CLINICAL REVIEW

Application Type	NDA
Application Number(s)	203313 and 203314
Priority or Standard	Standard
Submit Date(s)	February 15, 2016
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PDUFA Goal Date	December 16, 2016
Division / Office	DMEP/ ODEII
Reviewer Name(s)	Tania A. Condarco, M.D.
Review Completion Date	November 4, 2016
Established Name	Insulin degludec Insulin degludec/insulin aspart 70/30
(Proposed) Trade Name	Tresiba for insulin degludec Ryzodeg for insulin degludec/insulin aspart 70/30
Therapeutic Class	Degludec: Long-acting insulin analog. IDegAsp 70/30: Fixed ratio combination of long and short acting insulin analogs
Applicant	Novo Nordisk
Formulation(s)	Tresiba U-100 and U-200 and Ryzodeg 70/30 U-100 solutions for injections
Dosing Regimen	Individualized dose administered subcutaneously once daily
Indication(s)	To improve glycemic control
Intended Population(s)	Pediatric patients with diabetes mellitus from 1 to less than 18 years of age

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1 Recommendations/Risk Benefit Assessment

This document contains the clinical review for two efficacy supplements (supplement 2 for NDA 203313 and supplement 3 for NDA 203314) containing two pediatric studies. Each study was conducted as a Postmarketing Requirement (PMR) to fulfill the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). Study NN1250-3561 fulfills Post Marketing Requirement #2954 for Tresiba (NDA203314); while Study NN5401-3816 fulfills Post Marketing Requirement #2955-1 for Ryzodeg 70/30 (NDA203313).

Both Tresiba and Ryzodeg 70/30 were approved in September 2015 with an indication to improve glycemic control in adults with diabetes mellitus.

Tresiba (insulin degludec) is a once-daily long-acting human insulin analog, approved with two concentrations U-100 and U-200; while Ryzodeg (insulin degludec and insulin aspart injection) is a mixed (fixed-ratio) insulin analog product containing 70% insulin degludec (a long-acting insulin) and 30% insulin aspart (a rapid-acting insulin).

The data from these two PMR studies are provided to support use of Tresiba and Ryzodeg 70/30, respectively, in pediatric patients with diabetes mellitus from 1 to less than 18 years of age.

1.1 Recommendation on Regulatory Action

Based on my review of clinical efficacy and safety, I recommend **approval** of both of these supplemental NDAs pending agreement with the Sponsor on labeling.

1.2 Risk Benefit Assessment

This submission includes two open-labeled, randomized, pediatric (ages 1-18), phase 3 studies, in patients with type 1 diabetes mellitus: one study included a 26-week efficacy with 26 week safety extension for insulin degludec; the second study included a 16-week efficacy study for insulin degludec/insulin aspart. Each study was conducted to fulfill a Postmarketing Requirement (#2954 for Tresiba [NDA203314]; #2955-1 for Ryzodeg 70/30 [NDA203313]). Both studies were designed to support an indication in pediatric patients ages 1 to (b) (4) with diabetes mellitus.

In this section the benefit versus risk assessment is combined for insulin degludec and insulin degludec/insulin aspart, since both studies had similar efficacy and safety findings and were evaluated in the same population. Overall, the totality of the data for each program suggests that the benefit of insulin degludec and insulin degludec/insulin aspart for pediatric patients ages 1 to less than 18 outweighs its risk.

The benefit seen with insulin degludec and insulin degludec/insulin aspart is the glycemic lowering achieved. Although in both trials the difference between treatment arms was small (0.15 for insulin degludec- insulin detemir; and -0.04 for insulin degludec/insulin aspart- insulin detemir), both programs met the pre-specified non-inferiority margin, defined as the upper bound

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of the two-sided 95% confidence interval of the difference between insulin degludec or insulin degludec/insulin aspart and insulin detemir <0.4%. In both trials, glycemic control was achieved by smaller total daily insulin doses of insulin degludec or insulin degludec/insulin aspart (5 or more units less than the total insulin dose for the detemir arm, at the end of each trial). Exploratory, subgroup analyses by age did not suggest that the observed glycemic findings were driven by a particular age group.

Another potential clinical benefit for some pediatric patients is that both insulin degludec and insulin degludec/insulin aspart allow for the administration of fewer injections of basal insulin than twice a day regimens (e.g., insulin detemir or NPH).

The risk of hypoglycemia was the most notable safety concern in this review. Although all insulins are labeled for the risk of hypoglycemia, the persistent pattern for a higher risk with insulin degludec and insulin degludec/insulin aspart, than the risk with insulin detemir, was seen in numerical imbalances favoring the comparator. This increased risk was notable across multiple hypoglycemia definitions and across age subgroups (2-5, 6-11 and 12-17 years); however this imbalance was not statistically significant. The hypoglycemia trends differed between trials in that the majority of severe hypoglycemia events were seen in the first month in the insulin degludec trial, while the number of severe hypoglycemia events did not have a temporal pattern to the start of insulin degludec/insulin aspart. It does not appear that the hypoglycemia findings were explained by the overall glycemic control, (which was slightly better with insulin degludec/aspart or slightly better with insulin detemir than insulin degludec).

The interpretation of the hypoglycemia findings is confounded by trial design issues. For example, hypoglycemia should be in light of the fact that both trials excluded patients at high risk for hypoglycemia (i.e., exclude patients with hypoglycemic unawareness or recurrent severe hypoglycemia). Therefore, the absolute risk of hypoglycemia in a clinical setting may be higher than what was seen in these studies; however the relative risk should not be affected.

All currently approved insulins have labeled Warnings and Precautions for the risk of hypoglycemia. This language is applicable for both adult and pediatric patients and emphasizes the risk factors and risk mitigation strategies to decrease the risk of hypoglycemia. Although the statistical analyses for both trials do not suggest a clear difference in hypoglycemia between insulin degludec or insulin degludec/insulin aspart and insulin detemir, the reviewer suggest the consideration of pediatric-specific dosing based on the clinical trial data. For example, pediatric-specific dosing for both insulin degludec and insulin degludec/insulin aspart may include recommending once daily dosing and dosing at the same time of day. Dosing specific to insulin degludec/insulin aspart, may include recommending a dose reduction in the starting dose upon converting to insulin degludec/insulin aspart.

The differences in minimum dose titration allowed by Pen devices used in the clinical trials and Pen devices proposed to be-marketed, may also affect the postmarketing hypoglycemia risk. The Sponsor proposes to market the U-100 PDS290 pens (for insulin degludec and insulin degludec/aspart) which titrate by 1 unit increments; and the U-200 PDS290 pens (for insulin degludec) which titrate by 2 unit increments, in the pediatric population. These Pen devices are

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currently approved for use in adult patients. The Pen devices used in the pediatric trials were different than the Pen devices approved, and allowed titration by half-units.

The risk associated with the proposed and currently marketed pens in adults, will be discussed in terms of the U-100 concentration, since this concentration is applicable to both insulin degludec and insulin degludec/insulin aspart. However, it is important to remember that these risks would be magnified for the U-200 concentration of insulin degludec. Because the currently marketed U-100 PDS290 (FlexTouch) pens allow 1 unit increments (rather than the ½ unit increment pens that were used in the Phase 3 trials), there is a greater risk of overdose for the younger pediatric patients, who use small doses of basal insulin and in whom a 1 unit minimum dose increase may be a substantial change in dose (for example, in a patient on 1 unit of basal insulin, a minimum dose increase of 1 unit versus a minimum dose increase of half-a unit, may drastically affect his/her risk of hypoglycemia). These patients require a more granular titration than is provided by the 1 unit dose change.

Therefore, in order to provide adequate dosing for this subgroup, the ½ unit pens used in the Phase 3 studies could be marketed (the Sponsor does not currently plan on marketing the ½ unit pens), or the dosing of both products could be limited to a minimum dose; such as limiting the use to patients requiring more than 5 units of insulin degludec or insulin degludec/insulin aspart. The titration algorithms of both Phase 3 programs support the titration of insulin degludec and insulin degludec/aspart by 1 unit increments when the basal insulin dose (for insulin degludec) or the dose of insulin degludec/insulin aspart was greater than 5 units.

Extrapolation from the adult type 1 and type 2 diabetic trials in the original NDA support the use of the U-200 PDS 290 (FlexTouch) pen in certain subgroups of the pediatric population. As discussed above, this concentration is not appropriate for patients requiring small doses. The product label may select for the appropriate pediatric population, by specifying a minimum dose for use.

Other risks, including serious adverse events and immunological adverse events were not clinically worse than that observed in the adult clinical trial.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

There is no Risk Evaluation and Mitigation Strategy (REMS) for either insulin degludec (IDeg) or Insulin degludec/aspart (IDegAsp) that was identified at the time of approval and there were no safety concern in the current submission that would warrant a REMS.

1.4 Recommendations for Postmarket Requirements and Commitments

The current submission does not warrant a recommendation for either a new Postmarketing Requirement or Postmarketing Commitment. I recommend that the studies are satisfactory to fulfill both PMRs.

2 Introduction and Regulatory Background

The clinical trials conducted are identified by the project number NN5401, for IDegAsp and 1250 for IDeg, followed by a unique four-digit trial ID. For ease of the reader, the clinical trials will be referred to by their unique ID (i.e., the last 4 digits that follow the project number).

2.1 Product Information

Tresiba (insulin degludec) and Ryzodeg 70/30 (insulin degludec and insulin aspart) were approved on September 25, 2015 during the second review cycle. At the time of approval, Tresiba and Ryzodeg 70/30 were approved with an indication to improve glycemic control in adults with diabetes mellitus. Of note, at the time of approval, Tresiba was approved with two concentrations (U-100 and U-200).

Refer to the primary review in the first and second review cycle.

IDeg (Tresiba)
Insulin degludec (IDeg) is a long-acting basal insulin that has been modified from human insulin to allow IDeg to form soluble and stable multi-hexamers. These hexamers form a depot in the subcutaneous tissue after injection and gradually separate into IDeg monomers in a slowly, delivering IDeg from the subcutaneous injection site into the circulation. At the target tissues, IDeg monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake. The product presentation of Tresiba is the U-100 FlexTouch pen device and the U-200 FlexTouch pen device.

Ryzodeg 70/30
Insulin degludec and insulin aspart injection is a human insulin analog solution containing 70% insulin degludec and 30% insulin aspart. The insulin degludec component in Ryzodeg 70/30 forms multi-hexamers when injected into subcutaneous tissue, while insulin aspart monomers are released rapidly into the circulation. The product presentation of Ryzodeg 70/30 is the U-100 FlexTouch pen device.

2.2 Tables of Currently Available Treatments for Proposed Indications

Table 1 shows the currently approved products for the treatment of pediatric patients with diabetes mellitus. Except for metformin, all of the approved therapies for the treatment of diabetes in pediatrics are insulins. Notably, the Sponsor's proposed indication starts at age 1, while most of the other insulin products start at age 2 or older.

Table 1- approved drug products for the treatment of pediatric patients with diabetes

Drug name	Indication
Insulin	
Insulin aspart (Novolog)	Type 1 diabetes mellitus 2 years and older
Insulin glulisine (Apridra)	Diabetes mellitus 4 years of age and older
Insulin lispro (Humalog)	Diabetes mellitus 3 years and older
Insulin regular	Type 1 diabetes mellitus 2 years and older
Insulin detemir (Levemir)	Type 1 diabetes mellitus 2 years and older
Insulin glargine (Lantus)	Type 1 diabetes mellitus 6 years and older

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Insulin isophane (NPH)	Diabetes 12 years of age and older
Insulin isophane (NPH)/ insulin regular	Diabetes mellitus
Biguanides	
Metformin hydrochloride ***Immediate-release tablets/solution***	Type 2 diabetes 10 years and older

2.3 Availability of Proposed Active Ingredient in the United States

Tresiba and Ryzodeg 70/30 were approved in the United States in September 2015.

2.4 Important Safety Issues With Consideration to Related Drugs

Safety issues with insulins include the risks associated with over-/under-dosing, and the risk of immunogenic adverse events.

Safety issues related to over-dosing of insulins include the risk of hypoglycemia, which may be life-threatening.

Safety issues with under-dosing of insulins include the risk of hyperglycemia, which if severe can also be life-threatening (i.e. diabetic ketoacidosis- in type 1 diabetes or hyperglycemic hyperosmolar state in type 2 diabetes). Long term hyperglycemia may result in the macrovascular and microvascular complications of diabetes.

