-tolerated in subjects with different degrees of renal impairment.

**Overall Conclusions**

The conclusions from this single-centre, single dose, open-label, parallel-group trial investigating the pharmacokinetic properties and safety profile of IDeg in subjects with normal renal function and subjects with different degrees of renal impairment (including ESRD) are:

- Total exposure ( $AUC_{IDeg,0-120h,SD}$ ) of IDeg is similar in subjects with normal and impaired renal function.
- The pharmacokinetic properties of IDeg are similar in subjects with normal and impaired renal function.
- Haemodialysis does not affect clearance of IDeg ( $CL/F_{IDeg,SD}$ ) in subjects with ESRD.
- IDeg is well-tolerated in subjects with normal and impaired renal function, and no safety issues are identified in this trial.

*The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (2008).*

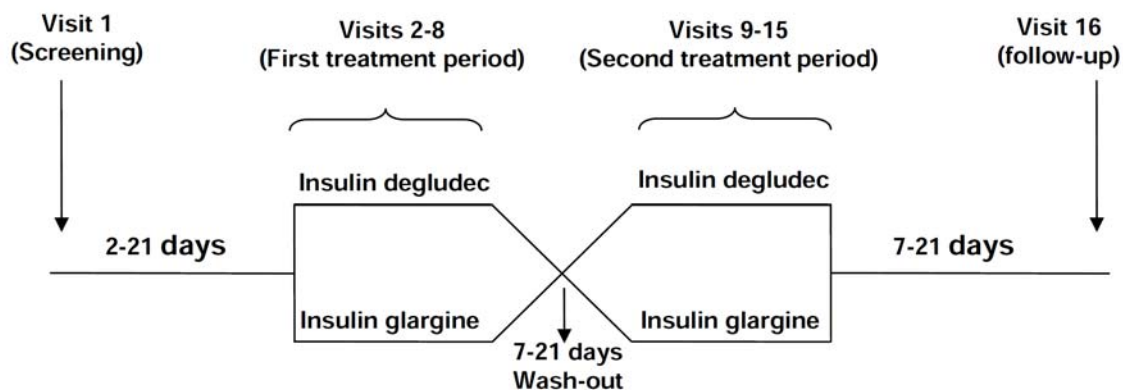
**Reviewer's Comments:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ ,  $\pm 6\%$ , and  $\pm 10\%$ , respectively.

#### 4.2.6 Intrinsic Factor PK Study in Geriatric Subjects and Young Adults with Type 1 DM (NN1250-1994)

**Rationale:** The rationale for this trial was to assess the pharmacodynamic (PD) and PK properties of IDeg at steady state in geriatric and younger subjects with type 1 diabetes. Furthermore, by assessing the PD and PK properties for both IDeg and IGLar (Insulin glargine) in the two age groups, it was possible to compare any age effects between the two products.

**Study Design:** The study design is presented in the figure below:



Groups based on age at screening:

Male or female aged 18-35 years (both inclusive) (younger adult group) or  $\geq 65$  years (geriatric group).

The study synopsis is as follows:

##### **Title of Trial**

A trial investigating the pharmacodynamic and pharmacokinetic properties of NN1250 in younger adult and geriatric subjects with Type 1 diabetes

##### **Objectives**

###### **Primary Objective:**

- To investigate the PD response to IDeg (based on the area under the glucose infusion rate curve from 0 to 24 hours at steady state [AUCGIR<sub>0-24h</sub>, SS]) in younger adult and geriatric subjects with type 1 diabetes

###### **Secondary Objectives:**

- To characterize the PD profile of IDeg at steady state in younger adult and geriatric subjects with type 1 diabetes
- To investigate the PK exposure of IDeg at steady state in younger adult and geriatric subjects with type 1 diabetes
- To characterize the PK profile of IDeg after single-dose and at steady state in younger adult<sup>i</sup> and geriatric subjects with type 1 diabetes
- To evaluate PK trough values towards the steady state level
- To compare the PK and PD properties of IDeg between the two different age groups
- To compare the effects of age on IDeg PK and PD properties with the effects of age on IGLar PK and PD properties

- To assess the safety and tolerability of IDeg in younger adult and geriatric subjects with type 1 diabetes

### **Methodology**

This was a single-centre, double-blind, randomized, two-period cross-over, multiple dose trial investigating the pharmacodynamic (PD) and pharmacokinetic (PK) properties of insulin degludec (IDeg) and insulin glargine (IGlar) in younger adult (18-35 years) and geriatric ( $\geq 65$  years) subjects with type 1 diabetes.

Each subject was randomly allocated to two treatment periods of 6 days of once-daily subcutaneous (s.c.) dosing with IDeg and IGLar, respectively; at a predefined fixed dose level (0.4 U/kg). During the treatment periods blood glucose levels were controlled by additional bolus injections of insulin aspart (IAsp) supervised by the investigator on a daily basis. The trial consisted of a screening visit (Visit 1) followed by two treatment periods (Visits 2-8 and 9-15) and a follow-up visit (Visit 16). The two treatment periods were separated by a wash-out period (7-21 days) where the subjects resumed their normal insulin treatment.

Treatment Period 1 consisted of an initial in-house period (Visit 2) where the subject stayed in-house for 48 hours after the first investigational product administration, or longer if deemed necessary by the investigator. During this period, the first 3 doses of IDeg or IGLar were administered. The PK response was evaluated by collecting blood samples for PK assessment before the first investigational product administration, frequently thereafter for 24 hours (IGlar and IDeg) and immediately before all subsequent investigational product administrations. On the fourth and fifth dosing day (Visits 3-4), the subject visited the clinic daily. At these daily visits, a blood sample for PK assessment was collected and thereafter the investigational product was administered. During the hours before (from arrival at the clinic) and for 48 hours after the last dose administration (Visit 5), blood samples were collected regularly for steady state PK assessment. The steady state PD response was evaluated during a 26-hour euglycemic glucose clamp starting after the last investigational product administration. The subject was discharged from the clinic 48 hours after the last investigational product administration and returned at 72, 96 and 120 hours after the last investigational product administration (Visits 6-8) in order to have blood samples taken for PK assessment and plasma glucose (PG) analysis. After a washout period of 7 to 21 days, subjects entered treatment Period 2. Treatment Period 2 procedures (Visits 9 to 12) were similar to Period 1. Finally, the subject attended a follow-up visit (Visit 16) 7-21 days after last dosing of the last treatment period (Visit 12).

### **Number of Subjects Planned and Analyzed**

Planned numbers of subjects to complete the trial were 24 (12 geriatric and 12 younger). A total of 42 subjects were screened, 27 were randomized (younger adult = 13; and geriatric = 14) and 26 completed the trial. All 13 and 14 subjects exposed to the trial products in the geriatric and younger groups, respectively were included in the full analysis set (FAS) and safety analysis set.

### **Diagnosis and Main Criteria for Inclusion**

Male or female subjects aged 18-35 years (both inclusive) (younger adult group) or  $\geq 65$  years (geriatric group), with type 1 diabetes mellitus (as diagnosed clinically)  $\geq 12$  months and a body mass index (BMI) of 18.0-28.0 kg/m<sup>2</sup> (both inclusive) were included in the trial.

Subjects were excluded from the trial if they had donated any blood or plasma in the past month or more than 500 mL within 3 months prior to screening, were smokers or used nicotine gum or transdermal nicotine patches during the inpatient period. A subject was to be withdrawn if there was a withdrawal of consent, protocol deviation or pregnancy or intention of becoming pregnant.

### **Test Product, Dose and Mode of Administration, Batch Number**

IDeg 100 U/mL, 3 mL <sup>(b)</sup><sub>(4)</sub> cartridges, 0.4 U/kg, administered s.c. into a lifted skin fold on the anterior surface of the thigh. Batch no.: VCQ0013

### **Duration of Treatment**

Two 6-day treatment periods with once-daily dosing of either IDeg and IGLar in the first period, and the alternate insulin in the second period

### **Reference Therapy, Dose and Mode of Administration, Batch Number**

- IGLar (Lantus<sup>®</sup>) 100 U/mL, 3 mL cartridges, 0.4 U/kg, administered s.c. into a lifted skin fold on the anterior surface of the thigh. Batch no.: 40U607.

## **Criteria for Evaluation – Pharmacodynamics and Pharmacokinetics**

### **Pharmacodynamics**

- Glucose infusion rate (GIR)
- PG concentration

### **Pharmacokinetics**

- Serum concentration of IDeg
- Serum concentration of IGlár

### **Criteria for Evaluation – Safety**

The secondary safety endpoints were:

- Adverse events (AEs)
- Laboratory safety variables (hematology, biochemistry, urinalysis, coagulation)
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Hypoglycemic episodes

### **Statistical Methods**

#### **Statistical Analysis of Primary Pharmacodynamic Endpoint:**

The primary endpoint  $AUC_{GIR,\tau,SS}$  (for IDeg) was derived from the individual GIR profiles for the IDeg treatment.  $AUC_{GIR,\tau,SS}$  was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. Last observation carried forward was used if there were missing values in the end of the assessment interval and if blood glucose levels escaped (i.e. increased to  $>11.1$  mmol/L [ $200$  mg/dL]). If blood glucose escaped before insulin action,  $AUC_{GIR,\tau,SS}$  was not calculated. If blood glucose had not escaped and there were missing values in the end of the assessment interval, a decision was taken during the blinded data review on how to handle the specific profile (possibly not to calculate  $AUC_{GIR,\tau,SS}$ ).

The log-transformed  $AUC_{GIR,\tau,SS}$  for the IDeg treatment was analyzed using an analysis of variance (ANOVA) method with age-group (Young/Geriatric) and treatment-period (Period 1/Period 2) as fixed factors. The estimated mean age effects for absolute values and estimated mean treatment differences (or ratios) were calculated together with two-sided 95% confidence intervals (CIs).

*Sensitivity Analysis:* The log-transformed  $AUC_{GIR,\tau,SS}$  for IDeg was analyzed using an ANOVA method with only age-group (Young/Geriatric) as a fixed factor.

#### **Statistical Analysis of Secondary Pharmacodynamic Endpoints:**

The following secondary PD endpoints were derived from the individual GIR profile at steady state:  $AUC_{GIR,\tau,SS}$ ,  $AUC_{GIR,0-12h,SS}$  (for IGlár),  $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ ,  $GIR_{max,SS}$ ,  $tGIR_{max,SS}$ ,  $AUC_{FGIR,\tau,SS}$ ,  $AUC_{FGIR,0-12h,SS}$ ,  $AUC_{FGIR,12-24h,SS}$ , Duration of action<sub>SS</sub> and  $PG_{24h,SS}$ .

*Age Analysis:* The log-transformed PD endpoints,  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$ , were analysed using the same model as for the primary endpoint. A separate analysis was made for the IDeg and IGlár treatments, noting that the analysis of  $AUC_{GIR,\tau,SS}$  for IDeg was the primary analysis.

*Drug-age Analysis:* The log-transformed PD endpoints,  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$ , for both treatments were analyzed using an ANOVA method with treatment, age group, interaction between treatment and age group, and treatment period as fixed factors, and subject as random effect. Based on this

model the difference between age groups was estimated for both IDeg and IGlar, and the p-value for the test of the interaction (i.e. a test for different age group effects for the two treatments) was calculated.

#### **Statistical Analysis of Secondary Pharmacokinetic Endpoints:**

The following secondary PK endpoints were to be derived from the insulin concentration-time curves:  $AUC_{Ins,0-24h,SD}$ ,  $C_{max,Ins,SD}$ ,  $t_{max,Ins,SD}$ , onset of appearance<sub>IDeg</sub>,  $AUC_{Ins,\tau,SS}$ ,  $AUC_{Ins,0-12h,SS}$ ,  $AUC_{Ins,0-12h,SS}/AUC_{Ins,\tau,SS}$ ,  $C_{max,Ins,SS}$ ,  $t_{max,Ins,SS}$ ,  $t_{1/2,Ins,ss}$ ,  $AUCF\%_{Ins,\tau,SS}$ ,  $AUCF\%_{Ins,0-12h,SS}$  and  $AUCF\%_{Ins,12-24h,SS}$ .

In addition, the following PK endpoints were to be derived:  $ITC_{Ins}$ ,  $AUC_{Ins,\tau,SS}/AUC_{Ins,0-24h,SD}$  and  $C_{max,Ins,SS}/C_{max,Ins,SD}$ .

*Age Analysis:* The log-transformed PK endpoints,  $AUC_{Ins,\tau,SS}$  and  $C_{max,Ins,SS}$ , were analysed using the same model as for the primary endpoint.

Note: Most of the endpoints were derived for both IDeg and Glar, therefore the term “Ins” is used in the endpoints.

#### **Statistical Analysis of Secondary Safety Endpoints:**

Safety analysis set included all subjects who received at least one dose of the investigational product or its comparator. The following secondary safety endpoints were listed and summarized using descriptive statistics: adverse events (AEs), laboratory safety variables (hematology, biochemistry, coagulation and urinalysis), physical examination, vital signs, ECG and hypoglycemic episodes.

#### **Demography of Trial Population**

Of the 27 randomised and exposed subjects, 14 (51.9%) were females and 13 (48.1%) were males. All 27 subjects were white. The mean age of the subjects in the younger adult group was 27.1 years (range: 19-34 years) and the geriatric group was 67.8 years (range: 65-78 years). The BMI was comparable between the 2 age groups. The mean baseline HbA<sub>1c</sub> value was 7.78% (range: 6.30-9.10%) in younger adult subjects and 7.70% (range: 6.80-8.90%) in the geriatric subjects.

#### **Pharmacodynamic and Pharmacokinetic Results and Conclusions**

- No statistically significant difference was found between younger adult and geriatric subjects with type 1 diabetes with respect to the primary endpoint  $AUC_{GIR,\tau,SS}$  for IDeg.
- No statistically significant difference was found between younger adult and geriatric subjects with type 1 diabetes with respect to the endpoints  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  for both IDeg and IGlar.
  - For IDeg the estimated mean age group ratio (geriatric/young) for  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  and corresponding two-sided 95% CIs were 0.78 [95% CI: 0.47, 1.31] and 0.80 [95% CI: 0.54, 1.17].
  - For IGlar the estimated mean age group ratios (geriatric/young) for  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  and corresponding two-sided 95% CIs were 0.87 [95% CI: 0.48, 1.60] and 0.84 [95% CI: 0.54, 1.30], respectively.
- No statistically significant difference was found for the effect of age between IDeg and IGlar for  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  ( $p=0.42$  and  $p=0.65$ , respectively) in subjects with type 1 diabetes.
- No statistically significant difference was found between younger adult and geriatric subjects with type 1 diabetes with respect to total exposure ( $AUC_{\tau,SS}$ ) and  $C_{max,SS}$  for IDeg and for IGlar.
  - The estimated mean age group ratios (geriatric/young) for  $AUC_{IDeg,\tau,SS}$  and  $C_{max,IDeg,SS}$  and corresponding two-sided 95% CIs were 1.04 [95% CI: 0.73, 1.47] and 1.02 [95% CI: 0.74, 1.39], respectively.
  - The estimated mean age group ratios (geriatric/young) for  $AUC_{IGlar,\tau,SS}$  and  $C_{max,IGlar,SS}$  and corresponding two-sided 95% CIs were 1.06 [95% CI: 0.80, 1.40] and 1.03 [95% CI: 0.80, 1.33], respectively.
- $t_{1/2}$  occurred after approximately 21 and 25 hours with IDeg in younger adult and geriatric subjects,

respectively, as compared with 13 and 15 hours with IGLar in younger adult and geriatric subjects, respectively.

- No differences were observed between younger adult and geriatric subjects with type 1 diabetes for the remaining secondary PD and PK endpoints at steady state for IDeg.
- The PK profiles appeared to be similar for younger adult and geriatric subjects with type 1 diabetes after single dose and at steady state for IDeg and IGLar.

#### **Safety Results and Conclusions**

- A total of 32 treatment emergent adverse events were reported in 16 subjects; 15 events in 8 (29.6%) subjects treated with IDeg and 17 events in 11 (42.3%) subjects treated with IGLar. There were no obvious differences in the distribution of adverse events between age groups with either treatment.
  - the most common adverse event (10 events of headache) was reported in 9 subjects: 4 events in 4 subjects with IDeg and 6 events in 5 subjects with IGLar.
  - one severe adverse event (hypoglycemia) was reported in the geriatric group after treatment with IDeg–
- One serious adverse event reported (severe hypoglycemia) was reported in the geriatric group after treatment with IDeg. The event was considered possibly related to IDeg and the subject was withdrawn from the trial.
- Two (2) injection site reactions were reported by 2 subjects, 1 with IDeg and 1 with IGLar- neither was considered to be related to trial product.
- No other medical events of special interest were reported
- A total of 280 treatment emergent hypoglycemic episodes (ADA classification) were reported for 26 (96.3%) subjects during the trial.
  - 176 episodes in 26 (96.3%) subjects with IDeg versus 104 episodes in 22 (84.6%) subjects with IGLar
  - although the number of episodes tended to be greater for geriatric subjects than for younger adult subjects with IDeg and IGLar, the proportion of subjects affected remained similar for both age groups
  - 38 nocturnal treatment emergent adverse events (ADA classification) were reported for 17 (63.0%) subjects.

The pattern of the incidence of between treatments and age groups was similar to that observed for all hypoglycaemia

- There were no clinically significant findings in laboratory parameters, vital signs, physical examination or ECG.

#### **Overall Conclusions**

The conclusions from this single-centre, double-blind, randomized, two-period, cross-over, glucose clamp, multiple dose trial investigating the pharmacodynamic and pharmacokinetic properties for IDeg in younger adult and geriatric subjects with Type 1 diabetes mellitus are:

- Glucose-lowering effect of IDeg is similar in younger adult (18-35 years of age) and geriatric ( $\geq 65$ ) subjects with type 1 diabetes.
- Total exposure ( $AUC_{\tau}$ ) and pharmacokinetics of IDeg is similar in younger adult (18-35 years of age) and geriatric ( $\geq 65$ ) subjects with type 1 diabetes
- IDeg is well-tolerated in both younger adult and geriatric subjects with type 1 diabetes and no safety issues are raised.

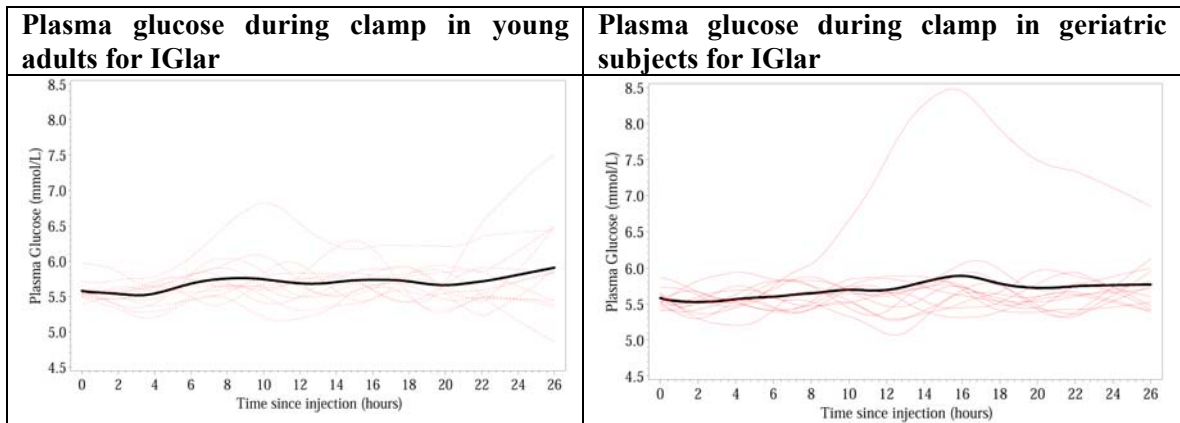
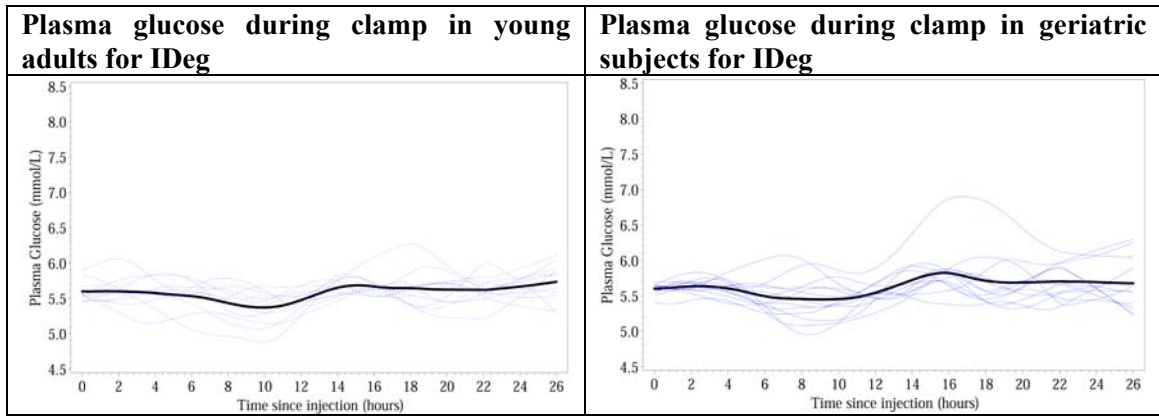
*The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice.*

**Reviewer’s Comments:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial.

The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ ,  $\pm 7\%$ , and  $\pm 9\%$ , respectively for IDeg. The analytical method adequately supported the results for IGLar with accuracy and precision for calibration standards (range of 20.0 to 750 pM) and QC samples lying within  $\pm 9\%$  and  $\pm 3\%$  respectively.

Overall, the integrity of clamp was evident from plasma glucose levels except in one geriatric subject in the IGLar treatment group.



**4.2.7 Intrinsic Factor PK Study in Children Adolescents and Adults with Type 1 DM (NN1250-1995)**

**Rationale:** This PK trial including both paediatric and adult subjects with type 1 diabetes mellitus compared the PK properties of IDeg between different age groups. (b) (4)

[Redacted]

[Redacted] (b) (4)

The study synopsis is as follows:

**Title of Trial**

A Trial Investigating the Pharmacokinetic Properties of NN1250 in Children, Adolescents and Adults with Type 1 Diabetes

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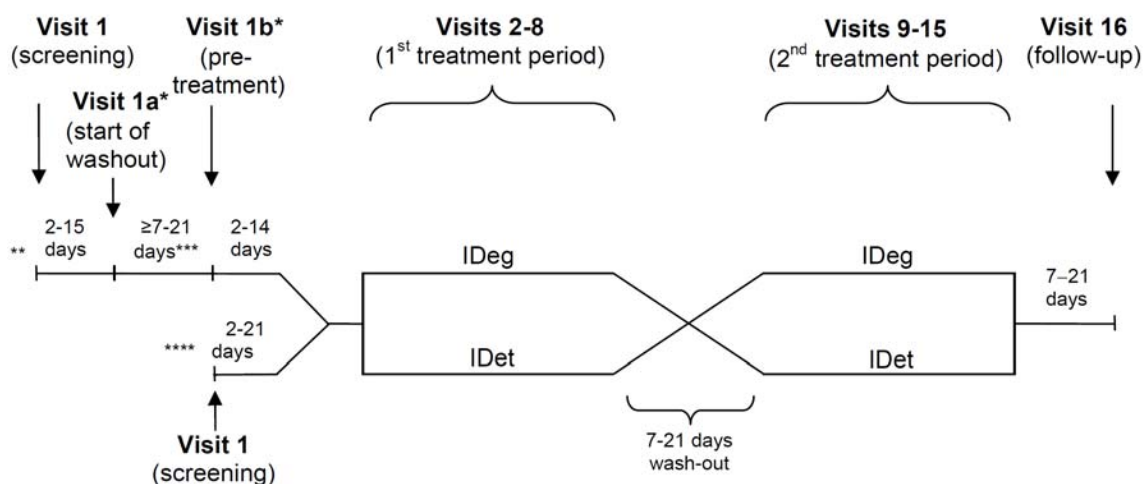
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#### 4.2.8 Intrinsic Factor PK Study in Subjects with Type 2 DM of different Race/Ethnicity (NN1250-3762)

**Rationale:** The aim of this trial was to investigate the combined effect of intrinsic (e.g. genetics and drug clearance) and extrinsic (e.g. diet, environmental exposure and sociocultural issues) factors on the pharmacodynamic and pharmacokinetic properties of IDeg in order to clarify if specific dosing recommendations should be given to certain racial and ethnic subgroups. Therefore, this trial compared the pharmacodynamic and pharmacokinetic response of IDeg in Black or African American subjects not of Hispanic or Latino origin, White subjects of Hispanic or Latino origin and White subjects not of Hispanic or Latino origin, all with type 2 diabetes. IDet, an already marketed long-acting insulin, was included in order to serve as a reference for any effects of race/ethnicity seen with IDeg.

**Study Design:** The study design is presented in the figure below:



\* Visit were performed only in subjects entering the trial on combination therapy with insulin plus oral anti-diabetic drugs (OADs)

\*\* Screening and run-in procedure were followed for subjects entering the trial on combination therapy with insulin plus OAD(s).

\*\*\* ≥7 days for subjects on sulfonylurea and/or acarbose therapy and ≥21 days for subjects on metformin therapy.

\*\*\*\* Screening procedure were followed for subjects entering the trial only on insulin therapy.

Groups based on age at screening:

Male or female, aged 29-68 years, Black or African American subjects not of Hispanic or Latino origin, White subjects of Hispanic or Latino origin and White subjects not of Hispanic or Latino origin, all with type 2 diabetes.

The subject demographics is as follows:

|                           | Black (not<br>Hispanic/Latino) | White<br>(Hispanic/Latino) | White (not<br>Hispanic/Latino) |
|---------------------------|--------------------------------|----------------------------|--------------------------------|
| Number of Subjects        | 18                             | 22                         | 23                             |
| Age (year)                |                                |                            |                                |
| N                         | 18                             | 22                         | 23                             |
| Mean (StD)                | 48.9 ( 8.4)                    | 51.5 ( 8.3)                | 55.1 ( 8.9)                    |
| Median                    | 49.0                           | 53.0                       | 54.0                           |
| Min ; Max                 | 35.0 ; 66.0                    | 29.0 ; 63.0                | 34.0 ; 68.0                    |
| Ethnicity, N (%)          |                                |                            |                                |
| N                         | 18 (100.0)                     | 22 (100.0)                 | 23 (100.0)                     |
| Hispanic or Latino        | 0 ( 0.0)                       | 22 (100.0)                 | 0 ( 0.0)                       |
| Not Hispanic or Latino    | 18 (100.0)                     | 0 ( 0.0)                   | 23 (100.0)                     |
| Race, N (%)               |                                |                            |                                |
| N                         | 18 (100.0)                     | 22 (100.0)                 | 23 (100.0)                     |
| White                     | 0 ( 0.0)                       | 22 (100.0)                 | 23 (100.0)                     |
| Black or African American | 18 (100.0)                     | 0 ( 0.0)                   | 0 ( 0.0)                       |
| Sex, N (%)                |                                |                            |                                |
| N                         | 18 (100.0)                     | 22 (100.0)                 | 23 (100.0)                     |
| Female                    | 7 ( 38.9)                      | 9 ( 40.9)                  | 10 ( 43.5)                     |
| Male                      | 11 ( 61.1)                     | 13 ( 59.1)                 | 13 ( 56.5)                     |
| Height (m)                |                                |                            |                                |
| N                         | 18                             | 22                         | 23                             |
| Mean (StD)                | 1.73 ( 0.09)                   | 1.65 ( 0.09)               | 1.71 ( 0.10)                   |
| Median                    | 1.75                           | 1.65                       | 1.73                           |
| Min ; Max                 | 1.50 ; 1.84                    | 1.49 ; 1.86                | 1.53 ; 1.85                    |
| Weight (kg)               |                                |                            |                                |
| N                         | 18                             | 22                         | 23                             |
| Mean (StD)                | 105.1 ( 14.4)                  | 82.2 ( 11.3)               | 94.7 ( 18.8)                   |
| Median                    | 107.9                          | 83.0                       | 95.8                           |
| Min ; Max                 | 81.1 ; 127.1                   | 54.3 ; 106.7               | 57.9 ; 129.7                   |
| BMI (kg/m <sup>2</sup> )  |                                |                            |                                |
| N                         | 18                             | 22                         | 23                             |
| Mean (StD)                | 35.3 ( 3.7)                    | 30.2 ( 4.4)                | 32.3 ( 5.6)                    |
| Median                    | 35.7                           | 30.5                       | 32.9                           |
| Min ; Max                 | 27.1 ; 40.4                    | 22.3 ; 38.2                | 20.4 ; 41.2                    |

BMI: body mass index, StD: standard deviation

Baseline information was recorded at screening and/or randomisation. If an assessment was recorded on both visits, the randomisation value was used as baseline value

The study synopsis is as follows:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                       |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------|
| <b>Trial Registration ID-number</b><br>NCT01043510                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>IND Number – US only</b><br>76,496 |
| <b>Title of Trial</b><br>A Trial Investigating the Pharmacodynamic and Pharmacokinetic Properties of NN1250 <sup>1</sup> at Steady State Conditions in Subjects with Type 2 Diabetes of Different Race and/or Ethnicity                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                       |
| <b>Investigator</b><br>Dr. Marcus Hompesch, Profil Institute for Clinical Research Inc., Chula Vista, United States of America (USA)                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |                                       |
| <b>Trial Site(s)</b><br>Profil Institute for Clinical Research Inc., 855 3rd Avenue, Suite 4400, Chula Vista, California (CA) 91911, USA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |                                       |
| <b>Publications</b><br>None as of the date of the final clinical trial report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                       |
| <b>Trial Period</b><br>7 January 2010–27 October 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Development Phase</b><br>Phase 1   |
| <b>Objectives</b><br><b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To compare the pharmacodynamic response of insulin degludec (IDeg) and insulin detemir (IDet) between Black or African American subjects not of Hispanic or Latino origin, White subjects of Hispanic or Latino origin and White subjects not of Hispanic or Latino origin, all with type 2 diabetes, based on the area under the glucose infusion rate curve during one dosing interval (0–24 hours) at steady state.</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To compare the pharmacokinetic exposure of IDeg and IDet between Black or African American subjects not of Hispanic or Latino origin, White subjects of Hispanic or Latino origin and White subjects not of Hispanic or Latino origin, all with type 2 diabetes, during one dosing interval (0–24 hours) at steady state.</li> <li>To characterise the pharmacodynamic properties of IDeg and IDet at steady state in subjects with type 2 diabetes of different race and/or ethnicity.</li> <li>To characterise the pharmacokinetic properties of IDeg after single-dose and of IDeg and IDet at steady state in subjects with type 2 diabetes of different race and/or ethnicity.</li> <li>To evaluate the pharmacokinetic trough values towards the steady state level.</li> <li>To assess the safety and tolerability of IDeg and IDet in subjects with type 2 diabetes of different race and/or ethnicity.</li> </ul>                                                                                                                                                                      |                                       |
| <b>Methodology</b><br>This was a randomised, single-centre, double-blind, two-period cross-over, multiple-dose trial investigating the pharmacodynamic and pharmacokinetic properties of IDeg and IDet in 3 different groups of subjects based on race and/or ethnicity (Black or African American subjects not of Hispanic or Latino origin, White subjects of Hispanic or Latino origin and White subjects not of Hispanic or Latino origin), all with type 2 diabetes. Each subject was randomly allocated to one sequence of two treatment periods, one with IDeg and one with IDet, at the predefined fixed dose level with 6 days of once-daily dosing per treatment period. The trial consisted of a Screening Visit (Visit 1), two treatment periods (Visits 2–8 and Visits 9–15) and a Follow-up Visit (Visit 16). In addition, two extra visits (Visit 1a: start of washout and Visit 1b: pre-treatment) were performed in subjects entering the trial on combination therapy with insulin plus oral antidiabetic drugs (OADs). The two treatment periods were separated by a washout period (7–21 days). Each treatment period consisted of an initial in-house period following the first trial product administration (Visits 2 and 9), two out-patient dosing visits (Visits 3–4 and 10–11), and an additional in-house period following the last trial product administration (Visits 5 and 12). The subject was discharged from the clinic 48 hours after the last trial product administration, or later if deemed necessary by the investigator, and returned at 72, 96 and 120 hours after the last trial product administration (Visits 6–8 and 13–15) in order to have |                                       |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p>blood samples taken for pharmacokinetic analysis (only analysed when dosed with IDeg) and for analysis of blood glucose. Finally, the subject attended a Follow-Up Visit (Visit 16), 7–21 days after the last dosing in the last treatment period. The planned total duration of the trial for the individual subject was between 27 and 103 days.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| <p><b>Number of Subjects Planned and Analysed</b></p> <p>A total of at least 52 subjects were planned to complete the trial. In total, 233 subjects were screened, 72 subjects entered the trial, 63 subjects were randomised and exposed to trial products (18 Black subjects not of Hispanic/Latino origin, 22 White subjects of Hispanic/Latino origin and 23 White subjects not of Hispanic/Latino origin) and 57 subjects completed the trial. All 63 randomised and exposed subjects were included in the full analysis set and the safety analysis set.</p>                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>Diagnosis and Main Criteria for Inclusion</b></p> <p>Male or female aged 18–70 years (both inclusive) with type 2 diabetes (as diagnosed clinically) <math>\geq 12</math> months either Black or African American not of Hispanic or Latino origin; or White of Hispanic or Latino origin; or White not of Hispanic or Latino origin, treated with insulin <math>\geq 3</math> months, alone or in combination with <math>\leq 2</math> oral antidiabetic drugs (OADs) and body mass index <math>\leq 40.0</math> kg/m<sup>2</sup>.</p> <p>Key exclusion criteria were: history or presence of cancer, cardiac diseases, supine blood pressure at screening <math>\geq 180</math> mmHg for systolic and/or <math>\geq 100</math> mmHg for diastolic blood pressure, proliferative retinopathy or maculopathy and/or severe neuropathy as well as recurrent severe hypoglycaemia or hypoglycaemic unawareness.</p> |
| <p><b>Test Product, Dose and Mode of Administration, Batch Number</b></p> <p>Insulin degludec (M) in 3 mL (b) (4) cartridges (100 U/mL) was administered at a dose level of 0.6 U/kg body weight (BW) as a subcutaneous (s.c.) injection into a lifted skin fold on the anterior surface of the thigh. Batch no. VCQ0014</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| <p><b>Duration of Treatment</b></p> <p>Each subject was allocated to two treatment periods of 6 days of once-daily dosing of 0.6 U/kg BW of either IDeg or IDet. It was possible to schedule up to 5 additional dosing visits per treatment period.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Reference Therapy, Dose and Mode of Administration, Batch Number</b></p> <p>Insulin detemir (Levemir<sup>®</sup>, 100 U/mL) in 3 mL Penfill<sup>®</sup> cartridges was administered at a dose level of 0.6 U/kg BW as an s.c. injection into a lifted skin fold on the anterior surface of the thigh. Batch no. XQ50422</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| <p><b>Criteria for Evaluation – Efficacy</b></p> <p><i>Pharmacodynamic variables</i></p> <p>Glucose infusion rate (GIR) during a euglycaemic clamp running for 24 hours following the last dosing of each treatment period.</p> <p>Serum C-peptide concentrations during the first 24 hours following the last dose of each treatment period.</p> <p><i>Pharmacokinetic variables</i></p> <p>Serum IDeg concentration after administration of IDeg</p> <p>Serum IDet concentration after administration of IDet</p>                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>Criteria for Evaluation – Safety</b></p> <p>Adverse events</p> <p>Laboratory safety variables</p> <p>Physical examination</p> <p>Vital signs</p> <p>Electrocardiogram (ECG)</p> <p>Hypoglycaemic episodes</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| <p><b>Statistical Methods</b></p> <p>The pharmacodynamic and pharmacokinetic analyses were based on the full analysis set (FAS), which included all randomised subjects. The analyses of the safety endpoints were based on the safety analysis set (including data from baseline and Follow-Up) and on the safety analysis set for OAD Washout (including data from the Screening, Pre-treatment and Follow-Up Visits).</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |

#### *Statistical Analysis of Primary Endpoint*

The primary endpoint was derived from the individual GIR profiles:  $AUC_{GIR,\tau,SS}$ , the area under the glucose infusion rate curve during one dosing interval at steady state (0–24 hours).  $AUC_{GIR,\tau,SS}$  was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points.

The primary endpoint ( $AUC_{GIR,\tau,SS}$ ) was analysed on the untransformed original scale using an analysis of variance (ANOVA) method with treatment period (period 1/period 2) and an interaction between race/ethnicity and treatment (i.e. with different race/ethnicity effects for each treatment) as fixed factors and subject as a random effect. In order to account for potential heteroscedasticity, the error-term was dependent on the treatment. The planned model to be used was based on the log-transformed scale. However, this was not feasible due to an outlier (Subject 1001), and therefore the analysis was performed for FAS using the same model but in the original scale. Furthermore, a sensitivity analysis (excluding Subject 1001) was performed using the planned model. In addition, a post-hoc analysis was performed, where body mass index (BMI) at baseline was included as covariate and Subject 1001 was excluded.

From the above model, the race/ethnicity contrasts with corresponding 95% confidence intervals (CIs) were estimated for IDeg and IDet, respectively. In order to assess any difference in the race/ethnicity effects between IDeg and IDet, the p-value for a test of interaction between race/ethnicity and treatment was also computed.

#### *Statistical Analysis of Secondary Pharmacodynamic Endpoints*

The secondary pharmacodynamic endpoints included: area under the GIR curve from 0 to 12 hours at steady state ( $AUC_{GIR,0-12h,SS}$ ) only for IDeg, ratio of areas under the GIR curve at steady state ( $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ ) only for IDeg, maximum GIR at steady state ( $GIR_{max,SS}$ ) and time to the maximum GIR at steady state ( $tGIR_{max,SS}$ ).

For consistency,  $GIR_{max,SS}$  was analysed using the same approach as for the primary endpoint. All other secondary PD endpoints were summarised using descriptive statistics.

#### *Statistical Analysis of Secondary Pharmacokinetic Endpoints*

The secondary pharmacokinetic endpoints derived from the insulin concentration–time curves after single-dose administration included: area under the serum IDeg concentration–time curve from 0 to 24 hours after single dose ( $AUC_{IDeg,0-24h,SD}$ ), maximum observed serum IDeg concentration ( $C_{max,IDeg,SD}$ ) and time to maximum observed serum IDeg concentration ( $t_{max,IDeg,SD}$ ).

The secondary pharmacokinetic endpoints derived from the individual insulin concentration–time curves at steady state included: area under the serum insulin concentration–time curve during one dosing interval for IDeg and IDet ( $AUC_{Ins,\tau,SS}$ ), area under the serum insulin concentration–time curve from 0 to 12 hours for IDeg only ( $AUC_{Ins,0-12h,SS}$ ), ratio of areas under the serum insulin concentration–time curve for IDeg only ( $AUC_{Ins,0-12h,SS}/AUC_{Ins,\tau,SS}$ ), maximum observed serum insulin concentration for IDeg and IDet ( $C_{max,Ins,SS}$ ), time to maximum observed serum insulin concentration for IDeg and IDet ( $t_{max,Ins,SS}$ ), terminal half-life for insulin ( $t_{1/2,Ins,SS}$ ) and terminal rate constant ( $\lambda_z,Ins$ ).

In addition, other pharmacokinetic endpoints derived were: IDeg trough concentration measured at the end of each dosing interval ( $ITC_{IDeg}$ ), IDet trough concentration measured at the end of each dosing interval ( $ITC_{IDet}$ ), ratio of  $AUC_{IDeg,0-24h}$  at steady state and  $AUC_{IDeg,0-24h}$  after single dose ( $AUC_{IDeg,\tau,SS}/AUC_{IDeg,0-24h,SD}$ ), ratio of  $C_{max,IDeg,0-24h}$  at steady state and  $C_{max,IDeg,0-24h}$  after single-dose ( $C_{max,IDeg,SS}/C_{max,IDeg,SD}$ ).

$AUC_{Ins,\tau,SS}$  and  $C_{max,Ins,SS}$  were logarithm transformed and analysed using the same approach as for the primary endpoint, including a post-hoc analyses (with BMI at baseline as a covariate). All other secondary pharmacokinetic endpoints were summarised using descriptive statistics.

#### *Statistical Analyses of Safety Endpoints*

Adverse events were evaluated based on the safety analysis set. All the other safety endpoints were evaluated based on the safety analysis set and also based on the safety analysis set for OAD washout.

#### **Demography of Trial Population**

All randomised and exposed subjects were either Black subjects (not Hispanic/Latino origin) or White subjects (Hispanic/Latino origin) or White subjects (not Hispanic/Latino origin). Of the 63 subjects randomised, there were 26 females and 37 males. The subjects had a mean age of 52.1 years and a BMI of 32.4 kg/m<sup>2</sup>. The average duration

of diabetes was 11.7 years and mean HbA<sub>1c</sub> was 8.2%. Based on the safety analysis set, 35 subjects were using OADs plus insulin products, 17 subjects were using both basal and bolus insulin, whereas 11 subjects were using basal insulin alone at screening.

### **Efficacy Results and Conclusions**

#### *Pharmacodynamic Endpoints*

- The total glucose-lowering effect of IDeg at steady state conditions ( $AUC_{GIR,t,SS}$ ) was not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- The maximum glucose-lowering effect of IDeg at steady state conditions ( $GIR_{max,SS}$ ) was not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- The  $AUC_{GIR,t,SS}$  and  $GIR_{max,SS}$  of IDet at steady state conditions were not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- There were no statistically significant differences in the race/ethnicity pattern between IDeg and IDet for  $AUC_{GIR,t,SS}$  ( $p=0.8484$ ) and  $GIR_{max,SS}$  ( $p=0.9338$ ), respectively
- The glucose infusion rate profiles of IDeg were flat and stable compared to IDet
- The glucose-lowering effect of IDeg extended beyond 24 hours at a clinically relevant dose of 0.6 U/kg
- Overall, the secondary pharmacodynamic endpoints at steady state conditions for IDeg were comparable among the 3 race/ethnicity groups based on descriptive statistics.

#### *Pharmacokinetic Endpoints*

- Total exposure of IDeg at steady state conditions ( $AUC_{IDeg,t,SS}$ ) was not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- Maximum exposure of IDeg at steady state conditions ( $C_{max,IDeg,SS}$ ) was not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- The  $AUC_{IDet,t,SS}$  and  $C_{max,IDet,SS}$  of IDet at steady state conditions were not statistically significantly different in the pair-wise comparisons among the 3 race/ethnicity groups
- No statistically significant differences were shown in the race/ethnicity pattern between IDeg and IDet for  $AUC_{Ins,t,SS}$  ( $p=0.5797$ ) and  $C_{max,Ins,SS}$  ( $p=0.7630$ ), respectively
- The shape of the mean concentration–time profiles for IDeg at steady state conditions was similar for the 3 race/ethnicity groups
- The pharmacokinetic profiles of IDeg were flat and stable compared to IDet
- Based on pharmacokinetic profiles, IDeg appeared to have reached steady state after 48 to 72 hours in all 3 race/ethnicity groups
- For IDeg, exposure at steady state was approximately 2 times greater than exposure after a single dose ( $AUC_{IDeg,t,SS}/AUC_{IDeg,0-24h,SD}$ ) in all 3 race/ethnicity groups based on descriptive statistics
- Overall, the secondary pharmacokinetic endpoints for IDeg at steady state conditions and after single dose were comparable among the 3 race/ethnicity groups based on descriptive statistics.

### **Safety Results and Conclusions**

- A total of 65 adverse events were reported in 34 (55%) of the subjects during treatment with IDeg and 64 adverse events were reported in 36 (60%) of the subjects during treatment with IDet. Overall, there were no observed differences between the 3 race/ethnicity groups in the pattern of adverse events, whereas fewer adverse events with possible or probable relation to trial product were reported for IDeg (6 events) than for IDet (22 events)
  - No severe adverse events were reported. The majority of adverse events were mild, and all subjects recovered, except for 3 subjects, who were reported to be recovering (myalgia, cough and dermatitis) at or shortly after their Follow-up Visit
  - The most common adverse events reported during treatment with IDeg were headache (16 events) and back

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
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| <p>pain (5 events), and the most common adverse events reported during treatment with IDet were headache (9 events) and injection site reaction (7 events)</p> <ul style="list-style-type: none"> <li>• No serious adverse events or medical events of special interest were reported in this trial</li> <li>• A total of 24 injection site reactions were reported in 15 (24%) subjects: one (1) during the screening period, 2 during treatment with IDeg and 21 during treatment with IDet. The majority of these were considered possibly or probably related to trial product. Most of the injection site reactions were mild in severity except for 2 (during treatment with IDet), which were of moderate severity</li> <li>• A total of 133 and 95 treatment-emergent hypoglycaemic episodes were reported during the treatment periods with IDeg and IDet, respectively, according to the ADA classification of hypoglycaemia. This included 4 and 3 severe episodes during treatment with IDeg and IDet, respectively. Approximately 17% and 26% of the episodes during treatment with IDeg and IDet, respectively, were nocturnal episodes. There were no obvious differences in the pattern of hypoglycaemic episodes between the 3 race/ethnicity groups. Hypoglycaemic episodes were reported for slightly more of the subjects during treatment with IDeg (71%) than during treatment with IDet (58%). The observed number of hypoglycaemic episodes may be artificially high due to the fixed dosing level of 0.6 U/kg of IDeg and IDet</li> <li>• Two (2) mild events of anaemia were reported as treatment emergent adverse events. No other clinically significant findings in laboratory parameters, vital signs, physical examination or ECG were reported.</li> </ul> |
| <p><b>Overall Conclusions</b></p> <p>The conclusions from this randomised, single-centre, double-blind, two-period cross-over, multiple-dose trial investigating the pharmacodynamic and pharmacokinetic properties of IDeg and IDet at steady state conditions in subjects with type 2 diabetes of different race and/or ethnicity (White non-Hispanic/Latino, White Hispanic/Latino and Black/African American non-Hispanic/Latino subjects) are:</p> <ul style="list-style-type: none"> <li>• Total glucose-lowering effect (<math>AUC_{GIR,\tau,SS}</math>) of IDeg is comparable in the three race/ethnicity groups</li> <li>• Total exposure (<math>AUC_{IDeg,\tau,SS}</math>) of IDeg is similar in the three race/ethnicity groups</li> <li>• The glucose-lowering effect of IDeg extends beyond 24 hours at a clinically relevant dose of 0.6 U/kg</li> <li>• IDeg has a flat and stable glucose-lowering effect compared to IDet</li> <li>• IDeg has a flat and stable pharmacokinetic profile compared to IDet</li> <li>• IDeg is well tolerated and no safety issues are identified in this trial.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><i>The trial was conducted in accordance with the Declaration of Helsinki (last amended by the 59<sup>th</sup> WMA General Assembly, Seoul, 2008) and ICH Good Clinical Practice (1996).</i></p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

**Reviewer’s Comments:**

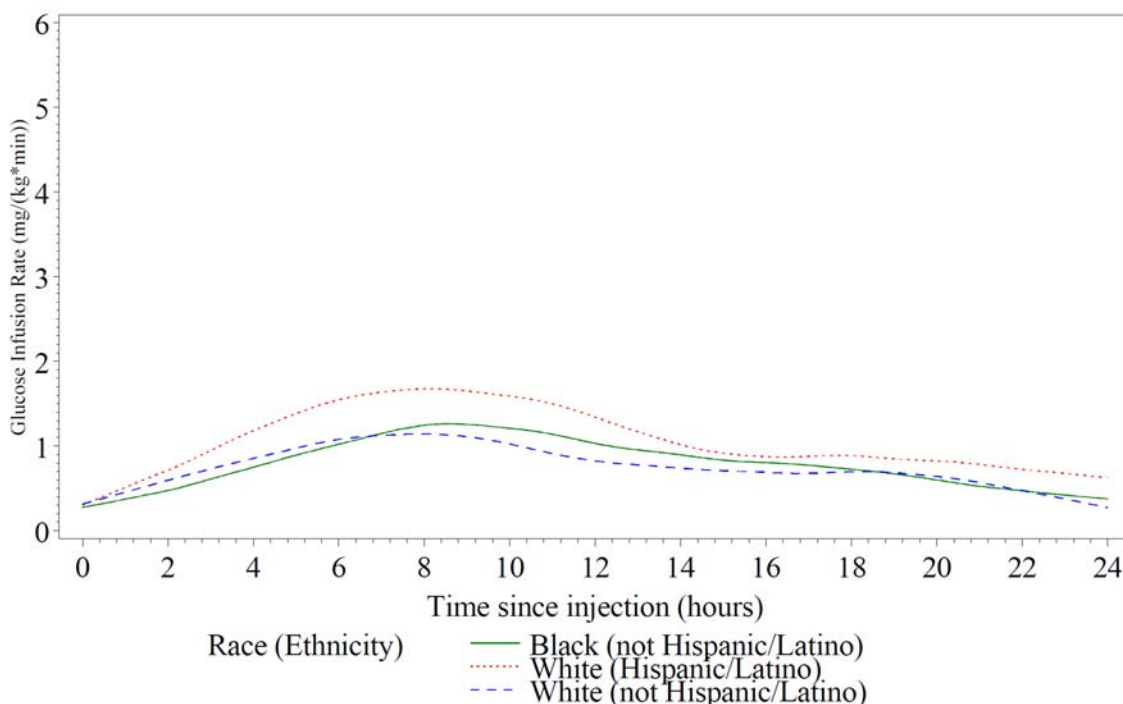
The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 1.5\%$ ,  $\pm 10\%$ , and  $\pm 15\%$ , respectively for IDeg. The analytical method adequately supported the results for IDet with accuracy and precision for calibration standards (range of 20.0 to 750 pM) and QC samples lying within  $\pm 3\%$  and  $\pm 14\%$  respectively. The statistical analysis conducted by this reviewer showed lower response for IDeg in black subjects in comparison to non-Hispanic/Latino white subjects based on mean ratio (90% CI).

### Statistical Comparison of IDeg PK/PD Parameters

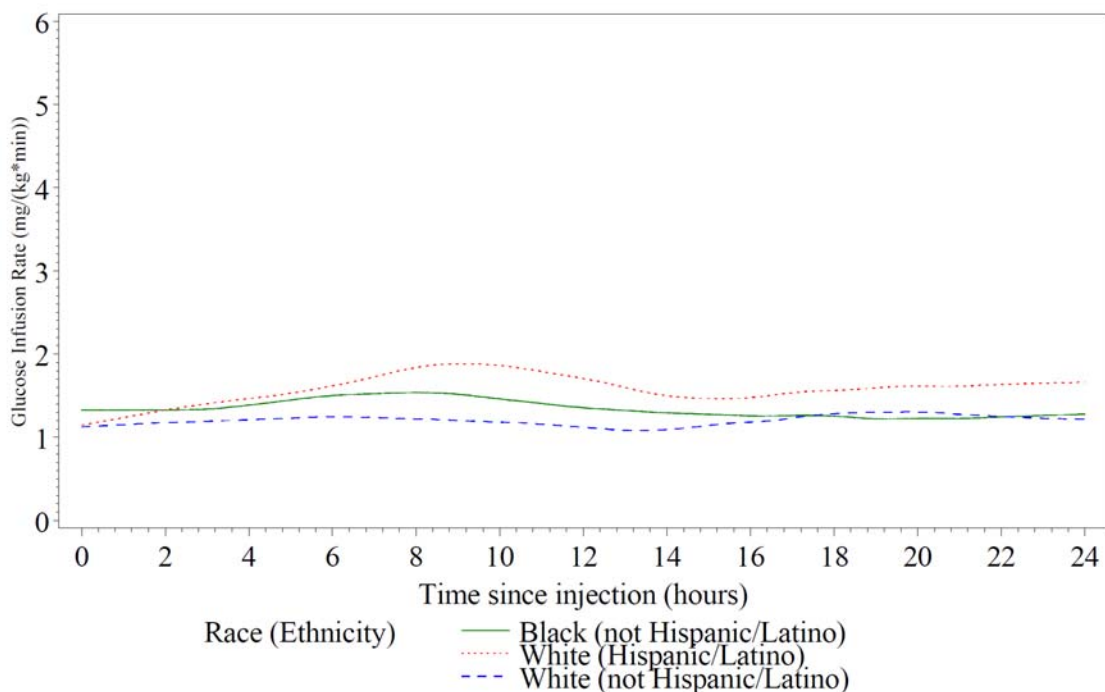
| Test                        | Ref                         | PK/PD Parameter | Units     | Ratio(%) | 90% CI         |
|-----------------------------|-----------------------------|-----------------|-----------|----------|----------------|
| Black (not Hispanic/Latino) | White (Hispanic/Latino)     | AUCGIR(0-tau)   | mg/kg     | 64.48    | 42.49 - 97.85  |
|                             |                             | GIRmax          | mg/kg/min | 77.35    | 57.85 - 103.41 |
|                             |                             | IDeg AUC(0-tau) | pmol.hr/L | 112.52   | 97.21 - 130.23 |
|                             |                             | IDeg Cmax       | pmol/L    | 106.09   | 91.28 - 123.29 |
| White (Hispanic/Latino)     | White (not Hispanic/Latino) | AUCGIR(0-tau)   | mg/kg     | 94.97    | 61.67 - 146.23 |
|                             |                             | GIRmax          | mg/kg/min | 101.97   | 75.5 - 137.72  |
|                             |                             | IDeg AUC(0-tau) | pmol.hr/L | 109.3    | 93.95 - 127.16 |
|                             |                             | IDeg Cmax       | pmol/L    | 106.04   | 90.76 - 123.89 |
| White (not Hispanic/Latino) | White (not Hispanic/Latino) | AUCGIR(0-tau)   | mg/kg     | 147.28   | 97.64 - 222.16 |
|                             |                             | GIRmax          | mg/kg/min | 131.83   | 99.02 - 175.5  |
|                             |                             | IDeg AUC(0-tau) | pmol.hr/L | 97.14    | 84.11 - 112.2  |
|                             |                             | IDeg Cmax       | pmol/L    | 99.96    | 86.2 - 115.92  |

**Comparison of IDeg versus IDet PD:** On average, both IDeg and Insulin Detemir show a lower PD response in Black subjects in comparison to the White subjects of non-Hispanic/Latino Origin and Hispanic/Latino appear to be the most sensitive population among blacks and white type 2 diabetic subjects. However, the difference could not be verified statistically for any other comparisons except for lower AUCGIR0-tau in black versus white (Non-H/L).

#### IDeg PD Profile at steady-state:



**Insulin Detemir PD profile at steady-state:**



Numerically, in each group PD effect of IDeg was higher than that of Insulin Detemir at steady-state after 0.6 U/kg/day administration. No formal statistical comparison was conducted.

**Summary statistics of primary PD parameter for IDeg:**

|                          | Black (not Hispanic/Latino) | White (Hispanic/Latino) | White (not Hispanic/Latino) |
|--------------------------|-----------------------------|-------------------------|-----------------------------|
| Number of Subjects       | 18                          | 22                      | 23                          |
| AUC GIR, tau, SS (mg/kg) |                             |                         |                             |
| N                        | 18                          | 22                      | 19                          |
| Mean (Std)               | 1940.1 (1373.2)             | 2286.3 (1060.5)         | 1735.0 (1056.9)             |
| Geometric mean (CV)      | 1328.1 ( 70.8)              | 2059.7 ( 46.4)          | 1398.5 ( 60.9)              |
| Min ; Max                | 63.7 ; 4186.3               | 734.6 ; 4458.3          | 306.1 ; 4431.9              |

**Summary statistics of primary PD parameter for Insulin Detemir:**

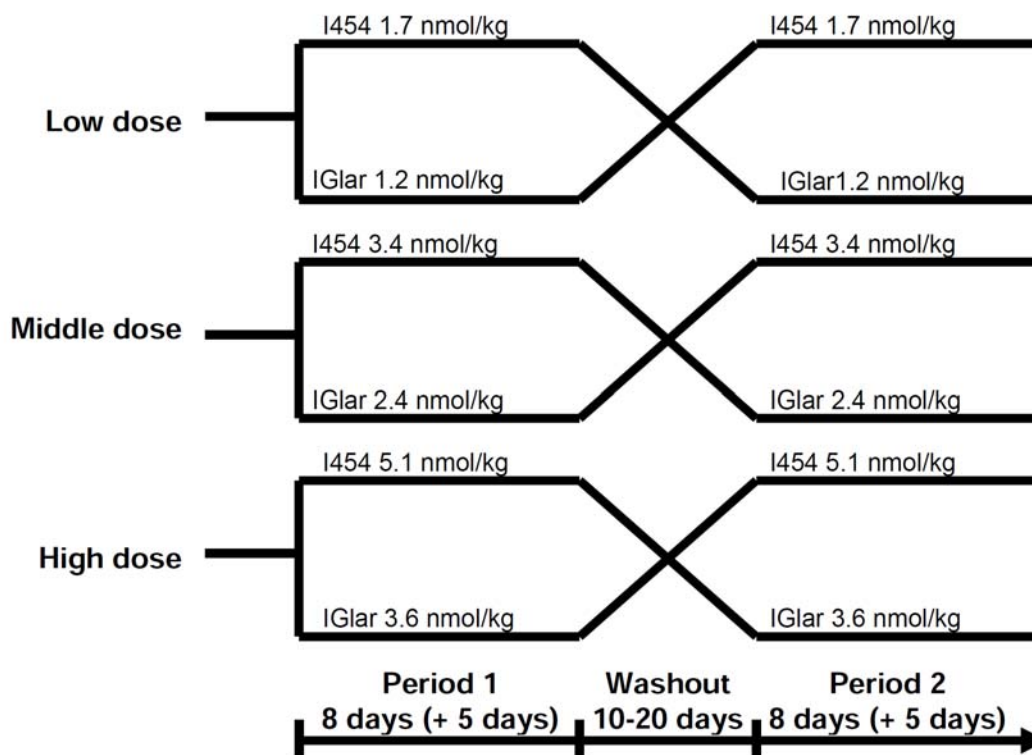
|                          | Black (not Hispanic/Latino) | White (Hispanic/Latino) | White (not Hispanic/Latino) |
|--------------------------|-----------------------------|-------------------------|-----------------------------|
| Number of Subjects       | 18                          | 22                      | 23                          |
| AUC GIR, tau, SS (mg/kg) |                             |                         |                             |
| N                        | 18                          | 22                      | 18                          |
| Mean (Std)               | 1149.5 (1073.9)             | 1544.4 ( 840.8)         | 1089.1 (1047.8)             |
| Geometric mean (CV)      | 553.8 ( 93.4)               | 1248.4 ( 54.4)          | 668.3 ( 96.2)               |
| Min ; Max                | 0.9 ; 3746.9                | 251.0 ; 3322.0          | 59.2 ; 3973.9               |

Std: Standard deviation, CV: Coefficient of variation in %

#### 4.2.9 Dose-response Study in Subjects with Type 1 DM (NN1250-1876)

**Rationale:** The current trial was designed to estimate the molar dose ratio between insulin 454 and insulin glargine under steady state conditions in order to establish the doses at which these two insulin products cause similar effect in subjects with type 1 diabetes. The assessment was based on the pharmacodynamic response obtained during a 24-hours euglycemic clamp procedure following administration of trial product at steady state conditions and at three clinically relevant dose levels for each trial product. In this trial, insulin 454 was administered as SIBA (E) containing insulin 454 solution for injection, 600 nmol/mL (1 DU = 6 nmol/mL).

**Study Design:** The study design is presented in the figure below:



The study synopsis is as follows:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |
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| <b>Trial Registration ID-number</b><br>Not applicable                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          | <b>EudraCT number</b><br>2007-003534-41 |
| <b>Title of Trial</b><br>A Randomised, Single Centre, Double-blind, Two-Period Cross-over, Multiple Dose Trial Comparing the Pharmacodynamic Response of Insulin 454 with Insulin Glargine at Steady-State Conditions in Subjects with Type 1 Diabetes Mellitus                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |
| <b>Investigator</b><br>Tim Heise, MD, Profil Institut für Stoffwechselforschung GmbH                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |
| <b>Trial Site</b><br>Profil Institut für Stoffwechselforschung GmbH, Hellersbergstr. 9, D-41460 Neuss, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                         |
| <b>Publications</b><br>None at the time of reporting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                         |
| <b>Trial Period</b><br>04 January to 11 June 2008                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | <b>Development Phase</b><br>Phase I     |
| <b>Objectives</b><br><b>Primary Objective:</b> <ul style="list-style-type: none"> <li>• To estimate the molar dose ratio between insulin 454 and insulin glargine at steady-state conditions</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>• To compare the pharmacodynamic response of insulin 454 and insulin glargine with respect to: <ul style="list-style-type: none"> <li>– duration of action in an exploratory 42-hours clamp experiment</li> <li>– suppression of free fatty acids (FFA) in response to insulin action</li> <li>– peak-to-trough fluctuation at steady state in a 24-hours dosing interval</li> </ul> </li> <li>• To compare and estimate the pharmacokinetic parameters of insulin 454 and insulin glargine with respect to: <ul style="list-style-type: none"> <li>– ratios of single dose and steady state levels</li> <li>– peak-to-trough fluctuation at steady state in a 24-hours dosing interval</li> <li>– trough values towards steady state level</li> <li>– terminal half life</li> </ul> </li> <li>• To describe the pharmacokinetic and pharmacodynamic profile of both insulin 454 and insulin glargine at steady-state</li> <li>• To assess safety and tolerability</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |
| <b>Methodology</b><br>This trial was a randomised, single centre, double-blind, two-period cross-over, multiple dose trial with an incomplete block design comparing the pharmacodynamic and pharmacokinetic properties of insulin 454 and insulin glargine at steady state conditions in subjects with type 1 diabetes mellitus. Each subject was randomised to one of three dose levels (low, middle or high dose) and one of two sequences with two periods of eight days of once daily dosing with SIBA or insulin glargine. The trial consisted of 18 visits: a screening visit, seven dosing visits, one combined dosing and clamp visit, a washout period followed by seven dosing visits, one combined dosing and clamp visit, and a follow-up visit. The subjects attended a screening visit followed by 2 to 21 days screening period before the randomisation and first dosing visit. The first dosing visit lasted for 24 hours and was the first of three 24-hour dosing visits adding up to a 72 hours in-house stay. The following four dosing visits were daily out-patient visits. The eighth dosing visit included the 42-hour clamp experiment. The subject was discharged from the clinic 48 hours after administration of the last dose and returned with 24-hour intervals at 72, 96, 120 and 144 hours after administration of the last dose to have blood samples taken for pharmacokinetic analysis. The treatment period thus consisted of eight days with once daily dosing. After a washout period of 10 to 20 days, where the subject resumed their normal insulin treatment, the second treatment period was conducted. The first and second treatment periods were identical. Finally, a follow-up visit occurred 7 to 21 days after last dosing. The total duration of the trial for the individual subject was 27 to 83 days. |                                         |

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| <p><b>Number of Subjects Planned and Analysed</b></p> <p>A total of 57 subjects (19 at each dose level) were planned to complete the trial. A total of 86 subjects were screened, 63 subjects were randomised and exposed to trial products. All 63 subjects completed the trial and were included in the pharmacokinetic, pharmacodynamic and safety analyses.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>Diagnosis and Main Criteria for Inclusion</b></p> <p>Subjects with type 1 diabetes treated with insulin (<math>\leq 1.2</math> U/kg/day) for <math>\geq 12</math> months, between 18 and 69 years of age, with <math>HbA_{1c} \leq 10.0\%</math>, BMI between 18.0 and 28.0 <math>kg/m^2</math> and fasting C-peptide <math>&lt; 0.3</math> nmol/L.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>Test Product, Dose and Mode of Administration, Batch Number</b></p> <ul style="list-style-type: none"> <li>SIBA (E), insulin 454 100 DU/mL (600 U/mL) in 3.0 mL FlexPen® cartridges, administered as 1.7, 3.4 or 5.1 nmol/kg s.c. in the thigh.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><b>Duration of Treatment</b></p> <p>Two periods of eight days of once daily dosing with SIBA or insulin glargine.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <p><b>Reference Therapy, Dose and Mode of Administration, Batch Number</b></p> <ul style="list-style-type: none"> <li>Insulin glargine (Lantus®), 100 U/mL in 3 mL Optiset® cartridges, administered as 0.2, 0.4 or 0.6 U/kg s.c. in the thigh.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| <p><b>Criteria for Evaluation – Pharmacodynamics and Pharmacokinetics</b></p> <p><b>Pharmacodynamics</b></p> <ul style="list-style-type: none"> <li>Glucose infusion rate (GIR)</li> <li>Blood glucose concentration</li> <li>Free fatty acids (FFA)</li> <li>Glycerol, lactate, pyruvate, beta-hydroxybutyrate, urea and CRP</li> <li>Human insulin (HI) concentration and insulin infusion rate (IIR)</li> <li>Quantitative assessments of glucose, albumin and urea in urine</li> <li>Selected metabolic and hormonal serum markers</li> </ul> <p><b>Pharmacokinetics</b></p> <ul style="list-style-type: none"> <li>Serum concentration of insulin 454</li> <li>Plasma concentration of insulin glargine</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| <p><b>Criteria for Evaluation – Safety</b></p> <ul style="list-style-type: none"> <li>Adverse Events (AEs), including injection site reactions</li> <li>Laboratory safety variables (haematology, biochemistry, urinalysis, coagulation, lipids)</li> <li>Vital signs</li> <li>Physical examination</li> <li>ECG (electrocardiogram)</li> <li>Hypoglycaemic episodes</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| <p><b>Statistical Methods</b></p> <p><b>Primary and Secondary Endpoints</b></p> <p>The primary endpoint was <math>AUC_{GIR,0-24h}</math>, area under the glucose infusion rate curve from 0 to 24 hours, derived for insulin 454 and insulin glargine.</p> <p>Secondary pharmacodynamic endpoints describing the time-action profiles of insulin 454 and insulin glargine included <math>GIR_{max}</math>, <math>tGIR_{max}</math> and <math>AUC_{GIR}</math> for various time intervals, as well as endpoints describing onset of action, duration of action and end of action for insulin 454 and insulin glargine and. In addition, endpoints describing the suppression of free fatty acids included <math>AUC_{FFA,0-42h}</math>, <math>AOC_{FFA,0-42h}</math>, <math>FFA_{min}</math> and <math>tFFA_{min}</math>.</p> <p>Secondary pharmacokinetic endpoints described the pharmacokinetic profiles of insulin 454 and insulin glargine after single dose and in steady-state for insulin, <math>C_{max}</math>, <math>t_{max}</math> and AUC for various time intervals.</p> <p>In addition, <math>AUC_{SS,0-24h}/AUC_{SD,0-24h}</math>, <math>C_{max,SS,0-24h}/C_{max,SD,0-24h}</math>, <math>PTF_{0-24h}</math>, <math>t_{1/2}</math>, CL/F and MRT were derived.</p> |

### **Primary and Secondary Analysis**

The primary analysis estimated the molar dose ratio between insulin 454 and insulin glargine, i.e. the relative dose potency of insulin 454 compared to insulin glargine. The molar dose ratio was estimated by fitting a linear mixed effect model to the log-transformed  $AUC_{GIR,0-24h}$  values. The model included insulin preparation (insulin 454 or glargine) and period as fixed factors, subject as a random factor, and the log-transformed dose (in nmol) as a fixed covariate. The model used independent within- and between-subject errors with equal variances for all treatments. The secondary endpoints, estimated ratios, were compared between treatments using a linear mixed effect model with treatment (including both insulin preparation and dose) and period as fixed factors and subject as a random factor. The model used independent within- and between-subject errors with equal variances for all treatments. The ratios were log-transformed before analysis. From the model, the mean ratios were estimated for each treatment and also as an overall ratio for insulin 454 and for insulin glargine. Pairwise treatment ratios for the ratios were further estimated for insulin 454 vs. insulin glargine (overall and for each dose level) and for dose comparisons within insulin 454 and within insulin glargine. 95% confidence intervals were calculated for all estimates and p-values were presented for treatment ratios. Other secondary endpoints were summarised using descriptive statistics.

### **Demography of Trial Population**

Of the 63 randomised and exposed subjects, 54 (86%) were male and 9 (14%) were female. A total of 58 (92%) were White, whereas 4 (6%) were Black and 1 (2%) had other origin. The subjects' mean age was 39 years and the mean BMI was 24.1 kg/m<sup>2</sup>. Subjects had had diabetes for 3 to 43 years, and HbA<sub>1c</sub> ranged from 6.2% to 9.9%.

### **Efficacy Results**

#### **Pharmacodynamics**

- Based on  $AUC_{GIR,t,SS}$  at steady state, the molar dose ratio between SIBA (E) and insulin glargine was 0.81 [0.72; 0.93], i.e. 1 nmol of SIBA (E) produced the same effect on  $AUC_{GIR,t,SS}$  as 0.81 nmol of insulin glargine.
- The glucose lowering action of SIBA (E) and insulin glargine increased with increasing dose, and  $tGIR_{max,SS}$  occurred later with SIBA (E) than with insulin glargine (approximately 10 vs 6 hours).
- Dose linearity was demonstrated for both  $AUC_{GIR,t,SS}$  and  $GIR_{max,SS}$  at steady state within the investigated dose ranges (1.7 to 5.1 nmol/kg for SIBA (E)).
- At steady state, both SIBA (E) and insulin glargine had an action profile that extended beyond 24 hours in subjects with type 1 diabetes.
- At the medium and high doses of SIBA (E), almost horizontal mean blood glucose profiles throughout the glycaemic clamp indicated a near constant pharmacodynamic action of close to 42 hours at steady state.
- Peak-to-Trough fluctuation in GIR was lower with SIBA (E) than with insulin glargine (estimated ratio approximately 0.7).
- FFA was more suppressed with SIBA (E) than with insulin glargine.

#### **Pharmacokinetics**

- Median  $t_{max,SD}$  after single dose was 15 hours for both insulin 454 and insulin glargine, whereas median  $t_{max,SS}$  at steady state was 10 hours for insulin 454 and 4 to 9 hours for insulin glargine.
- Following the last of 8 consecutive daily doses, insulin 454 was detectable in the serum for up to 144 hours; however with >95% of total exposure observed within 120 hours. Insulin glargine was detectable up to 48 to 120 hours.
- Dose proportionality was demonstrated for both  $AUC_{t,SS}$  and  $C_{max,SS}$  at steady state within the investigated dose range (1.7 to 5.1 nmol/kg for SIBA (E)).
- The mean  $t_{1/2,SS}$  was approximately 26 hours for insulin 454 and approximately 14 hours for insulin glargine. There was no indication of dose dependency.
- Steady state was reached after 2 to 4 days for both SIBA (E) and insulin glargine following once daily dosing.
- It was not possible to estimate insulin 454 accumulation due to an artefact of the blood sampling procedure during the euglycaemic clamp. However, it was clear that multiple dosing with SIBA (E) gave rise to stable pharmacokinetic profiles at steady state.

**Safety Results**

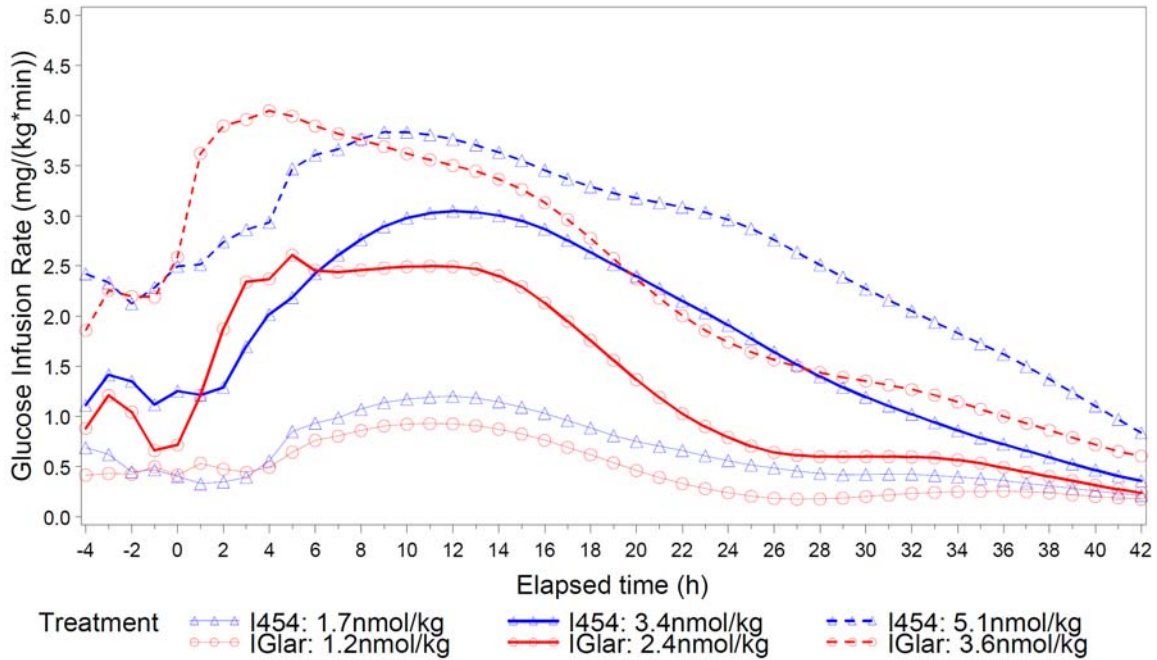
- A total of 64 AEs were reported by 30 out of 63 exposed subjects. Of these, 35 AEs were considered to be possibly or probably related to trial products. The majority of the AEs (46 out of 64) were moderate in severity, 18 AEs were mild.
- The AEs were equally divided between the three dose levels with 19, 21 and 24 events in 10, 11 and 9 subjects for the low, middle and high dose level, respectively.
- The most commonly reported AE was headache (35 out of 64 AEs). The remaining AEs were only reported once or twice at each dose level.
- No SAEs or deaths were reported during the trial.
- There were no clinically significant findings in clinically laboratory tests, vital signs, ECGs or physical examinations.
- Assessment of injection sites did not reveal any findings.
- Overall, 371 hypoglycaemic episodes were reported in 56 out of 63 subjects exposed with SIBA, and 272 hypoglycaemic episodes were reported in 57 out of 63 subjects exposed with insulin glargine. The incidence increased with increasing dose level. The majority of the episodes were classified as minor and were reported during day-time.

**Conclusions**

- Based on  $AUC_{GIR,\tau,SS}$  at steady state, the molar dose ratio between SIBA (E) and insulin glargine was 0.81 [0.72: 0.93].
- Dose linearity was demonstrated at steady state for  $AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  for SIBA (E).
- At steady state, both SIBA (E) and insulin glargine had a pharmacodynamic action profile that extended beyond 24 hours.
- At higher doses of SIBA (E), the almost horizontal mean blood glucose profiles throughout the glycaemic clamp indicated a near constant pharmacodynamic action of close to 42 hours at steady state.
- Dose proportionality was demonstrated for  $AUC_{\tau,SS}$  and  $C_{max,SS}$  at steady state for SIBA (E).
- Steady state in pharmacokinetics was reached after 2 to 4 days following once daily dosing of both SIBA (E) and insulin glargine.
- SIBA (E) and insulin glargine were well tolerated and no safety issues were raised. Assessment of injection sites did not reveal any findings. Due to the higher pharmacodynamic effect with SIBA (E), more hypoglycaemic episodes were reported compared to insulin glargine.

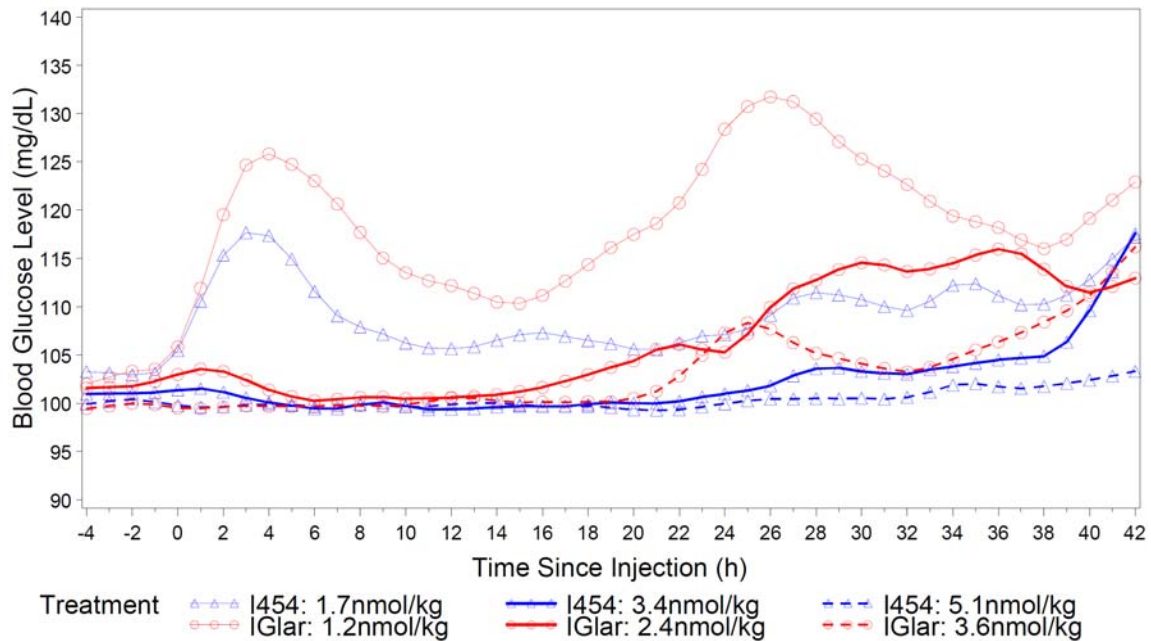
*The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).*

**Comparative PD Profiles:**

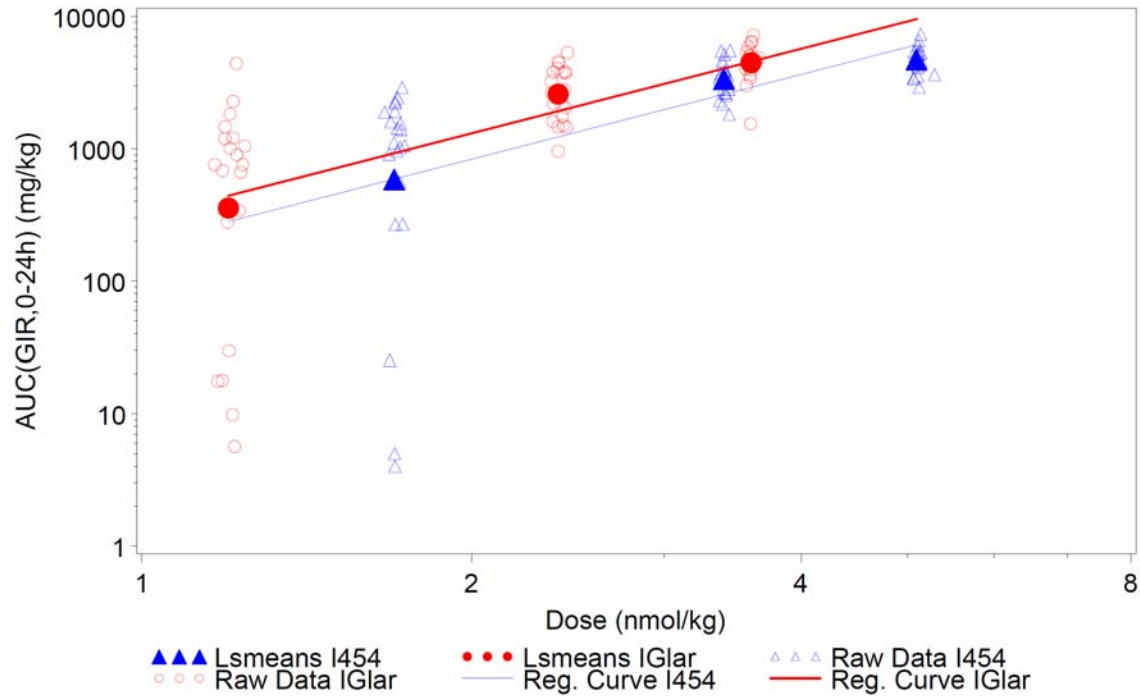


The GIR necessary to maintain the blood glucose concentration at 5.5 mmol/L (100 mg/dL) during the euglycaemic clamp was monitored for 42 hours at steady state conditions (following 8 days of once daily dosing of SIBA (IDeg-E) or insulin glargine). Overall, GIR increased with increasing doses for both SIBA (E) and insulin glargine. The increase in mean GIR was more pronounced and occurred earlier with insulin glargine than with SIBA (E), and the decline towards zero was observed earlier with insulin glargine than with SIBA (E).

**Blood glucose during clamp:**



Increased mean blood glucose concentrations were observed especially for the low dose levels of both SIBA (E) and insulin glargine indicating inadequate pharmacodynamic effect to maintain glucose clamp levels at these doses for some subjects. This was reflected in exceptionally low response in a number of individuals for the low dose groups for IDeg as well as IGLar, rendering the molar dose ratio assessment challenging.



**Estimated Molar Dose Ratio:**

|                                                                               | N   | Estimated Mean | 95%CI       |
|-------------------------------------------------------------------------------|-----|----------------|-------------|
| AUC(GIR,0-24h) - Primary Analysis<br>Potency<br>Parallel Dose-Response Curves | 126 | 0.81           | (0.72-0.93) |

**Descriptive statistics for the primary and secondary PD parameters:**

| Dose Level |       |            | AUC(GIR)0-24h (mg/kg) | GIRmax (mg/kg/min) | Time to GIRmax (h) |
|------------|-------|------------|-----------------------|--------------------|--------------------|
| Low        | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 1227.3 ( 851.6)       | 1.3 (0.7)          | 9.7 (4.7)          |
|            |       | Median     | 1107.                 | 1.2                | 10.4               |
|            |       | Min; Max   | 4.0; 2893.0           | 0.1; 2.5           | 0.0; 17.6          |
| Middle     | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 3505.2 (1066.7)       | 3.2 (0.9)          | 11.7 (3.5)         |
|            |       | Median     | 3463.                 | 3.1                | 13.3               |
|            |       | Min; Max   | 1817.7; 5536.8        | 1.9; 5.5           | 0.0; 16.2          |
| High       | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 4813.7 (1105.4)       | 4.1 (1.0)          | 7.9 (4.7)          |
|            |       | Median     | 4999.                 | 4.0                | 6.1                |
|            |       | Min; Max   | 2918.6; 7350.2        | 2.5; 6.3           | 0.3; 20.4          |
| Low        | IGlar | N          | 20                    | 20                 | 20                 |
|            |       | Mean (STD) | 943.9 (1033.7)        | 1.2 (0.9)          | 10.0 (10.9)        |
|            |       | Median     | 757.8                 | 1.1                | 9.0                |
|            |       | Min; Max   | 5.7; 4406.9           | 0.0; 3.8           | 0.0; 42.0          |
| Middle     | IGlar | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 2853.0 (1231.1)       | 3.3 (1.3)          | 6.5 (4.2)          |
|            |       | Median     | 2685.                 | 3.3                | 5.0                |
|            |       | Min; Max   | 955.6; 5329.1         | 1.2; 5.5           | 1.4; 13.3          |
| High       | IGlar | N          | 22                    | 22                 | 22                 |
|            |       | Mean (STD) | 4652.0 (1244.3)       | 5.0 (1.9)          | 5.5 (4.1)          |
|            |       | Median     | 4592.                 | 4.6                | 4.1                |
|            |       | Min; Max   | 1540.2; 7212.1        | 2.0; 9.6           | 1.1; 16.2          |

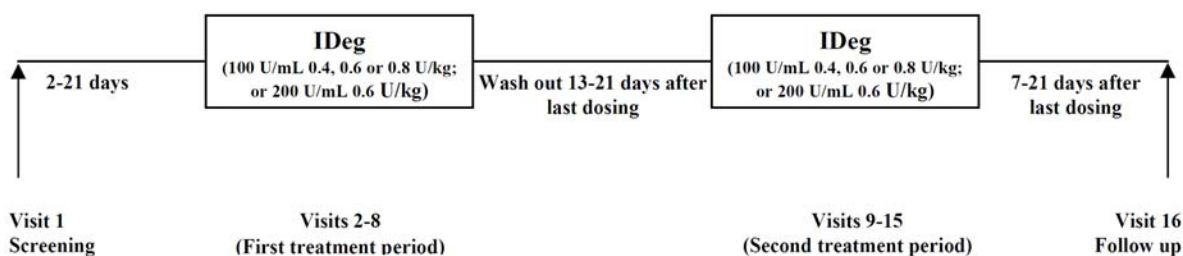
**Reviewer's Comments:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method used had calibration range of 23.8 to 805 pM). The precision of the assay, as determined from analysis of quality control samples ranged between 4.5 % and 15.3 %. The mean inaccuracy ranged between -4.3% and 2.4 %. The dilution linearity was not determined by the analytical laboratory neither the extent of dilution was reported for study samples. Study samples with >ULOQ levels were analyzed after dilution for IDEg. Therefore, the PK results should be interpreted with caution. Since the trial was intended to assess molar dose ratio based on PD comparison, this issue does not impact the trial results and interpretation. The analytical method adequately supported the results for IGlar with accuracy and precision for calibration standards (range of 16.0 to 750 pM) and QC samples lying within ±12% and ±7% respectively.

#### 4.2.10 Dose-response Study in Subjects with Type 2 DM (NN1250-1987)

**Rationale:** The rationale of this trial was to characterize the pharmacodynamic dose-response relationship of IDeg in subjects with type 2 diabetes with the main objective to evaluate the pharmacodynamic dose-response relationship of IDeg 100 U/mL over a range of three therapeutically relevant subcutaneous doses in subjects with type 2 diabetes. The pharmacodynamic and pharmacokinetic profile of IDeg 200 U/mL was characterized (at one dose level of 0.6 U/kg) in subjects with type 2 diabetes.

**Study Design:** The study design is presented in the figure below:



A 26-hour euglycemic clamp was conducted at steady-state conditions following the last dose of 0.4, 0.6 or 0.8 U/kg IDeg 100 U/mL in each treatment period. The glucose infusion rate necessary to maintain a constant blood glucose concentration of 5.0 mmol/L was recorded.

The study synopsis is as follows:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------|
| <b>Trial Registration ID-number</b><br>NCT01154881                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>EudraCT number</b><br>2009-017281-23 |
| <b>Title of Trial</b><br>A Trial Evaluating the Pharmacodynamic Response of NN1250 <sup>a</sup> at Steady State in Subjects with Type 2 Diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                         |
| <b>Investigator</b><br>Tim Heise, MD, Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |
| <b>Trial Site</b><br>Profil Institut für Stoffwechselforschung GmbH, Hellersbergstrasse 9, D-41460 Neuss, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |
| <b>Publications</b><br>None at the time of reporting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                         |
| <b>Trial Period</b><br>29 June to 19 November 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Development Phase</b><br>Phase 1     |
| <b>Objectives</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                         |
| <b>Primary Objective</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                         |
| <ul style="list-style-type: none"> <li>To evaluate the pharmacodynamic dose-response relationship of insulin deglude (IDeg) 100 U/mL over a range of three clinically relevant doses based on the area under the glucose infusion rate curve during one dosing interval (0-24 hours) at steady state</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                         |
| <b>Secondary Objectives</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                         |
| <ul style="list-style-type: none"> <li>To characterise the pharmacodynamic properties of three dose levels of IDeg 100 U/mL and one dose level of IDeg 200 U/mL at steady state</li> <li>To evaluate the pharmacokinetic dose-concentration relationship of IDeg 100 U/mL at steady state</li> <li>To characterise the pharmacokinetic properties of three dose levels of IDeg 100 U/mL and one dose level of IDeg 200 U/mL after single-dose and at steady state</li> <li>To evaluate pharmacokinetic trough concentrations of IDeg towards the steady state level</li> <li>To assess the safety and tolerability of three dose levels of IDeg 100 U/mL and one dose level of IDeg 200 U/mL</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |
| <b>Methodology</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                         |
| <p>This trial was a randomised, single-centre, double-blind, two-period, incomplete block cross-over, multiple-dose trial evaluating the dose-response relationship of IDeg 100 U/mL and characterising the pharmacodynamic response of IDeg 200 U/mL at steady state conditions in subjects with type 2 diabetes. Each subject was randomly allocated to two of four possible treatments: IDeg 100 U/mL (0.4, 0.6 or 0.8 U/kg) or IDeg 200 U/mL (0.6 U/kg). Each treatment period consisted of 6 days of once daily dosing with IDeg followed by 5 days with pharmacokinetic sampling until 120 hours after the last dose. The pharmacodynamic response was evaluated during a 26-hour euglycaemic clamp performed after the last dose. The trial consisted of a screening visit (2-21 days before randomisation), followed by two treatment periods (each of 11 days duration), and a follow-up visit (7-21 days after last dosing). Randomisation took place at the first dosing visit. The two treatment periods were separated by a wash out period (13-21 days) during which the subjects resumed their normal insulin treatment. The planned duration of the trial for the individual subject was between 34 and 75 days from screening to follow-up.</p> |                                         |
| <b>Number of Subjects Planned and Analysed</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                         |
| <p>A total of 45 subjects were planned to complete the trial. In total, 67 subjects were screened, 49 subjects were randomised and exposed to trial products. One subject was withdrawn from the trial due to personal reasons, and 48 subjects completed the trial. All 49 randomised subjects were included in the full analysis set and the safety analysis set.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                         |

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|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Diagnosis and Main Criteria for Inclusion</b></p> <p>Males and females with type 2 diabetes (<math>\geq 12</math> months) treated with insulin (basal insulin <math>\geq 0.2</math> (I)U/kg/day, and total insulin <math>&lt; 1.2</math> (I)U/kg/day), between 18 and 70 years of age, <math>HbA_{1c} \leq 10.0\%</math>, <math>BMI \leq 35.0</math> kg/m<sup>2</sup> and fasting C-peptide <math>&lt; 1.0</math> nmol/L.</p> <p>Key exclusion criteria were history or presence of cancer, cardiac diseases, supine blood pressure at screening outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic blood pressure, proliferative retinopathy or maculopathy and/or severe neuropathy as well as recurrent severe hypoglycaemia or hypoglycaemic unawareness, and smoking.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><b>Test Product, Dose and Mode of Administration, Batch Number</b></p> <ul style="list-style-type: none"> <li>• Insulin degludec (M) in 3 mL (b) (4) cartridges (100 U/mL) was administered at the dose levels 0.4, 0.6 or 0.8 U/kg as a subcutaneous injection in the thigh once daily for 6 days. Batch no. XCQ0001.</li> <li>• Insulin degludec (P) in 3 mL (b) (4) cartridges (200 U/mL) was administered at the dose level 0.6 U/kg as a subcutaneous injection in the thigh once daily for 6 days. Batch no. XCQ0018.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Duration of Treatment</b></p> <p>Subjects received once daily doses of IDeg for 6 days during the two treatment periods. The total duration of the trial for the individual subject was 34 to 75 days.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <p><b>Reference Therapy, Dose and Mode of Administration, Batch Number</b></p> <p>No reference therapy was used in this trial</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Criteria for Evaluation – Efficacy</b></p> <p><i>Pharmacodynamic variables</i></p> <ul style="list-style-type: none"> <li>• Glucose infusion rate</li> <li>• Blood glucose concentration</li> <li>• C-peptide concentration</li> </ul> <p><i>Pharmacokinetic variables</i></p> <ul style="list-style-type: none"> <li>• Serum IDeg concentration</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Criteria for Evaluation – Safety</b></p> <ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Physical examination</li> <li>• Vital signs</li> <li>• ECG</li> <li>• Hypoglycaemic episodes</li> <li>• Clinical laboratory safety variables</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| <p><b>Statistical Methods</b></p> <p>The pharmacodynamic and pharmacokinetic analyses were based on the full analysis set, which included all randomised subjects. The safety analyses were based on the safety analysis set, including all subjects, who received at least one dose of the investigational product or its comparator.</p> <p><i>Primary Endpoint</i></p> <p>The primary endpoint was <math>AUC_{GIR,\tau,SS}</math>, area under the glucose infusion rate (GIR) curve for IDeg (100 U/mL) during one dosing interval (0-24 hours) at steady state. <math>AUC_{GIR,\tau,SS}</math> was calculated as the area under the smoothed glucose infusion rate curve using the linear trapezoidal technique on interpolated points. Last observation carried forward was used if there were missing values in the end of the assessment interval. The log-transformed <math>AUC_{GIR,\tau,SS}</math> was analysed based on all data using a linear mixed model with period and an interaction term between treatment and dose level as fixed effects, and subject as random effect. As an exploratory analysis, the dose-response relationship for IDeg 100 U/mL was investigated further by attempting to use a functional form (e.g. a linear relationship between the log-transformed endpoint and dose).</p> <p><i>Secondary Pharmacodynamic Endpoints</i></p> <p>The secondary pharmacodynamic endpoints were derived from the individual glucose infusion rate profiles and blood glucose profiles at steady state and included <math>AUC_{GIR,\tau,SS}</math> (for IDeg 200 U/mL), <math>AUC_{GIR,0-12h,SS}</math>, <math>AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}</math>, <math>GIR_{max,SS}</math>, <math>tGIR_{max,SS}</math>, and <math>BG_{24h,SS}</math> and Duration of action<sub>SS</sub>. Duration of action was defined as the time from trial product administration until blood glucose exceeded 8.3 mmol/L (defined as end of</p> |

action). All secondary pharmacodynamic endpoints were summarised by treatment.  $AUC_{GIR,\tau,SS}$  for IDeg 200 U/mL and  $GIR_{max,SS}$  were analysed in the same model as for the primary endpoint.  $AUC_{GIR,\tau,SS}$  (IDeg 200 U/mL) was compared to  $AUC_{GIR,\tau,SS}$  (IDeg 100 U/mL) at dose level 0.6 U/kg.

#### Secondary Pharmacokinetic Endpoints

The secondary pharmacokinetic endpoints for IDeg 100 U/mL and IDeg 200 U/mL at steady state and after single dose were derived from the IDeg concentration-time curves.

Steady state:  $AUC_{IDeg,\tau,SS}$ ,  $AUC_{IDeg,0-12h,SS}$ ,  $AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$ ,  $C_{max,IDeg,SS}$ ,  $t_{max,IDeg,SS}$ ,  $ITC_{IDeg}$ ,  $t_{1/2,IDeg,SS}$ ,  $AUC_{IDeg,\tau,SS}/AUC_{IDeg,0-24h,SD}$ ,  $C_{max,IDeg,SS}/C_{max,IDeg,SD}$  and  $\lambda_z,IDeg,SS$ .

Single dose:  $AUC_{IDeg,0-24h,SD}$ ,  $C_{max,IDeg,SD}$ ,  $t_{max,IDeg,SD}$  and Onset of appearance<sub>IDeg,SD</sub>.

All pharmacokinetic endpoints were summarised by treatment.  $AUC_{IDeg,\tau,SS}$  and  $C_{max,IDeg,SS}$  were log-transformed and analysed in a linear mixed model with period, trial product and dose level as categorical effects and subject as random effect. In order to account for potential heteroscedasticity the residual error variance depended on trial product. As an exploratory analysis, the dose-concentration relationship for IDeg 100 U/mL was investigated further by attempting to use a functional form (e.g. a linear relationship between the log-transformed endpoint and log-transformed dose).

#### Safety Endpoints

The safety endpoints included adverse events, physical examination, vital signs, ECG, hypoglycaemic episodes and clinical laboratory safety variables. All safety endpoints were listed and summarised using descriptive statistics.

#### Demography of Trial Population

All 49 randomised and exposed subjects were white, and the majority of the subjects were males. They had a mean age of 58.7 years and a mean BMI of 29.6 kg/m<sup>2</sup>. The average duration of diabetes was 14 years, mean HbA<sub>1c</sub> was 7.6%, and mean C-peptide was 0.44 nmol/L.

#### Efficacy Results and Conclusions

##### Pharmacodynamics

- Total glucose-lowering effect ( $AUC_{GIR,\tau,SS}$ ) increased linearly with increasing dose of IDeg 100 U/mL (0.4, 0.6 and 0.8 U/kg).
- $GIR_{max}$  increased with increasing dose, and  $tGIR_{max,SS}$  was observed after 11–13 hours for the doses of IDeg 00 U/mL and after 12 hours for 0.6 U/kg IDeg 200 U/mL.
- The ratio between  $AUC_{GIR,0-12h,SS}$  and  $AUC_{GIR,\tau,SS}$  was close to 0.5 for both IDeg 100 U/mL and IDeg 200 U/mL, indicating similar glucose-lowering effect for the first 12 hours compared to the following 12 hours of one dosing interval.
- The glucose-lowering effect of IDeg 100 U/mL and IDeg 200 U/mL was similar and extended beyond 26 hours at all dose levels, as the blood glucose did not exceed 8.3 mmol/L (defined as end of action) within the 26-hour clamp period for any subject.
- The glucose infusion rate profiles of IDeg 100 U/mL and IDeg 200 U/mL were flat and stable.

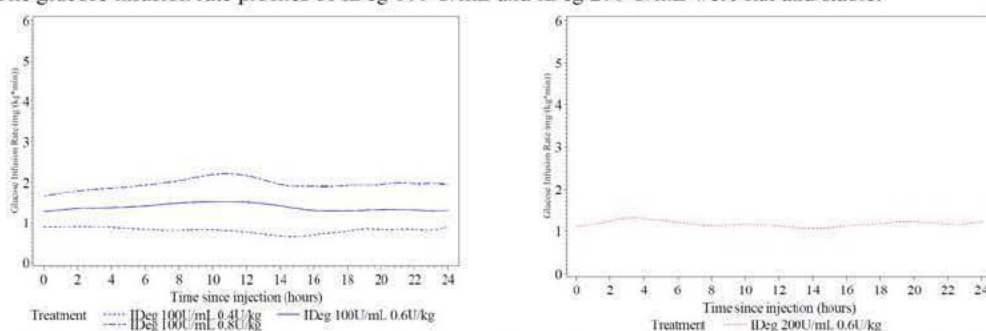
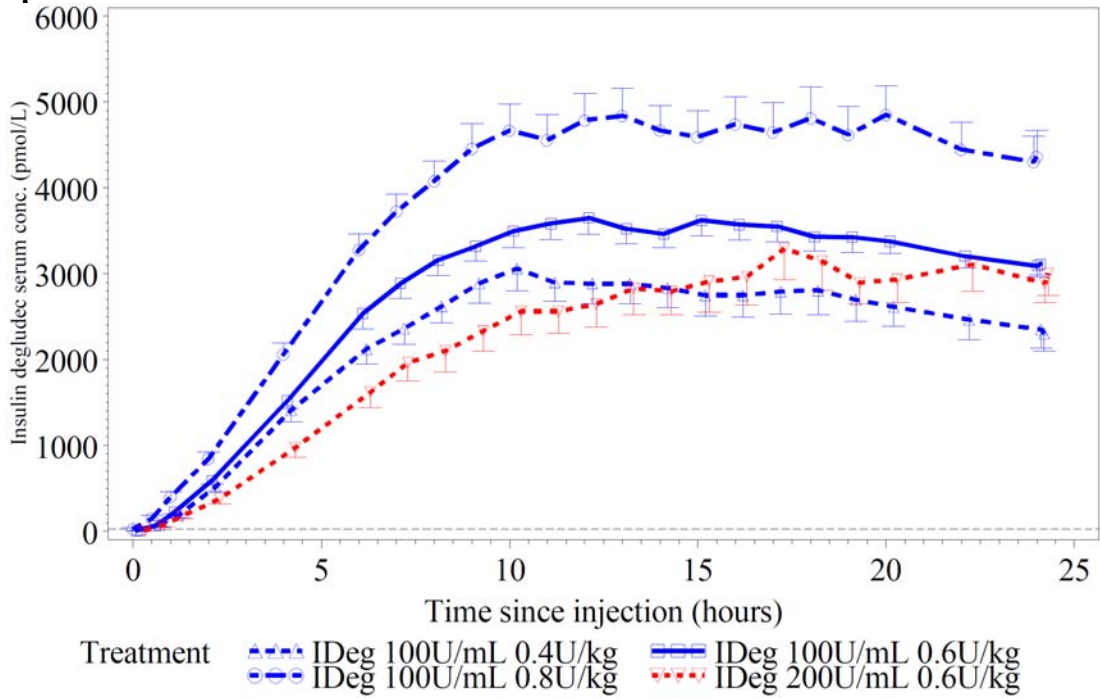


**Figure 1 24-Hour Mean Steady State Glucose Infusion Rate Profiles following 0.4, 0.6 and 0.8 U/kg IDeg 100 U/mL (Left) and 0.6 U/kg IDeg 200 U/mL (Right)**

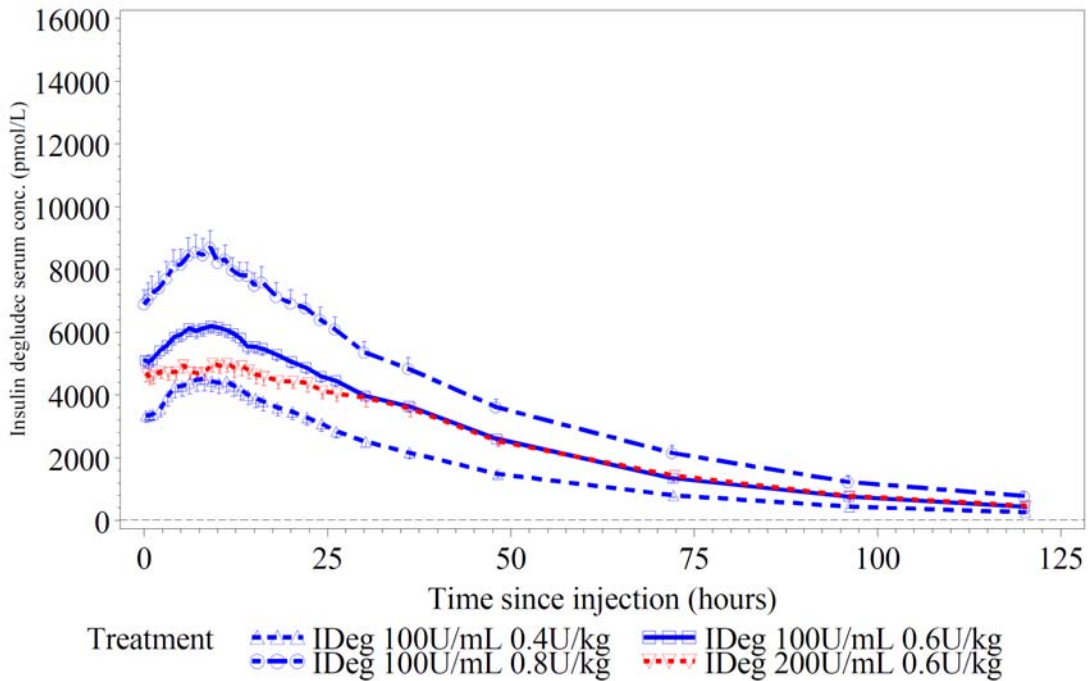
|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <p><b>Pharmacokinetics</b></p> <ul style="list-style-type: none"> <li>• Total exposure of IDeg 100 U/mL increased proportionally with increasing dose with estimated log-dose slope of 0.93 [0.82; 1.03]<sub>95%CI</sub> for <math>AUC_{\tau,SS}</math>.</li> <li>• Maximum exposure of IDeg 100 U/mL increased proportionally with increasing dose with estimated log-dose slope of 0.94 [0.81; 1.08]<sub>95%CI</sub> for <math>C_{max,SS}</math>.</li> <li>• The ratio between <math>AUC_{0-12h,SS}</math> and <math>AUC_{\tau,SS}</math> was close to 0.5 for IDeg 100 U/mL and IDeg 200 U/mL, indicating that IDeg exposure was similar for the first 12 hours compared to the following 12 hours of one dosing interval.</li> <li>• The pharmacokinetic profiles of IDeg 100 U/mL and IDeg 200 U/mL were flat and stable, and <math>AUC_{IDeg,\tau,SS}</math> and <math>C_{max,IDeg,SS}</math> appeared to be slightly lower for IDeg 200 U/mL compared to IDeg 100 U/mL.</li> <li>• The terminal <math>t_{1/2}</math> (harmonic mean) was for 25.1 hours for IDeg 100 U/mL across the three dose levels, and 26.2 hours for 0.6 U/kg IDeg 200 U/mL.</li> <li>• Onset of appearance of IDeg 100 U/mL was 35–46 minutes after dosing; earlier for the higher doses. Onset of appearance of 0.6 U/kg IDeg 200 U/mL was 51 minutes after dosing.</li> <li>• Steady state was reached after 48 to 72 hours (2–3 days) for both IDeg 100 U/mL and IDeg 200 U/mL, and the ratio between total exposure at steady state and total exposure during the first dosing interval was 1.8–2.2.</li> </ul>            |
| <p><b>Safety Results and Conclusions</b></p> <ul style="list-style-type: none"> <li>• A total of 21 AEs were reported in 13 (27%) subjects treated with IDeg 100 U/mL, and 3 AEs were reported in 3 (19%) subjects treated with IDeg 200 U/mL. The majority (19 AEs with IDeg 100 U/mL and 3 with IDeg 200 U/mL) were reported as mild or moderate in severity. A total of 6 AEs with IDeg 100 U/mL and 1 AE with IDeg 200 U/mL (headache, nausea and vomiting) were reported as possibly related; no AEs were reported as probably related.</li> <li>• The most commonly reported AEs were headache (6 events with IDeg 100 U/mL and 1 event with IDeg 200 U/mL), back pain (3 events with IDeg 100 U/mL) and nasopharyngitis (2 events with IDeg 100 U/mL).</li> <li>• Two SAEs (syncope and thoracic vertebral fracture) occurred in the same subject 6 days after the last dosing with 0.8 U/kg IDeg 100 U/mL. Both events were evaluated as severe and unlikely related to trial product. The subject has recovered completely from the syncope and is recovering from the fracture.</li> <li>• No injection site reactions were recorded with IDeg 100 U/mL or IDeg 200 U/mL.</li> <li>• A total of 33 hypoglycaemic episodes were reported in 20 (41%) subjects treated with IDeg 100 U/mL, and 6 episodes were reported in 3 (19%) subjects treated with IDeg 200 U/mL. None of the episodes were severe.</li> <li>• No clinically significant changes in vital signs, ECG or safety laboratory parameters from screening to follow-up were observed with IDeg 100 U/mL or IDeg 200 U/mL.</li> </ul> |
| <p><b>Overall Conclusions</b></p> <p>The conclusions from this randomised, single-centre, multiple-dose, double-blind, two-period, incomplete block cross-over trial evaluating the pharmacodynamic and pharmacokinetic properties of IDeg 100 U/mL (0.4, 0.6 and 0.8 U/kg) and IDeg 200 U/mL (0.6 U/kg) at steady state conditions in subjects with type 2 diabetes mellitus are:</p> <ul style="list-style-type: none"> <li>• Total glucose-lowering effect of IDeg (<math>AUC_{GIR,\tau,SS}</math>) increases linearly with increasing dose</li> <li>• The glucose-lowering effect of IDeg 100 U/mL and IDeg 200 U/mL extends beyond 26 hours at clinically relevant doses</li> <li>• IDeg has a flat and stable glucose-lowering effect</li> <li>• IDeg 100 U/mL and IDeg 200 U/mL have a similar glucose-lowering effect</li> <li>• Total exposure of IDeg (<math>AUC_{IDeg,\tau,SS}</math>) increases proportionally with increasing dose</li> <li>• IDeg 100 U/mL and IDeg 200 U/mL have a flat and stable pharmacokinetic profile</li> <li>• IDeg 100 U/mL and 200 U/mL are well tolerated, and no safety issues were identified in this trial</li> </ul> <p><i>The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice (refer to applicable edition).</i></p>                                                                                                                                                                                                                                                                                         |

**Comparative PD Profiles:**



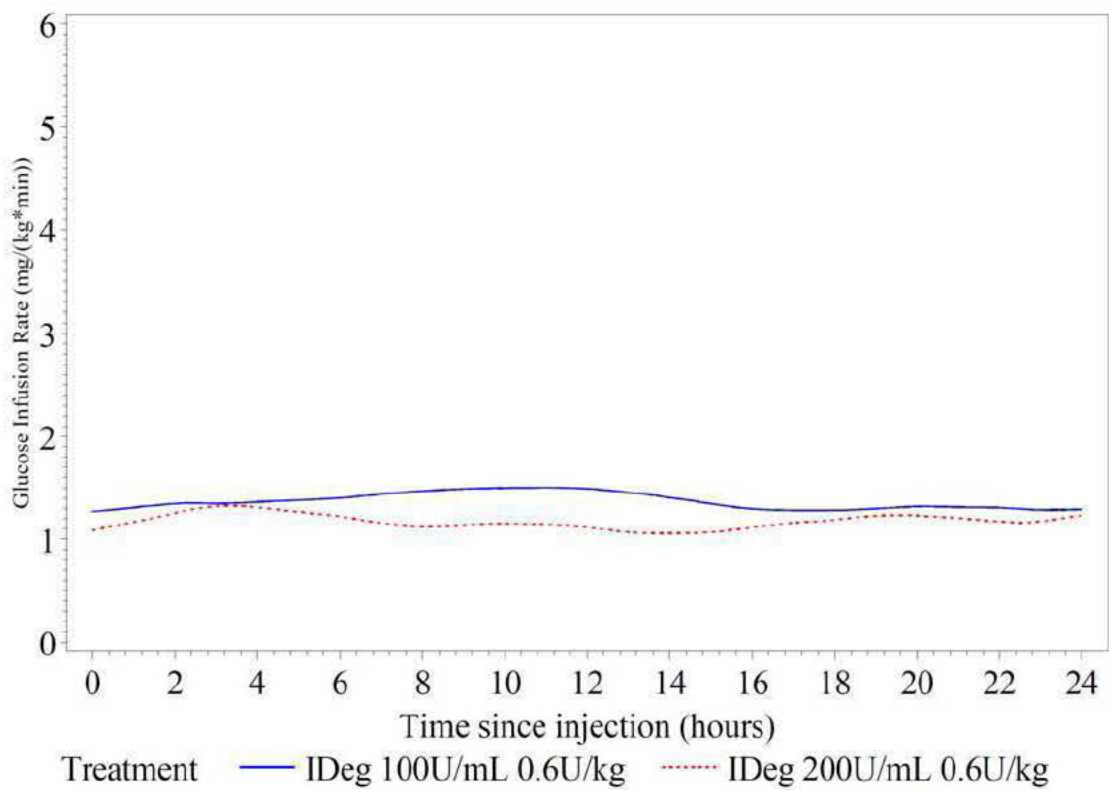
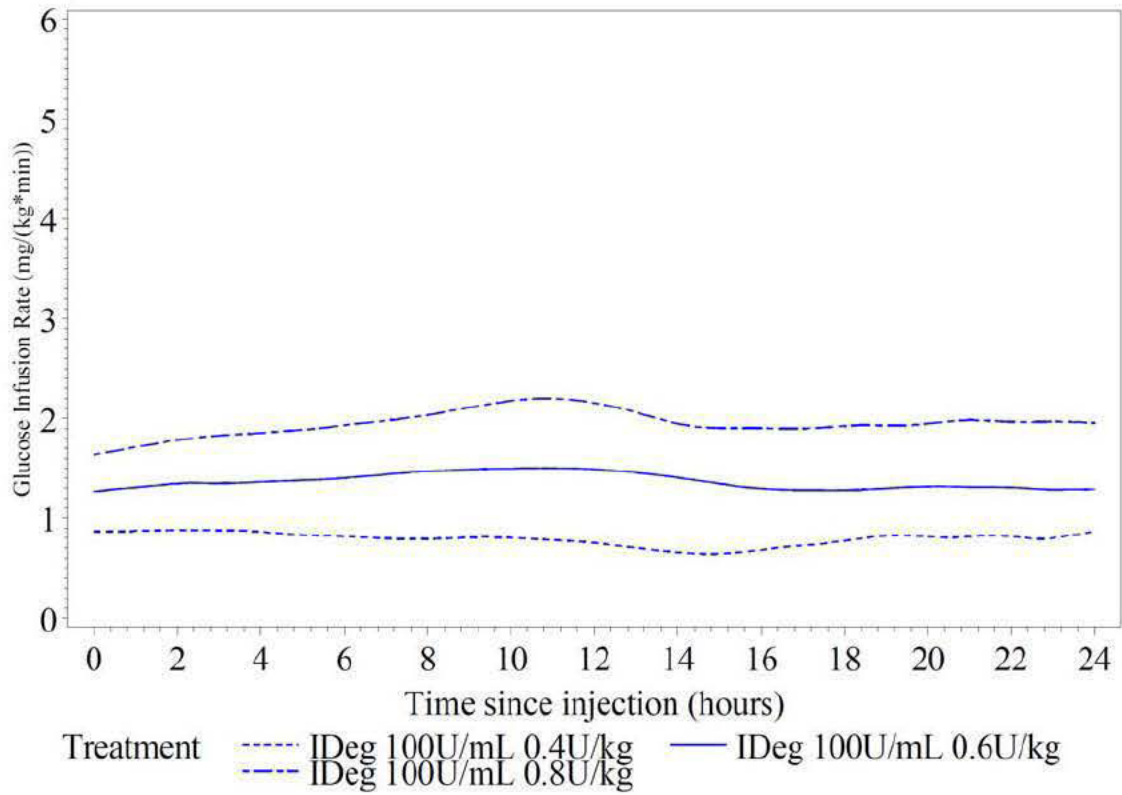
Horizontal dashed line represents the lower limit of quantification  
 Error bars represent the standard error of the mean (SEM)

**Comparative PD Profiles:**



Horizontal dashed line represents the lower limit of quantification  
 Error bars represent the standard error of the mean (SEM)

**Comparative PD Profiles:**



|                             | FAS | N  | Estimate | 95% CI      |
|-----------------------------|-----|----|----------|-------------|
| AUC GIR, tau, SS (mg/kg)    |     |    |          |             |
| LSMeans                     |     |    |          |             |
| IDeg 100U/mL 0.6U/kg        | 38  | 37 | 1658     |             |
| IDeg 200U/mL 0.6U/kg        | 16  | 16 | 1460     |             |
| Dose contrasts              |     |    |          |             |
| IDeg 200 vs 100U/mL 0.6U/kg |     |    | 0.88     | [0.70;1.12] |
| GIR max, SS (mg/(kg*min))   |     |    |          |             |
| LSMeans                     |     |    |          |             |
| IDeg 100U/mL 0.6U/kg        | 38  | 37 | 1.66     |             |
| IDeg 200U/mL 0.6U/kg        | 16  | 16 | 1.61     |             |
| Dose contrasts              |     |    |          |             |
| IDeg 200 vs 100U/mL 0.6U/kg |     |    | 0.97     | [0.87;1.08] |

The endpoints are log-transformed and analysed using a linear mixed model with period, treatment and dose level as fixed effects, subjects as a random effect, and the residual error variance depending on treatment group.