Other risks with insulin use include the risk of hypokalemia, weight gain and immunogenic adverse events (including the risk of local and systemic hypersensitivity and the development of anti-drug antibodies).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The following topics, regarding the proposed pediatric plan, were discussed between the Agency and the Sponsor:

For IDeg:

- There was agreement from the Agency that the 6-month trials comparing insulin degludec and insulin detemir in children with type 1 diabetes could be initiated prior to IDeg approval.

Statistical comments:

- Analyzing the number of hypoglycemic episodes by a negative binomial regression model was acceptable. More transparent analysis using the Wilcoxon test for the following two endpoints: the number of episodes per subject and the number of episodes per subject per patient year was encouraged.

Inadequate study request for a written request

- The Sponsor submitted a Written Request on December 2013 for trial 3561 in children and adolescents with type 1 diabetes. The written request was not issued because it did not include individuals with type 2 diabetes, therefore omitting meaningful safety and efficacy information for an important segment of the pediatric population. In addition, the IDeg data suggested a higher cardiovascular disease in adults with T2DM.

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- ***For IDegAsp:***

  Statistical comment
  - The FDA expressed concern regarding the use of Last Observation Carried Forward (LOCF) for the primary analysis and asked the Sponsor to specify a primary statistical analysis which does not rely on LOCF and which is in line with National Academy of Sciences (NAS) recommendations.
  - The Sponsor was asked to use the full analysis set (FAS) population for analysis "as randomized," not "as treated" as stated on the protocol

  For both IDeg and IDegAsp:

  Waivers
  - The Division agreed that a partial waiver in pediatric patients less than one year of age is appropriate as clinical trials would be impossible or highly impracticable due to the low incidence of diabetes mellitus in this age group.
  - The Division agreed that clinical studies in pediatric patients with type 2 diabetes mellitus will likely not be required under PREA, if data from studies in adult and pediatric patients with type 1 diabetes mellitus and studies in adults with type 2 diabetes mellitus are adequate to support use of IDeg(or IDegAsp) in the pediatric population with type 2 diabetes

  Comparators
  - The Division felt it was acceptable to use insulin detemir as the comparator in these trials.

  Indication
  - The Division felt that it would be a review issue to determine if the trials supported a pediatric indication down to 1 year.

  Toxicology
  - Juvenile toxicity studies were not necessary based on the animal data with IDeg and the approved product for insulin aspart (Asp).

  Population outside the US
  - The Agency also confirmed that data generated in pediatric populations outside the US could qualify for approval of a pediatric indication if the data demonstrate safety and effectiveness in pediatric patients and the trials are conducted in a manner relevant to how the product will be used in the United States. The pediatric patient population studied in these trials should represent the pediatric population in the United States who will use these products. In addition, the manner in which the insulins are used in these trials (e.g., titration goals) must be consistent with how insulins are used in clinical practice in the United States. The Sponsor was asked that some patients (e.g., ~20-25% of those enrolled in these trials) come from sites in the United States.

As part of the approval of Tresiba and Ryzodeg 70/30, the Sponsor had the following post marketing requirement (PMR) in pediatric studies:

2955-1 An open-label, 16-week, randomized, controlled efficacy and safety trial comparing Ryzodeg 70/30 (insulin degludec and insulin aspart injection) administered once daily with a main meal and insulin aspart for additional meals to insulin detemir, in combination with

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mealtime insulin aspart at each meal, in pediatric patients with type 1 diabetes mellitus ages 1 to 17 years (inclusive).

2954-1 An open-label, 26-week, randomized, controlled efficacy and safety trial comparing Tresiba (insulin degludec injection) with insulin detemir in pediatric patients with type 1 diabetes ages 1 to 17 years (inclusive) using insulin aspart at each meal, followed by a 26-week safety extension.

I note that the trials submitted to fulfill the PMRs are consistent with the PMR language.

2.6 Other Relevant Background Information

None.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

A routine site inspection from the Office of Scientific Investigations was not requested.

The submission quality was acceptable.

3.2 Compliance with Good Clinical Practices

The Sponsor states that both trial 3561 (IDeg) and trial 3516 (IDegAsp) were conducted in accordance with the Declaration of Helsinki, ICH good clinical practice and FDA 21 CFR 312.120.

The Sponsor provided listings of protocol deviations for each study.

Both Study 3561 and 3816 had protocol deviations related to the lack of collection of blood ketones for hyperglycemia:

- Trial **3561:** There were 202 patients who did not have blood ketone values measured, as the protocol specified for SMPG values above 250 mg/dL.
- Trial **3816:** Ketone bodies were not measured for approximately 26% in the IDegAsp and for 33% in IDet group

Reviewer's comment: Missing ketone measurement may result in underestimating the number of patients/cases of diabetic ketoacidosis in the trial overall. For a discussion on hyperglycemia in each trial refer to section 7.3.4 Significant Adverse Events.

3.3 Financial Disclosures

The Sponsor has adequately disclosed financial arrangements with the clinical investigators as recommended in the FDA guidance for industry on *Financial Disclosure by Clinical investigators.* These arrangements do not raise any questions about the integrity of the data

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submitted in the NDA. See section **Clinical investigator Financial Disclosure** for further details.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Pen devices will be discussed in this section. Refer to the original NDA for a full review of chemistry manufacturing and controls.

Pen devices

The reviewer created this section because the discussion regarding pen devices is extensive and is applicable to both trial 3561 and 3816. In this section, the reviewer will discuss the insulin pens used in the pediatric clinical trials and the Sponsor's justification for labeling the PDS290 pens.

Please refer to the review by Lana Shiu, M.D. from Center of Devices and Radiological Health (CDRH) and to the review by Sarah K. Vee, PharmD from the Division of Medication Error Prevention and Analysis (DMEPA) for a comprehensive review of the pen devices. Per the CDRH review[1], the Sponsor demonstrated that "their internal manufacturing release specifications are much tighter than as required by the ISO11608-1:2002 and is able to deliver precise and accurate targeted volume of the drug at the minimum dose (b) (4)[2]".

DMEPA's reviews on August 15, 2016 and August 29, 2016, agreed that pediatric patients could safely and effectively use Ryzodeg 70/30 and Tresiba U-100 FlexTouch pens and found the risk analysis and justification provided by the Sponsor acceptable for the Tresiba U-200 FlexTouch pen with regard to medication error.

Insulin pens used in the pediatric clinical trials

Table 2 shows the durable pen devices used in trials 3561 and 3816. All pens used in these trials were used with 100 U/ml, Penfill 3 ml cartridge of the corresponding insulin[3]. Of note, the Sponsor's proposed Package Insert (PI) in this supplement lists the already labeled pen devices in adults (FlexTouch pen devices using the PDS290 platform) for use in children, and *not* the actual pen devices studied in the pediatric trials, shown in **Table 2** . The FlexTouch pen does not allow for refilling with an insulin containing cartridge; it is a prefilled disposable pen.

Table 2 – Pen devices used in Phase 3 trials

	Trial 3561[a]	**Trial 3816[b]**

[1] CDRH review by Lana Shiu, dated 6/30/16, entered by Callie Cappel-Lynch into DARRTS on 7/14/16
[2] equal to 1 unit of insulin.
[3] *Trial 3561*- Insulin degludec 100 U/ml, Penfill 3 ml cartridge; Insulin detemir (Levemir) 100 U/ml, Penfill® 3 ml cartridge; *Trial 3816*- Insulin aspart (IAsp) 100 U/mL, 3 mL Penfill cartridge; Insulin detemir (Levemir) 100 U/ml, Penfill 3 ml cartridge

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Basal insulin		
USA	NovoPen Junior (green pen*)	NovoPen Junior (green pen)
Outside the USA	NovoPen 300 Demi (lime pen) NovoPen Echo (blue pen) NovoPen 4 (blue/silver pen)	NovoPen Echo (blue pen, covered by a green skin)
Prandial insulin (IAsp for all)		
USA	NovoPen Junior (yellow pen)	NovoPen Junior (yellow pen)
Outside the USA	NovoPen Echo (red pen) NovoPen 300 Demi (apricot pen)	NovoPen Echo (red pen, covered by an orange skin)
[a]For Trial 3561, basal insulin was IDeg and IDet [b]For Trial 3816, basal insulin was IDegAsp and IDet		

*Initially a yellow pen with green sticker was used in the trial

Reviewer's comments: The following differences in pen devices between the pediatric trials and the adult trials (that are labeled) are noted:

The pen devices used in the pediatric trials used penfill cartridges: *During the second cycle review of Tresiba and Ryzodeg 70/30 for the initial approval, the product presentation using the durable Penfill devices were withdrawn by the Sponsor from both NDAs due to DMEPAs concerns* (b) (4) (b) (4) (b) (4) *Therefore Tresiba and Ryzodeg 70/30 are only labeled for the FlexTouch pen devices using the PDS290 platform (prefilled disposable pen devices). DMEPA stated that since the FlexTouch platform has an "integrated cartridge, the step to insert a cartridge is eliminated compared to NovoPen Echo/Junior, thereby eliminating the possibility of a use error associated with this step."*

Differences in dose-increments allowed by pen device: *The U-100 concentrations of the approved Tresiba and Ryzodeg 70/30 pen devices (FlexTouch) allow for 1 unit increment increase/decrease, while the Penfill reusable cartridge devices used in the pediatric trials are able to dial half-unit increments.*

Previous pediatric studies (by the same Sponsor)[4] *with insulin detemir (Levemir, NDA 21536, supplement 41), evaluated pediatric patients ages 2-16 years of age, comparing insulin detemir to NPH using a ½ unit titration algorithm and resulted in approval for the pediatric indication, without the approval of a pen device able to dial ½ unit increments.*

The U-200 Tresiba pen device allows for a dose change by 2 unit increments, which were not studied in pediatric patients.

Sponsor's justification of labeling the proposed pen devices

[4] NDA 21536 (supplement 41), review by Dr. Balakrishnan (dated July 22, 2011)

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This section discusses the Sponsor's rationale in support of the use of the PDS290 pen devices (for Tresiba: 3 mL FlexTouch disposable prefilled pen (U-100) and FlexTouch disposable prefilled pen (U-200); for Ryzodeg 70/30: FlexTouch disposable prefilled pen) for use in the pediatric population. Since the Sponsor presented the same rationale in support for the use of PDS290 pens for both Tresiba and Ryzodeg 70/30 (since both drug products use a PDS290 pen platform), the information in this section of the review, pertains to both products.

Per the Sponsor, support of use of PDS290 pen injectors in the pediatric population is based on the following:

- **Justification of Device Effectiveness:** The prefilled pen devices are ISO 11608(-1) compliant and can deliver the drug product subcutaneously to achieve similar glycemic results. All pens have the same operating principle. Therefore (per the Sponsor) the safety and effectiveness in the pediatric clinical development program for Tresiba or Ryzodeg 70/30 are expected to be the same with the PDS290 pen-injector.
- **Extrapolations from adult data for pediatric use:** The Sponsor states that the FDA Guidance[5] supports the applicability of the PDS290 pen-injector data (for Tresiba and Ryzodeg 70/30) to the pens used in the pediatric trials
- **Human factors/usability validation:** As part of the development of the PDS290 pen injector for Tresiba or Ryzodeg 70/30, the Sponsor conducted summative usability test in the pediatric population to demonstrate that the PDS290 could be used by the intended users.

Reviewer's comment: Although from a device standpoint, there are no engineering or human factors issues identified, the reviewer is concerned that the proposed pens may not be clinically useful for younger patients, who use small insulin doses. The rationale for this concern is that the proposed FlexTouch pens allow dose changes of 1 unit increment/decrement while the pen devices used in the clinical phase 3 trials allowed 0.5 unit changes.

In order to explore dose relationship at different age groups, the reviewer sent an information request to the Sponsor asking for the mean dose by age groups for each study. **Table 3** *and* **Table 4** *show the insulin doses used in patients ages 1 to 5.*[6]

As would be expected, younger patients had the lowest insulin doses. Therefore in this age group, an increase of 1 unit of insulin was a larger proportion of their mean basal insulin dose.

[5] Draft Guidance for Industry and FDA Staff: Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices, May 6, 2015

[6] The reviewer sent an information request to the Sponsor to evaluate a pre-pubertal age range (initially ages 1-11), since this age group were thought to have lower insulin requirements than children undergoing puberty. Upon review of the submitted data, the reviewer chose to show (in this review) the age groups with mean doses <5 units of basal insulin, since this group was pre-specified to titrate basal insulin by ½ units, in the protocols. The Sponsor's full response is located in \\CDSESUB1\evsprod\NDA203314\0095\m1\us

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Table 3 – Trial 3561- Actual insulin dosing – safety analysis set

Age at baseline (years)	Age 1	Age 2	Age 3	Age 4	Age 5
Starting dose – week 1					
IDEG BASAL INSULIN Mean insulin dose U (mean U/kg)	N=2 0.92 (0.07)	N=6 3.69 (0.28)	N=10 4.10 (0.24)	N=9 5.31 (0.29)	N=16 4.55 (0.22)
1 unit of IDeg is this percentage of the mean dose of IDeg *	108%	27%	24%	19%	22%
Week 26 dose (observed)					
IDEG BASAL INSULIN Mean insulin dose U (mean U/kg)	N=2 2.08 (0.14)	N=6 3.72 (0.26)	N=9 4.23 (0.24)	N=9 6.35 (0.30)	N=15 5.28 (0.23)
1 unit of IDeg is this percentage of the mean dose of IDeg *	48%	27%	24%	16%	19%
Week 52 dose (observed)					
IDEG BASAL INSULIN Mean insulin dose U (mean U/kg)	N=2 3.00 (0.20)	N=5 4.45 (0.28)	N=7 4.31 (0.23)	N=9 6.39 (0.29)	N=13 6.19 (0.26)
1 unit of IDeg is this percentage of the mean dose of IDeg *	33%	22%	23%	16%	16%

*this was calculated by dividing 1 ÷ by the mean insulin dose in units.

For a patient with an age of 1year: with a mean insulin dose of 0.92 units, an increase of 1 unit of IDeg would be an increase of 108% of the original dose.
For a patient with an age of 5 years: with a mean insulin dose of 4.55 units, an increase of 1 unit of IDeg would be an increase of 22% of the original dose.

For a patient with an age of 1year: with a mean insulin dose of 2.08 units, an increase of 1 unit of IDeg would be an increase of 48% of the original dose.
For a patient with an age of 5 years: with a mean insulin dose of 5.28 units, an increase of 1 unit of IDeg would be an increase of 19% of the original dose.

For a patient with an age of 1year: with a mean insulin dose of 3 units, an increase of 1 unit of IDeg would be an increase of 33% of the original dose.
For a patient with an age of 5 years: with a mean insulin dose of 6.19 units, an increase of 1 unit of IDeg would be an increase of 16% of the original dose.

Table 4 – Trial 3816- Actual insulin dosing – safety analysis set

Age at baseline (years)	Age 1	Age 2	Age 3	Age 4	Age 5
Starting dose – week 1					
IDEGASP INSULIN~ Mean insulin dose U (mean U/kg)	N=0 --	N=3 3 33 (0.22)	N=12 6.82 (0.39)	N=8 7.02 (0.41)	N=17 8.32 (0.39)
1 unit of IDeg is this percentage of the mean dose of IDeg *	--	30%	15%	14%	12%
Week 16 dose (observed)					
IDEGASP INSULIN~ Mean insulin dose U (mean U/kg)	N=0 -	N=2 5.00 (0.32)	N=11 8.42 (0.46)	N=8 9.00 (0.47)	N=17 9.71 (0.42)
1 unit of IDeg is this percentage of the mean dose of IDeg *	--	20%	12%	11%	10%

~ The total IDegAsp dose is presented which includes the basal component (70% of the total IDegAsp dose) and the prandial component (30% of the total IDegAsp dose).
*this was calculated by dividing 1 ÷ by the mean insulin dose in units.

For a patient with an age of 2years: with a mean insulin dose of 3.33 units, an increase of 1 unit of IDegAsp would be an increase of 30% of the original dose.
For a patient with an age of 5 years: with a mean insulin dose of 8.32 units, an increase of 1 unit of IDegAsp would be an increase of 12% of the original dose.

For a patient with an age of 2years: with a mean insulin dose of 5 units, an increase of 1 unit of IDegAsp would be an increase of 20% of the original dose.
For a patient with an age of 5 years: with a mean insulin dose of 9.71 units, an increase of 1 unit of IDegAsp would be an increase of 10% of the original dose.

Reviewer's comment: A limitation of the analysis in the tables above is that the number of patients within subgroups is very small.

The above exploratory analysis suggests that younger patients would have a less granular titration using the already labeled FlexTouch pen device (which uses 1 unit increments). The FlexTouch pen would result in larger changes in dose, relative to the patient's dose, unlike the pen devices used in the clinical trials which could titrate by ½ unit increments.

These findings suggest that younger patients may benefit more from ½ unit titration (as was carried out in the phase 3 trials) than 1 unit titration.

Because of concern regarding patients who may require lower doses of insulin, there was internal discussion regarding: why the Sponsor was not planning on marketing the ½ unit pens used in the clinical trials and the dose accuracy of the PDS290 pen device vs. the pen devices used in the clinical trials. An information request was sent to the Sponsor on September 1, 2016 to clarify these issues. The Sponsor responded on September 14, 2016:[7]

Rationale for not planning on marketing the ½ unit pens:

The pediatric phase 3 trials were conducted in accordance with the EMA PIPs for Tresiba and Ryzodeg, which included a 0.5 unit increment pens as a PIP binding element. The Sponsor notes that "all basal insulins for the pediatric indication available in prefilled pen-injectors in the US are currently marketed in 1 unit increment only. Hence, the use of a 1 unit increment prefilled pen-injector for basal insulin injection is considered well established in the pediatric segment." The Sponsor states that a small proportion of patients would benefit from the half unit increments; this population would likely use another therapy, i.e., an insulin pump.

Dose Accuracy Specifications

The dose accuracy for the pen devices is shown in **Table 5**. The PDS290 pen device has an accuracy for a 1 unit increment ±1/2 unit, which is similar to the accuracy of the pens used in the clinical trials (with the exception of the NovoPen Junior 300 Demi, which had a lower accuracy).

Table 5 – Dose accuracy development specifications for PDS290 and clinical trial devices

Pen-injector	Minimum Set Dose	Novo Nordisk Internal Development specification	ISO11608-1 specification
PDS290, 100 U/mL (for Tresiba and Ryzodeg) and 200 U/mL (for Tresiba)	10µL (1U/2U)	(b) (4)	
NovoPen® Echo	5µL (0.5U)		
NovoPen® 4	10µL (1U)		
NovoPen® Junior/300 Demi*	10µL (1U)		

*NovoPen® Junior/300 Demi is no longer manufactured

[7] \\CDSESUB1\evsprod\NDA203314\0098\m1\us

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Reviewer's comment: Since the Sponsor is not planning on marketing the ½ unit pens, and in order to reduce the potential risks in patients who may require ½ dose titration of basal insulin, the reviewer suggests limiting use of the FlexTouch pen device to pediatric patients requiring above 5 units of basal insulin; this approach would be consistent with the submitted clinical trials.

U-200 FlexTouch pen

On August 11, 2016, DMEPA sent an information request which stated that there was no agreement that the adult data can be extrapolated to pediatric use from the Tresiba U-200 pen device. The Sponsor was asked to submit a comprehensive risk analysis and justification or rationale that Tresiba U-200 pen device can be used safety and effectively in pediatric patients.

On August 16, 2016 the Sponsor responded, clarifying that they conducted a comprehensive risk analysis for the PDS290 pen-injector for insulin degludec 200U/mL, including use by pediatric patients; therefore the Sponsor did not think that it was necessary to perform additional human factors validation. Please refer to the review by Sarah Vee regarding the adequacy of the human factors testing for this pen device.

Reviewer's comment: The current submission does not include any clinical data to support the use of the U-200 pen in the pediatric population. However given the efficacy and safety findings in the original NDA review and the DMEPA and CDRH review of this pen device, extrapolation to the pediatric population may be appropriate.

As discussed above, the U-200 FlexTouch pen may not be appropriate for use for younger patients, however, this device could potentially be useful for older pediatric patients with T1DM or T2DM, for whom titration by more than 2 units at a time would be acceptable,

4.2 Clinical Microbiology

There is no new information in this application that applies to this section. Refer to the original NDA review for details regarding this section.

4.3 Preclinical Pharmacology/Toxicology

Refer to the original NDA review for details regarding this section. Specific studies in juvenile animals have not been conducted given the well-known physiology and pharmacology of insulin in pediatric and adult populations.

Reviewer's comment: In previous correspondence, the Division agreed that juvenile toxicity studies were not necessary based on the animal data from the original NDAs.

4.4 Clinical Pharmacology

Please see the Clinical Pharmacology review by Dr. Renu Singh for approval recommendations.

The following section pertains to the clinical pharmacology studies in support the pediatric indication, and submitted as part of this efficacy supplement; refer to the original NDA reviews for a comprehensive review of clinical pharmacology in the Tresiba and Ryzodeg 70/30 programs respectively.

4.4.1 Mechanism of Action

The mechanism of action of Tresiba, and Ryzodeg 70/30 lowers glucose by stimulating peripheral glucose uptake by skeletal muscle and fat and by inhibiting hepatic glucose production. Insulin also inhibits lipolysis and proteolysis and enhances protein synthesis.

Degludec (for Tresiba and Ryzodeg 70/30) forms multi-hexamers when injected into the subcutaneous tissue forming a degludec depot that release slowly. The aspart component of Ryzodeg 70/30 is released rapidly into the circulation.

4.4.2 Pharmacokinetics (PK)/Pharmacodynamics (PD)

The Sponsor's clinical pharmacology program aimed to characterize the PK properties of the drug product in children and adolescents with T1DM.

Since both IDeg and IDegAsp share the "IDeg" component, the clinical pharmacology program in support of IDeg (discussed below) will also apply in support of IDegAsp. To avoid redundancy, the clinical pharmacology findings for IDeg will be discussed first, followed by the clinical pharmacology findings of IDegAsp.

IDeg and IDegAsp used in the clinical pharmacology trials were the same as the drug product used in the adult therapeutic confirmatory trials in the original NDAs.

4.4.2.1 Pediatric clinical pharmacology evaluation for IDeg

The clinical pharmacology program consisted of:

- A single-dose trial of IDeg in children/adolescents/adults (Trial 1995)[8]
- Sparse PK and PD measurements during the 26 week period of trial 3561
- PK/PD modelling analysis to develop a population PK model for IDeg in children younger than 6 years and conduct an exposure-response analysis focusing on this age group.

Pharmacokinetic analyses

Single-dose analyses

The single dose PK study in Trial 1995 shows that the prolonged PK profile of IDeg in adults was preserved in children and adolescents with type 1 diabetes. The mean PK profiles showed a greater IDeg exposure in children (6-11 years) and adolescents (12-18 years) than adults (age 18-65 years) but all groups had a similar shape of the PK profile, with a maximum concentration at 12 hours after drug administration; see Figure 1.