### Descriptive statistics for the primary and secondary PD parameters:

| Dose Level |       |            | AUC(GIR)0-24h (mg/kg) | GIRmax (mg/kg/min) | Time to GIRmax (h) |
|------------|-------|------------|-----------------------|--------------------|--------------------|
| Low        | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 1227.3 ( 851.6)       | 1.3 (0.7)          | 9.7 (4.7)          |
|            |       | Median     | 1107.                 | 1.2                | 10.4               |
|            |       | Min; Max   | 4.0; 2893.0           | 0.1; 2.5           | 0.0; 17.6          |
| Middle     | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 3505.2 (1066.7)       | 3.2 (0.9)          | 11.7 (3.5)         |
|            |       | Median     | 3463.                 | 3.1                | 13.3               |
|            |       | Min; Max   | 1817.7; 5536.8        | 1.9; 5.5           | 0.0; 16.2          |
| High       | I454  | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 4813.7 (1105.4)       | 4.1 (1.0)          | 7.9 (4.7)          |
|            |       | Median     | 4999.                 | 4.0                | 6.1                |
|            |       | Min; Max   | 2918.6; 7350.2        | 2.5; 6.3           | 0.3; 20.4          |
| Low        | IGlar | N          | 20                    | 20                 | 20                 |
|            |       | Mean (STD) | 943.9 (1033.7)        | 1.2 (0.9)          | 10.0 (10.9)        |
|            |       | Median     | 757.8                 | 1.1                | 9.0                |
|            |       | Min; Max   | 5.7; 4406.9           | 0.0; 3.8           | 0.0; 42.0          |
| Middle     | IGlar | N          | 21                    | 21                 | 21                 |
|            |       | Mean (STD) | 2853.0 (1231.1)       | 3.3 (1.3)          | 6.5 (4.2)          |
|            |       | Median     | 2685.                 | 3.3                | 5.0                |
|            |       | Min; Max   | 955.6; 5329.1         | 1.2; 5.5           | 1.4; 13.3          |
| High       | IGlar | N          | 22                    | 22                 | 22                 |
|            |       | Mean (STD) | 4652.0 (1244.3)       | 5.0 (1.9)          | 5.5 (4.1)          |
|            |       | Median     | 4592.                 | 4.6                | 4.1                |
|            |       | Min; Max   | 1540.2; 7212.1        | 2.0; 9.6           | 1.1; 16.2          |

### Reviewer's Comments:

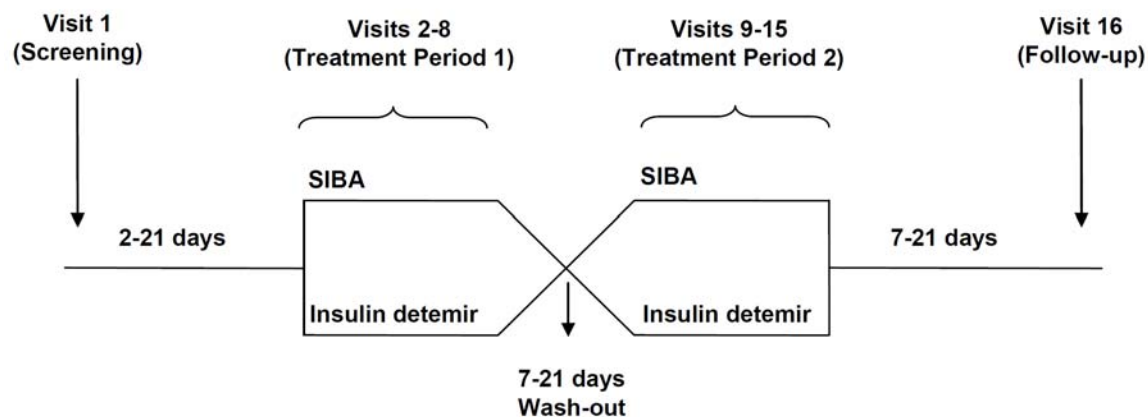
The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results for IDeg. Precision (%CV) ranged from 2.3% to 4.3% and the accuracy (%Bias) ranged from -1.0% to 2.3% for calibration standards (range of 20.0 to 1000 pM). For QC samples, the precision (%CV) ranged from 5.8% to 9.0% and the accuracy (%Bias) ranged from -3.1% to -1.0%. Precision (%CV) ranged from 5.4% to 7.2% and accuracy (%Bias) ranged from -2.6% to -1.2% for dilution QC samples. Based on the study results, the PK profile from U200 formulation showed distinct slower absorption in comparison to the U100 formulation. However, at steady-state the PD profiles were comparable. Although, the caveat with the multiple dose evaluation for formulation

comparison is that sensitivity to detect differences is low. Therefore, a single dose comparison is ideal for establishing PKPD comparability between formulations. The long duration of action however limits the PD comparison to partial AUC over 24 hour duration due to practical limitations of conducting >24 h euglycemic clamp. One likely solution to this problem could be that PD comparison is performed after first dose and at steady state.

#### 4.2.11 Dose-response Study in Japanese Subjects with Type 1 DM (NN1250-1996)

**Rationale:** This trial was planned to assess the pharmacodynamic and pharmacokinetic properties of IDeg at steady state in Japanese subjects with diabetes at therapeutic dose levels. The results obtained from this trial could contribute to the development of improved treatments for Japanese with diabetes in the future.

**Study Design:** The study design is presented in the figure below:



**SIBA:** Soluble Insulin Basel Analogue, NN1250, Synonym previously used for IDeg

**Dose:** 0.4 U/kg/day of IDeg or IDet

The study synopsis is as follows:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------|
| <b>Trial Registration ID-number</b><br>NCT01135927                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Japanese Registration number</b><br>21-4003 |
| <b>Title of Trial</b><br>A Trial Investigating the Pharmacodynamic Properties of NN1250 <sup>1</sup> in Japanese Subjects with Type 1 Diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                |
| <b>Investigator(s)</b><br>Dr. Ipppei Ikushima, MD, PhD, Sumida Hospital, Tokyo, Japan                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                |
| <b>Trial Site(s)</b><br>Sumida Hospital, 1-29-1, Honjo, Sumida-ku, Tokyo 130-0004, Japan                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                |
| <b>Publications</b><br>None at the time of the final clinical trial report                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |                                                |
| <b>Trial Period</b><br>01 June to 13 October 2010                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>Development Phase</b><br>Phase 1            |
| <b>Objectives</b><br><b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To characterise the pharmacodynamic response of insulin degludec (IDeg) based on the area under the glucose infusion rate curve from 0 to 24 hours at steady state</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To characterise the other pharmacodynamic properties of IDeg and insulin detemir (IDet) at steady state</li> <li>To characterise the pharmacokinetic properties of IDeg and IDet after single dose and at steady state</li> <li>To evaluate pharmacokinetic trough values towards the steady state level</li> <li>To assess the safety and tolerability of IDeg in Japanese subjects with type 1 diabetes</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                            |                                                |
| <b>Methodology</b><br>This was a randomised, single-centre, double-blind, two-period cross-over, multiple dose trial comparing the pharmacodynamic and pharmacokinetic properties of IDeg with IDet at steady state conditions in Japanese subjects with type 1 diabetes. Each subject was randomised to one of the two possible treatment sequences: IDeg/IDet or IDet/IDeg. The trial consisted of a screening visit (Visit 1) followed by two treatment periods (Visits 2 to 8 and Visits 9 to 15) and a follow-up visit (Visit 16). There was 2 to 21 days between the screening visit and the first treatment period. Each treatment period had duration of 11 days consisting of 6 days with once daily dosing with IDeg or IDet followed by a period of 5 days with blood sampling until 120 hours after last dosing (including a glucose clamp period of 26 hours). The two treatment periods were separated by a wash-out period (7 to 21 days after last trial product administration at Visit 5 Day 6) during which the subjects resumed their normal insulin treatment. There was a follow-up visit 7 to 21 days after the last injection of trial product. |                                                |
| <b>Number of Subjects Planned and Analysed</b><br>A total of 20 subjects were planned to complete the trial. In total, 24 subjects were screened, 22 subjects were randomised and exposed to trial products. One subject withdrew consent after Visit 10 due to an accidental change of the subject's schedule, and 21 subjects completed the trial. All 22 randomised subjects were included in the full analysis set and the safety analysis set                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                |
| <b>Diagnosis and Main Criteria for Inclusion</b><br>Male and female Japanese subjects with type 1 diabetes treated with insulin ( $\geq 0.3$ IU/kg/day) for $\geq 12$ months, between 20 and 65 years of age, with $HbA_{1c} \leq 10.0\%$ , BMI 18.0-28.0 kg/m <sup>2</sup> and fasting C-peptide $< 0.3$ nmol/L. Key exclusion criteria were history or presence of cancer, cardiac diseases, supine blood pressure at screening outside the range of 90–140 mmHg for systolic or 50–90 mmHg for diastolic blood pressure, proliferative retinopathy or maculopathy and/or severe neuropathy as well as recurrent severe hypoglycaemia or hypoglycaemic unawareness, and smoking.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                                |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
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| <p><b>Test Product, Dose and Mode of Administration, Batch Number</b><br/> Insulin degludec (M), 100 U/mL in 3 mL (b) (4) cartridges (batch no. XCQ0001). IDeg (0.4 U/kg) was administered s.c. in the thigh once daily for 6 days</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>Duration of Treatment</b><br/> Subjects received once daily doses of IDeg for 6 days and once daily doses of IDet for 6 days during the two treatment periods. The total duration of the trial for the individual subject was 27 to 74 days.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| <p><b>Reference Therapy, Dose and Mode of Administration, Batch Number</b><br/> Insulin detemir (100 U/mL) in 3 mL Penfill® cartridges (batch no. XQ50242). IDet (0.4 U/kg) was administered s.c. in the thigh once daily for 6 days.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Criteria for Evaluation – Efficacy</b><br/> <b>Pharmacodynamic variables</b></p> <ul style="list-style-type: none"> <li>• Glucose infusion rate</li> <li>• Blood glucose concentration</li> </ul> <p><b>Pharmacokinetic variables</b></p> <ul style="list-style-type: none"> <li>• Serum IDeg concentration</li> <li>• Serum IDet concentration</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| <p><b>Criteria for Evaluation – Safety</b></p> <ul style="list-style-type: none"> <li>• Adverse events</li> <li>• Physical examination</li> <li>• Vital signs</li> <li>• ECG</li> <li>• Hypoglycaemic episodes</li> <li>• Clinical laboratory safety variables</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| <p><b>Statistical Methods</b><br/> The pharmacodynamic and pharmacokinetic analyses were based on the full analysis set, which included all randomised subjects. The safety analyses were based on the safety analysis set, including all subjects, who received at least one dose of the investigational product or its comparator.</p> <p><b>Primary Endpoint</b><br/> The primary endpoint was <math>AUC_{GIR,t,SS}</math>, area under the glucose infusion rate (GIR) curve during one dosage interval at steady state for the IDeg treatment (0-24 hours). <math>AUC_{GIR,t,SS}</math> was calculated as the area under the smoothed glucose infusion rate curve using the linear trapezoidal technique on interpolated points. Last observation carried forward was used if there were missing values in the end of the assessment interval. The log-transformed <math>AUC_{GIR,t,SS}</math> was analysed using an analysis of variance (ANOVA) method with treatment (IDeg/IDet), treatment period as fixed factors and subjects as random effect. In order to account for potential heteroscedasticity, the error-term was dependent on the treatment.</p> <p><b>Secondary Pharmacodynamic Endpoints</b><br/> The secondary pharmacodynamic endpoints were derived from the individual glucose infusion rate profiles at steady state and included <math>GIR_{max,SS}</math>, <math>tGIR_{max,SS}</math>, <math>AUC_{GIR,t,SS}</math> (for IDet), <math>AUC_{GIR,0-12h,SS}</math>, <math>AUC_{GIR,0-12h,SS}/AUC_{GIR,t,SS}</math>, <math>AUCF_{GIR,t,SS}</math>, <math>AUCF_{GIR,0-12h,SS}</math>, <math>AUCF_{GIR,12-24h,SS}</math>, Duration of action<sub>SS</sub> and <math>BG_{24h,SS}</math>. Using the same model as for the primary endpoint the mean and 95% confidence interval for <math>AUC_{GIR,t,SS}</math> (IDet) and <math>GIR_{max,SS}</math> (IDeg and IDet) were estimated. Duration of action at steady state was illustrated using Kaplan-Meier plots, and all other pharmacodynamic endpoints were summarised by treatment using descriptive statistics.</p> <p><b>Secondary Pharmacokinetic Endpoints</b><br/> The secondary pharmacokinetic endpoints for IDeg and IDet after single dose and at steady state were derived from the insulin concentration-time curves. The term “ins” is used for both IDeg and IDet.<br/> Single dose: <math>AUC_{ins,0-24h,SD}</math>, <math>C_{max,ins,SD}</math>, <math>t_{max,ins,SD}</math> and Onset of appearance<sub>IDeg,SD</sub>.<br/> Steady state: <math>AUC_{ins,t,SS}</math>, <math>AUC_{ins,0-12h,SS}</math>, <math>AUC_{ins,0-12h,SS}/AUC_{ins,t,SS}</math>, <math>C_{max,ins,SS}</math>, <math>t_{max,ins,SS}</math>, <math>t_{1/2,ins,SS}</math>, <math>AUCF\%_{ins,t,SS}</math>, <math>AUCF\%_{ins,0-12h,SS}</math>, <math>AUCF\%_{ins,12-24h,SS}</math>, <math>ITC_{ins}</math>, <math>AUC_{ins,t,SS}/AUC_{ins,0-24h,SD}</math>, <math>C_{max,ins,SS}/C_{max,ins,SD}</math> and <math>\lambda_{z,ins,SS}</math>.<br/> The mean and 95% confidence interval of the logarithm of <math>AUC_{ins,t,SS}</math> and <math>C_{max,ins,SS}</math> were estimated assuming normal</p> |

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
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| <p>distribution. The mean and 95% confidence interval were back-transformed to the original scale. All other pharmacokinetic endpoints were summarised by treatment using descriptive statistics.</p> <p><b>Safety Endpoints</b></p> <p>The safety endpoints included adverse events, physical examination, vital signs, ECG, hypoglycaemic episodes and clinical laboratory safety variables. All safety endpoints were listed and summarised using descriptive statistics.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| <p><b>Demography of Trial Population</b></p> <p>All randomised and exposed subjects were Japanese and the majority of the subjects were males. They had a mean age of 42 years and a mean BMI of 22.3 kg/m<sup>2</sup>. The average duration of diabetes was 18 years, mean HbA<sub>1c</sub> was 7.5%, and mean C-peptide was 0.04 nmol/L.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| <p><b>Efficacy Results</b></p> <p><b>Pharmacodynamics</b></p> <ul style="list-style-type: none"> <li>• The glucose infusion rate profile of IDeg was flatter and more stable compared to IDet</li> <li>• Based on descriptive statistics, mean AUC<sub>GIR,τ,SS</sub> was 1446 mg/kg for IDeg.</li> <li>• The ratio between AUC<sub>GIR,0-12h,SS</sub> and AUC<sub>GIR,τ,SS</sub> was 0.48 for IDeg indicating similar glucose lowering effect for the first 12 hours compared to the last 12 hours of one dosing interval. For IDet, the ratio was 0.66 indicating higher glucose lowering effect during the first 12 hours compared to the last 12 hours of one dosing interval.</li> <li>• The fluctuation in the glucose infusion rate was lower for IDeg compared to IDet (AUCF<sub>GIR,τ,SS</sub>: 0.28 vs. 0.49 mg/(kg*min)).</li> <li>• The maximum glucose infusion rate (GIR<sub>max,SS</sub>) was similar for IDeg (1.7 mg/(kg*min)) and IDet (1.8 mg/(kg*min)) and the median time of the maximal glucose infusion rate (tGIR<sub>max,SS</sub>) was 10.6 hours for IDeg and 8.9 hours for IDet.</li> <li>• Duration of action exceeded 26 hours for all 21 subjects when dosed with IDeg, whereas 7 subjects experienced end of action before 26 hours with IDet.</li> <li>• The mean blood glucose concentration during the last 10 minutes of one dosing interval (BG<sub>24h,SS</sub>) was 5.6 mmol/L for IDeg and 7.3 mmol/L for IDet, indicating that the glucose target level was not kept throughout the clamp for IDet in some subjects.</li> </ul> <p><b>Pharmacokinetics</b></p> <ul style="list-style-type: none"> <li>• The pharmacokinetic profile of IDeg was flat and stable compared to IDet.</li> <li>• The ratio between AUC<sub>0-12h,SS</sub> and AUC<sub>τ,SS</sub> was 0.53 for IDeg and 0.65 for IDet indicating that IDeg exposure was similar for the first 12 hours compared to the following 12 hours of one dosing interval, whereas IDet exposure was higher during the first 12 hours of one dosing interval.</li> <li>• The relative fluctuation of the serum concentration-time curve (AUCF %) was lower for IDeg compared to IDet (11.6% vs. 39.1%, respectively).</li> <li>• Based on descriptive statistics the terminal t<sub>1/2</sub> (harmonic mean) was longer for IDeg compared to IDet (18.3 vs. 6.3 hours).</li> <li>• Steady state was reached after approximately 48 to 72 hours for IDeg and after approximately 24 hours for IDet, and the mean ratio between AUC<sub>τ,SS</sub> and AUC<sub>0-24h,SD</sub> was 1.7 for IDeg and 1.1 for IDet.</li> <li>• Onset of appearance of IDeg after single dose occurred approximately 49 minutes after dosing.</li> </ul> |
| <p><b>Safety Results</b></p> <ul style="list-style-type: none"> <li>• A total of 3 adverse events were reported in 3 (14%) subjects when treated with IDeg and 1 adverse event was reported in 1 (5%) subject when treated with IDet. All adverse events were mild in severity and were unlikely related to trial product.</li> <li>• No adverse events were reported more than once.</li> <li>• No serious adverse events or deaths were reported in this trial.</li> <li>• No injection site reactions were recorded.</li> <li>• In total, 195 treatment emergent hypoglycaemic episodes were reported by 21 subjects when treated with IDeg and 143 episodes were reported by 20 subjects when treated with IDet. For IDeg a total of 112 out of 195 hypoglycaemic episodes were asymptomatic, while 71 out of 143 hypoglycaemic episodes were asymptomatic with IDet. Of these, 30 episodes with IDeg and 23 episodes with IDet were nocturnal. None of the episodes were evaluated as severe.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |

- No clinically significant changes in vital signs, ECG or safety laboratory parameters from screening to follow-up were observed.

**Conclusions**

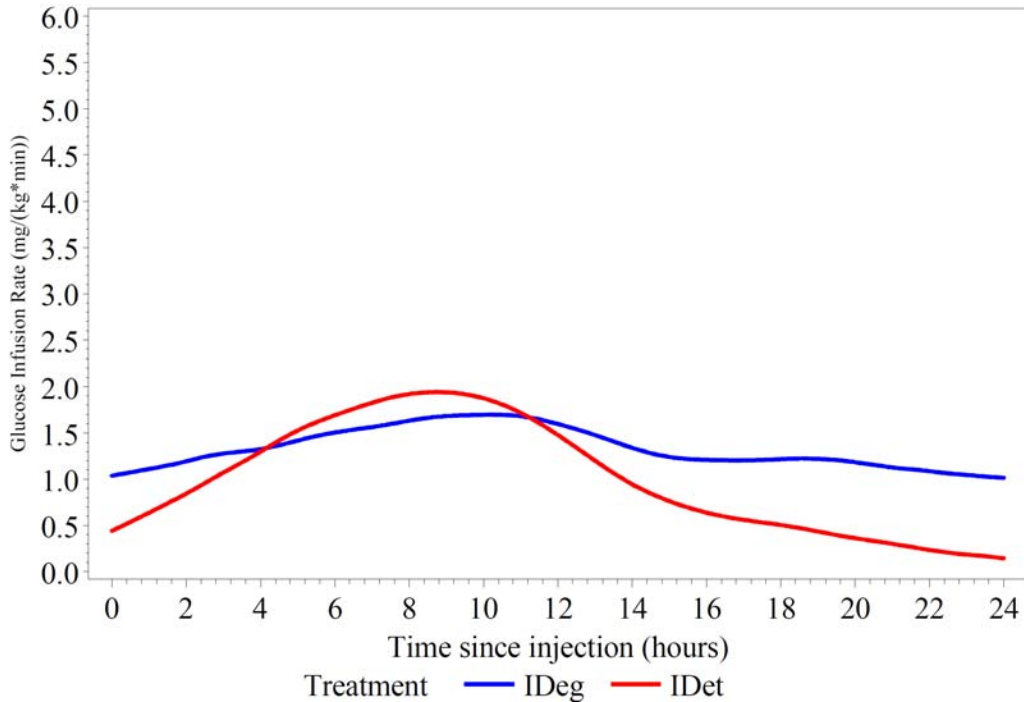
The conclusions from this randomised, single-centre, double-blind, two-period, cross-over, multiple-dose trial evaluating the pharmacodynamic and pharmacokinetic properties of IDeg and IDet at steady state condition at a clinically relevant dose of 0.4 U/kg in Japanese subjects with type 1 diabetes mellitus are:

- The glucose-lowering effect of IDeg extends beyond 26 hours at a clinically relevant dose
- IDeg has longer duration of action compared to IDet
- IDeg has a flat and stable glucose-lowering effect compared to IDet
- IDeg has a flat and stable pharmacokinetic profile compared to IDet
- IDeg is well tolerated and no safety issues are identified in this trial

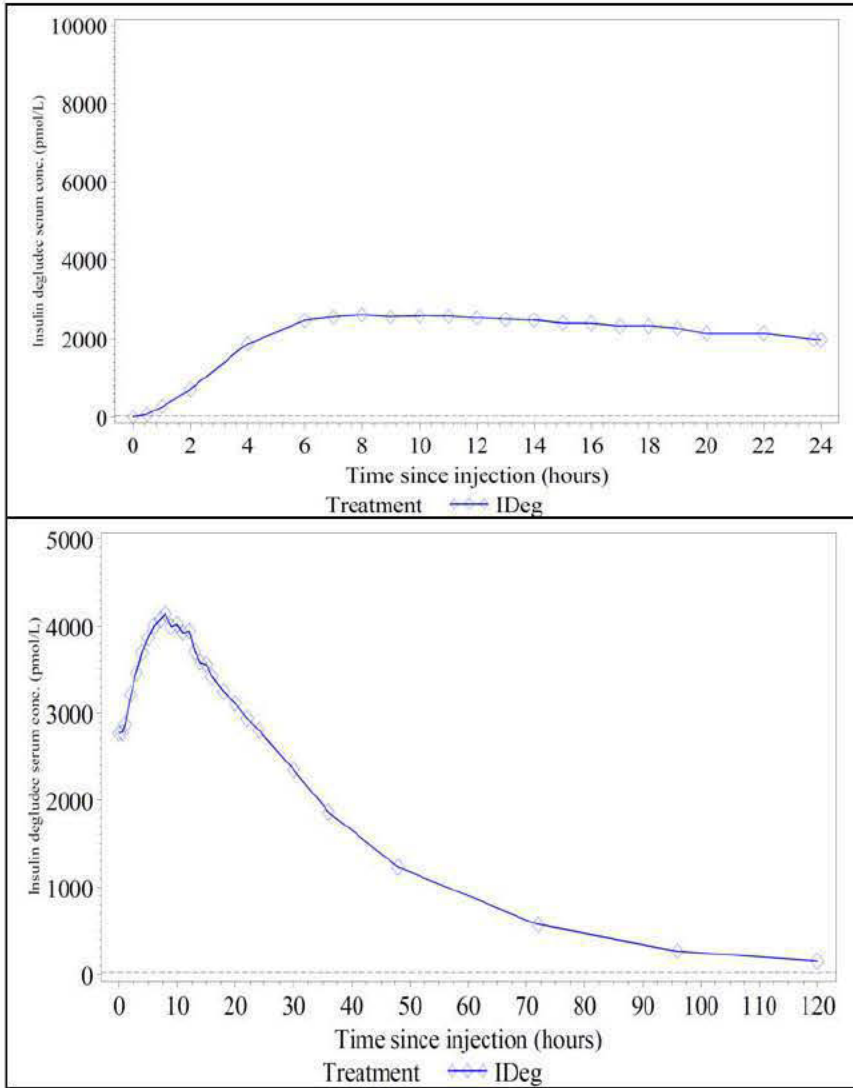
*The trial was conducted in accordance with the Declaration of Helsinki (Last amended by the 59th WMA General Assembly, Seoul, 2008) and Good Clinical Practice (GCP) as defined by the International Conference on Harmonisation (ICH) (1996) and regulatory requirements as stated in the protocol.*

**Key PK/PD Results:**

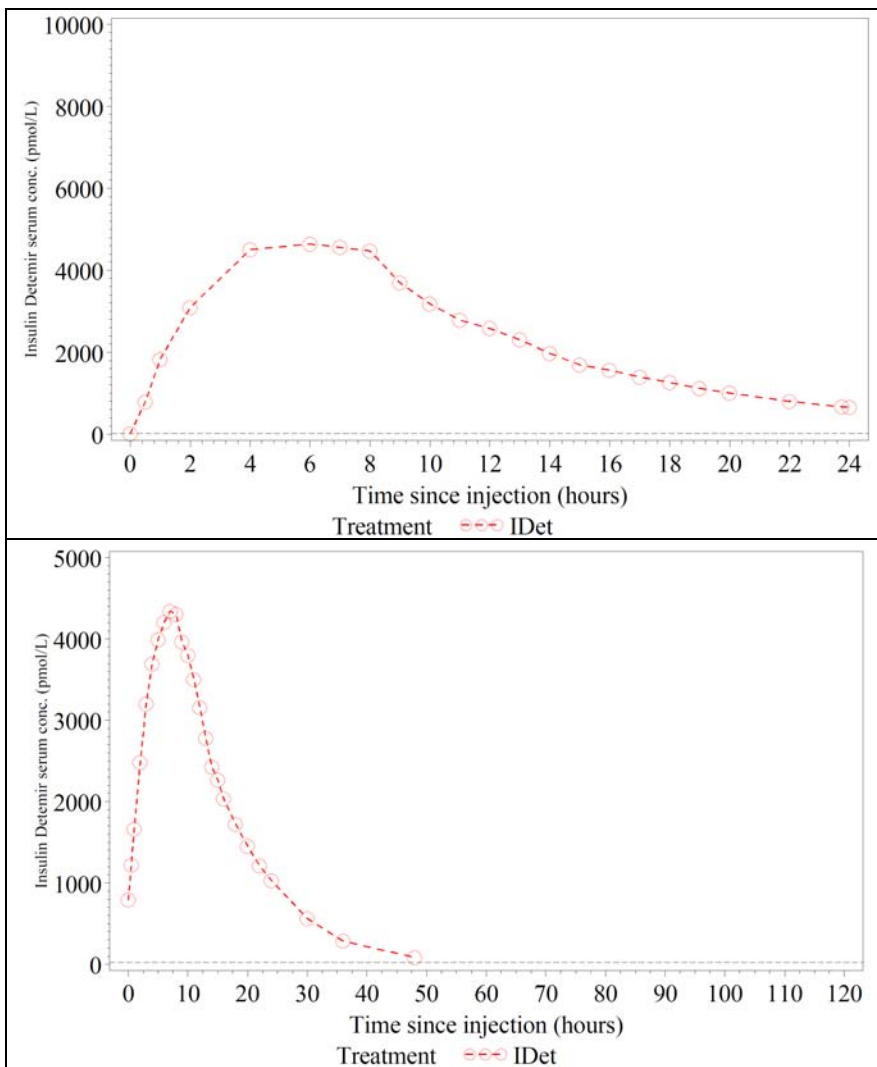
The PK parameters of IDeg were in the similar range as observed in other PK/PD studies conducted in non-Japanese subjects. For IDeg at steady state, geometric mean (%CV) AUCGIR,τ,SS was 1446 (55) mg/kg, GIRmax,SS was 1.7 (43) mg/(kg\*min) and tGIRmax,SS was observed after approximately 10.6 (0-26) hours. The ratio between AUCGIR,0-12h,SS and AUCGIR, τ,SS was close to 0.5 indicating that the glucose-lowering effect of IDeg was similar for the first 12 hours compared to the following 12 hours of one dosing interval. Whereas for insulin detemir (IDet) at steady state, geometric mean (%CV) AUCGIR,τ,SS was 1093 (61) mg/kg, GIRmax,SS was 1.8 (48) mg/(kg\*min) and tGIRmax,SS was observed 8.9 (4-21) hours after trial product administration. The ratio between AUCGIR,0-12h,SS and AUCGIR, τ,SS was above 0.5 indicating that more glucose-lowering effect of IDet occurred during the first 12 hours compared to the following 12 hours of one dosing interval. The IDeg PD effect was numerically higher than that of IDet from same 0.4 U/kg/day dose.



**Mean IDeg PK Profile (Day 1 and at steady state):**



### Mean IDet PK Profile (Day 1 and at steady state):



### Reviewer's Comments:

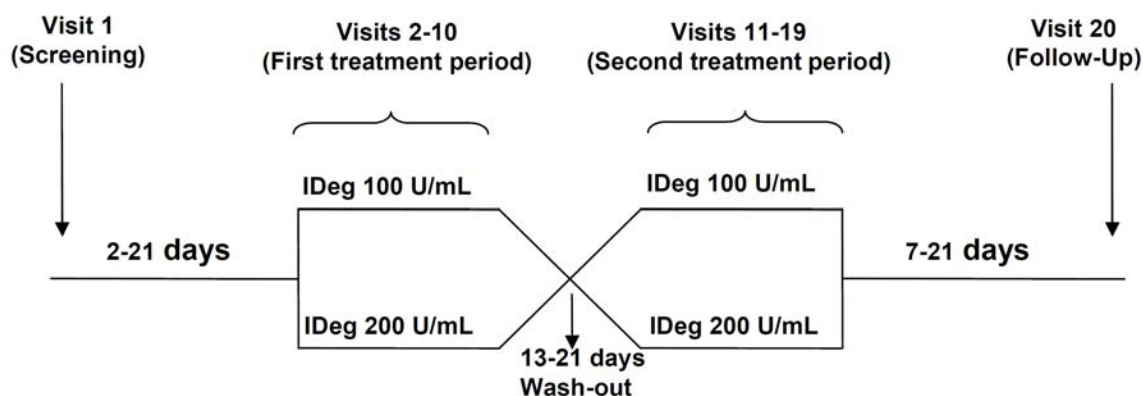
The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results for IDeg. For calibration standards, accuracy (expressed as %Bias) ranged between 2.1% and -1.0%. For QC sample analysis, precision was less than or equal to 10.5%. Accuracy ranged between 93.9% and 98.2%. with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ ,  $\pm 7\%$ , and  $\pm 9\%$ , respectively for IDeg. The analytical method adequately supported the results for and IDet with accuracy and precision for calibration standards (range of 25.0 to 800 pM) lying within  $\pm 3\%$ . For QC sample analysis, precision was less than or equal to 11.5%. Accuracy ranged between 100.1% and 109.1%.

#### 4.2.12 PKPD Comparison of U200 versus U100 in Subjects with Type 1 DM (NN1250-3678)

**Rationale:** IDeg has been developed as two different strengths: a 100 U/mL strength and a 200 U/mL strength. Sponsor anticipated that the IDeg 200 U/mL strength will provide advantages to subjects needing doses that require more than one injection in one administration with already marketed 100 U/mL formulations/injection devices, a practice that often leads to under-dosing and suboptimal glucose control. These subjects would benefit from the 200 U/mL product by having the opportunity of administering the same dose in smaller volumes and the possibility of being able to administer larger doses in one injection rather than two.

This trial was conducted to characterize the PD response of IDeg 100 U/mL and IDeg 200 U/mL at steady state in subjects with type 1 diabetes..

**Study Design:** The study design is presented in the figure below:



The study synopsis is as follows:

##### **Title of Trial**

A Trial Investigating the Pharmacodynamic Properties of NN1250<sup>1</sup> in Subjects with Type 1 Diabetes

##### **Objectives**

###### **Primary Objective:**

- To evaluate the pharmacodynamic response to insulin degludec (IDeg) 100 U/mL and IDeg 200 U/mL (based on the area under the glucose infusion rate curve from 0 to 24 hours at steady state) in subjects with type 1 diabetes.

###### **Secondary Objectives:**

- To characterize the pharmacodynamic profile of IDeg 100 U/mL and IDeg 200 U/mL, respectively, at steady state
- To characterize the pharmacokinetic profile of IDeg 100 U/mL and IDeg 200 U/mL, respectively, after single dose and at steady state
- To evaluate pharmacokinetic trough values towards the steady state level
- To assess the safety and tolerability of IDeg 100 U/mL and IDeg 200 U/mL.

##### **Methodology**

This was a randomized, single-centre, double-blind, two-period cross-over, multiple-dose trial investigating the pharmacokinetic and pharmacodynamic properties of IDeg 100 U/mL and IDeg 200 U/mL at steady state conditions in subjects with type 1 diabetes.

Each subject was randomly allocated to one of two sequences with 2 treatment periods of 8 days of once-daily dosing with IDeg 100 U/mL and IDeg 200 U/mL, respectively, at a predefined fixed dose level. During the 2 treatment periods, the plasma glucose level was controlled by additional bolus injections of insulin

aspart (IAsp) supervised by the investigator at the daily visits to the clinic. Moreover, subjects were instructed to follow their plasma glucose level closely when they were not at the clinic. The trial consisted of a screening visit (Visit 1) followed (2-21 days after) by 2 treatment periods (Visits 2-10 and Visits 11-19, respectively) and a follow-up visit (Visit 20) 7-21 days after the last dosing (Visit 16).

Each treatment period consisted of an initial in-house period following the first trial product administration (Visits 2 and 11), three dosing visits where the subject visited the clinic daily (Visits 3 and 12), a second in-house period, where the pharmacokinetic properties were to be evaluated at steady state after the sixth dosing (Visits 6 and 15) and, finally, a third in-house stay, where the pharmacodynamic and pharmacokinetic properties were evaluated during a euglycaemic glucose clamp after the eighth and last trial product administration (Visits 7 and 16). During

the first in-house period and second in-house period, the subjects were to stay in-house for 24 hours. The steady state pharmacodynamic response was evaluated during a euglycaemic glucose clamp continuing for 26 hours after the last trial product administration. The subjects were discharged from the clinic 48 hours after the last trial product administration and were to return at 72, 96 and 120 hours after the last trial product administration. The 2 treatment periods were separated by a wash-out period lasting 1321 days, during which the subjects were to resume their normal insulin treatment. The planned total duration of the trial for each individual subject was 38-79 days.

#### **Number of Subjects Planned and Analyzed**

A total of 30 subjects were planned to complete the trial. In total, 52 subjects were screened, 33 subjects were randomized and exposed to trial products. All 33 exposed subjects completed the trial and were included in the full analysis set and the safety analysis set. Of these, 17 and 16 subjects were exposed to the trial products in the IDeg 100 U/mL/IDeg 200 U/mL treatment sequence and IDeg 200 U/mL/IDeg 100 U/mL treatment sequence, respectively.

#### **Diagnosis and Main Criteria for Inclusion**

Men and women aged 18-65 years (both inclusive) with type 1 diabetes mellitus (as diagnosed clinically)  $\geq 12$  months and body mass index 18.0 - 28.0 kg/m<sup>2</sup> (both inclusive).

Key exclusion criteria were history or presence of cancer, cardiac diseases, supine blood pressure at screening outside the range of 90-140 mmHg for systolic or 50-90 mmHg for diastolic blood pressure, proliferative retinopathy or maculopathy and/or severe neuropathy, as well as recurrent severe hypoglycaemia or hypoglycaemic unawareness, and smoking.

#### **Test Product, Dose and Mode of Administration, Batch Number**

- IDeg 200 U/mL in 3 mL (b) (4) cartridges, batch number XCQ0018.
- IDeg 100 U/mL in 3 mL (b) (4) cartridges, batch number VCQ0013 and XCQ0001.

Each trial product was administered at the dose level 0.4 U/kg body weight as a subcutaneous (s.c.), once-daily injection into a lifted skin fold on the anterior surface of the thigh.

#### **Duration of Treatment**

Two treatment periods of 8 days of once-daily dosing of IDeg 100 U/mL and IDeg 200 U/mL, respectively.

#### **Criteria for Evaluation – Efficacy**

##### **Pharmacodynamic Variables**

- Glucose infusion rate (GIR) during a euglycaemic clamp running for 26 hours following the last of 8 once-daily doses in each treatment period.
- Plasma glucose concentration

##### **Pharmacokinetic Variables**

- Serum IDeg concentration

#### **Criteria for Evaluation – Safety**

- Adverse events
- Laboratory safety variables
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Hypoglycaemic episodes

#### **Statistical Methods**

The pharmacodynamic and pharmacokinetic analyses were based on the full analysis set, which included all randomized subjects. The safety analyses were based on the safety analysis set, including all subjects, who received at least one dose of the investigational medicinal products.

#### **Statistical Analysis of Primary Endpoint**

The primary endpoint was  $AUC_{GIR,\tau,SS}$ , the area under the glucose infusion rate curve during one dosing interval at steady state (0-24 hours) (after 8 days of treatment).

$AUC_{GIR,\tau,SS}$  was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. Last observation carried forward was used if there were missing values at the end of the assessment interval and if the PG escaped (i.e., the PG concentration consistently exceeded 13.9 mmol/L [250 mg/dL] with no glucose infusion for the last 30 minutes) after insulin action. If PG escaped before insulin action  $AUC_{GIR,\tau,SS}$  was not calculated. The log-transformed  $AUC_{GIR,\tau,SS}$  was analysed using an analysis of variance (ANOVA) method with treatment (IDeg 200 U/mL versus IDeg 100 U/mL) and period (treatment period 1 versus treatment period 2) as fixed factors, and subject as a random effect. In order to account for potential heteroscedasticity, the error-term was dependent on the treatment.

#### **Secondary Endpoints Pharmacodynamics**

The secondary PD endpoints were area under the GIR curve from 0-12 hours at steady state ( $AUC_{GIR,0-12h,SS}$ ), maximum GIR at steady state ( $GIR_{max,SS}$ ), time to maximum GIR at steady state ( $t_{GIR_{max,SS}}$ ), duration of action<sub>SS</sub> (time from investigational product administration until PG concentration was consistently above 8.3 mmol/L [150 mg/dL] during the glucose clamp at steady state), mean PG concentration during the last 10 minutes of one dosing interval at steady state ( $PG_{24h,SS}$ ) and ratio of areas under the GIR curve at steady state ( $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$ ). All secondary PD endpoints were summarized for each of the two treatments.

#### **Secondary Endpoints Pharmacokinetics**

The secondary PK endpoints for single dose were area under the serum IDeg concentration-time curve from 0-24 hours after single dose ( $AUC_{IDeg,0-24h,SD}$ ), maximum observed serum IDeg concentration after single dose ( $C_{max, IDeg,SD}$ ), time to maximum observed serum IDeg concentration after single dose ( $t_{max, IDeg,SD}$ ) and onset of appearance<sub>IDeg,SD</sub> (time from trial product administration until the first time serum IDeg concentration > 100 pmol/L after single dose [using linear interpolation]).

The secondary PK endpoints for steady state were area under the serum IDeg concentration-time curve during one dosing interval at steady state conditions ( $AUC_{IDeg,\tau,SS}$ ), area under the serum IDeg concentration-time curve from 0-12 hours at steady state ( $AUC_{IDeg,0-12h,SS}$ ), ratio of areas under the serum IDeg concentration curve at steady state ( $AUC_{IDeg,0-12h,SS}/AUC_{IDeg,\tau,SS}$ ), maximum observed serum IDeg concentration at steady state ( $C_{max, IDeg,SS}$ ), time to maximum observed serum IDeg concentration at steady state ( $t_{max, IDeg,SS}$ ) and terminal serum half-life for IDeg at steady state ( $t_{1/2, IDeg,SS}$ ).

The secondary PK endpoints for build-up to steady state were  $ITC_{IDeg,dose i}$ , determined from the serum IDeg trough concentrations measured at the end of each dosing interval as well as ratio of areas under the serum IDeg concentration curves at steady state and after single dose ( $AUC_{IDeg,\tau,SS}/AUC_{IDeg,0-24h,SD}$ ) and ratio of the maximum of the serum IDeg concentration curve at steady state and after single dose ( $C_{max, IDeg,SS}/C_{max, IDeg,SD}$ ).

The secondary PK endpoints were derived from the insulin concentration-time curves.  $AUC_{IDeg,\tau,SS}$  and  $C_{max, IDeg,SS}$  derived from the first insulin concentration-time profile at steady state (following the sixth dosing) were used when computing  $AUC_{IDeg,\tau,SS}/AUC_{IDeg,0-24h,SD}$  and  $C_{max, IDeg,SS}/C_{max, IDeg,SD}$ .  $T_{1/2, IDeg,SS}$  was derived from the last insulin concentration-time profile at steady state (following the eighth and last dosing). All other PK endpoints at steady state were derived from both insulin concentration-time profiles at steady state.

The trough concentrations  $ITC_{IDeg,dose 1}$  to  $ITC_{IDeg,dose 8}$  were plotted over the sampling period to determine if steady state was attained. All other secondary PK endpoints were summarised for each of the two treatments.

#### **Secondary Safety Endpoints**

The safety endpoints included AEs, laboratory safety variables, physical examination, vital signs, ECG and

hypoglycaemic episodes. All safety endpoints were listed and summarised using descriptive statistics.

#### ***Post-hoc Bioequivalence Analysis***

Test for bioequivalence at steady state was performed as extra analyses. For the endpoints AUC<sub>IDeg, □SS</sub> and C<sub>max, IDeg, SS</sub>, the same statistical model as for the primary analysis was employed with the change that the error term was assumed independent of the treatment. Bioequivalence is declared when the 90% CI for both the treatment ratios falls completely within the interval [0.80; 1.25].

#### ***Re-calculation of Terminal Half-life***

The mean terminal t<sub>1/2</sub> was re-calculated post database lock as it was decided that an individualised estimation of t<sub>1/2</sub> would yield a physiologically more relevant t<sub>1/2</sub> than the approach used pre-database lock. For most profiles, time points from 36 hours and onwards were included in the estimation of the terminal phase as decided pre-database

lock. Four time points from four subjects (Subject 2: time point 36 hour; Subject 12: time point 120 hour; Subject 13:

time point 120 hour; Subject 15: time point 72 hour) were however, excluded as they were considered physiologically implausible.

#### ***Demography of Trial Population***

Of the 33 randomised and exposed subjects, 31 (93.9%) were men and 2 (6.1%) were women. All subjects were white. The subjects mean age was 40.3 years and mean BMI was 25.3 kg/m<sup>2</sup>. Subjects mean duration of diabetes was

20.1 years (range: 3.645 years), and their mean HbA<sub>1c</sub> was 7.3% (range: 5.58.8%).

#### ***Efficacy Results and Conclusions***

##### ***Pharmacodynamic Endpoints***

□ Mean AUC<sub>GIR,τ, SS</sub> was similar for IDeg 100 U/mL and IDeg 200 U/mL (estimated ratio 200 U/mL/100 U/mL:

0.94 [0.86; 1.03]95%CI) in subjects with type 1 diabetes

□ Based on descriptive data (AUC<sub>GIR,0-12h,SS</sub> and GIR<sub>max,SS</sub>), IDeg 100 U/mL and IDeg 200 U/mL provided similar

glucose-lowering effect in subjects with type 1 diabetes at steady state

□ The glucose-lowering effect of IDeg 100 U/mL and IDeg 200 U/mL extended beyond 26 hours at a clinically relevant dose.

##### ***Pharmacokinetic Endpoints - Steady State***

□ Mean 120-hour serum IDeg 100 U/mL and IDeg 200 U/mL concentrationtime profiles appeared similar for subjects with type 1 diabetes at steady state

□ Mean 24-hour serum IDeg 100 U/mL and IDeg 200 U/mL concentrationtime profiles appeared similar for

subjects with type 1 diabetes at steady state

□ Based on descriptive data, the PK endpoints of IDeg 100 U/mL and IDeg 200 U/mL were similar for subjects with type 1 diabetes at steady state

□ Based on descriptive data, the terminal half-life (t<sub>1/2</sub>) was similar for IDeg 100 U/mL and IDeg 200 U/mL, the harmonic mean being 19.5 and 19.4 hours, respectively, in subjects with type 1 diabetes

□ IDeg 100 U/mL and IDeg 200 U/mL were bioequivalent based on AUC<sub>IDeg, □SS</sub> and C<sub>max, IDeg, SS</sub>. Estimated mean ratios were 0.99 [0.91; 1.07]90%CI for AUC<sub>IDeg, □SS</sub> and 0.93 [0.84; 1.02]90%CI for C<sub>max, IDeg, SS</sub> (post-hoc analysis – steady state).

##### ***Pharmacokinetic Endpoints – Single Dose***

□ Based on descriptive data, AUC<sub>IDeg,0-24h,SD</sub> and C<sub>max, IDeg,SD</sub> were higher after single-dose administration with IDeg 100 U/mL than with IDeg 200 U/mL

□ Based on descriptive data, t<sub>max</sub> and onset of appearance were earlier after single-dose administration of IDeg 100 U/mL than IDeg 200 U/mL.

##### ***Build-up to Steady State***

□ Based on descriptive data C<sub>max, IDeg,SS</sub>/C<sub>max, IDeg,SD</sub> and AUC<sub>IDeg,τ,SS</sub>/AUC<sub>IDeg,0-24h,SD</sub> were lower for IDeg 100 U/mL compared to IDeg 200 U/mL for subjects with type 1 diabetes, however as

shown above total exposure at steady state was similar

- Based on PK profiles, both IDeg 100 U/mL and IDeg 200 U/mL appeared to have reached steady state after 2-3 days.

#### **Safety Results and Conclusions**

- A total of 29 AEs were reported in 17 (52%) out of 33 subjects; 13 events in 12 (36%) subjects when treated with IDeg 100 U/mL group and 16 events in 13 (39%) subjects when treated with IDeg 200 U/mL. There were no apparent differences between IDeg 100 U/mL and IDeg 200 U/mL in the pattern of AEs. All events were of mild (29 events) severity, and all subjects recovered. All AEs were unlikely related to IDeg, NPH insulin and IAsp and not related to Device. The most common AE was headache (8 events in the IDeg 100 U/mL and 9 events in the IDeg 200 U/mL), no other AEs were reported more than twice in each group.
- No SAEs or MESIs were reported. No injection site reactions were reported.
- In total, 573 treatment emergent hypoglycaemic episodes were reported, including 1 severe episode, 308 documented symptomatic episodes, 242 asymptomatic episodes, 7 probably symptomatic episodes and 15 relative episodes. Approximately 14% (80 episodes) of the total number of episodes were nocturnal episodes. Overall, the number of hypoglycaemic episodes was similar between IDeg 100 U/mL and IDeg 200 U/mL treatments. The observed number of hypoglycaemic episodes may be artificially high due to the fixed dosing level of 0.4 U/Kg of IDeg 100 U/mL and IDeg 200 U/mL.
- There were no clinically significant findings in laboratory parameters, vital signs, physical examination or ECG.

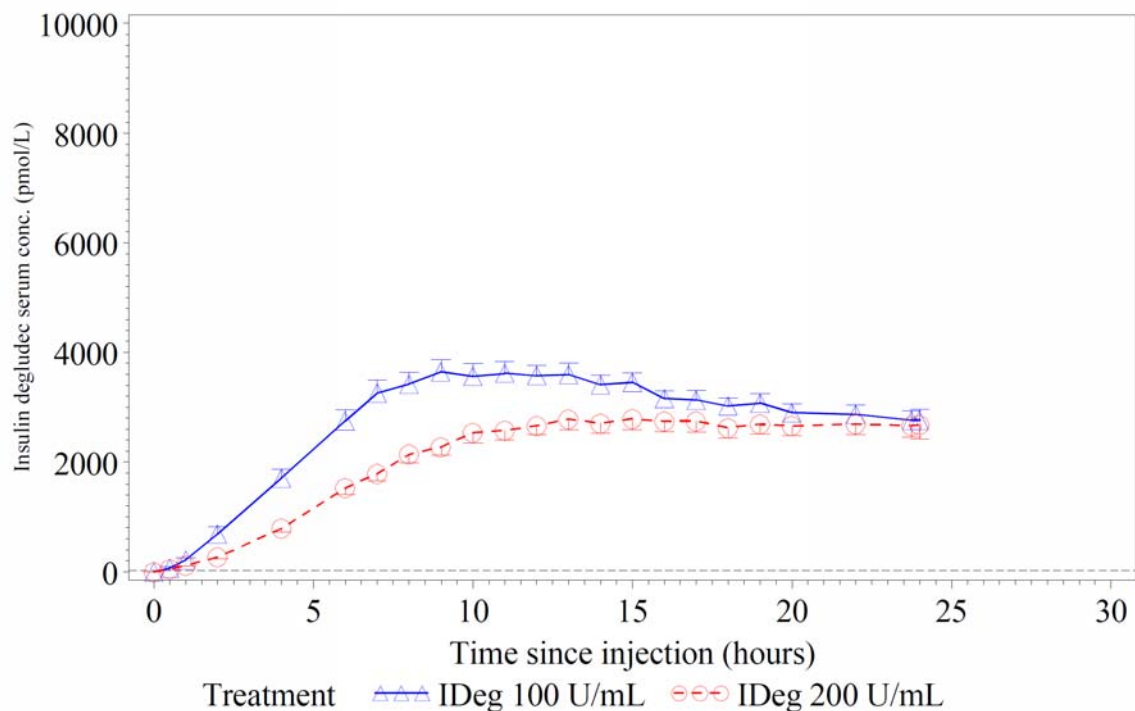
#### **Overall Conclusions**

The conclusions from this randomised, single-centre, double-blind, two-period cross-over, multiple-dose trial investigating the pharmacokinetic and pharmacodynamic properties of IDeg 100 U/mL and IDeg 200 U/mL at steady state conditions in subjects with type 1 diabetes mellitus are:

- IDeg 100 U/mL and IDeg 200 U/mL have similar glucose-lowering effect
- IDeg 100 U/mL and IDeg 200 U/mL have similar total exposure ( $AUC_{IDeg,\tau,SS}$ )
- IDeg 100 U/mL and IDeg 200 U/mL are bioequivalent based on  $AUC_{IDeg,\tau,SS}$  and  $C_{max, IDeg,SS}$  (post-hoc analysis)
- IDeg 100 U/mL and IDeg 200 U/mL are well tolerated and no safety issues are identified in this trial.

*The trial was conducted in accordance with the Declaration of Helsinki (Last amended by the 59th WMA General Assembly, Seoul 2008) and ICH Good Clinical Practice (1996).*

### **Comparison of PK after first dose on Day 1:**

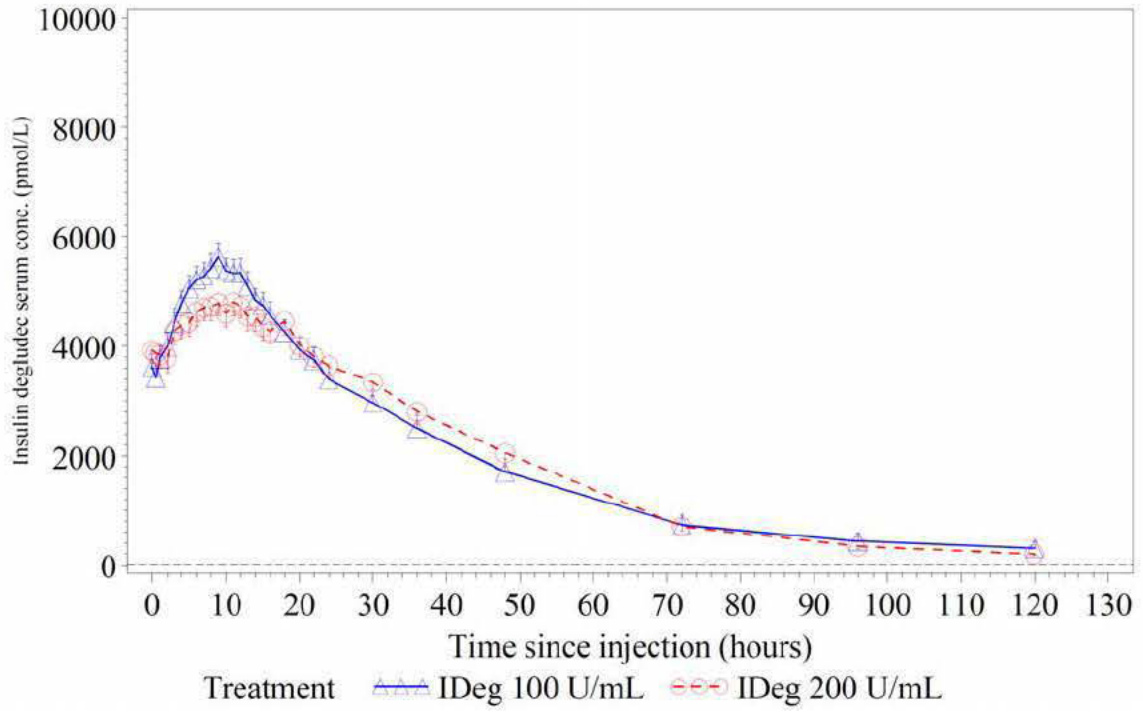


The mean maximum IDeg concentration after single dose ( $C_{max}$ , IDeg, SD) was higher with IDeg 100 U/mL compared to IDeg 200 U/mL, and the median time to maximum IDeg concentration ( $t_{max}$ , IDeg,SD) occurred earlier with IDeg 100 U/mL compared to IDeg 200 U/mL.

|                                     | IDeg 100 U/mL  | IDeg 200 U/mL |
|-------------------------------------|----------------|---------------|
| Number of Subjects                  | 33             | 33            |
| AUC IDeg, 0-24h, SD (pmol*h/L)      |                |               |
| N                                   | 33             | 33            |
| Geometric mean (CV)                 | 63015 ( 29.6)  | 46415 ( 36.4) |
| Min ; Max                           | 33874 ; 127143 | 25140 ; 86292 |
| $C_{max}$ IDeg, SD (pmol/L)         |                |               |
| N                                   | 33             | 33            |
| Geometric mean (CV)                 | 4037 ( 32)     | 3089 ( 40)    |
| Min ; Max                           | 1949 ; 8897    | 1714 ; 6274   |
| $t_{max}$ IDeg, SD (h)              |                |               |
| N                                   | 33             | 33            |
| Median                              | 12.0           | 14.1          |
| Min ; Max                           | 7.0 ; 24.0     | 10.0 ; 24.0   |
| Onset of appearance, IDeg, SD (min) |                |               |
| N                                   | 33             | 33            |
| Median                              | 48             | 70            |
| Min ; Max                           | 5 ; 84         | 10 ; 152      |

CV: Coefficient of variation in %

### Comparison of PK Profile at steady state:



|                                                 | IDeg 100 U/mL  | IDeg 200 U/mL  |
|-------------------------------------------------|----------------|----------------|
| Number of Subjects                              | 33             | 33             |
| AUC IDeg, tau, SS (pmol*h/L)                    |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 112358 ( 27)   | 110805 ( 33)   |
| Min ; Max                                       | 73512 ; 223214 | 74499 ; 274239 |
| AUC IDeg, 0-12h, SS (pmol*h/L)                  |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 61305 ( 24)    | 58928 ( 38)    |
| Min ; Max                                       | 39324 ; 110562 | 37269 ; 150455 |
| AUC IDeg, 0-12h, SS / AUC IDeg, tau, SS (ratio) |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 0.55 ( 6.14)   | 0.53 ( 8.42)   |
| Min ; Max                                       | 0.50 ; 0.64    | 0.45 ; 0.69    |
| Cmax IDeg, SS (pmol/L)                          |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 6568 ( 26)     | 6065 ( 37)     |
| Min ; Max                                       | 4290 ; 11560   | 3793 ; 14960   |
| tmax IDeg, SS (h)                               |                |                |
| N                                               | 33             | 33             |
| Median                                          | 9.0            | 9.0            |
| Min ; Max                                       | 3.1 ; 13.2     | 0.0 ; 15.9     |
| AUC IDeg, tau, SS / AUC IDeg, 0-24h, SD (ratio) |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 1.78 ( 25.29)  | 2.39 ( 37.51)  |
| Min ; Max                                       | 1.07 ; 2.94    | 1.01 ; 5.03    |
| Cmax IDeg, SS / Cmax IDeg, SD (ratio)           |                |                |
| N                                               | 33             | 33             |
| Geometric mean (CV)                             | 1.63 ( 33.97)  | 1.96 ( 42.18)  |
| Min ; Max                                       | 0.89 ; 3.23    | 0.81 ; 4.60    |

CV: Coefficient of variation in %

### Post-hoc assessment for bioequivalence at steady-state:

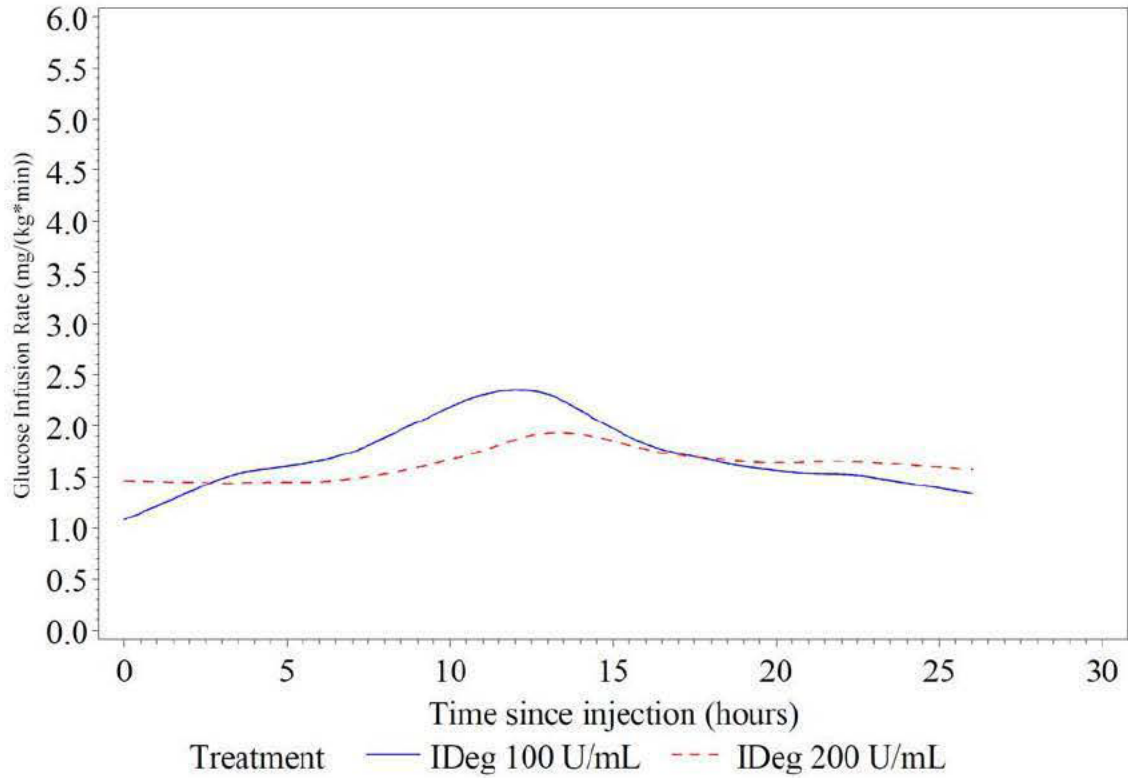
|                              | FAS | N     | Estimate | 90% CI       |
|------------------------------|-----|-------|----------|--------------|
| AUC IDeg, tau, SS (pmol*h/L) |     |       |          |              |
| Mean ratio                   |     |       |          |              |
| 200 U/mL/100 U/ml            | 33  | 33/33 | 0.99     | [0.91; 1.07] |
| Cmax IDeg, SS (pmol/L)       |     |       |          |              |
| Mean ratio                   |     |       |          |              |
| 200 U/mL/100 U/ml            | 33  | 33/33 | 0.93     | [0.84; 1.02] |

The endpoints are log-transformed and analysed using an ANOVA model with treatment and period as fixed effects, subject as random effect.

ANOVA: analysis of variance; CI: confidence interval; FAS: full analysis set

N: number of subjects contributing to the analysis

**Comparison of PD Profile at steady state:**



|                          | FAS | N  | Estimate | 95% CI       |
|--------------------------|-----|----|----------|--------------|
| AUC GIR, tau, SS (mg/kg) |     |    |          |              |
| Least square means       |     |    |          |              |
| IDeg 100 U/mL            | 33  | 33 | 2255     |              |
| IDeg 200 U/mL            | 33  | 33 | 2123     |              |
| Mean ratio               |     |    |          |              |
| 200 U/mL/100 U/mL        |     |    | 0.94     | [0.86; 1.03] |

The endpoints are log-transformed and analysed using an ANCOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.

**Statistical analysis of PD data:**

|                          | FAS | N  | Estimate | 95% CI       |
|--------------------------|-----|----|----------|--------------|
| AUC GIR, tau, SS (mg/kg) |     |    |          |              |
| Least square means       |     |    |          |              |
| IDeg 100 U/mL            | 33  | 33 | 2255     |              |
| IDeg 200 U/mL            | 33  | 33 | 2123     |              |
| Mean ratio               |     |    |          |              |
| 200 U/mL/100 U/mL        |     |    | 0.94     | [0.86; 1.03] |

The endpoints are log-transformed and analysed using an ANOVA model with treatment and period as fixed effects, subject as random effect, and with different error-terms for each treatment.

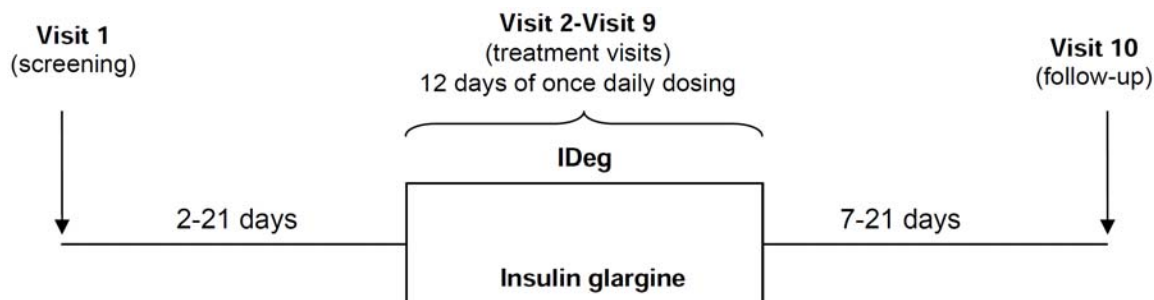
**Reviewer's Comments:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results for IDeg with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ , 11%, and  $\pm 3\%$  respectively. Based on the study results, the PK profile from U200 formulation showed distinct slower absorption in comparison to the U100 formulation. However, at steady state the PK and PD profiles were comparable. Although, the BE analysis was of post-hoc nature. Moreover, the caveat with the multiple dose evaluation for formulation comparison is that sensitivity to detect differences is low limiting the utility of this trial for establishing PKPD comparability. A single dose comparison is ideal for establishing PKPD comparability between the formulations. However, the long duration of action limits the PD comparison to partial AUC over 24 hour duration due to practical limitations of conducting  $>24$  h euglycemic clamp. One likely solution to this problem could be that PD comparison is performed after first dose and at steady state, at least if a multiple dose PKPD comparison is considered.

#### 4.2.13 Within-Subject variability in PD response in Type 1 DM (NN1250-1991)

**Rationale:** Clinically, it is important to obtain an estimate of the within-subject variability of the PD response for IDeg, because a low variability would be a major advantage when titrating the individual insulin dose, especially when aiming for a low glycemic target. Low within-subject variability would provide a more predictable therapeutic effect. Therefore, the aim of this trial is to compare the within-subject variability of the PD response at steady state between IDeg and IGLar in subjects with type 1 diabetes.

**Study Design:** The study design is presented in the figure below:



At the first treatment visit, each subject was randomly allocated to treatment with IDeg or IGLar at a predefined fixed dose level of 0.4U/kg body weight. Treatment consisted of 12 days of once daily dosing (dosing days/treatment days). During the treatment period, blood glucose levels were controlled by self-administered bolus injections of insulin aspart supervised by the investigator on a daily basis.

The study synopsis is as follows:

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                        |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|
| <b>Trial Registration ID-number</b><br>NCT00961324                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | <b>EudraCT number</b> – 2008-008308-42 |
| <b>Title of Trial</b><br>A Randomised, Single-centre, Double-blind, Parallel-group, Multiple Dose Trial Comparing the Within-subject Variability of NN1250 and Insulin Glargine with Respect to Pharmacodynamic Response at Steady State Conditions in Subjects with Type 1 Diabetes                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
| <b>Investigator(s)</b><br>Dr Tim Heise, Profil Institut für Stoffwechselforschung GmbH, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                        |
| <b>Trial Site(s)</b><br>Profil Institut für Stoffwechselforschung GmbH, Hellersbergstrasse 9, D-41460 Neuss, Germany                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
| <b>Publications</b><br>None at the time of reporting                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                        |
| <b>Trial Period</b><br>27th July 2009 to 26th October 2009                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Development Phase</b><br>Phase 1    |
| <b>Objectives</b><br><b>Primary Objective:</b> <ul style="list-style-type: none"> <li>To compare the within-subject variability of the pharmacodynamic (PD) response during one dosing interval at steady state (derived on treatment days 6, 9 and 12) between insulin degludec (IDeg) and insulin glargine (IGlar) in subjects with type 1 diabetes</li> </ul> <b>Secondary Objectives:</b> <ul style="list-style-type: none"> <li>To compare the within-subject variability of the pharmacodynamic (PD) properties at steady state between IDeg and IGlar</li> <li>To compare the within-subject variability of the pharmacokinetic (PK) properties at steady state between IDeg and IGlar</li> <li>To characterise the PD properties of IDeg and IGlar at steady state</li> <li>To characterise the PK properties of IDeg and IGlar at steady state</li> <li>To assess the safety and tolerability of IDeg</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                        |
| <b>Methodology</b><br>This trial was a randomised, single-centre, double-blind, parallel-group trial comparing the within-subject variability of the PD response at steady state between IDeg and IGlar in subjects with type 1 diabetes. Each subject was randomly allocated to treatment with IDeg or IGlar at a predefined fixed dose level of 0.4U/kg body weight (BW). Treatment consisted of 12 days of once-daily dosing (dosing days/treatment days). During the treatment period, subjects were self-administering bolus injections of insulin aspart for prandial glucose control. This was supervised by the investigator on a daily basis. The trial consisted of 10 visits: a screening visit followed by the treatment visits 2-21 days after screening (Visits 2-9 with a total duration of 13 days) and a follow-up visit 7-21 days after last dosing. At Visit 2, the subject remained in-house for the first 48 hours following first trial drug administration. During this in-house period, the first 3 doses of IDeg/IGlar were administered. The following daily visits (Visits 3-4) were out-patient visits where the subject visited the clinic for collection of blood samples and administration of the trial drug. At Day 6 (first clamp visit), the subject returned to the clinic and stayed in-house. The steady state PD response was evaluated during a euglycaemic glucose clamp continuing for 24 hours after trial drug administration. In addition, blood samples for PK assessment were taken during the clamp. At the end of the glucose clamp, the next day's trial drug was administered (Day 7). The subject remained at the clinic (Visit 6) for collection of additional PK samples without clamp running. After administration of the eighth dose of trial drug, the subject was discharged from the clinic and asked to return to the clinic the following day for Visit 7, the second clamp visit during which the ninth dose was administered. Clamp procedures were similar to those for the first clamp |                                        |

visit. After 24-hours, the tenth dose of trial drug was administered. The subject was discharged from the clinic approximately 2 hours after termination of the glucose clamp or later if deemed necessary by the investigator. The following day (Visit 8) was an out-patient visit where the eleventh dose of trial drug was administered and blood samples collected. On dosing day 12, the subjects attended the clinic for the last glucose clamp experiment (Visit 9), which was similar to the previous two glucose clamps. Finally, a follow-up visit (Visit 10) took place 7-21 days after dosing at Visit 9. The total duration of the trial for the individual subject was planned to be between 22-55 days.

**Number of Subjects Planned and Analysed**

A total of 50 subjects were planned to complete the trial. A total of 68 subjects were screened, 54 subjects were randomised to the trial and were exposed to trial products, and 52 subjects completed the trial. The 2 subjects who withdrew consent during the trial were included in the full analysis set.

**Diagnosis and Main Criteria for Inclusion**

Subjects with type 1 diabetes treated with multiple injections of insulin ( $< 1.2$  (IU/kg/day)  $\geq 12$  months, between 18 and 65 years of age with  $HbA_{1c} \leq 10.0\%$ , BMI between  $18.0$ - $28.0$   $kg/m^2$  and fasting C-peptide  $< 0.3$  nmol/L

**Test Product, Dose and Mode of Administration, Batch Number**

IDeg (100 U/mL; Novo Nordisk) in 3 mL (b) (4) cartridges administered as 0.4U/kg BW subcutaneously (s.c.) in the thigh, batch number VCQ0013.

**Duration of Treatment**

Twelve (12) days of once daily dosing with either IDeg or IGLar

**Reference Therapy, Dose and Mode of Administration, Batch Number**

IGlar (Lantus<sup>®</sup>, 100 U/mL; Sanofi Aventis) in 3 mL cartridges administered as 0.4U/kg BW s.c. in the thigh, batch number 40U607.

**Criteria for Evaluation – Pharmacodynamic and Pharmacokinetics**

**Pharmacodynamics**

- Glucose infusion rate (GIR)
- Blood glucose concentration (BG)

**Pharmacokinetics**

- Serum concentration of IDeg
- Serum concentration of IGLar

**Criteria for Evaluation – Safety**

- Adverse events (AEs)
- Physical examination
- Vital signs
- Electrocardiogram (ECG)
- Laboratory safety variables (haematology, biochemistry, urinalysis, coagulation, lipids)
- Hypoglycaemic episodes

**Statistical Methods**

**Primary Analysis**

The primary endpoint,  $AUC_{GIR,t,SS}$ , the area under the glucose infusion rate curve during one dosing interval at steady state (0-24 hours) was derived from the individual GIR profiles measured on treatment days 6, 9 and 12 during the three euglycaemic clamp visits. The primary endpoint was calculated as the area under the smoothed GIR curve using the linear trapezoidal technique on interpolated points. The analysis addressed the differences in within-subject variability of  $AUC_{GIR,t,SS}$  comparing IDeg with IGLar. In order to account for heteroscedasticity, the primary endpoint was log-transformed and analysed with a linear mixed model with insulin type and period as fixed effects, subjects as random effects depending on insulin type and an error variance depending on the insulin type. The difference in within-subject variability for the different insulin types was assessed as the ratio between the error variances. The test for no difference between the within-subject variability for any two insulin types was evaluated in an F-distribution, with a significance level of 5%. The 95% confidence limits for the estimated variance ratio between the two treatment groups (IGlar is the reference) was calculated assuming a F-distribution using Satterthwaite approximation for the degrees of freedom. Coefficients of variation (CV%) were derived from the within-subject variability estimated on the log-scale in the statistical analyses.

#### Analysis of Pharmacodynamic Secondary Endpoints

The secondary PD endpoints were derived from the individual GIR profiles at steady state at each of the three glucose clamp visits on treatment days 6, 9 and 12. The PD secondary endpoints  $AUC_{GIR,2-24h,SS}$ ,  $AUC_{GIR,0-12h,SS}$ ,  $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$  and  $GIR_{max,SS}$  were log-transformed. To compare the within-subject variability between IDeg and IGlár, a mixed model with insulin type and period as fixed effects, subjects as random effects depending on insulin type and an error variance depending on the insulin type was used. The differences in within-subject variability for the different insulin types were assessed as the ratio between the error variances. The test for no difference between the within-subject variability for any two insulin types was evaluated in an F-distribution, with a significance level of 5%, as presented in the analysis of the primary endpoint. The PD fluctuation endpoints  $AUC_{GIR,\tau,SS}$ ,  $AUC_{GIR,0-12h,SS}$  and  $AUC_{GIR,12-24h,SS}$  and blood glucose level  $BG_{24h,SS}$  were log-transformed and the difference in means between IDeg and IGlár was assessed in a linear mixed model with a significance level of 5% with insulin type and period as fixed effects and subject as random effects depending on insulin type and an error variance depending on the insulin type. Within-subject variation was assessed using summary statistics. All other PD secondary endpoints were summarised within each treatment group.

#### Analysis of Pharmacokinetic Secondary Endpoints

The two PK secondary endpoints  $AUC_{\tau,SS}$  and  $AUC_{0-12h,SS}$  were log-transformed and the within-subject variability was estimated separately for IDeg and IGlár in a linear mixed model with period as a fixed effect and subjects as random effects. No formal statistical test was made to compare IDeg and IGlár with respect to within-subject variability. For the statistical analysis only the insulin concentration-time curves at steady state at each of the three glucose clamp visits on treatment days 6, 9 and 12 were used.

#### Demography of Trial Population

Of the 54 randomised and exposed subjects, 48 (89%) were male and 6 (11%) female. A total of 53 were white and 1 was of black or African American origin. The subjects' mean age was 38.3 years and mean BMI was 24.6kg/m<sup>2</sup>. Subjects had had diabetes for 3 to 51 years, and HbA<sub>1c</sub> ranged from 5.4% to 9.8% with a mean of 7.66%.

#### Efficacy Results

- IDeg had statistically significantly less within-subject variability at steady state as measured by CV% compared to IGlár with respect to  $AUC_{GIR,\tau,SS}$ ,  $AUC_{GIR,0-12h,SS}$ ,  $AUC_{GIR,2-24h,SS}$  and  $GIR_{max,SS}$ . The within-subject variability at steady state was approximately four times larger with IGlár compared with IDeg.

#### Within-subject Variability

|                      | Insulin Degludec<br>(CV%)* | Insulin Glargine<br>(CV%)* | p value  |
|----------------------|----------------------------|----------------------------|----------|
| $AUC_{GIR,\tau,SS}$  | 20                         | 82                         | p<0.0001 |
| $AUC_{GIR,2-24h,SS}$ | 22                         | 92                         | p<0.0001 |
| $AUC_{GIR,0-12h,SS}$ | 23                         | 80                         | p<0.0001 |
| $GIR_{max,SS}$       | 18                         | 60                         | p<0.0001 |

\*CV: within-subject coefficient of variation in %

- With IDeg, the ratio  $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$  was 0.5 indicating a similar action profile for the first and second 12 hours of the clamp, whereas with IGlár more of its action occurred during the first 12 hours. Furthermore, IDeg had significantly less within-subject variability at steady state for the ratio  $AUC_{GIR,0-12h,SS}/AUC_{GIR,\tau,SS}$  compared with IGlár (CV IDeg =10%, CV IGlár =17%, p=0.0005).

- Based on the estimated within-subject CV of the glucose-lowering effect ( $AUC_{GIR,t,SS}$ ), the risk of experiencing less than half of the average effect on any given day (i.e., potential hyperglycaemia) is <0.1% for IDeg and 17% for IGLar.
- Based on the estimated within-subject CV of maximum glucose-lowering effect ( $GIR_{max,ss}$ ), the risk of experiencing more than twice the average effect on any given day (i.e., potential hypoglycaemia) is <0.1% for IDeg and 11% for IGLar.
- The PK endpoints support the PD results, for  $AUC_{ins,t,SS}$  a lower CV was calculated for IDeg (13%) compared with IGLar (24%), and also for  $AUC_{ins,0-12h,SS}$ : CV = 14% with IDeg compared to CV = 23% with IGLar. No formal statistical test was made to compare the IDeg and IGLar PK endpoints.

#### Safety Results

- A total of 36 AEs were reported by 19 out of 54 exposed subjects. Of these, 22 AEs were possibly related to basal insulin, 12 with IDeg and 10 with IGLar. All AEs were either mild (19 of 36) or moderate (17 of 36) and were equally divided between the treatment groups.
- The most commonly reported AE was headache (24 out of 36 AEs). Of these, 19 events of headache were possibly related to basal insulin. In all, 3 mild AEs of abdominal pain were reported. The remaining AEs were only reported once or twice.
- No SAEs, MESIs or deaths were reported during the trial.
- There were no clinically significant findings in clinically laboratory tests, vital signs, ECGs or physical examinations.
- There were no injection site findings.
- Of 54 exposed subjects, 53 reported hypoglycaemic episodes. Overall, 318 hypoglycaemic episodes were reported, 151 with IDeg and 167 with IGLar. No severe hypoglycaemia was reported. The majority of the hypoglycaemic episodes were classified as documented symptomatic and were reported during daytime. Fewer nocturnal hypoglycaemic episodes were reported in the IDeg group (19 episodes in 9 subjects) compared to the IGLar group (36 episodes in 17 subjects). The observed number of hypoglycaemic episodes may be artificially high due to the fixed dosing level of 0.4U/Kg of IDeg and IGLar.

#### Conclusions

The results of this trial, comparing within-subject variability of IDeg and IGLar in subjects with type 1 diabetes showed that:

- IDeg has approximately four times lower within-subject variability in pharmacodynamic response compared to IGLar.
- IDeg has a similar action profile for the first and second 12 hours of the clamp, whereas with IGLar, more of its action occurs during the first 12 hours.
- The results show a less variable and more predictable glucose lowering effect with IDeg compared to IGLar.
- The PK data is supportive of the PD analysis as within-subject variability is lower with IDeg than with IGLar.
- IDeg was well tolerated and no safety issues were raised during this trial

*The trial was conducted in accordance with the Declaration of Helsinki and ICH Good Clinical Practice*

#### Reviewer's Comments:

The study results are reasonable from a clinical pharmacology perspective. However, the study results are limited by the parallel design nature for product comparison. On other hand, the longer than 24 hour duration poses difficulty in assessing the within-subject variability (WSV; also known as intra-subject variability) in a crossover fashion. Nevertheless, the WSV estimates for individual products are reliable. With known higher WSV of insulin glargine, the choice of this

insulin as a comparator also seems to create a bias and provides artificially favorable contrast for IDeg as opposed to the situation if insulin detemir was used as comparator. The clinical pharmacology review for insulin detemir (Levemir®<sup>1</sup> NDA 21-536) noted significantly lower WSV in PK and PD parameters (CV% up to 15% and 27%, respectively) than insulin glargine (up to 34% and 46%, respectively).

No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ ,  $\pm 7\%$ , and  $\pm 10\%$ , respectively for IDeg. The analytical method adequately supported the results for IGLar with accuracy and precision for calibration standards (range of 20.0 to 750 pM) and QC samples lying within  $\pm 9\%$  and  $\pm 3\%$  respectively.

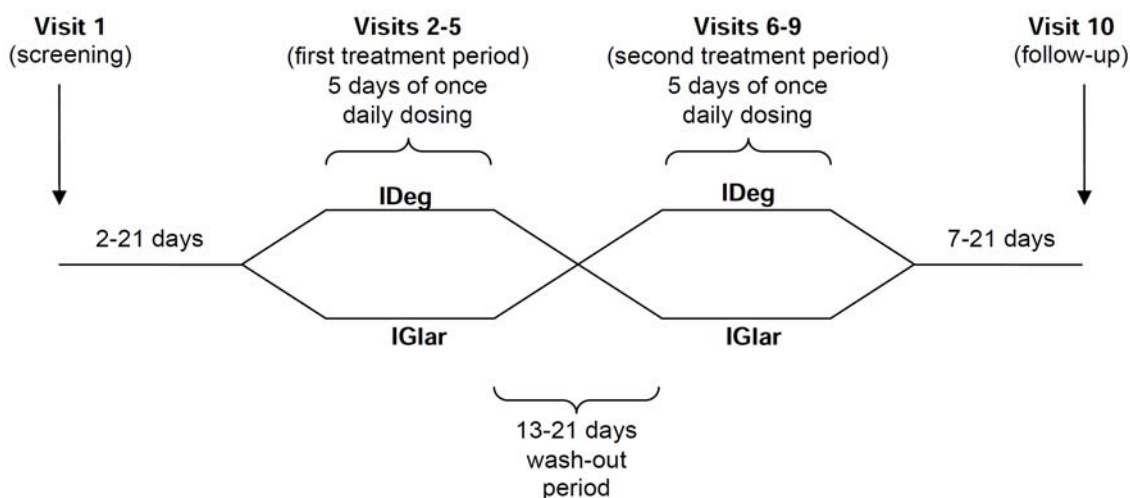
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<sup>1</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/021-536\\_Levemir\\_biopharmr.PDF](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021-536_Levemir_biopharmr.PDF)

#### 4.2.14 Hypoglycemic-response in Subjects with Type 1 DM (NN1250-3538)

**Rationale:** This trial was conducted to characterize the various symptoms, reactions and responses seen during development of hypoglycaemia induced by IDeg. Moreover, since the glucose lowering effect could extend beyond 24 hours at clinically relevant doses, it is also highly relevant to investigate IDeg action during recovery from hypoglycaemia.

**Study Design:** The study design is presented in the figure below:



The study synopsis is as follows:

**Title of Trial:**

A Trial Investigating the Hypoglycemic Response to NN1250 in Subjects with Type 1 Diabetes

**Objectives**

**Primary Objective**

- To compare symptoms of hypoglycemia during a hypoglycemic episode induced by insulin degludec (IDeg) versus one induced by insulin glargine (IGlar) in subjects with type 1 diabetes

**Secondary Objectives**

- To compare autonomic response, counterregulatory hormone response, cognitive function and hypoglycemic awareness during a hypoglycemic episode induced by insulin degludec versus one induced by insulin glargine
- To compare plasma glucose profiles during a hypoglycemic episode induced by insulin degludec versus one induced by insulin glargine
- To compare insulin action, symptoms of hypoglycemia, vital signs, counterregulatory hormones, cognitive function and hypoglycemic awareness during the recovery from a hypoglycemic episode induced by insulin degludec versus one induced by insulin glargine
- To characterize the pharmacokinetic profile before, during and after a hypoglycemic episode induced by insulin degludec and one induced by insulin glargine

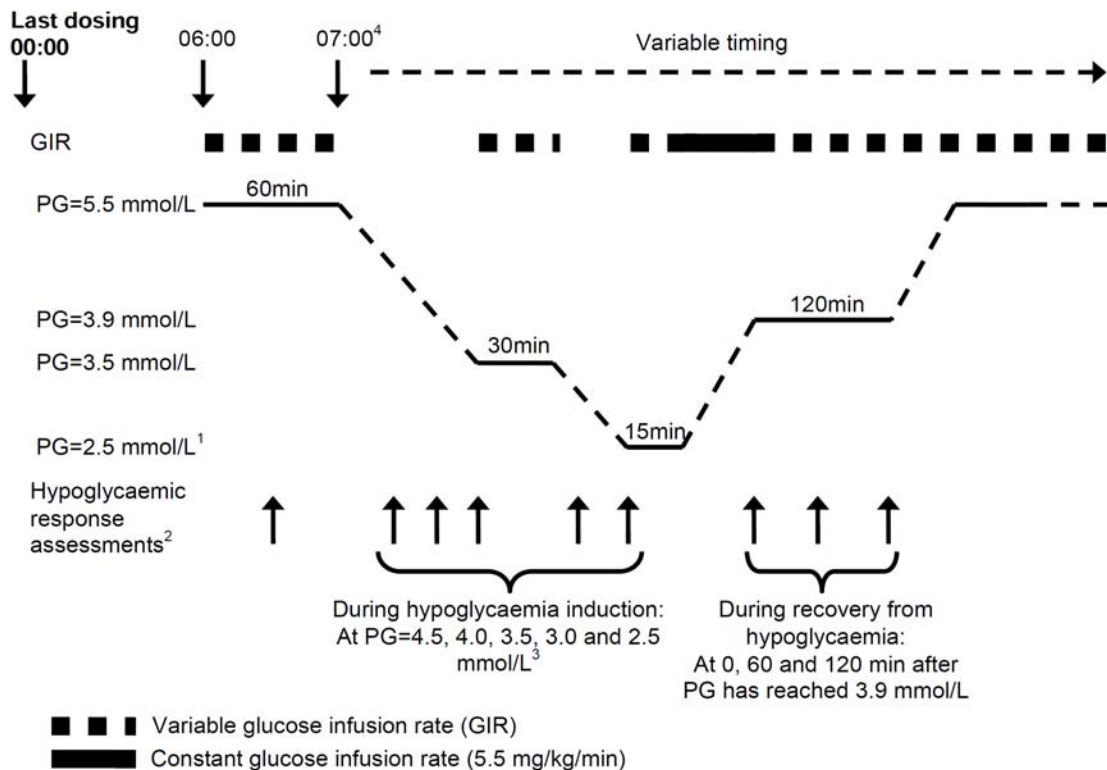
**Methodology**

This was a randomized, single-centre, double-blind, two-period cross-over, multiple dose trial in subjects with type 1 diabetes mellitus comparing the hypoglycemic response between IDeg and IGlar. Each subject was randomly allocated to two treatment periods of 5 days of once daily dosing with IDeg or IGlar at an individual, predefined dose level. The first four dose levels were 80% of the subject's own individual basal insulin treatment, and the fifth dose level was three times the subject's own individual basal insulin treatment.

The trial consisted of a screening visit (2 to 21 days before the first treatment period) followed by two treatment periods separated by a wash out period of 13 to 21 days during which the subjects resumed their normal insulin treatment, and a follow-up visit. During each treatment period, the subjects stayed in-house for at least 24 hours after the first trial product administration. During this time the first two doses of IDeg or IGlar were administered. On Days 3 and 4, the subjects visited the clinic in order to have trial product administered. On Day 5, the subjects attended the clinical unit for an in-house stay of at least 50 hours. After the fifth and last dose, subjects were clamped using a

variable glucose infusion at a plasma glucose level of 5.5 mmol/L. After 7 to 9 hours of euglycemia, plasma glucose was allowed to decline to 3.5 mmol/L which was kept steady for 30 min and then was allowed to further decline to a nadir level of 2.5 mmol/L. After the nadir plasma glucose level had been maintained for 15 min, a fixed glucose infusion of 5.5 mg/kg/min was initiated until plasma glucose reached 3.9 mmol/L. This level was kept for 2 hours where after euglycemia was restored. During this experimental procedure, blood samples were collected for assessment of plasma glucose, counterregulatory hormones and pharmacokinetic analysis. Moreover, a hypoglycemic symptoms questionnaire, hypoglycemic awareness, vital signs and cognitive function were frequently recorded. Subjects stayed at the clinic for observation for at least 46 hours after the last dose administration.

**Stepwise glucose clamp:**



- <sup>1</sup> Nadir plasma glucose. If a plasma glucose level of 2.5 mmol/L was not reached, nadir plasma glucose could occur at a higher level.
- <sup>2</sup> Hypoglycaemic symptoms questionnaire, hypoglycaemic awareness, blood sampling for measurement of counterregulatory hormones, vital signs and cognitive function tests
- <sup>3</sup> Performed the first time a specific plasma glucose concentration was reached
- <sup>4</sup> Hypoglycaemia induction may be initiated between 07:00 and 09:00 hours

**Number of Subjects Planned and Analyzed**

A total of 26 subjects were planned to complete the trial. A total of 36 subjects were screened, 28 subjects were randomized and exposed to trial products, 2 subjects were withdrawn due to adverse events, and 26 subjects completed the trial. All 28 exposed subjects were included in the full analysis set and the safety analysis set.

**Diagnosis and Main Criteria for Inclusion**

Subjects with type 1 diabetes treated with insulin (< 1.2 (IU/kg/day) for ≥ 12 months, between 18 and 65 years of age, with HbA1c 6.7-10.0%, BMI 18.0-28.0 kg/m<sup>2</sup> and fasting C-peptide < 0.3 nmol/L.

Key exclusion criteria were: donation of any blood or plasma in the past month or more than 500 mL within 3 months prior to screening; supine blood pressure at screening (after resting for 5 min) outside the range of 90-140 mmHg for systolic blood pressure or 50-90 mmHg for diastolic blood pressure; and smoking (any smoking within 3 months prior to screening).

**Test Product, Dose and Mode of Administration, Batch Number**

IDeg (100 U/mL) in 3 mL (b) (4) cartridges (batch number VCQ0013). IDeg was administered as single s.c. doses once daily for 5 days. The dose level at Days 1-4 was 80% of the subject's own individual basal insulin treatment, and the dose level at Day 5 was 3 times the subject's own individual basal insulin treatment.

**Duration of Treatment**

Subjects received once daily doses of IDeg for 5 days and once daily doses of IGLar for 5 days during the two treatment periods. The total duration of the trial was 17 to 64 days for the individual subject.

**Reference Therapy, Dose and Mode of Administration, Batch Number**

IGlar (Lantus<sup>®</sup> 100 U/mL) in 3 mL cartridges (batch number 40U607). IGLar was administered as single s.c. doses once daily for 5 days. The dose level at Days 1-4 was 80% of the subject's own individual basal insulin treatment, and the dose level at Day 5 was 3 times the subject's own individual basal insulin treatment.

**Criteria for Evaluation – Efficacy****Pharmacodynamics**

- Hypoglycemic symptoms score (HSS)
- Hypoglycemic awareness (HA)
- Vital signs (systolic blood pressure, diastolic blood pressure, pulse)
- Counterregulatory hormone concentrations (adrenaline, growth hormone, cortisol, noradrenaline and glucagon)
- Cognitive function [digit symbol substitution test (DSST), four-choice reaction time (4CRT), trail making B (TMB)]
- Glucose infusion rate
- Plasma glucose (PG)

**Pharmacokinetics**

- Serum IDeg
- Serum IGLar

**Criteria for Evaluation – Safety**

- Adverse events (incl. local injection site reactions)
- Laboratory safety variables
- Physical examination
- Vital signs
- ECG
- Hypoglycemic episodes (other than those being investigated)

**Statistical Methods****Primary Endpoint**

The primary endpoint was baseline-adjusted hypoglycemic symptoms score at nadir plasma glucose concentration, HSSPG<sub>nadir</sub>. Rating of hypoglycemic symptoms was based on the Edinburgh Hypoglycemia Scale including autonomic symptoms (sweating, palpitations, shaking, and hunger), neuroglycopenic symptoms (confusion, drowsiness, odd behaviour, speech difficulty, incoordination) and general malaise (headache, nausea). Each of the 11 symptoms was rated by the subject on an interval-scale ranging from 1 (not at all) to 7 (a great deal).

**Primary Analysis**

To compare symptoms of hypoglycemia during a hypoglycemic episode induced by IDeg versus one induced by IGLar, HSSPG<sub>nadir</sub> was baseline-adjusted and analyzed using a linear mixed effect model with treatment and treatment period as fixed effects, baseline HSS as a continuous covariate and subject as a random effect.

**Secondary Endpoints**

- Secondary pharmacodynamic endpoints related to the gradual development of hypoglycemia were derived from hypoglycemic response assessments and individual plasma glucose concentration-time profiles:
  - HSSPG decline, PulsePG decline, DBPPG decline, SBPPG decline, Chormone<sub>PG</sub> decline, AUC<sub>hormone</sub>, PG decline, TMBPG decline, DSSTPG decline, 4CRTPG decline, tPG decline, HAPG decline, PG $\Delta$ HSS, PG<sub>HA</sub>=yes, PG $\Delta$ TMB, PG $\Delta$ DSST, PG $\Delta$ 4CRT, tPG 5.5 - 3.5 mmol/L, tPG 3.5 - 2.5 mmol/L, PG<sub>HA</sub>=yes – PG<sub>nadir</sub>, tPG 3.9 mmol/L – PG nadir end, tPG 3.1 mmol/L - PG nadir end, tPG nadir - PG nadir end, AUC<sub>GIR</sub> PG 5.5 mmol/L, AUC<sub>GIR</sub> PG 3.5 mmol/L
- Secondary pharmacodynamic endpoints related to nadir plasma glucose were derived from the various hypoglycemic response assessments:
  - PulsePG nadir, DBPPG nadir, SBPPG nadir, Chormone<sub>PG</sub> nadir, TMBPG nadir, DSSTPG nadir, 4CRTPG nadir, PG<sub>nadir</sub>, AUC<sub>GIR</sub>, PG nadir
- Secondary pharmacodynamic endpoints related to the recovery from hypoglycemia were derived from the various hypoglycemic response assessments:
  - tPG nadir - 3.9 mmol/L, AUC<sub>GIR,0-2h,recovery</sub>, AUC<sub>GIR,PG nadir end - 2h</sub>, HSS<sub>recovery</sub>, Pulse<sub>recovery</sub>, DBP<sub>recovery</sub>, SBP<sub>recovery</sub>, Chormone<sub>recovery</sub>, TMB<sub>recovery</sub>, DSST<sub>recovery</sub>, 4CRT<sub>recovery</sub>, HA<sub>recovery</sub>
- Standard pharmacokinetic endpoints were derived from the insulin concentration-time curves after the last dosing.

**Secondary Analyses**

- To further compare symptoms of hypoglycemia and to compare the autonomic response, counterregulatory hormone

response, cognitive function and hypoglycemic awareness during hypoglycemia induced by IDeg versus IGLar:

- HSSPG decline, PulsePG decline, DBPPG decline, SBPPG decline, Chormone,PG decline, TMBPG decline, DSSTPG decline and 4CRTPG decline were analyzed using a mixed linear model with treatment effect (IDeg or IGLar), plasma glucose effect (4.5, 4.0, 3.5, 3.0 and 2.5 mmol/L), treatment\*plasma glucose interaction, period effect and baseline measurement of the given endpoint as a continuous covariate (not for Chormone,PG decline which was logarithm transformed and not baseline-adjusted) and a random subject effect. The random subject effect and error term were assumed independent.
- PulsePG nadir, DBPPG nadir, SBPPG nadir, Chormone,PG nadir, TMBPG nadir, DSSTPG nadir and 4CRTPG nadir were analyzed using the same approach as for the primary endpoint (for Chormone,PG nadir, baseline Chormone was not included as a continuous covariate).
- HAPG decline, PG $\Delta$ HSS, PGHA=yes, PG $\Delta$ TMB, PG $\Delta$ DSST and PG $\Delta$ 4CRT were presented using descriptive statistics.
- PG<sub>nadir</sub>, AUC<sub>Chormone,PG</sub> decline, AUCGIR, PG 5.5 mmol/L, AUCGIR, PG 3.5 mmol/L and AUCGIR, PG nadir were logarithm transformed and analyzed post hoc using the same approach as for the primary endpoint (without baseline-adjustment). For AUCGIR, PG nadir, zero values were set to the lowest non-zero observation. In addition, Chormone,PG decline was analyzed post hoc at plasma glucose 5.5 mmol/L using the same approach.
  - To compare plasma glucose profiles during hypoglycemia induced by IDeg versus IGLar:
    - tPG decline was logarithm transformed and analyzed using the same model as for the hormones during decline with the exception that baseline time (which by definition is 0) was not included in the model.
    - tPG 5.5 - 3.5 mmol/L, tPG 3.5 - 2.5 mmol/L and PGHA=yes - PG<sub>nadir</sub> were presented using descriptive statistics.
  - To compare insulin action, symptoms of hypoglycemia, vital signs, counterregulatory hormones, cognitive function and hypoglycemic awareness during the recovery from hypoglycemia induced by IDeg versus IGLar:
    - tPG nadir - 3.9 mmol/L and AUCGIR,0-2h,recovery were logarithm transformed and analyzed using a mixed linear model with treatment (IDeg or IGLar) and treatment period as fixed effects and subject as a random effect. The random subject effect and error term were assumed independent. AUCGIR,PG nadir end - 2h was analyzed post hoc using the same approach. For AUCGIR,0-2h,recovery, zero values were set to the lowest non-zero observation in the treatment group.
    - HSS<sub>recovery</sub>, Pulse<sub>recovery</sub>, DBP<sub>recovery</sub>, SBP<sub>recovery</sub>, Chormone<sub>recovery</sub>, TMB<sub>recovery</sub>, DSST<sub>recovery</sub> and 4CRT<sub>recovery</sub> were analyzed using a linear mixed effect model with a treatment effect (IDeg or IGLar), a time effect (0, 60 and 120 min), a treatment\*time interaction, a period effect, the baseline measurement of the given endpoint as a continuous covariate (not for Chormone<sub>recovery</sub> which was log transformed and not baseline adjusted) and a random subject effect. The random subject effect and error term were assumed independent.
    - HA<sub>recovery</sub> was presented using descriptive statistics.
- All secondary pharmacokinetic endpoints were derived from the insulin concentration-time curves and presented using descriptive statistics.

#### **Demography of Trial Population**

All exposed subjects were white, and the majority of the subjects were males. They had a mean age of 40 years and a mean BMI of 25.1 kg/m<sup>2</sup>. The average duration of diabetes was 20.6 years and mean HbA<sub>1c</sub> was 7.80%.