[8] Was a single-dose trial conducted at a single center in Germany with 13 children (6-11 years, 13 adolescents (12-17 years) and 12 adults (18-65 years) exposed to IDeg

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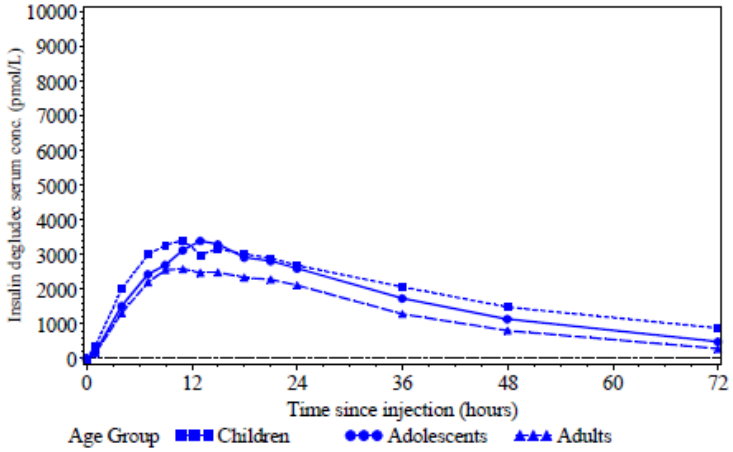
Figure 1 – Trial 1995- 72-hour mean concentration-time profiles for IDeg after single dose in children (ages 6-11 years), adolescents (12-17 years) and adult (18-65 years) subjects with T1DM



Trial 1995: 0.4 units/kg
Horizontal dashed line represents the lower limit of quantification for IAsp (10 pmol/L).
Source: 2.7.2 summary of clinical pharmacology, Figure 3-1 page 16

Statistical analysis showed that total IDeg exposure ($AUC_{IDeg,0-\infty,SD}$) was greater in children (6−11 years) and adolescents (12−17 years) compared to adults after single-dose administration; however, the difference was only statistically significant between adolescents and adults.[9] No statistically significant difference was demonstrated for $C_{max,IDeg,SD}$.[10]

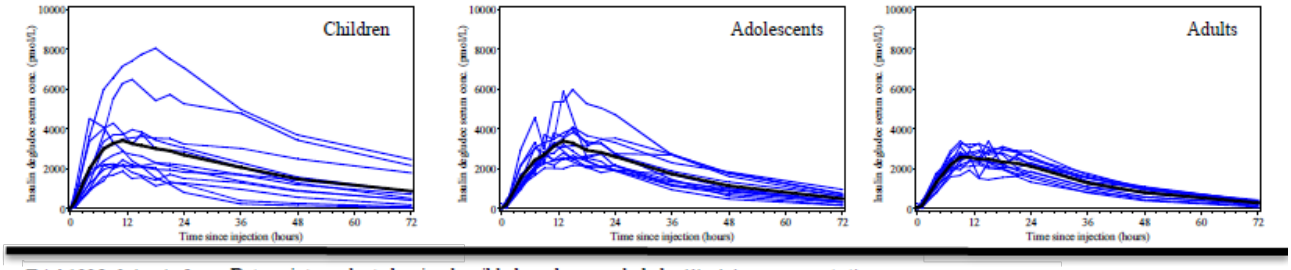
The between subject variability in the IDeg exposure was greater in children (6-11 years) and adolescents (12-17 years) compared with adults.

Reviewer's comment: it is unclear to what extent the inter-subject variability with insulin degludec affected the hypoglycemia findings seen in both studies, see discussion of hypoglycemia in section **7.3.4 Significant Adverse Events**.

[9] Total exposure ($AUC_{IDeg,0-\infty,SD}$) of IDeg tended towards being higher in children than in adults (estimated ratio (children/adults) 1.48 [0.98; 2.24]95%CI) and was higher in adolescents than in adults (1.33 [1.08; 1.64]95%CI) with T1DM after single-dose administration.
[10] Between children and adults for IDeg (estimated ration (children/adults) 1.20 [0.90; 1.60] 95%CI) or between adolescents and adults for IDeg (estimated ratio (adolescents/adults) 1.23 [1.00; 1.51] 95%CI).

Reference ID: 4009596

Figure 2 – Study 1915- 72-hour mean and compiled individual concentration-time profiles for IDeg after single dose in children (6-11 years), adolescents (12-17 years), and adults (18-65 years)

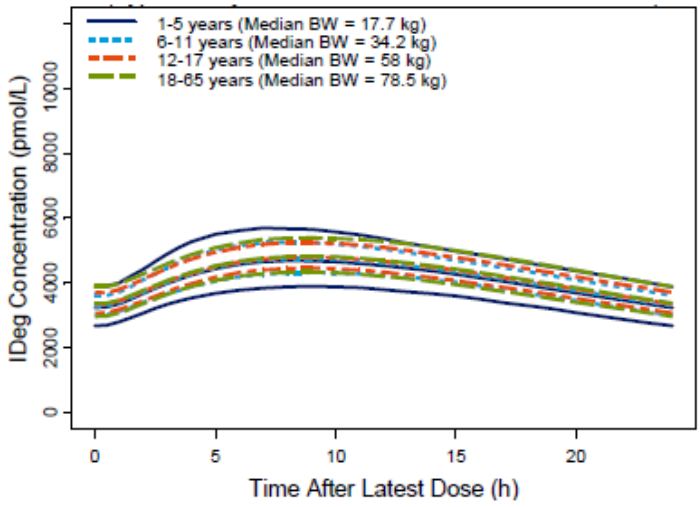


Trial 1995: 0.4 units/kg Data points evaluated as implausible have been excluded. Black line represents the mean.
Horizontal dashed line represents the lower limit of quantification for IDeg (20 pmol/L).
Source: 2.7.2 summary of clinical pharmacology, Figure 3-2 page 18

Population pharmacokinetic analyses

The population PK analysis showed that the IDeg concentration-time profile in children 1-5 years was similar to the concentration-time profiles in children 6-11 years, adolescents (12-17 years) and adults (18-65 years) when IDeg is dosed per body weight (kg). Body weight was the most important covariate. Age group was highly correlated with body weight, but was not significant by itself when body weight was included.

Figure 3 - Trial 3561- Model-derived concentration-time profiles over a 24 hour dosing interval at steady state following once daily dosing of 0.4 units of IDeg per kg body weight to a typical subject (based on median body weight) in 4 age groups



Data are medians with 95% CI obtained from the final population PK model.
BW: Body weight
Source: 2.7.2 summary of clinical pharmacology, Figure 3-3 page 19

Reviewer's comment: Although the age specific IDeg concentration-over-time in the population PD analysis appears similar, the age-specific differences may have been diminished by the scale used in the Sponsor's graph.

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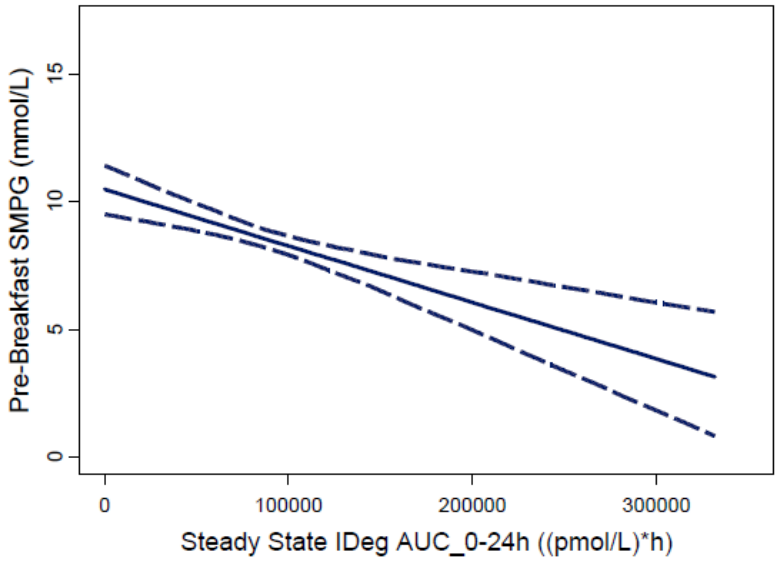
Per the Sponsor, the single dose study (Trial 1915), which showed higher exposure and variability in children and adolescents than adults, differed from the population pharmacokinetic analysis (which included data from Trials 3561 and 1995) because of the differences in numbers in each trial.[11]

Modeling derived exposure-response analyses
Data from the first 26 weeks of treatment of trial 3561 were used for an exposure-response analysis of IDeg exposure (from PK assessments to pre-breakfast SMPG levels).

The exposure-response analysis for pre-breakfast SMPG was similar across pediatric age groups. However the analysis is limited by the small changes in dose during the 26 week period and the large variability in pre-breakfast SMPG. These results also did not reflect the expected differences in insulin requirements in the different age groups, particularly during puberty (which would be expected to have higher insulin resistance and a ~40% increase of insulin). A common exposure-response relationship is shown for all age groups since age was not a significant covariate in the final model (see Figure 4). Figure 4 shows that a decrease in pre-breakfast SMPG with increasing IDeg exposure.

Figure 4 – Model-derived exposure-response relationship at steady state following once-daily dosing of IDeg for a typical subject independent of age group



Data is median with 95% CI obtained from the final exposure–response model.
Source: 2.7.2 summary of clinical pharmacology, Figure 3-4 page 21

4.4.2.1 Pediatric clinical pharmacology evaluation for IDegAsp

In addition to the pediatric clinical pharmacology studies for IDeg discussed above, the clinical pharmacology program to support use of IDegAsp in pediatrics consisted of:

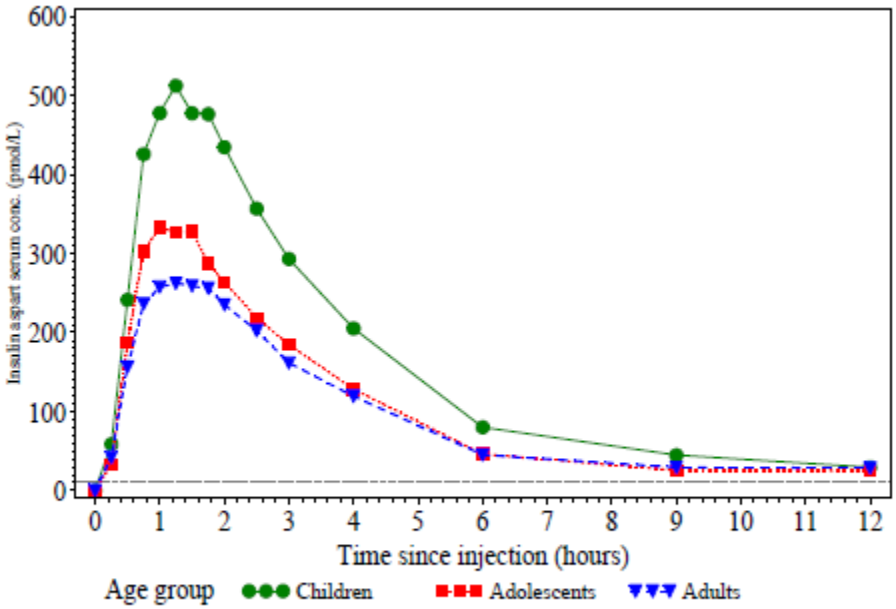
- A single-dose trial of IDegAsp in children/adolescents/adults (Trial 1982)[12]

11 Trial 1995 had 38 patients (with 12-13 patients per age group), while trial 3561 had 174 patients (with 43 to 70 patients per age group).

Pharmacokinetic properties of IAsp from IDegAsp

After a single-dose administration of IDegAsp, the rapid absorption characteristics of IAsp that was observed in adults were preserved in children and adolescents with T1DM. There was a rapid increase in the serum concentration of IAsp in all pediatric age groups with peak concentration after approximately 1.2 hours (~75 minutes). Total exposure and peak concentration of IAsp in IDegAsp were statistically significantly higher in children than in adults, but comparable in adolescents and adults (see **Figure 5**).

Figure 5 – Trial 1982- 12 hour mean concentration-time profiles for IAsp after single dose IDegAsp in children (6-11 years), adolescents (12-17 years) and adults with T1DM



Trial 1982: 0.5 units/kg IDegAsp (equal to 0.15 units/kg IAsp).
Horizontal dashed line represents the lower limit of quantification for IAsp (10 pmol/L).
Source: 2.7.2 Summary of clincal pharmacology, IDegAsp, Figure 3-1 page 20

Statistical analysis showed that the total IAsp exposure from IDegAsp ($AUC_{IAsp,0-12h,SD}$) was significantly higher in children (6−11 years) than in adults[13]; no statistically significant difference was seen between adolescents and adults.[14] The Maximum serum IAsp concentration was also significantly higher in children (6-11 years) than adults.[15]

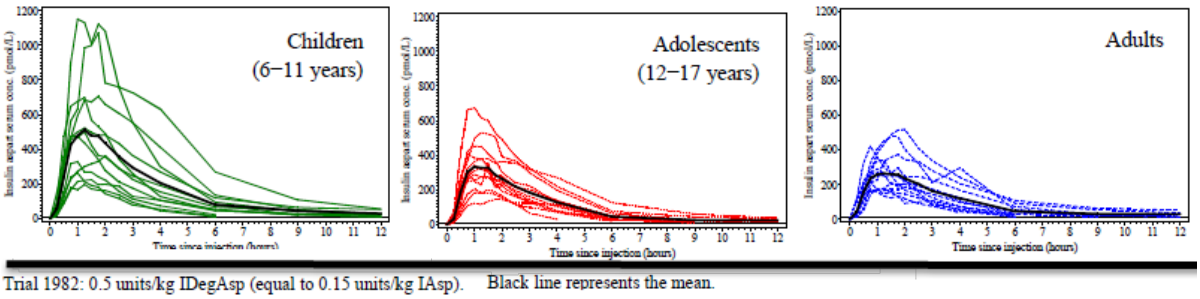
[12] In Trial 1982, a meal test was performed for all subjects in order to investigate the PD properties of IDegAsp in a clinically relevant setting. Metabolic control (blood glucose level within the target range of 89−178 mg/dL) was achieved prior to the meal test using a variable intravenous infusion of human insulin. During the meal test, plasma glucose levels were monitored using a blood glucose meter. Subjects received a single dose of 0.5 units/kg of IDegAsp (containing 0.35 units/kg of IDeg and 0.15 units/kg of IAsp) on a single occasion.
[13] Children (6−11 years) versus adults 1.69 [1.02; 2.80]
[14] Adolescents (12−17 years) versus adults
[15] Children (6−11 years) versus adults1.66 [1.10; 2.51]

Reference ID: 4009596

The between subject variability in IAsp exposure is shown in **Figure 6**. The individual variability was higher in children (6-11 years) than in adolescents or adults.