#### **Efficacy Results and Conclusions**

##### ***Development of Hypoglycemia***

- **Plasma glucose during development of hypoglycemia:** The overall rate at which plasma glucose declined from 5.5 mmol/L to nadir was slower for IDeg compared to IGLar (0.84 [0.72; 0.99]95%CI). However, statistical analysis showed that from 4.5 mmol/L to nadir plasma glucose, there was no difference between IDeg and IGLar (1.02 [0.89; 1.18]95%CI).
- **Plasma glucose at nadir:** Nadir plasma glucose levels below 2.70 mmol/L approaching the target of 2.5 mmol/L were obtained for the majority of the subjects for both IDeg and IGLar, and similar nadir plasma glucose, PG<sub>nadir</sub>, was obtained for IDeg and IGLar (1.03 [0.99; 1.08]95%CI).
- **Glucose infusion rate:** The amount of glucose required to maintain euglycemia at 5.5 mmol/L during the last 30 min before hypoglycemia induction was statistically significantly lower for IDeg compared to IGLar (0.55 [0.41; 0.74]95%CI), whereas no statistically significant difference was observed at 3.5 mmol/L (0.62 [0.37; 1.06]95%CI) or at nadir plasma glucose (0.43 [0.15; 1.22]95%CI).
- **Hypoglycemic symptoms:** Hypoglycemic symptoms score increased at plasma glucose values below 4.0 mmol/L, and statistical analysis showed that the increase was similar for IDeg and IGLar (-0.05 [-0.40; 0.31]95%CI). There was no statistically significant difference in the primary endpoint (baseline-adjusted hypoglycemic symptoms score at nadir plasma glucose (HSSPG nadir) between IDeg and IGLar (0.17

[-1.71; 2.05]95%CI).

- **Hypoglycemic awareness:** Hypoglycemic awareness was similar for IDeg and IGLar at all plasma glucose levels, increasing from 8% and 4%, respectively, at 5.5 mmol/L, to 74% and 68% at nadir plasma glucose.
- **Counterregulatory hormones:** During development of hypoglycemia, a greater increase in adrenaline and growth hormone levels (1.07 [1.01; 1.14]95%CI and 1.35 [1.19; 1.54]95%CI), and a trend towards greater increase in cortisol (1.03 [1.00; 1.06]95%CI) was observed with IDeg compared to IGLar. The difference between IDeg and IGLar at nadir plasma glucose was statistically significant for growth hormone and cortisol (p-values 0.0311 and 0.0491). The effect on noradrenaline and glucagon was similar for IDeg and IGLar. Results were supported by post hoc analyses of the area under the hormone concentration-time curves.
- **Vital signs:** A similar decrease in diastolic blood pressure was observed with IDeg and IGLar during development of hypoglycemia (-0.42 [-1.18; 0.35]95%CI), whereas no effect on systolic blood pressure or pulse was observed with either IDeg or IGLar. At nadir plasma glucose, there was no statistically significant difference between IDeg and IGLar with regard to pulse or blood pressure.
- **Cognitive function:** There was a smaller drop in the digit symbol substitution test with IDeg compared to IGLar during development of hypoglycemia, and the difference at nadir plasma glucose was statistically significant (5.93 [1.23; 10.62]95%CI). The increase in four-choice reaction time was similar for IDeg and IGLar, and there was no change in performance with regard to percentage of correct responses in four-choice reaction time or time in trail making B for either IDeg or IGLar.

#### **Recovery from Hypoglycemia**

- **Plasma glucose:** Recovery from hypoglycemia and the re-establishment of euglycemia occurred within the same timeframe for IDeg and IGLar (0.75 [0.56; 1.02]95%CI).
- **Glucose infusion rate:** Less glucose was needed to alleviate hypoglycemia for IDeg compared to IGLar as shown by glucose infusion rate profiles and statistical analysis of AUCGIR<sub>0-2h, recovery</sub> and AUCGIR<sub>PG nadir end - 2h</sub> (0.68 [0.49; 0.95]95%CI and 0.71 [0.53; 0.93], respectively).

**Hypoglycemic assessments:** All assessments (hypoglycemic symptoms, hypoglycemic awareness, counterregulatory hormones, vital signs and cognitive function) returned to baseline by a similar rate for IDeg and IGLar.

#### **Pharmacokinetics**

- Pharmacokinetic steady state, which was a prerequisite for comparing hypoglycemic symptoms score and other assessments, was reached before the hypoglycemic experiment.
- Steady state was achieved within 48 to 72 hours, and the 24-hour pharmacokinetic profiles obtained during the hypoglycemic experiment were flat and smooth.

#### **Safety Results and Conclusions**

- A total of 28 AEs (14 with IDeg and 14 with IGLar) were reported in 18 out of 28 exposed subjects. The majority of the AEs were mild (one was moderate and none were severe); two AEs (myopia and anaphylactic reaction) were possibly and probably, respectively, related to IDeg.
- The most commonly reported AE was headache with 16 out of 28 AEs (7 with IDeg and 9 with IGLar).
- One SAE (anaphylactic reaction) reported as moderate in severity and probably related to IDeg led to withdrawal of the subject. The episode resolved spontaneously and the subject recovered without need for medical intervention
- No injection site reactions were recorded.
- A total of 110 treatment emergent hypoglycemic episodes (other than those intentionally induced) were reported in 22 subjects, 18 of these were nocturnal hypoglycemic episodes. None were severe and no safety problems were detected. There was an even distribution between IDeg and IGLar.
- No clinically significant changes in vital signs, ECG or safety laboratory parameters from screening to follow-up were observed.

#### **Overall Conclusions**

The conclusions from this randomized, single-centre, double-blind, two-period cross-over, multiple-dose trial in subjects with type 1 diabetes mellitus comparing the hypoglycemic response between IDeg and IGLar are:

During hypoglycemia, the rate of decline of plasma glucose (from 4.5 mmol/L to nadir) is comparable for IDeg and IGLar.

- Symptoms during hypoglycemia are similar for IDeg and IGLar.
- Counterregulatory hormone response during hypoglycemia is greater with IDeg compared to IGLar.
- During hypoglycemia, cognitive function assessed by digital symbol substitution test is better maintained with IDeg compared to IGLar.
- Recovery from hypoglycemia occurs within the same timeframe for IDeg and IGLar.
- During recovery, less glucose is required to alleviate hypoglycemia with IDeg compared to IGLar.
- Generally, IDeg and IGLar are well tolerated in this trial.

**Reviewer's Comments:**

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 3\%$ ,  $\pm 7\%$ , and  $\pm 9\%$ , respectively for IDeg. The analytical method adequately supported the results for IGLar with accuracy and precision for calibration standards (range of 20.0 to 750 pM) and QC samples lying within  $\pm 9\%$  and  $\pm 3\%$  respectively.

#### 4.2.15 Dose-response in Subjects with Type 1 and Type 2 DM (NN5401-1719)

**Rationale:** The main purpose of the present trial was to establish a potency estimate of I454 (IDeg) both in subjects with type 1 and type 2 diabetes. Because IDeg has been shown to have a long action profile, it was reasonable to compare IDeg with a currently marketed long-acting insulin analogue. The present trial compared the pharmacodynamic dose-response relationship between IDeg and Insulin glargine (IGlar) over a clinically relevant dose range in subjects with type 1 and type 2 diabetes, thereby estimating the molar dose ratio between the two compounds. Furthermore, the present trial aimed at comparing several characteristics of the PK and PD profiles between IDeg and IGlar.

In this trial, the IDeg formulation contained (b) (4) IDeg molecules. IDeg will be mostly in (b) (4) to further enhance the protraction of IDeg.

The study synopsis is as follows:

##### **Title of Trial**

A Randomised, Double-Blind, Single Dose, Six-Period Cross-over Dose Response Trial Comparing the Pharmacodynamics and Pharmacokinetics of Insulin 454 with Insulin Glargine in Subjects with Type 1 and Type 2 Diabetes

##### **Objectives**

###### **Primary Objective:**

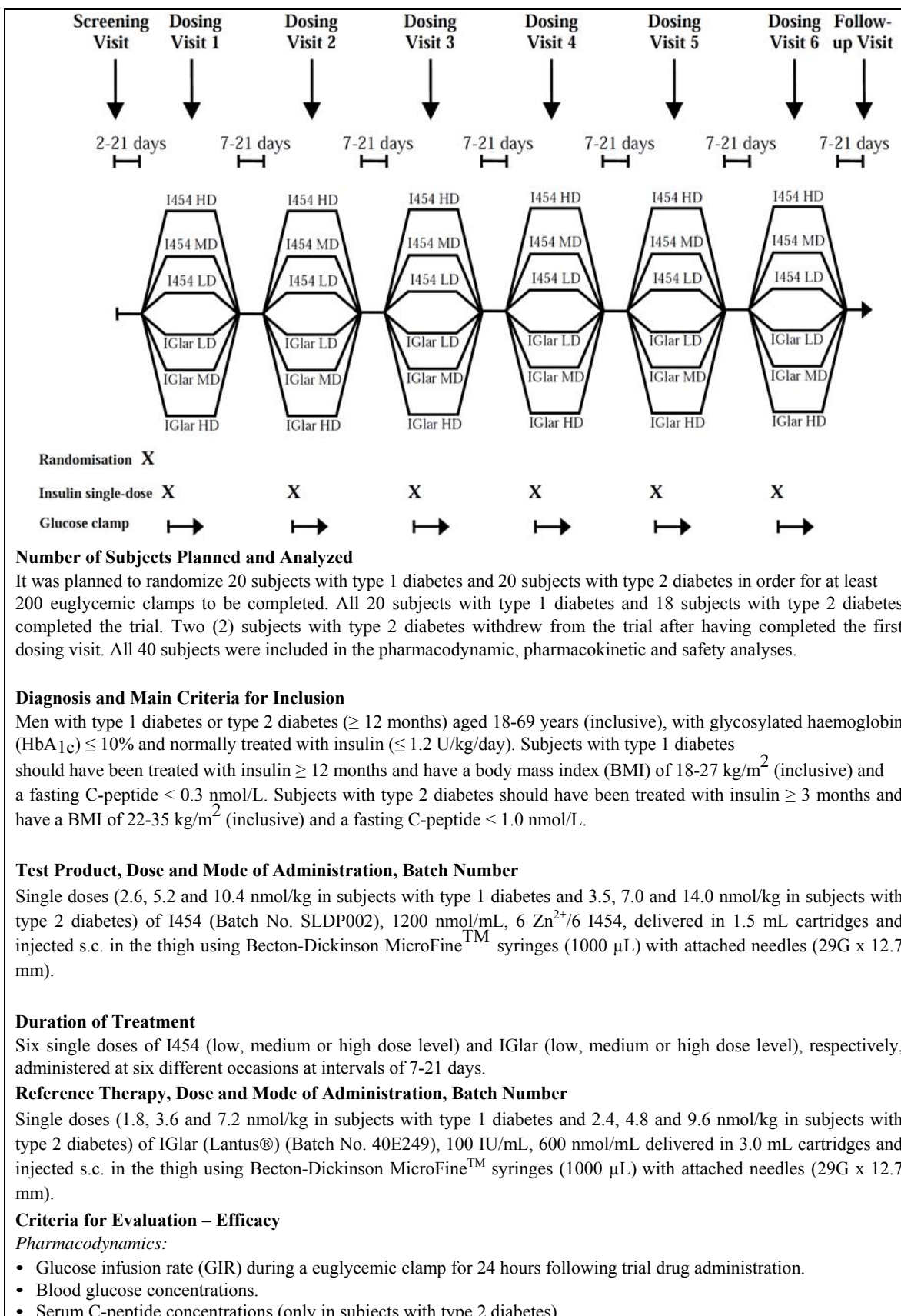
- To compare the dose-response, i.e. pharmacodynamic response, of insulin 454 and insulin glargine over a clinically relevant dose range in order to estimate the molar dose ratio between the two insulin preparations in subjects with type 1 diabetes and in subjects with type 2 diabetes.

###### **Secondary Objectives:**

- To compare the pharmacodynamic and pharmacokinetic properties of insulin 454 and insulin glargine.
- To evaluate the safety profile and local tolerability of insulin 454.

##### **Methodology**

- This was a randomized, double-blind, single centre, six-period cross over trial to compare the dose-response relationship of insulin 454 (I454) and insulin glargine (IGlar) in subjects with type 1 diabetes and type 2 diabetes, respectively, in order to estimate the molar dose ratio between the two insulin products.
- After successful screening, subjects were randomised to one of 18 treatment sequences, involving subcutaneous (s.c.) single-dose administration of 2.6, 5.2 and 10.4 nmol/kg I454 and 1.8, 3.6 and 7.2 nmol/kg IGlar in subjects with type 1 diabetes or 3.5, 7.0 and 14.0 nmol/kg I454 and 2.4, 4.8 and 9.6 nmol/kg IGlar in subjects with type 2 diabetes, respectively, at 6 different dosing visits.
- Wash-out periods of 7-21 days separated the 6 dosing visits.
- At each dosing visit subjects received a controlled intravenous infusion of glucose and human soluble insulin (Actrapid for 4-6 hours prior to trial drug administration in order to keep the blood glucose concentration stable at a level of 90 mg/dL (5.0 mmol/L), i.e. a euglycaemic clamp with a target blood glucose level of 90 mg/dL (5.0 mmol/L) was initiated. The euglycaemic clamp was terminated at 24 hours post-dosing but earlier if blood glucose levels increased to concentrations above 160 mg/dL (8.9 mmol/L) with no glucose infusion during the last 30 min.
- During the period from 24 to 30 hours after trial drug administration, subjects remained fasting. If the blood glucose declined to near or below 70 mg/dL (3.9 mmol/L) during this 6-hour period, the subject received one or more 10 g oral carbohydrate administrations.
- Blood samples for measurement of serum I454/plasma IGlar, serum free fatty acids, serum C-peptide (only subjects with type 2 diabetes) and blood glucose were drawn before dosing and for up to 96 hours after dosing.
- Safety assessments included adverse events (AEs), physical examination, vital signs, electrocardiograms (ECGs), clinical laboratory tests (hematology, biochemistry, urinalysis, coagulation parameters and lipids), blood glucose after the euglycemic clamp, hypoglycemic episodes and local tolerability at the injection site.



- Serum FFA concentrations.
- Number of oral carbohydrate administrations given from 24 to 30 hours post-dose to avoid hypoglycemia.

*Pharmacokinetics:*

- Serum I454/plasma IGlAr concentrations for 96 hours following a single dose of either I454 (low, medium or high dose level) or IGlAr (low, medium or high dose level).

**Criteria for Evaluation – Safety**

The safety evaluation was based on adverse events, physical examination, vital signs, ECGs, clinical laboratory tests (hematology, biochemistry, urinalysis, coagulation parameters and lipids), blood glucose after the euglycemic clamp, hypoglycemic episodes and local tolerability at the injection site.

**Statistical Methods**

**Primary Endpoint:**

- AUC<sub>GIR(0-24h)</sub>, the area under the curve (AUC) of the GIR curve from 0 to 24 hours

The AUC<sub>GIR(0-24h)</sub> dose-response relationship was evaluated in an ANOVA approach using the log-transformed AUC<sub>GIR(0-24h)</sub> as the dependent variable, visit and the interaction between insulin product and dose as fixed effects and subject as a random effect. The effect of treatment period was removed, if insignificant. Then, it was tested if, for the two insulin products, the dose-response relationship for the log-transformed AUC<sub>GIR(0-24h)</sub> could be fitted by straight lines (in log-dose) that were not necessarily parallel or had similar intercept. Finally, if the latter test was accepted, it was tested whether the two straight dose-response relationships were parallel. If this was the case, the potency (molar dose-ratio) was calculated as  $\exp((\beta_{I454} - \beta_{IGlAr})/\gamma)$ , where  $\beta$  is the intercept of the dose-response relationship and  $\gamma$  is the common slope of the dose-response relationships for I454 and IGlAr. For all model reductions, a significance level of  $p < 0.01$  was used.

**Secondary Endpoints:**

*Glucose Infusion Rate*

- GIR<sub>max</sub>, maximum GIR
- tGIR<sub>max</sub>, time to maximum GIR
- AUC<sub>GIR(0-6h)</sub>, area under the GIR curve from 0 to 6 hours
- AUC<sub>GIR(0-12h)</sub>, area under the GIR curve from 0 to 12 hours
- AUC<sub>GIR(12-24h)</sub>, area under the GIR curve from 12 to 24 hours
- AUC<sub>GIR(12-24h)</sub>/AUC<sub>GIR(0-24h)</sub>, ratio of areas under the GIR curve
- GIR<sub>max</sub>/average GIR, maximum GIR divided by the average GIR over 24 hours (AUC<sub>GIR(0-24h)</sub>/1440)
- t75%,AUC<sub>GIR(0-24h)</sub>, time to reach 75% of AUC<sub>GIR(0-24h)</sub>
- t50%,AUC<sub>GIR(0-24h)</sub>, time to reach 50% of AUC<sub>GIR(0-24h)</sub>
- t25%,AUC<sub>GIR(0-24h)</sub>, time to reach 25% of AUC<sub>GIR(0-24h)</sub>
- t75%,AUC<sub>GIR(0-24h)</sub> - t25%,AUC<sub>GIR(0-24h)</sub>, time from reaching 25% to reaching 75% of AUC<sub>GIR(0-24h)</sub>
- tGIR>50% GIR<sub>max</sub>, total amount of time when the smoothed GIR profile is above 50% of GIR<sub>max</sub>
- tGIR>1 mg/kg/min, total amount of time when the smoothed GIR profile is above 1 mg/kg/min
- tGIR>2 mg/kg/min, total amount of time when the smoothed GIR profile is above 2 mg/kg/min

*Serum C-peptide*

- AOCC-peptide(0-30h), area over the baseline-adjusted C-peptide curve from 0 to 30 hours
- C-peptide<sub>min</sub>, minimum C-peptide concentration
- C-peptide<sub>min</sub> (baseline-adjusted), baseline-adjusted minimum C-peptide concentration
- tC-peptide<sub>min</sub>, time to minimum C-peptide concentration
- tC-peptide<sub>baseline</sub>, time where the C-peptide concentration returned to baseline

*Serum FFA*

- AOCCFA(0-30h), area over the baseline-adjusted FFA curve from 0 to 30 hours
- FFA<sub>min</sub>, minimum FFA concentration
- FFA<sub>min</sub> (baseline-adjusted), baseline-adjusted minimum FFA concentration
- tFFA<sub>min</sub>, time to minimum FFA concentration
- tFFA<sub>baseline</sub>, time where the FFA concentration returned to baseline

*Oral Carbohydrate Administration*

- Noral carbohydrate, number of oral carbohydrate administrations to avoid hypoglycaemia during the period from 24 to 30 hours after dosing

#### *Pharmacokinetics*

- $AUC_{ins(0-\infty)}$ , area under the serum I454/plasma IGlár concentration curve from 0 to infinity
- $AUC_{ins(0-96h)}$ , area under the serum I454/plasma IGlár concentration curve from 0 to 96 hours
- $AUC_{ins(0-24h)}$ , area under the serum I454/plasma IGlár concentration curve from 0 to 24 hours
- $AUC_{ins(0-12h)}$ , area under the serum I454/plasma IGlár concentration curve from 0 to 12 hours
- $AUC_{ins(0-6h)}$ , area under the serum I454/plasma IGlár concentration curve from 0 to 6 hours
- $AUC_{ins(12-24h)}$ , area under the serum I454/plasma IGlár concentration curve from 12 to 24 hours
- $AUC_{ins(12-24h)}/AUC_{ins(0-24h)}$ , ratio of areas under the serum I454/plasma IGlár concentration curve
- $C_{max}$ , maximum serum I454/plasma IGlár concentration
- $t_{max}$ , time to maximum serum I454/plasma IGlár concentration
- $t_{1/2}$ , terminal half-life

#### **Statistical Methods (Continued)**

- $t_{50\%,AUC}$ , time to reach 50% of  $AUC_{0-\infty}$
- CL/F, clearance of fraction absorbed
- MRT, mean residence time
- $V_{z/f}$ , volume of distribution during terminal phase

The secondary pharmacodynamic endpoints,  $GIR_{max}$ ,  $AOCFFA(0-30h)$  and  $FFA_{min}$  (baseline-adjusted) as well as the pharmacokinetic endpoints,  $AUC_{ins(0-\infty)}$  and  $C_{max}$  were analyzed using the ANOVA approach described for the primary endpoint.  $GIR_{max}$ ,  $AUC_{ins(0-\infty)}$  and  $C_{max}$  were all log-transformed, whereas  $AOCFFA(0-30h)$  and  $FFA_{min}$  were not log-transformed before analysis. For  $GIR_{max}$ ,  $AOCFFA(0-30h)$  and  $FFA_{min}$ , the same model reductions as for the primary endpoint were evaluated. For  $AUC_{ins(0-\infty)}$  and  $C_{max}$ , the first two model reductions were evaluated to investigate whether the dose-response relationship for the endpoint of interest could be fitted by straight lines (in log-dose) that were not necessarily parallel or had similar intercept. It was then tested whether the slope of the dose-response relationship was equal to 1 for each of the two insulin products separately, in order to determine if the two insulin products had linear kinetics at the chosen dose interval. Noral carbohydrate was analyzed using a negative-binomial model with period and interaction between insulin type and dose as fixed effects and subject as a random effect. All other secondary endpoints were evaluated by descriptive statistics.

#### **Demography of Trial Population**

The 20 male subjects with type 1 diabetes were all Caucasians. Their mean age was 37 years (range 20 to 52 years), mean weight was 74 kg (range 54 to 90 kg), mean BMI was 24.1  $kg/m^2$  (range 20.0 to 26.8  $kg/m^2$ ), mean  $HbA_{1c}$  was 7.9% (range 6.7 to 9.6%), C-peptide was  $\leq 0.09$  nmol/L in all subjects and they had a mean diabetes duration of 21 years (range 9 to 36 years).

The 20 male subjects with type 2 diabetes were 19 Caucasians and 1 black. Their mean age was 56 years (range 39 to 68 years), mean weight was 93 kg (range 63 to 108 kg), mean BMI was 29.6  $kg/m^2$  (range 22.1 to 34.2  $kg/m^2$ ), mean  $HbA_{1c}$  was 7.7% (range 6.1 to 9.1%), C-peptide was 0.46 nmol/L (range  $<0.01$  to 1.15 nmol/L) and they had a mean diabetes duration of 14 years (range 2 to 39 years).

#### **Efficacy Results**

- The dose-response relationships for I454 and IGlár with respect to  $AUC_{GIR(0-24h)}$  and  $GIR_{max}$  were linear (on a logarithmic scale) within the investigated dose range in subjects with type 1 diabetes as well as in subjects with type 2 diabetes. However, the GIR data in the present trial should be carefully interpreted due to early blood glucose escape from the euglycemic clamp target level of 90 mg/dL seen especially with the low dose levels of I454 and IGlár. Moreover, in particular for I454,  $AUC_{GIR(0-24h)}$  did not capture the total insulin action, since pronounced levels of GIR were still present at clamp termination.
- The molar dose ratios between I454 and IGlár in the first 24 hours after injection were 0.32 in subjects with type 1 diabetes and 0.37 in subjects with type 2 diabetes. It should be noted that the potency estimates have little therapeutic relevance due to the large difference between I454 and IGlár in the shape of the GIR profiles.
- Mean GIR and FFA profiles indicated that I454 had a more protracted action profile than IGlár. Time to  $GIR_{max}$  was longer for I454 (13 to 20 hours) than for IGlár (11 to 13 hours) with no apparent dose dependency. The time for FFA concentrations to return to baseline levels also appeared to be longer for I454 (16, 26 and 30 hours in subjects with type 1 diabetes and 26, 29 and 29 hours in subjects with type 2 diabetes for increasing dose levels) than for

IGlar (12, 21 and 29 hours in subjects with type 1 diabetes and 18, 25 and 27 hours in subjects with type 2 diabetes for increasing dose levels) with a clear dose dependency (longer with higher dose level).

- The number of oral carbohydrate administrations necessary to keep blood glucose above 70 mg/dL (3.9 mmol/L) during the first 6 hours after euglycaemic clamp termination showed a linear dose-response relationship and appeared to be similar for I454 and IGLar when expressed on a nmol basis.
- For I454, there was a tendency towards dose proportionality with respect to  $AUC_{ins(0-\infty)}$  in both subjects with type 1 diabetes (95% CI for the slope of  $\log(AUC_{ins(0-\infty)})$  versus  $\log(\text{dose})$  was [0.77;0.97]) and in subjects with type 2 diabetes (95% CI was [0.79;0.97]). Dose proportionality could not be demonstrated for I454 with respect to  $C_{max}$ .
- For IGLar, dose proportionality was demonstrated with respect to  $C_{max}$  in subjects with type 1 diabetes and with respect to  $AUC_{ins(0-\infty)}$  and  $C_{max}$  in subjects with type 2 diabetes, whereas a tendency towards dose proportionality was observed with respect to  $AUC_{ins(0-\infty)}$  in subjects with type 1 diabetes (95% CI was [0.71;0.97]).
- The mean  $t_{max}$  was markedly longer for I454 (19 to 26 hours) than for IGLar (11-13 hours) with no apparent dose dependency.
- The mean terminal half-life was 18 to 19 hours for I454 and 13 to 25 hours for IGLar and did not differ between I454 and IGLar in subjects with type 1 diabetes and in subjects with type 2 diabetes.

#### Safety Results

- There were a total of 40 AEs occurring in 33% of the trial population (13 subjects). Twenty-five (25) AEs occurred in 7 subjects with type 1 diabetes and 15 AEs occurred in 6 subjects with type 2 diabetes.
- Twenty-one (21) AEs were mild and 19 were moderate. Twenty-three (23) AEs were assessed to be possibly related to trial product, while 17 AEs were assessed to be unlikely related to trial product.
- The most frequent AEs were headache (27 AEs), diarrhea (6) and nasopharyngitis (3).
- The incidence of AEs was comparable between I454 and IGLar.
- No serious AEs were reported.
- There were no clinically relevant findings for biochemistry, hematology, urinalysis, coagulation, vital signs, ECG and physical examination.
- No hypoglycemic episodes were reported.
- Mild injection site disorders were reported for 2 subjects following dosing with I454.
- In general, single-dose administration of I454 and IGLar, respectively, was well tolerated in subjects with type 1 diabetes and in subjects with type 2 diabetes.

#### Conclusions

- The pharmacodynamic dose-response relationship, based on  $AUC_{GIR(0-24h)}$ , was linear for I454 and IGLar in both subjects with type 1 and type 2 diabetes.
- I454 was less potent than IGLar on a molar scale over 24 hours (by a factor 0.32 in subjects with type 1 diabetes and by a factor 0.37 in subjects with type 2 diabetes). However, the potency estimates have little therapeutic relevance due to the large difference in the shape of the GIR profiles between I454 and IGLar.
- I454 appeared to have a more protracted action profile and a longer duration of action compared with IGLar as evidenced by the GIR and FFA profile characteristics and the number of carbohydrate administrations necessary to keep blood glucose above 70 mg/dL (3.9 mmol/L) during the first 6 hours after termination of the 24-hour euglycemic clamp.
- For I454, there was a tendency towards dose proportionality with respect to  $AUC_{ins(0-\infty)}$  in both subjects with type 1 and type 2 diabetes, whereas dose proportionality could not be demonstrated with respect to  $C_{max}$ . Dose proportionality was demonstrated for IGLar with respect to  $C_{max}$  in subjects with type 1 diabetes and with respect to both  $AUC_{ins(0-\infty)}$  and  $C_{max}$  in subjects with type 2 diabetes. A tendency towards dose proportionality was observed for IGLar with respect to  $AUC_{ins(0-\infty)}$  in subjects with type 1 diabetes.
- Single-dose administration of I454 and IGLar were well-tolerated with no indication of safety issues.

#### Reviewer's Comments:

The study results are reasonable from a clinical pharmacology perspective. No notable protocol deviations occurred during this trial. The analytical method adequately supported the results with accuracy and precision for calibration standards (range of 20.0 to 1000 pM), QC samples, and dilution QC samples lying within  $\pm 14\%$  for IDeg. The analytical method adequately supported the results for IGLar with accuracy and precision for calibration standards (range of 20.0 to 750 pM) and QC samples lying within  $\pm 16\%$  and  $\pm 6\%$  respectively.

### 4.3 OCP Filing Memo

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| <b>Office of Clinical Pharmacology</b>                                         |                                                   |                             |                                                                                                                   |                                                      |
|--------------------------------------------------------------------------------|---------------------------------------------------|-----------------------------|-------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| <i>New Drug Application Filing and Review Form</i>                             |                                                   |                             |                                                                                                                   |                                                      |
| <u>General Information About the Submission</u>                                |                                                   |                             |                                                                                                                   |                                                      |
|                                                                                | Information                                       |                             | Information                                                                                                       |                                                      |
| NDA/BLA Number                                                                 | 203314                                            | Brand Name                  | Tresiba®                                                                                                          |                                                      |
| OCP Division (I, II, III, IV, V)                                               | DCP II                                            | Generic Name                | Insulin Degludec                                                                                                  |                                                      |
| Medical Division                                                               | DMEP                                              | Drug Class                  | Anti-diabetic                                                                                                     |                                                      |
| OCP Reviewer                                                                   | Manoj Khurana, Ph.D.                              | Indication(s)               | An ultra-long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. |                                                      |
| OCP Team Leader                                                                | Jayabharathi Vaidyanathan, Ph.D. (Acting)         | Dosage Form                 | Solution for subcutaneous injection                                                                               |                                                      |
| Pharmacometrics Reviewer                                                       | Primary: Manoj Khurana<br>Secondary: Kevin Krudys | Dosing Regimen              | Once Daily any time of day                                                                                        |                                                      |
| Date of Submission                                                             | September 29, 2011                                | Route of Administration     | SC                                                                                                                |                                                      |
| Estimated Due Date of OCP Review                                               | May 29, 2012                                      | Sponsor                     | Novo Nordisk                                                                                                      |                                                      |
| Medical Division Due Date                                                      | June 01, 2012                                     | Priority Classification     | Standard                                                                                                          |                                                      |
| PDUFA Due Date                                                                 | July 29, 2012                                     |                             |                                                                                                                   |                                                      |
| <b><i>Clin. Pharm. and Biopharm. Information</i></b>                           |                                                   |                             |                                                                                                                   |                                                      |
|                                                                                | "X" if included at filing                         | Number of studies submitted | Number of studies reviewed                                                                                        | Critical Comments If any                             |
| <b>STUDY TYPE</b>                                                              |                                                   |                             |                                                                                                                   |                                                      |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                                                 |                             |                                                                                                                   |                                                      |
| Tabular Listing of All Human Studies                                           | X                                                 |                             |                                                                                                                   |                                                      |
| HPK Summary                                                                    | X                                                 |                             |                                                                                                                   |                                                      |
| Labeling                                                                       | X                                                 |                             |                                                                                                                   |                                                      |
| Reference Bioanalytical and Analytical Methods                                 | X                                                 |                             |                                                                                                                   |                                                      |
| <b>I. Clinical Pharmacology</b>                                                |                                                   |                             |                                                                                                                   |                                                      |
| Mass balance:                                                                  |                                                   |                             |                                                                                                                   |                                                      |
| Isozyme characterization:                                                      | X                                                 | 1                           |                                                                                                                   | 207440                                               |
| Blood/plasma ratio:                                                            |                                                   |                             |                                                                                                                   |                                                      |
| Plasma protein binding:                                                        | X                                                 | 4                           |                                                                                                                   | 208378, 208523, CES 10-January-2008, CES 01-May-2007 |
| <b>Pharmacokinetics (e.g., Phase I) -</b>                                      |                                                   |                             |                                                                                                                   |                                                      |
| <b>Healthy Volunteers-</b>                                                     |                                                   |                             |                                                                                                                   |                                                      |
| single dose:                                                                   |                                                   |                             |                                                                                                                   |                                                      |
| multiple dose:                                                                 |                                                   |                             |                                                                                                                   |                                                      |
| <b>Patients-</b>                                                               |                                                   |                             |                                                                                                                   |                                                      |
| single dose:                                                                   |                                                   |                             |                                                                                                                   |                                                      |
| multiple dose:                                                                 |                                                   |                             |                                                                                                                   |                                                      |

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|                                                            |          |           |  |                                                                                                                                                                            |
|------------------------------------------------------------|----------|-----------|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dose proportionality -</b>                              |          |           |  |                                                                                                                                                                            |
| fasting / non-fasting single dose:                         |          |           |  |                                                                                                                                                                            |
| fasting / non-fasting multiple dose:                       |          |           |  |                                                                                                                                                                            |
| <b>Drug-drug interaction studies -</b>                     |          |           |  |                                                                                                                                                                            |
| In-vivo effects on primary drug:                           |          |           |  |                                                                                                                                                                            |
| In-vivo effects of primary drug:                           |          |           |  |                                                                                                                                                                            |
| In-vitro:                                                  | <b>X</b> | 2         |  | CES 20-January-2009, CES 101123                                                                                                                                            |
| <b>Subpopulation studies -</b>                             |          |           |  |                                                                                                                                                                            |
| ethnicity:                                                 | <b>X</b> | 2         |  | NN1250-3762, NN1250-1996 (Japanese)                                                                                                                                        |
| gender:                                                    |          |           |  |                                                                                                                                                                            |
| pediatrics:                                                | <b>X</b> | 1         |  | NN1250-1995                                                                                                                                                                |
| geriatrics:                                                | <b>X</b> | 1         |  | NN1250-1994                                                                                                                                                                |
| renal impairment:                                          | <b>X</b> | 1         |  | NN1250-1990                                                                                                                                                                |
| hepatic impairment:                                        | <b>X</b> | 1         |  | NN1250-1989                                                                                                                                                                |
| <b>PD -</b>                                                |          |           |  |                                                                                                                                                                            |
| Phase 1:                                                   | <b>X</b> | 1         |  | NN1250-3538 (Hypoglycaemic response)                                                                                                                                       |
| Phase 2:                                                   |          |           |  |                                                                                                                                                                            |
| Phase 3:                                                   |          |           |  |                                                                                                                                                                            |
| <b>PK/PD -</b>                                             |          |           |  |                                                                                                                                                                            |
| Phase 1 and/or 2, proof of concept:                        | <b>X</b> | 4         |  | NN1250-1991 (T1DM, within-subject variability)<br>NN1250-1993 (T1DM SS, Dose-Resp)<br>NN1250-3678 (T1DM SS, U100 and U200)<br>NN1250-1987 (T2DM SS, Dose-Resp U100 & U200) |
| Phase 3 clinical trial:                                    |          |           |  |                                                                                                                                                                            |
| <b>Population Analyses -</b>                               |          |           |  |                                                                                                                                                                            |
| Data rich:                                                 |          |           |  |                                                                                                                                                                            |
| Data sparse:                                               | <b>X</b> | 1         |  | NN1250-3586 (One PopPK Report)                                                                                                                                             |
| <b>II. Biopharmaceutics</b>                                |          |           |  |                                                                                                                                                                            |
| Absolute bioavailability                                   | <b>X</b> | 1         |  | NN1250-1992                                                                                                                                                                |
| Relative bioavailability -                                 |          |           |  |                                                                                                                                                                            |
| solution as reference:                                     |          |           |  |                                                                                                                                                                            |
| alternate formulation as reference:                        |          |           |  |                                                                                                                                                                            |
| Bioequivalence studies -                                   |          |           |  |                                                                                                                                                                            |
| traditional design; single / multi dose:                   | <b>X</b> | 3         |  | NN1250-1988, NN1250-3769                                                                                                                                                   |
| replicate design; single / multi dose:                     |          |           |  |                                                                                                                                                                            |
| Food-drug interaction studies                              |          |           |  |                                                                                                                                                                            |
| Bio-waiver request based on BCS                            |          |           |  |                                                                                                                                                                            |
| BCS class                                                  |          |           |  |                                                                                                                                                                            |
| Dissolution study to evaluate alcohol induced dose-dumping |          |           |  |                                                                                                                                                                            |
| <b>III. Other CPB Studies</b>                              |          |           |  |                                                                                                                                                                            |
| Genotype/phenotype studies                                 |          |           |  |                                                                                                                                                                            |
| Chronopharmacokinetics                                     |          |           |  |                                                                                                                                                                            |
| Pediatric development plan                                 | <b>X</b> |           |  |                                                                                                                                                                            |
| Literature References                                      |          |           |  |                                                                                                                                                                            |
| <b>Total Number of Studies</b>                             |          | <b>23</b> |  |                                                                                                                                                                            |

Keys: T1DM- Type 1 diabetes mellitus, T2DM – Type 2 diabetes mellitus, SS – steady-state

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On **initial** review of the NDA/BLA application for filing:

|                                                                                     | Content Parameter                                                                                                                                                   | Yes | No | N/A | Comment                                                                                                                                                     |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Criteria for Refusal to File (RTF)</b>                                           |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 1                                                                                   | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?                                  | X   |    |     | To be marketed formulation has been used in the pivotal clinical trials. BE trials compared formulation changes due to process optimization during Phase 3. |
| 2                                                                                   | Has the applicant provided metabolism and drug-drug interaction information?                                                                                        | X   |    |     | Only in vitro studies.                                                                                                                                      |
| 3                                                                                   | Has the sponsor submitted bioavailability data satisfying the CFR requirements?                                                                                     | X   |    |     |                                                                                                                                                             |
| 4                                                                                   | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?                                                                        | X   |    |     |                                                                                                                                                             |
| 5                                                                                   | Has a rationale for dose selection been submitted?                                                                                                                  | X   |    |     |                                                                                                                                                             |
| 6                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?             | X   |    |     |                                                                                                                                                             |
| 7                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?                                                | X   |    |     |                                                                                                                                                             |
| 8                                                                                   | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?                                                            | X   |    |     |                                                                                                                                                             |
| <b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b> |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| <b>Data</b>                                                                         |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 9                                                                                   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?                                               | X   |    |     | Sponsor have not submitted nonmem dataset and control files for the population PK analysis and a request will be communicated in the filing letter          |
| 10                                                                                  | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?                                                                               |     |    | X   |                                                                                                                                                             |
| <b>Studies and Analyses</b>                                                         |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 11                                                                                  | Is the appropriate pharmacokinetic information submitted?                                                                                                           | X   |    |     |                                                                                                                                                             |
| 12                                                                                  | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed | X   |    |     |                                                                                                                                                             |

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|                |                                                                                                                                                                                                                                  |   |  |   |                                                                                                                                                                                                                         |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | dose-ranging or pivotal studies)?                                                                                                                                                                                                |   |  |   |                                                                                                                                                                                                                         |
| 13             | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?                                                                       | X |  |   |                                                                                                                                                                                                                         |
| 14             | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X |  |   | Insulin dose is titrated up and down based on the patients need.                                                                                                                                                        |
| 15             | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?                                                                                                         | X |  |   | FDA agreed with partial waiver in pediatric patients less than one year of age (correspondence dated 3/21/2011). Sponsor is planning to conduct clinical trial in T1DM pediatric subjects aged 1 to less than 18 years. |
| 16             | Did the applicant submit all the pediatric exclusivity data, as described in the WR?                                                                                                                                             |   |  | X |                                                                                                                                                                                                                         |
| 17             | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?                                                                                                   | X |  |   |                                                                                                                                                                                                                         |
| <b>General</b> |                                                                                                                                                                                                                                  |   |  |   |                                                                                                                                                                                                                         |
| 18             | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?                                                      | X |  |   |                                                                                                                                                                                                                         |
| 19             | Was the translation (of study reports or other study information) from another language needed and provided in this submission?                                                                                                  |   |  | X |                                                                                                                                                                                                                         |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**

  YES  

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**Although not a potential review issue, the following is an information request to be sent in the Day 74 letter for the Sponsor:**

1. Please provide raw data (CSV and/or SAS transport files) used for the population PK analysis conducted for Trial NN1250-3586.
2. Please provide the NONMEM Model Codes for the population PK analyses. In general, model codes or control streams and output listings should be provided for all major model-building steps, e.g., base structural model, covariates models, final model, and validation model. These

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files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

|                                    |          |
|------------------------------------|----------|
| Manoj Khurana                      | 11/18/11 |
| Reviewing Clinical Pharmacologist  | Date     |
| Jayabharathi Vaidyanathan (Acting) | 11/18/11 |
| Team Leader/Supervisor             | Date     |

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
06/27/2012

JAYABHARATHI VAIDYANATHAN  
06/27/2012

## CLINICAL PHARMACOLOGY REVIEW

|                                |                                                              |
|--------------------------------|--------------------------------------------------------------|
| NDA: 203313                    | Submission Date(s): 09/29/2011                               |
| Brand Name                     | Ryzodeg                                                      |
| Generic Name                   | Insulin degludec/ Insulin aspart                             |
| Clinical Pharmacology Reviewer | Ritesh Jain, Ph.D.                                           |
| Team Leader (Acting)           | Jayabharathi Vaidyanathan, Ph.D.                             |
| OCP Division                   | Clinical Pharmacology -2                                     |
| OND division                   | Metabolism and Endocrinology Products                        |
| Sponsor                        | Novo Nordisk                                                 |
| Submission Type; Code          | NDA 505(b)(1); Standard                                      |
| Formulation; Strength(s)       | 100 Units of insulin degludec/insulin aspart per mL (U-100)  |
| Proposed Indication            | To improve glycemic control in adults with diabetes mellitus |

|       |                                                                                                                                                                                                                 |    |
|-------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----|
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| 2.1.2 | What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?..... | 16 |
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| <hr/>  |                                                                                                                                                                                                                                         |    |
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## 1 Executive Summary

Insulin degludec/insulin aspart (IDegAsp) is a premix consisting of 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp). Insulin degludec (a new molecular entity) is long acting basal insulin, modified such that the amino acid <sup>(b) (4)</sup> threonine in position B30 of human insulin has been omitted, and the ε amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. Insulin aspart (B28Asp human insulin) is a well characterized fast-acting prandial insulin approved by the Agency in 2000 (NovoLog<sup>®</sup>).

IDegAsp is intended for subcutaneous (S.C.) injection for once or twice daily dosing at any main meal, and indicated to improve glycemic control in adults with diabetes mellitus. The formulation of IDegAsp has been optimized such that the individual components do not interact, with IAsp present as soluble and stable hexamers and IDeg as soluble and stable di-hexamers. Once injected into the subcutaneous tissue the IAsp hexamers immediately form monomers which are rapidly absorbed into the capillaries while the IDeg di-hexamers form soluble multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. IDegAsp is developed in a 100 unit (U)/mL strength for subcutaneous injection, provided in a prefilled pen injector with a dose range of 1-80 U per injection in one-unit increments <sup>(b) (4)</sup>

### 1.1 Recommendation

The Office of Clinical Pharmacology has reviewed the clinical pharmacology data submitted under NDA 203313 (dated 11/28/2011), and finds it acceptable.

### 1.2 Phase IV Commitments

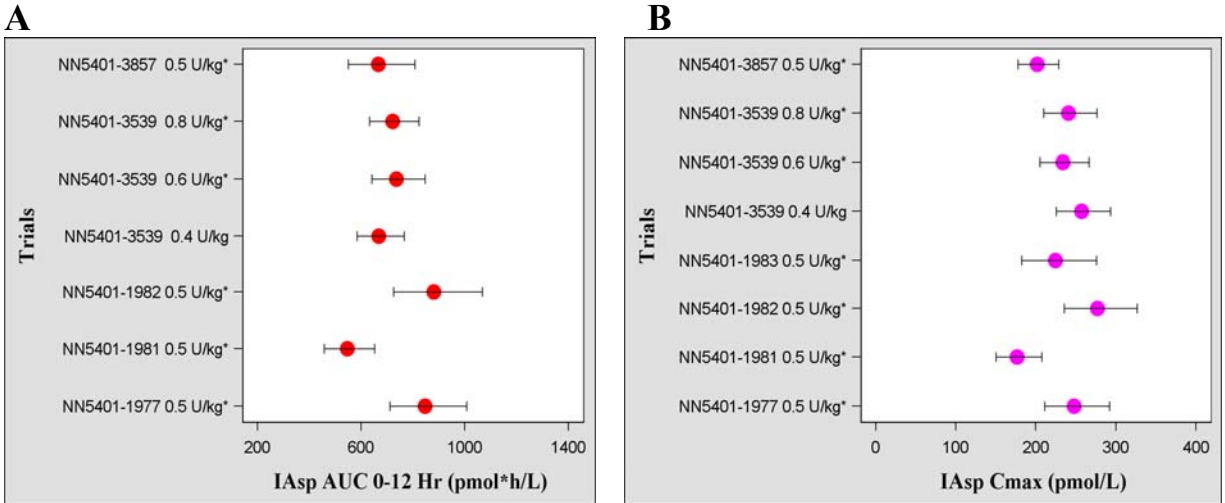
None

### 1.3 Summary of Important Clinical Pharmacology Findings

The IDegAsp clinical development program included in this application consists of 13 clinical pharmacology trials (**Table 3**), 3 exploratory trials of 6–16 weeks duration, 5 confirmatory trials of 26 weeks duration and one completed confirmatory, 26-week extension trial (**Figure 8**).

#### **Single Dose Pharmacokinetics Properties of IDegAsp in Type 1 Diabetic Mellitus (T1DM) Subjects:**

In this application, the pharmacokinetics of IDegAsp was evaluated in several Phase 1 clinical trials. Forest plots (**Figure 1**) shows the dose-normalized total exposure ( $AUC_{0-12h}$ , IAsp) and peak concentration ( $C_{max}$ , IAsp) for IAsp following IDegAsp single dose administration. Median  $T_{max}$  for IAsp in these trials ranged from 1 to 1.4 hrs. Cross study comparison of the pharmacokinetic parameters showed that the pharmacokinetic properties of IAsp were comparable across the trials.



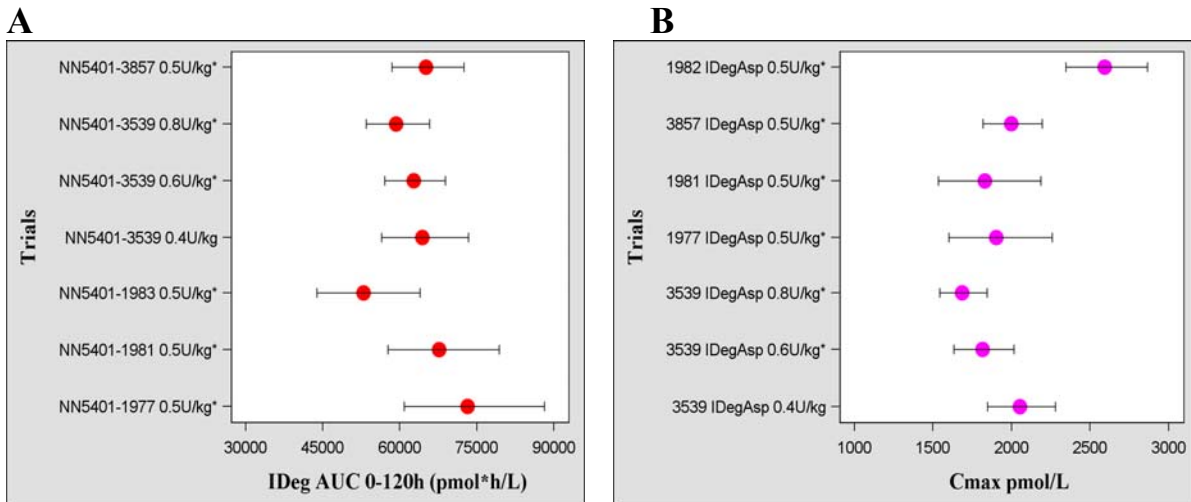
Geometric mean with 95% confidence intervals.

\* Dose-adjusted to 0.4 U/kg assuming dose proportionality (equal to a dose of 0.12 U/kg of the IAsp component)

Trial 1981: Analysis includes only younger adult subjects. Trial 1982: Analysis includes only adult subjects..

**Figure 1: IAsp Pharmacokinetic Endpoints (A) AUC<sub>0-12h</sub>, IAsp (B) C<sub>max</sub>, IAsp Adjusted for Dose after Single Dose IDegAsp in Adult Subjects with T1DM**

The pharmacokinetics parameters of IDeg following IDegAsp single dose administration is shown in **Figure 2**. Forest plots (**Figure 2**) shows the dose-normalized total exposure (AUC<sub>0-120h</sub>, IDeg) and peak concentration (C<sub>max</sub>, IDeg) for IDeg following IDegAsp single dose administration in T1DM subjects.



Trial 1981: Analysis younger adult subjects.

Geometric mean with 95% confidence intervals.

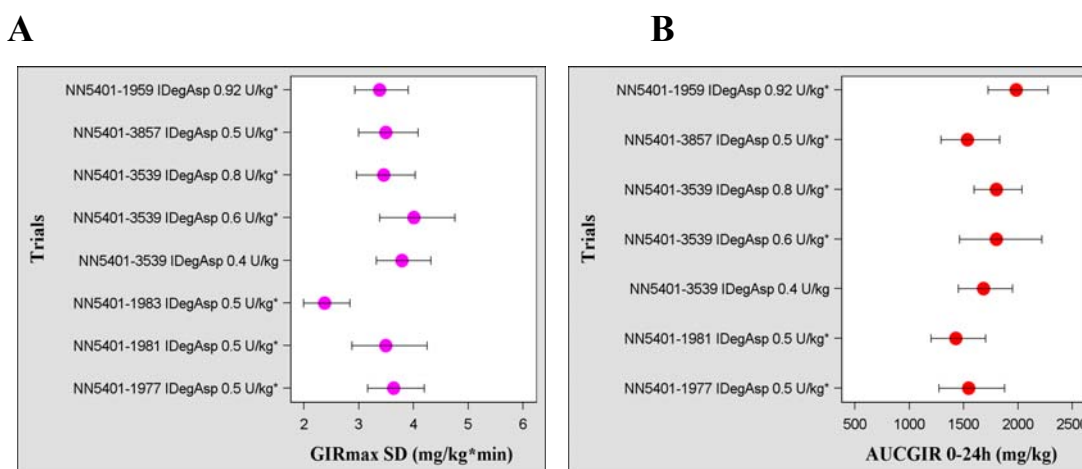
\* Dose-adjusted to 0.4 U/kg assuming dose proportionality (equal to a dose of 0.28 U/kg of the IDeg component).

**Figure 2: IDeg Pharmacokinetic Endpoints (A) AUC<sub>0-120h</sub> IDeg (B) C<sub>max</sub>, IDeg Adjusted for Dose after Single Dose IDegAsp in Adult Subjects with T1DM**

Median T<sub>max</sub> for IDeg in these trials ranged from 12 to 14 hrs. Similar to IAsp, cross study comparison showed that the pharmacokinetic properties of IDeg were comparable across the trials except for trial 1982 where C<sub>max</sub> seems to be different as compared to other trials.

### Single Dose Pharmacodynamic (PD) Characteristic of IDegAsp in T1DM adult subjects

In this application, pharmacodynamic effect (glucose-lowering effect) of IDegAsp was evaluated using the euglycemic clamp technique. In general, the glucose clamp target level was kept at 5.5 mmol/L (100 mg/dL) in subjects with T1DM. Similar to pharmacokinetic studies, pharmacodynamic parameters were evaluated only with single dose administration of IDegAsp. **Figure 3** shows the area under the glucose infusion rate curve from 0 to 24 hours ( $AUC_{GIR}$ , 0-24h) and maximum glucose infusion rate ( $GIR_{max}$ ) following single doses of IDegAsp. Similar to the pharmacokinetic properties, pharmacodynamic parameters across studies seems comparable (except  $GIR_{max}$  for trial 1983).



Geometric mean with 95% confidence intervals.

\* Dose-adjusted to 0.4 U/kg assuming dose proportionality.

Trial 1981: Analysis included only younger adult subjects.

Source: Sponsor's summary of clinical pharmacology report.

**Figure 3: Glucose Infusion Rate Endpoints (A)  $GIR_{max}$  (B)  $AUC_{GIR,0-24h}$  Adjusted for Dose after Single Dose IDegAsp in Subjects with T1DM**

### Pharmacokinetic and Pharmacodynamic Properties of IDegAsp in T1DM and T2DM subjects

#### Pharmacokinetics

Comparison of pharmacokinetic parameter in T1DM subjects (**Table 5 and Table 6**) and T2DM subject (**Table 7 and Table 8**) suggests that pharmacokinetics of both Insulin aspart and insulin degludec in similar between two population following single dose subcutaneous administration of IDegAsp.

#### Pharmacodynamics

Comparison of pharmacodynamic parameters showed that the pharmacodynamic response is different between two populations. Area under the curve for glucose infusion rate is much higher for subjects with T1DM as compared to T2DM subjects at all the dose levels following single dose administration of IDegAsp (**Figure 4**). Similarly,  $GIR_{max}$  was much lower in T2DM subjects as compared to T1DM subjects (**Figure 16 and Figure 18**).

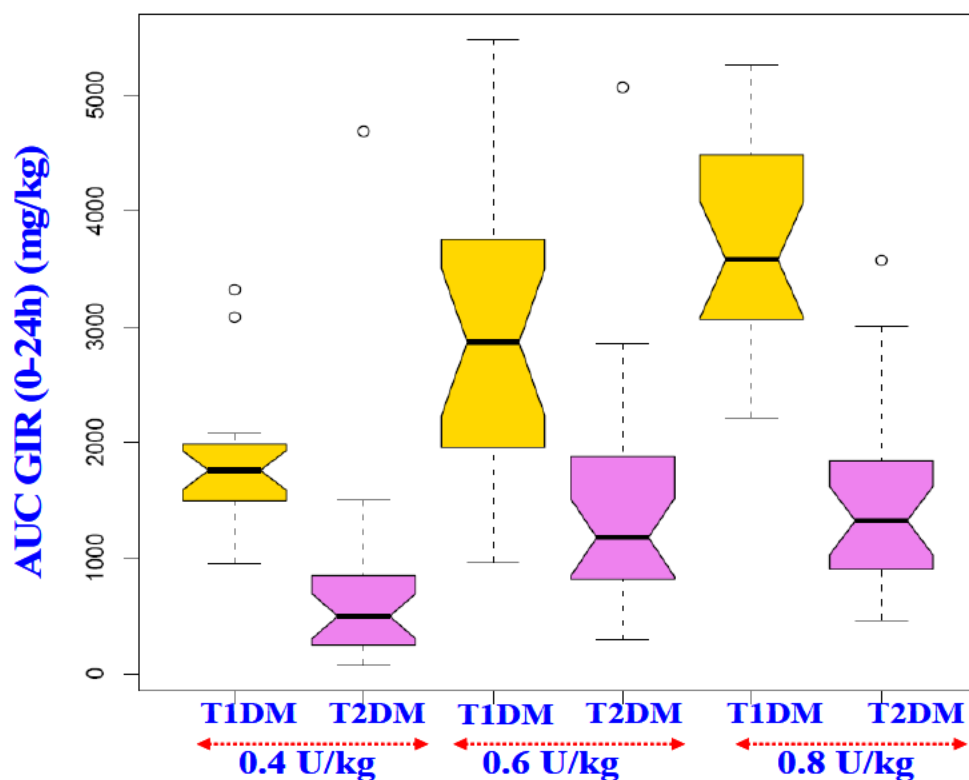


**Figure 4: Comparison of pharmacodynamic parameter ( $AUC_{GIR,0-24h}$ ) between T1DM Subjects (trial 3539) and T2DM Subject (trial 1978)**

These results suggest that T1DM subjects are more sensitive to insulin and thus require more glucose infusion rate as compared to T2DM subjects. However, caution should be made in the interpretation of these results because in clamp experiments different target glucose levels were set for T1DM (target glucose level of 5.5 mmol/L) and T2DM (target glucose level of 5 mmol/L) subjects. These different target glucose levels can affect the glucose infusion rate in T1DM and T2DM subjects and thus can affect  $AUC_{GIR,0-24h}$ .

### **Product Distinctiveness**

Current draft diabetes guidance recommends that a new formulation of premixed insulin (short- and long-acting insulin's) should demonstrate at least 20 % difference in pharmacodynamic and pharmacokinetic profiles when compared to each of its single components.

Pharmacokinetic analysis following single dose subcutaneous administration of IDegAsp, IDeg, or IAsp in T1DM subjects demonstrate that IDegAsp is more than 20% different from products of each of its components (IAsp and IDeg products) for all pre-specified pharmacokinetic endpoints (**Table 12 and Table 13**).

In terms of pharmacodynamics, product distinctiveness was demonstrated by comparing the area under the glucose infusion rate (GIR) between IDegAsp and IAsp (based on the

area under the GIR curve from 6 to 24 hours), and between IDegAsp and IDeg (based on the area under the GIR curve from 0 to 6 hours).

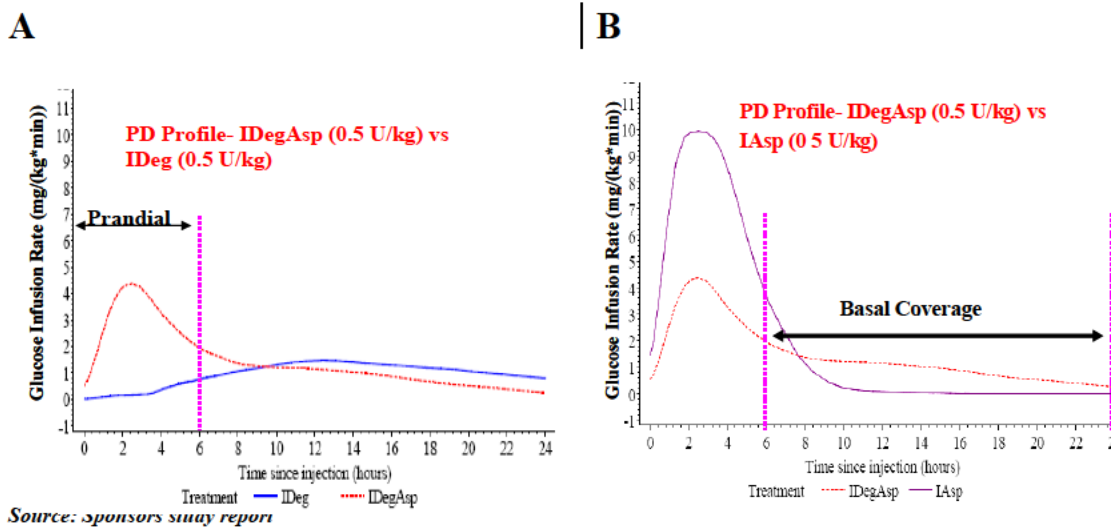


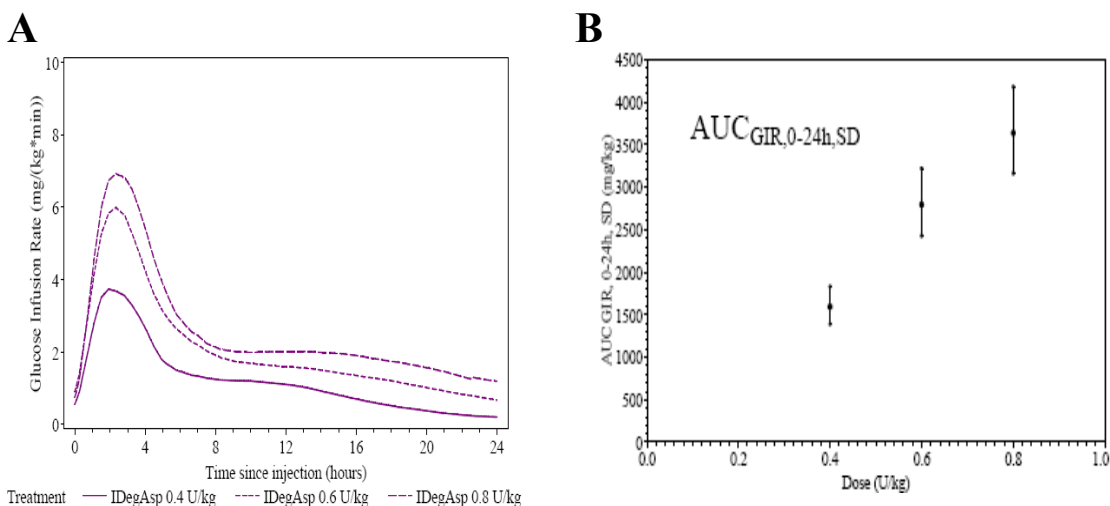
**Figure 5: (A) Glucose Infusion Rate, Mean Smoothed Profiles for IDegAsp and IDeg (0.5 U/kg) after Single Dose (B) Glucose Infusion Rate, Mean Smoothed Profiles – IDegAsp and IAsp (0.5 U/kg) after Single Dose.**

Prandial coverage (based on  $AUC_{GIR, 0-6h}$ ) showed that IDegAsp provided 7.8 times greater effect as compared to IDeg alone (Figure 5). Basal coverage (based on  $AUC_{GIR, 6-24h}$ ) showed that IDegAsp provided 3.9 times greater response as compared to IAsp alone.

#### **Dose Response-T1DM subjects:**

Single dose pharmacokinetic and pharmacodynamic properties of IDegAsp was evaluated at three different dose levels 0.4 U/kg, 0.6 U/kg, 0.8 U/kg in T1DM subjects. At doses from 0.4 U/kg-0.8 U/kg, the total exposure ( $AUC_{0-12h, IAsp}$ ) and peak concentration ( $C_{max, IAsp}$ ) of IAsp increased with increasing dose. The estimated log-dose slope and 95% CI was 0.88 [0.72; 1.04] and (1.09 [1.02; 1.17] for  $C_{max, IAsp}$  and  $AUC_{0-12h, IAsp}$ , respectively. Similarly, IDeg exposure increased with increasing dose (Figure 15 and Table 6) and the estimated log-dose slope for total exposure ( $AUC_{0-120h, IDeg}$ ) was 0.90 [0.78; 1.01] 95%CI, thus supporting dose proportionality.

The pharmacodynamic endpoints, total ( $AUC_{GIR, 0-24h}$ ) and maximum ( $GIR_{max}$ ) glucose-lowering effect of IDegAsp increased with increasing dose (Figure 6). The estimated log-dose slope and 95% CI was 1.19 [0.99; 1.40] and 0.89 [0.66; 1.13] for  $AUC_{GIR, 0-24h}$  and  $GIR_{max}$ , respectively.



Source: Sponsor's summary of clinical pharmacology report.

**Figure 6: (A) 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp in Subjects with T1DM (B) Glucose-lowering Effect vs. Dose after Single Dose IDegAsp in Subjects with T1DM**

**Intrinsic Factors:**

- **Renal Impairment:** Impact of renal impairment on the pharmacokinetics and pharmacodynamics of IDegAsp was not studied in this NDA. Pharmacokinetics of insulin aspart has been studied under NovoLog<sup>®</sup> application with no apparent effect of creatinine clearance on pharmacokinetics of insulin aspart. The pharmacokinetic properties of IDeg in subjects with or without renal impairment were investigated in Trial 1990 under the Insulin degludec program (NDA 203314). According to sponsor, pharmacokinetic profiles of IDeg were similar for subjects with normal and impaired renal function. Please refer to Clinical Pharmacology review (NDA 203314) by Dr. Manoj Khurana for further details.
- **Hepatic Impairment:** Impact of renal impairment on the pharmacokinetics and pharmacodynamics of IDegAsp was not studied in this NDA. Pharmacokinetics of insulin aspart has been studied under NovoLog<sup>®</sup> application with no apparent effect of hepatic impairment on pharmacokinetics of insulin aspart. The pharmacokinetic properties of IDeg in subjects with or without hepatic impairment were investigated in Trial 1989 under the Insulin degludec program (NDA 203314). According to sponsor, pharmacokinetic profiles of IDeg were similar for subjects with normal and impaired hepatic function. Please refer to Clinical Pharmacology review (NDA 203314) by Dr. Manoj Khurana for further details.
- **Age:** The mean pharmacokinetic profiles (**Figure 26**) showed that exposure of IAsp were greater in children (6-11 years) than in adolescents (12-17 years) and adults (18-65 years) following single dose administration of IDegAsp (0.5U/kg). The mean pharmacokinetic profiles showed that total exposure and maximum concentration of the IDeg component in IDegAsp was greater in children than in adults and

comparable between adolescents and adults (**Table 17**). Pharmacodynamics in terms of glucose lowering effect of IDegAsp following a meal challenge test was comparable for children, adolescents and adults (**Figure 27**).

- **Geriatric Subjects:** The mean IAsp concentration-time profiles showed that the exposures were slightly higher for geriatric ( $\geq 65$  years) than younger (18- 35 years) T1DM subjects following single dose administration of IDegAsp (0.5 U/kg). There was no difference in exposures of IDeg between geriatric and younger adult subjects. Pharmacodynamic profiles in terms of mean smoothed GIR profiles were similar for both age groups.
- **Gender:** Cross trial analysis was conducted to see the effect of gender on the pharmacokinetic and pharmacodynamic properties of IDegAsp. No difference in the pharmacokinetics and pharmacodynamics were seen between males and females.
- **Body Mass Index (BMI):** For IAsp there was no relationship between BMI and exposure in subjects with T1DM or T2DM when dosed per kg body weight. For IDeg when corrected for body weight, there was no significant relationship for subjects with T1DM. Whereas, for subjects with T2DM, total and maximum exposure (body weight adjusted), still increased with increasing BMI.

#### **Extrinsic Factors:**

- **Injection Site**

No clinical studies have been conducted to see the effect of injection site on the pharmacokinetics of IDegAsp. However, in the Phase 3 trials with IDegAsp the injection sites were rotated between thigh, abdomen and deltoid region. In addition, the use of various injection regions (abdominal wall, the thigh, the upper arm (deltoid region) or the gluteal region) has been established and demonstrated through several years of market use of the prandial component (IAsp) of IDegAsp. Sponsor also studied the effect of injection site on the pharmacokinetics of IDeg, under NDA 203314 and proposes to rotate the injection site for IDeg administration.

- **Pivotal BE Studies :**

There were no pivotal BE studies in this application. Sponsor used to be marketed commercial formulation in their pivotal clinical pharmacology and Phase 3 trials.

#### **Recommendation:**

In conclusion, overall there were no major clinical pharmacology issues and this NDA 203313 is acceptable.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes of the Drug and Drug Product

Insulin degludec (IDeg) is an analog of human insulin where threonine in position B30 has been omitted and where the  $\epsilon$ -amino group of lysine B29 has been coupled with hexadecanedioic acid via a  $\gamma$ -glutamic acid spacer. Insulin degludec is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*) and chemical modification.

Insulin aspart (IAsp) is an analog of human insulin where the amino acid proline has been replaced with aspartic acid in position B28. Insulin aspart is produced using recombinant DNA technology in yeast (*Saccharomyces cerevisiae*).

Insulin degludec/insulin aspart (IDegAsp) is a soluble premix of long-acting basal insulin, insulin degludec (IDeg) and the marketed rapid-acting insulin analog, insulin aspart (B28Asp human insulin; IAsp). IDegAsp is a clear and colorless solution containing the drug substances insulin degludec and insulin aspart. IDegAsp is a 100 U/mL premix of 420 nmol/mL insulin degludec (70%) and 180 nmol/mL insulin aspart (30%).

IDegAsp is intended to be marketed (b) (4) as a pre-filled disposable pen injector. The drug product is intended for subcutaneous (S.C.) injection indicated to improve glycemic control in patient with diabetes mellitus.

Insulin requirements vary on an individual basis and are adjusted on the basis of glycemic response. The proposed starting dose for insulin-naïve patients with type 2 diabetes mellitus is 10 units once-daily. Patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose.

#### **2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?**

Insulin degludec/insulin aspart (IDegAsp) is premix of a new molecular entity, insulin degludec, a long-acting human insulin analog and insulin aspart, rapid-acting human insulin analog. Insulin aspart is a well characterized fast-acting prandial insulin with global market experience since approval by the European Medicines Agency (EMA) in 1999 (NovoRapid<sup>®</sup>) and by the Food and Drug Administration (FDA) in 2000 (NovoLog<sup>®</sup>, NDA 20-986). Novo Nordisk has submitted a separate NDA (203314) for the approval of insulin degludec once daily subcutaneous injection.

**2.1.2 What are the highlights of the chemistry and physicochemical properties of the drug substance and the formulation of the drug product as they relate to clinical pharmacology and biopharmaceutics review?**

Highlights of the chemistry and physiological properties of the drug substance Insulin degludec is shown in **Table 1**. Such information for Insulin aspart can be found in NDA 20-986.

**Table 1: Chemistry and Physicochemical Properties of the Drug Substance**

|                           | Insulin Degludec                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|---------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Description</b>        | (b) (4)                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| <b>Chemical Name</b>      | LysB29(Nε-hexadecandioyl-γ-Glu) des(B30) human insulin                                                                                                                                                                                                                                                                                                                                                                                                            |
| <b>Molecular Formula</b>  | C <sub>274</sub> H <sub>411</sub> N <sub>65</sub> O <sub>81</sub> S <sub>6</sub>                                                                                                                                                                                                                                                                                                                                                                                  |
| <b>Molecular Weight</b>   | 6103.97 Da                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| <b>Structural Formula</b> | <p>The structural formula shows the A and B chains of insulin. The A chain (residues A1-A20) and B chain (residues B1-B29) are connected by interchain disulfide bonds. A hexadecanoyl chain is attached to the ε-amino group of the lysine residue at position B29. The amino acid sequences are: A1: NH<sub>2</sub>-G-I-V-E-Q-C-T-S-I-C-S-L-Y-Q-L-E-N-Y-C-NH-COOH; B1: NH<sub>2</sub>-F-V-N-Q-H-L-C-G-S-H-L-V-E-A-L-Y-L-V-C-G-E-R-G-F-Y-T-P-NH<sub>2</sub>.</p> |
| <b>Solubility</b>         | <ul style="list-style-type: none"> <li>The solubility in water is (b) (4) at neutral pH approximately pH 7.4. (b) (4)</li> <li>(b) (4)</li> <li>Insulin degludec is slightly soluble in methanol (b) (4).</li> <li>Insulin degludec is practically insoluble in ethanol (approximately (b) (4)).</li> </ul>                                                                                                                                                       |

**Formulation:** Insulin degludec/insulin aspart 100 U/ml is a clear, colourless solution. **Table 2** shows the composition of the to-be-marketed insulin degludec/insulin aspart 100

U/ml solution. The formulation contains glycerol (b) (4), zinc (b) (4) and sodium chloride as (b) (4), phenol and metacresol as (b) (4)

**Table 2: Composition of insulin degludec/insulin aspart 100 U/ml**

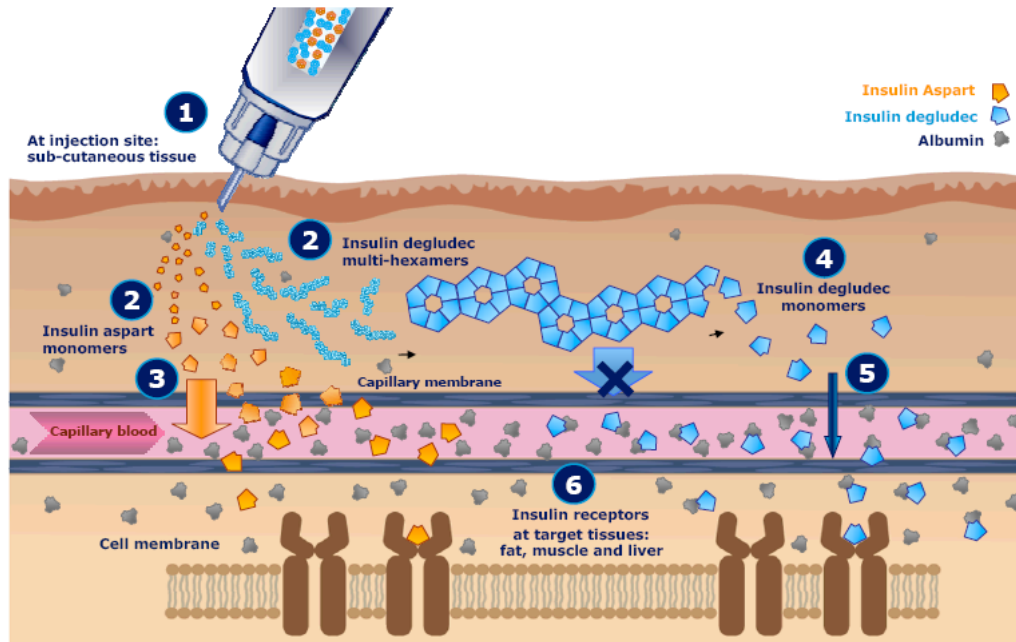
| Name of components             | Quantity per ml | Function       | Reference to standards        |
|--------------------------------|-----------------|----------------|-------------------------------|
| <b>Active substance</b>        |                 |                |                               |
| Insulin degludec               | 420 nmol        | Drug substance | Novo Nordisk                  |
| Insulin aspart                 | 180 nmol        | Drug substance | Novo Nordisk                  |
| <b>Excipients</b>              |                 |                |                               |
| Phenol <sup>1</sup>            | 1.50 mg         | (b) (4)        | Ph Eur, USP, JP               |
| Metacresol <sup>1</sup>        | 1.72 mg         | (b) (4)        | Ph Eur, USP                   |
| Glycerol                       | 19.0 mg         | (b) (4)        | Ph Eur, USP, JP               |
| Sodium chloride                | 0.58 mg         | (b) (4)        | Ph Eur, USP, JP               |
| Zinc                           | 27.4 µg         | (b) (4)        | Ph Eur, USP, JPE <sup>2</sup> |
| Hydrochloric acid <sup>3</sup> | q.s.            | pH adjustment  | Ph Eur, USP, JP               |
| Sodium hydroxide <sup>3</sup>  | q.s.            | pH adjustment  | Ph Eur, USP, JP               |
| Water for injections           | (b) (4)         | (b) (4)        | Ph Eur, USP, JP               |

Source: Sponsor's report on quality overall summary of drug product (2.3.P.1)

### 2.1.3 What is the mechanism of action and therapeutic indication?

The formulation of IDegAsp has been optimized such that the individual components do not interact on a molecular basis, with insulin aspart present as soluble and stable hexamers and insulin degludec as soluble and stable di-hexamers. Once injected into the subcutaneous tissue, the insulin aspart hexamers immediately form monomers which are rapidly absorbed into the capillaries while the insulin degludec di-hexamers form multi hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which insulin degludec monomers are slowly and continuously absorbed into the circulation (**Figure 7**). In addition, the fatty acid moiety of insulin degludec is able to bind to albumin, thus contributing to some extent to the overall slow release of IDegAsp in to the systemic circulation.

IDegAsp is indicated to improve glycemic control in patient with diabetes mellitus.



Source: Sponsor's report on nonclinical overview (section 2.4)

**Figure 7: Figure showing the proposed mechanism of rapid absorption of insulin aspart and slow absorption of insulin degludec in the IDegAsp premix**

#### 2.1.4 What are the proposed dosage and route of administration?

IDegAsp is developed in a 100 unit (U)/mL strength for subcutaneous injection and is intended to be marketed (b) (4) as a pre-filled disposable pen injector. The drug product is intended for subcutaneous injection indicated to improve glycemic control in patient with diabetes mellitus.

#### Proposed Dosage and Administration:

- Insulin requirements vary on an individual basis and should be adjusted on the basis of glycemic response.
- The proposed starting dose for Insulin-naïve patients with type 2 diabetes mellitus is 10 units once-daily.
- IDegAsp can be administered once or twice daily with any main meals alone or in combination with oral antidiabetic drugs (OADs).
- Patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose.
- Patients switching from more than once-daily basal or premix insulin therapy can be converted unit-to-unit to twice daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose.
- Patients switching from basal/bolus or self-mixed insulin therapy to IDegAsp will need to convert their dose based on individual needs.

### **2.1.5 Is any OSI (Office of Scientific Investigation) inspection requested for any of the clinical studies?**

Sponsor used proposed to-be-marketed formulation in their Phase 3 trials and hence there were no pivotal studies in this NDA. No, OSI inspection was not requested from clinical pharmacology standpoint.

## **2.2 General Clinical Pharmacology**

### **2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?**

The IDegAsp clinical development program included in this application consists of 13 clinical pharmacology trials, 3 exploratory trials of 6–16 weeks duration, 5 confirmatory trials of 26 weeks duration and one completed confirmatory, 26-week extension trial (Figure 8).

#### **Efficacy and Safety Program (Phase 2b/3 Program):**

The clinical development program for IDegAsp was designed to characterize the efficacy and safety of IDegAsp in patients with diabetes from early to late stage of the disease. In type 1 diabetes mellitus (T1DM) IDegAsp was studied with once daily (OD) dosing of IDegAsp in combination with IAsp dosed at remaining meals (Figure 8). For individuals with T2DM, IDegAsp was investigated for OD or twice daily (BID) administration as monotherapy or in combination with metformin, thiazolidinediones (TZDs) and dipeptidyl peptidase-4 (DPP-4) inhibitors.

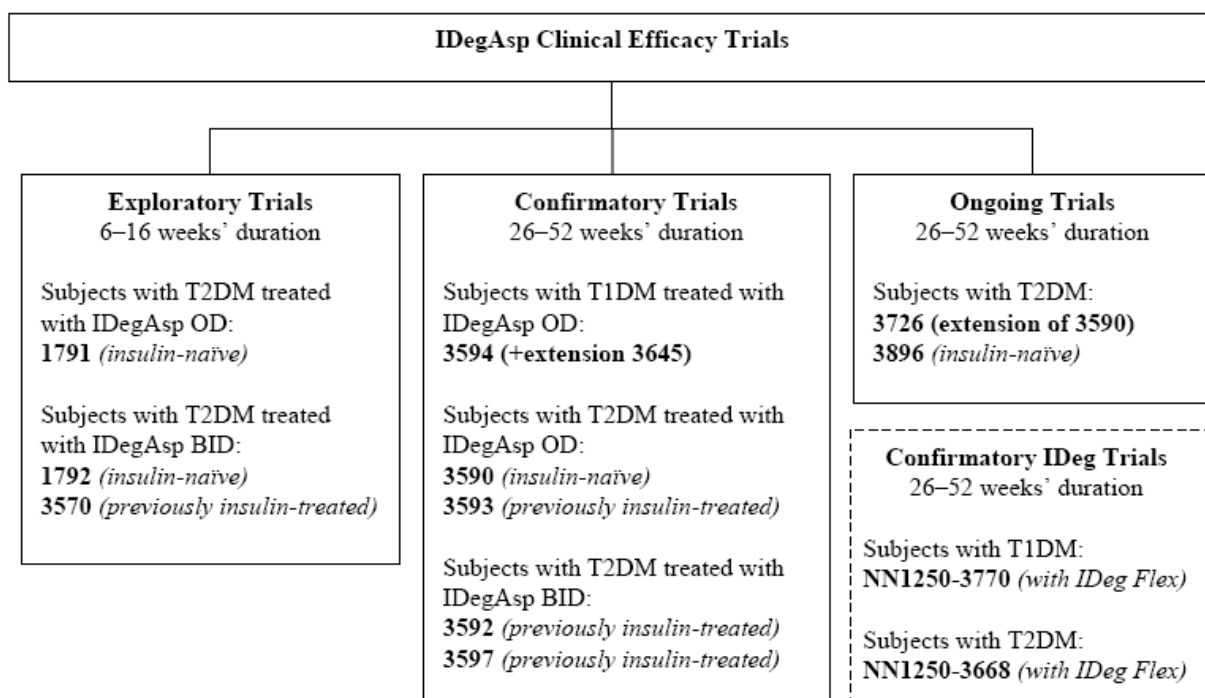


**Figure 8: Overview of Trials for Efficacy Evaluation**

The primary objective in all of the therapeutic confirmatory trials was to confirm the efficacy of IDegAsp in controlling glycemia as measured by change from baseline in glycosylated hemoglobin A1c (HbA1c) after 26 weeks of treatment in subjects with T1DM or T2DM. This was done by comparing the difference in change of HbA1c from baseline to end-of treatment between IDegAsp and the active comparator. All therapeutic confirmatory trials were treat-to-target trials, in which similar reductions in HbA1c from baseline were observed for IDegAsp and comparator products (**Figure 9**).

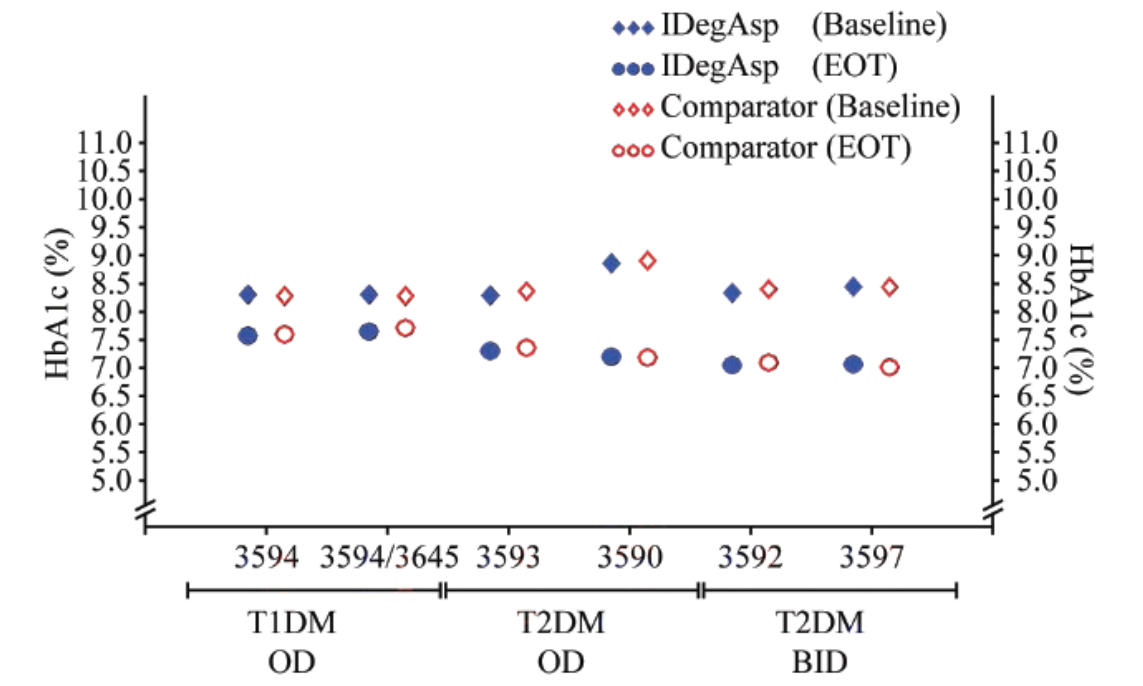


**Figure 9: Mean HbA1c (%) at Baseline and End-of-trial**

*Source: Sponsor's report on Summary of Clinical Efficacy*

**Clinical Pharmacology Program:**

The clinical pharmacology program for IDeg and IDegAsp consist a total of 31 trials. The IDeg program consists of a total of 18 trials and IDegAsp program consist of 13 trials (7 of which also included IDeg).

In general, clinical pharmacology program for IDegAsp consists of single dose (SD) dose PK/PD studies in healthy, T1DM and T2DM subjects, single dose PK/PD studies in pediatric and geriatric subjects, single dose PK/PD studies to demonstrate product distinctiveness, bioequivalence study between Phase 2 and Phase 3 formulation.

Effect of renal and hepatic impairment, drug-drug interaction was conducted under IDeg development program. **Table 3** summarizes the list of clinical pharmacology trials in IDegAsp and IDeg clinical development program. **Table 4** summarizes the list of key

clinical pharmacology trials in IDegAsp program. This review will focus on IDegAsp clinical development program and for IDeg clinical development program please refer to Clinical Pharmacology review by Dr. Manoj Khurana.

**Table 3 : IDegAsp and IDeg Clinical Pharmacology Trials**

| Clinical Pharmacology Trials                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | Other Clinical Trials                                                               |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|
| <p><b>Subjects with T1DM</b></p> <p><b>Key IDegAsp Trials</b><br/>           NN5401-1959<sup>a</sup><br/>           NN5401-1977<sup>a</sup><br/>           NN5401-1981<br/>           NN5401-1982<br/>           NN5401-1983<sup>d</sup><br/>           NN5401-3539<br/>           NN5401-3857<sup>a</sup></p> <p><b>Key IDeg Trials<sup>e</sup></b><br/>           NN1250-1991<br/>           NN1250-1993<br/>           NN1250-1994<br/>           NN1250-1995<br/>           NN1250-1996<sup>d</sup><br/>           NN1250-3538<br/>           NN1250-3678</p> <p><b>Supportive Trials<sup>b</sup></b><br/>           NN5401-1718<sup>c, e</sup><br/>           NN5401-1719<sup>e</sup><br/>           NN5401-1740<sup>e</sup><br/>           NN5401-1738<sup>c, a</sup><br/>           NN1250-1876<sup>e</sup></p> | <p><b>Subjects with T2DM</b></p> <p><b>Key IDegAsp Trials</b><br/>           NN5401-1978</p> <p><b>Key IDeg Trials<sup>e</sup></b><br/>           NN1250-1987<br/>           NN1250-3762</p> <p><b>Supportive Trials<sup>b</sup></b><br/>           NN5401-1718<sup>c, e</sup><br/>           NN5401-1719<sup>e</sup><br/>           NN5401-1738<sup>c, a</sup></p> | <p><b>Healthy Subjects</b></p> <p><b>Key IDegAsp Trials</b><br/>           NN5401-1980</p> <p><b>Key IDeg Trials<sup>e</sup></b><br/>           NN1250-1989<sup>f</sup><br/>           NN1250-1990<sup>f</sup><br/>           NN1250-1992<br/>           NN1250-3769</p> <p><b>Supportive Trials<sup>b</sup></b><br/>           NN5401-1718<sup>c, e</sup><br/>           NN5401-1788<sup>d, a</sup><br/>           NN5401-1790<sup>d, a</sup><br/>           NN5401-1985<sup>a</sup><br/>           NN1250-1988<sup>e</sup></p> | <p><b>Therapeutic Confirmatory Trial</b><br/>           NN1250-3586<sup>g</sup></p> |

<sup>1</sup> Trials conducted both with the IDeg and IDegAsp.  
<sup>2</sup> Supportive trials are not included in the summary text. Narratives of the individual trials are in [Appendix 5.1](#) and pharmacokinetic and pharmacodynamic endpoints are listed in [Appendix 5.2](#).  
<sup>3</sup> Trial 1718 included healthy subjects and subjects with either T1DM or T2DM; Trials 1719 and 1738 included subjects with either T1DM or T2DM.  
<sup>4</sup> Trials 1788, 1790, 1983 and 1996 were conducted in Japanese subjects.  
<sup>5</sup> Trials conducted with the IDeg product only.  
<sup>6</sup> Trials 1989 and 1990 included subjects with or without hepatic or renal impairment. Subjects with diabetes were included in the groups with impaired hepatic or renal function.  
<sup>7</sup> Trial 3586 was a therapeutic confirmatory trial including population pharmacokinetics for IDeg in Asian subjects.

**Source: Sponsor's summary of clinical pharmacology report.**

**Table 4: List of Key Clinical Pharmacology Studies**

| Trial ID                                    | Trial Design         | Trial Objectives                                                                                            | Treatment                                                                                                           |
|---------------------------------------------|----------------------|-------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| <b>IDegAsp Trials in Subjects with T1DM</b> |                      |                                                                                                             |                                                                                                                     |
| NN5401-1959                                 | RND, DB, CO, SD, INB | PK and PD of IAsp and IDeg when co-formulated in IDegAsp                                                    | IDegAsp: 0.92 U/kg<br>(0.28 U/kg IAsp + 0.64 U/kg IDeg)<br>IDeg: 0.64 U/kg + IAsp: 0.28 U/kg<br>BIAsp 30: 0.64 U/kg |
| NN5401-1977                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                                  | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| NN5401-1981                                 | RND, DB, CO, SD      | PK and PD in geriatric subjects and younger adult subjects                                                  | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-1982                                 | OL, PG, SD           | PK and safety profile in children, adolescents and adults                                                   | IDegAsp: 0.5 U/kg                                                                                                   |
| NN5401-1983                                 | RND, DB, CO, SD      | PK and PD in Japanese subjects                                                                              | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-3539                                 | RND, DB, INB, CO, SD | PK and PD (dose–response)                                                                                   | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| NN5401-3857                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                                  | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| <b>IDegAsp Trial in Subjects with T2DM</b>  |                      |                                                                                                             |                                                                                                                     |
| NN5401-1978                                 | RND, DB, INB, CO, SD | PK and PD (dose–response)                                                                                   | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| <b>IDegAsp Trial in Healthy Subjects</b>    |                      |                                                                                                             |                                                                                                                     |
| NN5401-1980                                 | RND, DB, CO, SD, BE  | BE between two IDeg products with identical formulations, and different drug substance manufacturing strain | IDegAsp: 0.5 U/kg                                                                                                   |

BE: bioequivalence; CO: cross-over; DB: double blind; MD: multiple dose; INB: incomplete block; OL: open label; PD: pharmacodynamics; PG: parallel group; PK: pharmacokinetics; RND: randomised; SD: single dose.

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*Source: Sponsor’s summary of clinical pharmacology report.*

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### **2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?**

The American Diabetes Association (ADA) recommends the use of glycosylated hemoglobin A1c (HbA1c) levels as an indicator of glycemic control. The primary objective in all of the therapeutic confirmatory trials was to confirm the efficacy of IDegAsp in controlling glycemia as measured by change from baseline in HbA1c after 26

weeks of treatment in subjects with T1DM or T2DM. This was done by comparing the difference in change of HbA1c from baseline to end-of-treatment between IDegAsp and the active comparator. In addition, to other glycemic parameters, PD parameter based on the mechanism of action of drug (such as fasting plasma glucose, self-measured plasma glucose) was measured in some clinical studies.

**2.2.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?**

Yes. Please refer to the analytical section for details.

## **2.3 Exposure-Response**

**2.3.1 What are the characteristics of the exposure/Dose-response relationship for effectiveness?**

In clinical practice, insulin dose is determined by individual need, considering the balance between the level of glycemic control and the risk of hypoglycemia. As the dose required to achieve similar glycemic targets varies widely from patient to patient, no formal dose-response assessments have been made in terms of clinical efficacy or clinical safety.

## **2.4 What are the PK characteristics of the drug?**

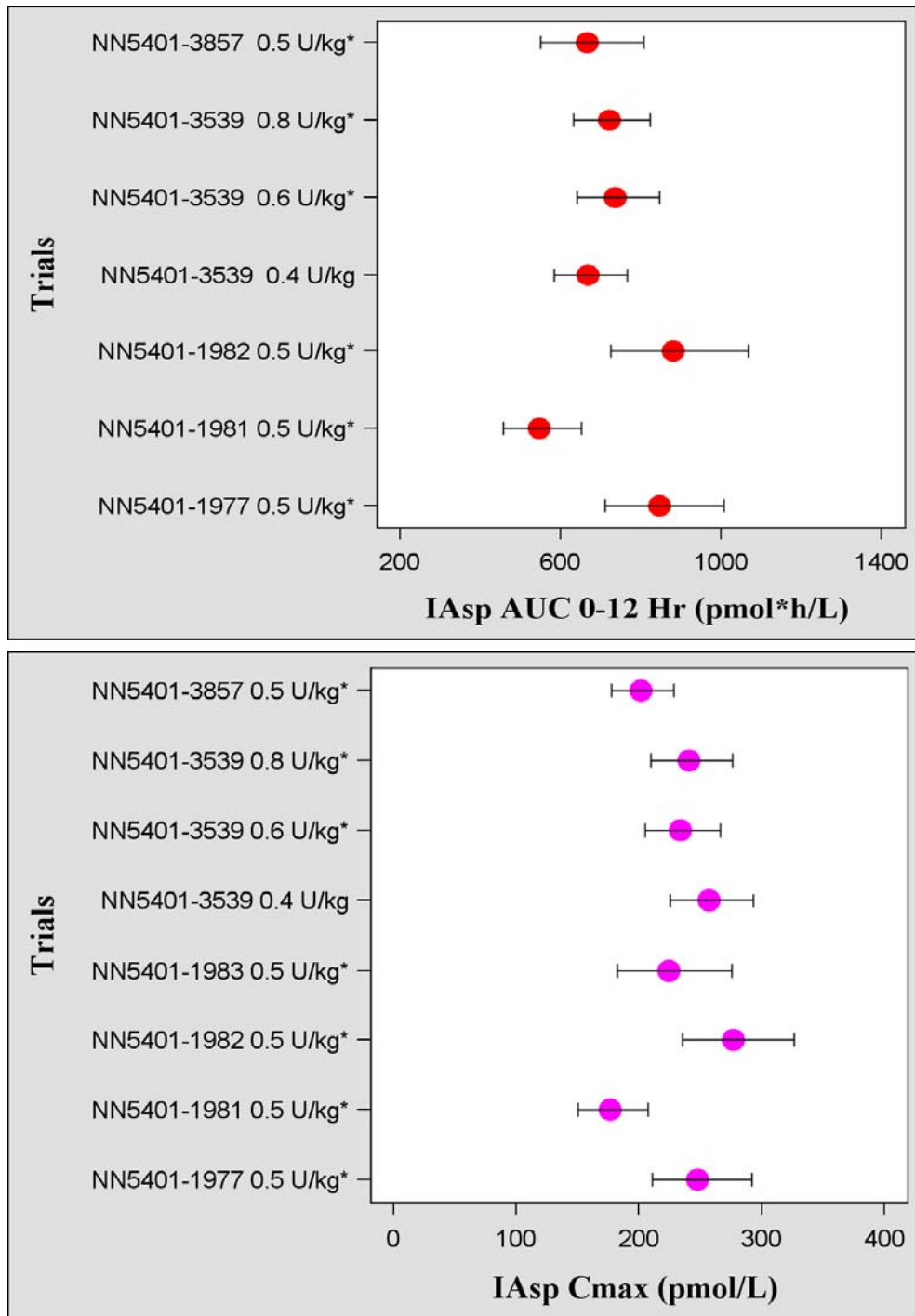
**2.4.1 What are the single and multiple dose PK characteristic of IDegAsp in T1DM adult subjects?**

### **Single Dose Pharmacokinetics**

In this NDA, sponsor has developed bioanalytical methods that can separately measure the two components (IDeg and IAsp) of IDegAsp. In the pharmacokinetic analysis the two components of IDegAsp were measured and evaluated separately.

The pharmacokinetics of IDegAsp was evaluated in several Phase 1 clinical trials. Forest plots (**Figure 10**) shows the dose-normalized total exposure ( $AUC_{0-12h}$ , IAsp) and peak concentration ( $C_{max}$ , IAsp) for IAsp following IDegAsp single dose administration. The CV% in  $AUC_{0-12h}$  ranged from 31% to 67% in these trials. The CV% in  $C_{max}$  ranged from 28 % to 57 %. Median  $T_{max}$  for IAsp in these trials ranged from 1 to 1.4 hrs.

Cross study comparison of the pharmacokinetic parameters showed that the pharmacokinetic properties of IAsp were comparable across the trials.



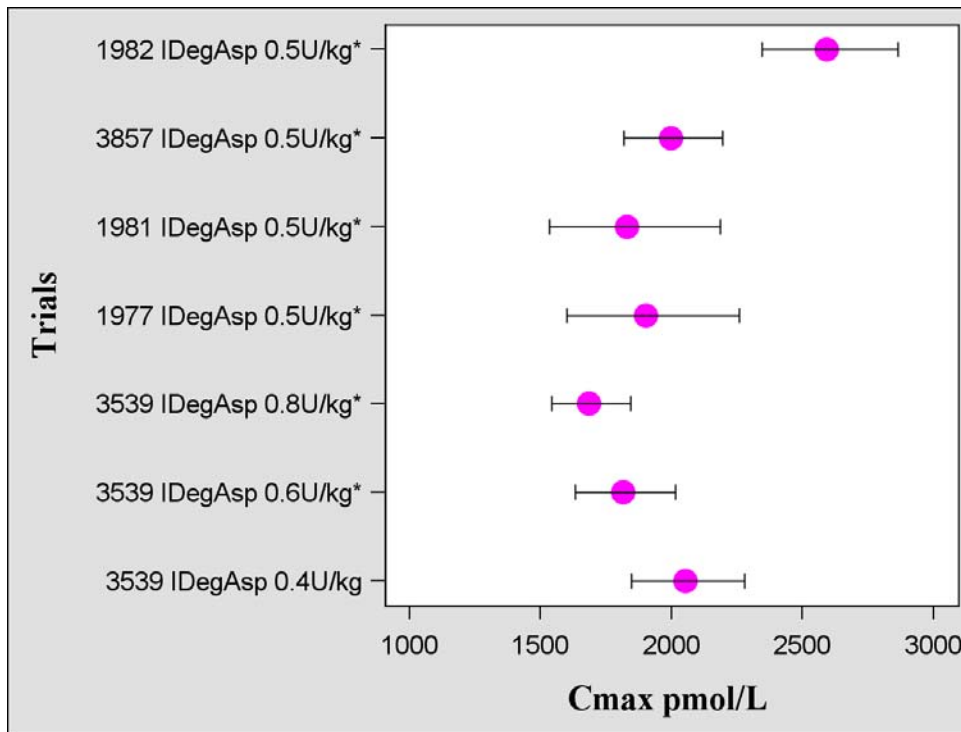
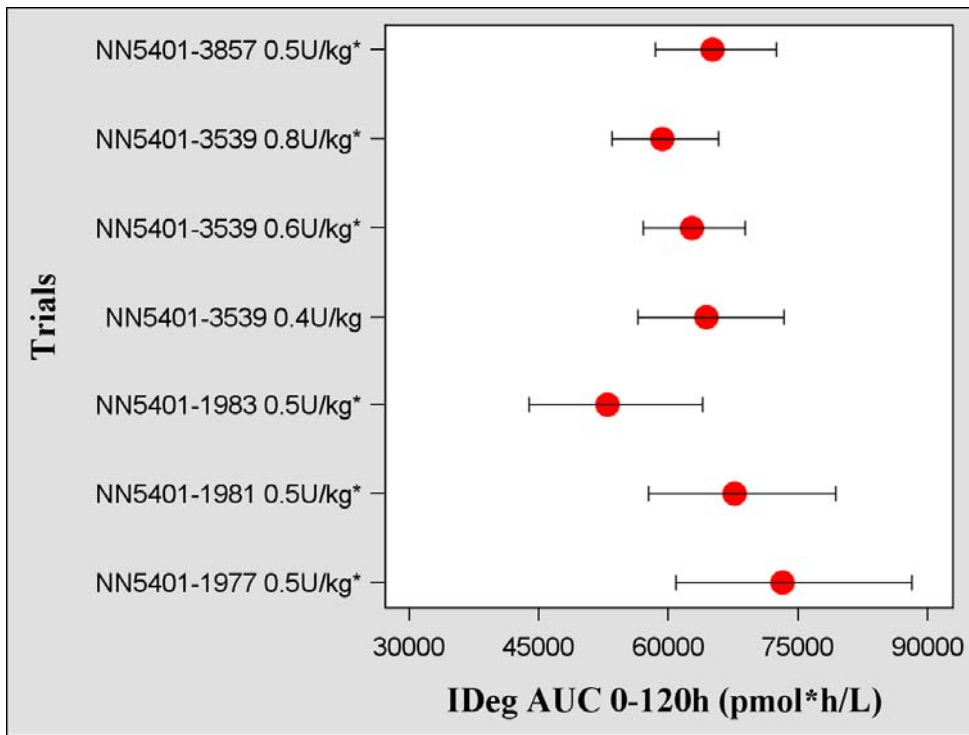
Geometric mean with 95% confidence intervals.

\* Dose-adjusted to 0.4 U/kg assuming dose proportionality (equal to a dose of 0.12 U/kg of the IAsp component)

Trial 1981: Analysis only included younger adult subjects. Trial 1982: Analysis included only adult subjects.

Source: Sponsor's summary of clinical pharmacology report.

**Figure 10: IAsp Pharmacokinetic Endpoints Adjusted for Dose after Single Dose IDegAsp in Adult Subjects with T1DM**



*Trial 1981: Analysis included only younger adult subjects.*

*Geometric mean with 95% confidence intervals.*

*\* Dose-adjusted to 0.4 U/kg assuming dose proportionality (equal to a dose of 0.28 U/kg of the IDeg component).*

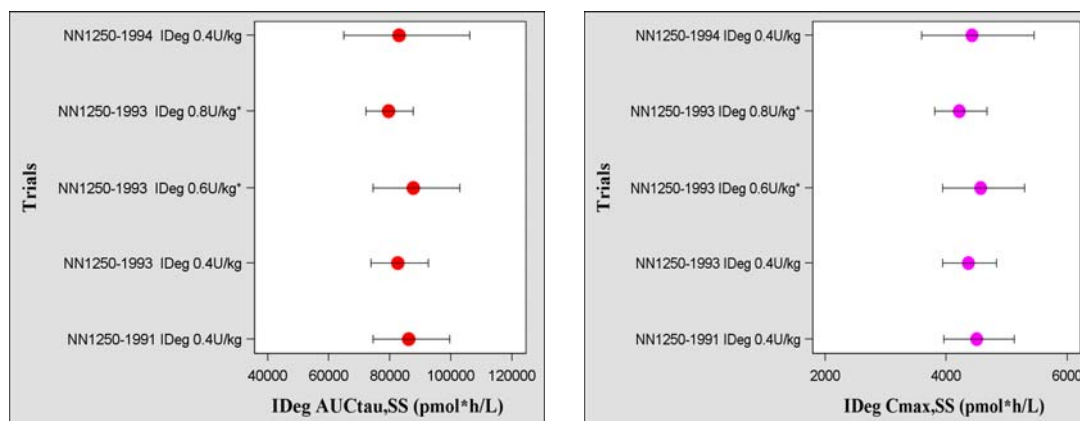
*Source: Sponsor's summary of clinical pharmacology report.*

**Figure 11: IDeg Pharmacokinetic Endpoints Adjusted for Dose after Single Dose IDegAsp in Adult Subjects with T1DM**

The pharmacokinetics parameters of IDeg following IDegAsp single dose administration is shown in **Figure 11**. Forest plots (**Figure 11**) shows the dose-normalized total exposure ( $AUC_{0-120h}$ , IDeg) and peak concentration ( $C_{max}$ , IDeg) for IDeg following IDegAsp single dose administration. The CV% in  $AUC_{0-120h}$  ranged from 21% to 80% in these trials. The CV% in  $C_{max}$  ranged from 19 % to 63 %. Median  $T_{max}$  for IDeg in these trials ranged from 12 to 14 hrs. Similar to IAsp, cross study comparison of the pharmacokinetic parameters showed that the pharmacokinetic properties of IDeg were comparable across the trials (**Figure 11**).

### **Multiple Dose Pharmacokinetics**

Multiple dose pharmacokinetics of IDegAsp is not characterized in this NDA. However in insulin degludec (NDA 203314) sponsor characterized the pharmacokinetics of IDeg following multiple dose administration of insulin degludec. **Figure 12** shows the pharmacokinetics of IDeg after multiple dosing of insulin degludec in T1DM subjects. Please refer to review by Dr. Manoj Khurana for further details (**Figure 12**).



*Geometric means with 95% confidence intervals.*

*Trial 1994: Analysis included only younger adult subjects.*

*\* Dose-adjusted to 0.4 U/kg assuming dose proportionality.*

**Figure 12: IDeg Pharmacokinetic Endpoints Adjusted for Dose at Steady State in Adult Subjects with T1DM**

#### **2.4.2 What are the highlights of the study design features for the pharmacodynamic (PD) assessment in this application?**

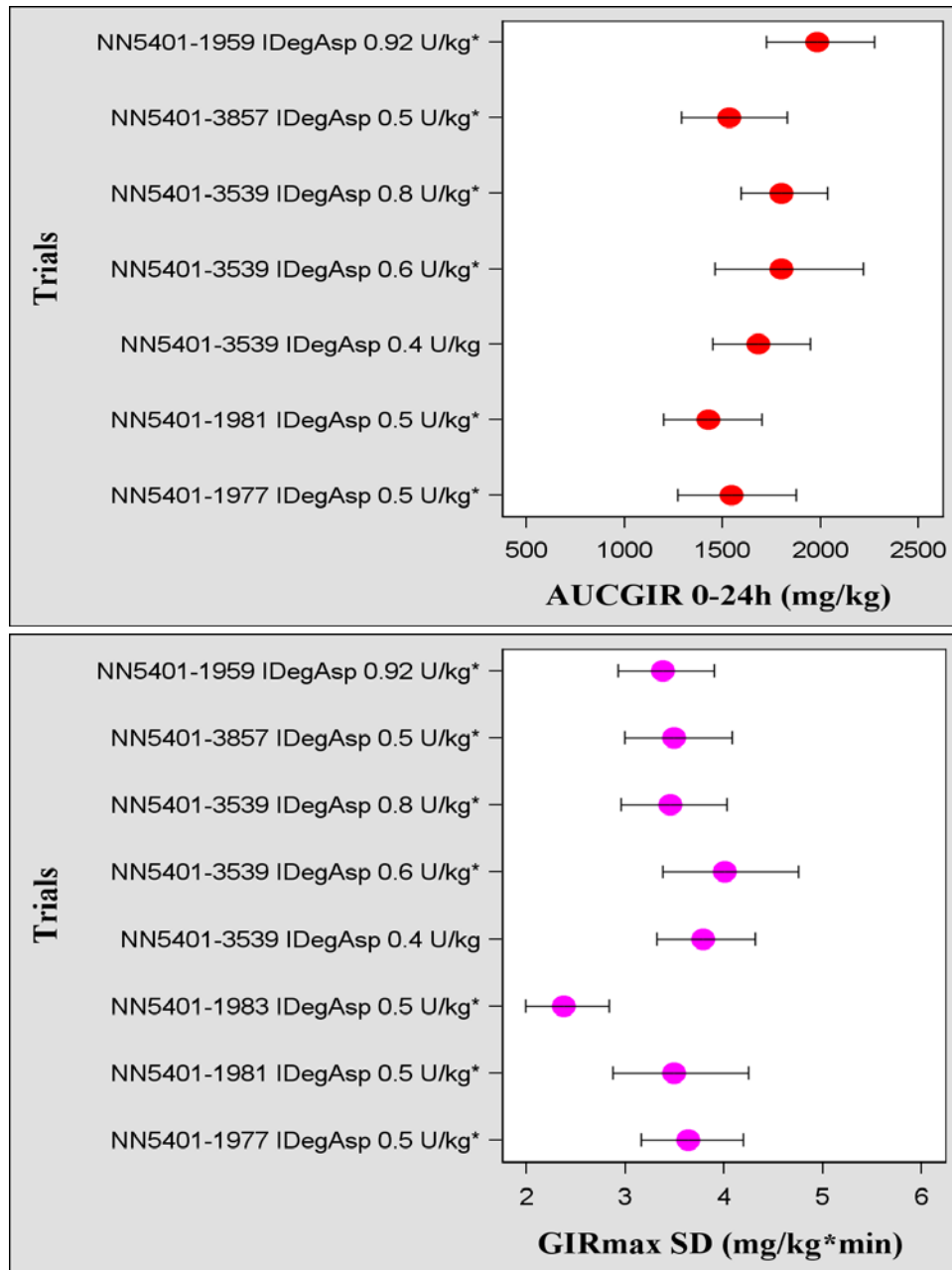
- In this application, the glucose-lowering effect of IDegAsp after single dose using the euglycemic clamp technique. Following are some of the highlights of the study design for pharmacodynamic assessment:
- In general, to accommodate for the difference in endogenous insulin, the glucose clamp target level was 5.5 mmol/L (100 mg/dL) in subjects with T1DM, 5.0

mmol/L (90 mg/dL) in subjects with T2DM, and 4.5 mmol/L (80 mg/dL) in healthy subjects.

- Before injection of IDegAsp or IDeg, a variable i.v. infusion of insulin or glucose was applied to ensure that the glucose clamp target level was achieved and maintained for at least 1 hour before dosing.
- In subjects with T2DM, insulin infusion was tapered off before administration of trial product, whereas insulin infusion was allowed as needed after dosing in healthy subjects and in subjects with T1DM until onset of action of the trial product administered. Onset of action in most of the trials is usually defined as time from trial product administration until the blood glucose concentration has decreased at least 5 mg/dL from the baseline
- The clamps continued for 24 or 26 hours after trial product administration in most trials.
- In the majority of the trials, continuous glucose infusion was automatically adjusted by a biostator to maintain blood glucose at a pre-defined level using a Biostator.
- The Biostator automatically calculates the appropriate adjustments of the i.v. glucose infusion rate using an algorithm based on the actual measured blood glucose concentration and the grade of variability in the preceding 5 minutes
- In most of the clinical studies plasma glucose, glucose infusion rate, insulin infusion rate, insulin levels were monitored throughout the clamp experiments.
- Glucose infusion rate data were smoothed using the Loess smoothing technique using a fixed smoothing parameter of 0.25 and sampling with 5-minute intervals.

#### **2.4.3 What are the single and multiple dose pharmacodynamic (PD) characteristic of IDegAsp in T1DM adult subjects?**

In this application the pharmacodynamic effect (glucose-lowering effect) of IDegAsp was evaluated using the euglycemic clamp technique. Similar to pharmacokinetic studies, pharmacodynamic parameters were evaluated only with single dose administration of IDegAsp. Glucose lowering effect following multiple dosing was evaluated with insulin degludec alone. **Figure 13** shows the area under the glucose infusion rate curve from 0 to 24 hours ( $AUC_{GIR}$  0-24h) and maximum glucose infusion rate ( $GIR_{max}$ ) following single doses of IDegAsp. **Figure 14** shows the area under the glucose infusion rate curve during one dosing interval at steady state ( $AUC_{GIR,\tau}$ , SS) and maximum glucose infusion rate at steady state ( $GIR_{max, SS}$ ) following multiple doses of IDeg. Dose normalized values (geometric mean with 95% confidence intervals) for pharmacodynamic parameters following single and multiple doses were similar across trials.



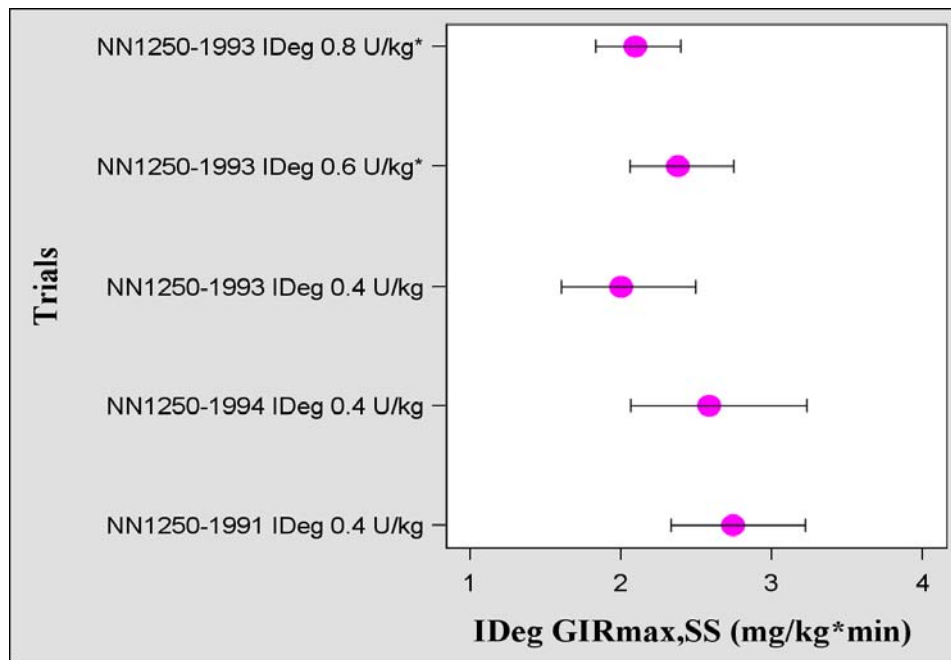
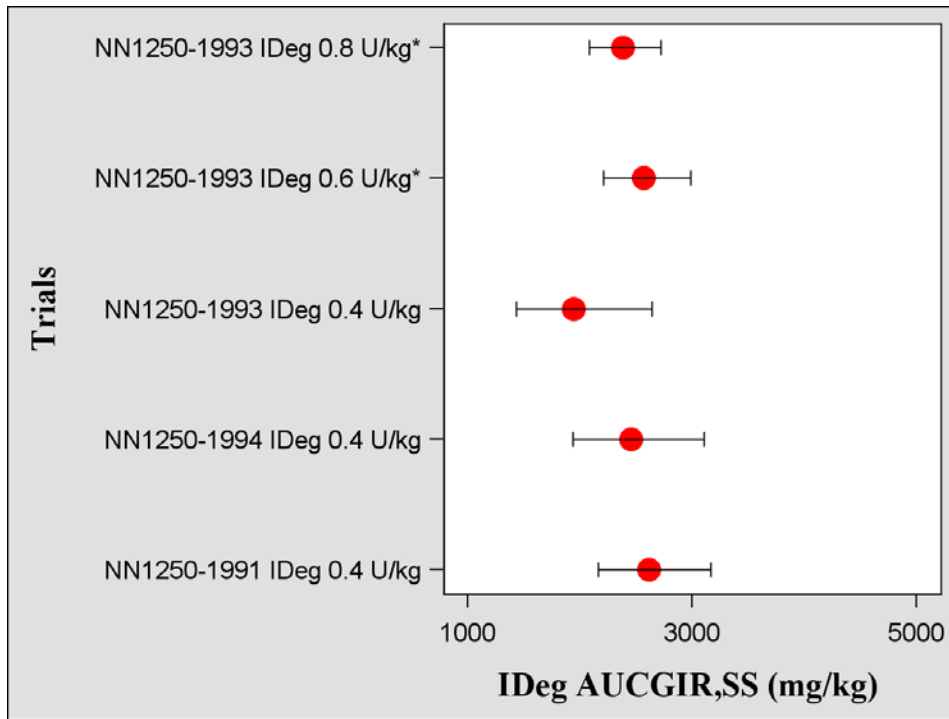
*Geometric mean with 95% confidence intervals.*

*\* Dose-adjusted to 0.4 U/kg assuming dose proportionality.*

*Trial 1981: Analysis included only younger adult subjects.*

*Source: Sponsor's summary of clinical pharmacology report.*

**Figure 13: Glucose Infusion Rate Endpoints Adjusted for Dose after Single Dose IDegAsp in Adult Subjects with T1DM**



*Geometric mean with 95% confidence intervals.  
 \* Dose-adjusted to 0.4 U/kg assuming dose proportionality.  
 Trial 1981: Analysis included only younger adult subjects.  
 Source: Sponsor's summary of clinical pharmacology report.*

**Figure 14: Glucose Infusion Rate Endpoints Adjusted for Dose for IDeg at Steady State in Adult Subjects with T1DM**

#### 2.4.4 What are the pharmacokinetic and pharmacodynamic properties of IDegAsp at different dose levels in T1DM subjects?

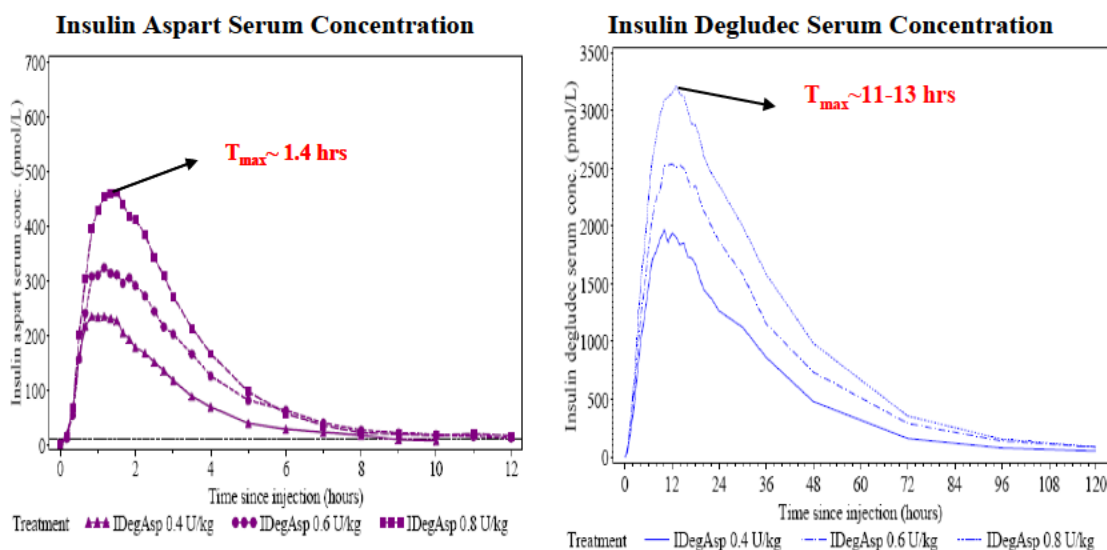
Single dose pharmacokinetic and pharmacodynamic properties of IDeg and IAsp when administered as IDegAsp were evaluated at three different dose levels 0.4 U/kg, 0.6 U/kg, 0.8 U/kg in T1DM subjects (trial 3539).

##### Pharmacokinetics

**Figure 15** shows the mean concentration time profiles of IAsp and IDeg and **Table 5** and **Table 6** shows the descriptive statistics of IAsp and IDeg following single dose administration of IDegAsp.

Following single dose s.c. administration of IDegAsp at doses from 0.4 U/kg-0.8 U/kg, the total exposure ( $AUC_{0-12h}$ , IAsp) and peak concentration ( $C_{max}$ , IAsp) of IAsp increased with increasing dose. The estimated log-dose slope and 95% CI was 0.88 [0.72; 1.04] and (1.09 [1.02; 1.17] for  $C_{max}$ , IAsp and  $AUC_{0-12h}$ , IAsp, respectively.

Results from this study suggest that for IAsp with increasing dose, there is a dose proportional increase in  $C_{max}$ . However, a slightly more than dose proportional increase in  $AUC_{0-12h}$ , of IAsp was seen following IDegAsp administration.



Source: Sponsor's summary of clinical pharmacology report.

#### **Figure 15: Mean Concentration-Time Profiles of Insulin Aspart and Insulin Degludec after a Single Dose of IDegAsp in Subjects with T1DM**

After a single dose of IDegAsp, IDeg exposure increased with increasing dose (**Figure 15** and **Table 6**) and the estimated log-dose slope for total exposure ( $AUC_{0-120h}$ , IDeg) was 0.90 [0.78; 1.01] 95%CI, thus supporting dose proportionality.

**Table 5: Insulin Aspart Pharmacokinetic Endpoints after Single Dose IDegAsp in Subjects with T1DM**

| Dose (U/kg) | N  | AUC <sub>0-12h</sub> , IAsp (pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IAsp (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-------------|----|------------------------------------------------------------|----------------------------------------------------|--------------------------------|
| 0.4         | 21 | 669 (35)                                                   | 257 (29)                                           | 1.2                            |
| 0.6         | 20 | 1105 (32)                                                  | 351 (28)                                           | 1.4                            |
| 0.8         | 20 | 1444 (31)                                                  | 481 (30)                                           | 1.4                            |

Source: Sponsor's summary report

**Table 6: Insulin Degludec Pharmacokinetic Endpoints after Single Dose IDegAsp in Subjects with T1DM**

| Dose (U/kg) | N  | AU <sub>0-120h</sub> , IDeg(pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IDeg (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-------------|----|-----------------------------------------------------------|----------------------------------------------------|--------------------------------|
| 0.4         | 21 | 64365 (33)                                                | 2053 (25)                                          | 11                             |
| 0.6         | 20 | 940003 (21)                                               | 2721 (21)                                          | 13                             |
| 0.8         | 20 | 118546 (22)                                               | 3373 (19)                                          | 12.5                           |

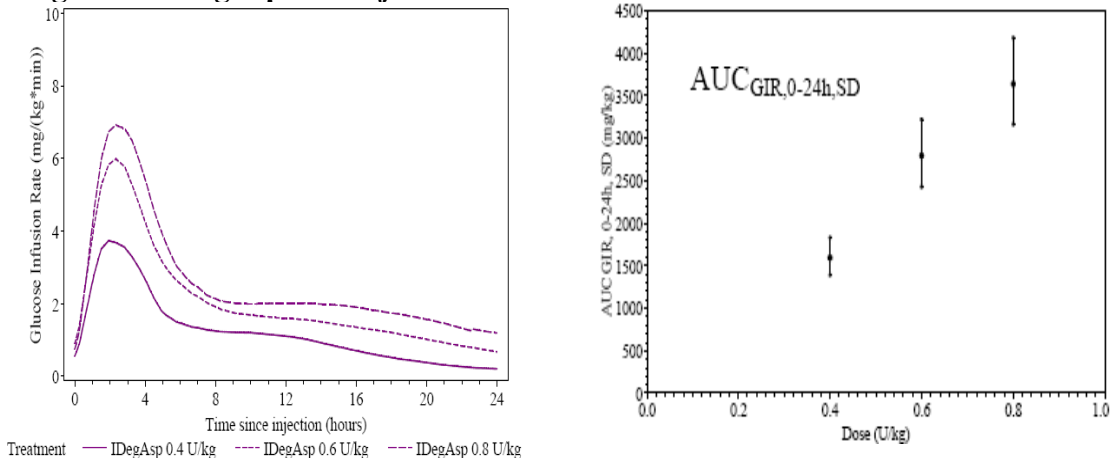
Source: Sponsor's summary report

**Pharmacodynamics:**

The pharmacodynamic properties were studied using a 26-hour euglycemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]) after a single dose of IDegAsp at 0.4 U/kg, 0.6U/kg, 0.8U/kg.

The total (AUC<sub>GIR</sub>, 0-24h) and maximum (GIR<sub>max</sub>) glucose-lowering effect of IDegAsp increased with increasing dose (**Figure 16A and Figure 16B**). The estimated log-dose slope and 95% CI was 1.19 [0.99; 1.40] 95%CI for AUC<sub>GIR</sub>, 0-24h and 0.89 [0.66; 1.13] 95% CI for GIR<sub>max</sub>, thus supporting dose proportionality.

**Figure 16: (A) 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp in Subjects with T1DM (B) Glucose-lowering Effect vs. Dose after Single Dose IDegAsp in Subjects with T1DM**



Source: Sponsor's summary of clinical pharmacology report.

**Reviewer's Comment:** In this study dose proportional increase in  $C_{max}$  and slightly more than dose proportional increase in  $AUC_{0-12h}$  of IAsp was seen following IDegAsp administration at dose ranges of 0.4U/kg-0.8U/kg. Also, dose proportional increase in  $AUC_{0-120h}$  of IDeg following IDegAsp administration at dose range of 0.4U/kg-0.8U/kg was observed. Given the within-subject day-to-day variability in total exposure generally seen with any insulin, the clinical implication is however considered negligible and, as with any insulin, IDegAsp should be dosed according to individual needs.

#### **2.4.5 What are the pharmacokinetic and pharmacodynamic properties of IDegAsp at different dose levels in T2DM subjects?**

Single dose pharmacokinetic and pharmacodynamic properties of IDeg and IAsp when administered as IDegAsp were evaluated at three different dose levels 0.4 U/kg, 0.6 U/kg, 0.8 U/kg in T2DM subjects (trial 1978).

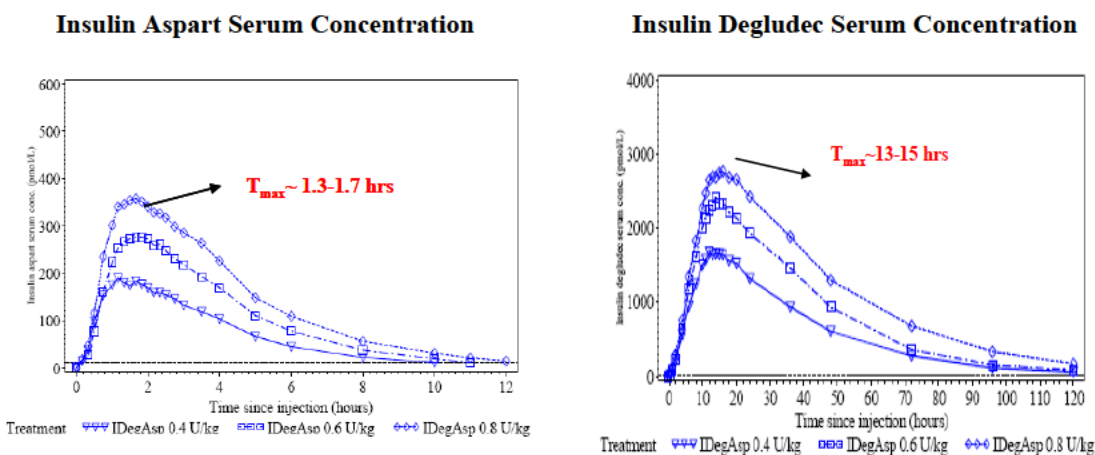
##### **Pharmacokinetics**

Figure 17 shows the mean concentration time profiles and Table 7 and Table 8 shows descriptive statistics of IAsp and IDeg following single dose s.c. administration of IDegAsp.

At doses from 0.4 U/kg-0.8 U/kg, the total exposure ( $AUC_{0-12h}$ , IAsp) and peak concentration ( $C_{max}$ , IAsp) of IAsp increased with increasing dose. The estimated log-dose slope and 95% CI was 0.98 [0.81; 1.14] and (1.17 [1.04; 1.30] for  $C_{max}$ , IAsp and  $AUC_{0-12h}$ , IAsp respectively.

Results from this study suggest that for IAsp with increasing dose there is a dose proportional increase in  $C_{max}$ . However, a slightly more than dose proportional increase in  $AUC_{0-12h}$  of IAsp was seen following IDegAsp administration at dose range of

0.4U/kg-0.8U/kg. The terminal half-life of IAsp after s.c. administration of IDegAsp was in the range 1.7 to 2.0 hours ( $t_{1/2}$ , harmonic mean) across the three dose levels. However, the  $t_{1/2}$  of IAsp is not relevant for the duration of action of IDegAsp, as duration of action of IDegAsp is determined by the  $t_{1/2}$  of the IDeg component which is the long acting insulin in this premix.



Source: Sponsor's summary of clinical pharmacology report.

**Figure 17: Mean Concentration-Time Profiles of Insulin Aspart and Insulin Degludec after a Single Dose of IDegAsp in Subjects with T2DM**

**Table 7: Insulin Aspart Pharmacokinetic Endpoints after Single Dose IDegAsp in Subjects with T2DM**

| Dose (U/kg) | N  | AUC <sub>0-12h</sub> IAsp, (pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IAsp (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-------------|----|-----------------------------------------------------------|----------------------------------------------------|--------------------------------|
| 0.4         | 24 | 712(47)                                                   | 193 (42)                                           | 1.3                            |
| 0.6         | 25 | 1141 (45)                                                 | 285 (41)                                           | 1.7                            |
| 0.8         | 25 | 1628 (20)                                                 | 377 (30)                                           | 1.7                            |

Source: Sponsor's summary report

**Table 8: Insulin Degludec Pharmacokinetic Endpoints after Single Dose IDegAsp in Subjects with T2DM**

| Dose (U/kg) | N  | AUC <sub>0-120h</sub> , IDeg (pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IDeg (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-------------|----|-------------------------------------------------------------|----------------------------------------------------|--------------------------------|
| 0.4         | 24 | 67280 (23)                                                  | 1722 (31)                                          | 13                             |
| 0.6         | 25 | 96507 (21)                                                  | 2403 (33)                                          | 15                             |
| 0.8         | 25 | 131932 (20)                                                 | 2854 (25)                                          | 15                             |

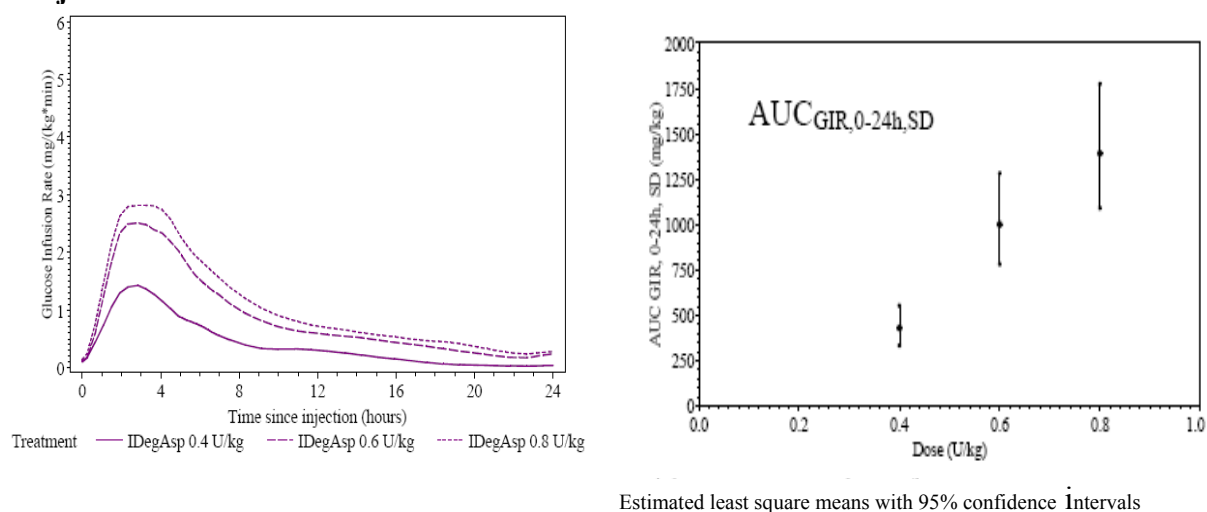
Source: Sponsor's summary report

### **Pharmacodynamics:**

The pharmacodynamic properties were studied using a 26-hour euglycemic clamp (target glucose level of 5.0mmol/L [90 mg/dL]) after a single dose of IDegAsp at 0.4 U/kg, 0.6U/kg, 0.8U/kg.

The total ( $AUC_{GIR, 0-24h}$ ) and maximum ( $GIR_{max}$ ) glucose-lowering effect of IDegAsp increased with increasing dose (**Figure 18A and Figure 18B**). The total and maximum glucose-lowering effect of IDegAsp ( $AUC_{GIR, 0-24h}$  and  $GIR_{max}$ ) increased linearly with increasing dose.

**Figure 18: (A) 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp in Subjects with T2DM (B) Glucose-lowering Effect vs. Dose after Single Dose IDegAsp in Subjects with T2DM**



Source: Sponsor's summary of clinical pharmacology report.

**Reviewer's Comment:** Similar to what seen with T1DM subjects, dose proportional increase in  $C_{max}$  and slightly more than dose proportional increase in  $AUC_{0-12h}$  of IAsp was seen following IDegAsp administration at dose ranges of 0.4U/kg-0.8U/kg. Also, dose proportional increase in  $AUC_{0-120h}$  of IDeg following IDegAsp administration at dose range of 0.4U/kg-0.8U/kg was observed.

#### **2.4.6 Does PK/PD of IDegAsp is comparable between T1DM subjects and T2DM subjects?**

Comparison of pharmacokinetic parameter in T1DM subjects (trial 3539) and T2DM subject (trial 1978) suggests that pharmacokinetics of both insulin aspart and insulin degludec in similar between two population (**5, 6 and Table 7, 8**). However, comparison of pharmacodynamic parameters showed that the pharmacodynamic response is different between two populations (**Figure 19**). Area under the curve for glucose infusion rate is much higher for subjects with T1DM as compared to T2DM subjects at all the dose

levels. Similarly,  $GIR_{max}$  was much lower in T2DM subjects as compared to T1DM subjects (**Figure 16 and Figure 18**). These results suggest that T1DM subjects are more sensitive to insulin and thus require more glucose infusion rate as compared to T2DM subjects. However, caution should be made in the interpretation of these results because in clamp experiments different target glucose levels were set for T1DM (target glucose level of 5.5 mmol/L) and T2DM (target glucose level of 5.0 mmol/L) subjects. These different target glucose levels can affect the glucose infusion rate in T1DM and T2DM subjects and thus can affect  $AUC_{GIR, 0-24h}$ .

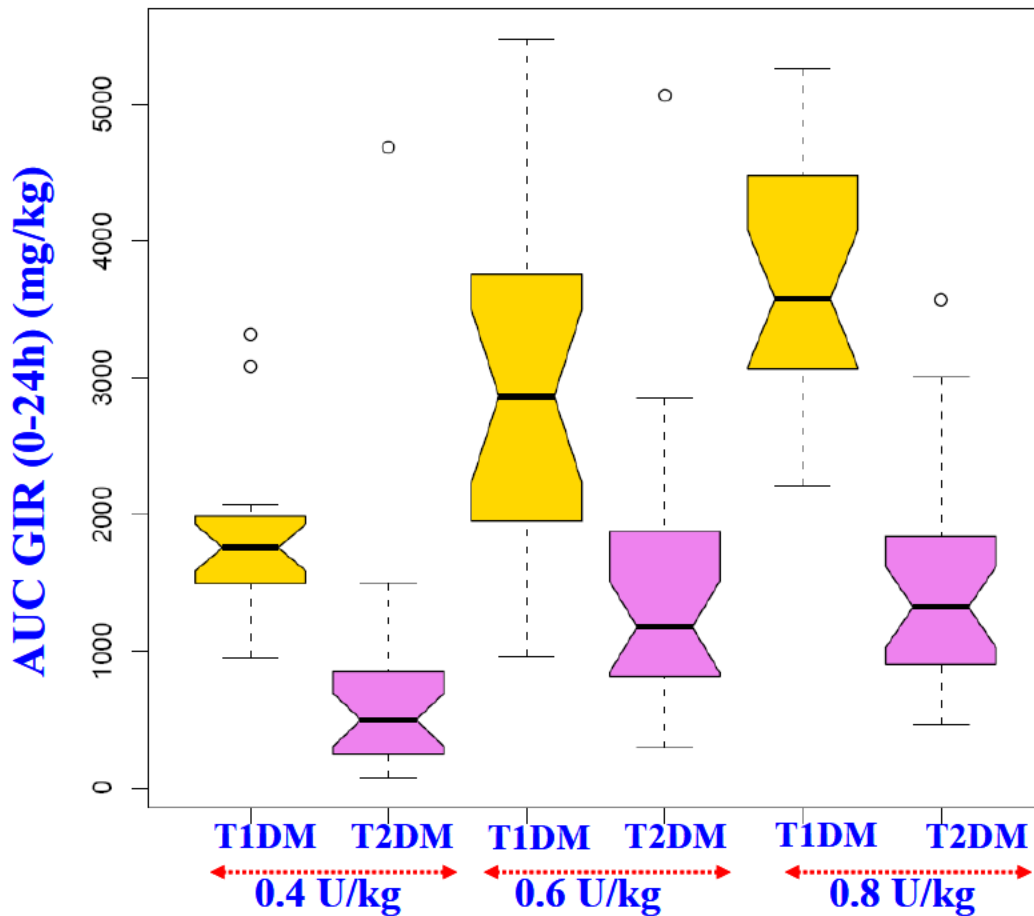


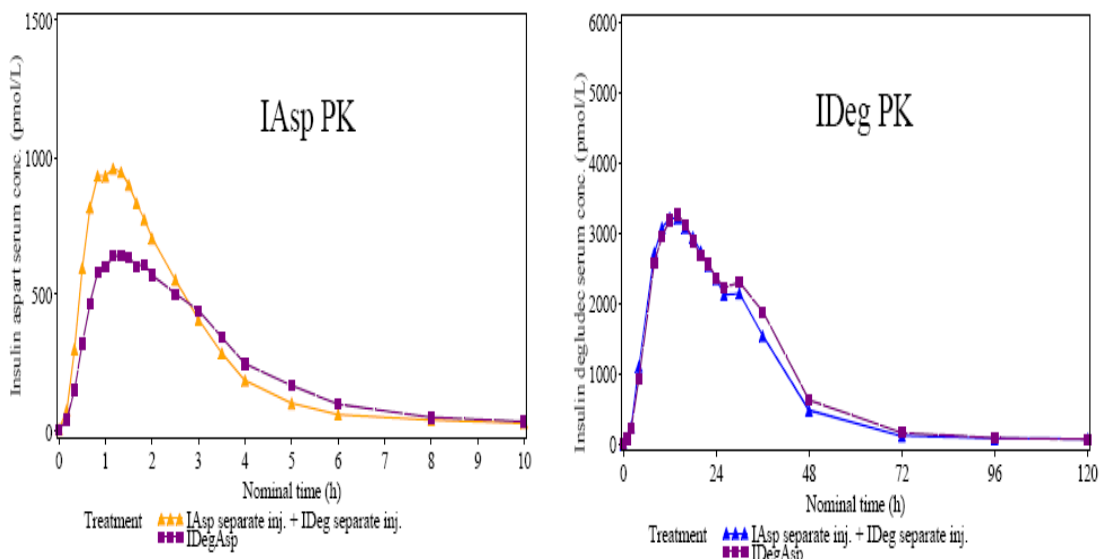
**Figure 19: Comparison of pharmacodynamic parameter ( $AUC_{GIR, 0-24h}$ ) between T1DM subjects (trial 3539) and T2DM subject (trial 1978)**

**2.4.7 What are the pharmacokinetic and pharmacodynamic properties of Insulin Degludec and Insulin Aspart when co-formulated as a premix IDegAsp as compared to separate simultaneous Injections of Insulin Aspart and Insulin Degludec?**

A single-center, randomized, double-blind, incomplete block cross-over design in T1DM subjects (Trial 1959) characterized the pharmacokinetic and pharmacodynamic properties

of insulin degludec and insulin aspart when co-formulated as a premix IDegAsp (IDegAsp 30 B) as compared to separate simultaneous s.c. injections of insulin degludec and insulin aspart.

The mean IDeg and IAsp concentration-time profiles following a single s.c. injection of IDegAsp and corresponding separate simultaneous injections of the IDeg and IAsp products are shown in **Figure 20**.



*Trial 1959: 0.92 U/kg IDegAsp (equal to 0.28 U/kg IAsp + 0.64 U/kg IDeg) and 0.64 U/kg IDeg + 0.28 U/kg IAsp. The slight upwards parallel shift in IDeg concentrations seen at termination of the euglycaemic clamp was due to different blood sampling procedure between the clamp period (0–26 hours) and non-clamp period (26–120 hours). Since the blood sampling procedure was identical for both treatments there is no impact on the comparisons.*

*Source: Sponsor’s summary of clinical pharmacology report.*

**Figure 20: Mean Concentration-Time Profiles after Single Dose IDegAsp and IDeg+IAsp in Subjects with T1DM. IAsp (10 hour, Left) and IDeg (120-hour, Right)**

The pharmacokinetic profile of IDeg was not affected by premix with IAsp in the IDegAsp product. No statistically significant differences were observed between IDegAsp and corresponding separate simultaneous injections of the IDeg and IAsp products with respect to  $AUC_{0-6h}$  IDeg,  $AUC_{0-\infty}$  IDeg, and  $C_{max, IDeg}$  (**Table 9**).

**Table 9: IDeg Pharmacokinetic Endpoints after Single Dose IDegAsp vs. IDeg+IAsp in Subjects with T1DM**

| Endpoint                     | Estimated Ratio | 95% CI     | p-value for Ratio = 1 |
|------------------------------|-----------------|------------|-----------------------|
| <b>IDegAsp vs. IDeg+IAsp</b> |                 |            |                       |
| $AUC_{IDeg, 0-6h, SD}$       | 0.91            | 0.74; 1.14 | 0.41                  |
| $AUC_{IDeg, 0-\infty, SD}$   | 1.05            | 0.95; 1.16 | 0.36                  |
| $C_{max, IDeg, SD}$          | 1.03            | 0.93; 1.14 | 0.57                  |

Trial 1959: 0.92 U/kg IDegAsp (equal to 0.64 U/kg IDeg) and 0.64 U/kg IDeg.

Statistical analyses were based on 22 subjects exposed to IDegAsp and 21 subjects exposed to IAsp + IDeg as separate simultaneous injections.

*Source: Sponsor’s summary of clinical pharmacology report.*

Pharmacokinetics parameters for IAsp component, both  $AUC_{0-2h}$ , IAsp and  $C_{max}$ , IAsp were approximately 30% lower for IDegAsp compared to separate simultaneous injections of the IDeg and IAsp products (**Table 10**). IAsp exposure over the first 6 hours after trial product administration ( $AUC_{0-6h}$ , IAsp,) was slightly lower for IDegAsp compared to corresponding separate simultaneous injections of the IDeg and IAsp products.

**Table 10: IAsp Pharmacokinetic Endpoints after Single Dose IDegAsp vs. IDeg+IAsp in Subjects with T1DM**

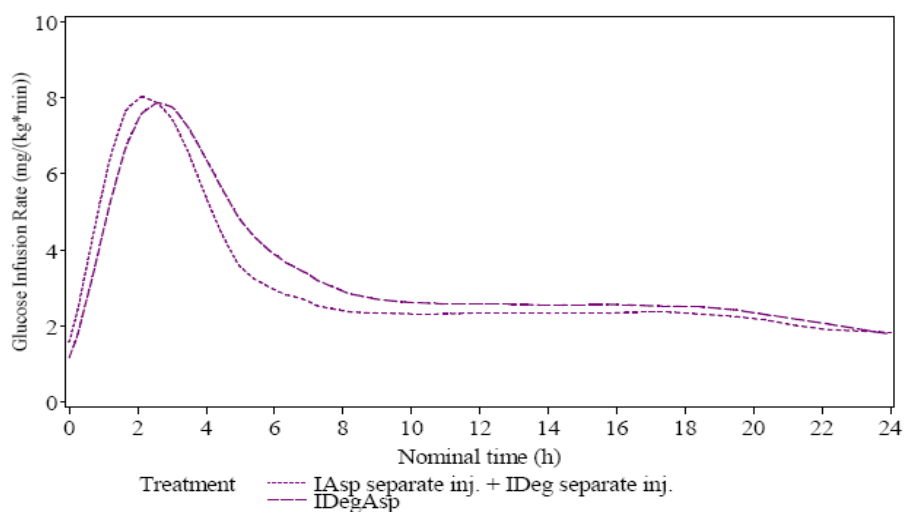
| Endpoint                     | Estimated Ratio | 95% CI     | p-value for Ratio = 1 |
|------------------------------|-----------------|------------|-----------------------|
| <b>IDegAsp vs. IDeg+IAsp</b> |                 |            |                       |
| $AUC_{IAsp,0-2h,SD}$         | 0.68            | 0.61; 0.75 | <0.001                |
| $AUC_{IAsp,0-6h,SD}$         | 0.89            | 0.83; 0.95 | <0.001                |
| $C_{max,IAsp,SD}$            | 0.72            | 0.64; 0.79 | <0.001                |

Trial 1959: 0.92 U/kg IDegAsp (equal to 0.28 U/kg IAsp) and 0.28 U/kg IAsp.

Statistical were analyses based on 23 subjects exposed to IDegAsp and 21 subjects exposed to IAsp + IDeg as separate simultaneous injections.

Source: Sponsor's summary of clinical pharmacology report.

The pharmacodynamic profiles following a single s.c. injection of IDegAsp and corresponding separate, simultaneous injections of the IAsp and IDeg products are shown in **Figure 21**.



Trial 1959: 0.92 U/kg IDegAsp or 0.28 U/kg IAsp + 0.64 U/kg IDeg.

Source: Sponsor's summary of clinical pharmacology report.

**Figure 21: 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp vs. IDeg+IAsp in Subjects with T1DM**

The observed differences in the pharmacokinetic profile of IAsp does not resulted in any significant changes in pharmacodynamics parameters based on  $GIR_{max}$ ,  $AUC_{GIR}$  0-6h, and  $AUC_{GIR}$  0-24h (Table 11). Furthermore, a comparable median time to  $GIR_{max}$  ( $tGIR_{max}$ ) was observed for IDegAsp (2.6 hours) and separate simultaneous IAsp and IDeg administration (2.2 hours).

**Table 11: Glucose Infusion Rate Endpoints after Single Dose IDegAsp vs. IDeg+IAsp in Subjects with T1DM**

| Endpoint                     | Estimated Ratio | 95% CI     | p-value for Ratio = 1 |
|------------------------------|-----------------|------------|-----------------------|
| <b>IDegAsp vs. IDeg+IAsp</b> |                 |            |                       |
| $AUC_{GIR,0-6h,SD}$          | 0.97            | 0.88; 1.06 | 0.48                  |
| $AUC_{GIR,0-24h,SD}$         | 1.04            | 0.94; 1.14 | 0.47                  |
| $GIR_{max,SD}$               | 0.94            | 0.86; 1.03 | 0.20                  |

Trial 1959: 0.92 U/kg IDegAsp or 0.28 U/kg IAsp + 0.64 U/kg IDeg.

Source: Sponsor's summary of clinical pharmacology report.

*Reviewer's Comment: Overall, the pharmacokinetic profile of IDeg was not affected by premix with IAsp in IDegAsp. Despite some difference in the pharmacokinetic profile of IAsp when co-formulated with IDeg in IDegAsp, this did not translate into statistically or clinically significant effects on the pharmacodynamic properties.*

#### **2.4.8 Does the IDegAsp premix satisfies the Agency's requirement of product distinctiveness for Insulin mixes?**

Current draft diabetes guidance recommends that a new formulation of premixed short- and long-acting insulin's has pharmacodynamic and pharmacokinetic profiles that have a target difference of at least 20% from each of its single components.

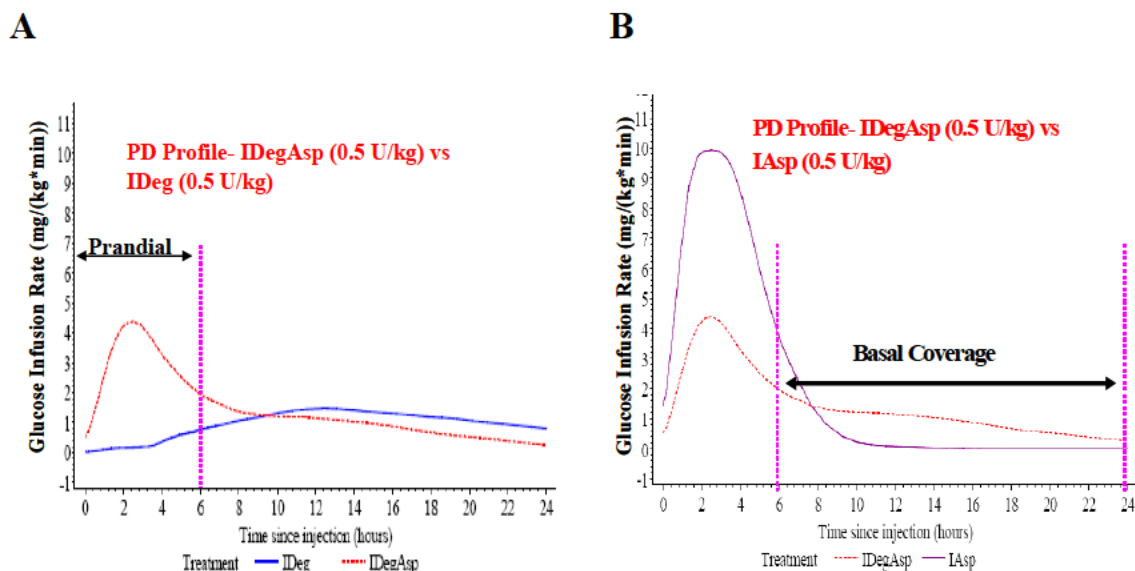
As IDegAsp is a premix of the rapid-acting IAsp and the ultra-long-acting IDeg sponsor conducted a PK/PD study to demonstrate product distinctness (Trial 3857). The distinctiveness of IDegAsp to each of its components (IAsp and IDeg) was investigated in a randomized, open-label, cross-over, single-dose trial in subjects with T1DM. The trial was designed to demonstrate the PK/PD distinctiveness of IDegAsp compared to the IAsp and IDeg products, respectively. Subjects were allocated to receive a single dose (0.5 U/kg) of IDegAsp, IDeg and IAsp in random sequence. As IDegAsp comprises 30 vol.% IAsp and 70 vol.% IDeg, a dose of 0.5 U/kg of the IDegAsp drug product corresponded to 0.15 U/kg of IAsp drug substance and 0.35 U/kg of IDeg drug substance

#### **Pharmacodynamic Analysis**

The pharmacodynamic effect was measure by euglycemic clamp experiment with the target blood glucose concentration of 5.5 mmol/L (100 mg/dL). The sponsor demonstrated the product distinctiveness for pharmacodynamics effect by comparing the area under the glucose infusion rate (GIR) between IDegAsp and IAsp (based on the area

under the GIR curve from 6 to 24 hours), and between IDegAsp and IDeg (based on the area under the GIR curve from 0 to 6 hours).

Prandial coverage (based on  $AUC_{GIR, 0-6h}$ ) showed that IDegAsp provided 7.8 times greater effect as compared to IDeg alone (**Figure 22**). Basal coverage (based on  $AUC_{GIR, 6-24h}$ ) showed that IDegAsp provided 3.9 times greater response as compared to IAsp alone.



Source: sponsors study report

**Figure 22: A) Glucose Infusion Rate, Mean Smoothed Profiles for IDegAsp and IDeg after Single Dose B) Glucose Infusion Rate, Mean Smoothed Profiles – IDegAsp and IAsp after Single Dose**

### Pharmacokinetic Analysis:

**Figure 23A** shows the pharmacokinetic profiles of IAsp following single dose administration of IAsp (0.5 U/kg) and IDegAsp (0.5 U/kg). **Figure 23B** shows the pharmacokinetic profiles of IDeg following single dose administration of IDeg (0.5 U/kg) and IDegAsp (0.5 U/kg). Statistical analyses demonstrate that IDegAsp is more than 20% different from products of each of its components (IAsp and IDeg products) for all pre-specified pharmacokinetic endpoints (**Tables 12 and 13**).

**Table 12: IAsp Pharmacokinetic Endpoints after Single Dose IDegAsp vs. IAsp in Subjects with T1DM**

| Endpoint              | Estimated Ratio | 95% CI     | p-value for Ratio = 1 |
|-----------------------|-----------------|------------|-----------------------|
| $AUC_{IAsp,0-2h,SD}$  | 0.19            | 0.17; 0.21 | <0.0001               |
| $AUC_{IAsp,0-6h,SD}$  | 0.22            | 0.20; 0.23 | <0.0001               |
| $AUC_{IAsp,0-12h,SD}$ | 0.23            | 0.21; 0.24 | <0.0001               |
| $C_{max,IAsp,SD}$     | 0.19            | 0.16; 0.22 | <0.0001               |

Trial 3857: 0.5 U/kg IDegAsp (equal to 0.15 U/kg IAsp) and 0.5 U/kg IAsp.

Note: A more than 20% difference corresponds to an estimated ratio outside the interval [0.83;1.20].

Statistical analyses were based on 27 subjects exposed to IDegAsp and 27 subjects exposed to IAsp.

Source: Sponsor's summary of clinical pharmacology report.

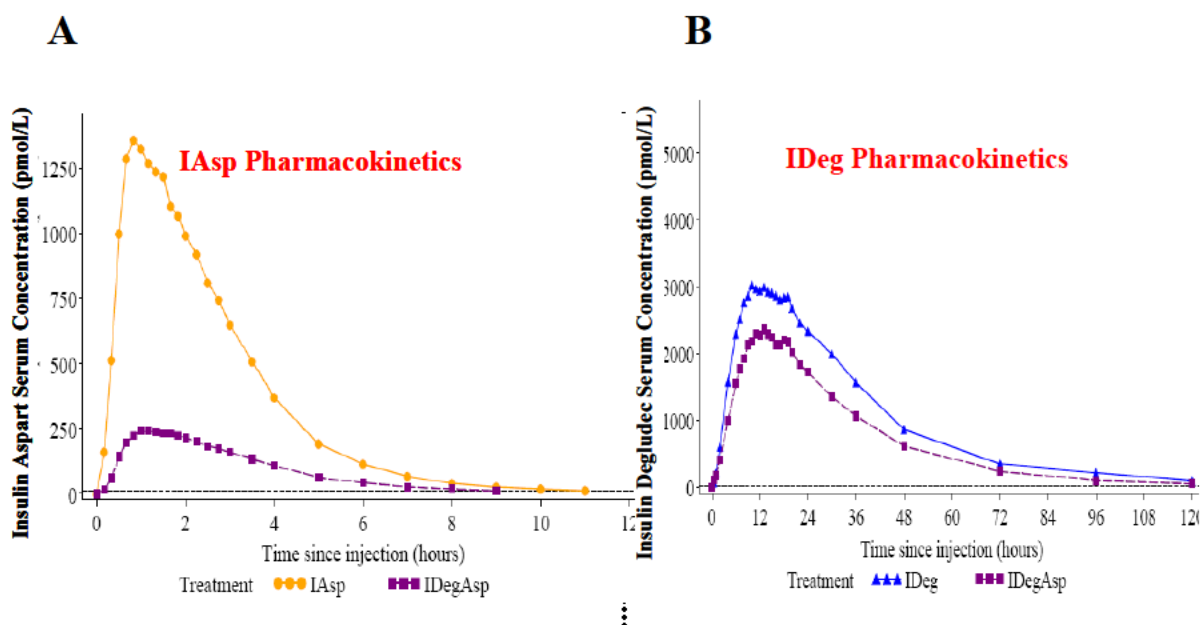


**Figure 23: A) 12-Hour IAsp Mean Concentration-Time Profiles after Single Dose IDegAsp and IAsp in Subjects with T1DM B) 120-hour IDeg Mean Concentration-Time Profiles after Single Dose IDegAsp and IDeg in Subjects with T1DM**

**Table 13: IDeg Pharmacokinetic Endpoints after Single Dose IDegAsp and IDeg in Subjects with T1DM**

| Endpoint               | Estimated Ratio | 95% CI     | p-value for Ratio = 1 |
|------------------------|-----------------|------------|-----------------------|
| $AUC_{IDeg,0-24h,SD}$  | 0.74            | 0.69; 0.80 | <0.0001               |
| $AUC_{IDeg,0-120h,SD}$ | 0.71            | 0.68; 0.74 | <0.0001               |
| $C_{max,IDeg,SD}$      | 0.75            | 0.69; 0.82 | <0.0001               |

Trial 3857: 0.5 U/kg IDegAsp (equal to 0.35 U/kg IDeg) and 0.5 U/kg IDeg.

Note: A more than 20% difference corresponds to an estimated ratio outside the interval [0.83; 1.20].

Statistical analyses were based on 27 subjects exposed to IDegAsp and 26 subjects exposed to IDeg.

Source: Sponsor's summary of clinical pharmacology report.

**Reviewer's Comment:** This study clearly demonstrated the product distinctiveness of more than 20% in terms of pharmacodynamics. In the same study, there were few subjects where the blood glucose level was not maintained throughout the experiment. The PD results presented above exclude those subjects from the analysis. The inclusion of those subjects in the PD analysis does not change the outcome of the conclusion that the pharmacodynamics of IDegAsp is more than 20% different when compared to the individual components.

Pharmacokinetic following administration of IDegAsp results in more than 20% lower exposures for IAsp and IDeg when compared to same dose level of individual component.

These results are expected since IDegAsp comprises of 30% IAsp and 70% IDeg. When dose normalized there the exposure was similar for IDeg component and slightly lower for IAsp component when administered as IDegAsp as compared to individual components. The current Agency's guidance of premix insulin is not fully applicable to this application. In this application the both insulin components can be measure separately as opposed to previous insulin premixes where the short and long acting components can not be separated. Although the dose normalized exposures were similar for IDeg when administered as IDegAsp and IDeg, the sponsor did demonstrate the differences in PD profiles for IDegAsp premix.

#### 2.4.9 What is the PK/PD of IDegAsp in healthy volunteers?

The pharmacokinetic properties of IAsp in IDegAsp were investigated in healthy subjects in Trial 1980. This was a randomized, single-center, double-blind, two-period cross-over trial with single-dose administration of 0.5 U/kg IDegAsp (bioequivalence between two products). The pharmacokinetic parameters for IDeg and IAsp following single dose administration of IDegAsp is shown in **Table 14**.

The pharmacodynamic properties of IDegAsp in healthy subjects were investigated during a 24-hour euglycemic clamp (target glucose level of 4.5 mmol/L [81 mg/dL]) following single dose administration of 0.5 U/kg IDegAsp. **Figure 24** show the PD profile and **Table 15** shows summary of PD parameters in healthy subjects.

| <b>Table 14: Summary of PK Parameters for IAsp and IDeg following Single Dose IDegAsp Administration in Healthy Subjects</b> |    |                                          |                                   |                              |                                              |
|------------------------------------------------------------------------------------------------------------------------------|----|------------------------------------------|-----------------------------------|------------------------------|----------------------------------------------|
| <b>IAsp pharmacokinetic Endpoints after Single Dose Administration of IDegAsp in Healthy Subjects.</b>                       |    |                                          |                                   |                              |                                              |
| Dose (U/kg)                                                                                                                  | N  | AUC <sub>IAsp,0-12h,SD</sub> (pmol·h/L)  | C <sub>max,IAsp,SD</sub> (pmol/L) | t <sub>max,IAsp,SD</sub> (h) | Onset of appearance <sub>IAsp,SD</sub> (min) |
|                                                                                                                              |    | Geom. mean (CV%)                         | Geom. mean (CV%)                  | Median (CV%)                 | Geom. mean (CV%)                             |
| 0.5                                                                                                                          | 26 | 645 (22)                                 | 218 (27)                          | 1.33 (33)                    | 18 (43)                                      |
| Trial 1980: 0.5 U/kg IDegAsp (equal to 0.15 U/kg IAsp)                                                                       |    |                                          |                                   |                              |                                              |
| N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.          |    |                                          |                                   |                              |                                              |
| <b>IDeg pharmacokinetic Endpoints after Single Dose Administration of IDegAsp in Healthy Subjects.</b>                       |    |                                          |                                   |                              |                                              |
| Dose (U/kg)                                                                                                                  | N  | AUC <sub>IDeg,0-120h,SD</sub> (pmol·h/L) | C <sub>max,IDeg,SD</sub> (pmol/L) | t <sub>max,IDeg,SD</sub> (h) |                                              |
|                                                                                                                              |    | Geom. mean (CV%)                         | Geom. mean (CV%)                  | Median (CV%)                 |                                              |
| 0.5 U/kg                                                                                                                     | 26 | 76398 (15)                               | 2400 (20)                         | 13.0 (24)                    |                                              |
| Trial 1980. 0.5 U/kg IDegAsp (equal to 0.35 U/kg IDeg).                                                                      |    |                                          |                                   |                              |                                              |
| N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.          |    |                                          |                                   |                              |                                              |

**Figure 24: 24-Hour Mean Glucose Infusion Rate Mean Profile after Single Dose IDegAsp in Healthy Subjects**

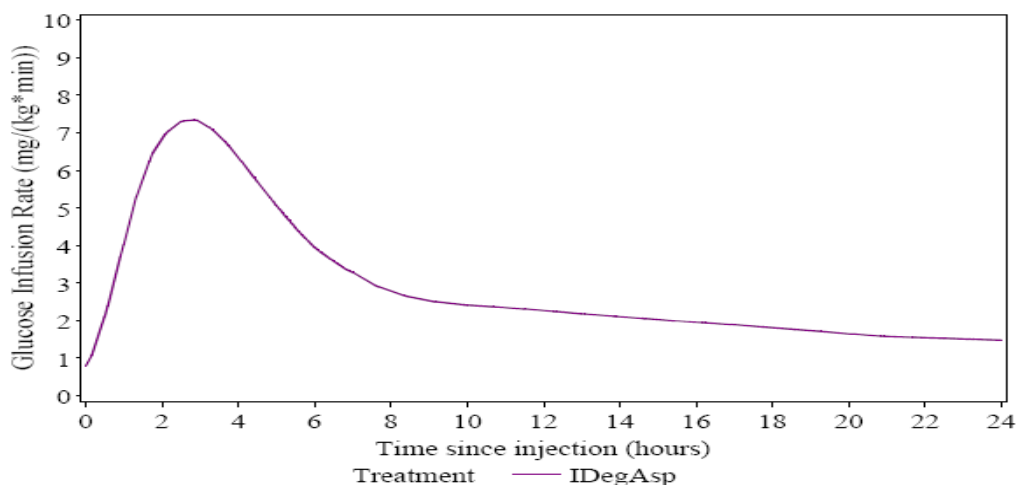


**Table 15: Glucose Infusion Rate Endpoints after Single Dose IDegAsp in Healthy Subjects**

| Dose (U/kg) | N  | AUC <sub>GIR,0-24h,SD</sub> (mg/kg) | GIR <sub>max,SD</sub> (mg/kg*min) | tGIR <sub>max,SD</sub> (h) |
|-------------|----|-------------------------------------|-----------------------------------|----------------------------|
|             |    | Geom. mean (CV%)                    | Geom. mean (CV%)                  | Median (CV%)               |
| 0.5         | 26 | 3947 (36)                           | 7.1 (43)                          | 2.7 (29)                   |

Trial 1980: 0.5 U/kg IDegAsp.

N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

**2.4.10 How do the PK/PD parameters change with time following chronic dosing?**

Multiple doses PK/PD studies were not conducted in this NDA. Under degludec NDA (NDA 203314) sponsor conducted several multiple dose PK/PD studies. Please refer to Clinical Pharmacology review by Dr. Manoj Khurana for further details.

**2.4.11 How are the PK/PD features of IDegAsp as compared to biphasic insulin aspart 30 (BIAsp 30)?**

In several Phase 3 trials, biphasic insulin aspart 30 (BIAsp 30) was used as comparator to IDegAsp. In addition, in the proposed IDegAsp label sponsor recommends that the patients switching from once-daily basal or premix insulin therapy can be converted unit-to-unit to once-daily IDegAsp at the same total insulin dose as the patient’s previous total daily insulin dose.

Sponsor conducted single dose PK/PD studies in T1DM subjects (Trial 3539) and T2DM subjects (Trial 1978) to compare pharmacokinetics and pharmacodynamic profiles following s.c. administration of IDegAsp and BIAsp 30. **Figure 25** shows the observed mean IAsp concentration–time profiles following IDegAsp and BIAsp 30 administration at three different dose levels in subjects with T1DM. Time of onset was defined as time from the two products administration until the first time serum IAsp concentration is

above 30 pmol/L. After single dose, the time of onset were comparable between IDegAsp and BIAsp 30 (Table 16). In addition, time to maximum IAsp concentration (median) was comparable between IDegAsp and BIAsp 30 (Table 16). However, pharmacokinetic profiles shows that the lower maximum IAsp concentration was observed if its given as IDegAsp as compared to BIAsp 30. Also, the AUC<sub>0-6</sub> of insulin aspart was lower following the IDegAsp administration.

**Figure 25: 8-Hour IAsp Mean Concentration-Time Profiles after Single Dose IDegAsp (Left) and BIAsp 30 (Right) in Subjects with T1DM**

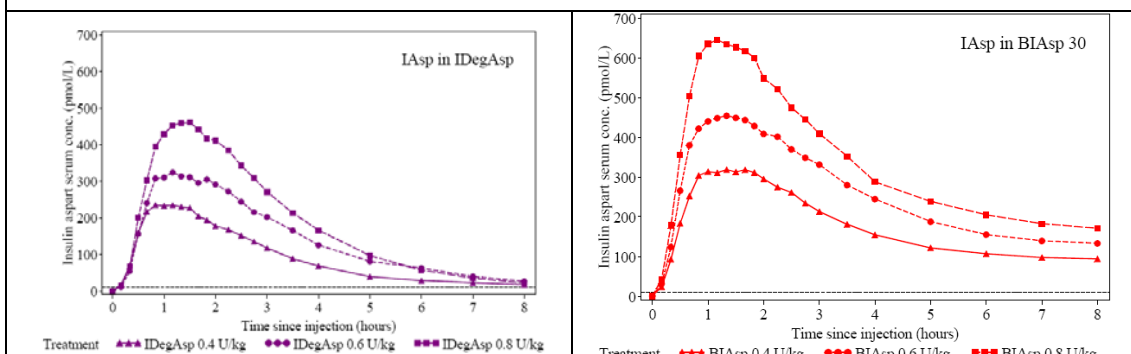


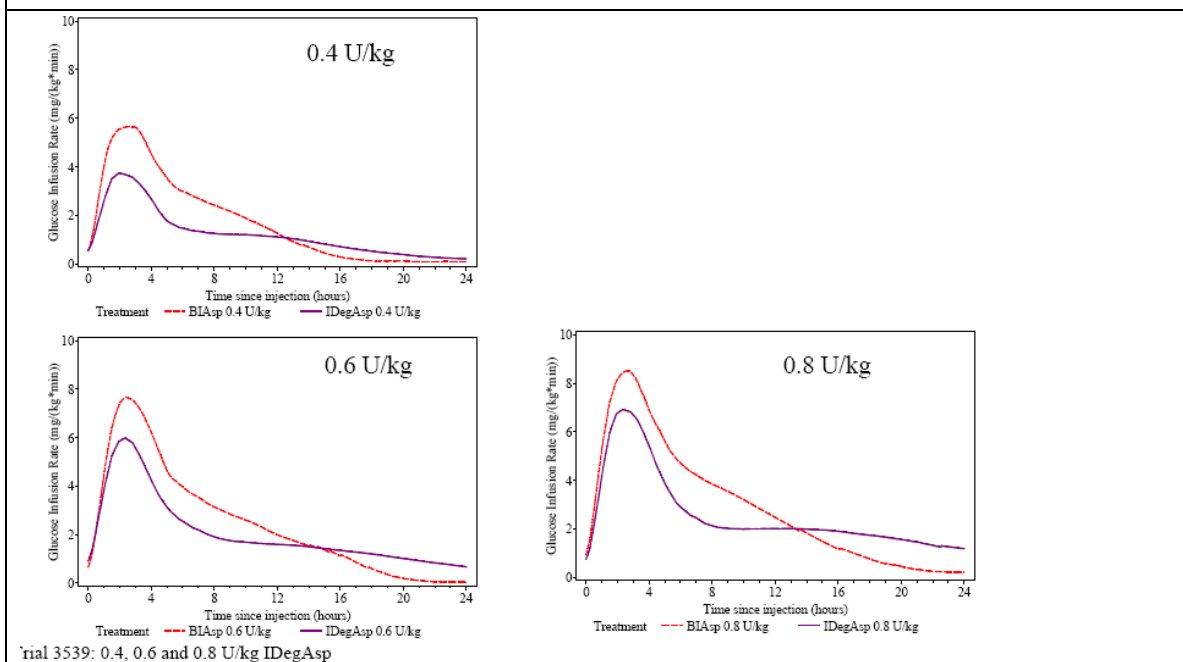
**Table 16: IAsp Pharmacokinetic Endpoints after Single Dose IDegAsp and BIAsp 30 in Subjects with T1DM**

| Dose (U/kg) | N       |          | Onset of appearance <sub>IAsp,SD</sub> (min)<br>Geom. mean (CV%) |          | $t_{max,IAsp,SD}$ (h)<br>Median (CV%) |          |
|-------------|---------|----------|------------------------------------------------------------------|----------|---------------------------------------|----------|
|             | IDegAsp | BIAsp 30 | IDegAsp                                                          | BIAsp 30 | IDegAsp                               | BIAsp 30 |
| 0.4         | 21      | 22       | 14 (32)                                                          | 12 (34)  | 1.2 (31)                              | 1.4 (38) |
| 0.6         | 20      | 20       | 17 (34)                                                          | 11 (43)  | 1.4 (38)                              | 1.5 (40) |
| 0.8         | 20      | 21       | 15 (30)                                                          | 8 (52)   | 1.4 (27)                              | 1.4 (28) |

Trial 3539: 0.4, 0.6 and 0.8 U/kg IDegAsp (equal to 0.12, 0.18 and 0.24 U/kg of the IAsp component).  
N: number of subjects contributing to the analysis; Geom. mean: geometric mean; CV%: coefficient of variation in %.

Figure 26 shows the observed mean glucose infusion rate profiles following IDegAsp and BIAsp administration at three different dose levels in subjects with T1DM subjects. The glucose infusion rate profiles suggest that the early (AUC<sub>GIR 0-4 hrs</sub>) glucose lowering effect was lower with IDegAsp as compared to BIAsp 30.

**Figure 26: 24-hour Mean Glucose Infusion Rate Profiles after Single Dose IDegAsp and BIAsp 30 in Subjects with T1DM**



**Reviewer’s comment:** This single dose study provides very limited information on dosing recommendation for patients switching from once-daily basal or premix insulin therapy to once-daily IDegAsp, at the same total insulin dose as the patient’s previous total daily insulin dose. Pharmacokinetic profiles shows that the lower maximum IAsp concentration was observed if its given as IDegAsp as compared to BIAsp 30. Similar to pharmacokinetics, pharmacodynamics response in terms of glucose infusion rate profiles were different between these two products. The early glucose-lowering effect (AUC GIR 0-4 hrs) was lower with IDegAsp than BIAsp 30. However, it should be noted that following multiple doses, the basal component reaches steady state within 2-3 days of once daily dosing. At steady state exposure of IDeg being approximately two-fold higher as compared to following single dose. However, Phase 3 studies were conducted where patients switched from BIAsp 30 to IDegAsp on unit to unit basis and provides support regarding the switch on unit to unit basis.

## 2.5 Intrinsic Factors

### 2.5.1 What intrinsic factors (e.g., age, gender, race, weight, height, , pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response(PD)?

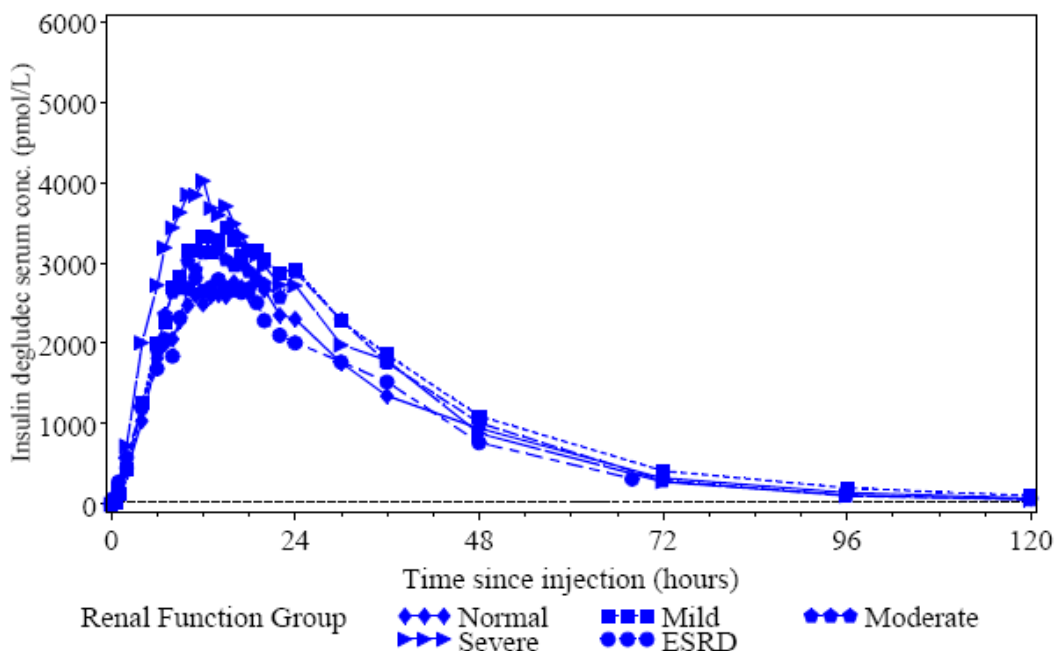
#### **Renal Impairment:**

Impact of renal impairment on the pharmacokinetics and pharmacodynamics of IDegAsp is not studied in this NDA. Pharmacokinetics of insulin aspart has been studied under

Novolog application with no apparent effect of creatinine clearance values on AUC and  $C_{max}$  of NovoLog.

The pharmacokinetic properties of IDeg in subjects with or without renal impairment were investigated in Trial 1990 under the Insulin degludec program (NDA 203314). This trial was a single center, open-label, parallel-group trial with single doses of 0.4 U/kg IDeg in subjects with different grades of renal impairment (including subjects with end-stage renal disease (ESRD) requiring hemodialysis) and subjects with normal renal function. In addition, the influence of hemodialysis on clearance of IDeg was investigated in subjects requiring hemodialysis (ESRD subjects) by administration of two single doses of IDeg, one before and one just after hemodialysis (**Figure 27**).

According to sponsor, pharmacokinetic profiles of IDeg were similar for subjects with normal and impaired renal function, and total exposure ( $AUC_{0-120h}$ , IDeg) was not affected by renal function measured by creatinine clearance ( $p = 0.26$ ). Please refer to Clinical Pharmacology review (NDA203313) by Dr. Manoj Khurana for further details.



Source: Sponsor's summary of clinical pharmacology report.

**Figure 27: 120-Hour IDeg Mean Concentration-Time Profiles after Single Dose IDeg in Subjects with Normal Renal Function and Subjects with Mild, Moderate, Severe or ESRD Renal Impairment**

**Reviewers Comments:** Although no changes in PK was seen with insulin aspart the approved Novolog<sup>®</sup> label still recommends careful glucose monitoring and dose adjustments if necessary in renally impaired patients. In the insulin degludec application sponsor proposed that the insulin degludec should be used with caution in patients with acute renal failure and also recommends glucose monitoring and adjustment on individual basis in patients with renal impairment. Similar labeling language is proposed in this application for renally impaired patients which seems reasonable.

- **Hepatic Impairment:**

Impact of renal impairment on the pharmacokinetics and pharmacodynamics of IDegAsp is not studied in this NDA. Pharmacokinetics of insulin aspart has been studied under Novolog<sup>®</sup> application with no effect of hepatic impairment of the pharmacokinetics of insulin aspart.

The pharmacokinetic properties of IDeg in subjects with or without hepatic impairment were investigated in Trial 1989 under the Insulin degludec program (NDA 203314). This trial was a single-center, open-label, parallel-group trial with single dose administration of 0.4 U/kg IDeg in subjects with different grades of hepatic impairment and in subjects with normal hepatic function. According to sponsor the mean pharmacokinetic profiles of IDeg were similar for subjects with normal and impaired hepatic function (**Table 17**). Please refer to Clinical Pharmacology review (NDA203314) by Dr. Manoj Khurana for further details.

**Table 17: Pair-wise Comparison of IDeg Total Exposure and Maximum Concentration after Single Dose IDeg between Subjects with Normal Hepatic Function and Subjects with Mild, Moderate or Severe Hepatic Impairment**

| Grade of hepatic impairment                                       | AUC <sub>IDeg,0-120h,SD</sub> |         | C <sub>max,IDeg,SD</sub> |
|-------------------------------------------------------------------|-------------------------------|---------|--------------------------|
|                                                                   | Ratio [90% CI]                | p-value | Ratio [90% CI]           |
| Mild vs. normal                                                   | 0.95 [0.77; 1.16]             |         | 0.90 [0.67; 1.20]        |
| Moderate vs. normal                                               | 1.00 [0.82; 1.22]             |         | 0.77 [0.58; 1.03]        |
| Severe vs. normal                                                 | 0.92 [0.74; 1.14]             |         | 0.75 [0.55; 1.02]        |
| Test of trend with increased hepatic function                     |                               | 0.63    |                          |
| Trial 1989: 0.4 U/kg IDeg. No adjustment for body weight.         |                               |         |                          |
| CI: confidence interval.                                          |                               |         |                          |
| N: Normal=6; Mild=6; Moderate=6; Severe=6                         |                               |         |                          |
| <i>Source: Sponsor's summary of clinical pharmacology report.</i> |                               |         |                          |

**Reviewers Comments:** Although no changes in PK was seen with insulin aspart the approved Novolog<sup>®</sup> label still recommends careful glucose monitoring and dose adjustments in need in hepatic impaired patients. In the insulin degludec application sponsor proposed that the insulin degludec should be used with caution in patients with acute liver failure and also recommends glucose monitoring and adjustment on individual basis in patients with hepatic impairment. Similar labeling language is proposed in this application for patients with hepatic dysfunction which seems reasonable.

- **Age**

The pharmacokinetic properties of IDegAsp in children and adolescents in comparison to adults were investigated in Trial 1982. (b) (4)  
 with T1DM.

**In this NDA sponsor is requesting waiver for pediatric studies in the following age group:**

- patients below 1 year of age with type 1 diabetes mellitus (T1DM)
- patients below 10 years of age with type 2 diabetes mellitus (T2DM)
- [redacted] (b) (4)

In addition sponsor is also requesting deferrals for conducting pediatric studies in the following group:

- patients between 1 and [redacted] (b) (4) years of age with [redacted] (b) (4) diabetes mellitus [redacted] (b) (4)

***Reviewers Comments:***

(b) (4)

• **Geriatric Subjects:**

The pharmacokinetic properties of IDegAsp in geriatric subjects in comparison to younger adult subjects were investigated in Trial 1981. The trial was randomized, single-center, double-blind, cross-over trial with single-dose administration of 0.5 U/kg of IDegAsp in younger adult (18–35 years) and geriatric ( $\geq 65$  years) subjects with T1DM.

The mean IAsp and IDeg concentration-time profiles showed that the exposure was slightly higher for geriatric than younger adult subjects (**Figure 30 and Table 21 and**

**Table 22).** A statistically significant difference is seen between geriatric and younger adult subjects with an estimated mean age group ratio (geriatric/young) of 1.37 [1.01; 1.87]95% CI. The total exposure of IDeg in IDegAsp (based on AUC<sub>0-120h</sub> IDeg) was not statistically significantly different between geriatric and younger adult subjects with an estimated mean age group ratio (geriatric/young) of 1.24 [0.90; 1.70] 95% CI.

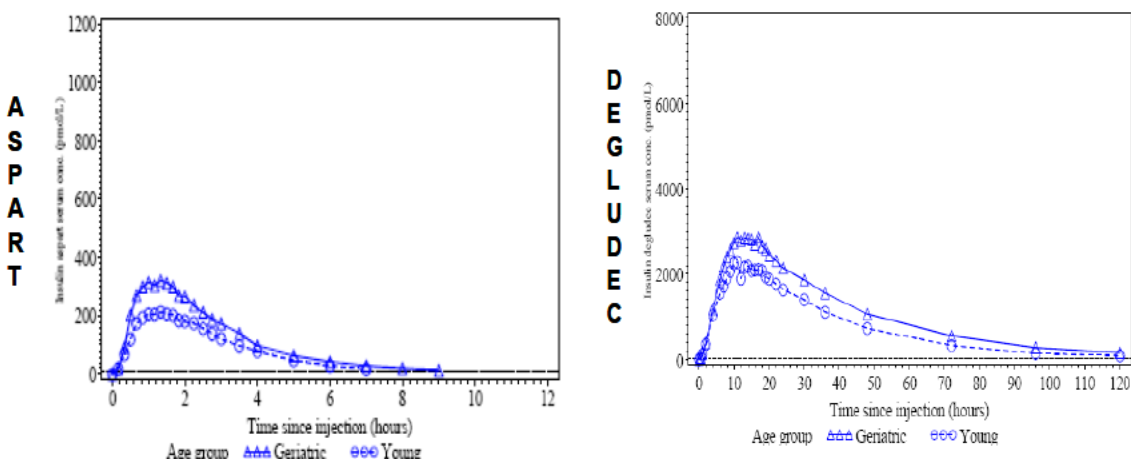


**Figure 30: Mean Pharmacokinetic Profile of IAsp and IDeg Following Single Dose Administration of IDegAsp in (18–35 years) and geriatric (≥65 years) subjects**

**Table 21: Insulin Aspart Pharmacokinetic Endpoints after Single Dose IDegAsp in Young Adults and Geriatric Subjects**

| Age Group | N  | AUCIAsp, 0-12h (pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IAsp (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-----------|----|-----------------------------------------------|----------------------------------------------------|--------------------------------|
| Young     | 13 | 683 ( 32)                                     | 221 ( 28)                                          | 1.3                            |
| Geriatric | 15 | 863 ( 37)                                     | 305 ( 59)                                          | 1.2                            |

Source: Sponsor's summary report

**Table 22: Insulin Degludec Pharmacokinetic Endpoints after Single Dose IDegAsp in Young Adults and Geriatric Subjects**

| Age Group | N  | AUCIDeg, 0-120h (pmol*h/L)<br>Geom. Mean (CV%) | C <sub>max</sub> IDeg (pmol/L)<br>Geom. Mean (CV%) | T <sub>max</sub> (h)<br>Median |
|-----------|----|------------------------------------------------|----------------------------------------------------|--------------------------------|
| Young     | 13 | 84590 ( 30)                                    | 2289.8 ( 31.2)                                     | 14                             |
| Geriatric | 15 | 94300 ( 34)                                    | 2842.4 ( 25.7)                                     | 12.5                           |

Source: Sponsor's summary report

The pharmacodynamic properties comparison of IDegAsp in young and geriatric subjects were investigated during a 26-hour euglycemic clamp (target glucose level of 5.5 mmol/L [100 mg/dL]) following single dose administration of 0.5 U/kg IDegAsp. **Figure 31** shows the mean GIR profile and **Table 23** shows summary of PD parameters in young and geriatric subjects. Mean smoothed GIR profiles for IDegAsp were similar for both age groups.

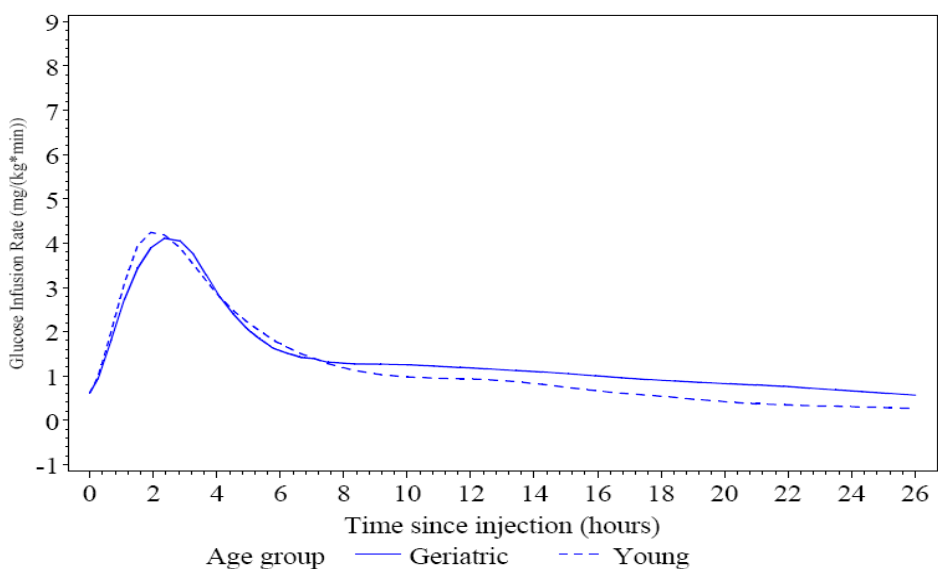


**Figure 31: Mean Smoothed Glucose Infusion Rate Profiles for IDegAsp after Single Dose**

**Table 23: Glucose Infusion Rate, 0-24 hours for IDegAsp after Single Dose – Statistical Analysis**

|                            | FAS | N  | Estimate | 95% CI        |
|----------------------------|-----|----|----------|---------------|
| AUC GIR, 0-24h, SD (mg/kg) |     |    |          |               |
| IDegAsp                    |     |    |          |               |
| Least square means         |     |    |          |               |
| Young                      | 13  | 13 | 1780     |               |
| Geriatric                  | 15  | 15 | 1789     |               |
| Mean ratio                 |     |    |          |               |
| Geriatric/Young            |     |    | 1.01     | [ 0.69; 1.47] |

The endpoint is log-transformed and analysed using a linear mixed model with age group and treatment period as fixed effects

*Reviewer's Comments: The total exposure of the prandial component (IAsp) of IDegAsp is higher in geriatric subjects than in younger adult. This increase in exposure of IAsp is believed to have limited clinical implication considering that IDegAsp should be dosed according to individual needs. Also, pharmacodynamic properties seem to be similar in both the age group as measured by area under the curve of GIR.*

- **Gender:**

Across trial analysis was conducted by the sponsor to see the effect of gender on the pharmacokinetic and pharmacodynamic properties of IDegAsp.

Cross trial analysis of data from trials 1977, 1981 (only younger adult subjects), 3539 and 3857 including 13 women and 85 men showed no difference in the pharmacokinetics of IAsp following IDegAsp administration (**Table 24**)

**Table 24: IAsp Pharmacokinetic Endpoints after Single Dose IDegAsp in Women and Men with T1DM**

| Sex       | N  | AUC <sub>IAsp,0-12h,SD</sub> (pmol <sup>2</sup> h/L) |                     | C <sub>max,IAsp,SD</sub> (pmol/L) |                     |
|-----------|----|------------------------------------------------------|---------------------|-----------------------------------|---------------------|
|           |    | Estimate                                             | Mean ratio [95% CI] | Estimate                          | Mean ratio [95% CI] |
| Women     | 13 | 711                                                  |                     | 239                               |                     |
| Men       | 85 | 683                                                  |                     | 213                               |                     |
| Women/Men |    |                                                      | 1.04 [0.83; 1.30]   |                                   | 1.12 [0.93; 1.35]   |

Trial 1977: 0.5 U/kg IDegAsp; Trial 1981: 0.5 U/kg IDegAsp (only younger adult subjects); Trial 3539: 0.4, 0.6 and 0.8 U/kg IDegAsp; Trial 3857 0.5 U/kg IDegAsp.  
 The endpoints are dose-adjusted to 0.4 U/kg (equal to 0.12 U/kg IAsp).  
 N: number of subjects contributing to the analysis. CI: confidence interval  
 Two subjects were excluded due to implausible IAsp concentration profiles.

Analysis of data for IDeg at steady state from Trials 1991, 1993, 1994 and 3678 including 22 women and 114 men with T1DM following IDeg administration showed similar PK properties between men and women (**Table 25**).

**Table 25: IDeg Pharmacokinetic Endpoints at Steady State in Women and Men with T1DM**

| Sex       | N   | AUC <sub>IDeg,t,SS</sub> (pmol <sup>2</sup> h/L) |                     | C <sub>max,IDeg,t,SS</sub> (pmol/L) |                     |
|-----------|-----|--------------------------------------------------|---------------------|-------------------------------------|---------------------|
|           |     | Estimate                                         | Mean ratio [95% CI] | Estimate                            | Mean ratio [95% CI] |
| Women     | 22  | 79522                                            |                     | 4350                                |                     |
| Men       | 110 | 85854                                            |                     | 4586                                |                     |
| Women/Men |     |                                                  | 0.93 [0.82, 1.05]   |                                     | 0.95 [0.84, 1.07]   |

Trial 1991: 0.4 U/kg IDeg; Trial 1993: 0.4, 0.6, 0.8 U/kg IDeg (dose-adjusted to 0.4 U/kg); Trial 1994: 0.4 U/kg IDeg (only younger adult subjects); Trial 3678: 0.4 U/kg IDeg.  
 N: number of subjects contributing to the analysis; CI: confidence interval.  
 Four subjects were excluded due to implausible IDeg concentration profiles.

Similarly the pharmacodynamic properties ( $AUC_{GIR, 0-24h}$ ) of IDegAsp at single dose were similar between female and male subjects with type 1 diabetes when compared in a cross trial analysis using data from Trials 3539, 1977, 3857 and 1981. The mean ratio for  $AUC_{GIR, 0-24h}$  between female vs. male was 1.03 with 95% CI of 0.79 to 1.33.

- **Body Mass Index (BMI)**

**IAsp Component**

The effect of BMI on total and maximum concentration of IAsp was studied after a single dose of IDegAsp in subjects with T1DM across Trials 1977, 1981, 3539 and 3857, and in subjects with T2DM in Trial 1978.

The scatter plots did not indicate a relationship between BMI and total exposure ( $AUC_{IAsp,0-12h,SD}$ ) or maximum concentration ( $C_{max,IAsp,SD}$ ) of IAsp in subjects with either T1DM (**Figure 32**) or T2DM (**Figure 33**) when dosed per kg body weight. Overall, there was no relationship between BMI and exposure in subjects with T1DM or T2DM when dosed per kg body weight.

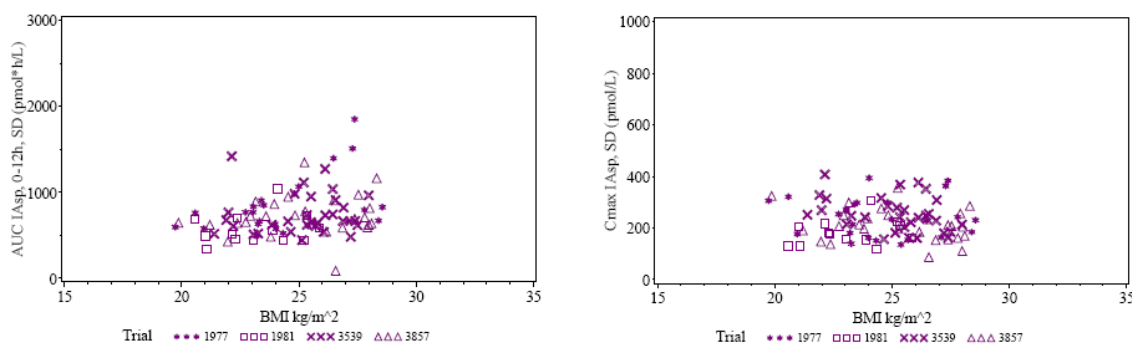


**Figure 32: IAsp Total Exposure (Left) and Maximum Concentration (Right) vs. BMI after Single Dose IDegAsp in Subjects with T1DM**

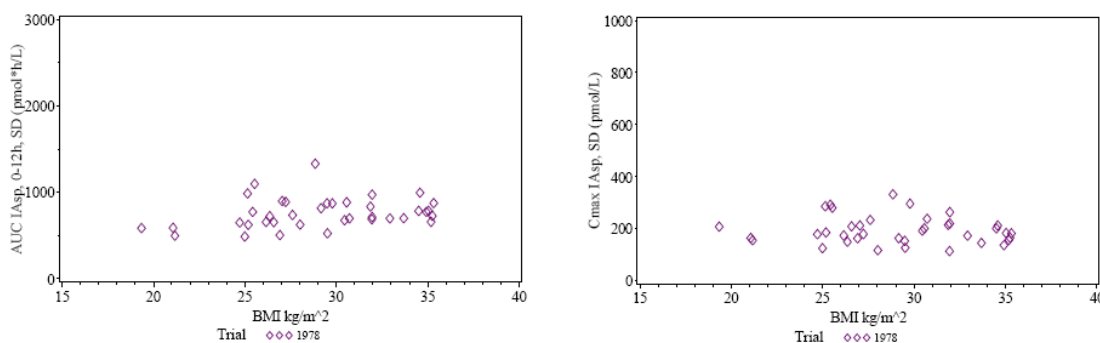


**Figure 33: IAsp Total Exposure (Left) and Maximum Concentration (Right) vs. BMI after Single Dose IDegAsp in Subjects with T2DM**

**IDeg Component**

Sponsor studied the effect of BMI on total exposure and maximum concentration of IDeg in subjects with T1DM across Trials 1991, 1993, 1994 and 3678, and in subjects with T2DM across Trials 1987 and 3762. The trials are conducted under IDeg clinical development program.

For IDeg when corrected for body weight, there was no significant relationship for subjects with T1DM, whereas for subjects with T2DM, total and maximum exposure still increased with increasing BMI. Please refer to Clinical Pharmacology review by Dr. Manoj Khurana for further details regarding the effect of BMI on pharmacokinetics of IDeg.

- **Race/Ethnicity:**

Pharmacokinetics of IDeg in African American, Hispanic and Caucasian subjects were studied under IDeg clinical development program. Sponsor claims that there is no difference in the pharmacokinetic properties of IDeg between subjects of different race and ethnicity. Please refer to Clinical Pharmacology review by Dr. Manoj Khurana for further details regarding the effect of race on pharmacokinetics of IDeg.

No studies were conducted with IDegAsp in African American, Hispanic and Caucasian subjects. Sponsor did single dose pharmacokinetic studies with IDegAsp in Japanese subjects (trial 1983). Comparing the pharmacokinetic parameters across the trials in Japanese and Caucasian subjects (trial 1983 vs. trial 3857) showed that exposure and peak concentration of IDeg and IAsp in Japanese subjects with T1DM were comparable to that seen in Caucasian subjects following single dose IDegAsp administration.

- **Smoking:**

In this NDA, No studies were done to see the effect of smoking on PK/PD of IDegAsp

## 2.6 Extrinsic Factors

### 2.6.1 What extrinsic factors (drugs, herbal products, diet, smoking, and alcohol use) influence dose-exposure and/or -response and what is the impact of any differences in exposure on response?

Elimination of IDeg is primarily mediated by the insulin receptor and non-specific degradation pathways. No clinical trials were conducted to investigate drug-drug interactions of IDegAsp with other drugs or vice versa.

### 2.6.2 Is there a known mechanistic basis for pharmacokinetics/ pharmacodynamic drug-drug interactions, if any?

IDeg has very high protein binding (>99%) to serum albumin. The fatty acid moiety of IDeg allows it to bind to plasma proteins and contributes to some extent to the protraction mechanism. To study the impact of other drugs on the protein binding of IDeg sponsor conducted in vitro protein binding studies.

In vitro studies showed that neither common protein-bound drugs (ibuprofen, warfarin, acetylsalicylate, salicylate), frequently used antidiabetic agents (glimepiride, metformin,

sitagliptin, liraglutide), nor fatty acids (palmitate, oleate, linoleate) affected IDeg binding to human serum albumin at therapeutically/physiologically relevant drug concentrations. This study was conducted under IDeg clinical development program. Please refer to Clinical Pharmacology review (NDA203314) by Dr. Manoj Khurana for further details.

### 2.6.3 What is the effect of injection site on the pharmacokinetics of IDegAsp?

No clinical studies have been conducted to see the effect of injection site on the pharmacokinetics of IDegAsp. However, in the Phase 3 trials with IDegAsp the injections sites were rotated between thigh, abdomen and deltoid region. In addition, the use of various injection regions (abdominal wall, the thigh, the upper arm (deltoid region) or the gluteal region) has been established and demonstrated through several years of market use of the prandial component (IAsp) of IDegAsp. Sponsor also studied the effect of injection site on the pharmacokinetics of IDeg, under NDA 203314 and proposes to rotate the injection site for IDeg. **Table 26** shows the relative bioavailability of IDeg in healthy subjects following administration at different injection sites. For details please refer to Clinical Pharmacology review (NDA203314) by Dr. Manoj Khurana for further details.

**Table 26: Relative Bioavailability of IDeg in Healthy Subjects**

| Trial ID | IDeg Product | Dose         | Injection Site            | AUC <sub>IDeg,0-120h,SD</sub><br>Ratio [95% CI] |
|----------|--------------|--------------|---------------------------|-------------------------------------------------|
| 1992     | IDeg (M)     | 0.4/0.4 U/kg | s.c. abdomen/s.c.thigh    | 1.07 [1.03; 1.11]                               |
|          |              | 0.4/0.4 U/kg | s.c. deltoid/s.c. thigh   | 1.06 [1.01; 1.10]                               |
|          |              | 0.4/0.4 U/kg | s.c. abdomen/s.c. deltoid | 1.01 [0.96; 1.06]                               |

## 2.7 General Biopharmaceutics

An overview of the IDegAsp drug products used in clinical trials during the development of IDegAsp is presented in **Table 27** and **Table 28**. In all the confirmatory Phase 3 trials and key clinical pharmacology studies sponsor used the proposed commercial formulation (IDegAsp (F)). However, during development, changes have been introduced in the (b) (4)

(b) (4) Please refer to CMC review by Drs Joseph Leginus, Muthukumar Ramaswamy Darrrts dated 02/08/2012 for further details.

In addition, sponsor conducted a BE study under NDA 203314 which investigated the bioequivalence between IDeg (M) drug products manufactured (b) (4) (b) (4) Also, under NDA 203314 sponsor used (b) (4) (b) (4) in their phase 3 trials. Please refer to review of NDA 203314 by Dr. Manoj Khurana for further details. In this NDA, sponsor used (b) (4) (b) (4) for all the clinical pharmacology and phase 3 studies.

**Table 27: Clinical Trials and IDegAsp Products Used**

|                                              | Early Drug Products<br>(Exploratory Formulations) |         |                    |                   |                   |                   |                    | Drug Products<br>(Proposed<br>Commercial<br>Formulation) |                |
|----------------------------------------------|---------------------------------------------------|---------|--------------------|-------------------|-------------------|-------------------|--------------------|----------------------------------------------------------|----------------|
|                                              | IDegAsp                                           | IDegAsp | IDegAsp<br>(b) (4) | IDegAsp<br>45 (B) | IDegAsp<br>40 (C) | IDegAsp<br>55 (C) | IDegAsp<br>(b) (4) | IDegAsp<br>30 (B)                                        | IDegAsp<br>(F) |
| IDeg<br>(nmol/mL)                            |                                                   |         |                    | 330               | 540               | 405               |                    | 420                                                      | 420            |
| IAsp<br>(nmol/mL)                            |                                                   |         |                    | 270               | 240               | 330               |                    | 180                                                      | 180            |
| <b>Clinical Pharmacology</b>                 |                                                   |         |                    |                   |                   |                   |                    |                                                          |                |
| 1738                                         | X                                                 | X       | X                  |                   |                   |                   |                    |                                                          |                |
| 1788                                         |                                                   |         | X                  |                   |                   |                   |                    |                                                          |                |
| 1790                                         |                                                   |         |                    | X                 |                   |                   |                    | X                                                        |                |
| 1959                                         |                                                   |         |                    | X                 | X                 | X                 |                    | X                                                        |                |
| 1977                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 1978                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 1980                                         |                                                   |         |                    |                   |                   |                   |                    | X                                                        | X              |
| 1981                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 1982                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 1983                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 1985                                         |                                                   |         |                    |                   |                   | X                 | X                  |                                                          |                |
| 3539                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| 3857                                         |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |
| <b>Therapeutic exploratory</b>               |                                                   |         |                    |                   |                   |                   |                    |                                                          |                |
| 1791                                         |                                                   |         |                    | X                 |                   |                   |                    | X                                                        |                |
| 1792                                         |                                                   |         |                    | X                 |                   |                   |                    | X                                                        |                |
| 3570                                         |                                                   |         |                    |                   |                   |                   |                    | X                                                        |                |
| <b>Therapeutic confirmatory <sup>1</sup></b> |                                                   |         |                    |                   |                   |                   |                    |                                                          |                |
|                                              |                                                   |         |                    |                   |                   |                   |                    |                                                          | X              |

See [Table 1-1](#) for description of the drug products.

<sup>1</sup> Trials 3590, 3592, 3593, 3594, 3597, 3645, 3726, 3896.

Source: Sponsor report on Summary of Biopharmaceutic Studies and Associated Analytical Methods

**Table 28: Composition of the IDegAsp Products used in Clinical Trials**

| Name of Ingredients               | IDegAsp | IDegAsp | IDegAsp (b) (4) | IDegAsp 55 (D) | IDegAsp 30 (B) <sup>1</sup> | IDegAsp 45 (B) | IDegAsp 40 (C) | IDegAsp 55 (C) | IDegAsp (F) <sup>1</sup> |
|-----------------------------------|---------|---------|-----------------|----------------|-----------------------------|----------------|----------------|----------------|--------------------------|
| Clinical development <sup>2</sup> |         |         |                 | Phase 2        | Phase 2                     | Phase 2        | Phase 2        | Phase 2        | Phase 3                  |
| Quantity per mL                   |         |         |                 |                |                             |                |                |                |                          |
| Drug substance <sup>3</sup>       |         |         |                 | (b) (4)        | 420                         |                |                | (b) (4)        | 420                      |
| IDeg (nmol/mL)                    |         |         |                 | (b) (4)        | 420                         |                |                | (b) (4)        | 420                      |
| IAsp (nmol/mL)                    |         |         |                 |                | 180                         |                |                |                | 180                      |
| Excipients                        |         |         |                 |                |                             |                |                |                |                          |
| Phenol <sup>4</sup> (mg/mL)       |         |         |                 |                | 1.50                        |                |                |                | 1.50                     |
| Metacresol <sup>4</sup> (mg/mL)   |         |         |                 |                | 1.72                        |                |                |                | 1.72                     |
| Glycerol (mg/mL)                  |         |         |                 |                | 19.0                        |                |                |                | 19.0                     |
| Trometamol (mg/mL)                |         |         |                 |                | -                           |                |                |                | -                        |
| Sodium chloride (mg/mL)           |         |         |                 |                | 0.58                        |                |                |                | 0.58                     |
| Zinc <sup>5</sup> (µg/mL)         |         |         |                 |                | 27.4                        |                |                |                | 27.4                     |
| Hydrochloric acid <sup>6,7</sup>  |         |         |                 |                | q.s.                        |                |                |                | q.s.                     |
| Sodium hydroxide <sup>6,8</sup>   |         |         |                 |                | q.s.                        |                |                |                | q.s.                     |
| Water for injections              |         |         |                 |                |                             |                |                |                | (b) (4)                  |
| Characteristics of drug product   |         |         |                 | (b) (4)        |                             |                |                |                | (b) (4)                  |
| pH                                |         |         |                 | (b) (4)        | 7.4                         |                |                |                | (b) (4)                  |

- <sup>1</sup> Same formulation as the proposed commercial product of IDegAsp 100 U/mL
- <sup>2</sup> This refers to the stage of clinical development and not the type of clinical trial. Please see Section 1.2 for a summary of drug product by type of clinical trial.
- <sup>3</sup> The varying concentrations and ratios of IAsp and IDeg across the drug products reflect that in the early stage of development, the potency of IDeg had not yet been established.
- <sup>4</sup> An overage of up to (b) (4) of (b) (4) is added to compensate for potential loss during manufacturing
- <sup>5</sup> Zinc is added (b) (4) Ph Eur, USP, JPE)
- <sup>6</sup> For pH adjustment to reach target pH
- <sup>7</sup> Hydrochloric acid (b) (4) is manufactured (b) (4) Ph Eur, USP, JP)
- <sup>8</sup> Sodium hydroxide (b) (4) is manufactured (b) (4) Ph Eur, USP, JP)

Source: Sponsor report on Summary of Biopharmaceutic Studies and Associated Analytical Methods

**Reviewer's Comment:** In this NDA (b) (4) which will be used for the commercial batch manufacturing. CMC review by Drs Joseph Leginus and Muthukumar Ramaswamy concluded that the comparability has been demonstrated between IDeg (b) (4) produced by different process with respect to (b) (4) Bioequivalence data from NDA 203314 supports the PK/PD comparability between drug product from (b) (4) (b) (4) In addition phase 3 trials in NDA 203314 used both (b) (4) (b) (4) Therefore, we conclude that comparability has been adequately established with respect to the IDeg and hence can be applied to (b) (4) used in the IDegAsp product.

**2.7.1 Is bioequivalence established between the proposed commercial formulation and formulation used in Phase 2 studies?**

Yes. Sponsor conducted trial 1980 to investigate bioequivalence between the IDegAsp 30 (B) and IDegAsp (F) drug products, manufactured with (b) (4) (phase 2) and (b) (4) (phase 3), respectively. Bioequivalence was confirmed for IDeg and IAsp as the 90% CIs for  $AUC_{IAsp,0-12h,SD}$ ,  $C_{max,IAsp}$ ,  $AUC_{IDeg,0-120h}$  and  $C_{max,IDeg}$  were fully within the bioequivalence limits [0.80; 1.25] (**Table 29**)

**Table 29: Bioequivalence of IDegAsp in Healthy Subjects**

| Trial ID | IDegAsp Product                | Dose     | Component | $AUC_{0-t,Ins,SD}$ <sup>1</sup><br>Ratio [90% CI] | $C_{max,Ins,SD}$<br>Ratio [90% CI] |
|----------|--------------------------------|----------|-----------|---------------------------------------------------|------------------------------------|
| 1980     | IDegAsp (F) vs. IDegAsp 30 (B) | 0.5 U/kg | IAsp      | 0.96 [0.93; 0.99]                                 | 1.01 [0.94; 1.09]                  |
|          |                                |          | IDeg      | 1.02 [0.99; 1.06]                                 | 1.00 [0.94; 1.06]                  |

<sup>1</sup> t = 12h for IAsp and t = 120h for IDeg

Ins: Abbreviation for IAsp or IDeg

Source: Sponsor's Summary of Biopharmaceutic Studies and Associated Analytical Methods

**2.8 Analytical**

**2.8.1 How are the active moieties identified and measured in the plasma/serum?**

In this NDA, Insulin aspart (IAsp) and insulin degludec was quantified by a specific sandwich enzyme-linked immuno sorbent assay (ELISA). The assay was validated in human plasma and serum at Novo Nordisk A/S and afterwards at different contract research organizations (CRO).

**2.8.2 What bioanalytical methods are used to assess Insulin Aspart concentrations?**

Insulin aspart (IAsp) was quantified by a specific sandwich enzyme-linked immuno sorbent assay (ELISA) method. The capture antibody coated on the microtitre plate was a monoclonal mouse antibody specific for human insulin (HI) (HUI-018), and the detection antibody, labeled with biotin, was an IAsp specific monoclonal mouse antibody (X14-6-F34).

The assay is specific for IAsp without cross-reactivity to HI, human pro-insulin or human C-peptide

The assay was validated in human plasma and serum at Novo Nordisk A/S (Study 970046) and afterwards at different contract research organizations (CRO) including (b) (4) (Study 970402), (b) (4) (Studies AA444469CH-EB) (b) (4) (Study AA81208), (b) (4) (Study ZZ29614) (b) (4) (Study ZZ32463-01). **Table 30** provides the summary of ELISA assay performance.

**Table 30: Insulin Aspart ELISA Assay Performance in Human Serum**

| Parameter              | Results                                                        | Validation Report             |
|------------------------|----------------------------------------------------------------|-------------------------------|
| Range <sup>1</sup>     | LLOQ = 10 pmol/L                                               | 970046, 970402, AA444469CH-EB |
|                        | ULOQ = 1000 pmol/L                                             |                               |
|                        | LLOQ = 10 pmol/L                                               | ZZ29614, AA81208, ZZ32463-01  |
|                        | ULOQ = 400 pmol/L                                              |                               |
| Accuracy               | Within the limits of 80 - 120%                                 | ZZ29614, AA81208, ZZ32463-01  |
| Dilution linearity     | Dilution up to 40 to 1000 fold within the limits of 80% - 120% | ZZ29614, AA81208, ZZ32463-01  |
| Intermediary precision | Within 20%                                                     | ZZ29614, AA81208, ZZ32463-01  |
| Stability              | 13 months at -20°C                                             | 970046                        |
|                        | 7 cycles of freezing and thawing at -20°C                      |                               |
|                        | 5 cycles of freezing and thawing at -20°C and -80°C            | AA81208, ZZ32463-01           |

LLOQ: Lower limit of quantification  
ULOQ: Upper limit of quantification  
<sup>1</sup> For all trials, the applicable limits were used. The range 10-400 pmol/L was used from phase 3 of the clinical development stage and forward. An overview of validation reports by trial is provided in [Appendix 4.3](#).

Interference in the ELISA was investigated with a series of compounds (**Table 31**), and generally no interference was observed (Study 208206 and 200184). The presence of severe hemolysis (more than 4%) in the samples generates invalid results for the determination of IAsp concentration.

**Table 31: Compounds tested for interference in insulin aspart ELISA**

| Compound tested   | Conclusion                                        | Study number |
|-------------------|---------------------------------------------------|--------------|
| Human insulin     | No interference up to a concentration of 1000 pM  | 970046       |
| Human pro-insulin | No interference up to a concentration of 1000 pM  | 970046       |
| Human C-peptide   | No interference up to a concentration of 1000 pM  | 970046       |
| Insulin degludec  | No interference up to a concentration of 15000 pM | 208206       |
| Insulin detemir   | No interference up to a concentration of 20000 pM | 200184       |
| Insulin glargine  | No interference up to a concentration of 5000 pM  | 208206       |
| Insulin lispro    | No interference up to a concentration of 5000 pM  | 208206       |

### 2.8.3 What bioanalytical methods are used to assess Insulin Degludec concentrations?

IDeg was quantified by a specific sandwich ELISA method. The capture antibody coated on the microtitre plate was a mouse monoclonal antibody specific for HI (HUI 001) and

the detection antibody, labeled with biotin, was an IDeg specific monoclonal mouse antibody (NN-454-1 F31).

The assay is specific for IDeg without cross-reactivity to insulin glargine, insulin detemir, insulin aspart and human insulin. The assay was validated in human serum at Novo Nordisk A/S (Study NN205498) and subsequently at different CROs including (b) (4) (Study NN206373) (b) (4) (Study AA444468CH-EB) (b) (4) (Study AA81207) (b) (4) (Study ZZ29613) and (b) (4) (Study ZZ32462). **Table 32** provides the summary of ELISA assay performance.

| Parameter              | Results                                                         | Validation Report                                  |
|------------------------|-----------------------------------------------------------------|----------------------------------------------------|
| Range <sup>1</sup>     | LLOQ = 32 pmol/L                                                | NN205498, AA444468CH-EB                            |
|                        | ULOQ = 750 pmol/L                                               |                                                    |
|                        | LLOQ = 20 pmol/L                                                | NN206373                                           |
|                        | ULOQ = 750 pmol/L                                               |                                                    |
| Accuracy               | LLOQ = 20 pmol/L                                                | NN206373, ZZ29613, AA81207, Z32462                 |
|                        | ULOQ = 1000 pmol/L                                              |                                                    |
| Accuracy               | Within the limits of acceptance (80%-120% )                     | NN205498, AA444468CH-EB, ZZ29613, AA81207, ZZ32462 |
| Dilution linearity     | Dilution up to 100 to 5000 fold within the limits of 80% - 120% | NN205498, AA81207, ZZ29613, ZZ32462                |
| Intermediary precision | 4.5% - 21.7%                                                    | NN205498                                           |
| Stability              | 2 years at -20°C                                                | NN205532, NN205498                                 |
|                        | 5 cycles of freezing and thawing at -20°C or -80°C <sup>2</sup> |                                                    |
|                        | 139 days at -80°C                                               | AA81207                                            |

LLOQ: Lower limit of quantification  
 ULOQ: Upper limit of quantification  
<sup>1</sup> For any trial, the applicable limits were used. The range 20-1000 pmol/L was used from phase 3 of the clinical development stage and forward. An overview of validation reports by trial is provided in [Appendix 4.3](#).  
<sup>2</sup> 8 cycles of freezing and thawing at -20 °C at (b) (4) study ZZ32462)

Interference in the ELISA was investigated with a series of compounds (**Table 33**), and generally no interference was observed. The presence of severe hemolysis (more than 5%) in the samples generates invalid results for the determination of IDeg concentration.

**Table 33:** Compounds tested for interference in insulin aspart ELISA

| Compound tested   | Conclusion                                        | Study number |
|-------------------|---------------------------------------------------|--------------|
| Human insulin     | No interference up to a concentration of 1000 pM  | 970046       |
| Human pro-insulin | No interference up to a concentration of 1000 pM  | 970046       |
| Human C-peptide   | No interference up to a concentration of 1000 pM  | 970046       |
| Insulin degludec  | No interference up to a concentration of 15000 pM | 208206       |
| Insulin detemir   | No interference up to a concentration of 20000 pM | 200184       |
| Insulin glargine  | No interference up to a concentration of 5000 pM  | 208206       |
| Insulin lispro    | No interference up to a concentration of 5000 pM  | 208206       |

*Reviewer's Comment:* Accepted validation indicates that method met the FDA guidance "Bioanalytical Method Validation" recommendations, and is therefore acceptable.

### **3 DETAILED LABELING RECOMMENDATION**

No labeling recommendations at this time. A separate memo will address the labeling comments later.

## **4 APPENDIX**

### **4.1 INDIVIDUAL STUDY REVIEWS**

Individual will be DARRTed separately as attachment to this review.