Reviewer's comment: differences in PK in adults versus children have been observed in previous studies with other insulins including studies with NPH [16], detemir, human insulin and insulin aspart [17]. Per the literature, the etiology of these observed differences in PK may arise from factors affecting the absorption/clearance of insulins as a result of differences in hormones between adults and children.

Figure 6 - Trial 1982 - 12-hour mean and compiled individual concentration-time profiles for IAsp after single dose IDegAsp in children, adolescents and adults with T1DM



Trial 1982: 0.5 units/kg IDegAsp (equal to 0.15 units/kg IAsp). Black line represents the mean.
Horizontal dashed line represents the lower limit of quantification for IAsp (10 pmol/L).
Source: 2.7.2 Summary of clincal pharmacology, IDegAsp, Figure 3-2 page 22

Pharmacokinetic properties of IDeg from IDegAsp

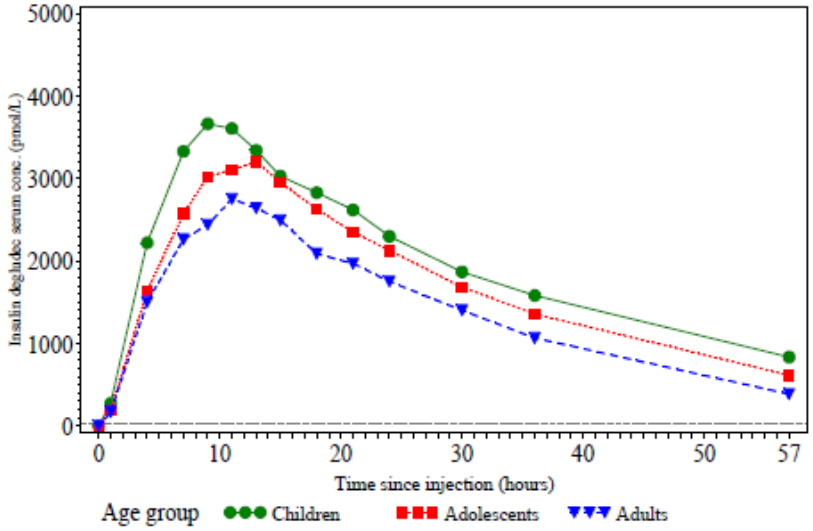
The single-dose PK study, Trial 1912, showed the prolonged PK profile of IDeg from IDegAsp in adults was preserved in children and adolescents. Mean PK profiles showed that IDeg exposure was greater in children and adolescents compared to adults but that the observed shape of the mean PK profiles was similar across the age groups, with a maximum concentration at 9 to 11 hours after product administration, see **Figure 7**.

[16] Danne T, Lupke K, Walte K, Von SW, Gall MA. Insulin detemir is characterized by a consistent pharmacokinetic profile across age-groups in children, adolescents, and adults with type 1 diabetes. Diabetes Care 2003; 6(11):3087-3092.

[17] Acerini CL, Cheetham TD, Edge JA, Dunger DB: Both insulin sensitivity and insulin clearance in children and young adults with type I (insulin-dependent) diabetes vary with growth hormone concentrations and with age. *Diabetologia* 43: 61–68, 2000

Reference ID: 4009596

Figure 7 – Trial 1982 – 57-hour mean concentration-time profiles for IDeg after single dose of IDegAsp in children (6-11 years), adolescents (12-17 years) and adults with T1DM



Trial 1982: 0.5 units/kg IDegAsp (equal to 0.35 units/kg IDeg).
Horizontal dashed line represents the lower limit of quantification for IDeg (20 pmol/L).
One subject was excluded to reflect the analysis of $AUC_{IDeg,0-\infty,SD}$ (which could not be calculated for one subject as it was not possible to determine the terminal phase).

Source: 2.7.2 Summary of clincal pharmacology, IDegAsp, Figure 3-3 page 23

The maximum serum IDeg concentration ($C_{max,IDeg,SD}$) was significantly higher in children (6−11 years) than in adults following administration of IDegAsp[18]. The total IDeg exposure from IDegAsp ($AUC_{IDeg,\ 0-\infty,SD}$) also tended to be higher in children (6−11 years) than in adults, but the difference was not statistically significant. The between subject variability in IDeg exposure was higher in children (6-11 years) than in adolescents (12-17) than adults (graphs not shown).

[18] Children (6−11 years) versus adults 1.38 [1.09; 1.76]

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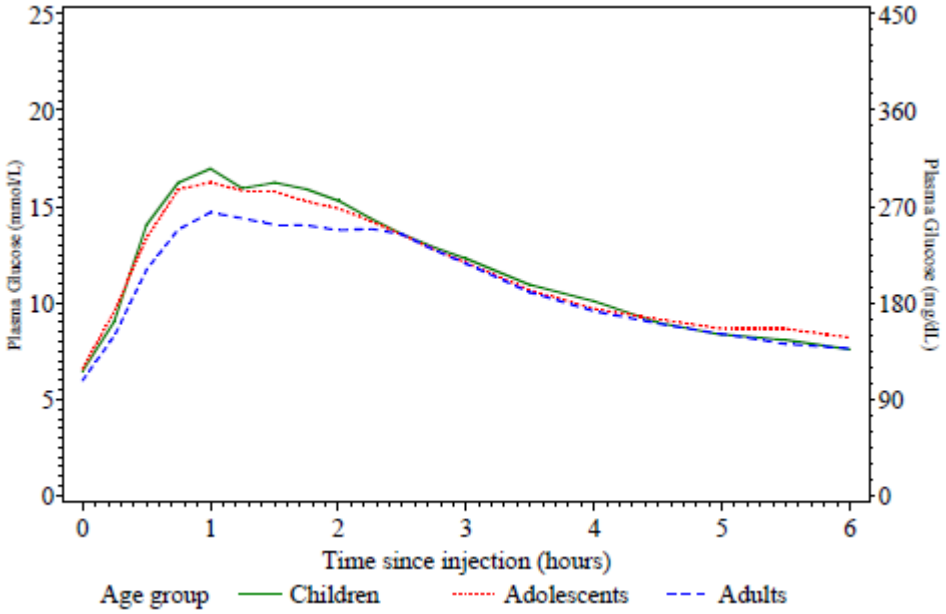
Pharmacodynamic assessment of IDegAsp

Figure 8 shows the mean plasma glucose profiles after IDegAsp administration and a standard meal by age groups. The glucose lowering effect of IDegAsp after a standard meal was comparable across age groups.

Figure 8 – Trial 1982 – Mean plasma glucose profiles, 0-6 hours for children (6-11 years), adolescents (12-17 years) and adults following single dose IDegAsp, dose adjusted by subjects' body weight



Source: 2.7.2 Summary of clincal pharmacology, IDegAsp, Figure 3-7 page 31

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

The pediatric clinical development program is shown in **Table 6.** Overall there was a clinical pharmacology, a therapeutic confirmatory trial and a PK/PD modelling analysis for IDeg and a clinical pharmacology clinical, a therapeutic confirmatory trial for IDegAsp.

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Table 6 – IDegAsp and IDeg pediatric clinical development program

Type of study	Novo Nordisk trial number	Description
Clinical trials with IDegAsp		
Clinical pharmacology trial with IDegAsp	NN5401-1982	A single-centre, single-dose, open-label trial investigating the PK and PD properties of IDegAsp in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM
Therapeutic confirmatory trial with IDegAsp	NN5401-3816	A 16-week multinational, multi-centre, randomised, open-label, two-arm, parallel group, treat-to-target, efficacy and safety trial comparing treatment with IDegAsp OD, with a main meal + IAsp for the remaining meals vs. IDet + mealtime IAsp in children and adolescents aged 1 to less than 18 years with T1DM
PK/PD modelling study		
PK/PD modelling analysis	--	A PK/PD modelling study in children aged 1 to less than 18 years, compared to adults, all with T1DM. The objectives were to develop a population PK model for IDeg in children younger than 6 years and to conduct an exposure–response analysis focusing on this age group. IDeg PK data from three trials (Trials 1982, 1995 and 3561) were combined for the population PK analysis and data from Trial 3561 were used for the exposure–response analysis
Clinical trials with IDeg		
Clinical pharmacology trial with IDeg	NN1250-1995	A single-centre, randomised, double-blind, two-period cross-over, single-dose trial investigating the PK properties of IDeg and IGlar in children (6–11 years), adolescents (12–17 years) and adults (18–65 years) with T1DM
Therapeutic confirmatory trial with IDeg	NN1250-3561	A 26-week multinational, multi-centre, randomised, open-label, two-arm, parallel group, efficacy and safety comparison of IDeg and IDet in children and adolescents aged 1 to less than 18 years with T1DM on a basal–bolus regimen with IAsp as bolus insulin, followed by a 26-week extension for further evaluation of safety and immunogenicity

IAsp: insulin aspart, IDeg: insulin degludec, IDegAsp: insulin degludec/insulin aspart, IDet: insulin detemir, IGlar: insulin glargine, OD: once daily, PD: pharmacodynamic(s), PK: pharmacokinetic(s), T1DM: type 1 diabetes mellitus.

Source: IDegAsp, Clinical overview, Table 1-1, page 14

5.2 Review Strategy

This review critically evaluates the efficacy findings from the phase 3 study for IDeg (3516) and the phase 3 study for IDegAsp (3816). Each trial was reviewed individually, and not pooled because each trial was submitted to meet an individual PMR requirement.

For clarity, headings which include the trial number and product name will be included throughout the document.

The reviewer used the information presented by the Sponsor in the individual Clinical Study Reports (CSR). Issues identified from the clinical summaries were addressed by in-depth review of the submitted narratives and datasets. Exploratory analyses carried out by the reviewer will be clearly outlined in the review.

5.3 Discussion of Individual Studies/Clinical Trials

Since there were similarities in study design, the reviewer discusses the common elements shared between trials 3561 and 3861 in the section titled **Common elements**.
The **Common elements** section will cover the following topics:

- Inclusion and exclusion criteria
- Withdrawal criteria
- Safety committees
- Dosing and titration

At the conclusion of the **Common elements** section, the reviewer discusses each trial separately emphasizing each trial's unique characteristics.

Common elements

The following inclusion and exclusion criteria were the same for both trials: **3561** and **3816**:

Common inclusion and exclusion criteria
Inclusion criteria

1. Informed consent and child assent (both obtained and signed-if possible) before any trial-related activities
2. Male or female diagnosed with T1DM (based on clinical judgment and supported by laboratory analysis as per local guidelines).
3. Age: 1 to less than 18 years of age at randomization.
4. Ongoing daily treatment with insulin (any regimen) for at least 3 months prior to Visit 1. No oral anti-diabetic drugs (OADs) are allowed.
5. Total daily dose of insulin: ≤ 2.0 U/kg.
6. HbA1c ≤ 11%.
7. Ability and willingness to adhere to the protocol including performance of 4-point and 8 point plasma glucose profiles according to the protocol (child and parent should be evaluated as a unit).

Exclusion criteria

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as randomization.
3. Girls who are pregnant, breastfeeding or intend to become pregnant.
4. Girls who have had menarche and are not using adequate contraceptive measures according to local requirements
5. Known hypoglycemic unawareness or recurrent severe hypoglycemic events as judged by the Investigator.
6. More than 1 diabetic ketoacidosis event requiring hospitalization within the last 3 months prior to Visit 1.
7. Significant concomitant disease, except for conditions associated with type 1 diabetes mellitus, which in the Investigator's opinion could interfere with the trial.
8. Mental incapacity, unwillingness or language barriers, precluding adequate understanding or cooperation (child and parent should be evaluated as a unit).
9. The receipt of any investigational drug within 1 month prior to Visit 1.