## 4.2 OCP FILING MEMO

### CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

| <b>Office of Clinical Pharmacology</b>                                         |                           |                             |                                                                        |                                                                                                                 |
|--------------------------------------------------------------------------------|---------------------------|-----------------------------|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| <i>New Drug Application Filing and Review Form</i>                             |                           |                             |                                                                        |                                                                                                                 |
| <u>General Information About the Submission</u>                                |                           |                             |                                                                        |                                                                                                                 |
|                                                                                | Information               |                             | Information                                                            |                                                                                                                 |
| NDA/BLA Number                                                                 | 203313                    | Brand Name                  | Ryzodeg                                                                |                                                                                                                 |
| OCP Division (I, II, III, IV, V)                                               | DCPII                     | Generic Name                | Insulin degludec/Insulin aspart                                        |                                                                                                                 |
| Medical Division                                                               | DMEP                      | Drug Class                  | Insulin Analog                                                         |                                                                                                                 |
| OCP Reviewer                                                                   | Ritesh Jain               | Indication(s)               | Indicated to improve glycemic control in adults with diabetes mellitus |                                                                                                                 |
| OCP Team Leader (Acting)                                                       | Jayabharathi Vaidyanathan | Dosage Form                 | 100 Units of insulin degludec/insulin aspart per mL (U-100)            |                                                                                                                 |
| Pharmacometrics Reviewer                                                       |                           | Dosing Regimen              | once or twice daily with any main meals                                |                                                                                                                 |
| Date of Submission                                                             | 11/28/2011                | Route of Administration     | subcutaneous                                                           |                                                                                                                 |
| Estimated Due Date of OCP Review                                               | 06/08/2012                | Sponsor                     | Novo Nordisk                                                           |                                                                                                                 |
| Medical Division Due Date                                                      | 07/06/2012                | Priority Classification     | S                                                                      |                                                                                                                 |
| PDUFA Due Date                                                                 | 07/29/2012                |                             |                                                                        |                                                                                                                 |
| <i>Clin. Pharm. and Biopharm. Information</i>                                  |                           |                             |                                                                        |                                                                                                                 |
|                                                                                | "X" if included at filing | Number of studies submitted | Number of studies reviewed                                             | Critical Comments If any                                                                                        |
| STUDY TYPE                                                                     |                           |                             |                                                                        |                                                                                                                 |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                         |                             |                                                                        |                                                                                                                 |
| Tabular Listing of All Human Studies                                           | X                         |                             |                                                                        |                                                                                                                 |
| HPK Summary                                                                    | X                         |                             |                                                                        |                                                                                                                 |
| Labeling                                                                       | X                         |                             |                                                                        |                                                                                                                 |
| Reference Bioanalytical and Analytical Methods                                 | X                         |                             |                                                                        |                                                                                                                 |
| I. Clinical Pharmacology                                                       |                           |                             |                                                                        |                                                                                                                 |
| Mass balance:                                                                  |                           |                             |                                                                        |                                                                                                                 |
| Isozyme characterization:                                                      |                           |                             |                                                                        |                                                                                                                 |
| Blood/plasma ratio:                                                            |                           |                             |                                                                        |                                                                                                                 |
| Plasma protein binding:                                                        | X                         | 4                           |                                                                        | Studies: 208378, 208523, CES 10-January-2008, CES 01-May-2007                                                   |
| Pharmacokinetics (e.g., Phase I) -                                             | X                         |                             |                                                                        |                                                                                                                 |
| Healthy Volunteers-                                                            |                           |                             |                                                                        |                                                                                                                 |
| single dose:                                                                   | X                         | 1                           |                                                                        | Study: NN5401-1980                                                                                              |
| multiple dose:                                                                 |                           |                             |                                                                        |                                                                                                                 |
| Patients-                                                                      |                           |                             |                                                                        |                                                                                                                 |
| single dose:                                                                   | X                         | 8                           |                                                                        | Studies: NN5401-1959, NN5401-1977, NN5401-1981, NN5401-1982, NN5401-1983, NN5401-3539, NN5401-3857, NN5401-1978 |
| multiple dose:                                                                 |                           |                             |                                                                        |                                                                                                                 |

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Reference ID: 3046386

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|                                                                   |   |    |  |                                                                                                                 |
|-------------------------------------------------------------------|---|----|--|-----------------------------------------------------------------------------------------------------------------|
| <b>Dose proportionality -</b>                                     |   |    |  |                                                                                                                 |
| fasting / non-fasting single dose:                                |   |    |  |                                                                                                                 |
| fasting / non-fasting multiple dose:                              |   |    |  |                                                                                                                 |
| <b>Drug-drug interaction studies -</b>                            |   |    |  |                                                                                                                 |
| In-vivo effects on primary drug:                                  | X |    |  |                                                                                                                 |
| In-vivo effects of primary drug:                                  |   |    |  |                                                                                                                 |
| In-vitro:                                                         | X | 3  |  | 207440, CES 20-January-2009, CES 101123                                                                         |
| <b>Subpopulation studies -</b>                                    |   |    |  |                                                                                                                 |
| ethnicity:                                                        | X | 1  |  | Study: NN5401-1983<br>Single dose PK/PD study in Japanese Subjects                                              |
| gender:                                                           |   |    |  |                                                                                                                 |
| pediatrics:                                                       | X | 1  |  | Study: NN5401-1982 Single dose PK/PD study in Pediatric Subjects                                                |
| geriatrics:                                                       | X | 1  |  | Study: NN5401-1981, Single dose PK/PD study in Geriatric subjects                                               |
| renal impairment:                                                 |   |    |  |                                                                                                                 |
| hepatic impairment:                                               |   |    |  |                                                                                                                 |
| <b>PD -</b>                                                       |   |    |  |                                                                                                                 |
| Phase 2:                                                          |   |    |  |                                                                                                                 |
| Phase 3:                                                          |   |    |  |                                                                                                                 |
| <b>PK/PD -</b>                                                    |   |    |  |                                                                                                                 |
| Phase 1 and/or 2, proof of concept:                               | X | 8  |  | Studies: NN5401-1959, NN5401-1977, NN5401-1981, NN5401-1980, NN5401-1983, NN5401-3539, NN5401-3857, NN5401-1978 |
| Phase 3 clinical trial:                                           |   |    |  |                                                                                                                 |
| <b>Population Analyses -</b>                                      |   |    |  |                                                                                                                 |
| Data rich:                                                        |   |    |  |                                                                                                                 |
| Data sparse:                                                      |   |    |  |                                                                                                                 |
| <b>II. Biopharmaceutics</b>                                       |   |    |  |                                                                                                                 |
| <b>Absolute bioavailability</b>                                   |   |    |  |                                                                                                                 |
| <b>Relative bioavailability -</b>                                 |   |    |  |                                                                                                                 |
| solution as reference:                                            |   |    |  |                                                                                                                 |
| alternate formulation as reference:                               |   |    |  |                                                                                                                 |
| <b>Bioequivalence studies -</b>                                   |   |    |  |                                                                                                                 |
| traditional design; single / multi dose:                          | X | 1  |  | Study: NN5401-1980                                                                                              |
| replicate design; single / multi dose:                            |   |    |  |                                                                                                                 |
| <b>Food-drug interaction studies</b>                              |   |    |  |                                                                                                                 |
| <b>Bio-waiver request based on BCS</b>                            |   |    |  |                                                                                                                 |
| <b>BCS class</b>                                                  |   |    |  |                                                                                                                 |
| <b>Dissolution study to evaluate alcohol induced dose-dumping</b> |   |    |  |                                                                                                                 |
| <b>III. Other CPB Studies</b>                                     |   |    |  |                                                                                                                 |
| <b>Genotype/phenotype studies</b>                                 |   |    |  |                                                                                                                 |
| <b>Chronopharmacokinetics</b>                                     |   |    |  |                                                                                                                 |
| <b>Pediatric development plan</b>                                 |   |    |  |                                                                                                                 |
|                                                                   | X |    |  |                                                                                                                 |
| <b>Literature References</b>                                      |   |    |  |                                                                                                                 |
| <b>Total Number of Studies</b>                                    |   | 16 |  |                                                                                                                 |

On **initial** review of the NDA/BLA application for filing:

|                                           | Content Parameter                          | Yes | No | N/A | Comment                              |
|-------------------------------------------|--------------------------------------------|-----|----|-----|--------------------------------------|
| <b>Criteria for Refusal to File (RTF)</b> |                                            |     |    |     |                                      |
| 1                                         | Has the applicant submitted bioequivalence |     |    | X   | Sponsor used the same formulation in |

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|                                                                                     |                                                                                                                                                                                                       |   |  |   |                                                                  |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|------------------------------------------------------------------|
|                                                                                     | data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?                                                                                                               |   |  |   | their pivotal clinical trial as to be marketed formulation.      |
| 2                                                                                   | Has the applicant provided metabolism and drug-drug interaction information?                                                                                                                          | X |  |   |                                                                  |
| 3                                                                                   | Has the sponsor submitted bioavailability data satisfying the CFR requirements?                                                                                                                       | X |  |   |                                                                  |
| 4                                                                                   | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?                                                                                                          | X |  |   |                                                                  |
| 5                                                                                   | Has a rationale for dose selection been submitted?                                                                                                                                                    | X |  |   |                                                                  |
| 6                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?                                               | X |  |   |                                                                  |
| 7                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?                                                                                  | X |  |   |                                                                  |
| 8                                                                                   | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?                                                                                              | X |  |   |                                                                  |
| <b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b> |                                                                                                                                                                                                       |   |  |   |                                                                  |
| <b>Data</b>                                                                         |                                                                                                                                                                                                       |   |  |   |                                                                  |
| 9                                                                                   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?                                                                                 | X |  |   |                                                                  |
| 10                                                                                  | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?                                                                                                                 |   |  | X |                                                                  |
| <b>Studies and Analyses</b>                                                         |                                                                                                                                                                                                       |   |  |   |                                                                  |
| 11                                                                                  | Is the appropriate pharmacokinetic information submitted?                                                                                                                                             | X |  |   |                                                                  |
| 12                                                                                  | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X |  |   |                                                                  |
| 13                                                                                  | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?                                            |   |  | X |                                                                  |
| 14                                                                                  | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the           |   |  | X | Insulin dose is titrated up and down based on the patients need. |

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|                |                                                                                                                                                                             |   |  |   |                                                                                                                             |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|-----------------------------------------------------------------------------------------------------------------------------|
|                | pharmacokinetic or pharmacodynamics?                                                                                                                                        |   |  |   |                                                                                                                             |
| 15             | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?                                                    | X |  |   | FDA agreed with partial waiver in pediatric patients less than one year of age (correspondence dated 3/21/2011).<br>(b) (4) |
| 16             | Did the applicant submit all the pediatric exclusivity data, as described in the WR?                                                                                        |   |  | X |                                                                                                                             |
| 17             | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?                                              | X |  |   |                                                                                                                             |
| <b>General</b> |                                                                                                                                                                             |   |  |   |                                                                                                                             |
| 18             | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X |  |   |                                                                                                                             |
| 19             | Was the translation (of study reports or other study information) from another language needed and provided in this submission?                                             | X |  |   |                                                                                                                             |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?**  
**YES, the Clinical Pharmacology section of the application is fileable.**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**From Clinical Pharmacology there are no comments for 74-day letter**

Ritesh Jain 11/16/2011

\_\_\_\_\_  
 Reviewing Clinical Pharmacologist Date

Jayabharathi Vaidyanathan 11/16/2011

\_\_\_\_\_  
 Team Leader/Supervisor Date

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for  
 NDA\_BLA or Supplement 090808

Reference ID: 3046386

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

### Filing Memo (Internal Memo)

#### **1. Background**

Insulin degludec/insulin aspart (IDegAsp; 70/30) is a co-formulation of insulin degludec (IDeg) and insulin aspart (IAsp) :

- Insulin degludec: a new-generation, ultra-long acting basal insulin modified such that the amino acid (b)(4) threonine in position B30 of human insulin has been omitted, and the ε amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer.
- Insulin aspart (B28Asp human insulin): a well characterized fast-acting prandial insulin with global market experience since approval by the European Medicines Agency (EMA) in 1999 (NovoRapid®) and by the Food and Drug Administration (FDA) in 2000 (NovoLog®).

The IDegAsp consists of 30% IAsp and 70% IDeg. The co-formulated product is intended for subcutaneous (S.C.) injection for once or twice daily dosing at any main meal, and indicated to improve glycemic control in adults with diabetes mellitus. The formulation of IDegAsp has been optimized such that the individual components do not interact, with IAsp present as soluble and stable hexamers and IDeg as soluble and stable di-hexamers. Once injected into the subcutaneous tissue the IAsp hexamers immediately form monomers which are rapidly absorbed into the capillaries while the IDeg di-hexamers form soluble multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. IDegAsp is developed in a 100 unit (U)/mL strength for subcutaneous injection, provided in a prefilled pen injector with a dose range of 1-80 U per injection in one-unit increments (b)(4). Sponsor used the similar formulation in their pivotal clinical trial as to be marketed formulation and there are no pivotal BE studies.

From Clinical Pharmacology there are no comments for 74-day letter. In addition, Clinical Pharmacology requests no DSI inspection.

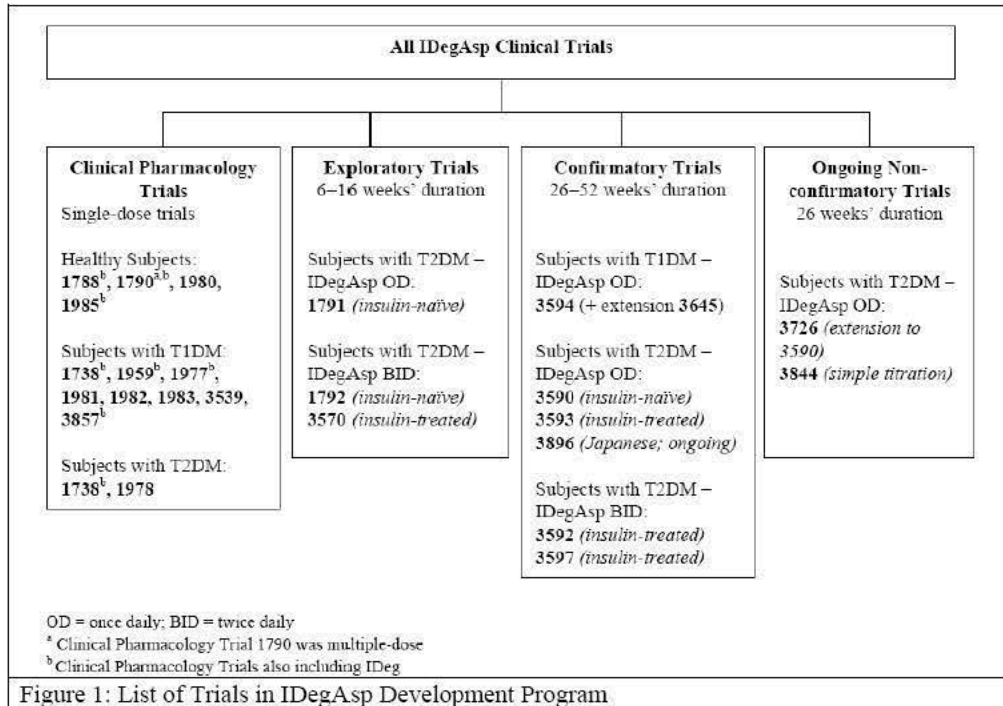
#### **2. Clinical Development Program:**

The completed clinical development program for IDegAsp comprises 13 clinical pharmacology trials, 3 therapeutic exploratory trials of 6–16 weeks duration, 5 therapeutic confirmatory trials of 26 weeks duration and one completed therapeutic confirmatory, 26-week extension trial. Figure 1 shows the lists of clinical trials in IDegAsp development program.

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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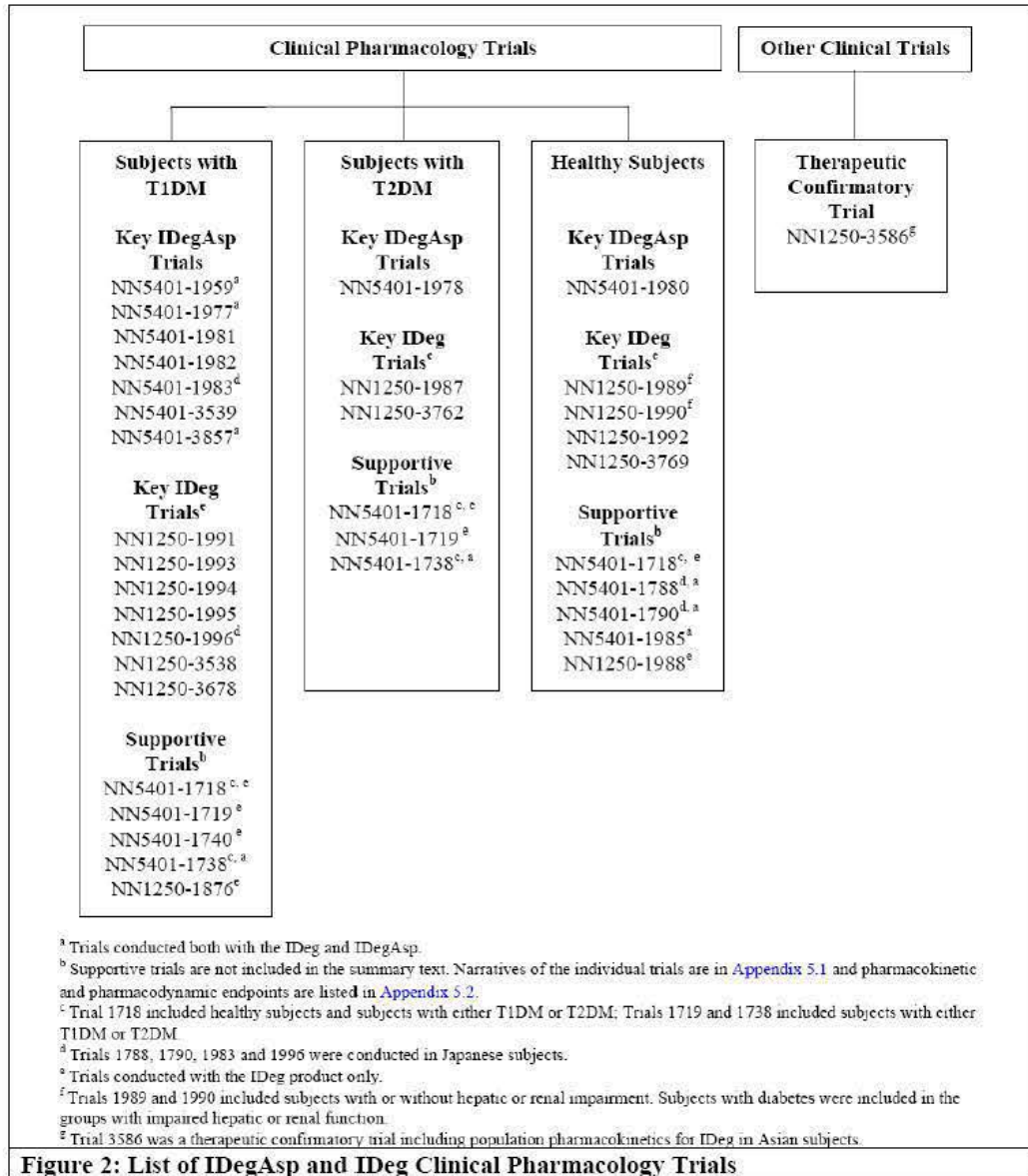
**3. Clinical Pharmacology Program:**

The clinical pharmacology program included 31 trials with IDegAsp (13 trials, 7 of which also included IDeg) or with IDeg alone (18 trials), see Figure 2. A list and brief descriptions of the individual key clinical pharmacology trials for this IDegAsp NDA is shown in Figure 3.

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

The Clinical Pharmacology Program Consists of 9 Key Studies:

| Trial ID                                    | Trial Design         | Trial Objectives                                                                                           | Treatment                                                                                                           |
|---------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| <b>IDegAsp Trials in Subjects with T1DM</b> |                      |                                                                                                            |                                                                                                                     |
| NN5401-1959                                 | RND, DB, CO, SD, INB | PK and PD of IAsp and IDeg when co-formulated in IDegAsp                                                   | IDegAsp: 0.92 U/kg<br>(0.28 U/kg IAsp + 0.64 U/kg IDeg)<br>IDeg: 0.64 U/kg + IAsp: 0.28 U/kg<br>BIAsp 30: 0.64 U/kg |
| NN5401-1977                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                                 | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| NN5401-1981                                 | RND, DB, CO, SD      | PK and PD in geriatric subjects and younger adult subjects                                                 | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-1982                                 | OL, PG, SD           | PK and safety profile in children, adolescents and adults                                                  | IDegAsp: 0.5 U/kg                                                                                                   |
| NN5401-1983                                 | RND, DB, CO, SD      | PK and PD in Japanese subjects                                                                             | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-3539                                 | RND, DB, INB, CO, SD | PK and PD (dose-response)                                                                                  | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| NN5401-3857                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                                 | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| <b>IDegAsp Trial in Subjects with T2DM</b>  |                      |                                                                                                            |                                                                                                                     |
| NN5401-1978                                 | RND, DB, INB, CO, SD | PK and PD (dose-response)                                                                                  | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| <b>IDegAsp Trial in Healthy Subjects</b>    |                      |                                                                                                            |                                                                                                                     |
| NN5401-1980                                 | RND, DB, CO, SD, BE  | BE between two IDeg products with identical formulations, and different drug substance manufacturing sites | IDegAsp: 0.5 U/kg                                                                                                   |

**Figure 3: Key Clinical Pharmacology Trials in IDegAsp Development Program**

### Potential Key Review Questions

- What are the PK and PD features of IDegAsp in T1DM and T2DM subjects?
- What are the effects of Intrinsic and Extrinsic Factors on PK/PD?
- Are PK and PD bioassay methods and their validation procedures adequate?
- Assessment of product distinctiveness when IDegAsp is given as premix or as individual IDeg and IAsp.
- Is BID dosing in T1DM subjects justified.

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11/17/2011

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RITESH JAIN  
06/15/2012

JAYABHARATHI VAIDYANATHAN  
06/15/2012

## CLINICAL PHARMACOLOGY REVIEW

|                                            |                                                                                                                  |
|--------------------------------------------|------------------------------------------------------------------------------------------------------------------|
| NDA: 203314                                | Submission Date(s): 09/29/2011                                                                                   |
| Brand Name                                 | Tresiba®                                                                                                         |
| Generic Name                               | Insulin Degludec (NN1250)                                                                                        |
| Clinical Pharmacology Reviewer             | Manoj Khurana, Ph.D.                                                                                             |
| Clinical Pharmacology Team Leader (Acting) | Jayabharathi Vaidyanathan, Ph.D.                                                                                 |
| OCP Division                               | Clinical Pharmacology -2                                                                                         |
| OND division                               | Metabolic and Endocrine Products                                                                                 |
| Sponsor                                    | Novo-Nordisk                                                                                                     |
| Submission Type; Code                      | NDA 505(b)(1); Standard                                                                                          |
| Formulation; Strength(s)                   | Solution for Subcutaneous (SC) Injection                                                                         |
| Proposed Indication                        | An ultra-long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus |

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## 1 Executive Summary

### 1.1 Recommendation

The Office of Clinical Pharmacology/Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the clinical pharmacology data submitted in support of NDA 203314 for Insulin Degludec (Tresiba®), found it acceptable, and recommend approval.

Required Office Level OCP briefing was held on 06/13/2012. Attendees included (but not limited to) Chandrahas Sahajwalla, Mehul Mehta, Nam Atiqur Rahman, Hae Young Ahn, Kevin Krudys, Nitin Mehrotra, Jeffry Florian, Vikram Arya, David Lee, Johnny Lau, Sang Chung, Immo Zadezensky, Ritesh Jain, and Jayabharathi Vaidyanathan from Office of Clinical Pharmacology, and Jean-Marc Guettier, Karim Calis, and Mary Parks from Office of New Drugs.

### 1.2 Phase IV Commitments

None

### 1.3 Summary of Important Clinical Pharmacology Findings

Novo Nordisk is seeking approval of Insulin degludec (proposed trade name: Tresiba®; IDeg, NN1250), a basal human insulin analog for the treatment of diabetes mellitus. IDeg is intended for treatment of diabetes mellitus, and is proposed to be administered once-daily at any time of the day, independent of meals, and can be injected subcutaneously (s.c.) in the thigh, the upper arm or the abdominal wall. IDeg is developed to cover basal insulin needs in patients with diabetes mellitus from early to late stages of the disease, either alone or in combination with bolus insulin as well as oral antidiabetic drugs (OADs). When needed, the patient has the option of changing the once daily injection time from day-to-day.

IDeg is available as clear and colorless solutions in two strengths:

- IDeg 100 U/ml (Insulin degludec 600 nmol/mL): Intended to be marketed (b) (4) as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialed in 1U increments.
- IDeg 200 U/ml, (Insulin degludec 1200 nmol/mL). Intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialed in 2U increments.

For patients with type 2 diabetes mellitus, the recommended daily starting dose of IDeg is 10 units, followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, IDeg is to be used once daily with mealtime insulin and requires individualized initiation dose, and subsequent individual dosage adjustments.

The clinical development program for IDeg comprises 41 completed clinical trials; 25 clinical pharmacology trials (7 of which include both IDeg and IDegAsp [70:30 premix of IDeg and Insulin Aspart, respectively]), 3 therapeutic exploratory trials, 11 therapeutic confirmatory trials, and 2 trials in the category 'other therapeutic trials'. The formulation of the IDeg drug products used in the phase 2 and 3a development programs is identical to the proposed commercial formulation.

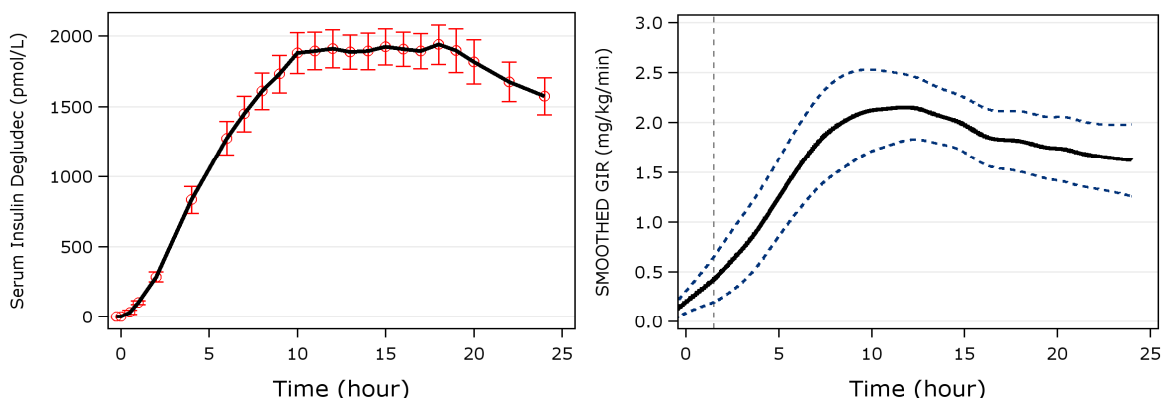
The therapeutic confirmatory program investigated the efficacy and safety of IDeg in subjects with T1DM and T2DM in combination with bolus insulin, and in both insulin-naïve and previously insulin-treated subjects with T2DM in combination with OADs.

The efficacy and safety of IDeg was investigated as once-daily (QD) treatment and as a three-times-weekly (3TW) dosing regimen. While clinically relevant improvement in glycosylated hemoglobin (HbA1c) was demonstrated with IDeg 3TW, non-inferiority versus IGLar QD was not confirmed for the primary endpoint. Therefore, the sponsor is not pursuing the 3TW dosing regimen for IDeg. The IDeg 3TW trials are included in the overall assessment of safety, and key results related to efficacy and dosing are included in the submission for completeness.

The clinical pharmacology evaluation included characterization of PK and PD profile after single dose in healthy, both single and multiple daily dose in subjects with Type 1 DM and Type 2 DM. The intrinsic factors included PK or PK/PD characterization in pediatric subjects (children and adolescents), geriatric subjects, and subjects of different ethnic origin. Injection site variation and in vitro DDI potential were evaluated among extrinsic factors.

**Summary of PK and PD (GIR; Time-action) Evaluation of IDeg:**

The single dose (0.4 U/kg) PK profile from proposed commercial formulation (U100, IM2) demonstrated protracted absorption of IDeg and primarily absorption driven PK. The associated mean glucose infusion rate (GIR)-time profile did not show a prominent peak over the 24 hour euglycemic clamp duration.



Initial 24 h Mean(SE) Insulin Degludec and Mean (95 % CI) Glucose Infusion Rate - Time Plots (0.4 U/kg Single SC Dose of IDeg; Trial 1250-3769)

**Figure 1 Mean (SE) IDeg pharmacokinetic (Top) and mean (95%CI) pharmacodynamic (GIR-time; Time-action) profile (Bottom), observed after single subcutaneous dose of 0.4 U/kg (2.4 nmol/kg) in healthy subjects**

GIR gradually deviated from baseline, exceeding by >10% of the maximum value from baseline at around 1.5 hours indicating slow onset, reaching a plateau by around 10 hours, and did not return to baseline during the 24 hour duration of clamp, indicating nearly flat time action profile and >24h duration of action after single SC administration. Collectively, both PK and PD profiles supported the use of IDeg as basal insulin in once daily regimen.

The PK profile was consistent between healthy, Type 1 and Type 2 diabetic subjects. The mean IDeg apparent clearance was 0.03 L/hr/kg (2.1 L/h in 70 kg individual) and apparent volume of distribution was 0.7 L/kg (49 L in 70 kg individual) after a single subcutaneous dose of 0.4 U/kg. IDeg demonstrated slow absorption into the systemic circulation, with maximum mean serum concentrations of 2000 pmol/L achieved at around 14 hour median  $t_{max}$ . The IDeg concentrations declined in a monoexponential fashion with elimination half-life of 17 hr. Even with uncertainty in the estimation due to over-dilution in intravenous fluids, elimination of IDeg after intravenous administration appeared to be rapid ( $t_{1/2}$  ~5 hr), suggesting that IDeg PK is primarily driven by absorption (flip-flop pharmacokinetics) after subcutaneous administration.

In all three groups, the slow appearance rate of IDeg in systemic circulation was associated with a gradually rising PD response (measured by GIR), which reached a plateau by around 10 hours, and did not return to baseline during the 24/26 hour duration of clamp. However, the magnitude of PD response appeared to decrease in the order of healthy>Type 1 DM>Type 2DM. The average GIR<sub>max</sub> was 2.8, 1.7, and 1.2 mg/kg/min from 2.4, 3.0, and 3.5 nmol/kg dose of IDeg in healthy, Type 1 DM, and Type 2 DM subjects, respectively. The average total glucose utilization (AUCGIR<sub>0-24h</sub>) translated as 5, 3, and 2 g glucose utilization over 24 hour per Unit IDeg dose in a representative 70 kg healthy individual, Type 1, and Type 2 DM patient, respectively.

The dose-proportionality assessment at steady state revealed that the IDeg exposure increased in proportion to the increase in dose over 0.4 U/kg to 0.8 U/kg after multiple once daily subcutaneous administrations. The accumulation ratio ( $R_A$ ) equaled 2, after multiple once daily subcutaneous administrations consistent with observed mean terminal half-life of 17 hr. The PD response measured at steady state was more or less proportional over the tested dose range of 0.4 U/kg to 0.8 U/kg in both Type 1 DM and Type 2 DM subjects, though dose-response relationship was shallower (numerically lower response/unit dose) in Type 2 DM than that of Type 1 DM subjects.

Molar dose ratio in comparison to Insulin Glargine (IGlar) was 0.3 after single dose and 1 at steady-state. Despite of the fact that single-dose comparison underestimated the total PD response of IDeg due to >24 h duration of action, the data demonstrates that after very first dose in a 1:1 switch from IGlar, equivalent response cannot be expected from a similar unit dose of IDeg over initial 24 hours. However, this difference will dissipate after 2-3 QD administrations of IDeg.

IDeg demonstrated low within-subject variability in PK and PD parameters when evaluated at 0.4 U/kg dose in subjects with Type 1 DM.

#### **Summary of Intrinsic Factors:**

***Body Weight, BMI, Gender:*** Across the PK and PK/PD studies, body weight based dosing (U/kg) and glucose infusion rates (mg/kg/min) were utilized, under the established understanding that both insulin exposure and glycemic response are influenced linearly by the body weight. Only body weight was found to influence the systemic IDeg exposure in Phase 3 trial, which utilized Unit based doses. Body weight also drives the total IDeg dose requirements in both Type 1 and Type 2 DM patients in Phase 3 clinical evaluation. Although BMI had minor effect on systemic exposure of IDeg, however, PD response decreased with increase in BMI. There was a distinct increase in insulin dose requirement with increase in BMI, especially in Type 2 DM patients. Gender had no clinically relevant effect on IDeg dosing, when corrected for body weight.

The effect of various other intrinsic factors are presented in the forest plots in Figures 2 and 3. The 90% confidence intervals and mean ratio was derived using general linear mixed model in SAS.

#### **Age:**

***Geriatric versus Young Adults (PK and PD):*** IDeg PK profile was comparable among young adults and geriatric subjects. Despite of comparable PK profile, geriatric subjects exhibited lower average PD response as compared to young adults. However, the statistical analysis did not reach significance, as 90% CIs for the mean ratio were wide and contained one, reflecting greater variability in PD response among geriatric subjects (~44% CV for AUCGIR,tau and GIR<sub>max</sub>) than young adults (33%CV for AUCGIR,tau and GIR<sub>max</sub>).

#### **Children, Adolescents, and Adults (PK Only):**

(b) (4)

**Race/Ethnicity:** IDeg PK profile was comparable among subjects of different race/ethnic origin. Despite of comparable PK profile, black subjects exhibited significantly lower AUCGIR,tau,ss response (36%) as compared to white subjects (not Hispanic/Latino). The GIRmax was 33% lower but the 90% CI contained 1. White subjects of Hispanic/Latino origin showed 47% and 32% higher AUCGIR and GIRmax, respectively than the non-Hispanic/Latino White subjects. However, the statistical analysis did not reach significance as 90% CIs for the mean ratio were wide and contained 1, reflecting greater variability in PD response among these subjects.

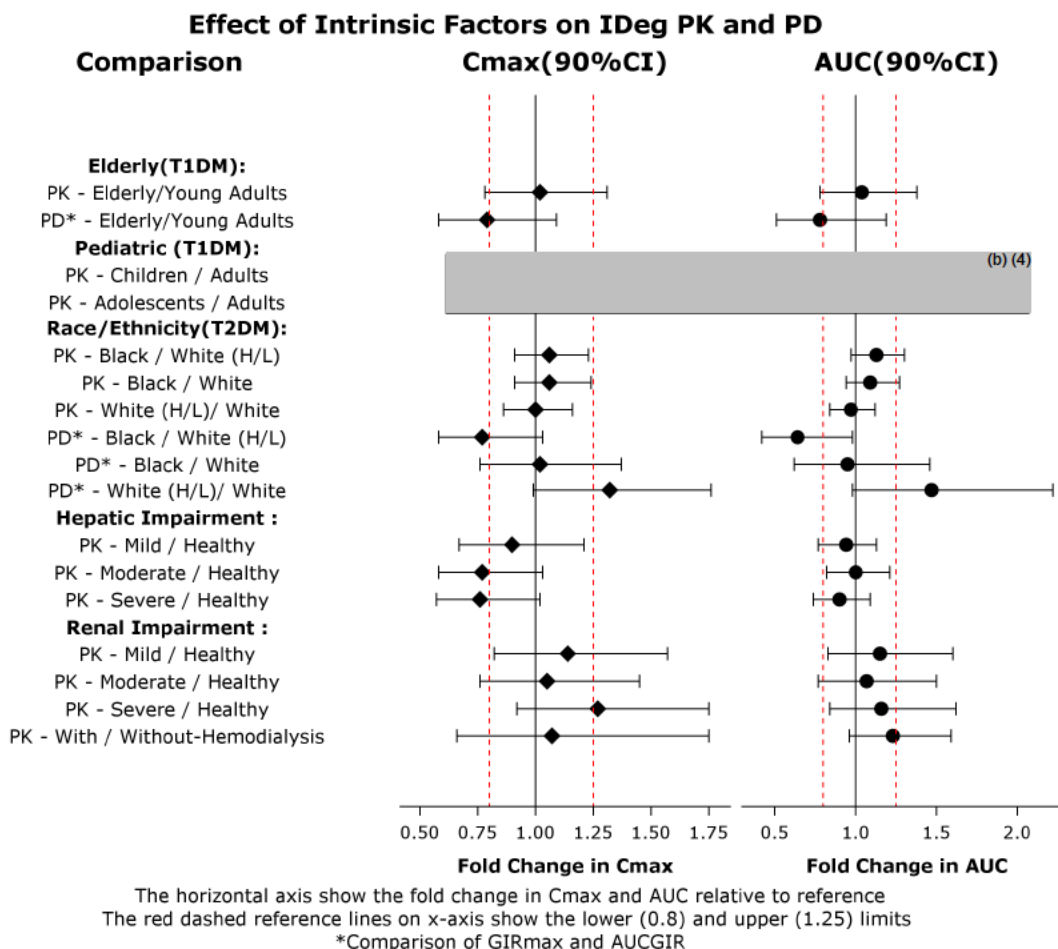


**Figure 2 Effect of Intrinsic Factors on IDeg PK and PD**

**Renal Impairment:** There was slight, albeit statistically insignificant, trend of decreased in IDeg clearance with decrease in creatinine clearance. Accordingly, the total IDeg exposures showed increasing trend with severity of renal impairment. The influence of hemodialysis on IDeg PK was minimal, which also means that the removal of IDeg with hemodialysis is unlikely. Considering that there were more hypoglycemic episodes (blood glucose values < 70 mg/dL) in the severe renal impairment category, general caution is recommended during initiation of IDeg in patients with renal impairment along with frequent glucose monitoring, until a stable dose is established.

**Hepatic Impairment:** The total IDeg exposures were statistically lower in moderate and severe hepatic impairment subjects than in subjects with normal hepatic function. Peak exposure to IDeg was statistically lower and magnitude of decrease was higher with increasing degree of hepatic impairment. Renal clearance of IDeg was negligible in these patients. However, as with all insulin products, IDeg should be initiated with caution in patients with hepatic impairment with frequent glucose monitoring, and dosage should be adjusted on an individual basis.

### **Summary of Extrinsic Factors:**

**Impact of different injection sites on PK and PD:** Subcutaneous administration of IDeg at abdomen and deltoid area results in about 7% higher total exposure of IDeg in comparison to thigh. Peak exposure was 23% and 27% higher from abdomen and deltoid area than thigh. Intramuscular administration yielded 60% higher peak exposure, however, only 7% higher total exposure than subcutaneous administration at thigh. Mean apparent clearance was same for this comparison with a corresponding decrease in apparent volume of distribution, and roughly, reduction in t<sub>1/2</sub> by 50%. T<sub>max</sub> was comparable from the four sites. Following the pattern of PK changes, PD parameters GIR<sub>max</sub> and AUCGIR<sub>0-24h</sub> showed comparable mean values. However, in comparison to subcutaneous administration at thigh, the magnitude of inter-individual variability (%CV) was higher from subcutaneous administration from abdomen and deltoid area, as well as from intramuscular administration at thigh. Notably, thigh was the principal site of administration in most of the clinical pharmacology evaluations. These findings support the sponsor's proposed use of thigh, abdomen, or deltoid area and within site rotation for subcutaneous IDeg administration. IDeg should not be administered as intramuscular injection due to altered time-action profile from this route and lack of safety and efficacy evaluation. However, in the event of accidental/suspected intramuscular administration during the clinical use, frequent monitoring of blood glucose is recommended, as there is a tendency of higher percentage of subjects being at higher GIR<sub>max</sub> in comparison to the subcutaneous route, which may increase the risk of hypoglycemia.

**Drug-drug Interactions:** Minor impact of IDeg on CYP expression in animal models was similar to that observed for human insulin. Therefore, DDI potential, if any, is expected to be similar to that of regular human insulin. The following drugs are unlikely to affect IDeg binding to human serum albumin at therapeutically/physiologically relevant concentrations:

- common protein-bound drugs: warfarin, acetylsalicylate, salicylate, and ibuprofen
- frequently used antidiabetic agents: sitagliptin, glimepiride, metformin,
- liraglutide, and
- the long-chain fatty acids: palmitate, oleate and linoleate

The *in vitro* DDI findings do not warrant for any further *in vivo* evaluation.

### **PK and PD Comparability of formulations:**

All therapeutic confirmatory trial utilized the proposed commercial formulations (U100 and U200). Therefore, the PK and PD comparison is supportive in nature.

**U100 Phase 2 versus Phase 3 Formulation:** PK and PD comparability was established between U100 Phase 2 (IDeg E) and Phase 3 (IDeg M) formulations, based on statistical evaluation of primary end points AUC<sub>0-120h</sub> and C<sub>max</sub>, and post-hoc in-house analysis by this reviewer of secondary endpoints: partial AUC<sub>0-24</sub>, GIRAUC<sub>0-24</sub>, and GIR<sub>max</sub>.

**U100 Phase 3 Formulation Before (IM1) and After (IM2) process optimization:** PK and PD comparability was established between U100 Phase 3 formulations, based on statistical evaluation of primary end points AUC<sub>0-120h</sub> and C<sub>max</sub>, and post-hoc in-house analysis by this reviewer of secondary endpoints: partial AUC<sub>0-24</sub>, GIRAUC<sub>0-24</sub>, and GIR<sub>max</sub>.

***U200 versus U100 Phase 3 Formulation:*** The U200 and U100 formulations cannot be regarded to have comparable PK and PD profile. Apparently, due to injection volume difference, the U200 formulation has a distinct absorption profile with lower amplitude of concentration and GIR versus time profile over 24 hour dosing interval, and thus demonstrates even lesser prominent peak than U100 after single and multiple once-daily doses. However, the available data establishes that difference in the PK and PD profile at steady-state may not be clinically meaningful in both Type 1DM and Type 2 DM subjects.

**Bioanalytical Methods:**

For the clinical pharmacology assessments, degludec was quantitated in serum and other biological fluids by a specific sandwich enzyme-linked immunosorbent assay (ELISA). The capture antibody was a mouse monoclonal antibody specific for HI (HUI 001) and the detection antibody was a biotin-labeled monoclonal mouse antibody (NN-454-1 F31) specific for IDeg. The ELISA was found to be valid for analyzing IDeg in serum, urine, and dialysis fluid samples regarding accuracy, linearity, intermediary precision, sensitivity, and stability. The storage stability was demonstrated for a maximum period of two years with no decrease in the measured degludec concentrations. There was no interference from other insulins and liraglutide up to 5000 pM level.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes

#### 2.1.1 What are the desired attributes and therapeutic utility of basal insulin like the proposed Insulin Degludec?

In human biological system, both glucose and insulin levels are regulated by the interaction of a multitude of substrates and hormones. Thus, endogenous insulin levels are typically not a simple reflection of blood glucose concentration and vice versa. Insulin-glucose co-regulation presents a unique picture of exposure-response in the sense that each could become an independent variable to drive the response for the other variable. Under normal physiological condition, insulin secretion is a result of the stimulatory response of the pancreatic beta cells to a substrate such as glucose after meal ingestion. However, between meals, insulin levels do not simply fall to zero. Rather, they decline to a low measurable level, referred to as “*basal*” level, which are maintained within a very narrow range. During a fast, there is a further slow parallel decline of glucose and insulin, suggesting the mutual control of insulin and glucose due to the presence of a direct feedback control mechanism for basal insulin secretion by glucose, and the delicate nature of glucose-homeostasis.

Under therapeutic use situation, the variables are reversed as insulin is administered exogenously to control plasma glucose. Therefore, insulin product design is geared towards mimicking the endogenous insulin secretion to optimize glucose control, and thus the therapeutic use (**Figure 3**).

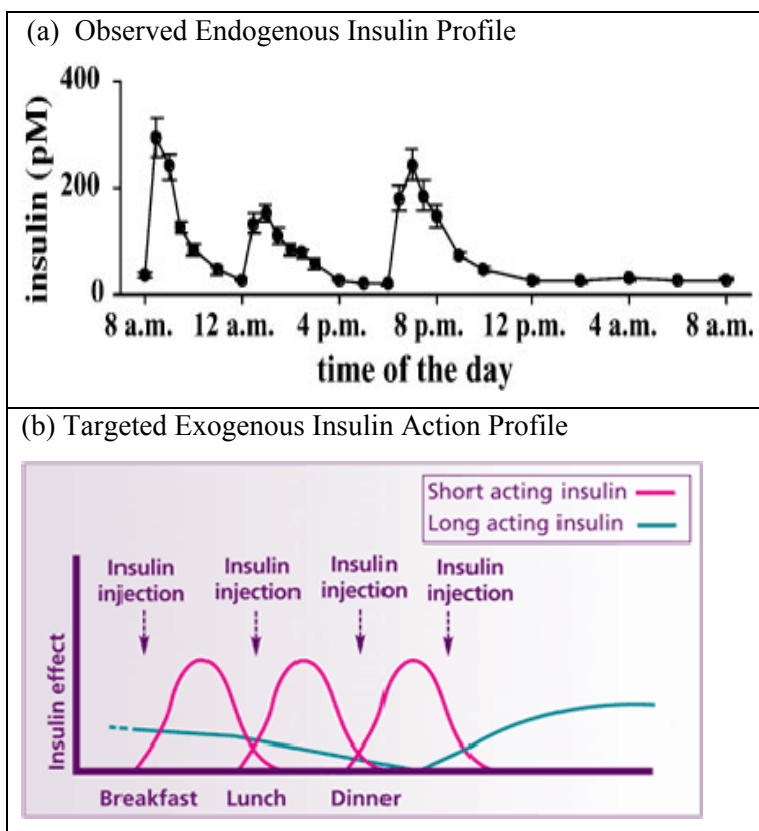


**Figure 3** Therapeutic objective drives the insulin product design – emphasis on time action profile

For simplification, there are two broad insulin product categories: *bolus* and *basal*, which is primarily based on the nature of PK/PD (or PK) profile and intended therapeutic use. *Bolus* insulin is designed to rapidly achieve high insulin levels over a short time duration (as seen after meal ingestion; thus *short-acting*) to provide control over plasma glucose excursion resulting from a meal (post-prandial), also referred to as *mealtime* insulin. Whereas, *basal* insulin is designed to achieve rather flat (peakless) insulin levels over longer time duration (to approximate physiologic basal insulin secretion; thus *long-acting*) and provide control over fasting plasma glucose.

Similar to the actions of endogenous insulin, the pharmacological action of exogenously administered insulin displays dual capability of shutting down endogenous hepatic glucose production and stimulation of peripheral glucose utilization, regardless of category<sup>1,2</sup>. However, the fact that EC<sub>50</sub> for suppression of glucose production is roughly half of that required for stimulation of glucose utilization for human insulin (greater sensitivity of hepatic glucose production towards circulating insulin levels)<sup>1</sup>, has allowed to attain different therapeutic utility for bolus and basal insulin products, based on the differences in the systemic insulin levels achieved.

The use of both mealtime and basal insulin as a regimen, generally referred to as “*basal-bolus*” therapy, is now standard of care for Type 1 diabetic patients. There is increased recognition of the use of insulin therapy in patients with type 2 diabetes, as with the progression of disease most patients eventually require insulin to maintain glucose control. However, there is heavy debate on the timing of initiation of insulin therapy as well as its intensity in Type 2 DM amid the results of several long-term outcome trials: U.K. Prospective Diabetes Study (UKPDS), ACCORD, ADVANCE and VADT<sup>3</sup>. Broadly, there are two schools of thoughts: one favoring the initiation in early stages with intensive insulin therapy<sup>4</sup> while others favoring the use in later stages when there is absolute deficiency<sup>5</sup>. The American Diabetes Association (ADA) consensus statement issued in 2009, recommended using insulin early in the disease if lifestyle management and monotherapy with metformin fail to control glucose, or if lifestyle management is not adequate and metformin is contraindicated<sup>4</sup>.

From a clinical pharmacology perspective, this highlights a remarkable difference in the intended therapeutic use of insulin in Type 1 and Type 2 diabetics. In Type 1 DM the therapy intends to replenish the total lack of endogenous insulin secretion while the insulin action is normal (forms the basis of Insulin Dependent Diabetes Mellitus; IDDM). Whereas, multiple layers of abnormalities in insulin secretion occur in type 2 diabetes: initially a loss of the early phase of meal-stimulated insulin secretion, followed by an inability of the  $\beta$ -cell to increase insulin secretion sufficient to overcome hepatic and peripheral insulin resistance. There is a progressive decrease in both  $\beta$ -cell mass and secretory function so that, in most individuals, absolute insulin deficiency occurs in the late stages of the disease. Therefore, in Type 2 DM (Non-Insulin

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<sup>1</sup> Dose-response characteristics for effects of insulin on production and utilization of glucose in man. R. A. Rizza, L. J. Mandarino, and J. E. Gerich. *American Journal of Physiology - Endocrinology* June 1981 Vol. 240 No. 6: E630-E639

<sup>2</sup> Intravenous glargine and regular insulin have similar effects on endogenous glucose output and peripheral activation/deactivation kinetic profiles. Mudaliar S, Mohideen P, Deutsch R, Ciaraldi TP, Armstrong D, Kim B, Sha X, Henry RR. *Diabetes Care*. 2002 Sep; 25(9):1597-602.

<sup>3</sup> ADA Position Statement on Standards of Medical Care in Diabetes-2012. *Diabetes Care*, Volume 35: S11-S63, Supplement 1, January 2012.

<sup>4</sup> Nathan DM, Buse JB, Davidson MB, et al. American Diabetes Association, European Association for Study of Diabetes. Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care* 2009; 32:193–203

<sup>5</sup> Insulin: Potential Negative Consequences of Early Routine Use in Patients With Type 2 Diabetes. Harold E. Lebovitz. *Diabetes Care*, Volume 34: S225-S230, Supplement 2, May 2011.

Dependent Diabetes Mellitus; NIDDM) the intent during primary stage of disease is to overcome the insulin resistance by providing excess insulin with some anticipated preservation of the pancreatic  $\beta$ -cell function. When  $\beta$ -cell failure occurs at more advanced stage of Type 2 DM, the intent of insulin therapy would be no different from that in Type 1 DM. Therefore, knowledge of time-action profile of any insulin product in both disease groups is essential to optimize the therapy.

The understanding of fundamental relationship between insulin exposure and glucose utilization has helped in designing the insulin products with systemic release (pharmacokinetic, PK) and action (pharmacodynamics, PD) profile that could approximate either a mealtime or basal insulin release, tailored to achieve a specific therapeutic objective. The longer-acting objective for previous insulin products was achieved through physicochemical (e.g. *Humulin Ultralente*, a crystalline suspension of human insulin with zinc, *Humulin Lente*, an amorphous and crystalline suspension of human insulin with zinc) and formulation changes (*Neutral Protamine Hagedorn* NPH insulin; addition of neutral protamine to human insulin). However, some of these products were discontinued partially due to the decline in use<sup>6</sup> and availability of newer options, including the longer-acting insulin products designed by structural modifications to the human insulin molecule (e.g. Insulin Glargine and Insulin Detemir).

The design of proposed insulin product IDeg involves structural modification to the human insulin molecule. The objective of this modification is to achieve a gradual release of IDeg from the injection site to the systemic circulation, thus resulting in a relatively flat concentration-time profile over a long duration of time. The therapeutic objective of IDeg is to function as basal insulin. The availability of IDeg would present another therapeutic option for management of diabetes among the currently available basal insulins: NPH (Novolin N®, Novo Nordisk NDA 19959, now available as over-the-counter), Insulin glargine (IGlar, Lantus®, Sanofi Aventis NDA 21081), and Insulin detemir (Levemir®, Novo Nordisk NDA 21536).

### 2.1.2 What are the highlights of the Insulin Degludec drug product?

IDeg (**Figure 4**) is structurally modified insulin such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the  $\epsilon$ -amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer.

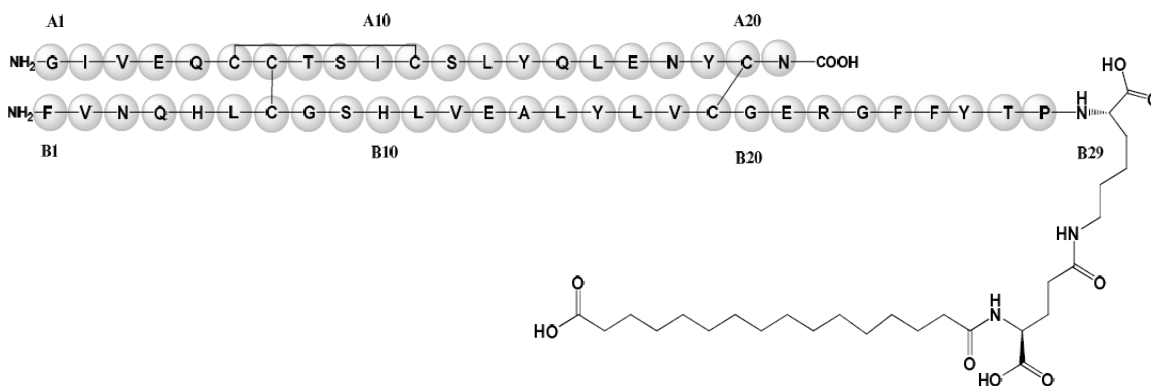


**Figure 4** Chemical Structure of Insulin Degludec

The structural formula is LysB29(N( $\epsilon$ )-hexadecandioyl- $\gamma$ -L-Glu)desB30 human insulin and the molecular formula C<sub>274</sub>H<sub>411</sub>N<sub>65</sub>O<sub>81</sub>S<sub>6</sub> giving a molecular mass of 6104.1 dalton.

<sup>6</sup> <http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/ucm086084.pdf>

IDeg drug product [other former names - *insulin 454/Soluble Insulin Basal Analogue (SIBA)*] is a new-generation basal insulin with long duration of action, and being a solution does not need re-suspension.

The proposed IDeg drug product is a clear and colorless solution in two strengths:

- IDeg 100 U/mL (Insulin degludec 600 nmol/mL): Intended to be marketed <sup>(b) (4)</sup> as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialed in 1U increments.
- IDeg 200 U/mL, (Insulin degludec 1200 nmol/mL): Intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialed in 2U increments.

IDeg exist as di-hexamers in the formulation. After subcutaneous (SC) injection, the di-hexamers apparently assemble to form soluble and stable multi-hexamers creating a depot of insulin in the subcutaneous tissue. Sponsor proposed that from this depot, IDeg monomers gradually separate from the multi-hexamers thus resulting in a slow and continuous delivery of IDeg into the circulation, leading to a pharmacokinetic and pharmacodynamic profile that could potentially approximate the basal insulin secretion (**Figure 5**).

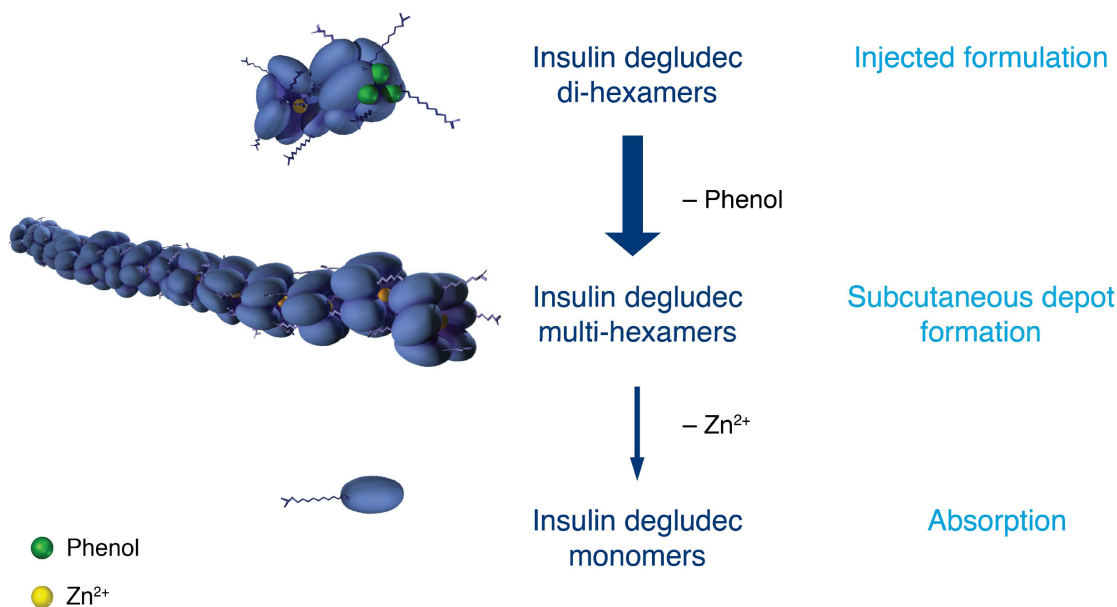


**Figure 5 Proposed mechanism of absorption for Insulin Degludec**

### 2.1.3 What is the composition of to-be-marketed formulation of Insulin Degludec and formulations used in clinical development?

Insulin Degludec 100 U/mL and 200 U/mL is a clear, colorless solution. The solution is filled in a <sup>(b) (4)</sup> The pH of the product is 7.6. The composition of Insulin Degludec 100 U/mL and 200 U/mL formulations is listed in Table 1 below.

**Table 1 Quantitative Composition of To-Be-Marketed Insulin Degludec 100 U/mL and 200 U/mL formulations**

| Name of components             | Quantity per ml           |                           | Function      | Reference to standards        |                 |
|--------------------------------|---------------------------|---------------------------|---------------|-------------------------------|-----------------|
|                                | Insulin degludec 100 U/ml | Insulin degludec 200 U/ml |               |                               |                 |
| <b>Active substance</b>        |                           |                           |               |                               |                 |
| Insulin degludec               | 600 nmol                  | 1200 nmol                 | (b) (4)       | Novo Nordisk                  |                 |
| <b>Excipients</b>              |                           |                           |               |                               |                 |
| Phenol <sup>1</sup>            | 1.50 mg                   | 1.50 mg                   |               | Ph Eur ,USP, JP               |                 |
| Metacresol <sup>1</sup>        | 1.72 mg                   | 1.72 mg                   |               | Ph Eur, USP                   |                 |
| Glycerol                       | 19.6 mg                   | 19.6 mg                   |               | Ph Eur ,USP, JP               |                 |
| Zinc                           | 32.7 µg                   | 71.9 µg                   |               | Ph Eur ,USP, JPE <sup>2</sup> |                 |
| Hydrochloric acid <sup>3</sup> | q.s.                      | q.s.                      |               | pH adjustment                 | Ph Eur ,USP, JP |
| Sodium hydroxide <sup>3</sup>  | q.s.                      | q.s.                      | pH adjustment | Ph Eur ,USP, JP               |                 |
| Water for injections           | (b) (4)                   |                           |               | Ph Eur ,USP, JP               |                 |

(b) (4)

<sup>3</sup> To reach pH 7.6

Sponsor tested a number of exploratory formulations in order to decide on an optimal composition. Following early clinical pharmacology and therapeutic exploratory trials, IDeg (E) was identified as the 100 U/mL (600 nmol/mL) formulation for further clinical development (See Table 2).

**Table 2 Overview of Quantitative Composition of Exploratory and Final Insulin Degludec 100 U/mL and 200 U/mL formulations used through the clinical development**

| Name of Ingredients                           | IDeg (A) | IDeg (B) | IDeg (C) | IDeg (J) | IDeg (D) | IDeg (E) <sup>1</sup> | IDeg (M) <sup>1</sup> | IDeg (P) <sup>2</sup> |
|-----------------------------------------------|----------|----------|----------|----------|----------|-----------------------|-----------------------|-----------------------|
| <b>Clinical development phase<sup>3</sup></b> | Phase 1  | Phase 1  | Phase 1  | Phase 2  | Phase 2  | Phase 2               | Phase 3               | Phase 3               |
| Quantity per mL                               |          |          |          |          |          |                       |                       |                       |
| <b>Drug substance<sup>4</sup></b>             |          |          |          |          |          |                       |                       |                       |
| IDeg (nmol/mL)                                | (b) (4)  |          |          |          |          | 600                   | 600                   | 1200                  |
| <b>Excipients</b>                             |          |          |          |          |          |                       |                       |                       |
| Phenol <sup>5</sup> (mg/mL)                   | (b) (4)  |          |          |          |          | 1.50                  | 1.50                  | 1.50                  |
| Metacresol <sup>5</sup> (mg/mL)               | (b) (4)  |          |          |          |          | 1.72                  | 1.72                  | 1.72                  |
| Glycerol (mg/mL)                              | (b) (4)  |          |          |          |          | 19.6                  | 19.6                  | 19.6                  |
| (b) (4)                                       | (b) (4)  |          |          |          |          | -                     | -                     | -                     |
| (b) (4)                                       | (b) (4)  |          |          |          |          | -                     | -                     | -                     |
| (b) (4)                                       | (b) (4)  |          |          |          |          | -                     | -                     | -                     |
| Sodium chloride (mg/mL)                       | (b) (4)  |          |          |          |          | -                     | -                     | -                     |
| Zinc <sup>6</sup> (µg/mL)                     | (b) (4)  |          |          |          |          | 32.7                  | 32.7                  | 71.9                  |
| Hydrochloric acid <sup>7,8</sup>              | (b) (4)  |          |          |          |          | q.s.                  | q.s.                  | q.s.                  |
| Sodium hydroxide <sup>7,9</sup>               | (b) (4)  |          |          |          |          | q.s.                  | q.s.                  | q.s.                  |
| Water for injections                          | (b) (4)  |          |          |          |          | (b) (4)               |                       |                       |
| <b>Characteristics of drug product</b>        |          |          |          |          |          |                       |                       |                       |
| pH                                            | (b) (4)  |          |          |          |          | 7.6                   | 7.6                   | 7.6                   |

<sup>1</sup> Same formulation as the proposed commercial product of IDeg 100 U/mL. <sup>2</sup> Same formulation as the proposed commercial product of IDeg 200 U/mL. <sup>3</sup> This refers to the stage of clinical development and not the type of clinical trial. <sup>4</sup>

(b) (4)

The IDeg 100 U/ml proposed commercial formulation, used throughout the therapeutic confirmatory trials and key clinical pharmacology trials, is claimed to be identical to IDeg (E), (b) (4)

Sponsor mentioned that all therapeutic confirmatory trials were conducted using (b) (4) change in product name from IDeg (E) to IDeg (M). During conduct of the therapeutic confirmatory trials, (b) (4). For the proposed 200 U/mL (1200 nmol/mL) formulation (IDeg (P)), the inactive ingredients are the same as for 100 U/mL and in the same concentration, except that the (b) (4) has been optimized for (b) (4). IDeg (P) is the 200 U/mL product used in the therapeutic confirmatory trials and the clinical pharmacology trials, and is identical to the IDeg 200 U/mL proposed commercial formulation.

**Table 3 Overview of Quantitative Composition of Exploratory and Final Insulin Degludec 100 U/mL and 200 U/mL formulations used through the clinical development**

|                                 | Early Drug Products<br>(Exploratory Formulations) |                       |                      |          |                     | Drug Products<br>(Proposed Commercial Formulation) |                                  |                                   |
|---------------------------------|---------------------------------------------------|-----------------------|----------------------|----------|---------------------|----------------------------------------------------|----------------------------------|-----------------------------------|
|                                 | IDeg (A)<br>(1200 mM)                             | IDeg (B)<br>(1200 mM) | IDeg (C)<br>(600 mM) | IDeg (D) | IDeg (J)<br>(b) (4) | 100 U/mL<br>IDeg (E)<br>(600 mM)                   | 200 U/mL<br>IDeg (M)<br>(600 mM) | 200 U/mL<br>IDeg (P)<br>(1200 mM) |
| <b>Clinical Pharmacology</b>    | (b) (4)                                           |                       |                      |          |                     |                                                    |                                  |                                   |
| 1987                            |                                                   |                       |                      |          |                     |                                                    | X                                | X                                 |
| 1988                            |                                                   |                       |                      |          |                     | X                                                  | X                                |                                   |
| 1989                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1990                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1991                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1992                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1993                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1994                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1995                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 1996                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 3538                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 3678                            |                                                   |                       |                      |          |                     |                                                    | X                                | X                                 |
| 3762                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| 3769                            |                                                   |                       |                      |          |                     |                                                    | X <sup>1</sup>                   |                                   |
| 3857                            |                                                   |                       |                      |          |                     |                                                    | X                                |                                   |
| <b>Therapeutic Exploratory</b>  |                                                   |                       |                      |          |                     |                                                    |                                  |                                   |
| 1835                            |                                                   |                       |                      | X        |                     | X                                                  |                                  | (b) (4)                           |
| <b>Therapeutic Confirmatory</b> |                                                   |                       |                      |          |                     |                                                    |                                  |                                   |
|                                 |                                                   |                       |                      |          |                     |                                                    | X <sup>2</sup>                   | X <sup>3</sup>                    |
| <b>Other Therapeutic</b>        |                                                   |                       |                      |          |                     |                                                    |                                  |                                   |
|                                 |                                                   |                       |                      |          |                     |                                                    |                                  | X <sup>4</sup>                    |

<sup>1</sup>This trial compared products manufactured before and after a minor optimization (b) (4) manufacturing process. <sup>2</sup>Trials 3583, 3585, 3582, 3668, 3579, 3586, 3580, 3725, 3643, 3644 and 3667 were conducted with products manufactured before, and Trial 3770 was conducted with trial products manufactured after the minor optimization of the (b) (4) manufacturing process. <sup>3</sup>U200 used in Trials 3672, 3718, 3724. (b) (4)

## 2.2 General Clinical Pharmacology

### 2.2.1 What is the mechanistic role of exogenously administered insulin in glycemic regulation in comparison to the endogenously secreted insulin, and translatory aspect of this role from a pharmacokinetic and pharmacodynamic perspective?

In animals and humans, nature has marvelously engineered the insulin secretion and its role in glucose homeostasis. In response to each meal/glucose intake there is precise delivery of insulin (along with GLP-1, GIP-1 and amylin) from pancreas to liver through the portal circulation to signal for shutting down the hepatic glucose production and stimulating the hepatic and other peripheral tissue uptake of glucose. On average peak endogenous insulin levels in response to a meal (50% Carbohydrate) are around 300 pM<sup>7</sup>. This transient rise is short-lived due to rapid elimination of insulin, and is followed by a gradual decline in insulin to basal level apparently a reflection of the basal secretion rate (see **Figure 3**). This stage is mostly a reflection of mutual regulatory control of insulin and glucose.

Human efforts to engineer insulin delivery have so far resulted in subcutaneously/intravenously (bolus/infusion) administered insulin products, which only approximate the endogenous insulin release. However, since both SC/IV routes bypass the hepatic first-pass extraction, exogenously administered insulin ends up providing a different insulin gradient than that occurring after endogenous insulin secretion (See **Figure 6**<sup>5</sup> below).

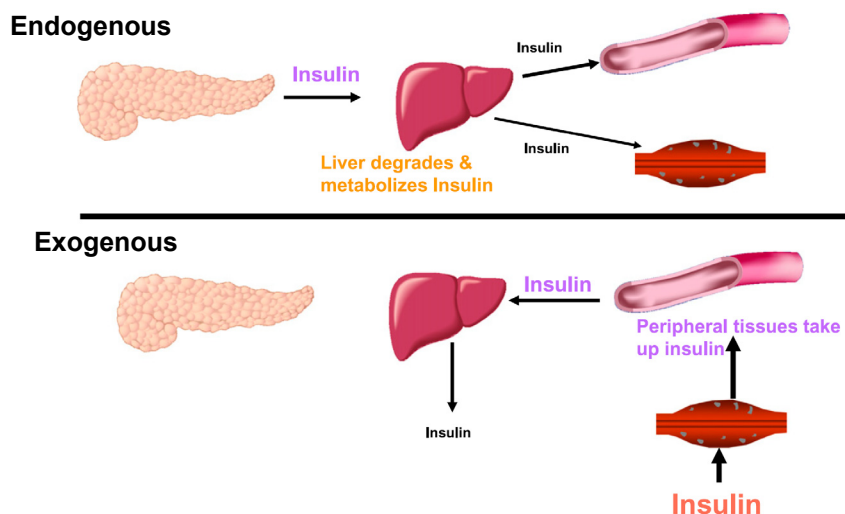


**Figure 6 Exogenous versus endogenous insulin action**

Endogenously secreted insulin acts initially on the liver where a major portion of insulin is taken up and <50% reaches the peripheral tissues. Whereas, exogenously administered insulin first circulates through the peripheral tissues before reaching the liver. Therefore, peripheral hyperinsulinemia is necessary to attain adequate insulin to regulate the liver. Consequently, exogenous insulin levels are generally higher than the physiologically observed insulin levels post-mealtime and at basal stage. The inherent potency difference between the exogenous and endogenous insulin due to molecular modification could also add to this difference. Moreover, strictly for exogenous basal insulin like IDeg one important fact to remember is that there is no influence of pertinent glucose levels on the insulin levels in contrast to that observed for endogenous insulin secretion in healthy and Type 2 DM.

<sup>7</sup> Meal and oral glucose tests for assessment of  $\beta$ -cell function: modeling analysis in normal subjects. Mari, Andrea, Ole Schmitz, Amalia Gastaldelli, Torben Oestergaard, Birgit Nyholm, and Ele Ferrannini. *Am J Physiol Endocrinol Metab* 283: E1159–E1166, 2002.

Both exogenous and endogenous insulin have dual effect of inhibiting the hepatic glucose production as well as stimulating peripheral utilization of glucose<sup>1</sup>. However, it requires special PD study design to distinguish these effects. To simplify the assessment of time-action profile, one can conduct a PKPD study, where insulin is administered without simultaneous exogenous glucose administration. This study would show hypoglycemic effect, which will be a net effect of dual insulin actions. Currently, almost all insulin PKPD studies are conducted utilizing an alternative euglycemic (*means "same glucose"*) clamp technique where, insulin is injected into subjects and glucose is infused to prevent the expected decrease in blood glucose concentration, thus "clamping" blood glucose to a predetermined basal level. The total amount of glucose infused and the rate of glucose infusion approximates the biological effect (i.e., glucose-lowering effect) of the tested insulin. The recorded glucose infusion rate (GIR) then constitutes a measure of the net effect of the insulin (i.e., it describes the resulting sum of the suppression of hepatic glucose production and the stimulation in glucose utilization)<sup>8</sup>. The euglycemic clamp design also allows for dose-response assessment without undue safety risk of hypoglycemia to the subjects, in contrast to the hypoglycemic effect technique.

A typical study schematic of the euglycemic clamp procedure used for evaluating PK and PD of IDeg in healthy subjects is shown in **Figure 7** below:

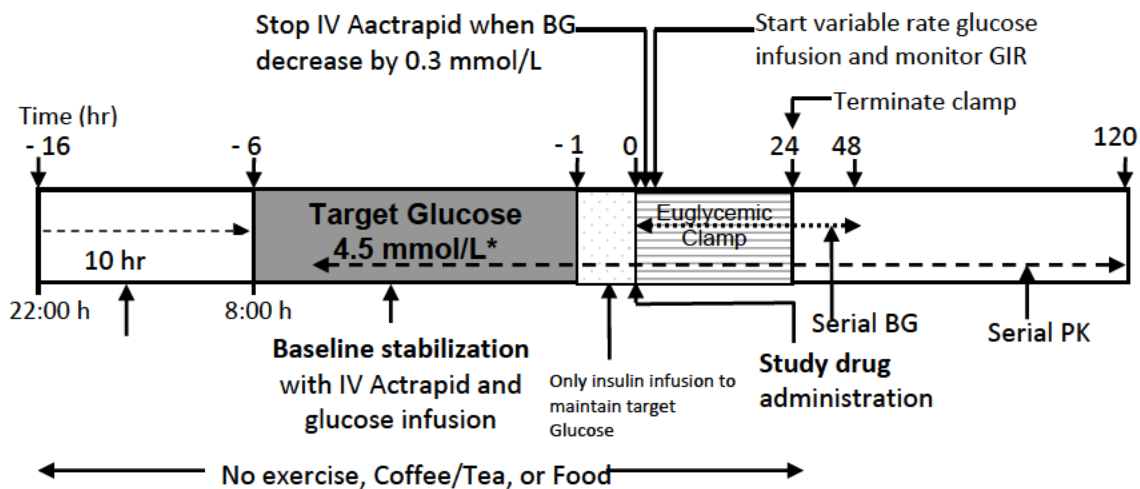


**Figure 7** Schematic of euglycemic clamp experiment used for PK and PD evaluation to characterize IDeg time-action profile

The experimental design in Type 1 and Type 2 diabetic subjects was similar to healthy subjects except some key differences with regards to the higher target blood glucose level 5 or 5.5 mmol/L, and presence or absence of C-peptide monitoring.

### 2.2.2 What are the key pharmacological properties of Insulin Degludec in comparison to the human insulin from a pharmacokinetic and pharmacodynamic perspective?

Insulin is a pleiotropic hormone, playing a central role in carbohydrate, lipid and protein metabolism as well as regulating appetite and cell proliferation (See **Figure 8** below).

<sup>8</sup> Pharmacokinetics and Pharmacodynamics of Basal Insulins. Francesca Porcellati, M.D., Ph.D., Geremia B. Bolli, M.D., and Carmine G. Fanelli. *Diabetes Technology & Therapeutics* Volume 13, Supplement 1, 2011.

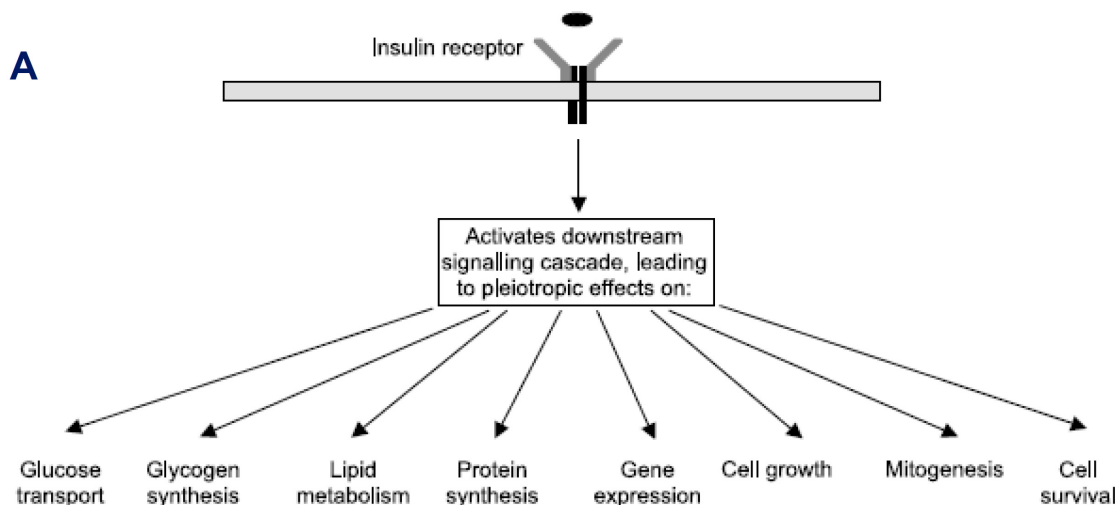


**Figure 8 Diverse biological actions of insulin**

Sponsor evaluated and compared the pharmacological properties of IDeg against human insulin in various mechanistic in vitro studies (For details, refer to Pharm-Tox Review). In brief, in vitro pharmacology studies demonstrated that:

- IDeg binds specifically to insulin receptors derived from the various species tested (rat, dog, pig and human), however, with a lower affinity than that of human insulin (**Table 4**). IDeg affinity for the related IGF-1 receptor was proportionately even lower than its binding to the insulin receptor. Insulin degludec was shown to activate the insulin receptor as exemplified by its ability to phosphorylate the insulin receptor and to stimulate post-receptor, down-stream intracellular signaling pathways in the same dose-dependent manner as human insulin. Thus, the mode of action of IDeg is expected to be identical to that of human insulin and other insulin analogs in vivo.

**Table 4 Binding Affinities of Human Insulin and Insulin degludec to Insulin Receptors from Different Species**

| Source      | Human insulin                                 | Insulin degludec                              | Affinity                                   |
|-------------|-----------------------------------------------|-----------------------------------------------|--------------------------------------------|
|             | IC <sub>50</sub> [CI <sub>95%</sub> ]<br>(nM) | IC <sub>50</sub> [CI <sub>95%</sub> ]<br>(nM) | relative to HI [CI <sub>95%</sub> ]<br>(%) |
| Rat liver   | 3.6 [1.7, 7.8]                                | 146 [57, 375]                                 | 3.3 [ 1.3, 4.8]                            |
| Dog liver   | 3.2 [1.8, 5.4]                                | 45 [29, 70]                                   | 7.0 [4.2, 11]                              |
| Pig liver   | 0.46 [0.24, 0.86]                             | 13 [7.6, 21]                                  | 3.6 [2.3, 3.8]                             |
| Human liver | 0.77 [0.41, 1.4]                              | 22 [14, 36]                                   | 3.5 [1.5, 8.2]                             |

CI<sub>95%</sub>, 95% confidence interval

- There was no significant difference between the apparent rate constants (Kobs) for association of <sup>125</sup>I-human insulin and <sup>125</sup>I-insulin degludec. The dissociation of both <sup>125</sup>I-human insulin and <sup>125</sup>I-insulin degludec could be resolved into a fast (koff<sup>2</sup>) and slow (koff<sup>1</sup>) component, reflecting the two binding sites for insulin on the receptor. The dissociation rate constants for each of these components were similar for insulin degludec and human insulin (Table 5). Rate at which insulin analogs dissociate from the insulin

receptor is considered an important factor in determining the duration of insulin signaling and action.

**Table 5 Apparent Rate Constants for Association and Dissociation of <sup>125</sup>I-Human Insulin and <sup>125</sup>I-Insulin degludec to the human insulin receptor**

|                                         | <sup>125</sup> I-Human insulin |        |   | <sup>125</sup> I-Insulin degludec |        |   | p-value <sup>a</sup> |
|-----------------------------------------|--------------------------------|--------|---|-----------------------------------|--------|---|----------------------|
|                                         | Mean                           | SEM    | n | Mean                              | SEM    | n |                      |
| k <sub>obs</sub> (min <sup>-1</sup> )   | 0.0239                         | 0.0024 | 4 | 0.0222                            | 0.0026 | 4 | NS                   |
| k <sub>off-1</sub> (min <sup>-1</sup> ) | 0.0181                         | 0.0081 | 4 | 0.0139                            | 0.0081 | 4 | NS                   |
| k <sub>off-2</sub> (min <sup>-1</sup> ) | 0.1232                         | 0.0557 | 4 | 0.1055                            | 0.0255 | 4 | NS                   |

a – Student’s t-test, NS: Not significant (p>0.05)

- Similar to the biological effects of human insulin, IDeg stimulated glycogen accumulation and inhibited phosphoenolpyruvate carboxykinase (PEPCK) mRNA expression, a rate-limiting enzyme involved in gluconeogenesis in primary rat hepatocytes. IDeg’s effects in the rat liver cells produced the same maximal response as human insulin, indicating that insulin degludec is a full insulin receptor agonist with full efficacy in hepatocytes. The relative in vitro potency of IDeg in stimulating glycogen accumulation (over a 24-hour period) was 21.3% compared to human insulin determined in the absence of any added albumin. With the addition of increasing concentrations of human serum albumin, the relative in vitro potency compared to human insulin decreased reflecting the increasing EC50 for IDeg, whereas the EC50 values for human insulin were unaffected by the presence of albumin consistent with the fact that human insulin does not bind to albumin (**Table 6**).

**Table 6 Effect of Albumin on the Potency of Insulin degludec compared to Human Insulin in stimulating Glycogen Storage in Primary Rat Hepatocytes**

| HSA (%)    | Relative Potency <sup>a</sup> (%) | Insulin degludec EC <sub>50</sub> (nM) | Human insulin EC <sub>50</sub> (nM) |
|------------|-----------------------------------|----------------------------------------|-------------------------------------|
| None added | 21.3 ± 4.4                        | 2.6 ± 0.3                              | 0.50 ± 0.08                         |
| 0.1%       | 10.1 ± 4.5                        | 8.0 ± 1.3                              | 0.67 ± 0.18                         |
| 0.5%       | 4.5 ± 1.2                         | 13.5 ± 4.2                             | 0.55 ± 0.14                         |
| 1%         | 3.3 ± 1.6                         | 92.4 ± 61                              | 0.62 ± 0.12                         |

Values are mean ± SEM of 6 independent assays

a – potency of insulin degludec relative to human insulin

- The right-shift in the dose-response curves compared to human insulin reflects a lower in vitro potency due to the lower insulin receptor affinity of insulin Degludec (**Figure 9**); however, the same maximum response signifies that insulin Degludec molecule has retained its efficacy as a full agonist of the insulin receptor.

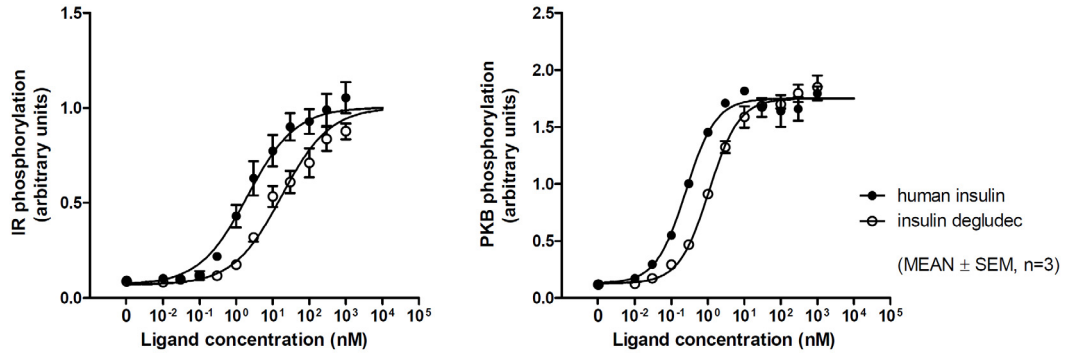


**Figure 9** Dose response curves for phosphorylation of the insulin receptor (IR) and protein kinase B (PKB) in L6-hIR cells

- The right-shift in the dose-response curve was also evident for glucose uptake and lipolysis in fat cells (**Figure 19**). In the human fat cell line [Simpson-Golabi-Behmel syndrome (SGBS) adipocytes], IDeg stimulated glucose uptake and utilization, and inhibited catecholamine-stimulated lipolysis and net fatty acid mobilization with the same efficacy as human insulin. The in vitro potency of IDeg in stimulating glucose utilization was determined to be 1.5% in comparison to human insulin in the presence of 1% albumin. IDeg also inhibited catecholamine-stimulated lipolysis (glycerol release) and net fatty acid mobilization in SGBS cells with an in vitro potency (relative to human insulin) of 1.8% and 1.7%, respectively, in the presence of 1% albumin.

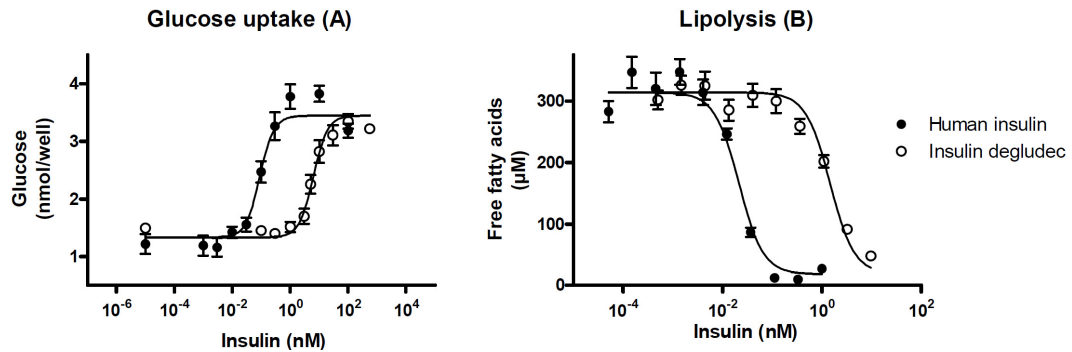


**Figure 10** SGBS cell dose-response curves for lipogenesis (A) and lipolysis (B)

- Furthermore, IDeg showed no sign of prolonged signaling based on comparable of rate of decline in insulin receptor phosphorylation to the human insulin (**Figure 11**).

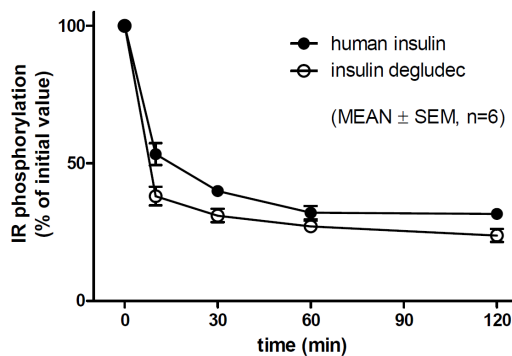


**Figure 11** Decline in insulin receptor signaling in CHO-hIR cells

- Protein Binding of IDeg to 96-99% HSA and essentially fatty acid free HSA resulted in mean dissociation rate constant (Kd) of  $32 \pm 6 \mu\text{M}$  and  $13 \pm 5 \mu\text{M}$ , respectively. Assuming HSA is the only plasma protein resulting in binding of IDeg, the mean percentage fraction unbound of IDeg was 4.7% and 2.0% when calculated for 96-99% HSA and essentially fatty acid free HSA, respectively. The binding affinity of IDeg for human serum albumin is 2.5 times greater relative to the reference, insulin detemir.

Considering remarkably low affinity of IDeg at IR and further reduction of activity due to protein binding observed *in vitro*, it is reasonable to expect that higher IDeg systemic levels (peripheral hyperinsulinemia) are necessary *in vivo* to achieve the glucodynamic effect, in comparison to the physiologically observed insulin levels. Section 2.2.3 below, which discusses *in vivo* PK and PD evaluation of IDeg elaborates this aspect in detail.

### 2.2.3 What are the characteristics of time-action profile of Insulin Degludec after single subcutaneous administration, how does it relate to the dose, and does it support the use of Insulin Degludec as a basal insulin?

Phase 1 PK and PD evaluation is fundamental in understanding the time-action profile of insulin products. This evaluation provides two critical sets of information: (i) the onset, peak, and duration of action, which compares the time-action profile, and (ii) the dose/exposure-glucose utilization relationship. Together, this information is important to tailor the evaluation of clinical use of insulin.

#### Single Dose PK and PD evaluation in Healthy:

Single dose PK and PD characteristics of IDeg were evaluated in Trial NN1250-3769, a randomized, single-center, double-blind, two-period cross-over trial in healthy subjects. The primary objective of the trial was to test for PK bioequivalence between two IDeg formulations resultant from minor process optimization of the intended commercial formulation. However, only the descriptive PK and PD results of this trial are highlighted here. PK samples were collected from -4, -0.5, -0.25, 0 (all pre-dose) to 120 h post dose. PD data (GIR) was obtained under euglycemic clamp from time 0 hour to 24 hour. The mean (SE) serum concentration-time and mean (95% CI) profiles of IDeg formulation IM2 are illustrated in the **Figure 12**. Table 7 summarizes the key PK and PD parameters for IDeg.

**Table 7 Summary of IDeg PK/PD parameters after single 0.4 U/kg SC dose [Intended commercial formulation IDeg M (IM1) NN1250-3769]**

| Parameter  |                                   | Geometric Mean (%CV) |
|------------|-----------------------------------|----------------------|
| <b>PK:</b> | Cmax (pmol/L):                    | 2083 (16)            |
|            | t <sub>max</sub> (hour)*:         | 14 (10-22)           |
|            | AUC <sub>0-120h</sub> (pmol*h/L): | 78437 (19)           |
|            | T1/2 (hour):                      | 16 (32)              |
|            | CL/F (L/h/kg):                    | 0.029 (17)           |
|            | Vd/F (L/kg):                      | 0.667 (27)           |
| <b>PD:</b> | GIRmax (mg/kg/min):               | 2.3 (41)             |
|            | t <sub>GIRmax</sub> (hour) *:     | 13 (6-24)            |
|            | AUCGIR <sub>0-24h</sub> (mg/kg):  | 2071 (43)            |

\*Median (Min., Max.)

As postulated in proposed absorption mechanism (see Section 2.1.2 of the QBR), upon SC administration, IDeg demonstrated slow absorption into the systemic circulation. Following single SC dose of 0.4 U/kg (2.4 nmol/kg), mean maximum concentrations of 2150 pmol/L were

achieved between 10-22 hour. Median onset of appearance time was around 1 hour. The mean apparent clearance was low 0.03 L/kg (2.1 L/h in 70 kg individual) and apparent volume of distribution was high 0.69 L/kg (48 L in 70 kg individual). Considering that after intravenous (IV) administration, the expected  $t_{1/2}$  is substantially lower than that observed after SC administration (regardless of some uncertainty in 5 hour value observed in Trial NN1250-1992 due to dilution of the formulation in IV fluid), the IDeg PK can be regarded as absorption limited or driven primarily by the absorption. As expected, IDeg exposure is substantially higher than endogenous insulin levels.

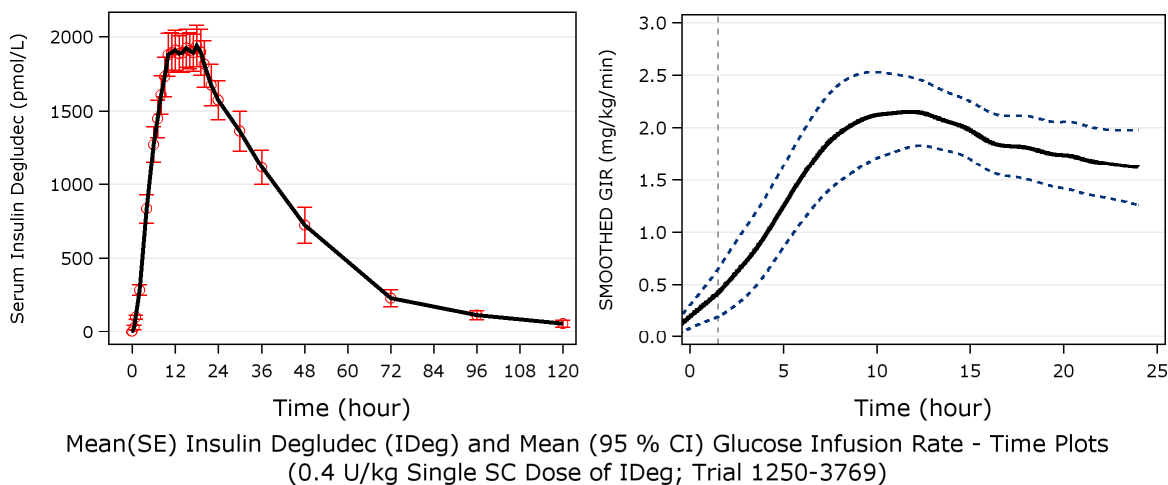


**Figure 12** Mean (SE) serum concentration-time (left) and mean (95% CI) GIR-time (right) profiles for IDeg (M) IM2 after single SC dose (0.4 U/kg or 2.4 nmol/kg) in healthy subjects (N=26)

The slow appearance rate of IDeg in systemic circulation was associated with a gradual deviation of GIR (PD Response) from baseline, which exceeded by >10% of the maximum value from baseline at around 1.5 hours indicating slow onset, reached a plateau over 8-14 hours with average maximum of 2.8 mg/kg/min, and did not return to baseline during the 24 hour duration of clamp, indicating nearly flat time action profile and >24h duration of action of IDeg after single SC administration. The mean AUCGIR<sub>0-24h</sub> of 2071 mg/kg translates as 145 g glucose being utilized over 24 hour, triggered by 28 U IDeg dose (5 g glucose/U IDeg) in a representative 70 kg healthy individual. Visual graphical evaluation of GIR versus time profile (**Figure 12**) reveals that onset of action could be as late as 6 hours and as early as 0.5 hour post-dose. On average, the GIR versus time profile showed no distinct peak indicating close to the desired peak-less time action profile of IDeg.

The integrity of the euglycemic clamp was evident from the blood glucose values that were tightly maintained at the target of 4.5 mmol/L on average, and were within the pre-specified limit of  $\pm 20\%$  (3.6 – 5.4 mmol/L) for all individuals (**Figure 13a**). On average, the c-peptide levels remained suppressed, due to the inhibitory effect of exogenous insulin on endogenous insulin secretion, over the duration of clamp indicating that interference from endogenous insulin in the PD profile is minimal (**Figure 13b**).

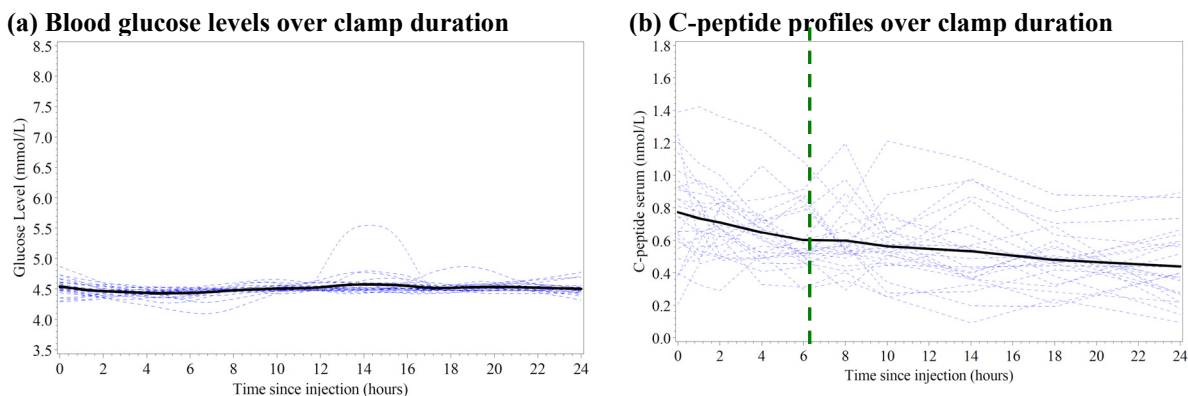
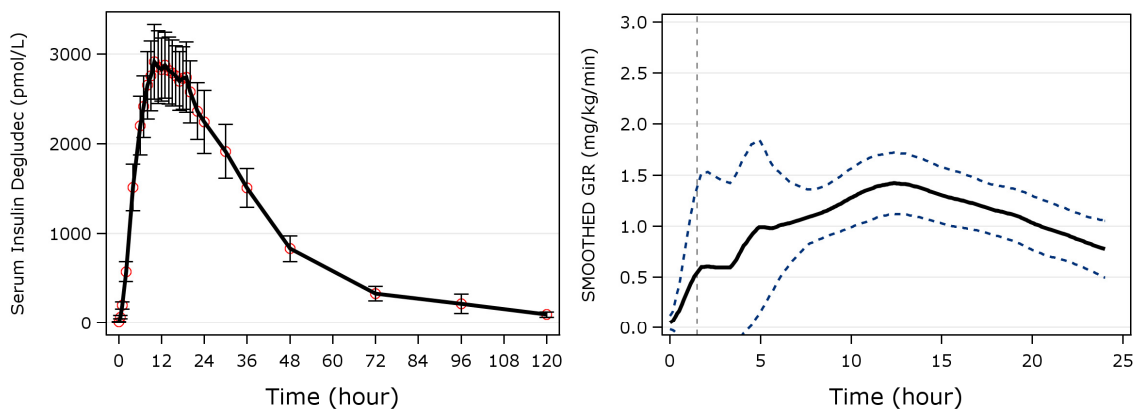


**Figure 13 Blood glucose levels (left) and C-peptide (right) Profiles over clamp duration – IDeg IM1**

**Single-Dose PK and PD in Type 1 DM:**

Single dose PK and PD characteristics of IDeg in Type 1 DM were evaluated in Trial NN5401-3857, a randomized, single-center, open-label, three-period crossover trial in subjects with Type 1 DM. Each subject was randomly allocated to three single-dose (SD) administrations (IDegAsp, IDeg and IAsp) on three separate dosing visits. The primary objective of the trial was to compare the pharmacodynamic response between IDegAsp and IDeg (based on the area under the glucose infusion rate curve from 0 to 6 hours) and between IDegAsp and IAsp (based on the area under the glucose infusion rate curve from 6 to 24 hours). This study is reviewed in detail under NDA 203313 (See Review by Dr. Ritesh Jain) and only the descriptive PK and PD results for IDeg arm of this trial are highlighted here. PK samples were collected at -4, -0.5, -0.25, 0 (all pre-dose) to 120 h post dose. PD data (GIR) was obtained under euglycemic clamp from time 0 hour to 24 hour. The mean (SE) serum concentration-time and mean (95% CI) GIR-time profiles of IDeg in subjects with Type 1 DM are illustrated in the **Figure 14** below.



Mean(SE) Insulin Degludec (IDeg) and Mean (95 % CI) Glucose Infusion Rate - Time Plots (0.5 U/kg Single SC Dose of IDeg; Trial 5401-3857)

**Figure 14 Mean (SE) concentration-time (left) and mean (95% CI) GIR-time (right) profiles for IDeg (M) after single SC dose (0.5 U/kg or 3.0 nmol/kg) in Type 1DM subjects (N=26)**

Similar to the healthy subjects, upon single SC administration in subjects with Type 1 DM, IDeg demonstrated slow absorption into the systemic circulation. Following single SC dose of 0.5 U/kg (3.0 nmol/kg), mean maximum concentrations of 3286 pmol/L were achieved between 5-24 hour. The mean apparent clearance was low 0.026 L/kg (1.8 L/h in 70 kg individual) and apparent volume of distribution was high 0.7 L/kg (49 L in 70 kg individual), comparable to the mean estimates in healthy subjects.

**Table 8 Summary of IDeg PK/PD parameters after single 0.5 U/kg SC dose in subjects with Type 1 DM [NN5401-3857]**

| Parameter  |                                   | Geometric Mean (%CV) |
|------------|-----------------------------------|----------------------|
| <b>PK:</b> | C <sub>max</sub> (pmol/L):        | 3286 (25)            |
|            | t <sub>max</sub> (hour)*:         | 13.5 (5.3-24)        |
|            | AUC <sub>0-120h</sub> (pmol*h/L): | 114809 (24)          |
|            | T <sub>1/2</sub> (hour):          | 19 (31)              |
|            | CL/F (L/h/kg):                    | 0.026 (34)           |
|            | V <sub>d</sub> /F (L/kg):         | 0.701 (54)           |
| <b>PD:</b> | GIR <sub>max</sub> (mg/kg/min):   | 1.6 (41)             |
|            | t <sub>GIRmax</sub> (hour) *:     | 14 (5-24)            |
|            | AUCGIR <sub>0-24h</sub> (mg/kg):  | 1219 (47)            |

\*Median (Min., Max.)

The slow appearance rate of IDeg in systemic circulation was associated with a gradual deviation of GIR from baseline. GIR exceeded by >10% of the maximum value from baseline at around 1.5 hours indicating slow onset. It reached a plateau over 8-14 hours with average maximum of 1.6 mg/kg/min, and did not return to baseline during the 24 hour duration of clamp, indicating nearly flat time action profile and >24h duration of action of IDeg after single SC administration (See **Figure 13** below). The mean AUCGIR<sub>0-24h</sub> of 1219 mg/kg translates as 85 g glucose being utilized over 24 hour, triggered by 35 U IDeg dose (2.4 g glucose/U IDeg) in a representative 70 kg Type 1 DM individual. On average, the GIR versus time profile showed no distinct peak, indicating close to the desired peak-less time action profile of IDeg in Type 1 DM subjects. Interestingly, in comparison to the healthy the mean PD response was lower in Type 1 DM based on GIR<sub>max</sub> and AUC<sub>0-24h</sub>, despite of higher IDeg systemic exposures (slightly higher dose of IDeg used in this Trial). This could be due to the difference in choice of target glucose level for the clamp (healthy: 4.5 mmol/L versus Type 1 DM: 5.5 mmol/L) or real sensitivity differences to the effects of IDeg in these two groups. Although latter appears to be the most likely reason as intuitively, a higher target glucose would require more glucose to be pushed in to counter the glucose lowering effect of insulin, resulting in higher GIR<sub>max</sub>/AUCGIR.

The integrity of the euglycemic clamp was evident only from the average blood glucose values, which were around the pre-specified target of 5.5 mmol/L. However, in 16 of the 27 total subjects the values escaped the target and were outside of the pre-specified limit of  $\pm 30\%$  (3.85 – 7.15 mmol/L) indicating unsuccessful clamp (no interference from endogenous insulin) during initial 6 hours post-dose making onset of action assessment difficult and overestimating AUCGIR in these subjects.

#### **Single-Dose PK and PD in Type 2 DM:**

Single dose PK and PD characteristics of IDeg in subjects with Type 2 DM were not evaluated using the intended commercial formulation. However, single dose dose-response trial using a developmental formulation (IDeg B, 1200 nmol/mL) was evaluated in Trial NN5401-1719. This was a randomized, single center, double-blind, six-period, cross-over trial in subjects with Type 1 DM and Type 2 DM. Subjects were randomly allocated to single-dose administration of three different dose levels of IDeg (I454) and three different dose levels of IGlax on six different

occasions. The primary objective of the trial was to compare the dose- pharmacodynamic response between IDeg and IGlár. The dose-response information is discussed later in this review. The descriptive PK and PD results for the lowest dose of IDeg tested in the subjects with Type 2 DM from this trial are highlighted here. PK samples for IDeg were collected at -4, -0.5, -0.25, 0 (all pre-dose) to 96 hour post dose. PD data (GIR) was obtained under euglycemic clamp from time 0 hour to 24 hour. The individual and mean serum concentration-time profiles of IDeg in subjects with Type 2 DM are illustrated in the **Figure 15** below.

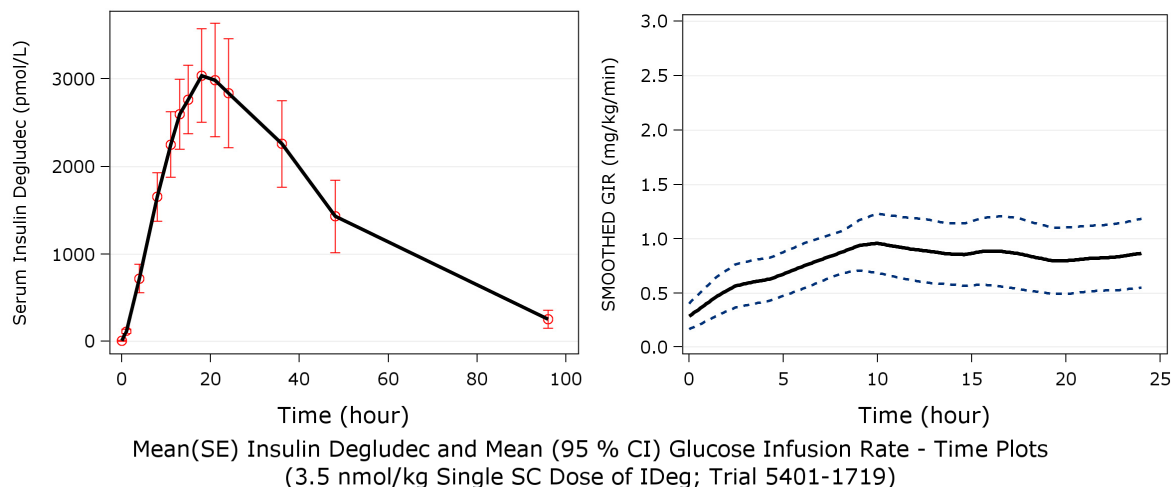


**Figure 15** Mean (SE) concentration-time (left) and mean (95% CI) GIR-time (right) profiles for IDeg (B) after single SC dose (3.5 nmol/kg) in Type 2 DM subjects (n=19)

Similar to the healthy subjects, upon single SC administration in subjects with Type 2 DM, IDeg demonstrated slow absorption into the systemic circulation. Following single SC dose of 3.5 nmol/kg, mean maximum concentrations of 3410 pmol/L were achieved between 11-36 hour. The mean apparent clearance was low 0.026 L/kg (2.1 L/h in 70 kg individual) and apparent volume of distribution was high 0.67 L/kg (47 L in 70 kg individual), comparable to the mean estimates in healthy or Type 1 DM subjects. However, qualitatively a longer  $t_{max}$  was apparent from this developmental formulation than that observed with 600 nmol/mL formulation used in healthy (IDeg E/M), and thus accordingly  $C_{max}$  was lower.

**Table 9** Summary of IDeg PK/PD parameters after single 3.5 nmol/kg SC dose IDeg (B) NN5401-1719]

| Parameter  |                                   | Geometric Mean (%CV) |
|------------|-----------------------------------|----------------------|
| <b>PK:</b> | $C_{max}$ (pmol/L):               | 3325 (37)            |
|            | $t_{max}$ (hour)*:                | 18 (11-36)           |
|            | AUC <sub>0-120h</sub> (pmol*h/L): | 148836 (44)          |
|            | T <sub>1/2</sub> (hour):          | 18 (27)              |
|            | CL/F (L/h/kg):                    | 0.026 (23)           |
| <b>PD:</b> | GIR <sub>max</sub> (mg/kg/min):   | 1.2 (47)             |
|            | $t_{GIRmax}$ (hour) *:            | 15 (0.5-24)          |
|            | AUCGIR <sub>0-24h</sub> (mg/kg):  | 1133 (56)            |

\*Median (Min., Max.)

The slow appearance rate of IDeg in systemic circulation was associated with a gradually rising pharmacodynamic response (as measured by GIR), which peaked at around 15 hour to an average of maximum of 1.2 mg/kg/min (See **Figure 15**). The mean AUCGIR0-24h of 1133 mg/kg translates as 79 g glucose being utilized over 24 hour triggered by 245 nmol of IDeg (~42U; 1.9 g glucose/U IDeg) in a representative 70 kg Type 2 DM individual. In comparison to the Type 1 DM PD response [AUCGIR0-24h=1046 mg/kg from 2.6 nmol/kg dose (~0.4U/kg) in the same trial; Glucose utilization ~ 2.8 g/U], numerically the response was lower. In comparison to the healthy subjects, the PD response was even lower magnitude based on GIRmax and AUC0-24h despite of higher IDeg systemic exposures (higher dose of IDeg used in this Trial), which indicates even lower sensitivity in the Type 2 DM subjects to the effects of IDeg in comparison to Type 1 DM and healthy subjects. On average, the GIR versus time profile showed no distinct peak indicating close to the desired peak-less time action profile of IDeg in subjects with Type 2 DM.

The integrity of the euglycemic clamp was evident for most of the subjects based on blood glucose values, which were around the pre-specified target of 90 mg/dL (5.0 mmol/L). However, in 3 subjects the values escaped the target. The c-peptide data showed a gradual rise in levels for most subjects up to 12 h which makes the interpretation of GIR data difficult, for instance, this could mean that initiation of glucose infusion could have triggered endogenous insulin secretion and vice versa in these subjects, thus inflating the onset of action. Therefore, interference due to endogenous insulin cannot be ruled out. Nevertheless, this does not impact the overall interpretation of data, as if this AUCGIR is over estimated then the true AUCGIR is likely of lower magnitude than that observed in Type 1 DM and healthy.

Collectively, close to peak-less shape of time-action profile following single dose and >24h duration of action support the use of IDeg U100 as a QD basal insulin in both Type 1 and Type 2 DM patients.

#### **2.2.4 What is the nature of the time-action profile of Insulin Degludec after once daily subcutaneous administration, how does it relate to the dose, and does it support the use of Insulin Degludec as a basal insulin?**

Typically, phase 1 PK and PD evaluations involve single SC insulin administration. However, a unique situation for PK and PD is presented by the long t<sub>1/2</sub> of IDeg and corresponding duration of action, which exceeds 24 hour. Sponsor evaluated steady-state PK and PD of IDeg in the patient population to determine glucodynamic effect offered by daily dosing at steady-state, and evaluate the molar dose ratio in comparison to insulin glargine. While evaluation of molar dose ratio is discussed in section 2.2.5, the PK and PD characteristics of IDeg after multiple doses are discussed here.

##### **Multiple Dose PK and PD evaluation in Type 1 DM:**

Multiple dose PK and PD characteristics of IDeg intended commercial formulation [IDeg (M)] in subjects with Type 1 DM were evaluated in Trial NN1250-1993. This was a randomized, single-center, double-blind, incomplete block cross-over, multiple dose trial evaluating the PD response of IDeg and IGl<sub>ar</sub> at steady-state conditions in subjects with type 1 diabetes. Each subject was randomized to one out of three dose levels (0.4, 0.6 or 0.8 U/kg) and one out of two sequences (either IDeg followed by IGl<sub>ar</sub> or IGl<sub>ar</sub> followed by IDeg).

PK samples were collected on after first-dose and at steady-state under non-clamp conditions. Both PK and GIR data was collected on Visits 7 and 16 (Period 1 and 2, respectively) at -6 to 42 h (End of clamp), and 48, 72, 96, and 24 h (all post-last dose). During the 3 hour run-in period (-6 to -3 h), i.v. Actrapid® infusion or glucose infusion was given to achieve glucose clamp target 5.5 mmol/L (100 mg/dL) ± 30%. The variable glucose infusion was used to keep glucose clamp

target 5.5 mmol/L (100 mg/dL). PD data (GIR) was obtained under euglycemic clamp from time 0 hour to 42 hour.

**Figures 16 and 17** below present the mean serum concentration-time profiles of IDeg after first dose, and full profile over eight days of once daily administration of 0.4, 0.6, and 0.8 U/kg doses, respectively. Figure 24 illustrates the PD profiles for the three dose levels as mean raw and mean smooth GIR profiles.

For the three dose levels, after first SC administration, IDeg demonstrated slow absorption into the systemic circulation. Median time to peak concentration was around 11-13 hour. On average, peak and 0-24h exposure increased in less than proportional manner with increase in dose. With once daily administration, the steady-state appear to be achieved by 72 hour with an accumulation ratio close to 2, as expected from IDeg's  $t_{1/2}$  of ~20 hours after multiple once daily dose.

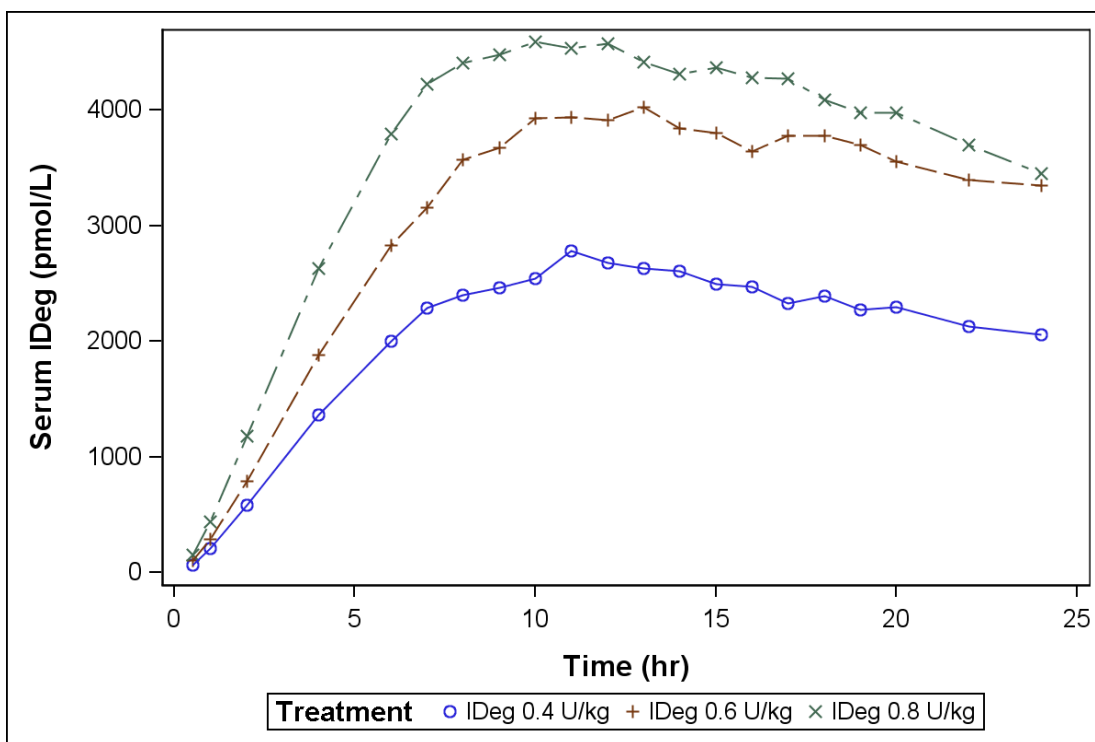


**Figure 16** Observed mean concentration-time profiles for IDeg (M) after first dose during eight days of once daily SC dose at three dose levels [0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg) and 0.8 U/kg (4.8 nmol/kg) in Type 1 DM subjects (N=21)

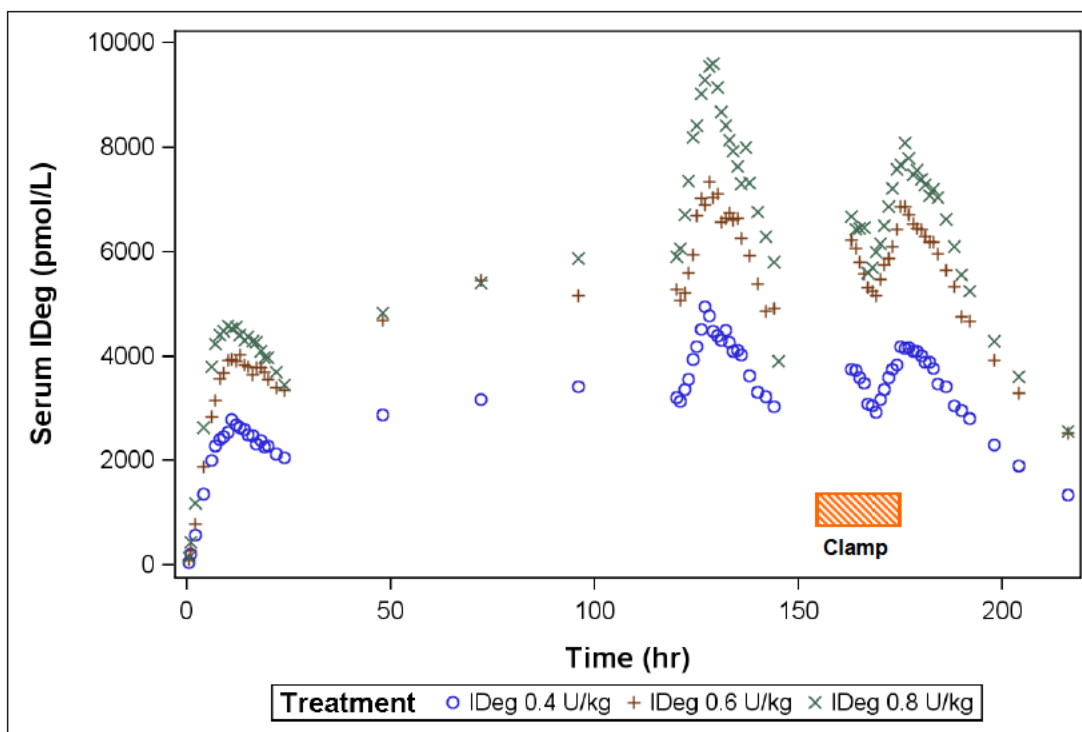


**Figure 17** Observed mean concentration-time profiles for IDeg (M) during eight days of once daily SC dose at three dose levels [0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg) and 0.8 U/kg (4.8 nmol/kg)] in Type 1 DM subjects (N=21)

**Table 10** Summary of IDeg PK parameters after first and last dose (NN1250-1993) for 0.4, 0.6, and 0.8 U/kg dose

| PK Parameter:<br>Geo. Mean (CV)                                                    | IDeg First Dose |             |             |
|------------------------------------------------------------------------------------|-----------------|-------------|-------------|
|                                                                                    | 0.4 U/kg        | 0.6 U/kg    | 0.8 U/kg    |
| C <sub>max</sub> (pmol/L):                                                         | 2896 (25)       | 4162 (42)   | 5029 (26)   |
| t <sub>max</sub> (hour)*:                                                          | 11 (8-22)       | 13 (10-24)  | 12 (6-22)   |
| AUC <sub>0-24h</sub> (pmol*h/L):                                                   | 47646 (24)      | 69350 (38)  | 84038 (25)  |
|                                                                                    | IDeg Day 8 Dose |             |             |
| C <sub>max</sub> (pmol/L):                                                         | 5376 (28)       | 7389 (38)   | 9731 (21)   |
| t <sub>max</sub> (hour)*:                                                          | 8 (0-12)        | 8 (5-18)    | 12 (6-22)   |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                  | 90941 (25)      | 137497 (38) | 179606 (23) |
| t <sub>1/2,ss</sub> :                                                              | 27 (26)         | 28 (27)     | 24 (29)     |
| AR <sub>AUC</sub> **:                                                              | 1.91 (28)       | 1.98 (25)   | 2.14 (24)   |
| AR <sub>C<sub>MAX</sub></sub> ***:                                                 | 1.86 (30)       | 1.78 (29)   | 1.93 (23)   |
| *Median (Min., Max)                                                                |                 |             |             |
| Accumulation Ratio AUC comparison; AR <sub>AUC</sub> **:                           |                 |             |             |
| Accumulation Ratio C <sub>max</sub> comparison; AR <sub>C<sub>MAX</sub></sub> ***: |                 |             |             |

The statistical analysis indicated dose proportionality in both C<sub>max</sub> and AUC<sub>tau,ss</sub> (Figure 18). Dose proportionality was also indicated for AUC<sub>IDeg,tau,ss</sub> and C<sub>max,IDeg,SS</sub> when outlier values (observed for 0.6 U/kg in 2 subjects) were excluded. The estimated slope [95%CI] was 1.00 [0.76; 1.23] for AUC<sub>IDeg,tau,ss</sub> and 1.01 [0.79; 1.24] for C<sub>max,IDeg,SS</sub>.

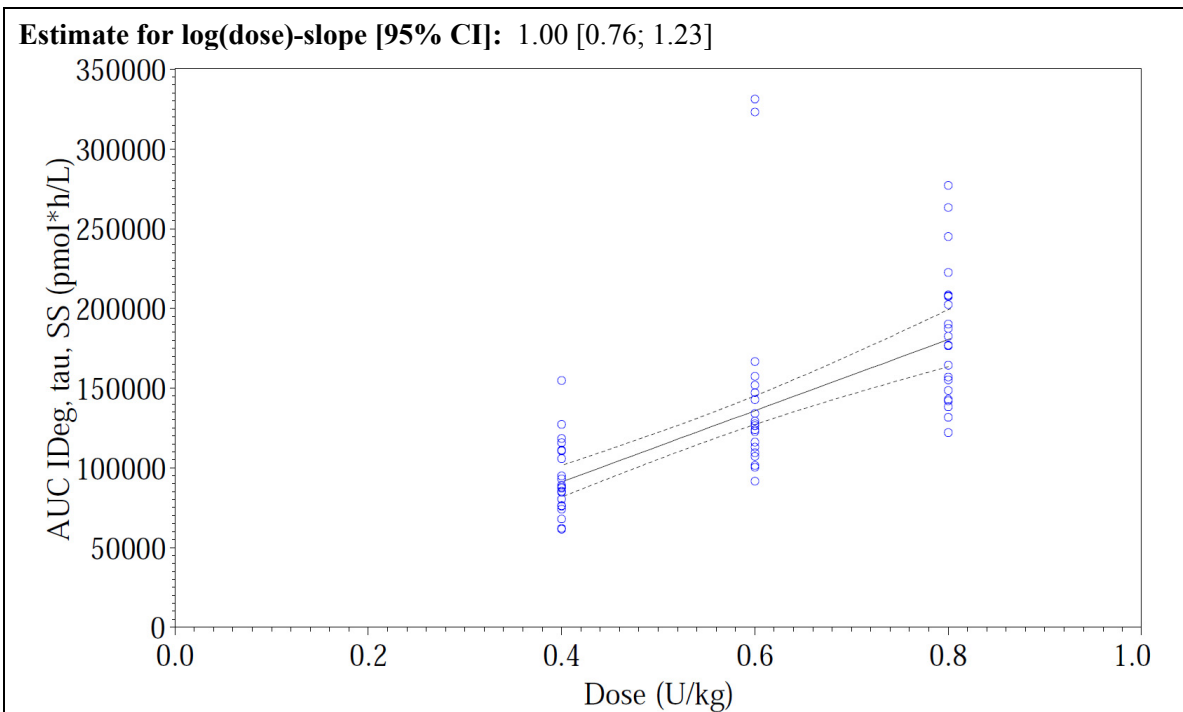
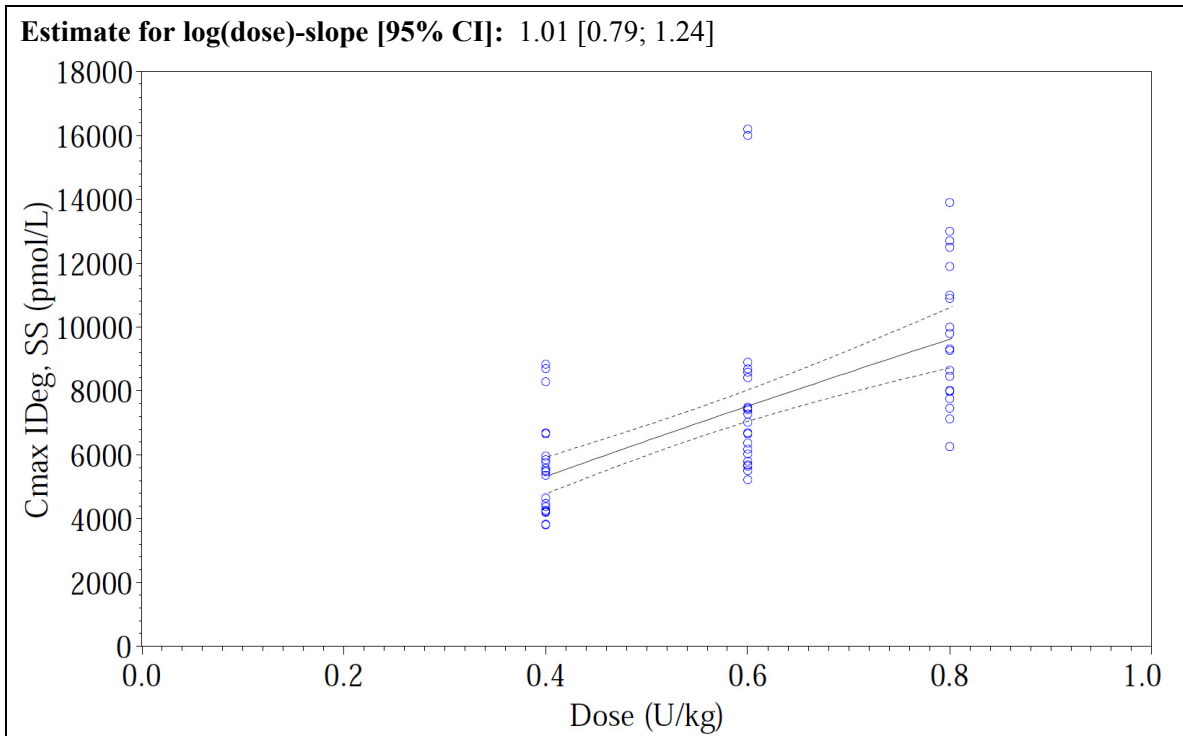


**Figure 18 Results of the dose-proportionality assessment for IDeg Cmax (top) and AUC (bottom) (N=64, all treatments)**

Pharmacodynamic response (as measured by GIR) after the eighth dose at steady-state showed no distinct peak at steady-state indicating close to the desired peak-less time action profile of IDeg (Figure 19).

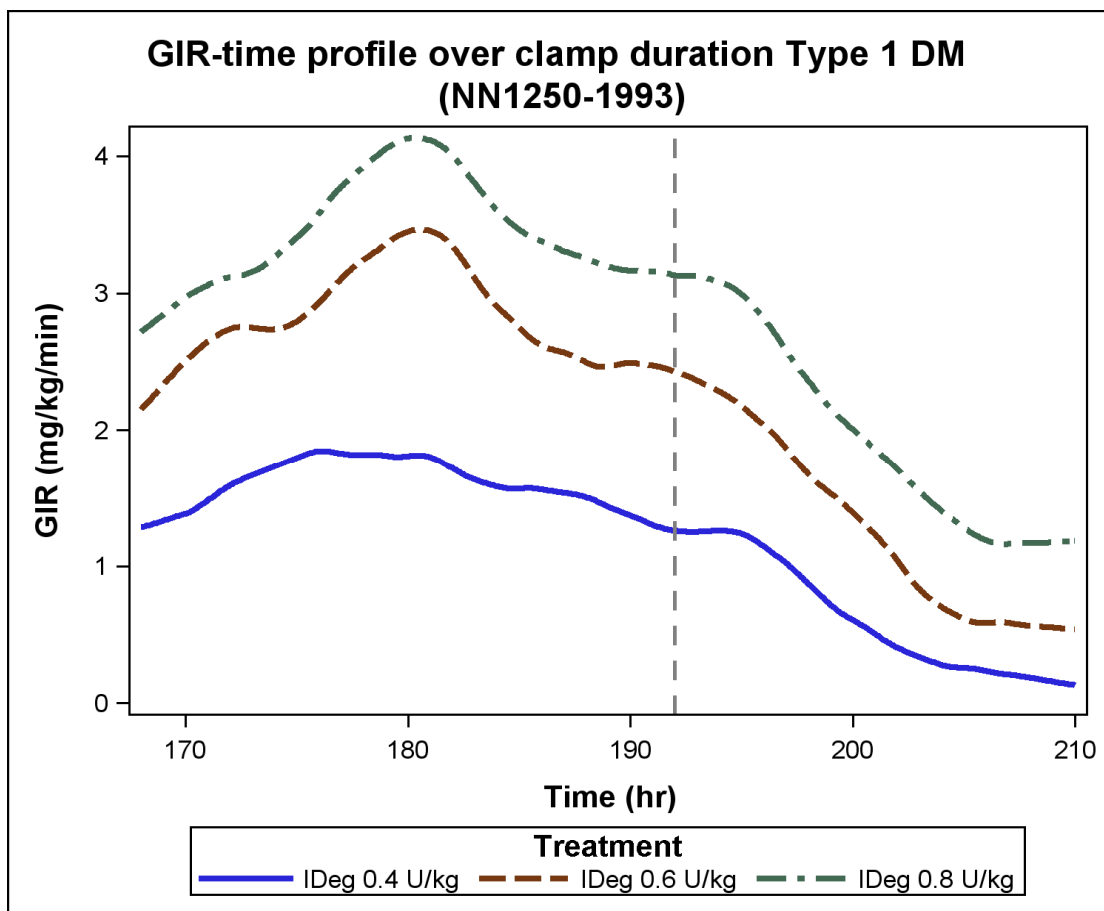


**Figure 19** Mean raw GIR and loess smooth GIR profiles for IDeg (M) on day 8 of once daily SC dose at three dose levels [0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg) and 0.8 U/kg (4.8 nmol/kg) in Type 1 DM subjects (N=21)

**Table 11** Summary of IDeg PD parameters after the last dose (NN1250-1993) for 0.4, 0.6, 0.8 U/kg dose from U100 formulation

| PD Parameter:<br>Geo. Mean (CV)                                             | IDeg Day 6 Dose         |                         |                         |
|-----------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|
|                                                                             | <u>0.4 U/kg</u><br>N=21 | <u>0.6 U/kg</u><br>N=21 | <u>0.8 U/kg</u><br>N=22 |
| GIR <sub>max</sub> (pmol/L):                                                | 2.0 (49)                | 3.6 (30)                | 4.2 (29)                |
| t <sub>GIR<sub>max</sub></sub> (hour)*:                                     | 12 (5-42)               | 12 (3-24)               | 12 (0-18)               |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):                                      | 1948 (54)               | 3854 (31)               | 4766 (27)               |
| <b>Dose contrasts for AUC<sub>GIR,tau,ss</sub> - LS Mean Ratio [95% CI]</b> |                         |                         |                         |
| IDeg 100U/mL 0.6 vs 0.4U/kg :                                               | 2.03 [ 1.53; 2.69]      |                         |                         |
| IDeg 100U/mL 0.8 vs 0.4U/kg :                                               | 2.50 [ 1.89; 3.32]      |                         |                         |
| IDeg 100U/mL 0.8 vs 0.6U/kg :                                               | 1.24 [ 0.93; 1.64]      |                         |                         |

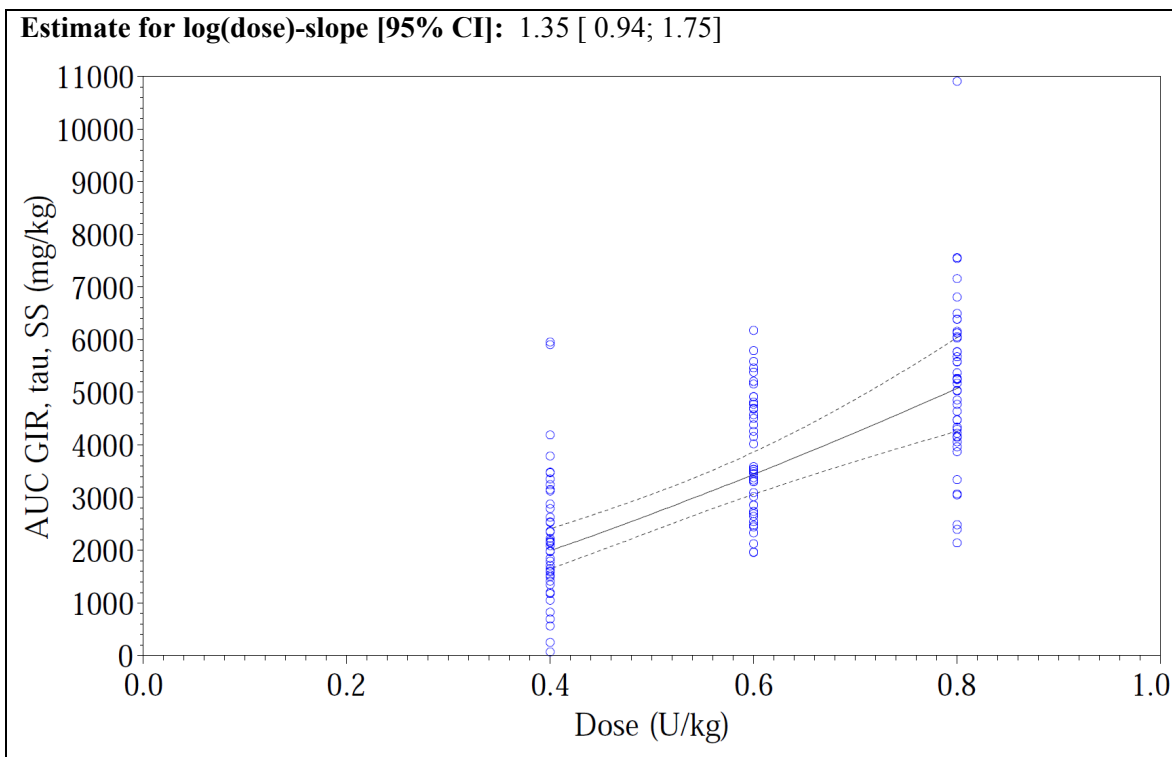


**Figure 20 Results of the dose-proportionality assessment for AUCGIR,tau,ss (N=64, all treatments)**

Based on pair wise comparison, the PD response appeared to increase in more than proportional manner when comparing 0.6 U/kg versus 0.4 U/kg dose and 0.8 U/kg versus 0.4 U/kg dose. The increase was less proportional when 0.8 U/kg was compared to 0.6 U/kg. However, the dose-proportionality analysis could not rule out lack of proportionality as even though the slope was greater than 1, the 95% CIs contained 1 (**Figure 20**).

At steady-state, the GIR at baseline was ~1.2 mg/kg for 0.4 U/kg dose, indicating a build-up of response at steady-state due to accumulation of IDeg. The baseline GIR increased with the dose as well as the GIRmax, which peaked at around 12 hour. The GIR tend to return to the baseline by 24 hour for all 3 dose levels. Beyond 24 hours, the GIR decreased with declining IDeg concentration. While on average, GIR tend to return to zero by ~30 hour for the lowest 0.4 U/kg dose, it was still higher than 0 for 0.6 and 0.8 U/kg dose levels (**Figure 19**). This was reflected in the blood glucose levels monitored during clamp, which start escaping the target value of 5.5 mmol/L for 0.4 U/kg dose around 30 hours, while still being within the acceptable limits of  $\pm 30\%$  (3.85 – 7.15 mmol/L). Whereas, the mean blood glucose values remained at target of 5.5 mmol/L for the two higher dose levels through 42 hours (**Figure 21**). This indicates that at steady-state, the duration of action of IDeg could be expected to be around 42 hour for doses > 0.4 U/kg as opposed to IGlir (used as comparator for dose-response), for which duration of action is less than or equal to 24 hours. In addition, while assessing duration of action one has to determine the clinical relevance of low GIR values observed during clamp experiment towards the end of clamp. This utility of duration of action parameter can only be confirmed during the efficacy/safety evaluation.

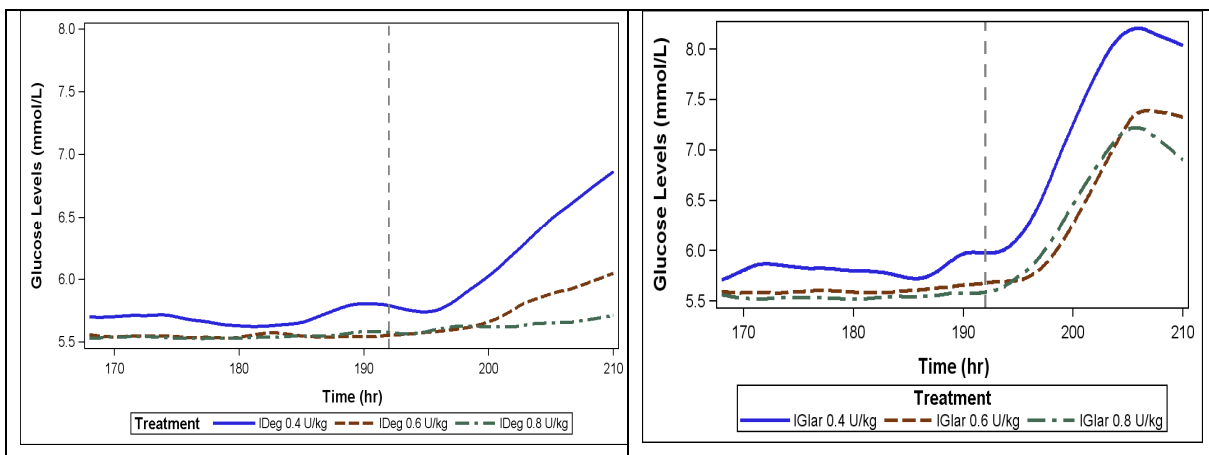


**Figure 21 Mean Blood Glucose Profiles over 42 h clamp duration after last dose of IDeg at Steady State in Type 1 DM subjects (N=21)**

The integrity of the euglycemic clamp was also evident from the blood glucose values.

**Multiple Dose PK and PD evaluation in Type 2 DM:**

Multiple dose PK and PD characteristics of IDeg intended commercial formulation [IDeg (M)] in subjects with Type 2 DM were evaluated in Trial NN1250-1987. This trial was a randomized, single-center, double-blind, two-period, incomplete block cross-over, multiple-dose trial. The primary objective of the trial was to evaluate the pharmacodynamic and pharmacokinetic dose-response relationship of IDeg 100 U/mL and characterizing the pharmacodynamic and pharmacokinetic properties of IDeg 200 U/mL formulation at steady state conditions in subjects with type 2 diabetes. Each subject was randomly allocated to two of four possible treatments: IDeg 100 U/mL (0.4, 0.6 or 0.8 U/kg) or IDeg 200 U/mL (0.6 U/kg). Each treatment period consisted of 6 days of once daily dosing with IDeg followed by pharmacokinetic sampling until 120 hours after the last dose. The pharmacodynamic response was evaluated during a 26-hour euglycemic clamp performed after the last (6th) dose of IDeg in each treatment period.

Each treatment period consisted of 6 days of once daily dosing with IDeg followed by 5 days with pharmacokinetic sampling until 120 hours after the last dose. On day of clamp, The subject was connected to the Biostator and a variable i.v. infusion of insulin (15 IU Actrapid®, 100 IU/mL in 49 mL saline and 1 mL of the subjects blood) or glucose, was initiated in order to obtain a glucose clamp target level of 5.0 mmol/L (90 mg/dL). If insulin was infused, glucose was not to be infused and vice versa. The insulin and glucose infusion rate was recorded. A blood glucose target level of 5.0 mmol/L (90 mg/dL)  $\pm$ 20% (upper and lower limit included) was kept continuously for at least 1 hour before the pre-dose clamp period was initiated., IDeg was administered. Actrapid®, infusion was gradually decreased until the glucose concentration had dropped by 0.3 mmol/L (5 mg/dL), where it was stopped. Then variable glucose infusion was initiated to keep glucose clamp target 5.0 mmol/L (90 mg/dL). PD data (GIR) was obtained under euglycemic clamp from time 0 hour to 42 hour.

**Figures 22 and 23** below present the mean serum concentration-time profiles of IDeg after first dose, and full profile over six days of once daily administration of 0.4, 0.6, and 0.8 U/kg doses from U100, respectively.

For the three dose levels from U100 formulation, IDeg demonstrated slow absorption into the systemic circulation after first SC administration. Median time to peak concentration was around 13-16 hour. With once daily administration, the steady-state appear to be achieved by 72 hour

with an accumulation ratio close to 2, as expected from once daily administration of a drug with  $t_{1/2}$  of ~20 hours.

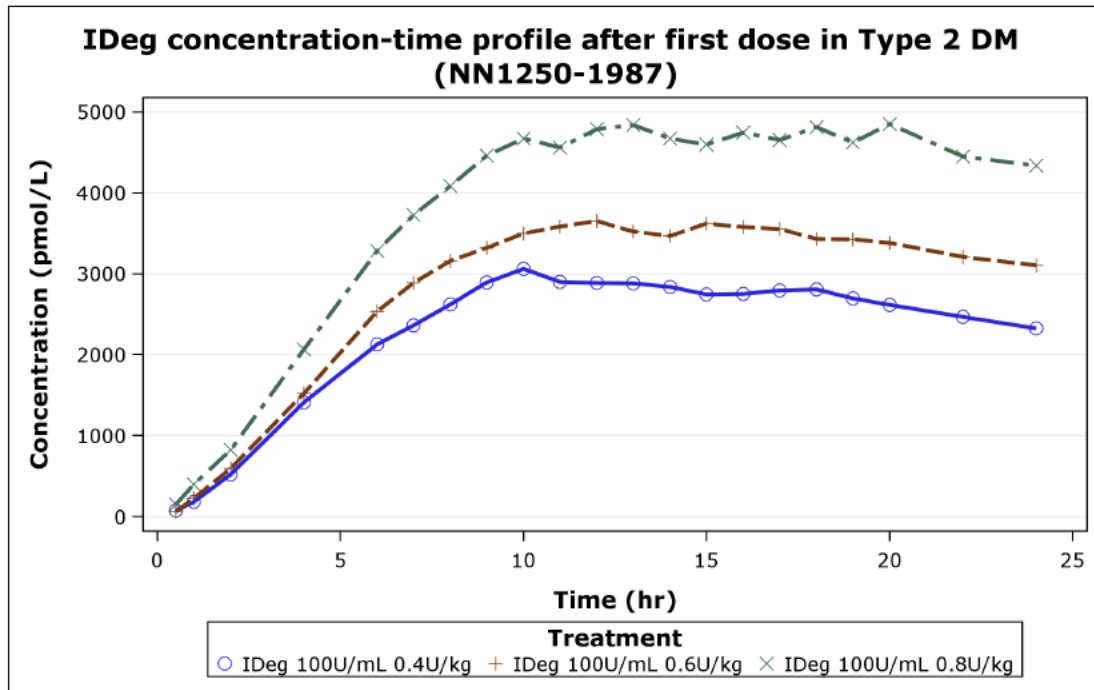


**Figure 22** Observed mean concentration-time profiles for IDeg (M) after first dose during six days of once daily SC dose of 0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg), 0.8 U/kg (4.8 nmol/kg) from U100 formulation in Type 2 DM subjects (N=22, 38, and 21, respectively)

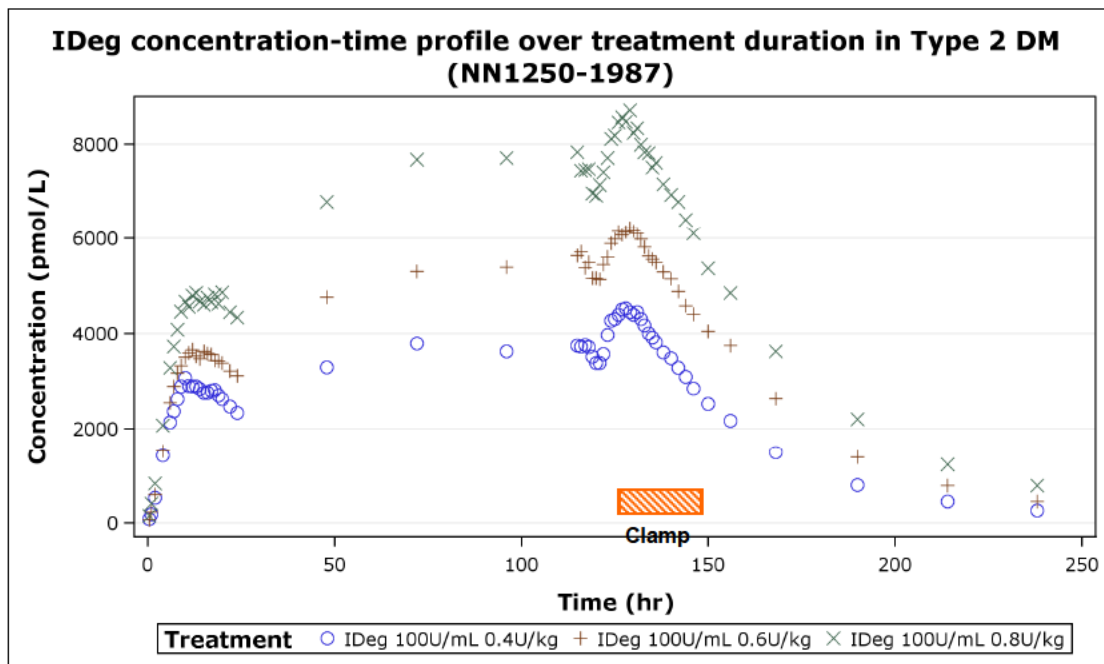
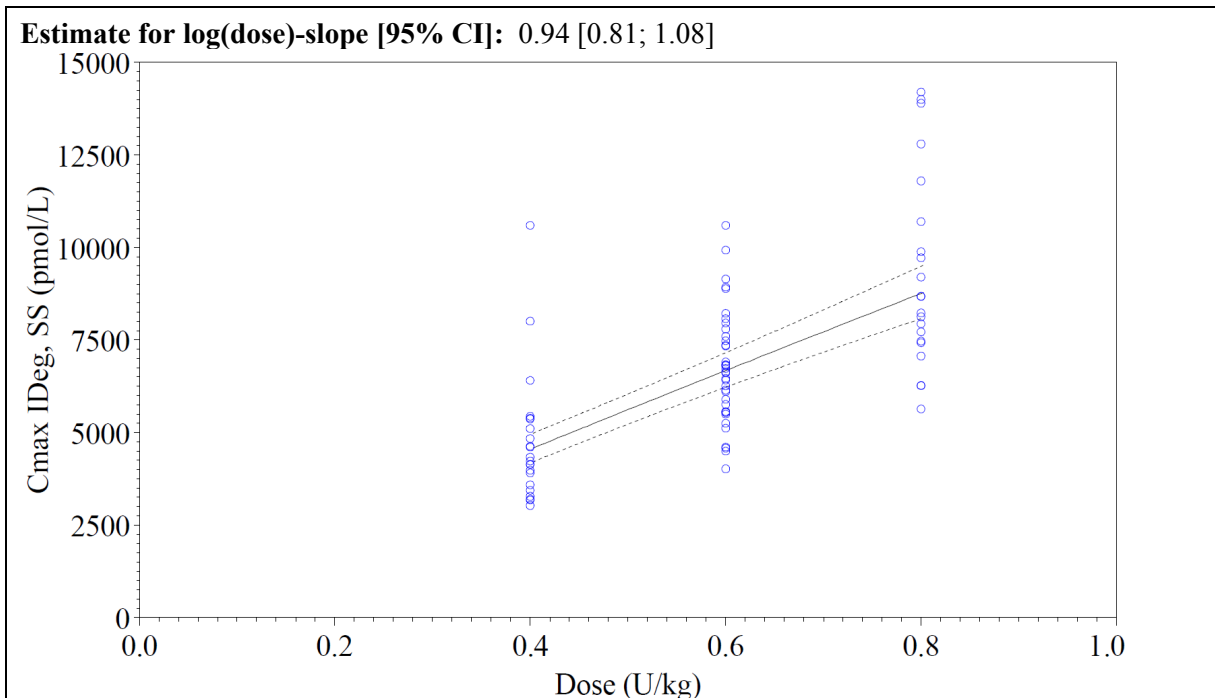


**Figure 23** Observed mean concentration-time profiles for IDeg (M) during six days of once daily SC dose of 0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg), 0.8 U/kg (4.8 nmol/kg) from U100 formulation in Type 2 DM subjects (N=22, 38, and 21, respectively)

**Table 12 Summary of IDeg PK parameters after first and last dose (NN1250-1987) for 0.4, 0.6, 0.8 U/kg dose from U100 formulation**

| PK Parameter:<br>Geo. Mean (CV)                                                                          | IDeg First Dose         |                         |                         |
|----------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|-------------------------|
|                                                                                                          | <u>0.4 U/kg</u><br>N=22 | <u>0.6 U/kg</u><br>N=38 | <u>0.8 U/kg</u><br>N=21 |
| Cmax (pmol/L):                                                                                           | 3143 (41)               | 3860 (32)               | 5280 (29)               |
| t <sub>max</sub> (hour)*:                                                                                | 13 (8-22)               | 15 (8-24)               | 16 (8-24)               |
| AUC <sub>0-24h</sub> (pmol*h/L):                                                                         | 51026 (38)              | 64418 (30)              | 87145 (27)              |
|                                                                                                          | IDeg Day 6 Dose         |                         |                         |
| Cmax (pmol/L):                                                                                           | 4534 (37)               | 6592 (23)               | 8987 (28)               |
| t <sub>max</sub> (hour)*:                                                                                | 8.5 (4-15)              | 9.0 (1-36)              | 8.0 (3-11)              |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                                        | 89643 (35)              | 130164 (38)             | 177408 (23)             |
| t <sub>1/2,ss</sub> :                                                                                    | 26 (27)                 | 25 (28)                 | 28 (38)                 |
| AR <sub>AUC</sub> **:                                                                                    | 1.8 (28)                | 2.0 (23)                | 2.0 (23)                |
| AR <sub>C<sub>MAX</sub></sub> ***:                                                                       | 1.4 (29)                | 1.7 (25)                | 1.7 (31)                |
| *Median (Min., Max)                                                                                      |                         |                         |                         |
| Accumulation Ratio AUC comparison; AR <sub>AUC</sub> ** : AUC <sub>tau,SS</sub> / AUC <sub>0-24,SD</sub> |                         |                         |                         |
| Accumulation Ratio Cmax comparison; AR <sub>C<sub>MAX</sub></sub> *** : Cmax,SS / Cmax,SD                |                         |                         |                         |

The statistical analysis indicated dose proportionality in both Cmax and AUC<sub>tau,ss</sub> (**Figure 24**). The estimated slope [95%CI] was 0.94 [0.81; 1.08] for Cmax, IDeg, SS and 0.93 [0.82; 1.03] for AUC<sub>IDeg,tau,ss</sub>.



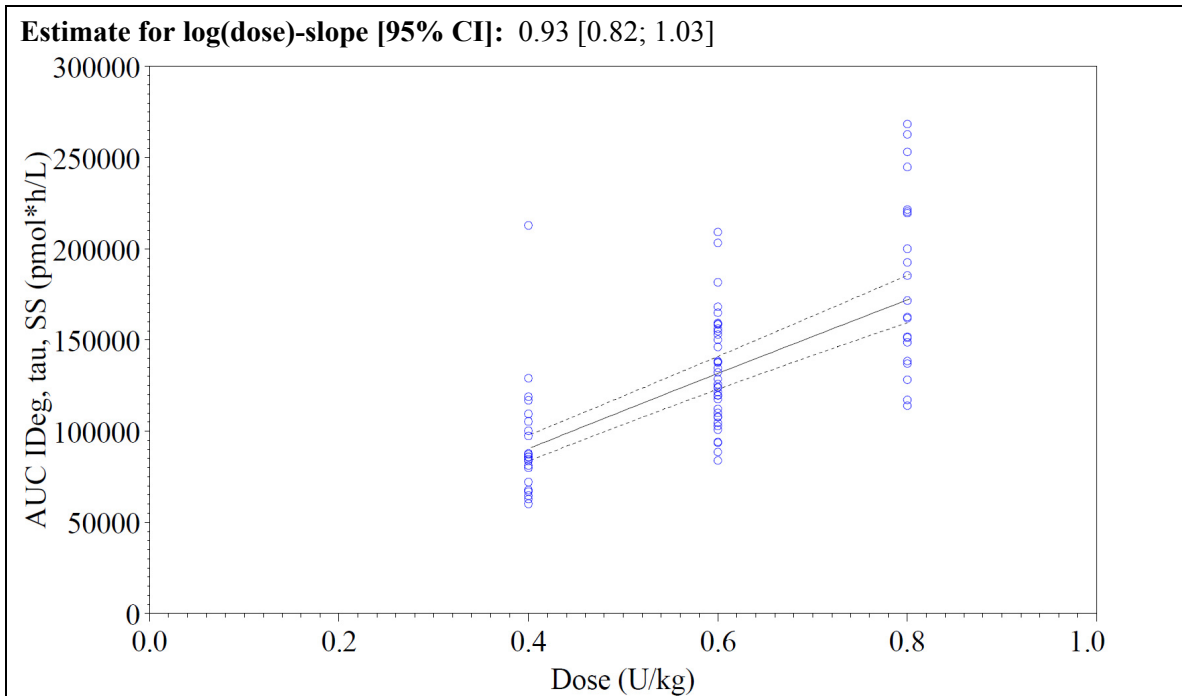


**Figure 24 Results of the dose-proportionality assessment for IDeg Cmax and AUC (N=49, all treatments)**

**Figure 25** illustrates the PD profiles for the three dose levels as mean smoothed GIR profiles. Pharmacodynamic response (as measured by GIR) after the sixth dose at steady-state showed no distinct peak at steady-state indicating close to the desired peak-less time action profile of IDeg. The GIR at baseline was ~1.2 mg/kg for 0.4 U/kg dose, indicating a build-up of response at steady-state due to accumulation of IDeg. The baseline GIR increased with the dose as well as the GIRmax, which peaked at around 12 hour. The GIR tend to return to the baseline by 24 hour for all 3 dose levels, it was still higher than 0 for 0.6 and 0.8 U/kg dose levels. This was reflected in the blood glucose levels, which did not escape the target value of 5.0 mmol/L for. This indicates that at steady-state, the duration of action of IDeg could extend beyond 24 hour for doses  $\geq 0.4$  U/kg.

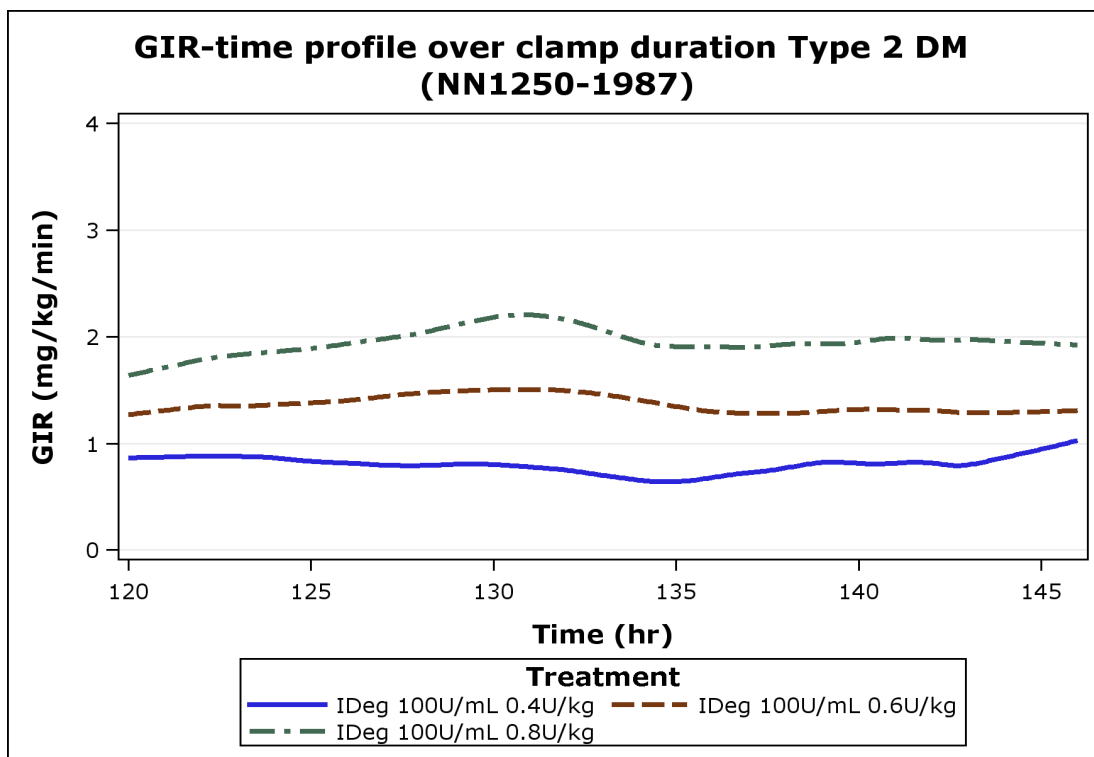


**Figure 25** Mean smoothed GIR profiles for IDeg (M) on day 6 of once daily SC dose of 0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg), 0.8 U/kg (4.8 nmol/kg) from U100 formulation in Type 2 DM subjects (N=22, 38, and 21, respectively)

**Table 13** Summary of IDeg PD parameters after the last dose (NN1250-1987) for 0.4, 0.6, 0.8 U/kg dose from U100 formulation

| PD Parameter:<br>Geo. Mean (CV)<br>(Min., Max.)                              | IDeg Day 6 Dose         |                           |                           |
|------------------------------------------------------------------------------|-------------------------|---------------------------|---------------------------|
|                                                                              | <u>0.4 U/kg</u><br>N=22 | <u>0.6 U/kg</u><br>N=37   | <u>0.8 U/kg</u><br>N=21   |
| GIRmax (pmol/L):                                                             | 1.1 (52)<br>(0.2 , 2.8) | 1.7 (49)<br>(0.7 , 4.4)   | 2.4 (54)<br>(0.7, 7.4)    |
| t <sub>GIRmax</sub> (hour)*:                                                 | 13 (0-26)               | 11 (0-26)                 | 11 (0-26)                 |
| AUC <sub>GIR,tau, ss</sub> (mg/kg/min):                                      | 828 (68)<br>(44 , 2830) | 1694 (56)<br>(531 , 4610) | 2482 (46)<br>(405 , 5843) |
| <b>Dose contrasts for AUC<sub>GIR,tau, ss</sub> - LS Mean Ratio [95% CI]</b> |                         |                           |                           |
| <b>IDeg 100U/mL 0.6 vs 0.4U/kg :</b> 2.03 [1.65;2.50]                        |                         |                           |                           |
| <b>IDeg 100U/mL 0.8 vs 0.4U/kg :</b> 3.01 [2.43;3.72]                        |                         |                           |                           |
| <b>IDeg 100U/mL 0.8 vs 0.6U/kg :</b> 1.48 [1.20;1.83]                        |                         |                           |                           |
| <b>Dose contrasts for GIRmax -</b>                                           |                         |                           |                           |
| <b>IDeg 100U/mL 0.6 vs 0.4U/kg :</b> 1.54 [1.33;1.79]                        |                         |                           |                           |
| <b>IDeg 100U/mL 0.8 vs 0.4U/kg :</b> 2.18 [1.87;2.54]                        |                         |                           |                           |
| <b>IDeg 100U/mL 0.8 vs 0.6U/kg :</b> 1.41 [1.21;1.65]                        |                         |                           |                           |

Based on pair wise comparison, the PD response appeared to increase in more than proportional manner for all comparisons: 0.6 U/kg versus 0.4 U/kg, 0.8 U/kg versus 0.4 U/kg, and 0.8 U/kg versus 0.6 U/kg dose. The GIRmax comparison showed almost proportional increase in GIRmax with dose.

The integrity of the euglycemic clamp was also evident from the blood glucose values that were tightly maintained at the target of 5.0 mmol/L on average, and were within the pre-specified limit of  $\pm 30\%$  (3.85 – 7.15 mmol/L). The c-peptide levels remained suppressed for most of the clamp duration, and suppression was greater with 0.6 and 0.8U/kg dose levels.

Collectively, close to peak-less shape of time-action profile was evident for IDeg following multiple once-daily doses. The duration of action at steady-state was >24h to support the once-daily use of IDeg U100 as a basal insulin in both Type 1 and Type 2 DM patients.

### 2.2.5 What is the molar dose ratio of Insulin Degludec to Insulin Glargine after subcutaneous administration?

As per WHO standards and standards adopted by the American Diabetes Association, for regular human insulin 1U (unit) equals 6 nmol<sup>9</sup> of human insulin. Very often insulin concentrations are also expressed as mU where, 1 microUnit = 6 pmol/L. Clinically, the concentrations in mU seem to be more relevant to the glucose lowering effect<sup>10</sup> (amount of glucose utilized per unit of insulin dose). However, measurements in molar units are more relevant in deciding formulation strength, comparing systemic levels. To claim that a test insulin is equipotent to reference insulin e.g. to RHI on a molar basis, one can formulate the new insulin as 600 nmol/mL of insulin and establish comparable glucose lowering effect to RHI, when same SC dose is administered as U/kg (injection volume is kept same) in a PKPD study. Typically, single dose PKPD comparison under euglycemic clamp provide this information as AUC<sub>GIR</sub> (mg/kg of glucose utilized for X Unit/kg dose). Alternatively, one could arrive at a decision on the concentration of the formulation by comparing dose-response of the new insulin to reference insulin using nmol/kg based doses in the PKPD evaluation. This comparison could establish that e.g., 12 nmol/kg of test insulin gives comparable AUC<sub>GIR</sub> to 6 nmol/kg of RHI (1U/kg) so as to formulate new insulin as 1200 nmol/mL to get 100 U/mL in the formulation.

Historically, the AUC<sub>glucose</sub> (hypoglycemic effect) of NPH was compared to RHI, AUC<sub>glucose</sub>/AUC<sub>GIR</sub> of insulin glargine (IGlar) was compared to NPH. Based on comparable PD response, both NPH and IGlar could be formulated as 600 nmol/mL (100 U/mL). However, comparison of AUC<sub>GIR</sub> of insulin detemir (detemir) versus that observed for NPH revealed a molar dose ratio of four, and thus Agency accepted 100 U/mL detemir to be formulated as 2400 nmol/mL<sup>11, 12</sup> (24 nmol of detemir correspond to 6 nmol of human insulin).

For IDeg, the sponsor attempted to establish IDeg molar dose ratio in Trial NN5401-1719, which was a randomized, double-blind, single dose, six-period crossover, dose response trial comparing the pharmacodynamics and pharmacokinetics of IDeg (IDeg) with insulin glargine in Type 1 and Type 2 Diabetic patients. The dose-response relationship was evaluated in an ANOVA approach using the log-transformed AUC<sub>GIR(0-24h)</sub> as the dependent variable, visit and the interaction between insulin preparation and dose as fixed effects and subject as a random effect as shown in the model below:

$$Y_{ij} = \beta_{ins(ij)} + \gamma \cdot \log(dose_{ij}) + U_i + \epsilon_{ij}$$

Where,  $Y_{ij}$  is the log-transformed AUC<sub>GIR(0-24h)</sub> for subject  $i$  at treatment visit  $j$   
 $\beta_{ins(ij)}$  is the intercept between the vertical axis and the dose-response curve for the specific insulin product given to subject  $i$  at treatment visit  $j$   
 $dose_{ij}$  denotes the dose level (in nmol/kg) given to subject  $i$  at treatment visit  $j$

<sup>9</sup> Table 1—Système International (SI) units for plasma, serum, or blood concentrations, Diabetes Care December 1997 20:1931.

<sup>10</sup> Comments and Responses. Insulin Assay Standardization: Leading to Measures of Insulin Sensitivity and Secretion for Practical Clinical Care. Lutz Heinemann. Diabetes Care, Volume 33, Number 6, June 2010 e83

<sup>11</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/021-536\\_Levemir\\_chemr.PDF](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021-536_Levemir_chemr.PDF)

<sup>12</sup> [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2005/021-536\\_Levemir\\_biopharmr.PDF](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2005/021-536_Levemir_biopharmr.PDF)

$\gamma_{ins}(ij)$  represents the coefficient (depending on insulin product given to subject  $i$  at treatment visit  $j$  of the effect of  $\log(\text{dose } ij)$   
 $U_i$  is the random effect of subject  $i$ , and  $\epsilon_{ij}$  is the residual error term for subject  $i$  at treatment visit  $j$   
The random effects  $U_{1 \text{ to } N}$  were independent and normally distributed with mean 0 and a common variance.

Potency was estimated using the following equation:

$$P_{I454/IGlar} = \exp\left(\frac{\hat{\beta}_{I454} - \hat{\beta}_{IGlar}}{\hat{\gamma}}\right)$$

Dose -  $AUC_{GIR(0-24h)}$  relationship for IDeg and IGLar in type 1 and type 2 diabetic patients is shown in **Figures 26a and 26b** below, respectively.

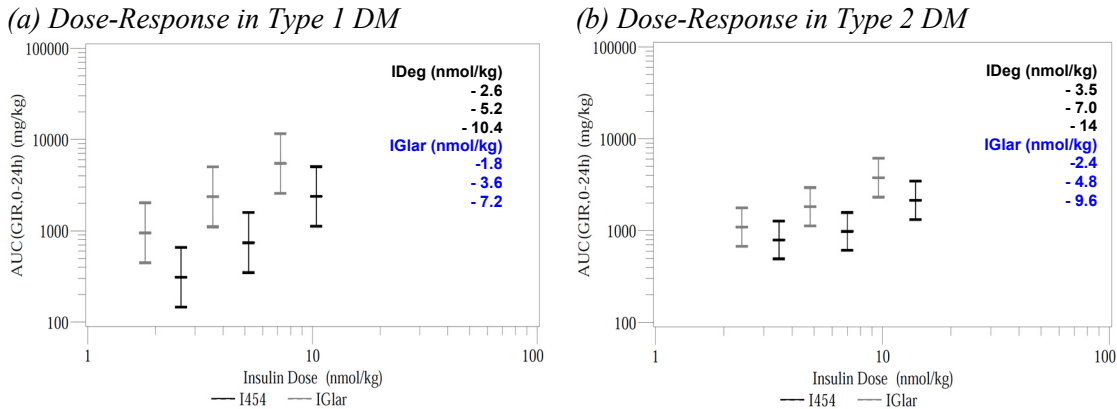


**Figure 26 Comparison of  $AUC_{GIR(0-24h)}$  versus Dose for IDeg and IGLar in patients with Type 1 or Type 2 Diabetes Mellitus (Trial NN5401-1719)**

**Table 14** below summarizes the estimates of relative potency of IDeg to IGLar in type 1 and type 2 diabetic patients.

**Table 14 Relative Potency of IDeg versus IGLar based on  $AUC_{GIR(0-24h)}$  after Single SC Dose (Trial NN5401-1719)**

| Type of Diabetes | Endpoint       | Potency (nmol to nmol) Estimate (95% CI) |
|------------------|----------------|------------------------------------------|
| TYPE 1           | AUC GIR(0-24h) | 0.32 (0.17, 0.49)                        |
| TYPE 2           | AUC GIR(0-24h) | 0.37 (0.23, 0.52)                        |

Despite of certain limitations with the clamp performance in this trial, the results showed that when given as a single SC dose in subjects with type 1 diabetes, 1 nmol of IDeg produced the same effect on glucose over 24 hour duration [ $AUC_{GIR(0-24h)}$ ] as produced by 0.32 nmol of IGLar. Whereas, in subjects with type 2 diabetes, 1 nmol of IDeg produced the same effect on  $AUC_{GIR(0-24h)}$  as 0.37 nmol of IGLar over 24 hour duration.

Apparently in past, for relative potency determination, the single dose PD comparison was feasible for NPH, Insulin glargine, or insulin detemir as for these insulin products, the duration of action (based on GIR versus time data) seemed to be contained within 24 hour, even if the PK profiles were different. However, when duration of action exceeds 24 hour, the in vivo potency comparison becomes challenging for the following reasons:

- (i) practical difficulties in conducting clamp experiments > 24 hour, and

- (ii) the fact that  $AUC_{GIR(0-24h)}$  will be an underestimation of total glucose utilization/unit dose for insulin that has duration of action exceeding 24 hour, and thus comparison with a reference insulin that has duration of action 24 hour or less, is not accurate.

**Figure 27** below illustrates this issue via the comparison of IDeg and IGLar PK and PD profiles observed for single SC dose of 5.2 nmol/kg and 3.6 nmol/kg, respectively. The comparison shows that, on average, use of  $AUC_{GIR(0-24h)}$  in this trial underestimates the total glucose utilization for IDeg.

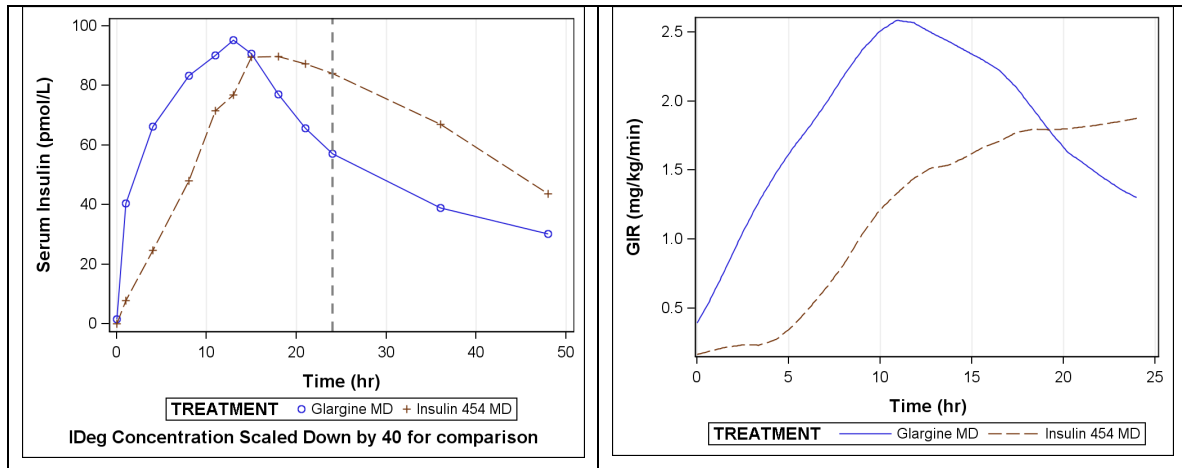


**Figure 27 Comparison of observed PK and PD profiles of IDeg and IGLar after single SC dose of 5.2 nmol/kg and 3.6 nmol/kg, respectively**

One way to get around this issue is to compare the dose-response at steady state (over the dosing duration), as the  $AUC_{\tau,ss}$  is equal to the  $AUC_{0-\infty}$  observed after single dose when a drug follows linear pharmacokinetics. Therefore,  $AUC_{GIR,\tau,ss}$  would approximate the  $AUC_{GIR0-\infty}$  after single dose. The sponsor attempted this approach in Trial NN1250-1876 (IDeg Formulation E). This trial was a randomized, single center, double-blind, two-period cross-over, multiple dose trial with an incomplete block design comparing the PD and PK properties of IDeg and IGLar at steady state conditions in subjects with type 1 diabetes mellitus.

Each subject was randomized to one of three dose levels (low, middle or high dose) and one of two sequences with two periods of eight days of once daily dosing with 1.7, 3.4 or 5.1 nmol/kg IDeg (SIBA (E)) or 0.2, 0.4 or 0.6 U/kg (1.2, 2.4 or 3.6 nmol/kg) IGLar. IDeg (E) and IGLar were administered in the morning as SC injections in the thigh. With the eighth and last dose administration during each treatment period, a 42-hour euglycemic clamp experiment was conducted.

The dose-response ( $AUC_{GIR0-\tau}$ ) analysis revealed that slopes of the response surfaces were linear though not exactly parallel. The log-log plot revealed that in both the treatments there were subjects with unusually low response in the low-dose groups (**Figure 28**). The estimated molar ratio was close to 1 [mean molar dose-ratio of 0.8 (95% CI: 0.72, 0.93)].

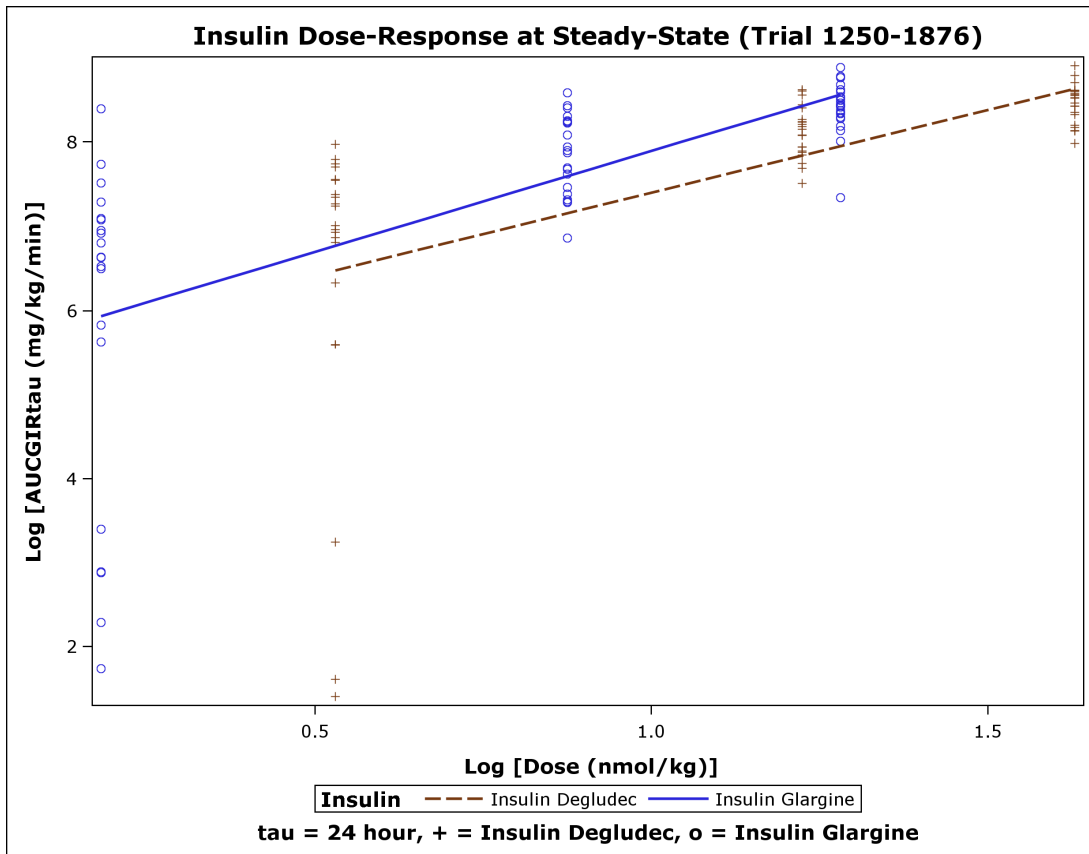


**Figure 28 Comparison of IDeg(E) and IGlار dose-response at steady state in subjects with Type 1 DM for molar dose ratio determination (NN1250-1876)**

Sponsor conducted another trial NN1250-1993 to evaluate and compare IDeg dose-response from the intended commercial formulation IDeg (M) versus IGlار. The trial utilized 0.4 U/kg (2.4 nmol/kg), 0.6 U/kg (3.6 nmol/kg), and 0.8 (4.8 nmol/kg) U/kg dose levels of IDeg or IGlار for comparison, which were numerically higher than doses tested in previous trial 1876, apparently to overcome the challenge posed by the low dose in that trial. Molar dose ratio was assessed in a post-hoc analysis.

The dose-response ( $AUC_{GIR0-\tau,ss}$ ) analysis revealed that slopes of the response surfaces were linear and parallel. The log-log plot revealed a consistent dose-response in both the treatment groups (**Figure 29**). The estimated molar ratio was one [mean molar dose-ratio of 1.03 (95% CI: 0.95; 1.12)].

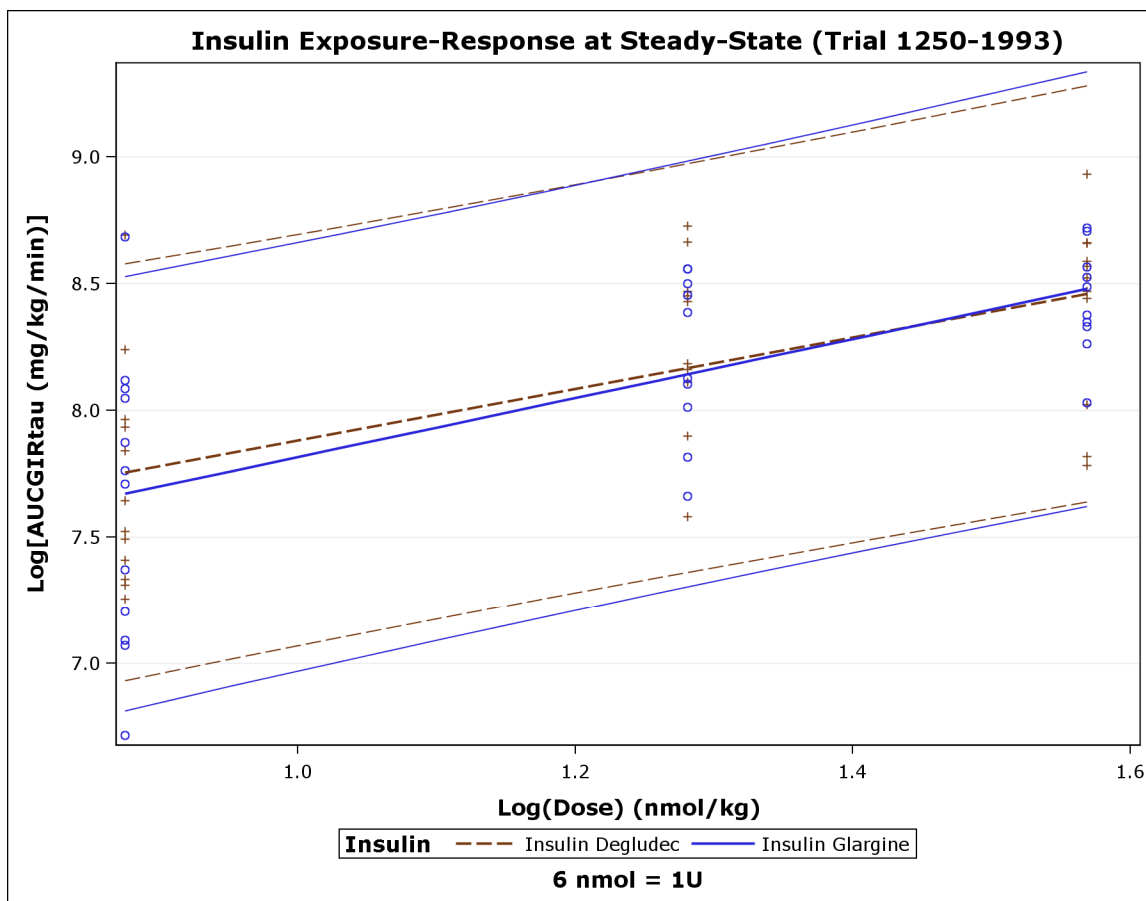


**Figure 29 Comparison of IDeg(M) and IGlar dose-response at steady state in subjects with Type 1 DM for molar dose ratio determination (NN1250-1993)**

Sponsor proposed molar dose of IDeg to IGlar as 1, suggesting equipotency to IGlar for 24-hour  $AUC_{GIR,tau,SS}$  with once-daily administration, and thus proposed IDeg U100 formulation has 600 nmol/mL strength. The proposed molar dose ratio, and thus 600 nmol/mL formulation of IDeg is adequately supported by the results of clinical pharmacology evaluations. However, regardless of the single dose PK and PD study limitations, the results do suggest that for first 24 h of initiation of IDeg therapy a lower glycemic response could be expected from IDeg in comparison to IGlar on a unit-to-unit basis. This difference from IGlar will dissipate at steady-state, which is achieved by 72 hours from initiation of once-daily regimen.

### 2.2.6 What is the extent of within-subject (intra-subject) variability in PK and PD profile of Insulin Degludec in comparison to Insulin Glargine after subcutaneous administration?

The importance of assessing within subject variability (WSV) in insulin action is highlighted well by Lutz Heinemann in his review quoting his colleague's statement "*The variability of insulin action appears to be the pestilence of insulin therapy*"<sup>13</sup>. As summarized in his review, there are multiple factors, which could independently contribute to this variability (**Table 15**).

<sup>13</sup> Variability of Insulin Absorption and Insulin Action. Lutz Heinemann. Diabetes Technology & Therapeutics. Volume 4: 673 - 682, Number 5, 2002.

**Table 15 Potential factors influencing absorption and action of subcutaneously injected insulin – intra and inter-subject variation**

| <i>Insulin preparation</i>                                                                                                                                                                                                               | <i>Differences between injection sites</i>                                                                                                                                        | <i>Changes on the injection site</i>                                                                                                                                                                                                                                                                                  |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Galenic principle of protraction</li> <li>• Dose</li> <li>• Physical status (soluble or suspension)</li> <li>• Concentration</li> <li>• Volume</li> <li>• Species</li> <li>• Shaking</li> </ul> | <ul style="list-style-type: none"> <li>• Injection site (i.m. vs. s.c.)</li> <li>• Injection depths</li> <li>• Anatomical region of injection</li> <li>• Lipodystrophy</li> </ul> | <ul style="list-style-type: none"> <li>• Temperature</li> <li>• Physical activity</li> <li>• Substances known to increase local blood flow</li> <li>• Massage</li> <li>• Hypoglycaemia</li> <li>• Ketoacidosis</li> <li>• Smoking</li> <li>• Age</li> <li>• Metabolic control</li> <li>• Local degradation</li> </ul> |

Irrespective of the cause, the inherent variability of insulin action negatively affects the reproducibility of insulin therapy and makes it challenging to reach an optimal metabolic control. Therefore, it is important to answer a clinically relevant question for any insulin preparation – “For a typical patient with diabetes, will the subcutaneous injection of identical doses of a new insulin preparation lead to a consistent metabolic effect? If not, then how variable is the effect?”. WSV assessment tries to answer this question. Typical of the scientific comparison philosophy, there is no one magic number to regard WSV as ideal. In general, lower value is better or the higher the worse, in contrast to a reference.

To estimate WSV in the PD response, sponsor conducted Trial NN1250-1991 and collected three repeated measurements of PK and PD response data, over the dosing interval ( $\tau=24$  hour) at steady state (derived on treatment day 5, 8, and 11 euglycemic clamp visits/treatment). This data was collected and compared among IDeg and IGl<sub>r</sub> in subjects with type 1 diabetes, in a randomized, single-center, double-blind, parallel-group design setting. The analysis addressed the differences in WSV of the primary endpoint  $AUC_{GIR,\tau,SS}$  comparing IDeg with IGl<sub>r</sub>. To account for heteroscedasticity, the primary endpoint was log-transformed and analyzed with a linear mixed model with insulin type and period as fixed effects, subjects as random effects depending on insulin type and an error variance depending on the insulin type. The difference in within-subject variability for the different insulin types was assessed as the ratio between the error variances.

The CV% was estimated using the following equation:

$$CV\% = (\sqrt{\exp(s^2)} - 1) * 100\% \quad \text{Where, } s^2 \text{ is the estimated variance}$$

To understand the extent of WSV, this reviewer analyzed the data graphically by plotting the regression of PK parameters observed at subsequent visits over the first visit observations as baseline using individual observations. This approach try to draw a relationship between the observations where, in ideal situation of one-to-one correlation, the regression line will pass through unity with tight 95% prediction limits. Alternatively, in absence of a strong correlation, the plot would show a shallow slope with wider 95% prediction limits.

**Figures 30 and 31** below present the relationship of  $AUC_{\tau,SS}$  at subsequent visits to the first observation (0.4 U/kg/day over 12 days) of IDeg and IGl<sub>r</sub>, respectively.

**Figures 32 and 33** below present the relationship of  $AUC_{GIR,\tau,SS}$  at subsequent visits to the first observation (0.4 U/kg/day over 12 days) of IDeg and IGl<sub>r</sub>, respectively.

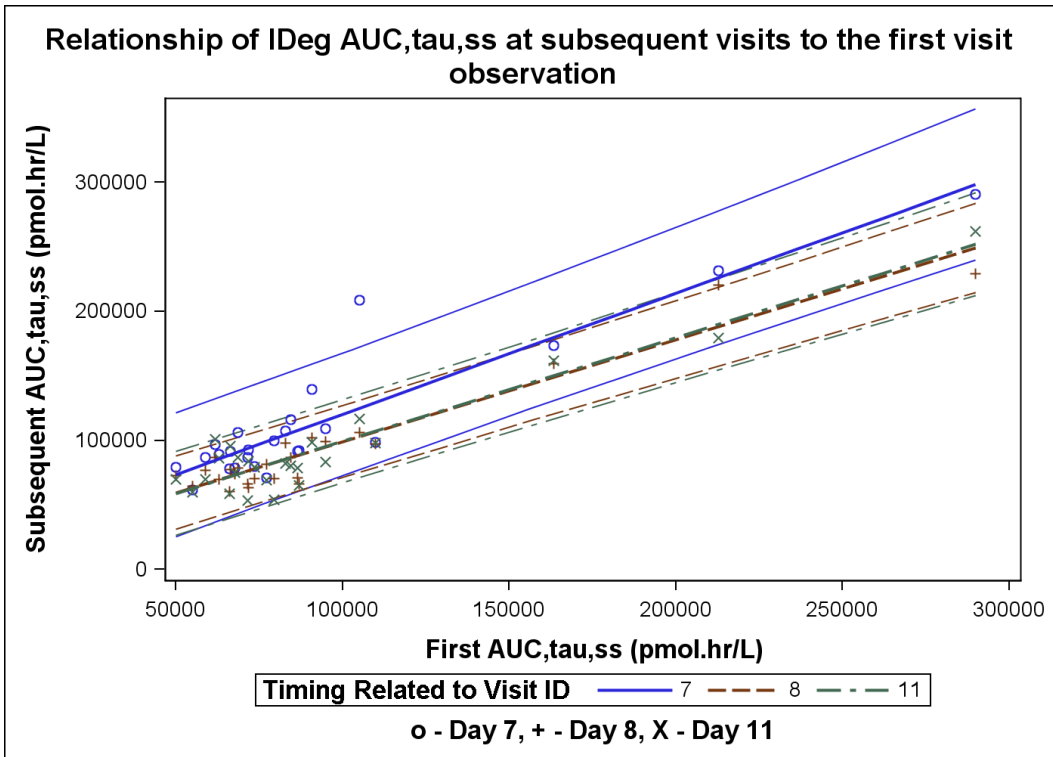


**Figure 30** Relationship of IDeg AUC,tau,ss at subsequent visits to the first observation (0.4 U/kg/day over 12 days).

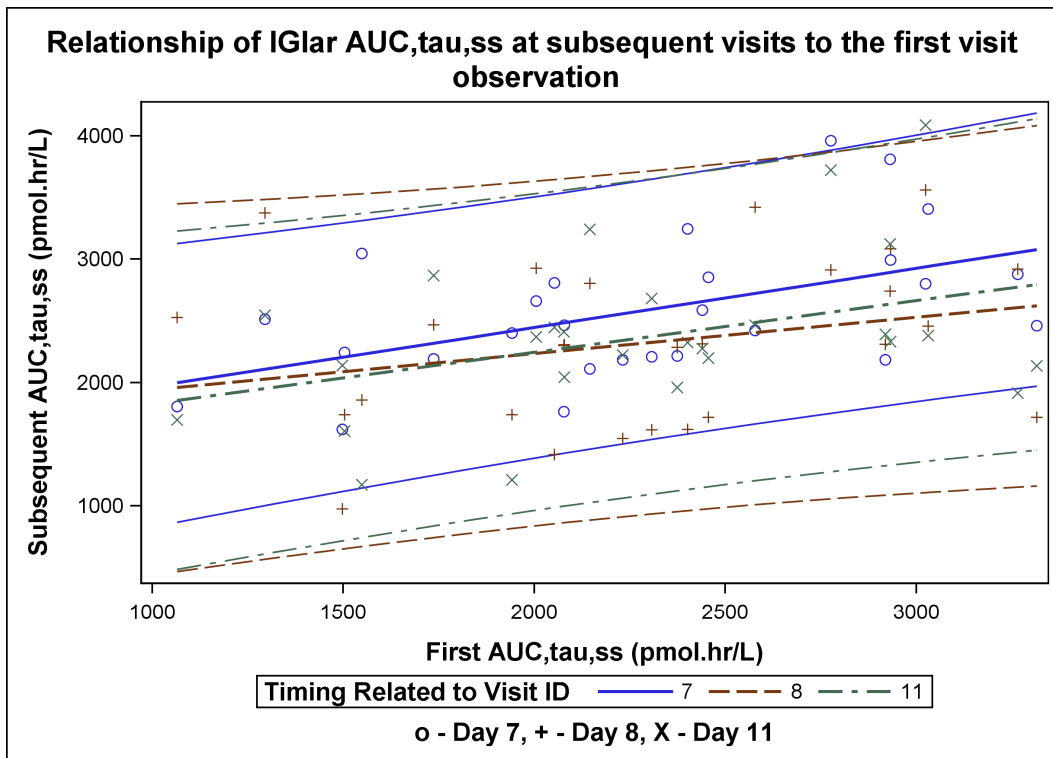


**Figure 31** Relationship of IGLar AUC,tau,ss at subsequent visits to the first observation (0.4 U/kg/day over 12 days).

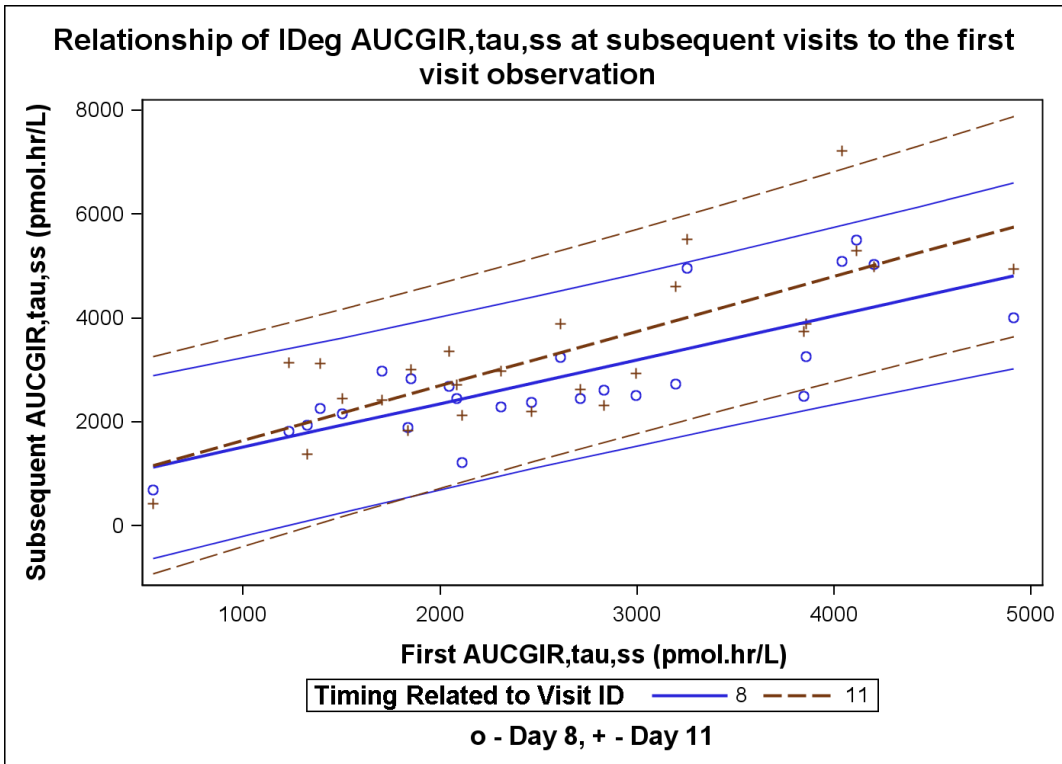


**Figure 32** Relationship of IDeg AUCGIR,tau,ss at subsequent visits to the first observation (0.4 U/kg/day over 12 days).

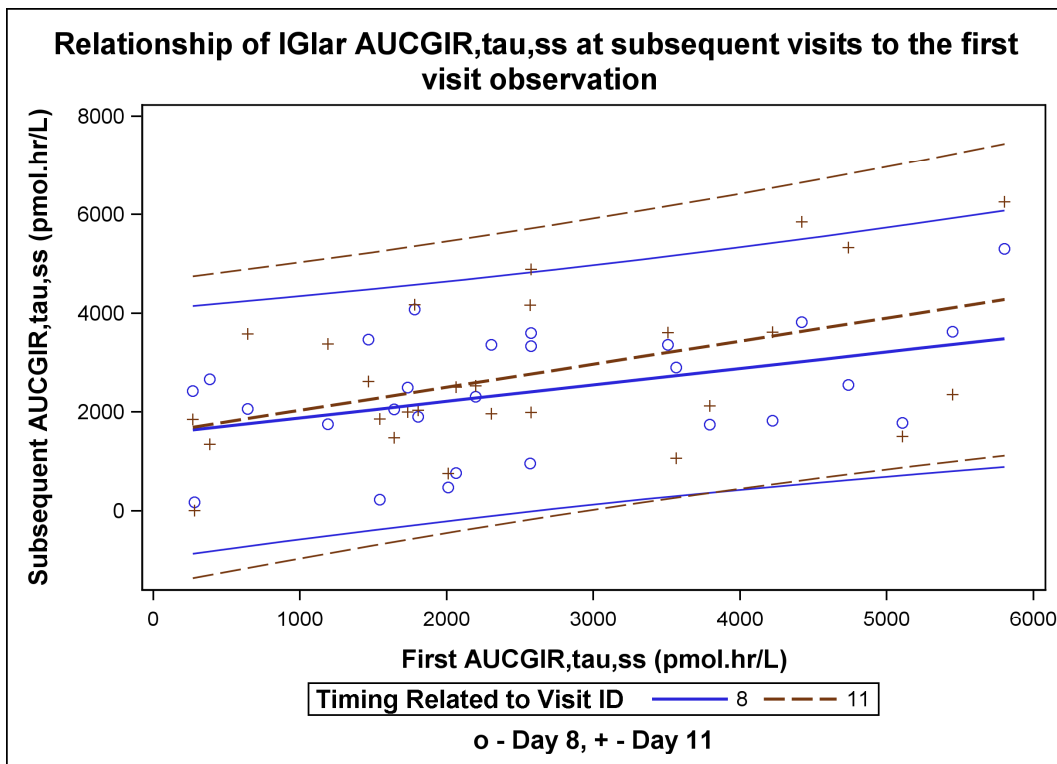


**Figure 33** Relationship of IGLar AUCGIR,tau,ss at subsequent visits to the first observation (0.4 U/kg/day over 12 days).

The results showed that:

For IDeg, both AUC,tau,ss and AUCGIR,tau,ss on subsequent visits were correlated in a better way to the first observation with tighter 95% prediction intervals, in contrast to the relationships observed for IGLar. This suggests that in comparison to IGLar, both PK and PD profiles are relatively more consistent (or less variable) within subjects. This supports the sponsors comparison based on CV comparison (shown in **Figure 34** below), which revealed a lower WSV in both PK and PD parameters for IDeg in comparison to IGLar.

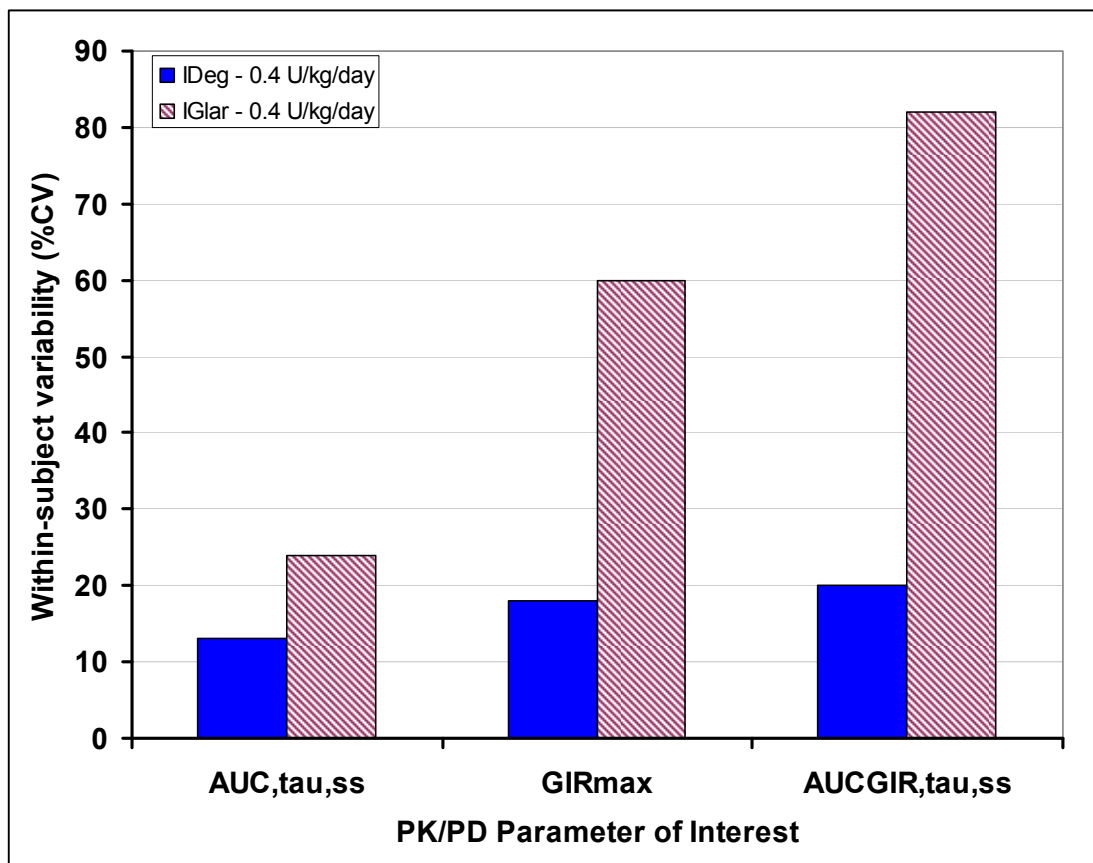


**Figure 34** Estimated within-subject variability in PK and PD parameters at steady-state for IDeg or IGLar (0.4 U/kg/day over 12 days).

### 2.2.7 Is major route of elimination in humans identified for IDeg?

The primary route of elimination for IDeg is via specific and non-specific metabolism (**Figure 36**). The metabolism of IDeg, which consists of a peptide with a fatty acid attached via a glutamate spacer results in amino acids and a fatty acid. Metabolism of IDeg was studied in two in vitro systems, cathepsin D (cleavage of the peptide backbone) and hepatocytes (general metabolism after uptake in the liver) as well as in the rat and dog in vivo.

In vitro incubation of IDeg and human insulin with Cathepsin D, yielded two identical metabolites. The metabolites were A<sup>1-21</sup>-B<sup>1-24</sup> and A<sup>1-21</sup>-B<sup>1-25</sup> (b) (4) respectively. In vitro incubations with [<sup>3</sup>H]-IDeg for 4 hours were conducted in the presence of rat, rabbit, dog and human hepatocytes at 10 and 500 nM to reflect observed clinical and toxicological concentrations. In total, 11 components were detected in samples from the incubations. The metabolite profile was the same at 10 and 500 nM, with a

tendency to fewer metabolites at the 10 nM incubations. The formation of the large number of components confirms that IDeg was extensively degraded in hepatocytes, most likely after receptor mediated uptake. All metabolites observed in human samples were detected in the rat samples and all but one minor metabolite in the dog samples (**Figure 35**). Consequently, no unique human metabolites were observed.

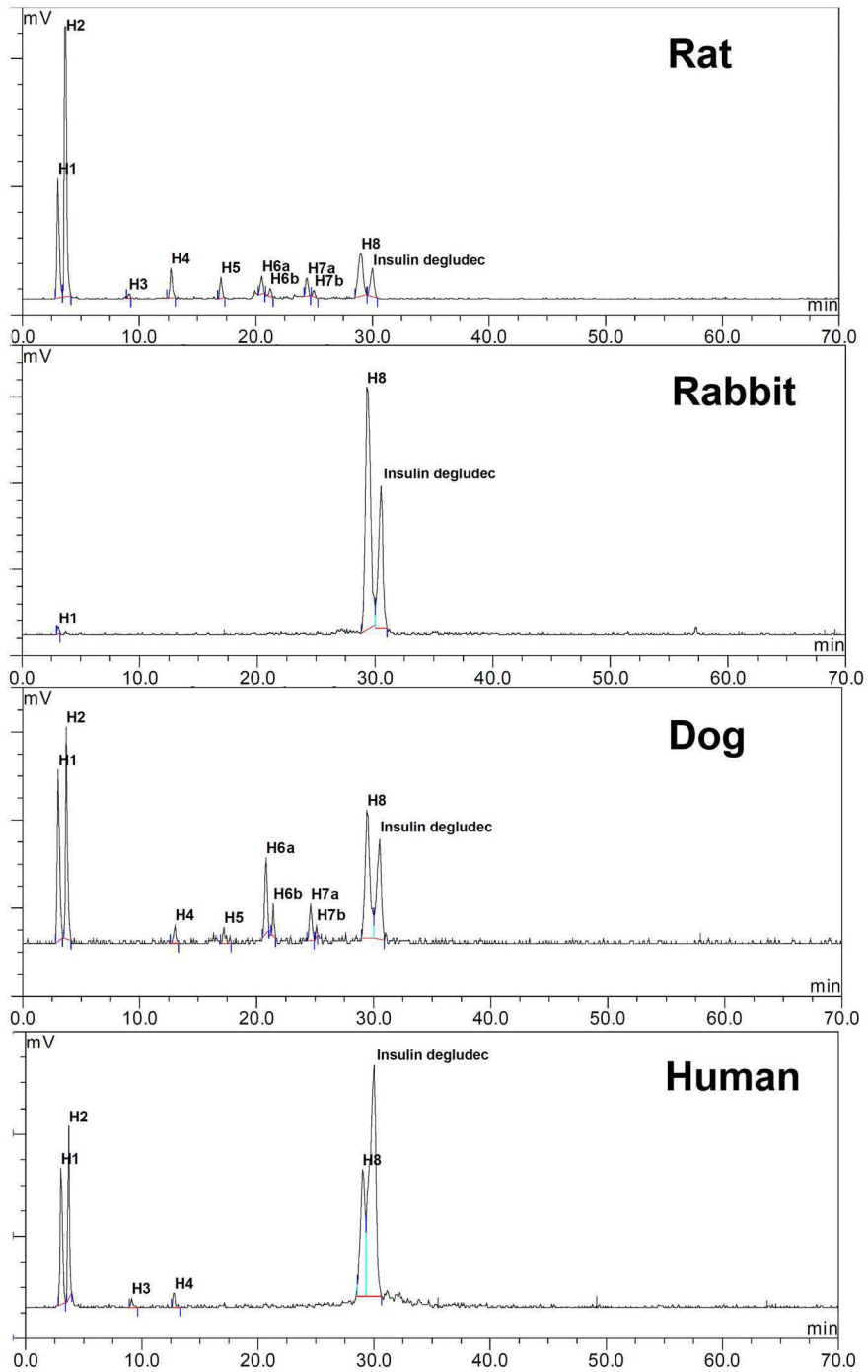


**Figure 35** In vitro metabolic profile of [<sup>3</sup>H]-Insulin Degludec in various species



**Figure 36** Proposed metabolic pathway of [<sup>3</sup>H]-Insulin Degludec

### **2.2.8 Is there any effect of IDeg on QT prolongation in T1DM, and T2DM population?**

As mutually agreed upon by the Agency during end-of-phase 2 meeting and pre-filing meeting, a thorough QT study was waived for IDeg considering long clinical experience with insulin products, availability of in vitro data (hERG receptor binding) and nonclinical evaluations for IDeg for review. However, upon Agency's request sponsor agreed to include 12-lead ECGs measured at baseline and at end of Phase 3 trial NN1250-3579, with evaluation by a blinded, independent, central cardiology reading center: The readers are referred to the Clinical Safety review for further details. In brief, no significant QT prolongation effect of IDeg was detected from trial results. Overall summary of findings is presented in **Table 16** below.

**Table 16 QTc Intervals Change from Baseline in Trial 3579 – Full Analysis Set**

|                           | IDeg OD<br>N (%) | IGlar OD<br>N (%) | Total<br>N (%) |
|---------------------------|------------------|-------------------|----------------|
| Number of Subjects        | 766              | 257               | 1023           |
| Ch. QTcB >= 30 (msec)     |                  |                   |                |
| Visit 41 (Week 52) (LOCF) |                  |                   |                |
| N                         | 736 (100.0)      | 241 (100.0)       | 977 (100.0)    |
| Yes                       | 51 ( 6.9)        | 30 ( 12.4)        | 81 ( 8.3)      |
| No                        | 685 ( 93.1)      | 211 ( 87.6)       | 896 ( 91.7)    |
| Ch. QTcB >= 60 (msec)     |                  |                   |                |
| Visit 41 (Week 52) (LOCF) |                  |                   |                |
| N                         | 736 (100.0)      | 241 (100.0)       | 977 (100.0)    |
| Yes                       | 2 ( 0.3)         | 3 ( 1.2)          | 5 ( 0.5)       |
| No                        | 734 ( 99.7)      | 238 ( 98.8)       | 972 ( 99.5)    |
| Ch. QTcF >= 30 (msec)     |                  |                   |                |
| Visit 41 (Week 52) (LOCF) |                  |                   |                |
| N                         | 736 (100.0)      | 241 (100.0)       | 977 (100.0)    |
| Yes                       | 41 ( 5.6)        | 18 ( 7.5)         | 59 ( 6.0)      |
| No                        | 695 ( 94.4)      | 223 ( 92.5)       | 918 ( 94.0)    |
| Ch. QTcF >= 60 (msec)     |                  |                   |                |
| Visit 41 (Week 52) (LOCF) |                  |                   |                |
| N                         | 736 (100.0)      | 241 (100.0)       | 977 (100.0)    |
| Yes                       | 2 ( 0.3)         | 0 ( 0.0)          | 2 ( 0.2)       |
| No                        | 734 ( 99.7)      | 241 (100.0)       | 975 ( 99.8)    |

N = Number of subjects, QTcB = Bazett correction, QTcF = Fridericia correction

#### 2.2.4 What are the characteristics of the exposure-response relationships (dose-response, concentration-response) with regards to efficacy?

The goal of an ideal insulin therapy is to achieve near-normoglycaemia with a low rate of hypoglycemic episodes. Both bolus and basal insulin doses are titrated individually to achieve optimal glycemic control.

The Phase 1 data on protracted time-action profile of IDeg with close to peak-less shape and duration of action >24h formed adequate basis to evaluate IDeg as a basal insulin in both Type 1 and Type 2 DM patients. Accordingly, sponsor conducted a number of exploratory and confirmatory efficacy and safety trials, primarily inspired by the duration of action, to test whether a fixed QD regimen, flexible-QD regimen, or 3TW (three times a week; every 48 h) regimen serves as appropriate baseline insulin therapy.

The starting dose was 10 U, and subsequent dose was titrated using predefined titration algorithm as per individual response.

**Table 17 Summary of dosing schedules used in therapeutic confirmatory trials for IDeg and Comparator in Type 1 DM and Type 2 DM patients**

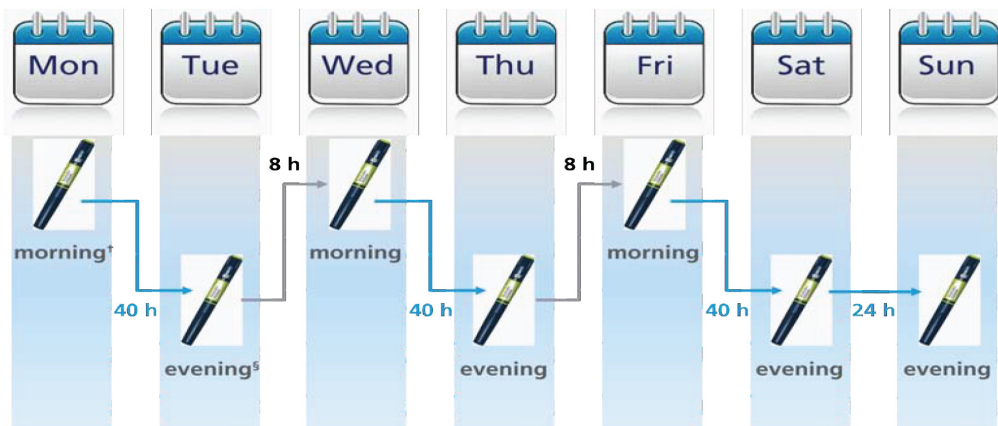
| Trial                                        | IDeg dosing time                                                                                                                        | Comparator                                                    |
|----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------|
| <b>T1DM, basal-bolus therapy</b>             |                                                                                                                                         |                                                               |
| 3583                                         | with main evening meal                                                                                                                  | IGlar OD according to label <sup>§</sup>                      |
| 3585                                         | from start of evening meal until bedtime                                                                                                | IDet OD <sup>#</sup> from start of evening meal until bedtime |
| 3770                                         | IDeg Flex:<br>– Monday, Wednesday, Friday: morning<br>– Tuesday, Thursday, Saturday, Sunday: evening<br>IDeg OD: with main evening meal | IGlar OD according to label <sup>§</sup>                      |
| <b>T2DM, basal-bolus therapy ±OADs</b>       |                                                                                                                                         |                                                               |
| 3582                                         | with main evening meal                                                                                                                  | IGlar OD according to label <sup>§</sup>                      |
| <b>T2DM, OAD-insulin combination therapy</b> |                                                                                                                                         |                                                               |
| 3579                                         | with main evening meal                                                                                                                  | IGlar OD according to label <sup>§</sup>                      |
| 3586                                         | from start of evening meal until bedtime                                                                                                | IGlar OD according to label <sup>§</sup>                      |
| 3580                                         | injection time as preferred (8–40 h between injections)                                                                                 | Sitagliptin 100 mg/day                                        |
| 3672                                         | with main evening meal                                                                                                                  | IGlar OD according to label <sup>§</sup>                      |
| 3668                                         | IDeg Flex:<br>– Monday, Wednesday, Friday: morning<br>– Tuesday, Thursday, Saturday, Sunday: evening<br>IDeg OD: with main evening meal | IGlar OD according to label <sup>§</sup>                      |

#Twice-daily dosing of IDet considered in case of inadequate glycemic control after 8 weeks of treatment and optimization of dosing;

§ any time of the day, but at the same time every day

Pertaining to almost flat time action profile, in Trial 3580 sponsor tested the efficacy and safety profile of IDeg by allowing subjects to inject IDeg flexibly at any time of the day, and at varying time from day to day. Wherever used, IGlar was dosed according to the approved label, hence at any time of the day, but at the same time every day.

The IDeg Flexible (FF) schedule is shown in **Figure 36** below:



<sup>†</sup>Morning defined as time period from waking up to first meal of the day.

<sup>§</sup>Evening defined as time period from start of main evening meal to bedtime.

Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h

**Figure 37 IDeg Flexible (FF) schedule (Trial 3770 and 3668).**

Readers are referred to clinical for a thorough evaluation of efficacy and safety, and statistical review with regards to the claims of non-inferiority. However, a brief overview of the efficacy and key clinical pharmacology components are described here. The efficacy results across various therapeutic confirmatory trials as reported by the sponsor are summarized in **Figure 38** below.

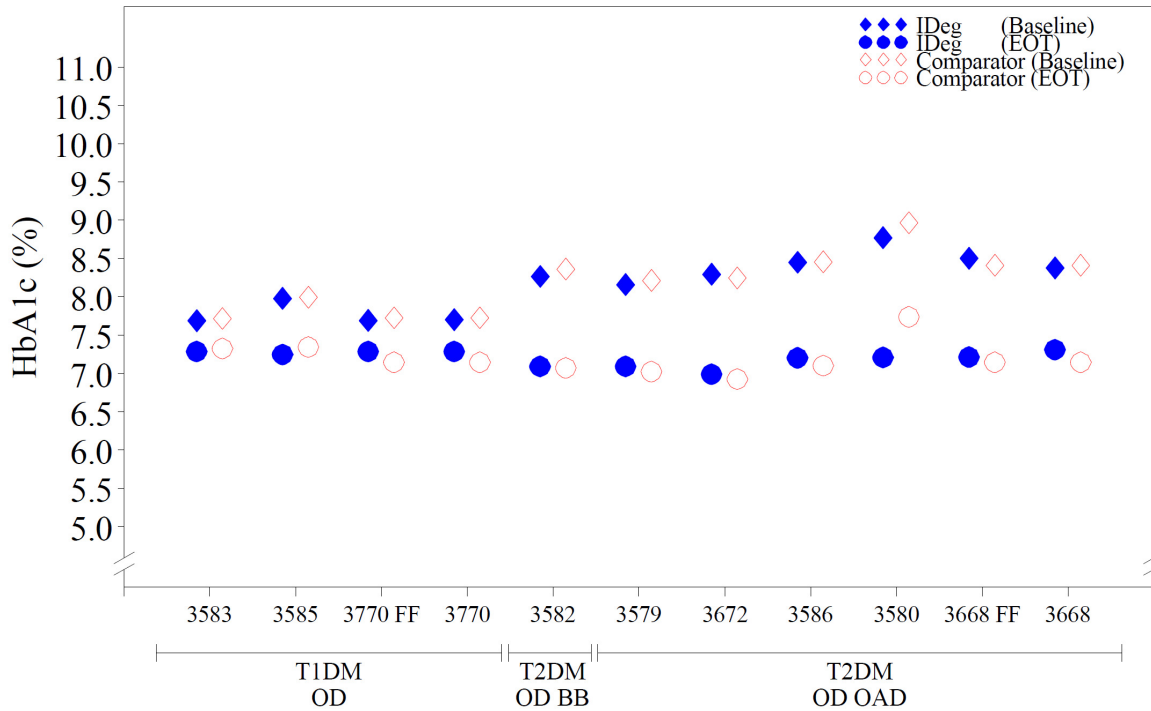


**Figure 38 Summary of efficacy results across therapeutic confirmatory trials.**

The comparison of week 26 or week 52 data among Phase 3 trial was also reasonable based on HbA1c (%) versus time profiles. The HbA1c (%) versus time profile from Phase 3 trials showed a comparable maximal decrease in mean HbA1c from baseline between IDeg and comparator, both in Type 1DM (**Figure 39**) and Type 2 DM patients (**Figure 40 and 41**) (*Source: 2.7.3 Summary of clinical efficacy*).