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10. Suffer from a life threatening disease (e.g. malignant cancer).

Reviewer's comment: Inclusion and exclusion criteria and their rationale are acceptable. Exclusion criteria attempt to limit risk of patients and exclude patients with advanced comorbid conditions. In particular, the exclusion of patients with known hypoglycemic unawareness may limit the interpretation of the hypoglycemia findings to patients with less severe disease.

Common withdrawal criteria
The following withdrawal criteria were the same for both trials 3561 and 3816:

Withdrawal criteria
The subject may withdraw at will at any time. Subjects who were withdrawn after randomization were not to be replaced. A withdrawn subject should be called in for the end of treatment visit and if possible for the follow-up visit 7−12 days after last treatment.

A subject must be withdrawn for the following:

- The subject, the parent(s) or legal representative of the subject withdraws informed consent.
- Investigator decision to withdraw subject from the trial due to a safety concern or if judged noncompliant with trial procedures.
- Randomized in error (not fulfilling the inclusion and/or exclusion criteria).
- Pregnancy or intention of becoming pregnant.
- Participation in other intervention trials throughout the trial.
- Development of any life threatening disease (e.g. cancer).
- Initiation or significant change of any systemic treatment which in the Investigator's opinion could interfere with glucose metabolism (inhaled corticosteroids are allowed).

Trial 3561 had additional withdrawal criteria, related to unacceptable hyperglycemia (which trial 3816 did not have); refer to the specific trial for details.

Safety committees
For both trials there was an external unblinded Data Monitoring Committee (DMC) which was established to independently review and evaluate accumulated safety data in order to protect the safety of the subjects, and to evaluate the evolving risk-benefit.

Both trials also had an internal Novo Nordisk A/S safety committee which performed ongoing blinded safety surveillance, which included monitoring of blinded laboratory data.

SMPG measurements
For both trials, the subjects were supplied with glucose meters and test strips. The glucose meters were calibrated to plasma glucose.

Commonalities in Dosing
Investigators were to be in contact with the subjects, at least once weekly to discuss glycemic control, hypoglycemic episodes and assist subjects in adjusting the insulin doses.

During the trial, members of the Novo Nordisk Insulin Titration Group or designated persons from Novo Nordisk's affiliates visited the sites/Investigators to discuss progress in glycemic control and titration of the individual subjects. This discussion was done in a blinded manner, i.e. without knowing the specific treatment.

During the trial, HbA1c was monitored by a Novo Nordisk representative for titration surveillance purpose and was used for discussions with the Investigator, both on a site level as well on an individual subject level.

Injection area
The site of injection was similar for both studies.
IDeg (for trial 3561) and IDegAsp (for trial 3816) were to be injected subcutaneously into the thigh, upper arm (deltoid) or abdomen.

In both trials, IDet and IAsp were to be administered according to local labeling.

Injection site was to remain unchanged, but rotation was recommended.

For injection time and dose selection refer to specific trial.

Titration of basal insulins
It was recommended that subject/investigators follow titration algorithm. If there was deviation from the algorithms, reason had to be documented in eCRF (electronic case report form). The investigator had to document within 24 hours (on weekdays) after subjects visit, the SMPG values and insulin doses for the previous 3 days[19].

Surveillance of insulin titration was performed centrally by Novo Nordisk personnel not otherwise involved in the trial. Significant deviations from the titration algorithm were to be followed up.

Titration of investigational product:
The following titration approach (in **Table 7**) applied to the basal insulin in both trials. The fasting glycemic goal was 90-145 mg/dL. Titration of IDeg, IDegAsp and IDet doses was done by ½ units for doses less than 5 units, by 1 unit for doses between 5-15 units; and by 2 units for doses >15 units.

Titration was to be done according to the lowest pre-breakfast SMPG value measured on the three days prior to the visit/phone contact.

For IDet BID: the morning dose adjustment was based on the lowest pre-dinner SMPG value measured on the three days prior to the visit/phone contact. The evening dose of IDet was determined by the lowest pre-breakfast SMPG value measured three days prior to the visit/phone contact[20].

[19] The Sponsor had to record: the following information for the 3 days prior to the visit: Pre-breakfast, pre-lunch, pre-main evening meal and bedtime plasma glucose values; last insulin doses taken prior to visit/phone contact; new insulin doses prescribed after titration; reason for deviation from the titration algorithm, if applicable.
[20] Information obtained in IR response dated 22 June 2016

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Specific to trial 3816, the IDegAsp dose could be switched from one meal to another for safety or efficacy reasons at the investigator's discretion.

Reviewer's comment: Currently, the Ryzodeg 70/30 PI states that "In patients switching from a multiple daily injections regimen that includes a basal and short-and rapid-acting insulin at mealtimes, start Ryzodeg 70/30 once daily with the main meal at the same unit dose as the basal insulin." Language in line with the design of study 3816, specifying that IDegAsp may be switched to another meal for safety issues could be potentially added for pediatric patients.

Table 7- Titration scheme for both trials: study 3561 adjustment of IDeg and IDet; study 3816 - adjustment of IDegAsp and IDet;

Current dose		**< 5U**	**5-15U**	**> 15U**
Pre-breakfast or pre-dinner plasma glucose		Adjustment (U)		
mmol/L	mg/dL			
< 5.0	< 90	-½	-1	-2
5.0-8.0	90-145	0	0	0
8.1-10.0	146-180	+½	+1	+2
10.1-15.0	181-270	+1	+2	+4
> 15.0	> 270	+1½	+3	+6

Source: CSR 3561, Table 9-2, page 58

Titration of IAsp (sliding scale or carbohydrate counting)
Titration of IAsp was done weekly using a sliding scale or carbohydrate counting. The adjustments based on the sliding scale included adjustments based on the lowest of the 3 premeal and bedtime SMPG measures in the 3 days prior to visit/contact were evaluated for titration (as per **Table 8** and **Table 9**)[21].

Reviewer's comment: the protocol did not specify if any patients had to remain with either the sliding scale or carbohydrate counting method throughout the trial.

Table 8- Study 3561– Adjustment of IAsp

Current bolus dose		**≤ 5U**	**> 5U**
Lowest pre-meal or bedtime plasma glucose		Adjustment (U)	
mmol/L	mg/dL		
< 5.0	< 90	-1	-2
5.0-8.0	90-145	0	0
8.1-10.0	146-180	+½	+1
10.1-15.0	181-270	+1	+2
> 15.0	> 270	+1½	+3

Source: Protocol 3861, Appendix C, Table 4-2, page 9; protocol 3816, Appendix A, Table 3-2, page 9.

Titration of IAsp using carbohydrate counting and correction factor for IAsp dose:

[21] Pre-breakfast IAsp was adjusted according to lowest SMPG measured pre-lunch; pre-lunch IAsp, was adjusted according to lowest SMPG measured before main evening meal; before main evening meal IAsp was adjusted according to lowest SMPG measured at bedtime

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- This method was applicable to subjects and care takers who had prior hands-on experience with this method. At Visit 2, the investigator had to ensure that the subject was adequately educated and comfortable with this method.
- The subject's insulin/carbohydrate ratio had to be recorded at trial start and could be adjusted at the discretion of the Investigator based on the subjects SMPG measurements. A sample of initial plasma glucose correction factors and insulin carbohydrate ratios are shown in **Table 9.**

Table 9 – Plasma glucose correction factors and insulin/carbohydrate ratios

Age group	Plasma glucose correction factor	Insulin/carbohydrate ratio
Infant/Toddler	1U:15 mmol/L (270 mg/dL)	1U:60g
Pre-Pubertal	1U:10 mmol/L (180 mg/dL)	1U:45g
Early Puberty	1U:5 mmol/L (90 mg/dL)	1U:15 g
Older Adolescent	1U:2.5 mmol/L (45 mg/dL)	1U:10g

Source: Protocol 3861, Appendix C, Table 4-3, page 10; Trial 3816 Protocol, Appendix A, Table 3-3, page 10

- Subjects (parents/care-providers) were to calculate the dose of insulin needed based on their SMPG measurement, insulin/carbohydrate ratio, correction factor and carbohydrate content of their meal.[22]

Of note, an extra IAsp dose was allowed. No dose adjustment recommendations were provided for this dose. The dose was to be entered in the diary as "extra insulin" dose.

Assessment of treatment compliance
The Investigator emphasized adherence to trial procedures at each visit. The Investigator was to assess the compliance of the subject at each visit based on a review of glycemic control, adherence of the visit schedule, completion of the subject's diary including the SMPG profiles. Substantial failure to comply with the insulin regimen could lead to withdrawal.

Commonalities in definitions of analysis sets
Both trial 3561 and 3816 defined analysis sets based on the ICH-E9 guidance. Randomized subjects who were lost to follow up and where no exposure information of the trial product or its comparator is available after randomization was to be handled as unexposed.

Reviewer's comment: The handing of randomized patients that were lost to follow up as unexposed is probably reasonable for the safety analyses. For the efficacy evaluation, typically ,all randomized subjects are analyzed regardless of exposure.

Both trials had the same definitions for the Full Analysis Set (FAS) and the Safety Analysis Set (SAS), and differed in the definition of the Per Protocol analysis set; see below.

- Full Analysis Set (FAS): includes all randomized subjects. In exceptional cases subjects from the FAS could be eliminated. In such cases the elimination was justified and documented. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and subjects contributed to the evaluation "as-randomized".

[22] Dose of IAsp = grams of carbohydrate in meal/(insulin/carbohydrate ratio) ; Dose of IAsp to correct pre-prandial glucose = (Actual plasma glucose- target plasma glucose)/ plasma glucose correction factor

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- Safety Analysis Set (SAS): includes all subjects receiving at least one dose of the trial product or its comparator. Subjects in the safety set contributed to the evaluation "as-treated".

For details regarding Per-Protocol analysis sets (PP), primary, secondary efficacy and safety endpoints refer to the individual study sections.

Study NN1250-3561 (IDeg)

The Sponsor submitted one new phase 3 trial as evidence of efficacy of IDeg in T1DM pediatric patients. The information pertaining to this study is summarized below.

There were 8 total amendments to the protocol, two amendments occurred prior to trial initiation; four amendments were specific to individual countries; only one amendment was considered important by this reviewer (described below).

Amendment #3- Described and clarified the endpoints measured in the extension period of the trial. Measurement of insulin antibodies (IDeg specific, IDet specific, IAsp specific and antibodies cross-reacting to human insulin) after 26 weeks and 52 weeks of treatment. [23]

Title: A trial investigating the efficacy and safety of insulin degludec in children and adolescents with type 1 diabetes mellitus (A 26-week, Multinational, Multi-centre, Open-Labelled, Randomized, Parallel, Efficacy and Safety Comparison of Insulin Degludec and Insulin Detemir in children and adolescents 1 to less than 18 years with type 1 Diabetes Mellitus on a basal-bolus regimen with insulin aspart as bolus insulin, followed by a 26- week extension investigating long term safety.)

Sites: The trial was conducted at 72 sites in 12 countries as follows: Bulgaria (2), Finland (5), France (4), Germany (3), Italy (2), Japan (15), Netherlands (5), Republic of Macedonia (2), Russian Federation (6), South Africa (2), United Kingdom (4), and United States (22).

Dates conducted: 16 January 2012 to 08 February 2013

Design: This was a 26-week, open labelled, randomized (1:1), multinational, multi-center, two arm parallel group, treat to target, safety and efficacy trial comparing IDeg with insulin detemir (IDet) as basal insulin in combination with insulin aspart (IAsp) as bolus insulin in subjects with T1DM between 1 and less than 18 years of age, followed by a 26-week extension investigating long term safety and immunogenicity.

Subjects: For inclusion, exclusion and withdrawal criteria refer to **Common elements** section.

Study procedures and visits:
For subjects who only completed the main period (26 weeks of treatment) the duration was approximately 29 weeks. For subjects who continued into the extension period, the duration of the trial was approximately 57 weeks. Visits included on site and phone visits, see **Figure 9**.