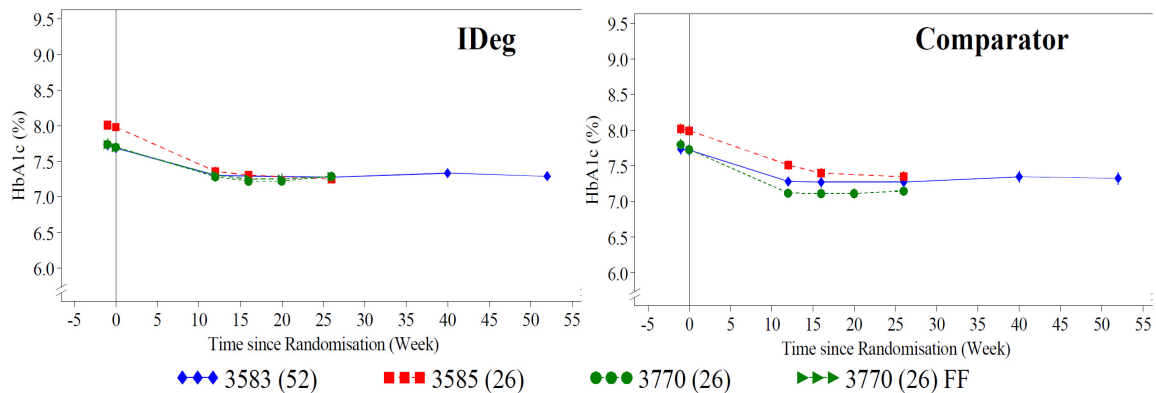


**Figure 39 Mean (±SEM) HbA1c (%) by time in Type 1 DM [LOCF data, Full Analysis Set (FAS)]**

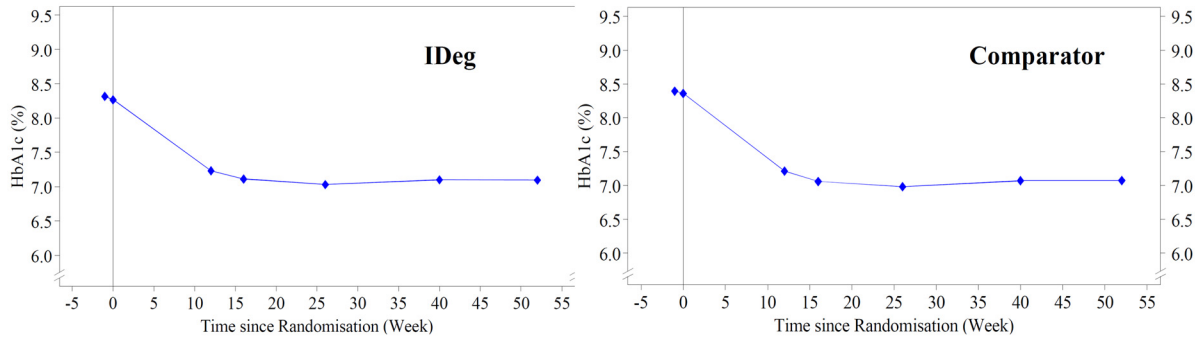


**Figure 40 Mean ( $\pm$ SEM) HbA1c (%) by time in Type 2 DM basal-bolus therapy – Trial 3582 (LOCF data, FAS)**

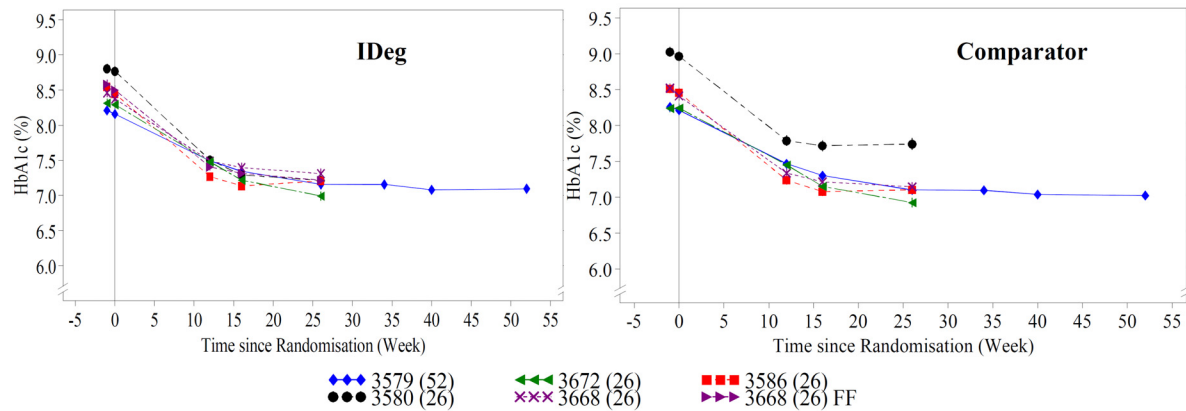


**Figure 41 Mean ( $\pm$ SEM) HbA1c (%) by time in Type 2 DM OAD-insulin combination (LOCF data, FAS)**

Graphical evaluation of change from baseline in HbA1c versus quartiles of dose-normalized systemic exposure revealed a flat response surface (Figure 42), as expected for individually titrated insulin regimen.

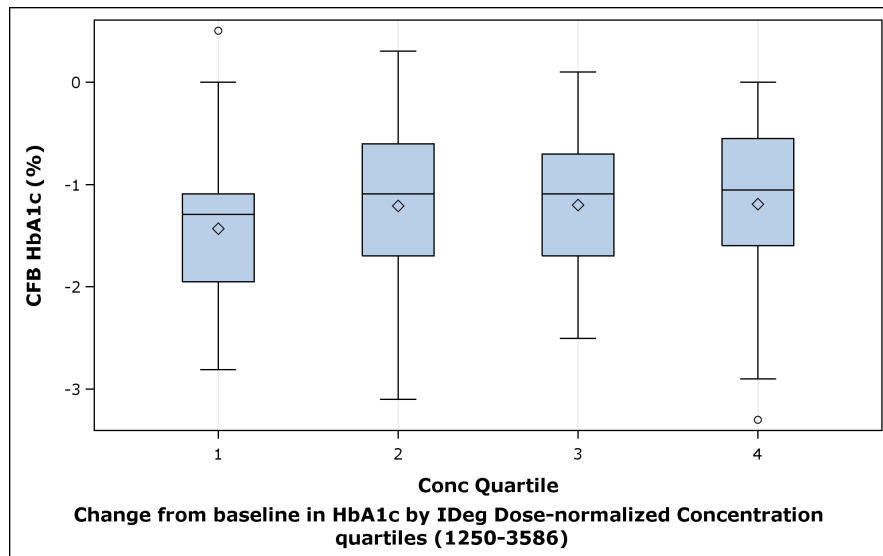


**Figure 42 Dose-normalized systemic IDeg exposure-response relationship in Pan-Asian Phase 3 trial (3586).**

Differences in therapeutic management of Type 1 DM and Type 2 DM are caused by the nature of insulin requirements: replenishment (Type 1) and overcoming resistance (Type 2), as evident from the actual IDeg or IGLar dose over time profiles in confirmatory trials (see **Fig. 43** below). The profile is almost stable over trial duration for both IDeg and IGLar, though on average requirements for IDeg dose was lower than IGLar in Type 1 DM patients.

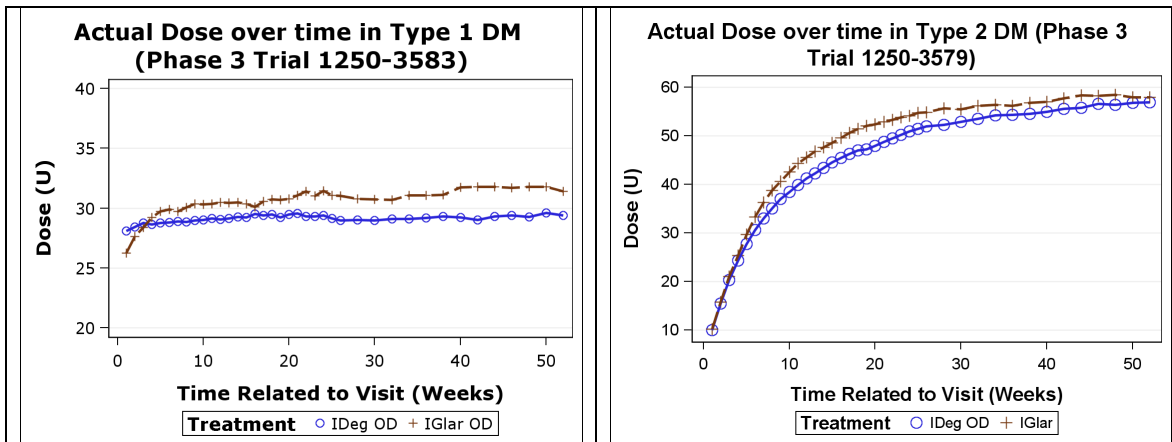


**Figure 43 Actual IDeg dose versus time by treatment in Type 1 DM (Phase 3 trial 3583) and Type 2 DM patients (Phase 3 trial 3579)**

The average actual dose gradually increased in Type 2 DM patients treated for a target HbA1c of 7%, with numerically higher dose requirement than Type 1 DM, and almost identical average dose requirements for IDeg and IGLar.

The proposed starting dose of 10 U in Type 2 DM, individualized initiation dose in Type 1 DM, and subsequent individual titration is adequately supported by the efficacy evaluation. The sponsor’s proposed dose regimen is acceptable from clinical pharmacology perspective.

## 2.3 Intrinsic Factors

**2.3.1 What intrinsic factors (e.g., weight, gender, race, age, height, disease, genetic polymorphism, pregnancy, and organ dysfunction) influence exposure (PK usually) and/or response, and what is the impact of any differences in exposure on efficacy or safety responses?**

**Body Weight:** Insulin doses in PKPD evaluations are often based on body weight (U/kg) based on the assumption that body weight is the most influential covariate affecting PK, such that higher dose is required per kg of body weight to achieve similar exposure, and thus similar response.

As illustrated below in **Figure 44**, the total IDeg exposure at steady state in trial 1250-1993 increased in relation to total dose (U/kg \*Body Weight), when three dose levels (0.4, 0.6, and 0.8 U/kg) were introduced to same group of Type 1 DM individuals (body weight range of 52-102 kg). Alternatively, if these subjects had received total dose of 30 U then a decreasing AUC would have been evident over increasing body weight.

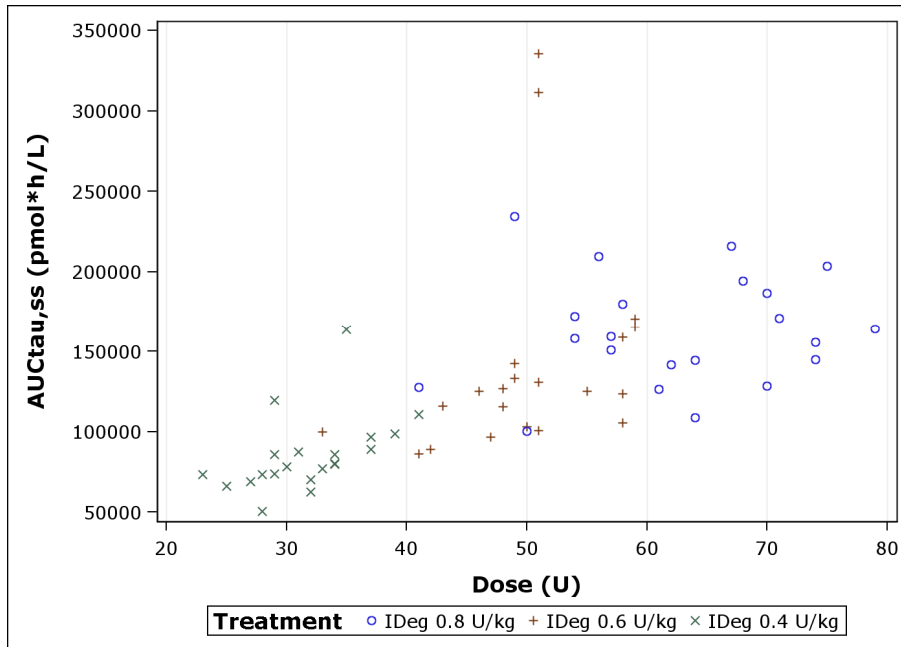


**Figure 44 IDeg AUC $\tau_{ss}$  versus total dose by treatment in Type 1 DM patients (Trial 1250-1993)**

The total response (AUCGIR, $\tau_{ss}$  \* Weight) also showed linear increase with total dose (Figure 45).

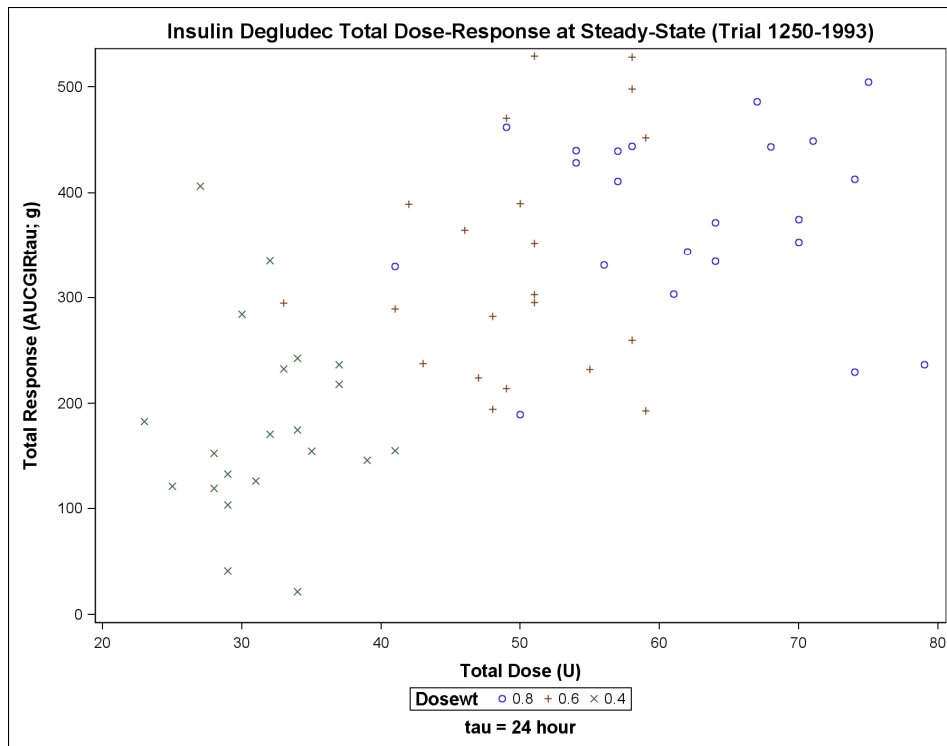


**Figure 45 Total Response (AUCGIR $\tau_{ss}$ , g) versus total dose by treatment in Type 1 DM patients (Trial 1250-1993)**

This information does provide confidence that with increase in dose, a better (Type 2 DM) or higher (Type 1 DM) response could be expected and forms the basis of titration in clinical evaluation. In clinical evaluation and therapeutic use, total dose (Units) was used for initiation and subsequent titration. Based on clinical pharmacology data, this means that higher body weight individual will likely be receiving higher total U based doses.

This aspect was further evaluated in two of the confirmatory Phase 3 trials (one each in Type 1 and Type 2 DM patients). The mean prescribed dose was plotted over trial visits by body weight quartiles for the test and comparator treatment.

The graphical evaluation showed an increase in the average Unit dose prescribed and used (Actual dose has similar trend; data not shown here) with increase in weight from Quartile 1 to 4, in both the patient populations (Figures 46 and 47). However, the difference in the dose-time trend between Type 1 DM and Type 2 DM patients was preserved.

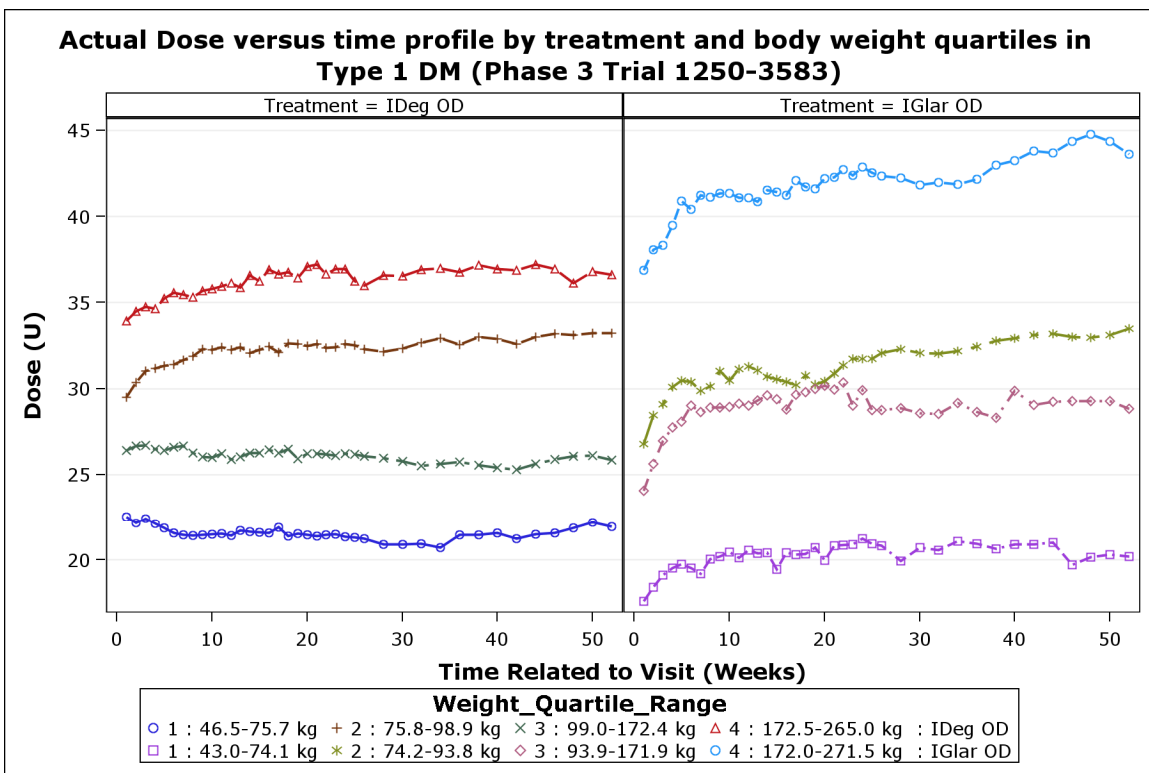


**Figure 46** Effect of body weight on insulin dose in Type 1 DM (Phase 3 trial NN1250-3583)

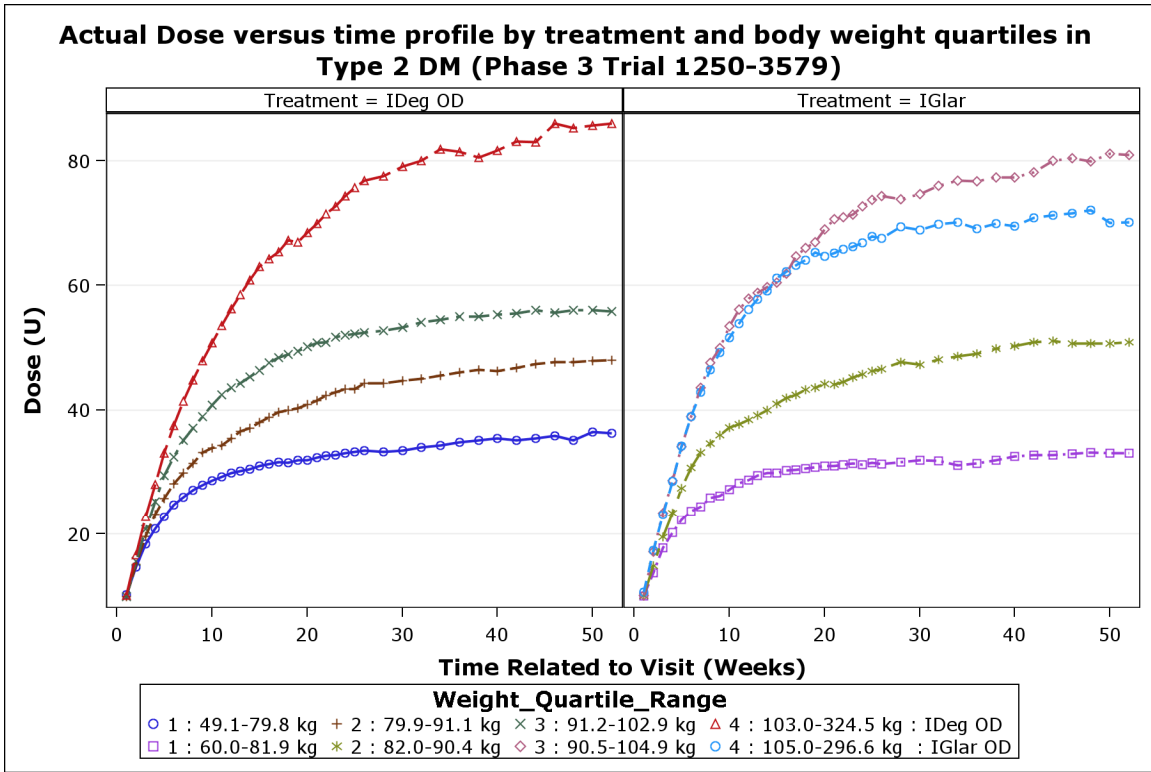


**Figure 47** Effect of body weight on insulin dose in Type 2 DM (Phase 3 trial NN1250-3579)

**BMI:** There was no major effect of BMI on IDeg exposure other than slightly lower dose-normalized concentration as illustrated in **Figure 47** below.

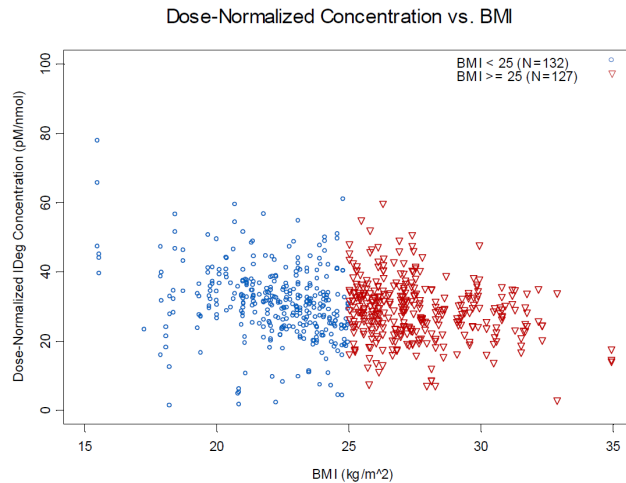


**Figure 48** Effect of BMI on Insulin Degludec exposure in Phase 3 trial NN1250-3586

However, there was evidence of decrease in PD response from Phase 1 PKPD evaluations as shown in **Figure 49** below:

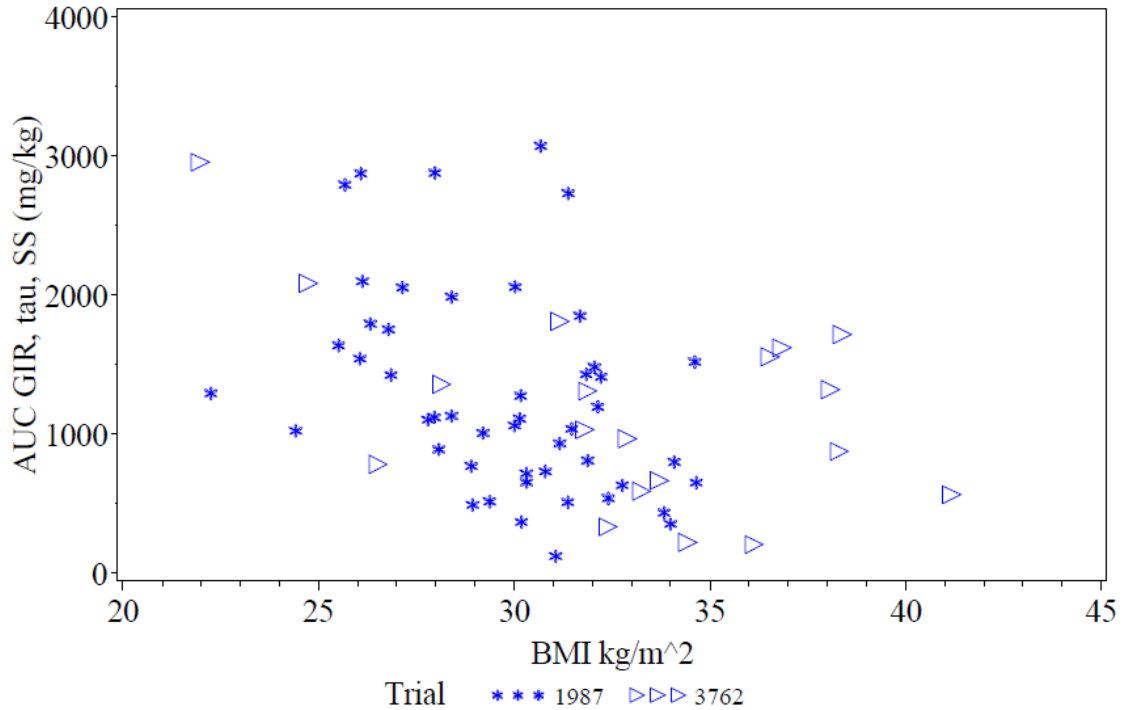


**Figure 49 Total Glucose-Lowering Effect vs. BMI in Phase 1 trial NN1250-1987 and 3760 [Trial 1987: dose-adjusted to 0.4 U/kg; Trial 3762: only Caucasian subjects]**

Sponsor mentioned that this is expected result based on known association of BMI to the insulin resistance. Therefore, Phase 3 dose data was evaluated to answer the question “Does BMI influences the insulin dose requirements in Type 1 and Type 2 DM population?”. Since weight was already found to influence the total dose requirement, mean body weight adjusted dose was plotted over trial visit by BMI quartiles. The results of graphical evaluation are presented in **Figures 50 and 51** below.

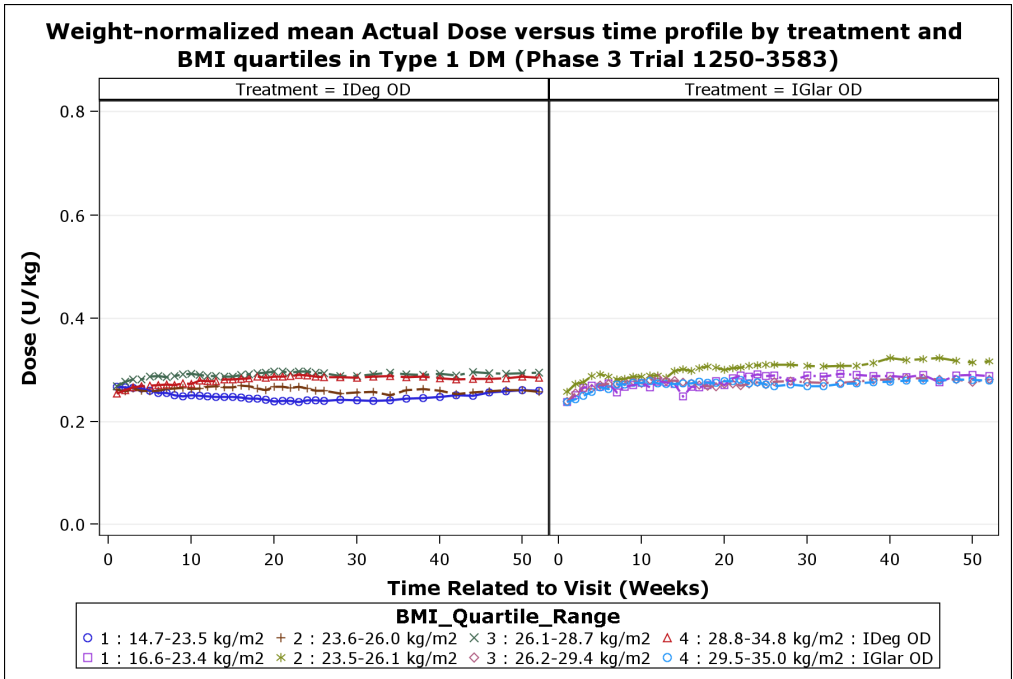


**Figure 50** Effect of BMI on weight adjusted insulin dose in Type 1 DM (Phase 3 trial NN1250-3583)

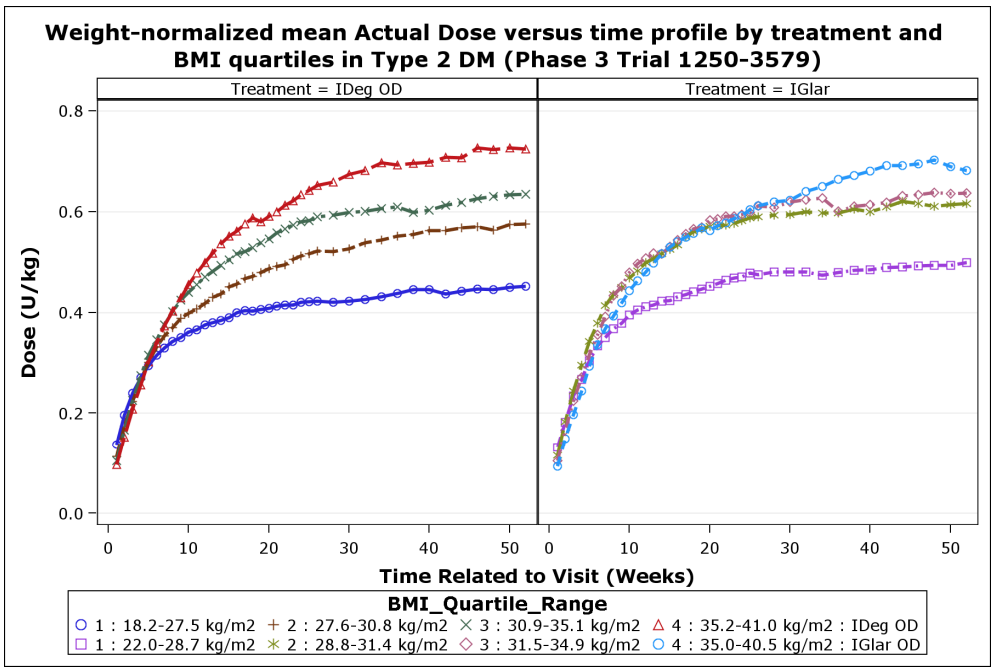


**Figure 51** Effect of BMI on weight adjusted insulin dose in Type 2 DM (Phase 3 trial NN1250-3579)

The graphical evaluation showed that in contrast to the Type 1 DM patients, an increase in the average Unit/kg dose with increase in BMI from Quartile 1 to 4, in Type 2 DM patient population (Figures 50 and 51). However, the difference in the dose-time trend between Type 1 DM and Type 2 DM patients was preserved.

**Age (Geriatric subjects versus Young Adults):** The effect of age on PK and PD of IDeg was assessed in a single-center, double-blind, randomized, two-period cross-over, multiple dose trial which compared the PK and PD properties of IDeg and IGLar in younger adult (18-35 years) and geriatric ( $\geq 65$  years) subjects with type 1 diabetes (Trial NN1250-1994). Each subject was randomly allocated to two treatment periods of 6 days of once daily subcutaneous dosing with IDeg (M) and IGLar, respectively, at a predefined fixed dose level (0.4 U/kg). During the treatment periods, blood glucose level was controlled by additional bolus injections of insulin aspart (IAsp) on a daily basis. The PK response was evaluated after first dose, pre-dose trough on subsequent doses, and for 120 hours post last dose.

The PD response was evaluated during a 26-hour euglycemic glucose clamp starting after the last dose on Day 6. IDeg and IGLar were administered at anterior region of thigh whereas IAsp was administered in the abdominal region. For all insulin products, the injection site remained within the same anatomical region throughout the trial, but location within the area was changed for each injection. The run-in period started approximately 5 hours before administration of investigational product and continued for 3 hours. The subject received a variable intravenous infusion of human insulin (40 IU Actrapid®, 100 IU/mL in 99.6 mL saline) or glucose (10%) in order to obtain a glucose clamp target level of 5.5 mmol/L (100 mg/dL). This level ( $\pm 30\%$ ) was kept continuously for at least 1 hour before the clamp period was initiated. The run-in period was extended with up to 1 hour if necessary to establish the clamp target. The euglycemic clamp continued for 26 hours after administration of trial product. The PK and PD profile of IDeg are illustrated in **Figure 52** below.

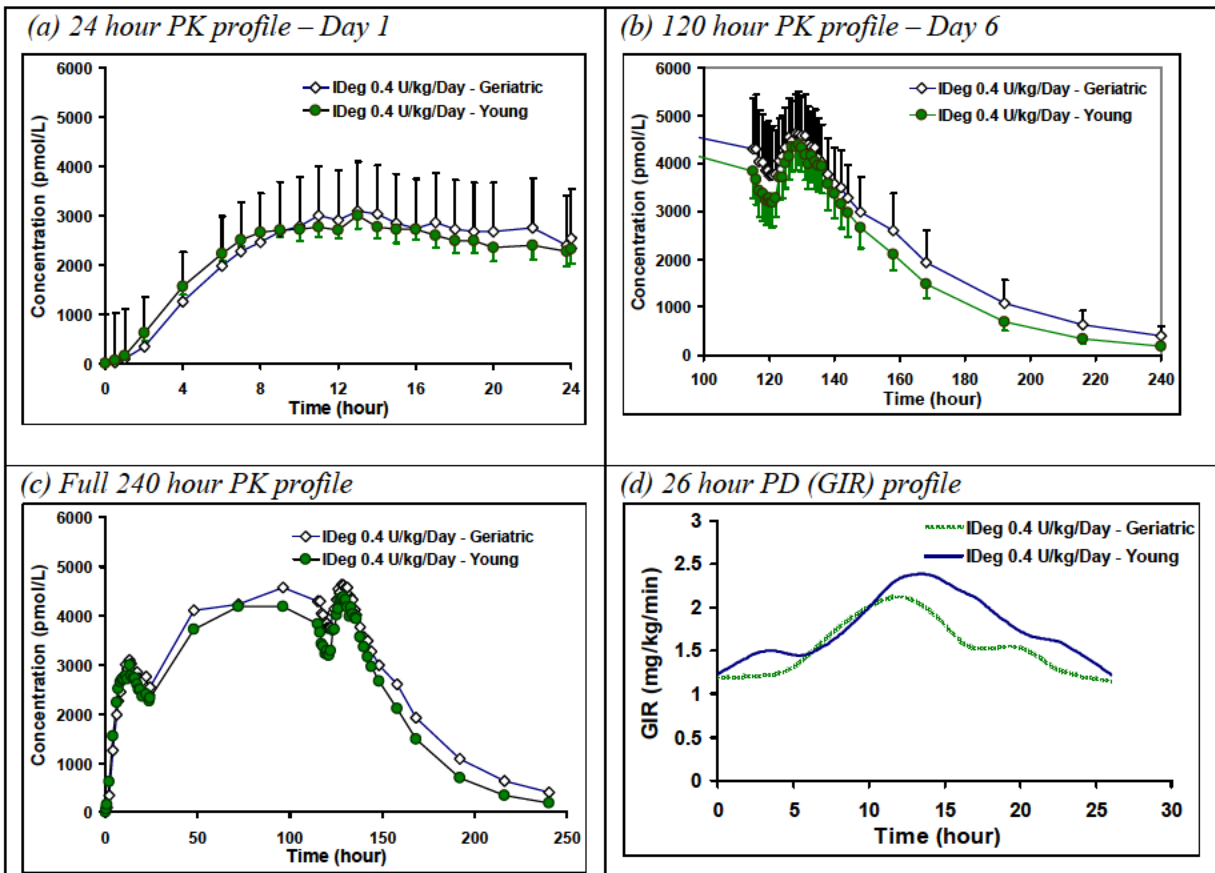


**Figure 52** Effect of Age on Insulin Degludec pharmacokinetics and pharmacodynamics (N=13 for Young; N=14 for Geriatric subjects).

The mean (SE) plots showed greater inter-individual variability in IDeg exposure among Type 1 DM geriatric subjects in comparison to the young adults. The statistical comparison of key PK parameters also yielded wide 95% confidence intervals.

Statistical analysis revealed that PK profile was comparable among young adults and geriatric subjects. Despite of comparable PK profile, geriatric subjects exhibited lower PD response as compared to young adults based on descriptive statistics. However, the statistical analysis did not reach significance as 95% CIs for the mean ratio were wide and contained 1, reflecting greater variability in PD response among geriatric subjects. These results were confirmed in reviewer's analysis, although as expected the CIs were tighter with the use of 90% confidence.

**Table 18 Descriptive statistics and statistical comparison of key PK and PD parameters for Insulin Degludec in young and geriatric subjects**

| PK/PD Parameter:<br>Geo. Mean (CV)                                                                      | Age Group                                |                                             |
|---------------------------------------------------------------------------------------------------------|------------------------------------------|---------------------------------------------|
|                                                                                                         | Young Adults (N=13)                      | Geriatric Subjects (N=14)                   |
| C <sub>max</sub> (pmol/L):                                                                              | 4425 (39)                                | 4493 (66)                                   |
| t <sub>max</sub> (hour)*:                                                                               | 9 (5-14)                                 | 10 (0-16)                                   |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                                       | 82998 (48)                               | 85953 (72)                                  |
| t <sub>1/2</sub> (hour):                                                                                | 22 (19)                                  | 26 (21)                                     |
| AR <sub>AUC</sub> **:                                                                                   | 1.6 (27)                                 | 1.7 (27)                                    |
| AUCGIR,tau,ss (mg/kg):                                                                                  | 2457 (33)                                | 1906 (44)                                   |
| GIR <sub>max,ss</sub> (mg/kg/min):                                                                      | 2.6 (32)                                 | 2.0 (45)                                    |
| tGIR <sub>max,ss</sub> (hour) *:                                                                        | 13.3 (0-24)                              | 12.3 (7-24)                                 |
| Parameter Compared                                                                                      | LS Mean Ratio [95%CI]<br>Geriatric/Young | LS Mean Ratio [90%CI]***<br>Geriatric/Young |
| AUC,tau,ss (pmol.h/L)                                                                                   | 1.04 [0.73; 1.46]                        | 1.04 [0.78; 1.38]                           |
| C <sub>max</sub> (pmol/L)                                                                               | 1.02 [0.74; 1.39]                        | 1.02 [0.78; 1.31]                           |
| AUCGIR,tau,ss (mg/kg)                                                                                   | 0.78 [0.47; 1.31]                        | 0.78 [0.51; 1.19]                           |
| GIR max,ss (mg/kg/min)                                                                                  | 0.79 [0.54; 1.16]                        | 0.79 [0.58; 1.09]                           |
| *Median (Min., Max.)                                                                                    |                                          |                                             |
| **Accumulation Ratio AUC comparison; AR <sub>AUC</sub> : AUC <sub>tau,SS</sub> / AUC <sub>0-24,SD</sub> |                                          |                                             |
| ***Reviewer's analysis                                                                                  |                                          |                                             |

There is no need to adjust the starting dose of IDeg in geriatric patients (Age≥65). However, consistent to the proposed use of IDeg in with young adults, IDeg should be titrated according to individual requirements in geriatric patients.

**Ethnicity/Race:** PK and PD of IDeg was evaluated at steady-state conditions in subjects with Type 2 DM of different race and/or ethnicity (NN1250-3762). The objective of the trial was to compare the pharmacodynamic response of IDeg and IDet between:

- Black or African American subjects not of Hispanic (H) or Latino (L) origin,
- White subjects of Hispanic or Latino origin, and
- White subjects not of Hispanic or Latino origin, all with type 2 diabetes.

The primary comparison was based on the area under the glucose infusion rate curve during one dosing interval (0-24 hours) at steady state. The PK and PD profile of IDeg are illustrated in **Figure 53** below.

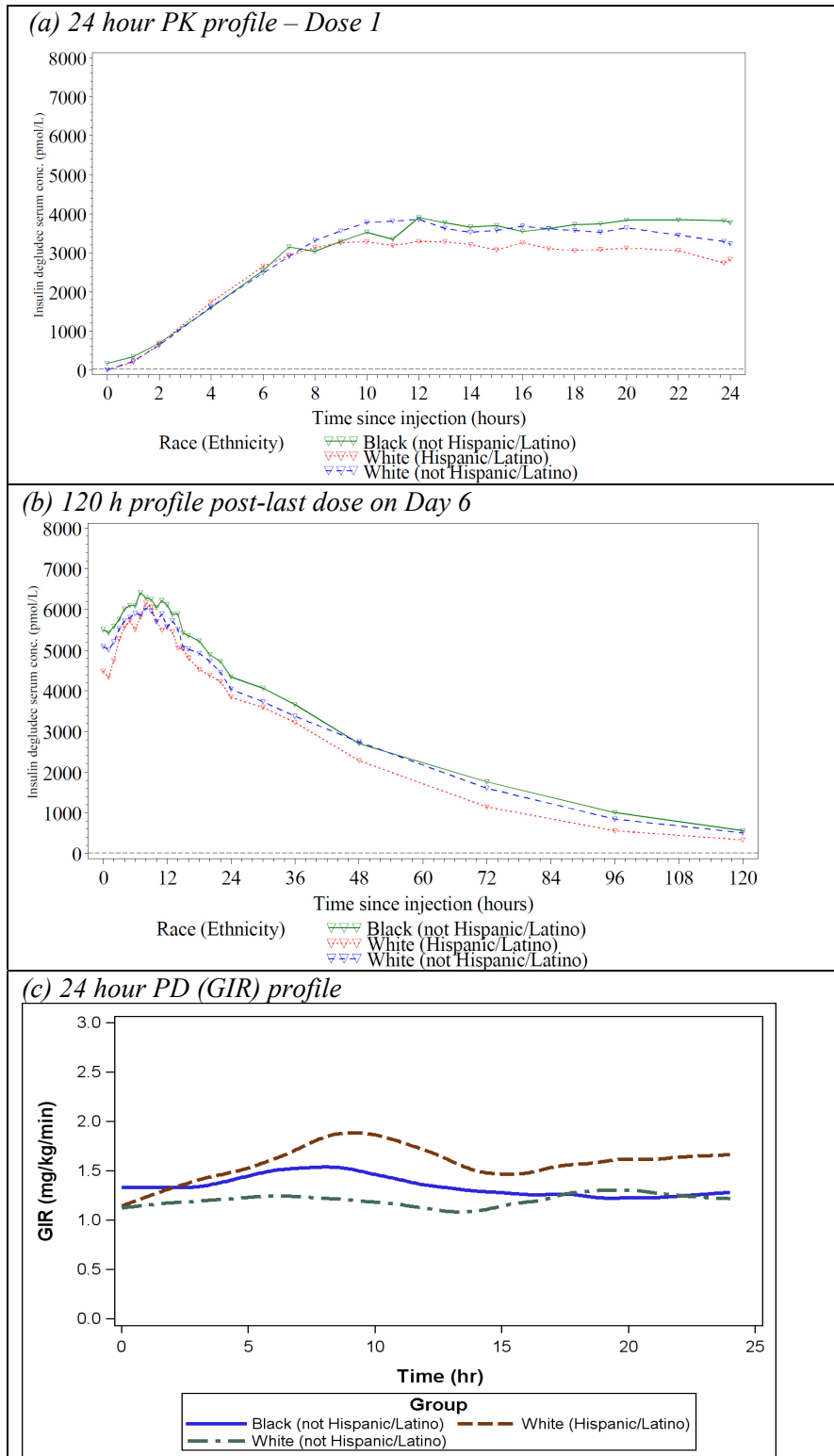


**Figure 53** Effect of Ethnicity/Race on Insulin Degludec pharmacokinetics and pharmacodynamics (N=18 for Black (NH/L); N=22 for White (H/L); N=19 for White (NH/L))

**Table 19 Descriptive statistics for key PK parameters and statistical comparison of AUC<sub>0-inf</sub> and C<sub>max</sub> of Insulin Degludec among subjects with Type 2 DM of different race and/or ethnicity (NN1250-3762) after 0.6 U/kg/d subcutaneous doses**

| PK Parameter:<br>Geo. Mean (CV)                                                                                                                                                                                                                                  | IDeg First Dose                        |                                    |                                        |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------|------------------------------------|----------------------------------------|
|                                                                                                                                                                                                                                                                  | Black (not<br>Hispanic/Latino)<br>N=18 | White<br>(Hispanic/Latino)<br>N=22 | White (not<br>Hispanic/Latino)<br>N=19 |
| C <sub>max</sub> (pmol/L):                                                                                                                                                                                                                                       | 4221 (32)                              | 3658 (27)                          | 4053 (36)                              |
| t <sub>max</sub> (hour)*:                                                                                                                                                                                                                                        | 19 (7-24)                              | 13 (8-24)                          | 12 (9-24)                              |
| AUC <sub>0-24h</sub> (pmol*h/L):                                                                                                                                                                                                                                 | 67863 (37)                             | 60656 (28)                         | 65317 (37)                             |
| IDeg Day 6 Dose                                                                                                                                                                                                                                                  |                                        |                                    |                                        |
| C <sub>max</sub> (pmol/L):                                                                                                                                                                                                                                       | 6718 (22)                              | 6332 (27)                          | 6335 (36)                              |
| t <sub>max</sub> (hour)*:                                                                                                                                                                                                                                        | 8.5 (0-22)                             | 8 (0-15)                           | 7 (0-18)                               |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                                                                                                                                                                                                | 131578 (22)                            | 116940 (25)                        | 120380 (36)                            |
| t <sub>1/2,ss</sub> :                                                                                                                                                                                                                                            | 30 (32)                                | 24 (35)                            | 29 (32)                                |
| AR <sub>AUC</sub> **:                                                                                                                                                                                                                                            | 1.94 (37)                              | 1.93 (42)                          | 2.01 (33)                              |
| AR <sub>C<sub>MAX</sub></sub> ***:                                                                                                                                                                                                                               | 1.59 (34)                              | 1.73 (39)                          | 1.69 (31)                              |
| *Median (Min., Max)<br>Accumulation Ratio AUC comparison; AR <sub>AUC</sub> ** : AUC <sub>tau,SS</sub> / AUC <sub>0-24,SD</sub><br>Accumulation Ratio C <sub>max</sub> comparison; AR <sub>C<sub>MAX</sub></sub> *** : C <sub>max,SS</sub> / C <sub>max,SD</sub> |                                        |                                    |                                        |

The endpoints are log-transformed and analyzed using a linear mixed model with period and an interaction term between treatment and race/ethnicity as fixed effects, subjects as a random effect, and the residual error variance depending on treatment group. The results of the statistical analysis are presented in **Table 20** below.

**Table 20 Descriptive statistics for key PD parameters and statistical comparison of AUC<sub>GIR,tau,ss</sub> and GIR<sub>max</sub> of Insulin Degludec among subjects with Type 2 DM of different race and/or ethnicity (NN1250-3762) after 0.6 U/kg/d subcutaneous doses**

| PD Parameter:<br>Geo. Mean (CV)<br>(Min., Max.)     | IDeg Day 6 Dose                                                |                                                         |                                        |
|-----------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------|----------------------------------------|
|                                                     | Black (not<br>Hispanic/Latino)<br>N=18                         | White<br>(Hispanic/Latino)<br>N=22                      | White (not<br>Hispanic/Latino)<br>N=19 |
| GIR <sub>max</sub> (pmol/L):                        | 1.5 (59)<br>(0.4, 3.7)                                         | 2.0 (44)<br>(0.7, 4.2)                                  | 1.5 (48)<br>(0.5, 3.9)                 |
| t <sub>GIR<sub>max</sub></sub> (hour)*:             | 13 (0-26)                                                      | 11 (0-26)                                               | 11 (0-26)                              |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):              | 1328 (71)<br>(64, 4186)                                        | 2060 (46)<br>(735, 4458)                                | 1399 (61)<br>(306, 4432)               |
|                                                     | <b>AUC<sub>GIR,tau,ss</sub> -<br/>Mean difference (95% CI)</b> | <b>GIR<sub>max</sub> -<br/>Mean difference (95% CI)</b> |                                        |
| <b>Black (NH)/White (H):</b>                        | -346.18 [-1088; 396.0]                                         | -0.32 [-0.93; 0.30]                                     |                                        |
| <b>Black (NH)/White (NH):</b>                       | 217.64 [-551; 985.9]                                           | 0.17 [-0.46; 0.81]                                      |                                        |
| <b>White (H)/White (NH):</b>                        | 563.83 [-168; 1295]                                            | 0.49 [-0.11; 1.10]                                      |                                        |
|                                                     | <b>Mean Ratio (90% CI)**</b>                                   | <b>Mean Ratio (90% CI)**</b>                            |                                        |
| <b>Black (NH)/White (H):</b>                        | 0.64 [0.42; 0.98]                                              | 0.77 [0.58; 1.03]                                       |                                        |
| <b>Black (NH)/White (NH):</b>                       | 0.95 [0.62; 1.46]                                              | 1.02 [0.76; 1.38]                                       |                                        |
| <b>White (H)/White (NH):</b>                        | 1.47 [0.98; 2.22]                                              | 1.32 [0.99; 1.76]                                       |                                        |
| <b>* Median (Min., Max.); **Reviewer's Analysis</b> |                                                                |                                                         |                                        |

Statistical analysis revealed that PK profile was comparable among subjects of different race/ethnic origin. Despite of comparable PK profile, black subjects exhibited significantly lower AUCGIR,tau,ss response (36%) as compared to white subjects (not Hispanic/Latino). The GIRmax was 33% lower but the 90% CI contained 1. White subjects of Hispanic/Latino origin showed 47% and 32% higher AUCGIR and GIRmax, respectively than the non-Hispanic/Latino White subjects. However, the statistical analysis did not reach significance as 90% CIs for the mean ratio were wide and contained 1, reflecting greater variability in PD response among these subjects.

**2.3.2 Does the Insulin Degludec pharmacokinetics differ among children, adolescents, and adults with Type 1 Diabetes?**

The pharmacokinetic profile of Insulin Degludec among children, adolescents, and adults with Type 1 Diabetes was evaluated in Trial NN1250-1995. (b) (4)

[Redacted]

[Redacted] (b) (4)

[Redacted] (b) (4)





(b) (4)



- Efficacy and safety of IDeg in pediatric population has not been established. (b) (4)

Sponsor has requested partial waiver for evaluation of IDeg in:

- children < 1 year of age with Type 1 DM as clinical trials would be impossible or highly impracticable due to the low incidence of cases as well as the special management considerations in this vulnerable population,
- children <10 year of age with Type 2 DM as clinical trials would be impossible or highly impracticable due to the extremely low incidence of T2DM in children below this age

(b) (4)

Sponsor has requested deferrals for conducting pediatric studies in the following group:

- children between 1 and (b) (4) years of age (b) (4)

Sponsor has proposed a pediatric efficacy and safety evaluation, Trial NN1250-3561- Long-term Efficacy and Safety of Insulin Degludec in Children and Adolescents with Type 1DM. This trial is proposed as a (b) (4) open-label, randomized, (b) (4) study comparing the efficacy and safety of insulin degludec (IDeg) and insulin detemir, both in combination with mealtime insulin aspart, in children and adolescents with type 1 diabetes mellitus, aged 1 to less than 18 years of age. (b) (4)

### 2.3.3 What is the effect of renal function impairment on Insulin Degludec pharmacokinetics?

The effect of renal impairment was assessed in a single-center, single-dose, parallel group, open-label trial investigating pharmacokinetic profiles of Insulin Degludec in four groups of subjects with normal, mild, moderate, severe renal impairment, and end-stage renal disease subject requiring hemodialysis (NN1250-1990). Six subjects were evaluated in each group as planned. Each subject received a single 0.4 U/kg subcutaneous dose of IDeg (M) into the thigh. The classification of renal impairment was based on the estimated creatinine clearance using Cockcroft-Gault equation (**Table 22**). The trial was conducted prior to the issuance of the revised of the renal impairment guidance. Therefore, the classification criterion was in accordance with that defined by the old Guidance document.

**Table 22 The classifications of renal impairment groups used in Trial NN1250-1990**

| Group | Description                    | Estimated Creatinine Clearance (mL/minute) |
|-------|--------------------------------|--------------------------------------------|
| 1     | Normal renal function          | Creatinine clearance > 80                  |
| 2     | Mild renal impairment          | 50 ≤ Creatinine clearance ≤ 80             |
| 3     | Moderate renal impairment      | 30 ≤ Creatinine clearance < 50             |
| 4     | Severe renal impairment        | Creatinine clearance < 30                  |
| 5     | End stage renal disease (ESRD) | Requiring dialysis                         |

The new classification criteria specifies the CrCL ≥ 90 mL/min for normal, CrCL = 60-89 mL/min for mild, and CrCL = 30-59 mL/min for moderate renal impairment. The concentration-time data was plotted based on re-classification, with no apparent impact on the overall results (See **Figure 57**). Therefore, the sponsor's assessment was accepted as is without further exploration of this issue.

Mean (SD) age of subjects was 65.2 (7.5) for normal renal function, 57.2 (10.2) for mild, 70.8 (7.5) for moderate, 71.8 (6.4) for severe renal impairment, and 62.8 (13.6) for ESRD subjects. Ratio of male to female subjects was 1 in normal and moderate categories. Whereas there were 2 females each in mild and ESRD categories, and 5 females in the severe renal impairment category.

The impact of renal impairment in Non-ESRD and ESRD on dialysis groups on mean IDeg concentration-time profile is depicted below in **Figures 58 and 59, respectively**. The IDeg mean concentration-time profile showed an increase in mean peak concentration with increase in degree of renal impairment.

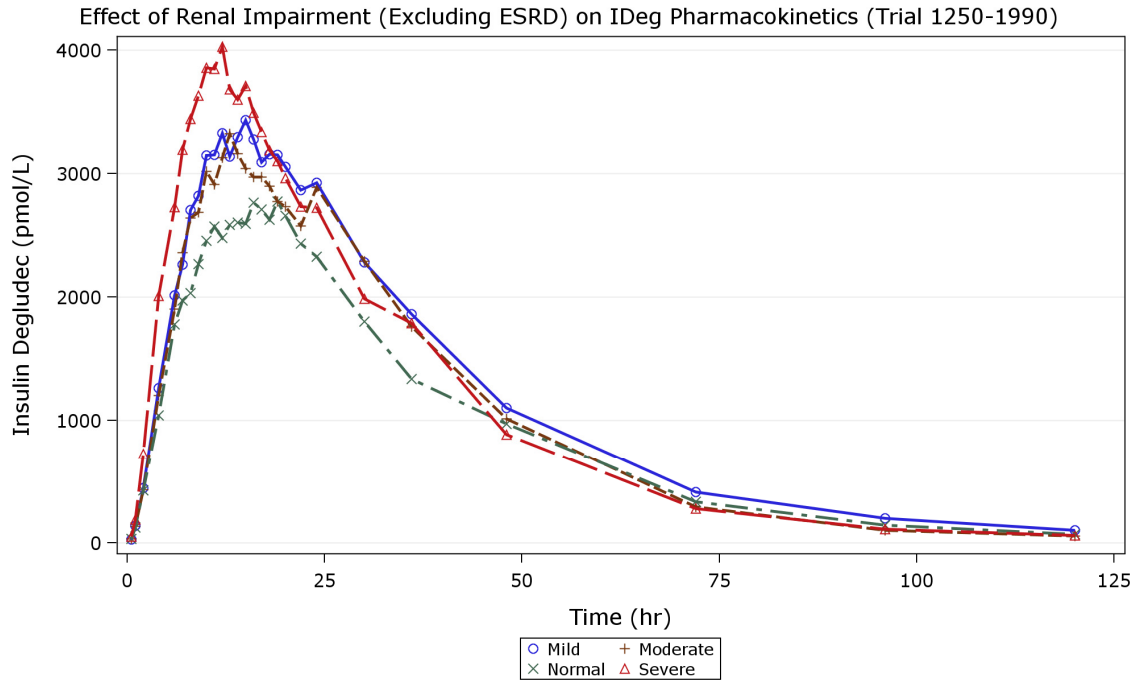
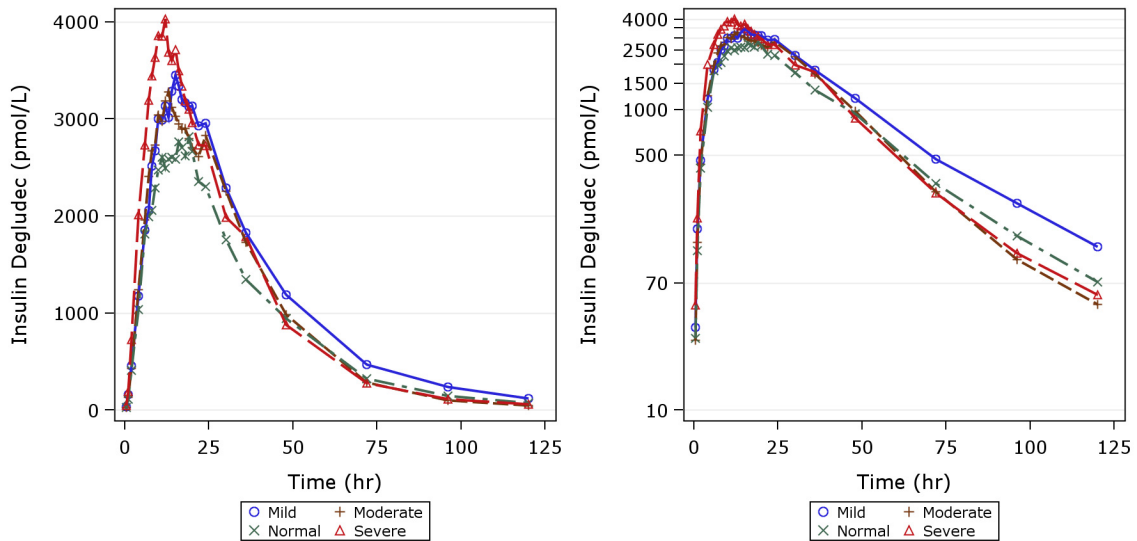


**Figure 57** Insulin Degludec pharmacokinetic profile in healthy and renal impairment subjects after single 0.4 U/kg subcutaneous dose according to sponsor’s classification



(Subjects re-classified based on CrCL specifications in the March 2010 Renal Impairment Guidance)

**Figure 58** Insulin Degludec pharmacokinetic profile in healthy and renal impairment subjects after single 0.4 U/kg subcutaneous dose according to revised classification based on March 2010 renal impairment guidance

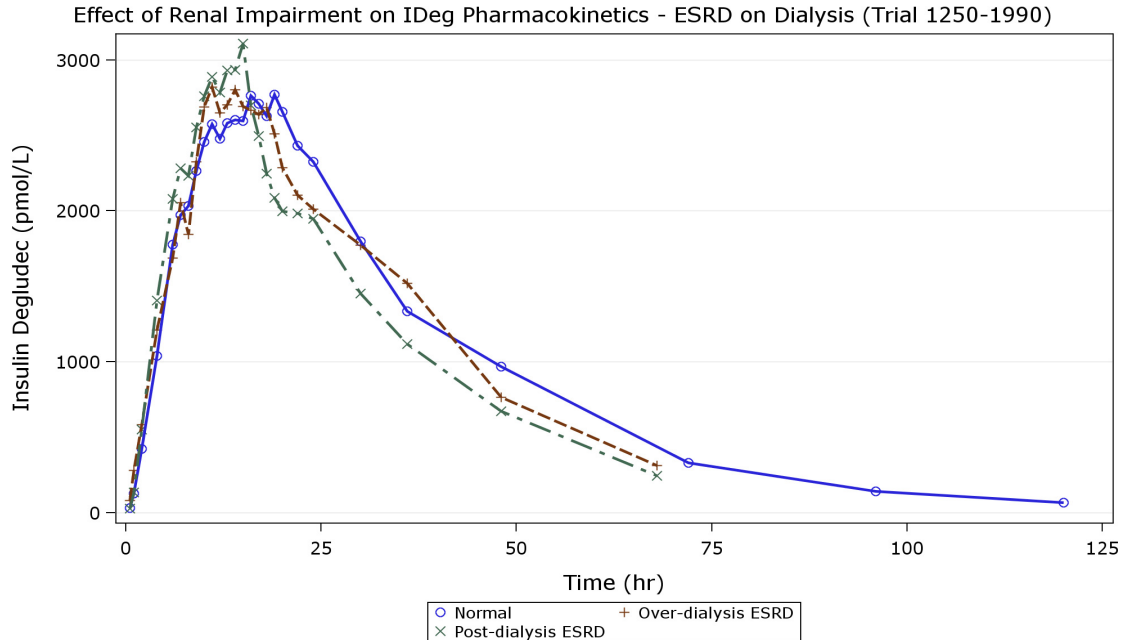


**Figure 59 Insulin Degludec pharmacokinetic profile in end-stage renal disease subjects requiring hemodialysis after single 0.4 U/kg subcutaneous dose immediately after hemodialysis (Post-dialysis ESRD) and 13-hour prior to initiation of hemodialysis (Over-dialysis ESRD)**

The mean IDeg concentration-time profile in ESRD (post or over-dialysis) was similar to that observed in subjects with normal renal function.

Descriptive statistics and the results from the statistical analysis of key PK parameters are summarized in the following tables.

**Table 23 Statistical comparison of AUC<sub>0-120h</sub> and C<sub>max</sub> of Insulin Degludec in subjects with normal renal function and with renal impairment**

| PK Parameter:<br>Geo. Mean (CV)                                                                                                                                                                                                                                                                     | Renal Impairment Group                            |              |              |             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------|--------------|--------------|-------------|
|                                                                                                                                                                                                                                                                                                     | Normal                                            | Mild         | Moderate     | Severe      |
| C <sub>max</sub> (pmol/L):                                                                                                                                                                                                                                                                          | 3085 (28)                                         | 3502 (30)    | 3237 (39)    | 3918 (28)   |
| t <sub>max</sub> (hour)*:                                                                                                                                                                                                                                                                           | 15.5 (12-19)                                      | 13.5 (12-24) | 12.5 (10-17) | 11 (10-14)  |
| AUC <sub>0-120h</sub> (pmol*h/L):                                                                                                                                                                                                                                                                   | 107332 (26)                                       | 124403 (47)  | 116153 (33)  | 125945 (28) |
| t <sub>1/2</sub> (hour):                                                                                                                                                                                                                                                                            | 19 (22)                                           | 16 (29)      | 17 (25)      | 15 (27)     |
| CL/F (L/h/kg):                                                                                                                                                                                                                                                                                      | 0.022 (32)                                        | 0.019 (31)   | 0.021 (39)   | 0.019 (24)  |
| V/F (L/kg):                                                                                                                                                                                                                                                                                         | 0.611 (52)                                        | 0.429 (27)   | 0.493 (65)   | 0.417 (34)  |
| <b>Statistical Comparison<br/>Parameter estimate**</b>                                                                                                                                                                                                                                              | <b>LS Mean Ratio [90%CI] AUC<sub>0-120h</sub></b> |              |              |             |
| Sex (Female)                                                                                                                                                                                                                                                                                        | 0.154 [-0.144; 0.452]                             |              |              |             |
| Age                                                                                                                                                                                                                                                                                                 | -0.010 [-0.026; 0.006]                            |              |              |             |
| Body Weight                                                                                                                                                                                                                                                                                         | 0.787 [ 0.055; 1.519]                             |              |              |             |
| Creatinine Clearance                                                                                                                                                                                                                                                                                | -0.254 [-0.507; 0.000] P-value 0.05               |              |              |             |
| *Median (Min., Max.)                                                                                                                                                                                                                                                                                |                                                   |              |              |             |
| **The endpoints are log-transformed and analyzed using an ANOVA model with log (Creatinine Clearance at screening), Sex, Age at baseline and log (Body Weight at baseline) as fixed effects. The estimate for the effect of Sex is for Female, with Male as reference group. ***Reviewer's Analysis |                                                   |              |              |             |

**Table 24 Descriptive statistics for key PK parameters and statistical comparison of CL/F of Insulin Degludec with and without hemodialysis in subjects with renal impairment**

| PK Parameter:<br>Geo. Mean (CV)    | Renal Impairment Group                |                         |                         |
|------------------------------------|---------------------------------------|-------------------------|-------------------------|
|                                    | Normal                                | ESRD<br>(Post-dialysis) | ESRD<br>(Over-dialysis) |
| C <sub>max</sub> (pmol/L):         | 3085 (28)                             | 3172 (37)               | 2955 (45)               |
| t <sub>max</sub> (hour)*:          | 15.5 (12-19)                          | 17.0 (10-19)            | 14.5 (11-24)            |
| AUC <sub>0-68</sub> (pmol*h/L):    | 107332 (26)                           | 92457 (22)              | 84028 (30)              |
| t <sub>1/2</sub> (hour):           | 19 (22)                               | 18 (155)                | 15 (33)                 |
| CL/F (L/h/kg):                     | 0.022 (32)                            | 0.021 (19)              | 0.026 (29)              |
| V/F (L/kg):                        | 0.611 (52)                            | 0.541 (131)             | 0.561 (63)              |
| <b>Statistical Comparison</b>      | <b>LS Mean Ratio [90%CI] for CL/F</b> |                         |                         |
| With dialysis/<br>Without dialysis | 1.23 [0.92; 1.66]                     |                         |                         |
| *Median (Min., Max.)               |                                       |                         |                         |

Results showed that:

- Based on the statistical analysis, there was slight, albeit statistically insignificant, trend of increased in clearance with increase in creatinine clearance. Accordingly, the total IDeg exposures showed increasing trend with severity of renal impairment. Both magnitude (C<sub>max</sub>) and time to peak exposure (t<sub>max</sub>) to IDeg were generally comparable across all categories.
- The results of this trial also suggested that renal clearance of IDeg was negligible. Little or no unaltered IDeg was detected in the urine samples collected up to 24 hour after administration from normal and non-ESRD subjects.
- The IDeg apparent clearance appeared to be affected by hemodialysis (23% higher clearance). However, The average concentration of intact IDeg recovered in the dialysate after a single dose (C<sub>dialysate, IDeg, SD</sub>) were negligible indicating that overall influence of hemodialysis on IDeg clearance is negligible.
- Twenty-eight (28) of the 31 hypoglycemic episodes reported during this trial were asymptomatic [American Diabetes Association (ADA) criteria: any plasma glucose concentration ≤ 3.9 mmol/L (or 70 mg/dL)]. No severe episodes were reported. Three documented symptomatic episodes were reported for 2 subjects with moderate or severe renal impairment, and 12 nocturnal hypoglycemic episodes were reported (1 documented symptomatic and 11 asymptomatic). The number of hypoglycemic episodes tended to be greater for subjects with ESRD as compared with subject with mild, moderate, or severe renal impairment. However, there was no obvious difference in the incidence of hypoglycemia in relation to whether or not subjects with ESRD underwent hemodialysis.
- Based on this reviewer’s analysis, in comparison to the subjects with normal renal function the mean ratio (90%CI) for mild, moderate and severe renal impairment were 1.15 (0.83 – 1.60), 1.07 (0.77 – 1.50), and 1.16 (0.84 – 1.62) respectively for AUC<sub>0-inf</sub>. The corresponding mean ratios (90%CI) for C<sub>max</sub> were 1.14 (0.82 – 1.57), 1.05 (0.76 – 1.45), and 1.27 (0.92 – 1.75) respectively.

Based on these findings:

There is no need to adjust the starting dose of IDeg based on degree of renal impairment. However, consistent to the proposed use of IDeg in with subjects with normal renal function, IDeg should be titrated according to individual requirements in patients with renal impairment as well. The influence of hemodialysis on IDeg PK was minimal, which also means that the removal of IDeg with hemodialysis is unlikely. Number of hypoglycemic episodes was higher in

subjects with ESRD. Considering there is a trend of increased exposure of IDeg with degree of renal impairment, IDeg should be used with caution in patients with renal impairment and frequent monitoring of blood glucose is recommended during IDeg use.

### 2.3.4 What is the effect of hepatic impairment on Insulin Degludec pharmacokinetics?

The effect of hepatic impairment on IDeg PK was assessed in a single-center, single-dose, parallel group, open-label trial investigating pharmacokinetic profiles of Insulin Degludec in four groups of subjects with normal, mild, moderate, and severe hepatic impairment (NN1250-1989). Each subject received a single 0.4 U/kg subcutaneous dose of IDeg (M) into the thigh. The classification of hepatic impairment was based on the Child-Pugh scores and was in accordance with that defined by the Guidance document. Six subjects were evaluated in each group as planned.

The impact of hepatic impairment on relevant pharmacokinetic parameters of Insulin Degludec is depicted below in **Figure 60**. The IDeg mean concentration-time profiles showed a decrease in mean peak concentration with increase in degree of hepatic impairment.

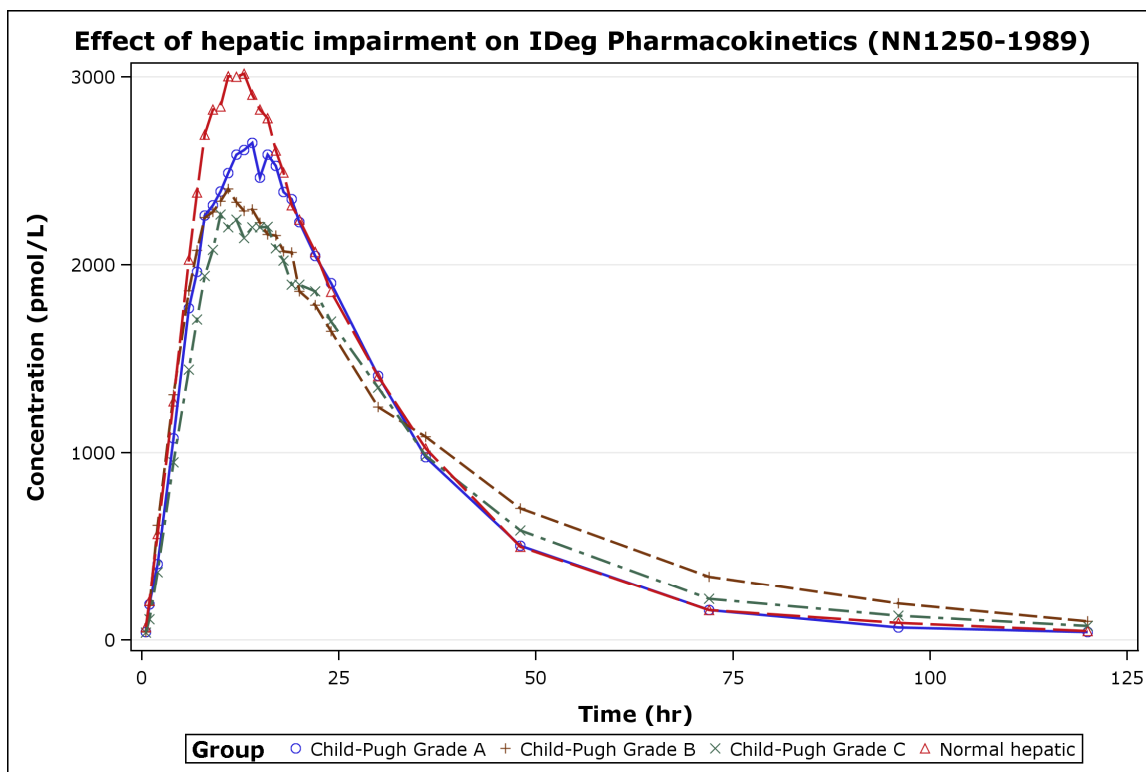


**Figure 60 Insulin Degludec pharmacokinetic profile among subjects with normal hepatic function and with hepatic impairment after single 0.4 U/kg subcutaneous dose**

Results of the statistical analysis of pharmacokinetic parameters are summarized in the following table.

**Table 25 Descriptive statistics for key PK parameters and statistical comparison of AUC<sub>0-120h</sub> and C<sub>max</sub> of Insulin Degludec among subjects with normal hepatic function and with hepatic impairment**

| PK Parameter:<br>Geo. Mean (CV)   | Hepatic Impairment Group (Child-Pugh Grade)    |                   |                                           |                     |
|-----------------------------------|------------------------------------------------|-------------------|-------------------------------------------|---------------------|
|                                   | Normal<br>Function                             | Mild<br>(Grade A) | Moderate<br>(Grade B)                     | Severe<br>(Grade C) |
| C <sub>max</sub> (pmol/L):        | 3099 (13)                                      | 2796 (18)         | 2394 (54)                                 | 2350 (31)           |
| t <sub>max</sub> (hour)*:         | 13.5 (11-16)                                   | 14.5 (11-17)      | 13.0 (8-19)                               | 13.5 (8-24)         |
| AUC <sub>0-120h</sub> (pmol*h/L): | 89092 (16)                                     | 83327 (15)        | 88944 (23)                                | 79846 (19)          |
| t <sub>1/2</sub> (hour):          | 17 (34)                                        | 16 (21)           | 20 (30)                                   | 19 (32)             |
| CL/F (L/h/kg):                    | 0.027 (16)                                     | 0.029 (13)        | 0.026 (28)                                | 0.029 (20)          |
| V/F (L/kg):                       | 0.656 (34)                                     | 0.665 (30)        | 0.740 (47)                                | 0.789 (43)          |
| Statistical Comparison            | LS Mean Ratio [90%CI]<br>AUC <sub>0-120h</sub> |                   | LS Mean Ratio [90%CI]<br>C <sub>max</sub> |                     |
| Mild/Normal                       | 0.99 [0.83; 1.19]                              |                   | 0.90 [0.67; 1.22]                         |                     |
| Moderate/Normal                   | 0.92 [0.76; 1.11]                              |                   | 0.76 [0.56; 1.04]                         |                     |
| Severe/Normal                     | 0.82 [0.66; 1.01]                              |                   | 0.74 [0.52; 1.04]                         |                     |
| *Median (Min., Max.)              |                                                |                   |                                           |                     |

Results showed that:

- Based on the LS-mean ratios and 90%CIs, the total IDeg exposures were statistically lower in moderate and severe hepatic impairment subjects than in subjects with normal hepatic function. Peak exposure to IDeg was statistically lower and magnitude of decrease was higher with increasing degree of hepatic impairment.
- The trend analysis, which is test of the hypothesis (trend=0) for a monotonous trend in the endpoint with severity of impaired hepatic function, indicated a negative slope -0.68 for the AUC<sub>IDeg,0-120h,SD</sub>, though statistically insignificant (P-value = 0.11).
- The serum albumin concentration in subjects with severe hepatic impairment was generally lower than that of the other three groups at baseline. A small positive correlation was evident between AUC<sub>IDeg,0-120h,SD</sub> and serum albumin (estimated correlation coefficient value: 0.51 and p-value: 0.01). However, the result of the analysis of the primary endpoint was not affected when repeated including serum albumin as an extra explanatory variable.
- Renal clearance of IDeg was negligible in subjects with hepatic impairment.
- Twelve hypoglycaemic episodes occurred (all with plasma glucose between 3.4 and 3.9 mmol/l). No relation between the incidence of hypoglycemia and severity of hepatic impairment was evident.

Based on these findings:

- There is no need to adjust the starting dose of IDeg based on degree of hepatic impairment. However, consistent to the proposed use of IDeg in with subjects with normal hepatic function, IDeg should be titrated according to individual requirements in patients with hepatic impairment as well. Considering the role of liver in glucose homeostasis and uncertainties surrounding the impact of hepatic impairment therein, the proposed cautionary use of IDeg in subjects with hepatic impairment with frequent glucose monitoring is reasonable and in accordance to the language in existing insulin labels.

## 2.4 Extrinsic Factors

### 2.4.1 What is the effect of different injection sites on the bioavailability of Insulin Degludec?

The relative bioavailability of Insulin Degludec from different injection sites was assessed in Trial 1250-1992. This was a randomized, single-center, open-label, five-period, cross-over trial in healthy subjects investigating the comparison of pharmacokinetic and pharmacodynamic properties of IDeg after different routes of administration. Twenty (20) subjects were randomized to pre-determined sequences of five single-dose administrations (0.4 U/kg IDeg subcutaneous in the thigh, the abdomen, and the deltoid area, 0.4 U/kg IDeg intra-muscular in the thigh, and 0.04 U/kg IDeg intravenous, respectively) on five separate dosing visits. The dosing visits were separated by washout periods lasting 13-21 days.

At the subcutaneous and intramuscular dosing visits, the subjects were hospitalized at the trial site for the first 48 hours after trial product administration. The pharmacodynamic response was evaluated during a 24-hour euglycemic clamp (blood glucose target: 4.5 mmol/L [81 mg/dL]). The pharmacokinetic profile of IDeg was evaluated for 120 hours. At the i.v. dosing visit, the subjects were hospitalized at the trial site for the first 30 hours after trial product administration. The pharmacodynamic response was evaluated during a 12-hour euglycemic clamp (blood glucose target: 4.5 mmol/L [81 mg/dL]), and the pharmacokinetic profile of IDeg was evaluated for 30 hours. The mean PK and PD profiles of IDeg by treatment are presented in **Figures 61 and 62**, respectively.

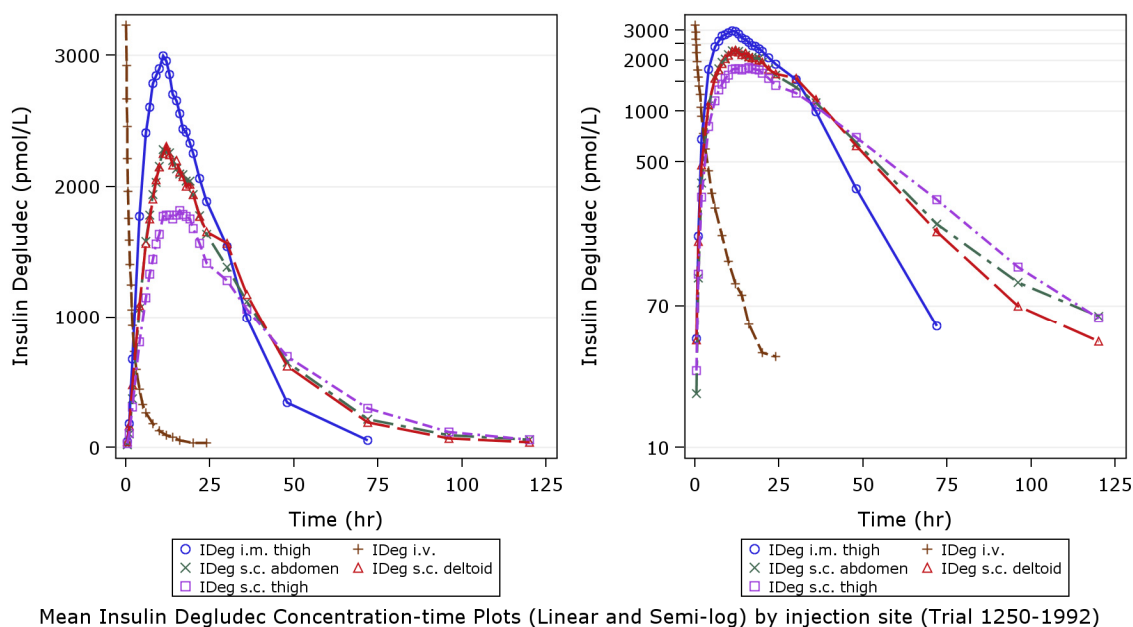
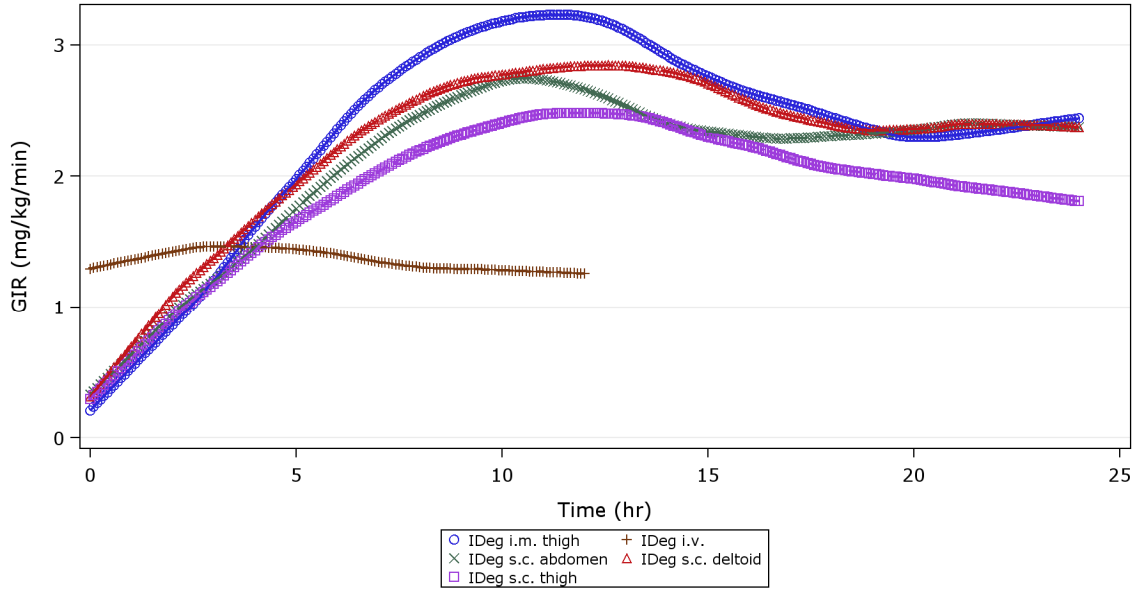


**Figure 61** Mean Insulin Degludec plasma concentrations from different injection sites



Mean Insulin Degludec GIR-time Plots (Linear and Semi-log) by injection site (Trial 1250-1992)

**Figure 62 Mean GIR from different injection sites**

To better visualize the degree of variation in key PK and PD parameters resulting from injection at different sites, the distribution of these parameters was plotted by injection site (**Figures 63 and 64**, respectively for PK and PD).

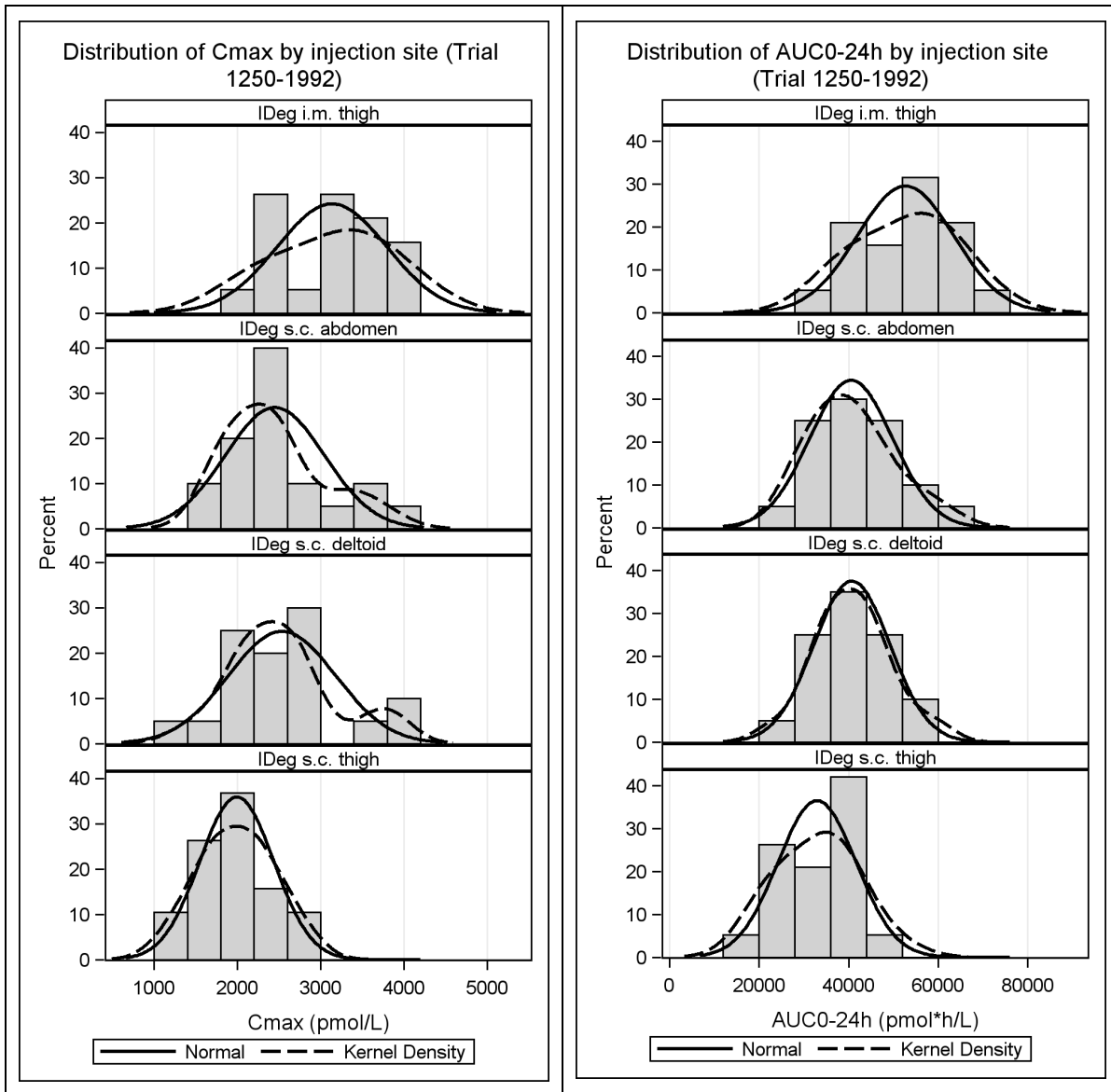


**Figure 63 Distribution of IDeg PK parameters by different injection sites**

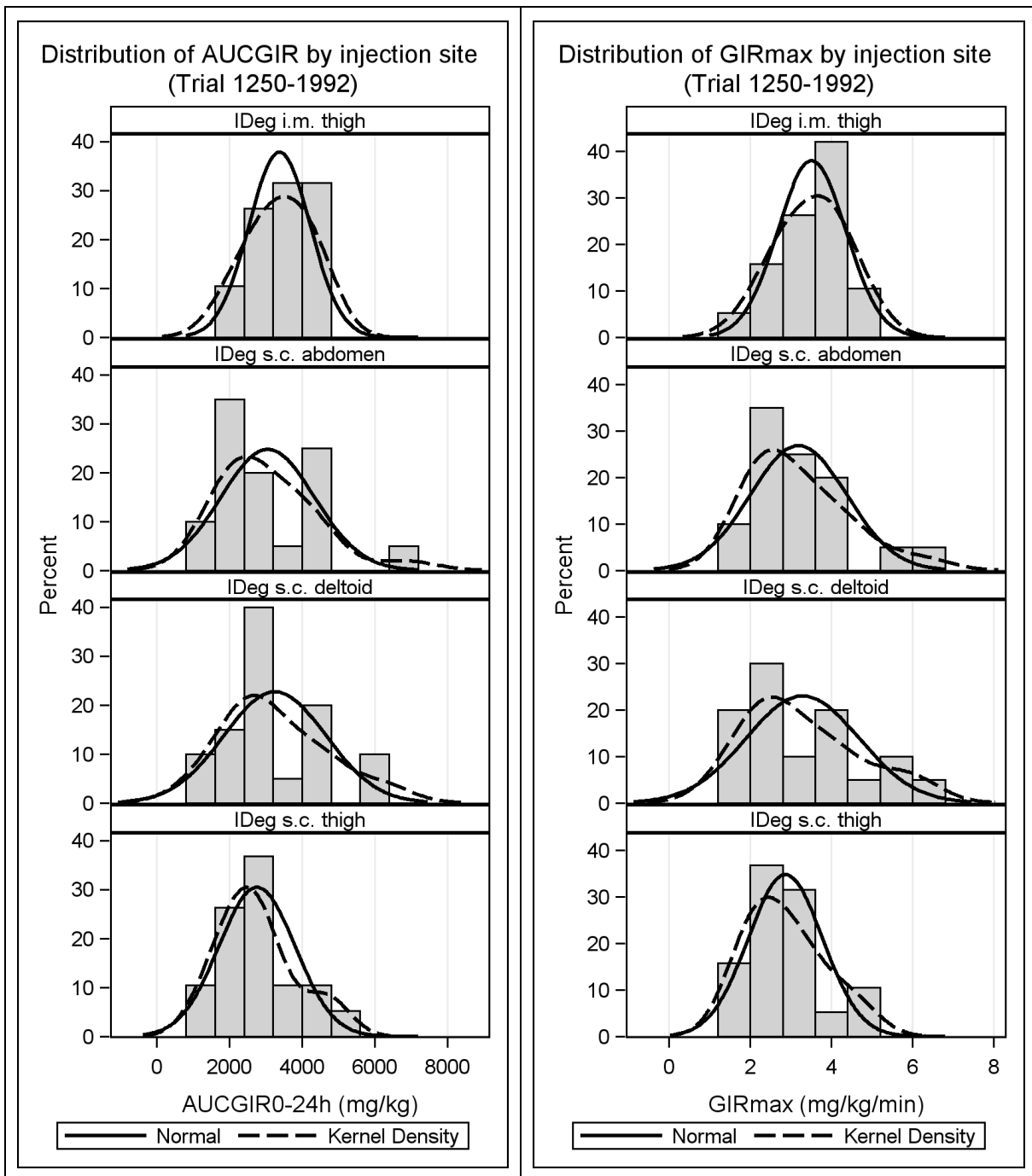


**Figure 64** Distribution of IDeg PD parameters by different injection sites

The summary of PK and PD parameters, and statistical comparisons is presented in **Table 26** below.

**Table 26 Effect of injection site on Insulin Degludec pharmacokinetics after single 0.4 U/kg SC administration in thigh, abdomen, and deltoid area, and 0.4 U/kg IM in thigh**

| PK Parameter:<br>Geo. Mean (CV)   | Injection Route/Site                           |            |                               |            |
|-----------------------------------|------------------------------------------------|------------|-------------------------------|------------|
|                                   | SC–Thigh                                       | SC–Abdomen | SC–Deltoid                    | IM–Thigh   |
| Cmax (pmol/L):                    | 1945 (22)                                      | 2388 (24)  | 2462 (25)                     | 3067 (21)  |
| t <sub>max</sub> (hour)*:         | 15 (11-30)                                     | 13 (7-20)  | 12 (8-20)                     | 11 (7-15)  |
| AUC <sub>0-120h</sub> (pmol*h/L): | 75853 (19)                                     | 83327 (15) | 82059 (17)                    | 81521 (18) |
| t <sub>1/2</sub> (hour):          | 16 (24)                                        | 14 (29)    | 17 (27)                       | 7 (32)     |
| CL/F (L/h/kg):                    | 0.029 (19)                                     | 0.029 (22) | 0.031 (21)                    | 0.029 (20) |
| V/F (L/kg):                       | 0.645 (18)                                     | 0.595 (29) | 0.739 (30)                    | 0.303 (42) |
| AUCGIR <sub>0-24h</sub> (mg/kg):  | 2572 (38)                                      | 2833 (42)  | 2960 (43)                     | 3269 (25)  |
| GIR max (mg/kg/min)               | 2.7 (32)                                       | 3.0 (37)   | 3.0 (42)                      | 3.4 (24)   |
| tGIR <sub>max</sub> (hour)*:      | 13 (8, 24)                                     | 11 (6, 24) | 12 (7, 24)                    | 12 (9, 24) |
| Statistical Comparison            | LS Mean Ratio [95%CI]<br>AUC <sub>0-120h</sub> |            | LS Mean Ratio [90%CI]<br>Cmax |            |
| SC-abdomen/thigh                  | 1.07 [1.03; 1.11]                              |            | 1.23 [1.07; 1.42]             |            |
| SC-deltoid/thigh                  | 1.06 [1.01; 1.10]                              |            | 1.27 [1.08; 1.49]             |            |
| SC-abdomen/deltoid                | 1.01 [0.96; 1.06]                              |            | 0.97 [0.84; 1.12]             |            |
| IM-Thigh/SC-Thigh                 | 1.07 [1.02; 1.13]                              |            | 1.58 [1.36; 1.84]             |            |
| *Median (Min., Max.)              |                                                |            |                               |            |

The total exposure of IDeg from abdomen and deltoid area was about 7% higher than thigh after subcutaneous administration at these sites. Peak total exposure was 23% and 27% higher from abdomen and deltoid area was about 7% higher than thigh. Intramuscular administration yielded 60% higher Cmax, however, 7% higher peak exposure than subcutaneous administration at thigh. Mean apparent clearance was same for this comparison with a corresponding decrease in apparent volume of distribution and roughly, reduction in t<sub>1/2</sub> by 50%. Tmax was comparable from the four sites.

Following the pattern of PK changes, PD parameters GIR<sub>max</sub> and AUCGIR<sub>0-24h</sub> showed comparable mean values. However, the magnitude of inter-individual variability (%CV) was higher from subcutaneous administration from abdomen and deltoid are as well as from intramuscular administration at thigh in comparison to subcutaneous administration at thigh. Perhaps, this is the reason sponsor used thigh as the principal site of administration in most of the clinical pharmacology evaluations. Based on the findings IDeg can be administered interchangeably at these injection sites subcutaneously. We agree to the proposed rotation of injection sites within the same region to reduce the risk of lipodystrophy as well as variability in PK and response. IDeg should not be administered as intramuscular injection due to altered time-action profile from this route and lack of safety and efficacy evaluation. However, in the event of accidental/suspected intramuscular administration during the clinical use, patients should frequently monitor their blood glucose. There was a tendency of higher percentage of subjects being at higher GIR<sub>max</sub> after intramuscular injection in comparison to the subcutaneous route (Figure 64), which may increase the risk of hypoglycemia.

## 2.4.2 Drug-Drug Interactions

### 2.4.2.1 What is the CYP induction potential of Insulin Degludec?

Minor effect on individual cytochrome P-450 (CYP) expression (less than 2-fold induction) was observed following insulin degludec treatment in rats. All effects of insulin Degludec were

similar to those elicited by human insulin. Therefore, this aspect was not considered for further evaluation in humans.

#### 2.4.2.2 What is the effect of other drugs on protein binding of Insulin Degludec?

The common protein-bound drugs, warfarin, acetylsalicylate, salicylate, ibuprofen, and frequently used antidiabetic agents sitagliptin, glimepiride, metformin and liraglutide as well as the long-chain fatty acids, palmitate, oleate and linoleate were evaluated for their potential to alter IDeg binding to human serum albumin at therapeutically/physiologically relevant concentrations (Study CES 101123).

Human serum albumin (HSA, 0.3  $\mu\text{M}$ ) covalently immobilized to Mini-Leak agarose beads was incubated for 2 hours with tracer amounts of [ $^{125}\text{I}$ ]-IDeg (25 pM) and increasing concentrations of palmitate, oleate, linoleate, liraglutide, sitagliptin, glimepiride, metformin, warfarin, ibuprofen, salicylate or acetylsalicylate (typically 0 – 1,000 times the HSA concentration). The reaction was terminated by centrifugation. The amount of tracer in the supernatant was measured on a gamma counter to estimate the free and bound fractions.

The summary of Insulin Degludec in vitro protein binding interaction evaluation is presented in **Table 26** below.

**Table 27 Summary table of concentrations giving half-maximal binding of  $^{125}\text{I}$ -IDeg to human serum albumin (mean IC<sub>50</sub> values, 95% confidence intervals, n=3, 0.3  $\mu\text{M}$  HSA) for fatty acids and commonly used antidiabetic and analgesic agents**

| Ligand           | IC <sub>50</sub> ( $\mu\text{M}$ ) | 95% CI ( $\mu\text{M}$ ) | IC <sub>50</sub> norm. [Ligand IC <sub>50</sub> ]/[HSA] | Typical Cmax* ( $\mu\text{M}$ ) |
|------------------|------------------------------------|--------------------------|---------------------------------------------------------|---------------------------------|
| Palmitate        | 3.2                                | 1.4 - 7.2                | 10.67                                                   | variable < 200                  |
| Oleate           | 5.5                                | 3.7 - 8.2                | 18.33                                                   | variable < 200                  |
| Linoleate        | 4.1                                | 2.8 - 6.0                | 13.67                                                   | variable < 200                  |
| Ibuprofen        | 11                                 | 7.2 - 15                 | 36.67                                                   | 90 - 265                        |
| Glimepiride      | > 100                              | -                        | > 333                                                   | 0.6 - 1.2                       |
| Metformin        | > 500                              | -                        | > 1666                                                  | 7 - 30                          |
| Sitagliptin      | > 500                              | -                        | > 1666                                                  | 1                               |
| Liraglutide      | > 100                              | -                        | > 333                                                   | 0.035                           |
| Warfarin         | > 100                              | -                        | > 333                                                   | 5.8 - 7.1                       |
| Acetylsalicylate | > 500                              | -                        | > 1666                                                  | 800 - 1600                      |
| Salicylate       | > 100                              | -                        | > 333                                                   | Metabolite of ASA               |

\* from drug label

The normalized IC<sub>50</sub> values give the concentration ratio between ligand and HSA leading to half-maximal inhibition of binding. From the normalized IC<sub>50</sub> ratios [Ligand]/[HSA] in Table 25 it is evident that all compound need to be present at a concentration greater than 10 times the HSA concentration to reduce the binding of IDeg by 50%. At a typical serum albumin concentration of 4% (600  $\mu\text{M}$ ) none of these agents are expected to have any noticeable effect on the binding of IDeg to serum albumin.

The following agents are not expected to affect IDeg binding to human serum albumin at therapeutically/physiologically relevant concentrations:

- common protein-bound drugs: warfarin, acetylsalicylate, salicylate, ibuprofen,
- antidiabetic agents: sitagliptin, glimepiride, metformin, and liraglutide
- long-chain fatty acids: palmitate, oleate and linoleate.

## 2.5 General Biopharmaceutics

### 2.5.1 What is absolute bioavailability of Insulin Degludec?

The absolute bioavailability of Insulin Degludec following subcutaneous dose could not be estimated due to unreliable data from the intravenous administration evaluated in Trial 1250-1992. For safety reasons, the pharmacokinetics of IDeg were investigated at a lower dose level for intravenous administration (0.04 U/kg) than for subcutaneous and intramuscular administration (0.4 U/kg). In order to be able to dose an appropriate volume during intravenous administration, IDeg (100 U/mL; 600 nmol/mL) was diluted by 20 times before intravenous dosing. IDeg concentrations in the diluted solution were within 1 nmol of the theoretical concentration (5 U/mL; 30 nmol/mL) for all subjects. Sponsor suspected the over-dilution of IDeg formulation as the cause of underestimation. The efficacy and safety of intravenous use of IDeg is also unknown. Considering altered disposition of IDeg following dilution in intravenous fluid, the therapeutic use from this route (bolus or infusion) is contraindicated from clinical pharmacology perspective.

### 2.5.2 Is pharmacokinetic/pharmacodynamic profile (time-action profile) of IDeg comparable among proposed commercial formulation (also Phase 3 formulation) before (IM1) and after (IM2) process optimization, and among the Phase 2 (IDeg E) and Phase 3 formulation (IDeg M)?

The IDeg (M) 100 U/mL proposed commercial formulation was used throughout the therapeutic confirmatory trials and key clinical pharmacology trials. IDeg (P) is the 200 U/mL product used in the therapeutic confirmatory trials and the clinical pharmacology trials, and is identical to the IDeg 200 U/mL proposed commercial formulation. Therefore, the PK/PD comparability trials were considered as supportive, and therefore OSI inspection was not requested.

Trial NN1250-1988 investigated bioequivalence between the IDeg (E) and IDeg (M) drug products, manufactured before and after a change in the (b) (4). Trial NN1250-3769 investigated bioequivalence between IDeg (M) drug products produced from (b) (4), before and after optimization of (b) (4).

**Trial 1250-1988:** The IDeg formulation used for the Phase 3 studies (IDeg M) is identical in composition to the formulation used for the Phase 2 studies (IDeg E), but (b) (4) were from different campaigns as the manufacturing process was optimized. Therefore, sponsor evaluated PK and PD comparability of the Phase 3 formulation to Phase 2 formulation. Rationale for this trial was to test for bioequivalence between the two formulations IDeg (E) and IDeg (M) (used in the studies for Phase 2 and Phase 3, respectively) under the assumption that, bioequivalence between the two formulations would imply that the safety and efficacy information obtained with IDeg (E) could be assumed as identical to that with IDeg (M).

This trial was a randomized, single-center, double-blinded, two-period cross-over trial in healthy subjects. Each subject was randomized to two single-dose administrations (one for each of the 2 IDeg formulations) on two separate dosing visits separated by a washout period of 13-21 days between the 2 dosing events. At each of the 2 dosing visits, the subjects stayed in-house for at least first 48 hours after trial drug administration. The PK profile of IDeg was evaluated for 120 hours, while the PD response was evaluated during a 24-hour euglycemic clamp.

The mean (95% confidence band) IDeg concentration-time profile by treatment is presented in **Figure 65** below.

The mean concentration profiles from the two formulations and overlapping 95% confidence bands indicated that the two profiles were comparable in shape to approximate congruency. The partial time-action profiles depicted by the GIR over 24 hours were also comparable in shape from the two formulations (**Figure 65**).

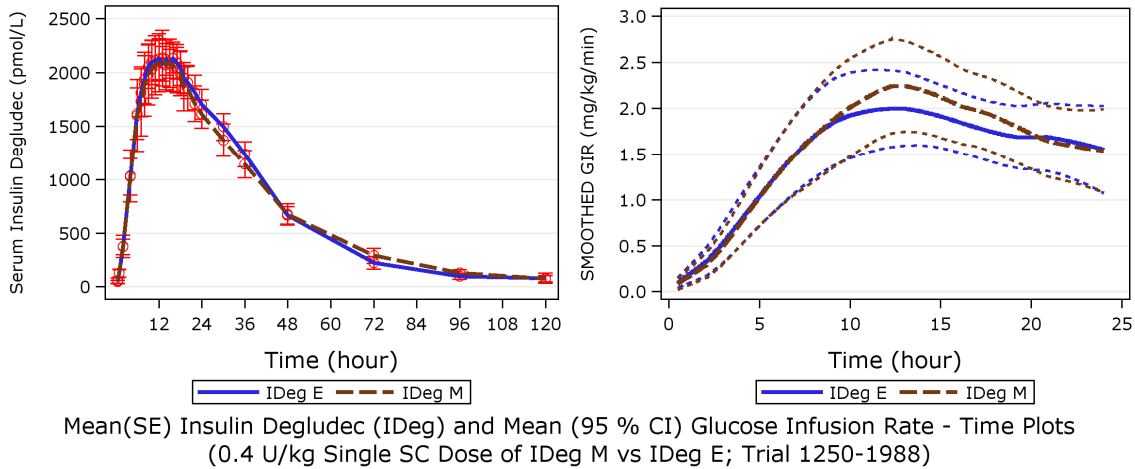


**Figure 65** Mean (SE) IDeg concentration-time (Left) and mean (95% confidence band) GIR-time profile (Right) by treatment

The euglycemic clamp integrity was evident from the glucose levels that were tightly maintained at target of 4.5 mmol/L over the clamp duration. On average the c-peptide levels remained suppressed over the clamp duration, indicating minimal interference from endogenous insulin (**Fig. 66**).

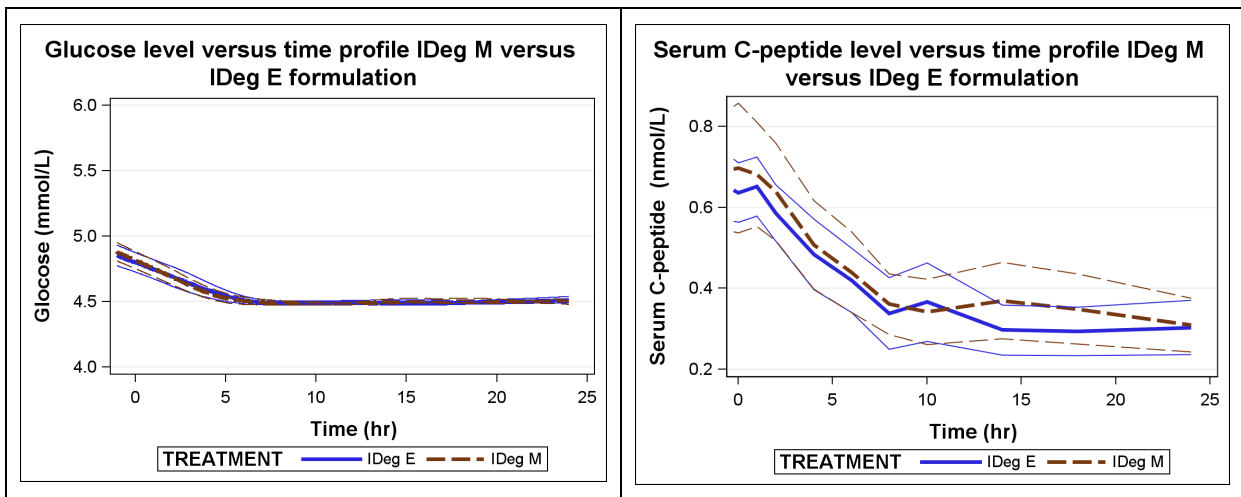


**Figure 66** Mean (95% confidence band) plots for glucose-time (Left) and c-peptide-time (Right) over clamp duration by treatment

The summary of select PK and PD parameters along with the results of the BE analysis are presented in **Table 27** below.

**Table 28 Summary of bioequivalence analysis for BE Trial 1250-1988**

| PK Parameter:<br>Geo. Mean (CV)                                                                            | IDeg Day 6 Dose                                     |                |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|----------------|
|                                                                                                            | IDeg E<br>N=25                                      | IDeg M<br>N=26 |
| Cmax (pmol/L):                                                                                             | 2345 (21)                                           | 2280 (29)      |
| tmax (hour):                                                                                               | 13 (6-22)                                           | 13.5 (6-36)    |
| AUCIDeg,0-120h (pmol*h/L):                                                                                 | 84346 (14)                                          | 83817 (16)     |
| GIRmax (pmol/L):                                                                                           | 2.2 (42)                                            | 2.3 (48)       |
| t <sub>GIRmax</sub> (hour)*:                                                                               | 15 (6-24)                                           | 14 (5-24)      |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):                                                                     | 1892 (50)                                           | 1907 (54)      |
| <b>Dose contrasts for AUCIDeg,0-120h -<br/>IDeg M vs. E :</b>                                              | <b>LS Mean Ratio (90% CI)</b><br>1.00 [ 0.94; 1.05] |                |
| <b>Dose contrasts for Cmax -<br/>IDeg M vs. E :</b>                                                        | 0.97 [0.89; 1.05]                                   |                |
| <b>Post-hoc assessments by this reviewer:<br/>Dose contrasts for Partial AUC0-24h -<br/>IDeg M vs. E :</b> | <b>LS Mean Ratio (90% CI)</b><br>0.99 [0.84; 1.17]  |                |
| <b>Dose contrasts for AUCGIR0-24h -<br/>IDeg M vs. E :</b>                                                 | 0.95 [0.88; 1.03]                                   |                |
| <b>Dose contrasts for GIRmax -<br/>IDeg M vs. E :</b>                                                      | 1.03 [0.90; 1.18]                                   |                |

Based on the statistical analyses

- Insulin Degludec formulation M and Insulin Degludec E were bioequivalent with respect to the primary endpoints AUCIDeg,0-120h and Cmax.

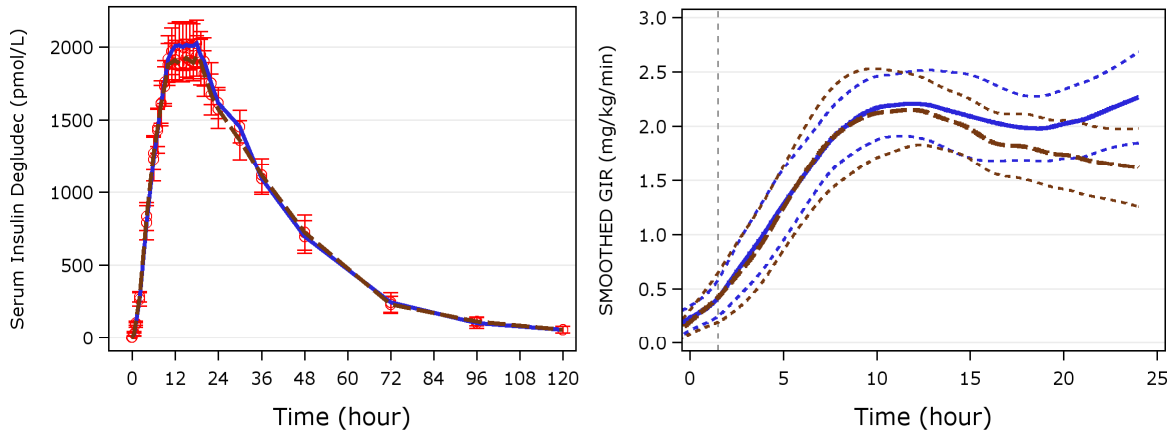
Post-hoc analysis for partial IDeg AUC0-24 conducted by this reviewer also provided additional support that relative bioavailability during initial absorption phase was consistent for the two formulations. Post-hoc analysis of secondary PD parameters (BE analysis in WinNonlin; 90% Confidence) conducted by this reviewer also indicated that relative response over first 24 hours was consistent for the two formulations. Overall, the PK and PD profiles were comparable for this intermediate change in the formulation.

**Trial NN1250-3769:** This was a randomized, single-center, double-blind, two-period cross-over trial in healthy subjects. Each subject was randomly allocated to two single-dose administrations (one for each of IDeg (M) IM1 and IDeg (M) IM2) on two separate dosing visits, separated by at least 13 days to ensure wash out from the previous dosing. Primary objective of the trial was to test for bioequivalence between formulations of IDeg (M) IM1 and IDeg (M) IM2 based on AUC0-120h and Cmax. Secondary objective was to compare the pharmacokinetic and pharmacodynamic profiles of formulations IDeg (M) IM1 and IDeg (M) IM2. The pharmacokinetic (PK) profile was evaluated by collecting blood samples for analysis of IDeg over 120 hours. The PK samples were collected before trial product administration and frequently thereafter. The PD response was evaluated during first 24-hour euglycemic glucose at a target blood glucose of 4.5 mmol/L (81 mg/dL) post-dose.

The mean (95% confidence band) IDeg concentration-time profile by treatment is presented in **Figure 67** below.

The mean concentration profiles from the two formulations and overlapping 95% confidence bands indicated that the two profiles were comparable in shape to approximate congruency

(Figure 67). The partial time-action profiles depicted by the GIR over 24 hours were also comparable in shape from the two formulations.



Mean(SE) Insulin Degludec (IDeg) and Mean (95 % CI) Glucose Infusion Rate - Time Plots (0.4 U/kg Single SC Dose of IDeg IM2 vs. IM1; Trial 1250-3769)

**Figure 67 Mean (SE) IDeg concentration-time (Left) and mean (95% confidence band) GIR-time profile (Right) by treatment**

The euglycemic clamp integrity was evident from the glucose levels that were tightly maintained at target of 4.5 mmol/L over the clamp duration. On average the c-peptide levels remained suppressed over the clamp duration, indicating minimal interference from endogenous insulin.

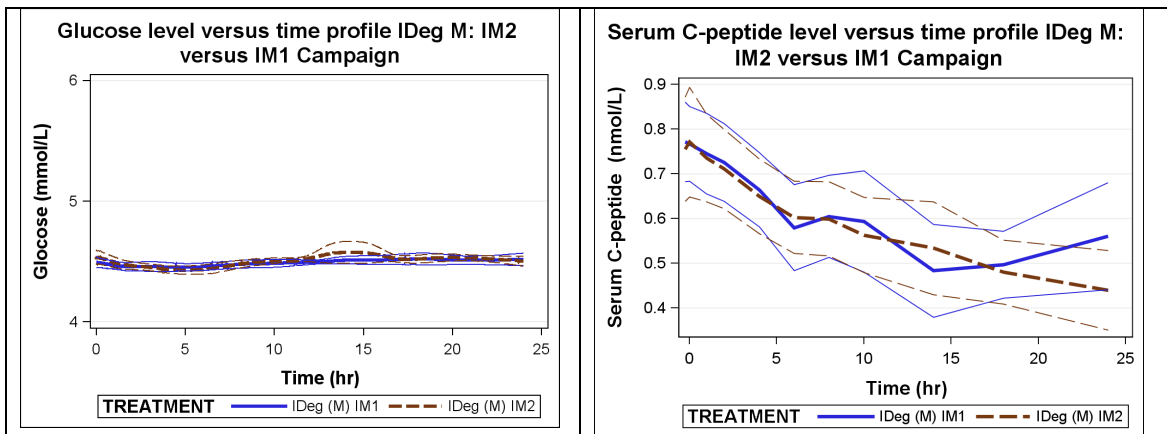


**Figure 68 Mean (95% confidence band) plots for glucose-time (Left) and c-peptide-time (Right) over clamp duration by treatment**

The summary of select PK and PD parameters along with the results of the BE analysis are presented in Table 29 below.

**Table 29 Summary of bioequivalence analysis for BE Trial 1250-3769**

| PK Parameter:<br>Geo. Mean (CV)                                                                               | Treatment                                           |                  |
|---------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|------------------|
|                                                                                                               | IDeg IM1<br>N=26                                    | IDeg IM2<br>N=26 |
| Cmax (pmol/L):                                                                                                | 2115 (19)                                           | 2083 (16)        |
| tmax (hour):                                                                                                  | 14 (10-22)                                          | 15 (10-20)       |
| AUCIDeg,0-120h (pmol*h/L):                                                                                    | 79840 (15)                                          | 78437 (19)       |
| GIRmax (pmol/L):                                                                                              | 2.7 (32)                                            | 2.3 (41)         |
| t <sub>GIRmax</sub> (hour)*:                                                                                  | 15 (6-24)                                           | 13 (6-24)        |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):                                                                        | 2348 (35)                                           | 2071 (43)        |
| <b>Dose contrasts for AUCIDeg,0-120h -<br/>IDeg IM2 vs IM1 :</b>                                              | <b>LS Mean Ratio (90% CI)</b><br>0.99 [ 0.95; 1.03] |                  |
| <b>Dose contrasts for Cmax -<br/>IDeg IM2 vs IM1 :</b>                                                        | <b>LS Mean Ratio (90% CI)</b><br>0.98 [ 0.92; 1.05] |                  |
| <b>Post-hoc assessments by this reviewer:<br/>Dose contrasts for Partial AUC0-24h -<br/>IDeg IM2 vs IM1 :</b> | <b>LS Mean Ratio (90% CI)</b><br>0.98 [0.91; 1.05]  |                  |
| <b>Dose contrasts for artial AUC0-12h -<br/>IDeg IM2 vs IM1 :</b>                                             | <b>LS Mean Ratio (90% CI)</b><br>1.01 [0.93; 1.09]  |                  |
| <b>Dose contrasts for AUCGIR0-24h -<br/>IDeg IM2 vs IM1 :</b>                                                 | <b>LS Mean Ratio (90% CI)</b><br>0.88 [0.80; 0.98]  |                  |
| <b>Dose contrasts for GIRmax -<br/>IDeg IM2 vs IM1 :</b>                                                      | <b>LS Mean Ratio (90% CI)</b><br>0.86 [0.79; 0.95]  |                  |

Based on the statistical analyses

- Insulin Degludec formulation IM2 and Insulin Degludec IM1 were bioequivalent with respect to the primary endpoints AUCIDeg,0-120h and Cmax.

Post-hoc analysis for partial IDeg AUCs: AUC0-12 and AUC0-24, and secondary PD parameters conducted by this reviewer also provided additional support that relative bioavailability during initial absorption phase was consistent for the two formulations. Post-hoc analysis of secondary PD parameters (BE analysis in WinNonlin; 90% Confidence) conducted by this reviewer also indicated that relative response over first 24 hours was consistent for the two formulations, albeit marginally lower with the IM2 formulation. Overall, the PK and PD profiles were comparable for this intermediate change in the formulation.

As this optimization is related to (b) (4) manufacturing process only, the bioequivalence demonstrated in Trial 3769 covers both 100 U/mL and 200 U/mL.

**2.5.2 Is pharmacokinetic/pharmacodynamic profile (time-action profile) of IDeg comparable from the two to-be-marketed formulations U100 and U200?**

**U200 versus U100 comparison in Type 1 DM:** PK and PD profile of IDeg from the U200 (1200 nmol/mL) and U100 (600 nmol/mL) formulations were compared in Trial NN1250-3678. This was a randomized, single-center, double-blind, two-period cross-over, multiple dose trial investigating the PK and PD properties of IDeg 100 U/mL and IDeg 200 U/mL at steady state conditions in subjects with type 1 diabetes.

Each subject was randomly allocated to one of two sequences with 2 treatment periods of 8 days of once-daily dosing with IDeg 100 U/mL and IDeg 200 U/mL, respectively, at a pre-defined

fixed dose level of 0.4 U/kg body weight. During the 2 treatment periods, the plasma glucose (PG) level was controlled by additional bolus injections of insulin aspart (IAsp) supervised the investigator at the daily visits to the clinic.

During each period, PK was evaluated after the first dose, pre-dose sampling from 2<sup>nd</sup> Day to 8<sup>th</sup> Day, and 120h post last dose on 8<sup>th</sup> Day. PD response was evaluated at steady-state post-last dose on 8<sup>th</sup> Day using 26 h euglycemic clamp on both the periods.

The Day 1 mean (95% confidence band) and Day 8 mean (SE) IDeg concentration-time profile by treatment are presented in **Figure 69** below, respectively.

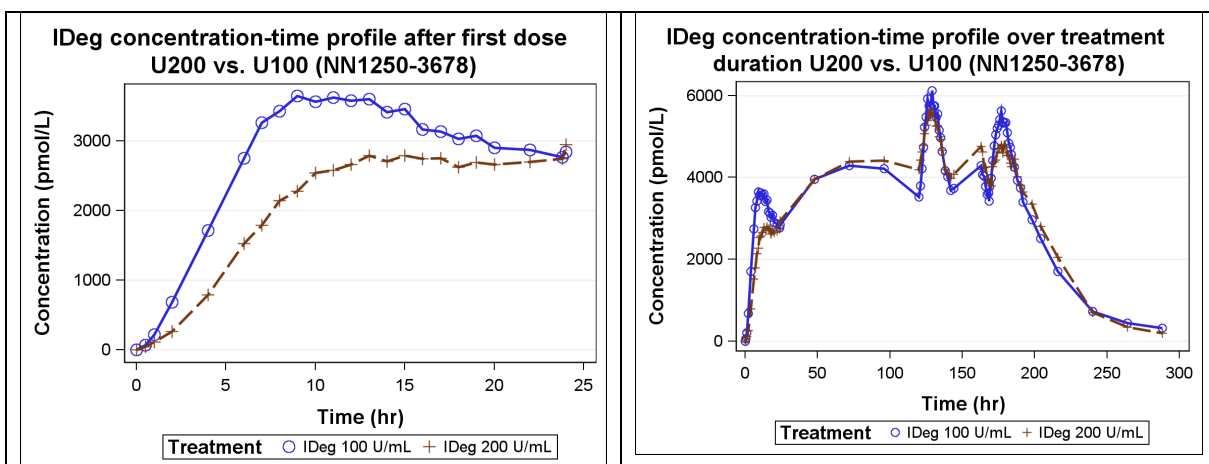


**Figure 69 Day 1 (Left) and full (Right) mean IDeg concentration-time profile by treatment in Type 1 Diabetic subjects (N=33)**

The mean concentration profiles from the two formulations indicated that U200 formulation provides a different absorption gradient than U100 formulation, resulting in less pronounced peak than that from U100. These differences tend to exist but lose their statistical significance at steady-state, as expected, due to lower sensitivity of the multiple-dose design.

The time-action profiles from the two formulations depicted by the GIR over 26 hours accordingly differed in shape (**Figure 70**).

On average, there was a reduction in the amplitude of response, meaning less peak-to-trough fluctuation evident for the GIR-time profile from U200 formulation. However, there was no significant difference in AUCGIR<sub>tau,ss</sub>, although post-hoc assessment of GIR (Smoothed) time data (using standard BE assessment and using 95% confidence) by this reviewer indicated lower GIR<sub>max</sub> from the U200 formulation at steady-state.

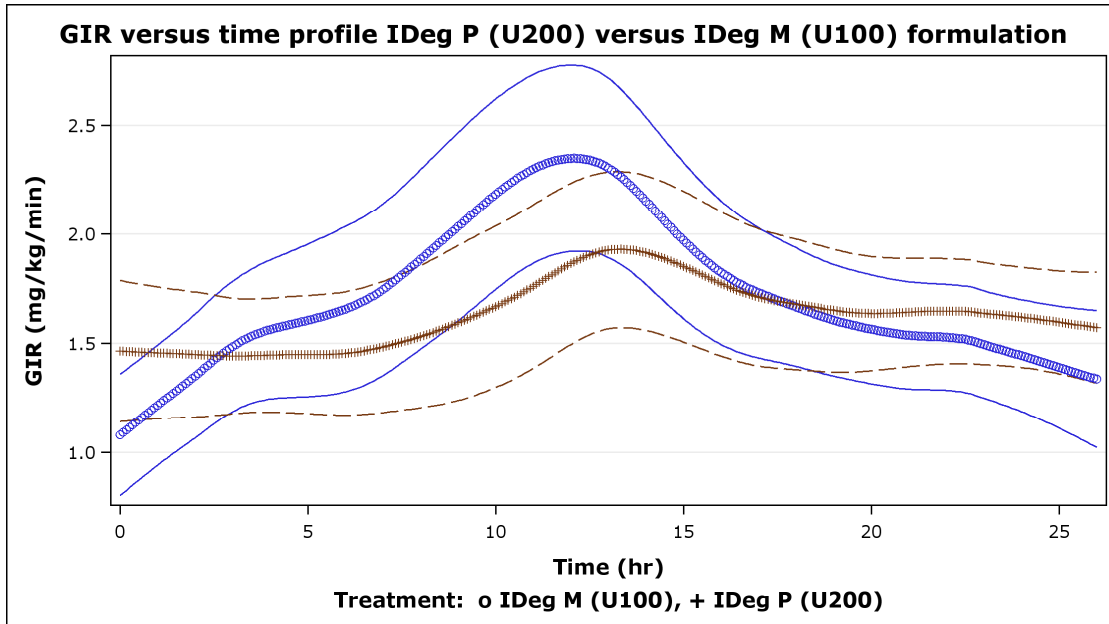


**Figure 70** Day 8 mean (95% confidence band) GIR-time profile by treatment in Type 1 Diabetic subjects (N=33)

**Table 30** Summary of IDeg PK parameters after first and last dose (NN1250-3678) for 0.4 U/kg/d dose from U100 formulation and U200 formulation

| PK Parameter:<br>Geo. Mean (CV)                                                                                               | IDeg First Dose              |                           |
|-------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------|
|                                                                                                                               | 0.4 U/kg/d (U100)<br>N=33    | 0.4 U/kg/d (U200)<br>N=33 |
| C <sub>max</sub> (pmol/L):                                                                                                    | 4037 (32)                    | 3089 (40)                 |
| t <sub>max</sub> (hour)*:                                                                                                     | 12 (7-24)                    | 14 (10-24)                |
| AUC <sub>0-24h</sub> (pmol*h/L):                                                                                              | 63015 (30)                   | 46415 (36)                |
|                                                                                                                               | IDeg Day 8 Dose              |                           |
| C <sub>max</sub> (pmol/L):                                                                                                    | 5980 (27)                    | 5269 (28)                 |
| t <sub>max</sub> (hour)*:                                                                                                     | 9.0 (3-16)                   | 9 (5-18)                  |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                                                             | 106861 (27)                  | 100497 (30)               |
| t <sub>1/2,ss</sub> :                                                                                                         | 22 (42)                      | 20 (26)                   |
| AR <sub>AUC</sub> **:                                                                                                         | 1.8 (25)                     | 2.4 (38)                  |
| AR <sub>C<sub>MAX</sub></sub> ***:                                                                                            | 1.6 (34)                     | 2.0 (42)                  |
| <b>Dose contrasts for AUC<sub>tau,ss</sub> -</b>                                                                              | <b>LS Mean Ratio [95%CI]</b> |                           |
| <b>IDeg 200 vs 100 U/mL 0.4U/kg/d (Day 6):</b>                                                                                | 0.99 [0.91; 1.07]            |                           |
| <b>IDeg 200 vs 100 U/mL 0.4U/kg/d (Day 8):</b>                                                                                | 0.94 [0.88; 1.00]            |                           |
| <b>Dose contrasts for C<sub>max</sub> -</b>                                                                                   |                              |                           |
| <b>IDeg 200 vs 100 U/mL 0.4U/kg/d (Day 6):</b>                                                                                | 0.93 [0.84; 1.02]            |                           |
| <b>IDeg 200 vs 100 U/mL 0.4U/kg/d (Day 8):</b>                                                                                | 0.88 [0.82; 0.96]            |                           |
| *Median (Min., Max)                                                                                                           |                              |                           |
| Accumulation Ratio AUC comparison; AR <sub>AUC</sub> ** = AUC <sub>tau,SS</sub> / AUC <sub>0-24,SD</sub>                      |                              |                           |
| Accumulation Ratio C <sub>max</sub> comparison; AR <sub>C<sub>MAX</sub></sub> *** = C <sub>max,SS</sub> / C <sub>max,SD</sub> |                              |                           |

**Table 31 Summary of IDeg PD parameters after the last dose (NN1250-1987) of 0.6 U/kg dose from U100 formulation and U200 formulation in subjects with Type 2 DM**

| PD Parameter:<br>Geo. Mean (CV)                                            | IDeg Day 8 Dose           |                           |
|----------------------------------------------------------------------------|---------------------------|---------------------------|
|                                                                            | 0.4 U/kg/d (U100)<br>N=33 | 0.4 U/kg/d (U200)<br>N=33 |
| GIRmax (pmol/L):<br>Mean (SD)                                              | 2.4 (46)<br>2.6 (1.2)     | 2.1 (42)<br>2.2 (0.9)     |
| t <sub>GIRmax</sub> (hour)*:                                               | 12 (0-22)                 | 14 (0-24)                 |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):                                     | 2255 (48)                 | 2123 (48)                 |
| <b>Dose contrasts for AUC<sub>GIR,tau,ss</sub> - LS Mean Ratio [95%CI]</b> |                           |                           |
| <b>IDeg 200 vs 100U/mL 0.4U/kg/d : 0.94 [0.86; 1.03]</b>                   |                           |                           |
| <b>Dose contrasts for GIRmax** -</b>                                       |                           |                           |
| <b>IDeg 200 vs 100U/mL 0.4U/kg/d : 0.88 [0.80; 0.96]</b>                   |                           |                           |
| **Post-hoc assessment by this reviewer                                     |                           |                           |

**U200 versus U100 comparison in Type 2 DM:** Comparison of multiple dose PK and PD characteristics of IDeg U100 (IDeg (M)) and U200 (IDeg (P)) in subjects with Type 2 DM was conducted in Trial NN1250-1987. This trial was a randomized, single-center, double-blind, two-period, incomplete block cross-over, multiple-dose trial. The primary objective of the trial was to evaluate the pharmacodynamic and pharmacokinetic dose-response relationship of IDeg 100 U/mL and characterizing the pharmacodynamic and pharmacokinetic properties of IDeg 200 U/mL formulation at steady state conditions in subjects with type 2 diabetes. Each subject was randomly allocated to two of four possible treatments: IDeg 100 U/mL (0.4, 0.6 or 0.8 U/kg) or IDeg 200 U/mL (0.6 U/kg). Each treatment period consisted of 6 days of once daily dosing with IDeg followed by pharmacokinetic sampling until 120 hours after the last dose. The pharmacodynamic response was evaluated during a 26-hour euglycemic clamp performed after the last (6th) dose of IDeg in each treatment period.

**Figure 71** below present the mean serum concentration-time profiles of IDeg after first dose, and full profile over six days of once daily administration of 0.4, 0.6, and 0.8 U/kg doses from U100. Figure 28 illustrates the PD profiles for the three dose levels as mean raw and mean smooth GIR profiles.

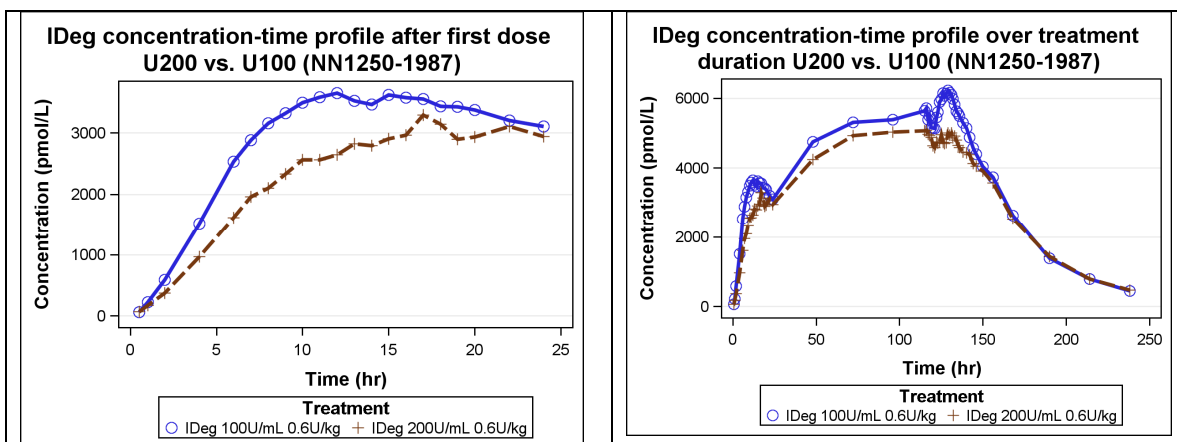


**Figure 71 Day 1 (Left) and full (Right) mean IDeg concentration-time profile Mean IDeg concentration-time profile by treatment in Type 2 Diabetic subjects (N=38)**

The mean concentration profiles from the two formulations in Type 2 DM subjects showed similar behavior as in Type 1 DM subjects.

U200 formulation provided a different absorption gradient than U100 formulation, resulting in less pronounced peak than that from U100 after first and last dose. These differences tend to exist but lose their statistical significance at steady-state as expected due to lower sensitivity of the multiple-dose design. The time-action profiles from the two formulations depicted by the GIR over 26 hours accordingly differed in shape (**Figure 72**).

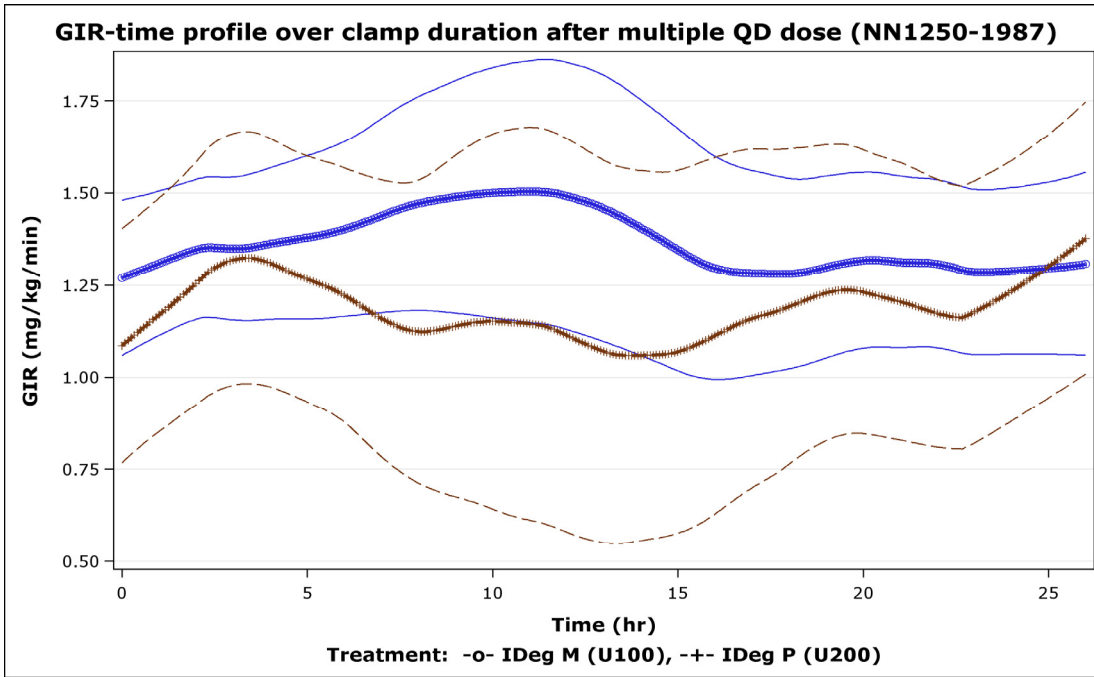


**Figure 72** Day 6 mean (95% confidence bands) GIR-time profile by treatment in Type 2 Diabetic subjects

**Table 32** Summary of IDeg PK parameters after first and last dose (NN1250-1987) for 0.6 U/kg dose from U100 formulation and U200 formulation

| PK Parameter:<br>Geo. Mean (CV)                                                    | IDeg First Dose         |                         |
|------------------------------------------------------------------------------------|-------------------------|-------------------------|
|                                                                                    | 0.6 U/kg (U100)<br>N=38 | 0.6 U/kg (U200)<br>N=16 |
| C <sub>max</sub> (pmol/L):                                                         | 3860 (32)               | 3400 (43)               |
| t <sub>max</sub> (hour)*:                                                          | 15 (8-24)               | 18 (13-24)              |
| AUC <sub>0-24h</sub> (pmol*h/L):                                                   | 64418 (30)              | 50280 (38)              |
|                                                                                    | IDeg Day 6 Dose         |                         |
| C <sub>max</sub> (pmol/L):                                                         | 6592 (23)               | 5365(23)                |
| t <sub>max</sub> (hour)*:                                                          | 9.0 (1-36)              | 7.5(0-30)               |
| AUC <sub>tau,ss</sub> (pmol*h/L):                                                  | 130164 (38)             | 109898 (21)             |
| t <sub>1/2,ss</sub> :                                                              | 25 (28)                 | 26 (31)                 |
| AR <sub>AUC</sub> **:                                                              | 2.0 (23)                | 2.2 (28)                |
| AR <sub>C<sub>MAX</sub></sub> ***:                                                 | 1.7 (25)                | 1.6 (30)                |
| *Median (Min., Max)                                                                |                         |                         |
| Accumulation Ratio AUC comparison; AR <sub>AUC</sub> **:                           |                         |                         |
| Accumulation Ratio C <sub>max</sub> comparison; AR <sub>C<sub>MAX</sub></sub> ***: |                         |                         |

Similar to the observation in Type 1 DM subjects, on average, there was a reduction in the amplitude of response based on the GIR-time profile from U200 formulation. However, there was no statistically significant difference in primary end points: AUC<sub>GIR,tau,ss</sub> and GIR<sub>max</sub> (Table 32), apparently due to blunted PD response in the Type 2 DM.

**Table 33 Summary of IDeg PD parameters after the last dose (NN1250-1987) of 0.6 U/kg dose from U100 formulation and U200 formulation in subjects with Type 2 DM**

| PD Parameter:<br>Geo. Mean (CV)<br>(Min. , Max.)                           | IDeg Day 6 Dose           |                           |
|----------------------------------------------------------------------------|---------------------------|---------------------------|
|                                                                            | 0.6 U/kg (U100)<br>N=37   | 0.6 U/kg (U200)<br>N=16   |
| GIR <sub>max</sub> (pmol/L):                                               | 1.7 (49)<br>(0.7 , 4.4)   | 1.5 (44)<br>(0.8 , 3.3)   |
| t <sub>GIRmax</sub> (hour)*:                                               | 11 (0-26)                 | 12 (0-26)                 |
| AUC <sub>GIR,tau,ss</sub> (mg/kg/min):                                     | 1694 (56)<br>(531 , 4610) | 1345 (64)<br>(270 , 4101) |
| <b>Dose contrasts for AUC<sub>GIR,tau,ss</sub> - LS Mean Ratio [95%CI]</b> |                           |                           |
| <b>IDeg 200 vs 100U/mL 0.6U/kg :</b> 0.88 [0.70;1.12]                      |                           |                           |
| <b>Dose contrasts for GIR<sub>max</sub> -</b>                              |                           |                           |
| <b>IDeg 200 vs 100U/mL 0.6U/kg :</b> 0.97 [0.87;1.08]                      |                           |                           |

These results brings up an important issue from a regulatory and scientific perspective. For basal insulin products such as IDeg with duration of action >24h, PK and PD assessment to claim comparability between two formulations will always be challenging. Considering data from PK and PD comparison in both Type 1 and Type 2 DM subjects, one can argue that a single dose study design would probably have detected PD differences given that PK differences were apparent after the first-dose in both Trials. However, PD evaluation would still be limited to 26 hours at the most, again limiting the capability to assess the impact of these changes in PK profile on the total glycemic response and duration of action. This reviewer acknowledges sponsor's difficulty and resultant choice of the multiple-dose study design, close to the strategy followed for molar dose ratio assessment. The key difference was that molar dose ratio assessment was performed using a dose-response at three dose levels. Nevertheless, single-dose PKPD data or PD data after first dose would have been of more help in accepting/rejecting the PK and PD comparability assessment as was followed for comparing formulation changes (e.g. IDeg E versus IDeg M).

Despite of the presumed lower sensitivity of design, the multiple-dose evaluation at one dose level still captured some key differences in the nature of IDeg PK and PD profile with bit higher sensitivity in Type 1 versus Type 2 DM subjects. From a regulatory perspective, it is difficult to accept that PK and PD profile of IDeg from these two formulations is comparable in Type 1 and Type 2 DM subjects. However, from a scientific perspective we accept that these results also indicate that these PK and PD differences are likely not clinically relevant at steady state for patients on once-daily regimen of either U100 or U200 IDeg with regards to efficacy. In future, sponsor need to consider single dose PK and PD evaluation to establish PK and PD comparability of IDeg formulation change. For steady-state approach, sponsor should consider evaluating PD response after first dose in addition to the steady-state response.

## 2.6 Analytical

### 2.6.1 Is the analytical method for Insulin Degludec appropriately validated?

IDeg was quantified by a specific sandwich enzyme-linked immunosorbent assay (ELISA). The capture antibody was a mouse monoclonal antibody specific for human insulin (HUI 001) and the detection antibody was a biotin-labeled monoclonal mouse antibody (NN-454-1 F31) specific for

IDeg. The ELISA was found to be valid for analyzing IDeg in serum, urine, and dialysis fluid samples regarding accuracy, linearity, intermediary precision, sensitivity, and stability. Calibrators, QC-samples, and samples are in human serum. If necessary, the samples were diluted in calibrator matrix, i.e. pooled human serum. Microtitre plates were coated with a monoclonal antibody recognizing insulins. Free binding sites were blocked with PBS 0.5% w/v BSA and 0.05% NaAZid. Calibrators, QC-samples, unknown samples and biotinylated antibody recognising IDeg were applied and incubated for 2 hours. The bound antibody was detected with a HRP-conjugated avidin and finally tetramethylbenzidine. The enzymatic reaction was stopped with H3PO4 and the absorbance was read at 450-620 nm.

Table 32 captures the overall performance summary of the different analytical method validations for IDeg throughout the development.

**Table 34 Summary of analytical method used for the CPB studies**

| Parameter              | Results                                                                             |
|------------------------|-------------------------------------------------------------------------------------|
| Range <sup>1</sup>     | LLOQ = 32 pmol/L<br>ULOQ = 750 pmol/L                                               |
|                        | LLOQ = 20 pmol/L<br>ULOQ = 750 pmol/L                                               |
|                        | LLOQ = 20 pmol/L<br>ULOQ = 1000 pmol/L                                              |
| Accuracy               | Within the limits of acceptance (80%-120%)                                          |
| Dilution linearity     | Dilution up to 100 to 5000 fold within the limits of 80% - 120%                     |
| Intermediary precision | 4.5% - 21.7%                                                                        |
| Stability              | 2 years at -20°C<br>5 cycles of freezing and thawing at -20°C or -80°C <sup>2</sup> |
|                        | 139 days at -80°C                                                                   |

LLOQ: Lower limit of quantification.

ULOQ: Upper limit of quantification.

<sup>1</sup>For all trials, the applicable limits were used. The range 20-1000 pmol/L was used from phase 3 of the clinical development stage and forward.

<sup>2</sup>8 cycles of freezing and thawing at -20°C.

Interference of different insulins with IDeg assay was evaluated by assessing cross-reactivity from human insulin, insulin detemir, insulin glargine and insulin aspart. As it was not expected that human insulin, insulin detemir, insulin glargine and insulin aspart were detected by the IDeg specific antibodies the crossreactivity was only validated in the presence of IDeg. The cross-reactivity was only evaluated in pooled dog EDTA plasma as the reactivity of the antibodies is not species dependent. Insulin Aspart in concentrations up to 5075 pM did not interfere with the measurement of IDeg, whereas Insulin Aspart in concentrations above 5075 interfered with the measurement of IDeg, when the concentration of IDeg was less than 4950 pM. When the concentration of IDeg was at or above 4950 pM, Insulin Aspart in concentrations up to 100000 pM did not interfere.

Liraglutide in concentrations up to approximately 400000 pM did not interfere with the measurement of IDeg. Insulin Lispro in concentrations of approximately 50000 pM interfered with the measurement of IDeg. Insulin Lispro in concentrations of 5000 pM did not interfere with the measurement of IDeg. Insulin Aspart (up to 100000 pM), Insulin LisPro (up to 50000 pM) and Liraglutide (up to 400000 pM) was not detected in the absence of IDeg confirming that the antibody was specific to IDeg.

**Table 35 Other insulins tested for interference with IDeg assay**

| <b>Compound tested</b> | <b>Conclusion</b>                                |
|------------------------|--------------------------------------------------|
| Human insulin          | No interference up to a concentration of 5000 pM |
| Insulin aspart         | No interference up to a concentration of 5000 pM |
| Insulin lispro         | No interference up to a concentration of 5000 pM |
| Insulin glargine       | No interference up to a concentration of 5000 pM |
| Insulin detemir        | No interference up to a concentration of 5000 pM |

The presence of severe hemolysis in the samples generated invalid results for determination of IDeg concentration. Further assessments of the haemolysis interference showed that more than 5% hemolysis in the samples generated invalid results for IDeg concentrations. Consequently, sponsor decided not to report samples with more than 5% hemolysis.

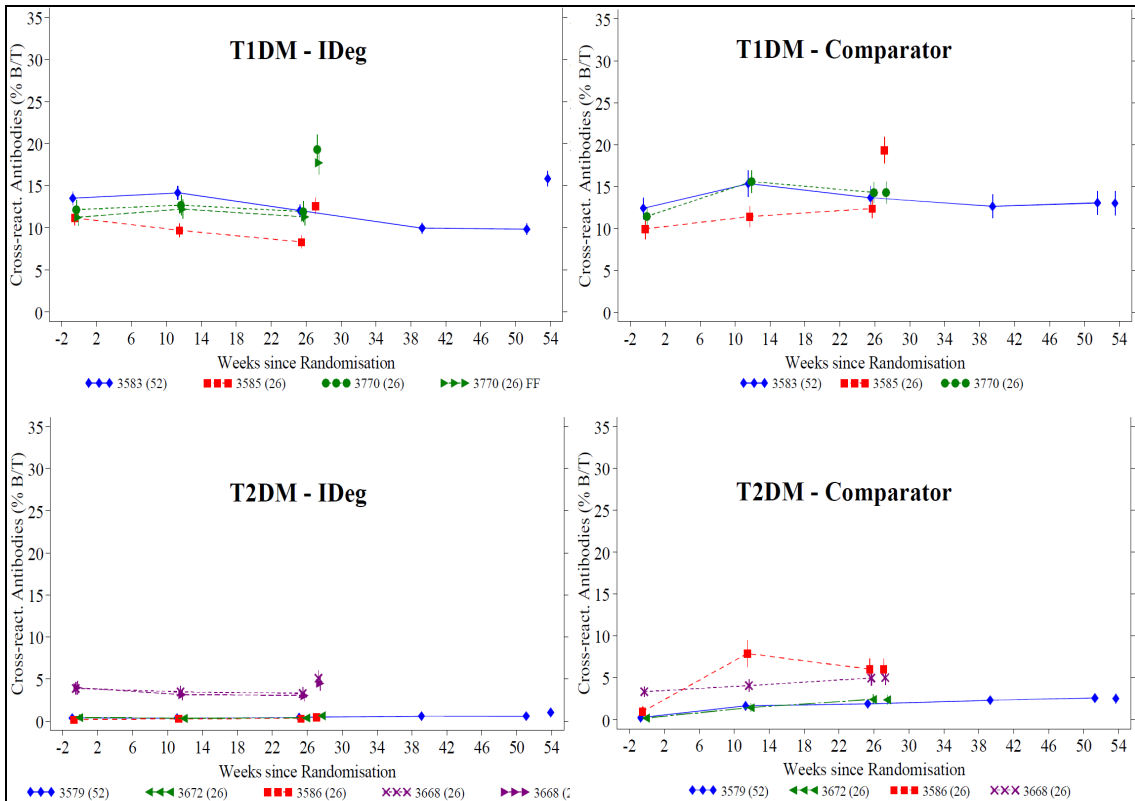
Antibody development against IDeg, IAsp, IDet and IGlar in the clinical trials was measured by a validated subtraction radio-immunoassay (RIA) using radioactively labelled IDeg, IAsp, IDet, IGlar. Briefly, serum samples (50 µL) were mixed with radiolabeled IDeg or another relevant insulin tracer and incubated overnight. Radiolabeled insulin bound to antibodies in the sample was precipitated using polyethylene glycol. The amount of precipitated radioactivity was measured, and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. Samples were analyzed as double determinations. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.

Antibodies specific for IDeg were measured by incubating serum samples with radioactively labeled IDeg in two parallel series, either with addition of excess unlabelled HI or with addition of excess unlabelled IDeg. The amount of IDeg specific antibodies was calculated by subtracting the %B/T values of the two.

The assay sensitivity was measured to be approximately 50 ng/mL and the intra- and inter-assay variations were below 15% (coefficient of variation) or HI.

Antibodies specific for IAsp, IDet and IGlar were measured the same way as the IDeg specific antibodies using the relevant tracer or unlabelled insulin analogue.

**Figure 73** below presents the antibody measurements across therapeutic trials.



% B/T: % bound over total radioactivity; Subjects temporarily discontinued trial product for a 1-week washout with NPH insulin at Weeks 26 and 52; Last antibody assessment was made 1 week after last trial product administration;

Comparator: IGLar (3583, 3770, 3579, 3672, 3586, 3668), IDEg (3585).

**Figure 73 Antibodies Cross-reacting to Human Insulin (% B/T) – Mean ( $\pm$ SEM) Observed Values**

The immunogenic response to treatment with IDEg was modest and similar to comparator did not result in reduced efficacy nor did it result in a consistent need for increased doses to maintain glycemic control.

### 3 Labeling Comments (Preliminary)

Note: Labeling statements to be removed are shown in ~~red strikethrough font~~ and suggested labeling to be included is shown in underline blue font.

#### Proposed Text:

|   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|---|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1 | <b>2 DOSAGE AND ADMINISTRATION</b><br><div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <p style="text-align: right;">(b) (4)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| 2 | <p><del>(b) (4)</del> <b>Renal impairment</b></p> <div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <p style="text-align: right;">(b) (4)</p> <p><del>(b) (4)</del> as with all insulin products, glucose monitoring should be intensified and the <del>(b) (4)</del> dosage adjusted on an individual basis in patients with renal impairment.</p> <p><del>(b) (4)</del> <b>Hepatic impairment</b></p> <div style="background-color: #cccccc; height: 30px; width: 100%;"></div> <p>No <del>(b) (4)</del> difference in the pharmacokinetics of <del>(b) (4)</del> was identified in a study comparing healthy subjects and subjects with hepatic impairment (mild, moderate, and severe hepatic impairment) [see Clinical Pharmacology (12.3)]. However, as with all insulin products, glucose monitoring should be intensified and the <del>(b) (4)</del> dosage adjusted on an individual basis in patients with hepatic impairment.</p> |
| 3 | <b>8.4 Pediatric use</b><br><div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <p style="text-align: right;">(b) (4)</p> <p>Safety and efficacy of <del>(b) (4)</del> in children and adolescents under the age of 18 have not been established.</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 4 | <b>12.2 Pharmacodynamics</b><br><div style="background-color: #cccccc; height: 100px; width: 100%;"></div> <p style="text-align: right;">(b) (4)</p>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

|                                        |                                                                                                                                          |
|----------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------|
|                                        | <p data-bbox="1404 191 1453 212">(b) (4)</p> <p data-bbox="1437 254 1485 275">(b) (4)</p> <p data-bbox="1274 1094 1323 1115">(b) (4)</p> |
| <p data-bbox="235 1371 251 1392">5</p> | <p data-bbox="284 1371 592 1392"><b>12.2 Pharmacodynamics</b></p> <p data-bbox="1388 1413 1437 1434">(b) (4)</p>                         |

(b) (4)

(b) (4)

**6 12.3 Pharmacokinetics**

(b) (4)

**7 12.3 Pharmacokinetics**

Distribution (b) (4)  
The affinity of insulin degludec to serum albumin corresponds to a plasma protein binding of >99% in human plasma. (b) (4)

**8 (b) (4) Elimination**

The half-life after subcutaneous administration is determined primarily by the rate of absorption from the subcutaneous tissue. The half-life is approximately 25 hours independent of dose. Degradation of (b) (4) is similar to that of insulin human; all metabolites formed are inactive.

(b) (4)

### Specific Populations

As with other insulin preparations, (b) (4) should always be titrated according to individual requirements.

#### Geriatrics-

Pharmacokinetic and pharmacodynamic response of (b) (4) in 13 younger adult (18–35 years) and 14 geriatric ( $\geq 65$  years) subjects with T1DM following two 6 day periods of once-daily subcutaneous dosing with (0.4 U/kg) of (b) (4) or insulin glargine. The pharmacokinetic and pharmacodynamic properties of (b) (4) at steady state were similar in younger adult and geriatric subjects. (b) (4)

#### Gender-

The effect of gender on the pharmacokinetics of (b) (4) was examined in an across-trial analysis of the pharmacokinetic and pharmacodynamic studies. Overall, there were no clinically differences in the pharmacokinetic properties of insulin degludec between female and male subjects.

#### Obesity-

The effect of BMI on the pharmacokinetics of (b) (4) was (b) (4) in a (b) (4) cross-trial analysis of (b) (4) pharmacokinetic and pharmacodynamic studies. (b) (4)

#### Race and ethnicity-

(b) (4) has been studied in a pharmacokinetic and pharmacodynamic study in Black or African American subjects not of Hispanic or Latino origin (n=18), White subjects of Hispanic or Latino origin (n=22) and White subjects not of Hispanic or Latino origin (n=23) with type 2 diabetes mellitus. There were no statistically significant differences between the racial and ethnic groups investigated. (b) (4)

#### Pregnancy-

The effect of pregnancy on the pharmacokinetics and pharmacodynamics of (b) (4) has not been studied [see Use in Specific Populations (8.1)]

#### Renal impairment-

(b) (4) study in 32 subjects (b) (4)/group) with normal or impaired renal function/end-stage renal disease following administration of a (b) (4) (0.4U/kg) of (b) (4) (b) (4)

Haemodialysis did not affect (b) (4) clearance of (b) (4) (CL/FIDeg,SD) in subjects with ESRD. (b) (4)

Hepatic impairment-

(b) (4) has been studied in a pharmacokinetic study in 24 subjects (n=6/group) with normal or impaired hepatic function (mild, moderate, and severe hepatic impairment) following administration of a (b) (4) (0.4U/kg) of (b) (4). ~~Hepatic function was defined using Child Pugh Scores ranging from 5 (mild hepatic impairment) to 15 (severe hepatic impairment).~~ No (b) (4) differences in the pharmacokinetics of (b) (4) were identified between healthy subjects and subjects with hepatic impairment (b) (4)

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
06/15/2012

JAYABHARATHI VAIDYANATHAN  
06/15/2012

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

|                                  | Information                                       |                         | Information                                                                                                       |
|----------------------------------|---------------------------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------|
| NDA/BLA Number                   | 203314                                            | Brand Name              | Tresiba®                                                                                                          |
| OCP Division (I, II, III, IV, V) | DCP II                                            | Generic Name            | Insulin Degludec                                                                                                  |
| Medical Division                 | DMEP                                              | Drug Class              | Anti-diabetic                                                                                                     |
| OCP Reviewer                     | Manoj Khurana, Ph.D.                              | Indication(s)           | An ultra-long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. |
| OCP Team Leader                  | Jayabharathi Vaidyanathan, Ph.D. (Acting)         | Dosage Form             | Solution for subcutaneous injection                                                                               |
| Pharmacometrics Reviewer         | Primary: Manoj Khurana<br>Secondary: Kevin Krudys | Dosing Regimen          | Once Daily any time of day                                                                                        |
| Date of Submission               | September 29, 2011                                | Route of Administration | SC                                                                                                                |
| Estimated Due Date of OCP Review | May 29, 2012                                      | Sponsor                 | Novo Nordisk                                                                                                      |
| Medical Division Due Date        | June 01, 2012                                     | Priority Classification | Standard                                                                                                          |
| PDUFA Due Date                   | July 29, 2012                                     |                         |                                                                                                                   |

***Clin. Pharm. and Biopharm. Information***

|                                                                                | "X" if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any                             |
|--------------------------------------------------------------------------------|---------------------------|-----------------------------|----------------------------|------------------------------------------------------|
| STUDY TYPE                                                                     |                           |                             |                            |                                                      |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                         |                             |                            |                                                      |
| Tabular Listing of All Human Studies                                           | X                         |                             |                            |                                                      |
| HPK Summary                                                                    | X                         |                             |                            |                                                      |
| Labeling                                                                       | X                         |                             |                            |                                                      |
| Reference Bioanalytical and Analytical Methods                                 | X                         |                             |                            |                                                      |
| <b>I. Clinical Pharmacology</b>                                                |                           |                             |                            |                                                      |
| Mass balance:                                                                  |                           |                             |                            |                                                      |
| Isozyme characterization:                                                      | X                         | 1                           |                            | 207440                                               |
| Blood/plasma ratio:                                                            |                           |                             |                            |                                                      |
| Plasma protein binding:                                                        | X                         | 4                           |                            | 208378, 208523, CES 10-January-2008, CES 01-May-2007 |
| Pharmacokinetics (e.g., Phase I) -                                             |                           |                             |                            |                                                      |
| <b>Healthy Volunteers-</b>                                                     |                           |                             |                            |                                                      |
| single dose:                                                                   |                           |                             |                            |                                                      |
| multiple dose:                                                                 |                           |                             |                            |                                                      |
| <b>Patients-</b>                                                               |                           |                             |                            |                                                      |
| single dose:                                                                   |                           |                             |                            |                                                      |
| multiple dose:                                                                 |                           |                             |                            |                                                      |

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

|                                                                   |   |    |  |                                                                                                                                                                            |
|-------------------------------------------------------------------|---|----|--|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Dose proportionality -</b>                                     |   |    |  |                                                                                                                                                                            |
| fasting / non-fasting single dose:                                |   |    |  |                                                                                                                                                                            |
| fasting / non-fasting multiple dose:                              |   |    |  |                                                                                                                                                                            |
| <b>Drug-drug interaction studies -</b>                            |   |    |  |                                                                                                                                                                            |
| In-vivo effects on primary drug:                                  |   |    |  |                                                                                                                                                                            |
| In-vivo effects of primary drug:                                  |   |    |  |                                                                                                                                                                            |
| In-vitro:                                                         | X | 2  |  | CES 20-January-2009, CES 101123                                                                                                                                            |
| <b>Subpopulation studies -</b>                                    |   |    |  |                                                                                                                                                                            |
| ethnicity:                                                        | X | 2  |  | NN1250-3762, NN1250-1996 (Japanese)                                                                                                                                        |
| gender:                                                           |   |    |  |                                                                                                                                                                            |
| pediatrics:                                                       | X | 1  |  | NN1250-1995                                                                                                                                                                |
| geriatrics:                                                       | X | 1  |  | NN1250-1994                                                                                                                                                                |
| renal impairment:                                                 | X | 1  |  | NN1250-1990                                                                                                                                                                |
| hepatic impairment:                                               | X | 1  |  | NN1250-1989                                                                                                                                                                |
| <b>PD -</b>                                                       |   |    |  |                                                                                                                                                                            |
| Phase 1:                                                          | X | 1  |  | NN1250-3538 (Hypoglycaemic response)                                                                                                                                       |
| Phase 2:                                                          |   |    |  |                                                                                                                                                                            |
| Phase 3:                                                          |   |    |  |                                                                                                                                                                            |
| <b>PK/PD -</b>                                                    |   |    |  |                                                                                                                                                                            |
| Phase 1 and/or 2, proof of concept:                               | X | 4  |  | NN1250-1991 (T1DM, within-subject variability)<br>NN1250-1993 (T1DM SS, Dose-Resp)<br>NN1250-3678 (T1DM SS, U100 and U200)<br>NN1250-1987 (T2DM SS, Dose-Resp U100 & U200) |
| Phase 3 clinical trial:                                           |   |    |  |                                                                                                                                                                            |
| <b>Population Analyses -</b>                                      |   |    |  |                                                                                                                                                                            |
| Data rich:                                                        |   |    |  |                                                                                                                                                                            |
| Data sparse:                                                      | X | 1  |  | NN1250-3586 (One PopPK Report)                                                                                                                                             |
| <b>II. Biopharmaceutics</b>                                       |   |    |  |                                                                                                                                                                            |
| Absolute bioavailability                                          | X | 1  |  | NN1250-1992                                                                                                                                                                |
| <b>Relative bioavailability -</b>                                 |   |    |  |                                                                                                                                                                            |
| solution as reference:                                            |   |    |  |                                                                                                                                                                            |
| alternate formulation as reference:                               |   |    |  |                                                                                                                                                                            |
| <b>Bioequivalence studies -</b>                                   |   |    |  |                                                                                                                                                                            |
| traditional design; single / multi dose:                          | X | 3  |  | NN1250-1988, NN1250-3769                                                                                                                                                   |
| replicate design; single / multi dose:                            |   |    |  |                                                                                                                                                                            |
| <b>Food-drug interaction studies</b>                              |   |    |  |                                                                                                                                                                            |
| <b>Bio-waiver request based on BCS</b>                            |   |    |  |                                                                                                                                                                            |
| <b>BCS class</b>                                                  |   |    |  |                                                                                                                                                                            |
| <b>Dissolution study to evaluate alcohol induced dose-dumping</b> |   |    |  |                                                                                                                                                                            |
| <b>III. Other CPB Studies</b>                                     |   |    |  |                                                                                                                                                                            |
| Genotype/phenotype studies                                        |   |    |  |                                                                                                                                                                            |
| Chronopharmacokinetics                                            |   |    |  |                                                                                                                                                                            |
| Pediatric development plan                                        | X |    |  |                                                                                                                                                                            |
| Literature References                                             |   |    |  |                                                                                                                                                                            |
| <b>Total Number of Studies</b>                                    |   | 23 |  |                                                                                                                                                                            |

Keys: T1DM- Type 1 diabetes mellitus, T2DM – Type 2 diabetes mellitus, SS – steady-state

File name: 5\_Clinical Pharmacology and Biopharmaceutics Filing Form/Checklist for NDA\_BLA or Supplement 090808

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

On **initial** review of the NDA/BLA application for filing:

|                                                                                     | Content Parameter                                                                                                                                                   | Yes | No | N/A | Comment                                                                                                                                                     |
|-------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----|----|-----|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Criteria for Refusal to File (RTF)</b>                                           |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 1                                                                                   | Has the applicant submitted bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?                                  | X   |    |     | To be marketed formulation has been used in the pivotal clinical trials. BE trials compared formulation changes due to process optimization during Phase 3. |
| 2                                                                                   | Has the applicant provided metabolism and drug-drug interaction information?                                                                                        | X   |    |     | Only in vitro studies.                                                                                                                                      |
| 3                                                                                   | Has the sponsor submitted bioavailability data satisfying the CFR requirements?                                                                                     | X   |    |     |                                                                                                                                                             |
| 4                                                                                   | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?                                                                        | X   |    |     |                                                                                                                                                             |
| 5                                                                                   | Has a rationale for dose selection been submitted?                                                                                                                  | X   |    |     |                                                                                                                                                             |
| 6                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?             | X   |    |     |                                                                                                                                                             |
| 7                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?                                                | X   |    |     |                                                                                                                                                             |
| 8                                                                                   | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?                                                            | X   |    |     |                                                                                                                                                             |
| <b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b> |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| <b>Data</b>                                                                         |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 9                                                                                   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?                                               | X   |    |     | Sponsor have not submitted nonmem dataset and control files for the population PK analysis and a request will be communicated in the filing letter          |
| 10                                                                                  | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?                                                                               |     |    | X   |                                                                                                                                                             |
| <b>Studies and Analyses</b>                                                         |                                                                                                                                                                     |     |    |     |                                                                                                                                                             |
| 11                                                                                  | Is the appropriate pharmacokinetic information submitted?                                                                                                           | X   |    |     |                                                                                                                                                             |
| 12                                                                                  | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed | X   |    |     |                                                                                                                                                             |

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

|                |                                                                                                                                                                                                                                  |   |  |   |                                                                                                                                                                                                                         |
|----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | dose-ranging or pivotal studies)?                                                                                                                                                                                                |   |  |   |                                                                                                                                                                                                                         |
| 13             | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?                                                                       | X |  |   |                                                                                                                                                                                                                         |
| 14             | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics? | X |  |   | Insulin dose is titrated up and down based on the patients need.                                                                                                                                                        |
| 15             | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?                                                                                                         | X |  |   | FDA agreed with partial waiver in pediatric patients less than one year of age (correspondence dated 3/21/2011). Sponsor is planning to conduct clinical trial in T1DM pediatric subjects aged 1 to less than 18 years. |
| 16             | Did the applicant submit all the pediatric exclusivity data, as described in the WR?                                                                                                                                             |   |  | X |                                                                                                                                                                                                                         |
| 17             | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?                                                                                                   | X |  |   |                                                                                                                                                                                                                         |
| <b>General</b> |                                                                                                                                                                                                                                  |   |  |   |                                                                                                                                                                                                                         |
| 18             | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?                                                      | X |  |   |                                                                                                                                                                                                                         |
| 19             | Was the translation (of study reports or other study information) from another language needed and provided in this submission?                                                                                                  |   |  | X |                                                                                                                                                                                                                         |

### IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?

  YES  

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

### Although not a potential review issue, the following is an information request to be sent in the Day 74 letter for the Sponsor:

1. Please provide raw data (CSV and/or SAS transport files) used for the population PK analysis conducted for Trial NN1250-3586.
2. Please provide the NONMEM Model Codes for the population PK analyses. In general, model codes or control streams and output listings should be provided for all major model-building steps, e.g., base structural model, covariates models, final model, and validation model. These

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

|                                    |          |
|------------------------------------|----------|
| Manoj Khurana                      | 11/18/11 |
| Reviewing Clinical Pharmacologist  | Date     |
| Jayabharathi Vaidyanathan (Acting) | 11/18/11 |
| Team Leader/Supervisor             | Date     |

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Internal Memo: Submission in Brief

Sponsor, Novo Nordisk has submitted a new drug application for Insulin degludec (proposed trade name: Tresiba<sup>®</sup>; IDeg), a basal human insulin analog for the treatment of diabetes mellitus.

IDeg is claimed to be an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the  $\epsilon$ -amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer.

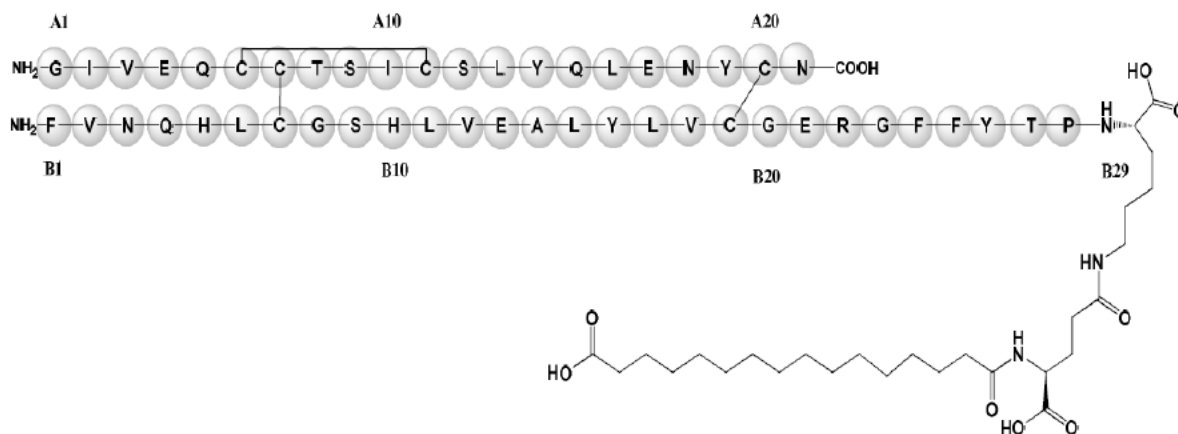


**Figure 1. Insulin Degludec**

The structural formula is LysB29(N( $\epsilon$ )-hexadecandioyl- $\gamma$ -L-Glu)desB30 human insulin and the molecular formula C<sub>274</sub>H<sub>411</sub>N<sub>65</sub>O<sub>81</sub>S<sub>6</sub> giving a molecular mass of (b) (4) dalton.

This structure apparently allows IDeg to form soluble and stable multi-hexamers, resulting in a depot in the subcutaneous tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the subcutaneous injection site into the circulation, leading to ultra-long pharmacokinetic and pharmacodynamic profiles.

IDeg is intended for treatment of diabetes mellitus, and is administered once-daily at any time of the day, independent of meals, and can be injected subcutaneously (s.c.) in the thigh, the upper arm or the abdominal wall. IDeg is developed to cover basal insulin needs in patients with diabetes mellitus from early to late stages of the disease, either alone or in combination with bolus insulin as well as oral antidiabetic drugs (OADs). When needed, the patient has the option of changing the once daily injection time from day-to-day.

IDeg is available as clear and colorless solutions in two strengths:

- IDeg 100 U/ml (Insulin degludec 600 nmol /mL): Intended to be marketed (b) (4) as a pre-filled disposable PDS290 pen-injector with a dose range of 1-80 U/injection, which can be dialed in 1U increments.

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## **CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

- IDeg 200 U/ml, (Insulin degludec 1200 nmol /mL). Intended for the market in a pre-filled disposable PDS290 pen-injector with a dose range of 2-160 U/injection, which can be dialed in 2U increments.

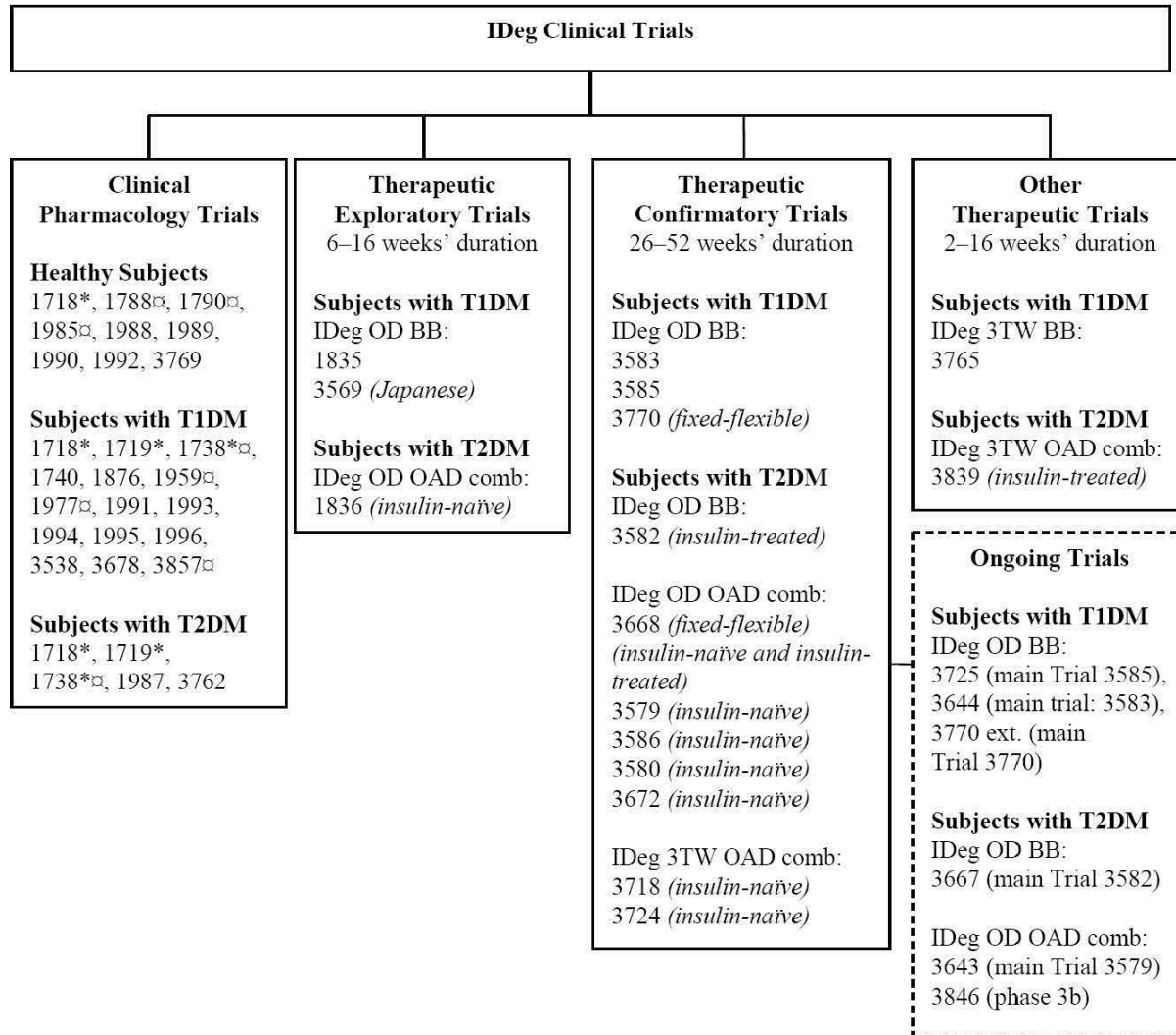
For patients with type 2 diabetes mellitus, the recommended daily starting dose of IDeg is 10 units, followed by individual dosage adjustments. For patients with type 1 diabetes mellitus, IDeg is to be used once-daily with meal-time insulin and requires subsequent individual dosage adjustments.

The clinical development program for IDeg comprises 41 completed clinical trials; 25 clinical pharmacology trials (7 of which include both IDeg and IDegAsp [70:30 premix of IDeg and Insulin Aspart, respectively]), 3 therapeutic exploratory trials, 11 therapeutic confirmatory trials, and 2 trials in the category ‘other therapeutic trials’. The formulation of the IDeg drug products used in the phase 2 and 3a development programs is identical to the proposed commercial formulation.

The therapeutic confirmatory program investigated the efficacy and safety of IDeg in subjects with T1DM and T2DM in combination with bolus insulin, and in both insulin-naïve and previously insulin-treated subjects with T2DM in combination with OADs.

IDeg was investigated as once-daily (QD) treatment and as a three-times-weekly (3TW) dosing regimen. Whereas clinically relevant improvement in glycosylated hemoglobin (HbA1c) was demonstrated with IDeg 3TW, non-inferiority versus IGLar QD could not be confirmed for the primary endpoint. Therefore, the sponsor is not pursuing the 3TW dosing regimen for IDeg. The IDeg 3TW trials are included in the overall assessment of safety, and key results related to efficacy and dosing are included in the submission for completeness.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement



Trials marked with \* included both subjects with T1DM and subjects with T2DM. Trial 1718 also included healthy subjects. Trials marked with □ included both IDeg and IDegAsp. 3TW: three times weekly, BB: basal-bolus, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart, OAD: oral antidiabetic drug, OD: once daily, T1DM: type 1 diabetes mellitus, T2DM: type 2 diabetes mellitus.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

A number of drug products have been produced during the development program and are differentiated by letter designation (see table below).

**Table 1–1 Composition of the Products Used in Clinical Trials**

| Name of Ingredients                           | IDeg (A) | IDeg (B) | IDeg (C) | IDeg (J) | IDeg (D) | IDeg (E) <sup>1</sup> | IDeg (M) <sup>1</sup> | IDeg (P) <sup>2</sup> |      |
|-----------------------------------------------|----------|----------|----------|----------|----------|-----------------------|-----------------------|-----------------------|------|
| <b>Clinical development phase<sup>3</sup></b> | Phase 1  | Phase 1  | Phase 1  | Phase 2  | Phase 2  | Phase 2               | Phase 3               | Phase 3               |      |
| Quantity per mL                               |          |          |          |          |          |                       |                       |                       |      |
| <b>Drug substance<sup>4</sup></b>             |          |          |          |          |          | (b) (4)               | 600                   | 600                   | 1200 |
| IDeg (nmol/mL)                                |          |          |          |          |          | (b) (4)               | 600                   | 600                   | 1200 |
| <b>Excipients</b>                             |          |          |          |          |          |                       |                       |                       |      |
| Phenol <sup>5</sup> (mg/mL)                   |          |          |          |          |          |                       | 1.50                  | 1.50                  | 1.50 |
| Metacresol <sup>5</sup> (mg/mL)               |          |          |          |          |          |                       | 1.72                  | 1.72                  | 1.72 |
| Glycerol (mg/mL)                              |          |          |          |          |          |                       | 19.6                  | 19.6                  | 19.6 |
| (b) (4)                                       |          |          |          |          |          |                       | -                     | -                     | -    |
| (b) (4)                                       |          |          |          |          |          |                       | -                     | -                     | -    |
| Sodium chloride (mg/mL)                       |          |          |          |          |          |                       | -                     | -                     | -    |
| Zinc <sup>6</sup> (µg/mL)                     |          |          |          |          |          |                       | 32.7                  | 32.7                  | 71.9 |
| Hydrochloric acid <sup>7,8</sup>              |          |          |          |          |          |                       | q.s.                  | q.s.                  | q.s. |
| Sodium hydroxide <sup>7,9</sup>               |          |          |          |          |          |                       | q.s.                  | q.s.                  | q.s. |
| Water for injections                          |          |          |          |          |          |                       | (b) (4)               |                       |      |
| <b>Characteristics of drug product</b>        |          |          |          |          |          |                       |                       |                       |      |
| pH                                            |          |          |          |          |          | (b) (4)               | 7.6                   | 7.6                   | 7.6  |

<sup>1</sup> Same formulation as the proposed commercial product of IDeg 100 U/mL

<sup>2</sup> Same formulation as the proposed commercial product of IDeg 200 U/mL

<sup>3</sup> This refers to the stage of clinical development and not the type of clinical trial. Please see Section 1.2 for a summary of drug product by type of clinical trial.

<sup>4</sup> The varying concentrations of IDeg across the drug products reflect that in the early stage of development, the potency of IDeg had not yet been established.

<sup>5</sup> An overage of up to (b) (4) is added to compensate for potential loss during manufacturing

<sup>6</sup> Zinc added (b) (4) Ph Eur, USP, JP)

<sup>7</sup> For pH adjustment to reach target pH

<sup>8</sup> Hydrochloric acid (b) (4) is manufactured (b) (4) Ph Eur, USP, JP)

<sup>9</sup> Sodium hydroxide (b) (4) is manufactured (b) (4) Ph Eur, USP, JP)

Initially, a number of exploratory formulations were produced in order to decide on an optimal composition (see table below for details). Following early clinical pharmacology and therapeutic exploratory trials, IDeg (E) was identified as the 100 U/mL (600 nmol/mL) formulation for further clinical development. The IDeg 100 U/ml proposed commercial formulation, used throughout the therapeutic confirmatory trials and key clinical pharmacology, is identical to IDeg (E), except that (b) (4)

(b) (4). All therapeutic confirmatory trials were conducted using (b) (4) (change in product name from IDeg (E) to IDeg (M)). During conduct of the therapeutic confirmatory trials, (b) (4) was further optimized.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

**Table 1–2 Clinical Trials and IDeg Products**

| Trials                          | Early Drug Products<br>(Exploratory Formulations) |          |          |          |                     | Drug Products<br>(Proposed Commercial Formulation) |                      |                                   |
|---------------------------------|---------------------------------------------------|----------|----------|----------|---------------------|----------------------------------------------------|----------------------|-----------------------------------|
|                                 | IDeg (A)                                          | IDeg (B) | IDeg (C) | IDeg (D) | IDeg (J)<br>(b) (4) | 100 U/mL<br>IDeg (E)<br>(600 mM)                   | IDeg (M)<br>(600 mM) | 200 U/mL<br>IDeg (P)<br>(1200 mM) |
| <b>Clinical Pharmacology</b>    |                                                   |          |          |          |                     |                                                    |                      |                                   |
| (b) (4)                         |                                                   |          |          |          |                     |                                                    |                      |                                   |
| 1987                            |                                                   |          |          |          |                     |                                                    | X                    | X                                 |
| 1988                            |                                                   |          |          |          |                     | X                                                  | X                    |                                   |
| 1989                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1990                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1991                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1992                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1993                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1994                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1995                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 1996                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 3538                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 3678                            |                                                   |          |          |          |                     |                                                    | X                    | X                                 |
| 3762                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| 3769                            |                                                   |          |          |          |                     |                                                    | X <sup>1</sup>       |                                   |
| 3857                            |                                                   |          |          |          |                     |                                                    | X                    |                                   |
| <b>Therapeutic Exploratory</b>  |                                                   |          |          |          |                     |                                                    |                      |                                   |
| 1835                            |                                                   |          |          | X        |                     | X                                                  |                      |                                   |
| (b) (4)                         |                                                   |          |          |          |                     |                                                    |                      |                                   |
| <b>Therapeutic Confirmatory</b> |                                                   |          |          |          |                     |                                                    |                      |                                   |
| (b) (4)                         |                                                   |          |          |          |                     |                                                    | X <sup>2</sup>       | X <sup>3</sup>                    |
| (b) (4)                         |                                                   |          |          |          |                     |                                                    |                      |                                   |

<sup>1</sup> This trial compared products manufactured before and after a minor optimisation of the (b) (4) manufacturing process.

<sup>2</sup> Trials 3583, 3585, 3582, 3668, 3579, 3586, 3580, 3725, 3643, 3644 and 3667 were conducted with products manufactured before, and Trial 3770 was conducted with trial products manufactured after the minor optimisation of the (b) (4) manufacturing process described in Section 1.1.

<sup>3</sup> Trials 3672, 3718, 3724  
(b) (4)

Bioequivalence was tested between products produced before and after the (b) (4) manufacturing process optimizations. Trial 1988 investigated bioequivalence between the IDeg (E) and IDeg (M) drug products, (b) (4). Trial 3769 investigated bioequivalence between IDeg (M) drug products produced from (b) (4) before and after optimization (b) (4). (b) (4) the bioequivalence demonstrated in Trial 3769 covers

## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

both 100 U/mL and 200 U/mL. In addition, the pharmacodynamic and pharmacokinetic properties of the 100 U/mL and 200 U/mL products have been compared (Trial 3678) including a *post-hoc* assessment of whether the requirements for bioequivalence between 100 U/mL and 200 U/mL were fulfilled. Relative bioavailability of IDeg between s.c. injections in the thigh, abdomen and deltoid (upper arm) and intramuscular injection was investigated in one trial (Trial 1992). As a secondary objective of this trial, sponsor investigated the absolute bioavailability of IDeg.

An extensive clinical pharmacology program has been conducted to evaluate the pharmacokinetic (PK) and pharmacodynamic (PD) properties of IDeg. The program included 25 clinical pharmacology trials. Sixteen (16) trials were conducted using the commercial IDeg formulation and are considered key trials in this summary (see table below).

The objectives of the program were to:

- Characterize the pharmacokinetic and pharmacodynamic properties of IDeg in subjects with T1DM and T2DM as well as in healthy subjects
- Compare the pharmacokinetic and pharmacodynamic properties of IDeg 100 U/mL and 200 U/mL in subjects with T1DM
- Compare the pharmacokinetic and pharmacodynamic properties of IDeg with those of marketed long-acting basal insulin analogues
- Evaluate the effects of intrinsic factors (BMI, age, sex, race/ethnicity, renal and hepatic function) on the pharmacokinetic and pharmacodynamic properties of IDeg
- Investigate the response to induced hypoglycaemia with IDeg in subjects with T1DM

In addition, population pharmacokinetic analyses are included from one therapeutic confirmatory trial (Trial 3586). This trial was conducted in Asian region.

(b) (4)

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

**Table 1–1 Summary of Key Clinical Pharmacology Trials**

| Trial ID                            | Trial Design         | Trial Objectives                                                                                                           | Treatment                                                   |
|-------------------------------------|----------------------|----------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------|
| <b>Trials in Subjects with T1DM</b> |                      |                                                                                                                            |                                                             |
| NN1250-1991                         | RND, DB, PG, MD      | Within-subject variability at steady state                                                                                 | IDeg: 0.4 U/kg<br>IGlar: 0.4 U/kg                           |
| NN1250-1993                         | RND, DB, INB, CO, MD | PK and PD (dose–response) at steady state                                                                                  | IDeg: 0.4; 0.6, 0.8 U/kg<br>IGlar: 0.4; 0.6 and 0.8 U/kg    |
| NN1250-1994                         | RND, DB, CO, MD      | PK and PD properties at steady state in geriatric and younger adult subjects                                               | IDeg: 0.4 U/kg<br>IGlar: 0.4 U/kg                           |
| NN1250-1995                         | RND, DB, CO, SD      | PK and safety profile in children, adolescents and adults                                                                  | IDeg: 0.4 U/kg<br>IGlar: 0.4 U/kg                           |
| NN1250-1996                         | RND, DB, CO, MD      | PK and PD at steady state in Japanese subjects                                                                             | IDeg: 0.4 U/kg<br>IDet: 0.4 U/kg                            |
| NN1250-3538                         | RND, DB, CO, MD      | Hypoglycaemic response after multiple doses                                                                                | IDeg: Individual doses<br>IGlar: Individual doses           |
| NN1250-3678                         | RND, DB, CO, MD      | PK and PD of IDeg 100 U/mL vs. 200 U/mL at steady state                                                                    | IDeg: 0.4 U/kg<br>IDeg 200 U/mL: 0.4 U/kg                   |
| NN5401-1977                         | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp                                                                           | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg       |
| NN5401-3857                         | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp                                                                           | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg       |
| <b>Trials in Subjects with T2DM</b> |                      |                                                                                                                            |                                                             |
| NN1250-1987                         | RND, DB, INB, CO, MD | PK and PD (dose–response) at steady state                                                                                  | IDeg: 0.4; 0.6, 0.8 U/kg<br>IDeg 200 U/mL: 0.6 U/kg         |
| NN1250-3762                         | RND, DB, CO, MD      | PK and PD at steady state in subjects of different race and/or ethnicity                                                   | IDeg: 0.6 U/kg<br>IDet: 0.6 U/kg                            |
| <b>Trials in Healthy Subjects</b>   |                      |                                                                                                                            |                                                             |
| NN1250-1988                         | RND, DB, CO, SD, BE  | BE between two IDeg products with identical formulations, and different (b) (4) and manufacturing (b) (4)                  | IDeg: 0.4 U/kg                                              |
| NN1250-1989                         | OL, PG, SD           | PK and safety profile in subjects with/without hepatic impairment                                                          | IDeg: 0.4 U/kg                                              |
| NN1250-1990                         | OL, PG, SD           | PK and safety profile in subjects with/without renal impairment                                                            | IDeg: 0.4 U/kg                                              |
| NN1250-1992                         | RND, OL, CO, SD, BA  | PK and PD after s.c. administration at three different injection regions, and i.m. and i.v. administration                 | IDeg: 0.4 U/kg (s.c.),<br>0.4 U/kg (i.m.), 0.04 U/kg (i.v.) |
| NN1250-3769                         | RND, DB, CO, SD, BE  | BE between IDeg drug product manufactured before (IM1) and after (IM2) minor optimisation of (b) (4) manufacturing process | IDeg: 0.4 U/kg                                              |

BA: bioavailability; BE: bioequivalence; CO: cross-over; DB: double-blind; MD: multiple dose; i.m.: intramuscularly; INB: incomplete block; i.v.: intravenously; OL: open label; PD: pharmacodynamics; PG: parallel group; PK: pharmacokinetics; RND: randomised; s.c.: subcutaneously; SD: single dose.

**Table 1–2 *In vitro* Studies with Human Biomaterials**

| Type of Study                           | Study ID                                             |
|-----------------------------------------|------------------------------------------------------|
| Plasma Protein Binding                  | 208378, 208523, CES 10-January-2008, CES 01-May-2007 |
| Hepatic Metabolism and Drug Interaction | 207440, CES 20-January-2009, CES 101123              |

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The objective of various clinical pharmacology trials is highlighted in the Table below:

| TYPE       | TRIAL                                                                | Commercial Formulation (Code)                                                                                  | OBJECTIVE                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|------------|----------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| PK/PD-BA   | 1992                                                                 | Yes (M)                                                                                                        | Absolute BA and injection site                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| PK/PD (BE) | 1988<br>3769                                                         | Yes (E versus M)<br>Yes (M1 and M2)                                                                            | Before and after a change of (b) (4) respectively (b) (4) produced before (IM1) and after (IM2) a minor optimization of the manufacturing process                                                                                                                                                                                                                                                                                                                                                                                                                             |
| PKPD       | 1994<br>3762<br>1876<br>1987<br>1991<br>1993<br>1996<br>3538<br>3678 | Yes (M)<br>Yes (M)<br>Yes (E)<br>Yes (M and P)<br>Yes (M)<br>Yes (M)<br>Yes (M)<br>Yes (M)<br>Yes (M versus P) | Multiple QD in young and geriatric T1DM (versus QD Glargine)<br>Multiple QD in 3 grps of different race/ethnicity T1DM (versus QD Detemir)<br>Multiple QD @ 3 dose levels DR in T1DM (versus QD Glargine)<br>Multiple QD @ 3 dose levels DR in T2DM<br>Multiple QD T1DM within-subject variability (versus QD Glargine)<br>Multiple QD @ 3 dose levels DR in T1DM (versus QD Glargine)<br>Multiple QD @ 3 dose levels DR in T1DM Japanese (versus QD Glargine)<br>Hypoglycemia counter-regulation in T1DM<br>Multiple QD in T1DM (Also post-hoc BE assessment @ steady-state) |
| PK         | 1989<br>1990<br>1995<br>3586                                         | Yes (M)<br>Yes (M)<br>Yes (M)<br>Yes (M)                                                                       | Hepatic impairment<br>Renal impairment<br>Children, adolescent and adult T1DM<br>Population PK in asian subjects with T2DM (Phase 3 trial)                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| In vitro   | 207440<br>CES &<br>CES<br>101123                                     | NA<br>NA                                                                                                       | In-vitro metabolism in hepatocytes across species<br>In vitro protein binding based DDI with warfarin, acetylsalicylate, salicylate, ibuprofen and frequently used antidiabetic agents sitagliptin, glimepiride, metformin and liraglutide as well as the long-chain fatty acids, palmitate, oleate and linoleate                                                                                                                                                                                                                                                             |

Based on the filing review of the submission the clinical pharmacology review will focus on answering the following questions.

### Clinical Pharmacology Review Questions:

- What are the PK/PD characteristics of IDeg and how do they support sponsor's claims?
- Is PK/PD profile IDeg similar among healthy, T1DM, and T2DM population?
- What is Dose-PK/PD relationship of IDeg?
- How does PKPD of IDeg compare among children, adolescent and adult T1DM subjects?
- What is the impact of renal impairment on PK of IDeg?
- What is the impact of hepatic impairment on PK of IDeg?
- What is the impact of BMI on PK/PD of IDeg?
- How does PKPD of IDeg compare among subjects with different race/ethnicity?
- What is the DDI potential of other protein bound drugs with IDeg?
- Is PK/PD profile of formulation IDeg (M) comparable to IDeg(E)?
- Is PK/PD profile of formulation IDeg (IM1) comparable to IDeg(IM2)?
- Is PK/PD profile of formulation Ideg (P) 200U/mL comparable to Ideg(M) 200 U/mL in Type 1DM?
- Are bioanalytical methods used in the clinical pharmacology evaluations adequate?

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MANOJ KHURANA  
11/20/2011

JAYABHARATHI VAIDYANATHAN  
11/20/2011

**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
FILING FORM/CHECKLIST FOR NDA/BLA or Supplement**

**Office of Clinical Pharmacology**

*New Drug Application Filing and Review Form*

General Information About the Submission

|                                  | Information               |                         | Information                                                            |
|----------------------------------|---------------------------|-------------------------|------------------------------------------------------------------------|
| NDA/BLA Number                   | 203313                    | Brand Name              | Ryzodeg                                                                |
| OCP Division (I, II, III, IV, V) | DCPH                      | Generic Name            | Insulin degludec/Insulin aspart                                        |
| Medical Division                 | DMEP                      | Drug Class              | Insulin Analog                                                         |
| OCP Reviewer                     | Ritesh Jain               | Indication(s)           | Indicated to improve glycemic control in adults with diabetes mellitus |
| OCP Team Leader (Acting)         | Jayabharathi Vaidyanathan | Dosage Form             | 100 Units of insulin degludec/insulin aspart per mL (U-100)            |
| Pharmacometrics Reviewer         |                           | Dosing Regimen          | once or twice daily with any main meals                                |
| Date of Submission               | 11/28/2011                | Route of Administration | subcutaneous                                                           |
| Estimated Due Date of OCP Review | 06/08/2012                | Sponsor                 | Novo Nordisk                                                           |
| Medical Division Due Date        | 07/06/2012                | Priority Classification | S                                                                      |
| PDUFA Due Date                   | 07/29/2012                |                         |                                                                        |

***Clin. Pharm. and Biopharm. Information***

|                                                                                | “X” if included at filing | Number of studies submitted | Number of studies reviewed | Critical Comments If any                                                                                        |
|--------------------------------------------------------------------------------|---------------------------|-----------------------------|----------------------------|-----------------------------------------------------------------------------------------------------------------|
| <b>STUDY TYPE</b>                                                              |                           |                             |                            |                                                                                                                 |
| Table of Contents present and sufficient to locate reports, tables, data, etc. | X                         |                             |                            |                                                                                                                 |
| Tabular Listing of All Human Studies                                           | X                         |                             |                            |                                                                                                                 |
| HPK Summary                                                                    | X                         |                             |                            |                                                                                                                 |
| Labeling                                                                       | X                         |                             |                            |                                                                                                                 |
| Reference Bioanalytical and Analytical Methods                                 | X                         |                             |                            |                                                                                                                 |
| <b>I. Clinical Pharmacology</b>                                                |                           |                             |                            |                                                                                                                 |
| Mass balance:                                                                  |                           |                             |                            |                                                                                                                 |
| Isozyme characterization:                                                      |                           |                             |                            |                                                                                                                 |
| Blood/plasma ratio:                                                            |                           |                             |                            |                                                                                                                 |
| Plasma protein binding:                                                        | X                         | 4                           |                            | Studies: 208378, 208523, CES 10-January-2008, CES 01-May-2007                                                   |
| Pharmacokinetics (e.g., Phase I) -                                             | X                         |                             |                            |                                                                                                                 |
| Healthy Volunteers-                                                            |                           |                             |                            |                                                                                                                 |
| single dose:                                                                   | X                         | 1                           |                            | Study: NN5401-1980                                                                                              |
| multiple dose:                                                                 |                           |                             |                            |                                                                                                                 |
| Patients-                                                                      |                           |                             |                            |                                                                                                                 |
| single dose:                                                                   | X                         | 8                           |                            | Studies: NN5401-1959, NN5401-1977, NN5401-1981, NN5401-1982, NN5401-1983, NN5401-3539, NN5401-3857, NN5401-1978 |
| multiple dose:                                                                 |                           |                             |                            |                                                                                                                 |

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

|                                                                   |   |           |  |                                                                                                                             |
|-------------------------------------------------------------------|---|-----------|--|-----------------------------------------------------------------------------------------------------------------------------|
| <b>Dose proportionality -</b>                                     |   |           |  |                                                                                                                             |
| fasting / non-fasting single dose:                                |   |           |  |                                                                                                                             |
| fasting / non-fasting multiple dose:                              |   |           |  |                                                                                                                             |
| <b>Drug-drug interaction studies -</b>                            |   |           |  |                                                                                                                             |
| In-vivo effects on primary drug:                                  | X |           |  |                                                                                                                             |
| In-vivo effects of primary drug:                                  |   |           |  |                                                                                                                             |
| In-vitro:                                                         | X | 3         |  | 207440, CES 20-January-2009, CES 101123                                                                                     |
| <b>Subpopulation studies -</b>                                    |   |           |  |                                                                                                                             |
| ethnicity:                                                        | X | 1         |  | Study: NN5401-1983<br>Single dose PK/PD study in<br>Japanese Subjects                                                       |
| gender:                                                           |   |           |  |                                                                                                                             |
| pediatrics:                                                       | X | 1         |  | Study: NN5401-1982 Single<br>dose PK/PD study in<br>Pediatric Subjects                                                      |
| geriatrics:                                                       | X | 1         |  | Study: NN5401-1981, Single<br>dose PK/PD study in<br>Geriatric subjects                                                     |
| renal impairment:                                                 |   |           |  |                                                                                                                             |
| hepatic impairment:                                               |   |           |  |                                                                                                                             |
| <b>PD -</b>                                                       |   |           |  |                                                                                                                             |
| Phase 2:                                                          |   |           |  |                                                                                                                             |
| Phase 3:                                                          |   |           |  |                                                                                                                             |
| <b>PK/PD -</b>                                                    |   |           |  |                                                                                                                             |
| Phase 1 and/or 2, proof of concept:                               | X | 8         |  | Studies: NN5401-1959,<br>NN5401-1977, NN5401-1981,<br>NN5401-1980, NN5401-1983,<br>NN5401-3539, NN5401-3857,<br>NN5401-1978 |
| Phase 3 clinical trial:                                           |   |           |  |                                                                                                                             |
| <b>Population Analyses -</b>                                      |   |           |  |                                                                                                                             |
| Data rich:                                                        |   |           |  |                                                                                                                             |
| Data sparse:                                                      |   |           |  |                                                                                                                             |
| <b>II. Biopharmaceutics</b>                                       |   |           |  |                                                                                                                             |
| <b>Absolute bioavailability</b>                                   |   |           |  |                                                                                                                             |
| <b>Relative bioavailability -</b>                                 |   |           |  |                                                                                                                             |
| solution as reference:                                            |   |           |  |                                                                                                                             |
| alternate formulation as reference:                               |   |           |  |                                                                                                                             |
| <b>Bioequivalence studies -</b>                                   |   |           |  |                                                                                                                             |
| traditional design; single / multi dose:                          | X | 1         |  | Study: NN5401-1980                                                                                                          |
| replicate design; single / multi dose:                            |   |           |  |                                                                                                                             |
| <b>Food-drug interaction studies</b>                              |   |           |  |                                                                                                                             |
| <b>Bio-waiver request based on BCS</b>                            |   |           |  |                                                                                                                             |
| <b>BCS class</b>                                                  |   |           |  |                                                                                                                             |
| <b>Dissolution study to evaluate alcohol induced dose-dumping</b> |   |           |  |                                                                                                                             |
| <b>III. Other CPB Studies</b>                                     |   |           |  |                                                                                                                             |
| <b>Genotype/phenotype studies</b>                                 |   |           |  |                                                                                                                             |
| <b>Chronopharmacokinetics</b>                                     |   |           |  |                                                                                                                             |
| Pediatric development plan                                        | X |           |  |                                                                                                                             |
| <b>Literature References</b>                                      |   |           |  |                                                                                                                             |
| <b>Total Number of Studies</b>                                    |   | <b>16</b> |  |                                                                                                                             |

On **initial** review of the NDA/BLA application for filing:

|                                           | Content Parameter                          | Yes | No | N/A | Comment                              |
|-------------------------------------------|--------------------------------------------|-----|----|-----|--------------------------------------|
| <b>Criteria for Refusal to File (RTF)</b> |                                            |     |    |     |                                      |
| 1                                         | Has the applicant submitted bioequivalence |     |    | X   | Sponsor used the same formulation in |

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## CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

|                                                                                     |                                                                                                                                                                                                       |   |  |   |                                                                  |
|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|------------------------------------------------------------------|
|                                                                                     | data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?                                                                                                               |   |  |   | their pivotal clinical trial as to be marketed formulation.      |
| 2                                                                                   | Has the applicant provided metabolism and drug-drug interaction information?                                                                                                                          | X |  |   |                                                                  |
| 3                                                                                   | Has the sponsor submitted bioavailability data satisfying the CFR requirements?                                                                                                                       | X |  |   |                                                                  |
| 4                                                                                   | Did the sponsor submit data to allow the evaluation of the validity of the analytical assay?                                                                                                          | X |  |   |                                                                  |
| 5                                                                                   | Has a rationale for dose selection been submitted?                                                                                                                                                    | X |  |   |                                                                  |
| 6                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA organized, indexed and paginated in a manner to allow substantive review to begin?                                               | X |  |   |                                                                  |
| 7                                                                                   | Is the clinical pharmacology and biopharmaceutics section of the NDA legible so that a substantive review can begin?                                                                                  | X |  |   |                                                                  |
| 8                                                                                   | Is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work?                                                                                              | X |  |   |                                                                  |
| <b>Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)</b> |                                                                                                                                                                                                       |   |  |   |                                                                  |
| <b>Data</b>                                                                         |                                                                                                                                                                                                       |   |  |   |                                                                  |
| 9                                                                                   | Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?                                                                                 | X |  |   |                                                                  |
| 10                                                                                  | If applicable, are the pharmacogenomic data sets submitted in the appropriate format?                                                                                                                 |   |  | X |                                                                  |
| <b>Studies and Analyses</b>                                                         |                                                                                                                                                                                                       |   |  |   |                                                                  |
| 11                                                                                  | Is the appropriate pharmacokinetic information submitted?                                                                                                                                             | X |  |   |                                                                  |
| 12                                                                                  | Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)? | X |  |   |                                                                  |
| 13                                                                                  | Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?                                            |   |  | X |                                                                  |
| 14                                                                                  | Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the           |   |  | X | Insulin dose is titrated up and down based on the patients need. |

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**CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS  
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|                |                                                                                                                                                                             |   |  |   |                                                                                                                                                                                                                        |
|----------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|--|---|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                | pharmacokinetic or pharmacodynamics?                                                                                                                                        |   |  |   |                                                                                                                                                                                                                        |
| 15             | Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?                                                    | X |  |   | FDA agreed with partial waiver in pediatric patients less than one year of age (correspondence dated 3/21/2011). Sponsor is planning to conduct clinical trial in T1DM pediatric subjects aged 1 to less than 18 years |
| 16             | Did the applicant submit all the pediatric exclusivity data, as described in the WR?                                                                                        |   |  | X |                                                                                                                                                                                                                        |
| 17             | Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?                                              | X |  |   |                                                                                                                                                                                                                        |
| <b>General</b> |                                                                                                                                                                             |   |  |   |                                                                                                                                                                                                                        |
| 18             | Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product? | X |  |   |                                                                                                                                                                                                                        |
| 19             | Was the translation (of study reports or other study information) from another language needed and provided in this submission?                                             | X |  |   |                                                                                                                                                                                                                        |

**IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE?  
YES, the Clinical Pharmacology section of the application is fileable.**

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

**From Clinical Pharmacology there are no comments for 74-day letter**

Ritesh Jain 11/16/2011

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Reviewing Clinical Pharmacologist Date

Jayabharathi Vaidyanathan 11/16/2011

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Team Leader/Supervisor Date

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# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

## Filing Memo (Internal Memo)

### **1. Background**

Insulin degludec/insulin aspart (IDegAsp; 70/30) is a co-formulation of insulin degludec (IDeg) and insulin aspart (IAsp) :

- Insulin degludec: a new-generation, ultra-long acting basal insulin modified such that the amino acid <sup>(b) (4)</sup> threonine in position B30 of human insulin has been omitted, and the ε amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer.
- Insulin aspart (B28Asp human insulin): a well characterized fast-acting prandial insulin with global market experience since approval by the European Medicines Agency (EMA) in 1999 (NovoRapid®) and by the Food and Drug Administration (FDA) in 2000 (NovoLog®).

The IDegAsp consists of 30% IAsp and 70% IDeg. The co-formulated product is intended for subcutaneous (S.C.) injection for once or twice daily dosing at any main meal, and indicated to improve glycemic control in adults with diabetes mellitus. The formulation of IDegAsp has been optimized such that the individual components do not interact, with IAsp present as soluble and stable hexamers and IDeg as soluble and stable di-hexamers. Once injected into the subcutaneous tissue the IAsp hexamers immediately form monomers which are rapidly absorbed into the capillaries while the IDeg di-hexamers form soluble multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. IDegAsp is developed in a 100 unit (U)/mL strength for subcutaneous injection, provided in a prefilled pen injector with a dose range of 1-80 U per injection in one-unit increments <sup>(b) (4)</sup>

<sup>(b) (4)</sup> Sponsor used the similar formulation in their pivotal clinical trial as to be marketed formulation and there are no pivotal BE studies.

From Clinical Pharmacology there are no comments for 74-day letter. In addition, Clinical Pharmacology requests no DSI inspection.

### **2. Clinical Development Program:**

The completed clinical development program for IDegAsp comprises 13 clinical pharmacology trials, 3 therapeutic exploratory trials of 6–16 weeks duration, 5 therapeutic confirmatory trials of 26 weeks duration and one completed therapeutic confirmatory, 26-week extension trial. Figure 1 shows the lists of clinical trials in IDegAsp development program.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

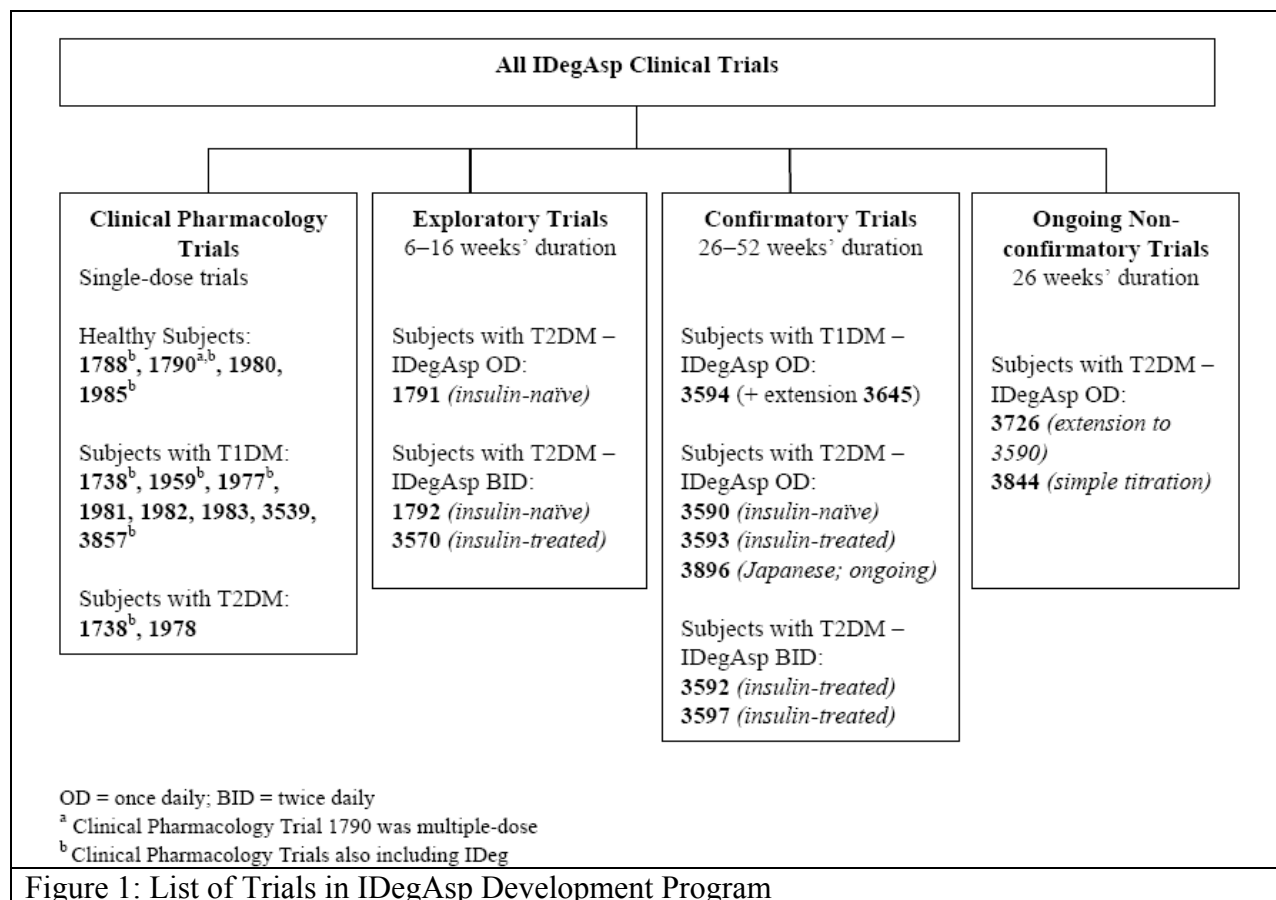


Figure 1: List of Trials in IDegAsp Development Program

### **3. Clinical Pharmacology Program:**

The clinical pharmacology program included 31 trials with IDegAsp (13 trials, 7 of which also included IDeg) or with IDeg alone (18 trials), see Figure 2. A list and brief descriptions of the individual key clinical pharmacology trials for this IDegAsp NDA is shown in Figure 3.

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

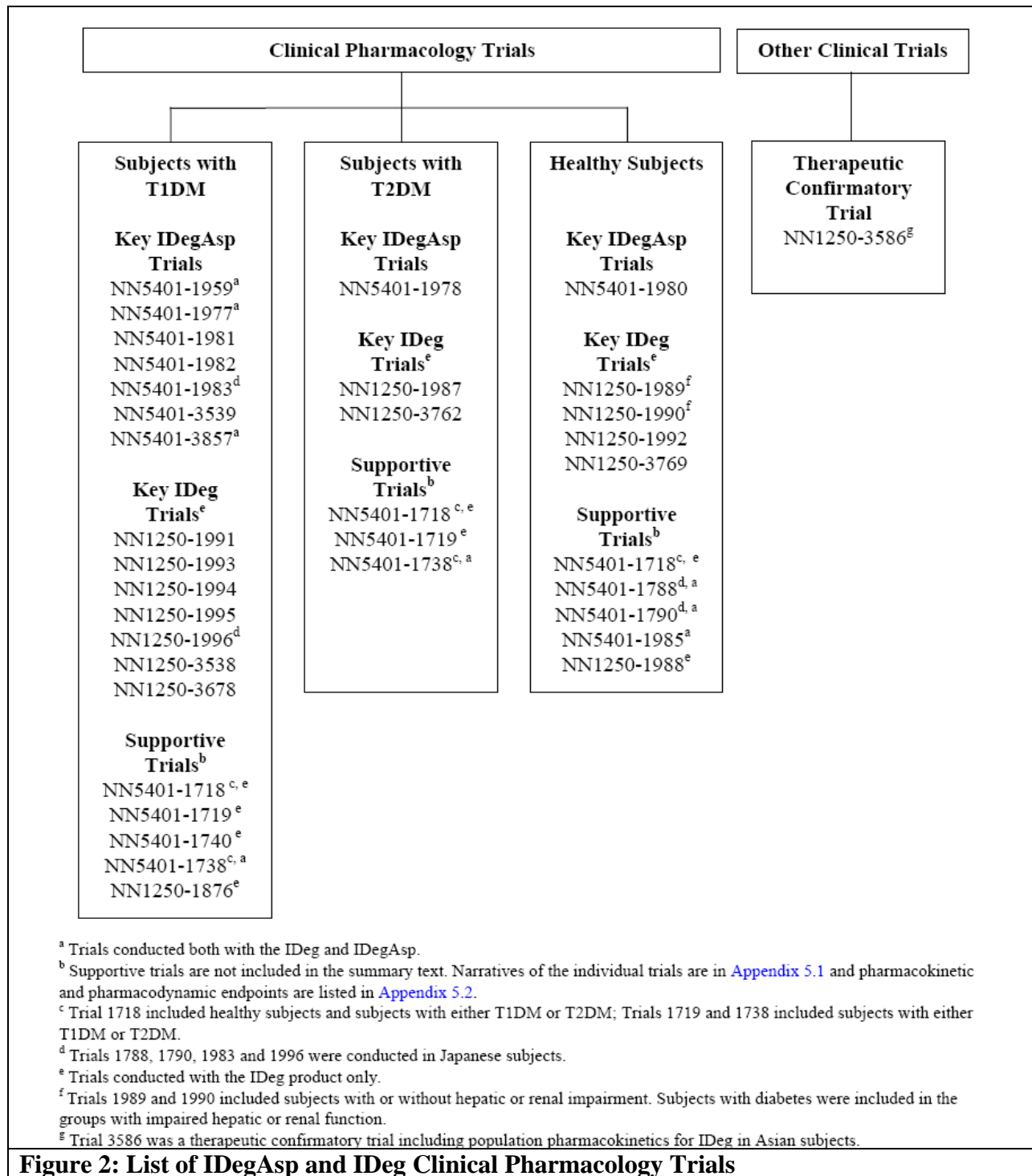


**Figure 2: List of IDegAsp and IDeg Clinical Pharmacology Trials**

# CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FILING FORM/CHECKLIST FOR NDA/BLA or Supplement

The Clinical Pharmacology Program Consists of 9 Key Studies:

| Trial ID                                    | Trial Design         | Trial Objectives                                                                                     | Treatment                                                                                                           |
|---------------------------------------------|----------------------|------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| <b>IDegAsp Trials in Subjects with T1DM</b> |                      |                                                                                                      |                                                                                                                     |
| NN5401-1959                                 | RND, DB, CO, SD, INB | PK and PD of IAsp and IDeg when co-formulated in IDegAsp                                             | IDegAsp: 0.92 U/kg<br>(0.28 U/kg IAsp + 0.64 U/kg IDeg)<br>IDeg: 0.64 U/kg + IAsp: 0.28 U/kg<br>BIAsp 30: 0.64 U/kg |
| NN5401-1977                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                           | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| NN5401-1981                                 | RND, DB, CO, SD      | PK and PD in geriatric subjects and younger adult subjects                                           | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-1982                                 | OL, PG, SD           | PK and safety profile in children, adolescents and adults                                            | IDegAsp: 0.5 U/kg                                                                                                   |
| NN5401-1983                                 | RND, DB, CO, SD      | PK and PD in Japanese subjects                                                                       | IDegAsp: 0.5 U/kg<br>BIAsp 30: 0.5 U/kg                                                                             |
| NN5401-3539                                 | RND, DB, INB, CO, SD | PK and PD (dose-response)                                                                            | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| NN5401-3857                                 | RND, OL, CO, SD      | PK and PD of IDegAsp compared with IDeg and IAsp (product distinctiveness)                           | IDegAsp: 0.5 U/kg<br>IDeg: 0.5 U/kg<br>IAsp: 0.5 U/kg                                                               |
| <b>IDegAsp Trial in Subjects with T2DM</b>  |                      |                                                                                                      |                                                                                                                     |
| NN5401-1978                                 | RND, DB, INB, CO, SD | PK and PD (dose-response)                                                                            | IDegAsp: 0.4, 0.6, 0.8 U/kg<br>BIAsp 30: 0.4, 0.6, 0.8 U/kg                                                         |
| <b>IDegAsp Trial in Healthy Subjects</b>    |                      |                                                                                                      |                                                                                                                     |
| NN5401-1980                                 | RND, DB, CO, SD, BE  | BE between two IDeg products with identical formulations, and different manufacturing stream (b) (4) | IDegAsp: 0.5 U/kg                                                                                                   |

**Figure 3: Key Clinical Pharmacology Trials in IDegAsp Development Program**

### Potential Key Review Questions

- What are the PK and PD features of IDegAsp in T1DM and T2DM subjects?
- What are the effects of Intrinsic and Extrinsic Factors on PK/PD?
- Are PK and PD bioassay methods and their validation procedures adequate?
- Assessment of product distinctiveness when IDegAsp is given as premix or as individual IDeg and IAsp.
- Is BID dosing in T1DM subjects justified.

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
-----

RITESH JAIN  
11/17/2011

JAYABHARATHI VAIDYANATHAN  
11/17/2011