[23] Substantial amendment 3 was not approved in South Africa due to administrative delay and therefore subjects in South Africa could not continue into the extension period of the trial

Figure 9 – Trial 3561- trial visits- main period

Trial NN1250-3561 – Type 1	Screen	Rand	0-26 weeks								FU						FU
Visit Number (V)	V1	V2	V3	V4	V6	V10	V14	V18	V23	V28	V29	V30	V36	V42	V49	V56	V57[16]
Phone Contact number (P)[1] (For details see separate flow chart)					P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	P19 P20 P21 P22	P24 P25 P26 P27			P31 P32 P33 P34 P35	P37 P38 P39 P40 P41	P43 P44 P45 P46 P47 P48	P50 P51 P52 P53 P54 P55		
Time of visit (weeks)[2]	-2[3]	0[3]	1	2	4	8	12	16	21	26	27[4]	26[15]	32	38	45	52	53
Visit window (days)			±3	±3	±3	±3	±3	±3	±3	±3	+5	±3	±3	±3	±3	±3	+5

1. A phone contact may be converted to a site visit, if needed
2. Time of visit is always calculated in relation to the actual date of the randomisation visit (Visit 2)
3. Randomisation should take place as soon as all screening (including laboratory) results are available, reviewed and the subject is confirmed eligible and no later than 14 days after visit 1.
4. Follow-up visit (Visit 29) must take place no earlier than 7 days after the actual date of the last treatment visit (Visit 28).

- **Screening visit (Visit 1)** - Enrolled subjects were supplied with a glucometer and instructions of use. Informed consent, demography information (including diabetes history and doses of treatment) were recorded. Physical exam and safety laboratories were drawn, including HbA1c. Re-screening failures were allowed once within the limits of the recruitment period.

- **Randomization visit (Visit 2) -** Inclusion and exclusion criteria were reviewed as well as concomitant medications. HbA1c and lipids were drawn. Subjects were administered drug product.
- **Main study visits Visit 3-Visit 29 -** For the main trial, key visits took place at week 0, 12, and 26 (Visit 2, 14 and 28 respectively) where assessments for primary and secondary endpoints were done.

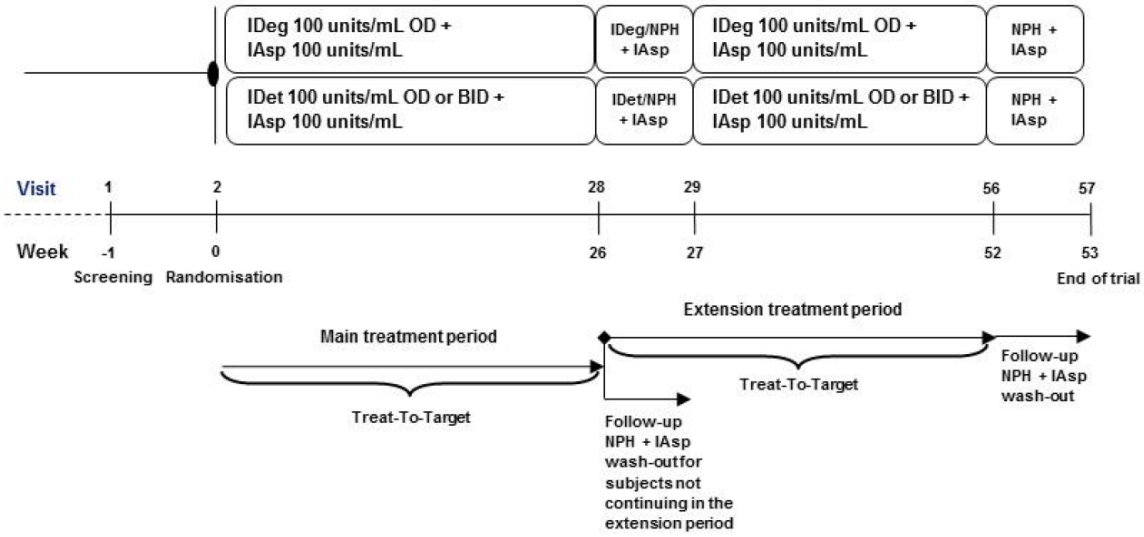
  At Visit 3, information on first date and dose on trial insulin (IDeg 100 U/mL or IDet 100 U/mL) was recorded. All subjects were instructed to record the date and doses of the insulin administered on 3 consecutive days immediately prior to each visit/phone contact throughout the treatment period (Visit 3-28) in the diary.

  At the last treatment visit, information on last date and dose on basal trial insulin was to be recorded. Subjects not continuing in the extension trial were to be switched to insulin NPH for the wash-out period between Visit 28 and Visit 29. Doses of insulin NPH were to be entered in the Visit 29 diary. At Visit 29 treatment was switched to a suitable marketed product at the Investigator's discretion.

- **Extension period -** Subjects continuing in the extension trial continued directly into Visit 30 where informed consent and assent forms were collected prior to starting extension period. Subjects were to continue the 6 month extension period according to the treatment allocation in the main period.

Reference ID: 4009596

Figure 10- Study 3561- Study Design



BID: twice daily, IAsp: insulin aspart, IDet: insulin detemir, IDeg: insulin degludec, OD: once daily, NPH: neutral protamine Hagedorn

Source: clinical overview trial 3861, Figure 4-1, page 21

Inclusion and exclusion criteria

Refer to section **Common elements** for inclusion and exclusion criteria. The following additional criteria were specific to study **3561:**

- Use of antidiabetic treatment during the treatment period other than the ones permitted by the protocol.
- Unacceptable hyperglycemia: at and after week 12, the subject must be withdrawn if there is:
  - No reduction in HbA1c **AND**
  - Three pre-breakfast SMPG readings higher than 14 mmol/L (250 mg/dL) within a two week period and FPG measured at the central laboratory exceeds 14 mmol/L (250 mg/dL) **AND**
  - There is no treatable cause for the hyperglycemia

The following investigational products were used in this trial:

- Insulin degludec 100 U/ml, Penfill 3 ml cartridge
- Insulin detemir (Levemir) 100 U/ml, Penfill 3 ml cartridge

Devices which permit 0.5 Unit dosing increments were used. For specific pen devices used with these cartridges refer to **.**

<u>Insulin dosing and Titration:</u>

All subjects received therapy with:

- IDeg once daily (QD) + meal time IAsp
- IDet once daily or twice daily (BID) + IAsp

Injection time:

- IDeg should be given once a day approximately at the same time of day
- IDet should be given QD or BID as per local labelling. If on BID regimen, should dose at breakfast and with the main evening meal or at bedtime.
- IAsp should be given immediately before meals (2-4 times daily)

Reviewer's labeling comment: The approved Tresiba PI dosing is different from the dosing used in the Phase 3 pediatric trials. The approved Tresiba PI states: "Inject TRESIBA subcutaneously once-daily at any time of day" and to "ensure that at least 8 hours have elapsed between consecutive TRESIBA injections."

Given the findings of the increased risk of hypoglycemia for IDeg (when compared to IDet), see section 7.3.4 Significant Adverse Events*; the reviewer does not believe that "flexible" dosing (as currently labeled for use in adult patients) is appropriate for pediatric patients. Instead, the injection time should be the same as what was evaluated in the pediatric trial, once a day, "approximately at the same time of day."*

Dose selection:
At randomization (Visit 2), the Investigator switched subjects to IDeg or IDet from their previous insulin dose (the protocol does not specify beyond stating "previous insulin dose," as to whether the dose refers to the screening or randomization dose); adjusting the bolus-basal ratio to either 50:50 or 70:30 at the Investigator's discretion as per **Table 46** (in appendix)**.** There were no specific recommendations regarding adjustments of the total insulin doses upon switching to trial product (i.e. there was no decrease in dose recommended).

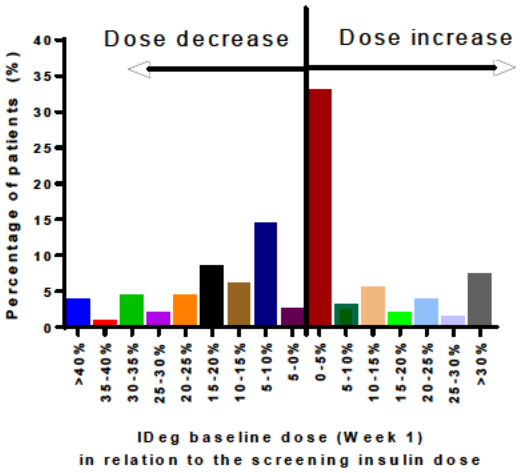
Reviewer's comment: The Sponsor does not provide a rationale for the two ratios (i.e. 50:50 or 70:30) used in the protocol.

Subjects on IDet QD were changed to BID if the mean pre-breakfast plasma glucose (PG) reached 90-145 mg/dL and mean pre-dinner PG >145 mg/dL. The start of the second dose of detemir should be 2-4 U.

Reviewer's labeling comment: in an information request, the Sponsor was asked to justify the starting dose in the pediatric trials, since the instructions for the starting dose in the approved PI for patients already on insulin are to "Start TRESIBA at the same unit dose as the total daily long or intermediate-acting insulin unit dose."

In an information request, dated August 18, 2016, the Sponsor stated that the difference in mean daily basal dose between baseline and screening for IDeg was 0.03 units/kg (1.24 units or less). Approximately 1/3 of patients started IDeg at the same unit dose as the pre-randomization total daily basal insulin dose, consistent with the proposed Physician Insert. Figure 11 *shows the relationship between the IDeg dose at baseline when compared to the screening dose. As can be seen, the majority of patients had a slight/increase in IDeg starting dose at week 1, from the baseline basal insulin dose.*

Figure 11 – Trial 3561 – Changes to the baseline (week 1) IDeg dose in relation to the screening basal insulin dose -safety analysis set



Source: Information request dated 17 August 2016, IR \\CDSESUB1\evsprod\NDA203314\0093\m1\us, reviewer generated graph of Table 5

Given the trends in starting dose in this trial, and the increased trends of hypoglycemia in the first month of switching to IDeg, (as discussed in section **7.3.4.1 Hypoglycemia - Trial NN1250-3561(IDeg)***) I would recommend a decrease in basal insulin dose when converting to IDeg.*

At randomization the subject switched to IAsp from previous bolus insulin. The dose of IAsp was as per **Table 46.** The total dose could be divided into 2 to 4 daily doses.

At the washout period, the total daily basal dose at the end of the treatment period was reduced by 20% and was administered as NPH in the morning and evening.

Titration and assessment of compliance
See **Common elements** for details regarding titration

Definitions of analysis sets
Refer to section **Common elements** for definition of the FAS and SAS. The PP analysis set is shown below.

- Per Protocol (PP) Analysis Set: Includes subjects without any major protocol violations that may affect the primary endpoint. Subjects should be exposed for more than 12 weeks and have a valid assessment after 12 weeks of exposure necessary for deriving the primary endpoint. Subjects in the PP set contribute to the evaluation "as treated." Subjects must have a non-missing HbA1c at screening or at randomization.
- Extension trial set (ETS): defined as subjects who consented to participate in the extension trial period and had received at least 1 dose of trial product in the extension period.
- Completer analysis set (CAS): defined as subjects who completed the 52-week trial and had a valid (not imputed) measurement on the last scheduled visit for HbA1c assessment.

Endpoints:
Only endpoints derived after 26 weeks of treatment were to be analyzed statistically; after 26 weeks descriptive statistics were presented based on observed and LOCF imputed data. All efficacy endpoints were summarized and analyzed based on the full analysis set (FAS) of all randomized subjects, following the intention-to-treat principle with subjects contributing to the evaluation 'as randomized'. Missing values (including intermittent missing values) were imputed using the last observation carried forward (LOCF) method.

Primary efficacy endpoint:
The primary endpoint was the change from baseline in centrally measured HbA1c (%) after 26 weeks of treatment.

The primary endpoint was analyzed using the variance (ANOVA) method with treatment, sex, region and age group as fixed factors and baseline HbA1c as covariate.

Region is a factor with four levels: 1. Europe (including Russia), 2.United States (US), 3. Japan, 4. South Africa.

Age group is a factor with the following three levels:
- 1 to less than 6 years of age
- 6 to less than 12 years of age
- 12 to less than 18 years of age

The primary objective was the demonstration of non-inferiority of IDeg +mealtime IAsp vs. IDet + mealtime IAsp.
- Non-inferiority was confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4% or equivalent if the p-value for the one-sided test of H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$, is less than or equal to 2.5%, where D is the mean treatment difference (IDeg minus IDet).

If non-inferiority was confirmed, the superiority of IDeg + mealtime IAsp over IDet + mealtime IAsp was investigated. Superiority was confirmed if the upper bound of the two-sided 95% confidence interval, which is calculated using the FAS, is below 0%.

Of note, the Sponsor justifies the use of the non-inferiority margin of 0.4% (absolute), in accordance with the Food and Drug Administration (FDA) guidance.

Sensitivity Analysis
The sensitivity analyses were repeated for the following analyses sets:
- Per Protocol (PP) analysis set
- Set of all completed subjects
- Full analysis set
    - Analyzed in a linear mixed model using an unstructured residual covariance matrix (if possible) and compared to the results of the LOCF analysis
    - Model with treatment as the only fixed factor and baseline HbA1c as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates

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Post hoc sensitivity analyses included multiple imputation and tipping point analyses for change in HbA1c after 26 and 52 weeks.

Secondary efficacy endpoints:
There were no confirmatory secondary endpoints that were adjusted for multiplicity.

The following were secondary endpoints were analyzed for both 26 and 52 weeks:

- Change from baseline in centrally measured HbA1c (%) after 52 weeks of treatment (analyzed by central laboratory)[24]
- Change from baseline in centrally measured Fasting Plasma Glucose (FPG)[25] (analyzed by central laboratory)
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustments
    - Mean plasma glucose (PG) before breakfast[26]
    - Within-subject variability as measured by the CV%[27]
- SMPG measurements (8-point profiles)[28]
    - 8-point profiles
    - Mean of the 8-point profiles
    - Fluctuation in the 8-point profiles
    - Prandial PG increment from 8-point profiles

Nocturnal increments of 8-point SMPG were summarized descriptively.

Additional *post hoc* sensitivity analyses were also conducted for FPG after 26 and 52 weeks.

Safety endpoints:
See **Table 10** for the safety endpoints assessed at baseline and at 26 and 52 weeks.

Safety endpoints were summarized using the SAS. Statistical analyses of safety endpoints were based on the FAS. In addition to the comparison between the two treatment groups, results were presented across age groups by treatment using descriptive statistics.

[24] Change from baseline in HbA1c after 52 weeks of treatment was analyzed for the ETS and the CAS analyses sets.
[25] Change from baseline in FPG after 26 weeks and 52 weeks of treatment will be analyzed separately using an ANOVA method with treatment, sex, region and age group as fixed factors and baseline FPG as covariate
[26] The mean of before breakfast PG values after 26 weeks and 52 weeks of treatment will be analyzed separately using an ANOVA method with treatment, sex, region and age group as fixed factors and the corresponding mean PG at baseline as covariate
[27] Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance σ^2 as $CV\% = 100\sqrt{(\exp(\sigma^2 - 1))}$. The confidence interval for the CV ratio between treatments will be calculated using the delta method.
[28] A mixed effect model will be fitted to the 8-point profile (SMPG) data after both 26 weeks and 52 weeks of treatment (analyzed separately). The model will include treatment, time, interaction between treatment and time, sex, region and age group as fixed factors and the values from the profile at baseline as covariate and subject as random effect. From this model, mean profile by treatment and relevant treatment differences will be estimated and explored. Mean and fluctuation in the 8-point profile (SMPG) and prandial PG increments after 26 weeks and 52 weeks of treatment will be analyzed separately using an ANOVA method with treatment, sex and region and age group as fixed factors and the relevant baseline value as covariate. Fluctuation in the 8-point profile (SMPG) will be logarithmically transformed before analyzed.

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Table 10 – Safety endpoints for trial 3561

Safety endpoints	Details
Incidence of treatment emergent adverse events (TEAEs)	
Hypoglycemia^ Number of the following TEAEs:	• confirmed hypoglycemic episodes (<56 mg/dL) or severe hypoglycemia • *nocturnal* [11 p.m. – 7 a.m. inclusively]confirmed hypoglycemic episodes (<56 mg/dL) or severe hypoglycemia • hypoglycemic episodes (PG≤ 70 mg/dL) with or without symptoms of hypoglycemia • *nocturnal* [11 p.m. – 7 a.m. inclusively] hypoglycemic episodes (PG≤ 70 mg/dL) with or without symptoms of hypoglycemia
Hyperglycemia Number of:	• Self-measured glucose >200 mg/dL • Self-measured blood ketones > 1.5 mmol/L for SMPG measures >250 mg/dL$^{\sigma}$
Change from baseline in **central laboratory assessments**	• Hematology $^{\sim}$ • Biochemistry$^{\$}$ • Lipid profile$^{€}$ • Insulin doses $^{\Omega}$ • Body weight and BMI • Vital signs • Physical examination$^{\infty}$
Insulin antibodies	• Insulin degludec specific, insulin detemir specific, insulin aspart specific and antibodies cross-reacting to human insulin. The antibody measurement was preceded by a washout period of one week, where the patient was switched to insulin NPH
^ refer to section 7.3.4 Significant Adverse Events for definitions of hypoglycemia $^{\sigma}$ all ketone measurements were self-measured $^{\sim}$hemoglobin, hematocrit, erythrocytes, thrombocytes and leucocytes $^{\$}$creatinine, ALAT, ASAT, alkaline phosphatase, sodium, potassium, albumin and total bilirubin) $^{€}$cholesterol, HDL and LDL $^{\Omega}$Units/day and Units/kg/day both for total, basal and bolus $^{\infty}$Physical exam will include: head, ears, eyes, nose, throat and neck, respiratory system, cardiovascular system, gastrointestinal system including mouth, musculoskeletal system, central and peripheral nervous system, skin	

Of note, *after* data base lock, the following post-hoc analyses were performed:

- Evaluation of the number of confirmed and nocturnal confirmed hypoglycemic episodes after 16 nominal weeks of treatment. This analysis was performed to explore the event rate of hypoglycemic episodes in the maintenance period.[29]
- Evaluation of the standard deviation scores for body weight (SD scores) in order to compare the body weight in the various age groups.[30] The SD scores were derived from the age and sex of the subjects and the body weight together with growth curves defined for reference population of each country. For countries with no reference values, the reference values for the US were used.[31]

[29] The statistical analysis was based on a negative binomial regression model with a log-link function and the logarithm of the exposure time after week 16 as offset. The model included treatment, sex, region and age group as fixed factors. Of note this analysis was not documented in the protocol amendment or SAP, but is noted in the CSR.
[30] Change from baseline in SD scores for body weight after 26 weeks of treatment was analyzed using an ANOVA method with treatment, sex, region and age group as fixed factors and baseline value as a covariate
[31] Bulgaria, Finland, Macedonia, Netherlands, Russia and South Africa

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Sample size calculation:
Sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in children and adolescents with type 1 diabetes treated with insulin, a conservative estimate for the standard deviation (SD) of 1.25% for HbA1c was used in the sample size calculation. [32]

The total number of randomized subjects is to be at least 346 subjects in order to have at least 80% power in the evaluation of the PP analysis set.[33]

Study NN5401-3816 (IDegAsp)

The Sponsor submitted one new phase 3 trial as evidence of efficacy of IDegAsp in T1DM pediatric patients. The information pertaining to this study is summarized below.

There were 2 total global amendments to the protocol (described below).

Amendment1- The protocol was updated upon request from FDA; the MMRM method (applied on non-imputed data) was used instead of the ANOVA method (applied to imputed data by use of LOCF) for analysis of continuous endpoints. Furthermore, the blood volume needed for blood sampling in the age group below 6 years was updated to a smaller volume due to a miscalculation.

Amendment 2 - global amendment corrected error corrected regarding definition of the Full Analysis Set (FAS).

Title: A trial investigating the efficacy and safety of insulin degludec/insulin aspart once daily plus insulin aspart for the remaining meals versus insulin detemir once or twice daily plus meal time insulin aspart in children and adolescents with type 1 diabetes mellitus.

Sites: 63 sites in 14 countries as follows: Belgium: 3 sites; Brazil: 1 sites; Canada: 3 sites; Czech Republic 3 sites; Croatia: 2 sites; Israel: 6 sites; Macedonia: 2 sites; Poland: 3 sites; Russian Federation: 5 sites; Serbia: 4 sites; Slovenia: 1 sites; South Africa: 2 sites; Spain: 5 sites; and Unites States: 23 sites.

Dates conducted: 17 October 2013 to 7 November 2014

Design: This was a 16-week multi-national, multi-centre, open-label, two-arm, parallel group, randomized (1:1), treat-to-target (T-T-T), efficacy and safety trial comparing treatment with IDegAsp OD, with a main meal + IAsp for the remaining meals vs. IDet + meal-time IAsp in children and adolescents with T1DM between 1 and less than 18 years of age.

[32] The standard deviation of 1.25% used in the sample size calculation was based on results from two previous pediatric trials with insulin detemir (Trials NN304-1379 and NN304-1689. In NN304- 1379 the SD was 0.95% for HbA1c (%) after 26 weeks of treatment in children with age ranging from 6 to 18 years. In NN304-1689, the SD was 1.13 % HbA1c (%) after 52 weeks in children with age ranging from 2 to 16 years. In both trials the drop-out rate was below 9% and of similar magnitude in the two treatment arms.
[33] In previous phase 3 trials, in insulin treated children and adolescents with type 1 diabetes, less than 9% of the randomized subjects were excluded from the PP analysis set. In this trial, an estimate of 10% will be used and sample size is capped in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (1:1).

Reference ID: 4009596

Subjects:
For inclusion, exclusion and withdrawal criteria refer to Common elements**.**

Study procedures and visits:
Visits included in site and phone visits, see the figure below. There were a total of 9 clinic visits and 10 phone contacts.

Figure 12 – Trial 3816- trial visits

Trial NN5401-3816 – Type 1	Screen	Rand	16 weeks						Follow up
Visit Number (V)	V1	V2	V3	V4	V6	V10	V14	V18	V19[3]
Phone Contact number (P) (For details see separate flow chart)					P5	P7 P8 P9	P11 P12 P13	P15 P16 P17	
Time of visit (weeks)[1]	-1[2]	0	1	2	4	8	12	16	17
Visit window (days)	-7/+3		±3	±3	±3	±3	±3	±3	+5

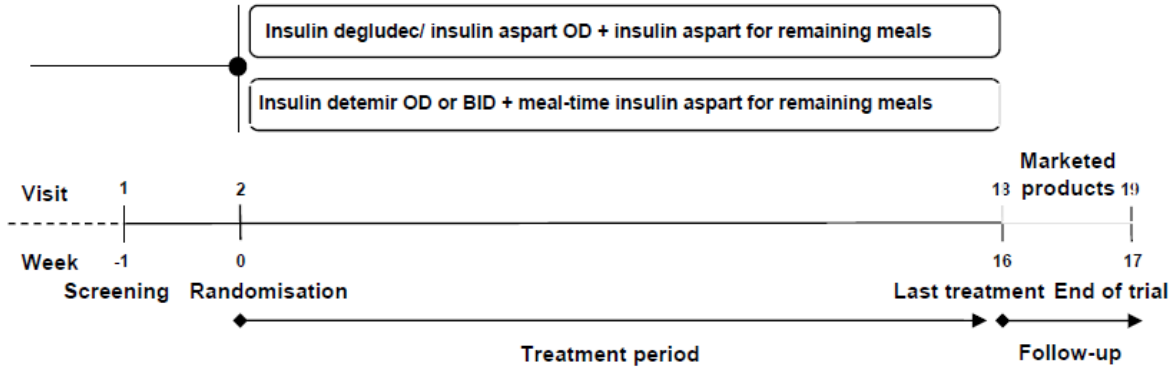
1. Time of visit is always calculated in relation to the actual date of the randomisation visit (Visit 2)
2. Visit 1 may take place no earlier than 14 days and no later than 4 days prior to randomisation
3. Follow-up visit (Visit 19) should take place 7-12 days after the last treatment visit (Visit 18)

- **Screening visit (Visit 1)** - Enrolled subjects were supplied with a glucometer and instructions for use. Informed consent, demography information (including diabetes history and doses of treatment) were recorded. Physical exam and safety laboratories were drawn, including HbA1c. Re-screening failures were not allowed for this trial.
- **Randomization visit (Visit 2) -** Inclusion and exclusion criteria were reviewed as well as concomitant medications. HbA1c and lipids were drawn. Subjects were administered drug product.
- **Study visits Visit 3-Visit 19 -** During each visit the investigator transcribed from the patient's diary hypo- and hyperglycemic episodes, AEs and changes in concomitant medication since last contact, 4-point profile performed prior to a contact, and dose of trial insulin on three consecutive days prior to a contact.

  Visit 18 was the end of treatment visit. Central laboratories were drawn, adverse events were recorded. Patients were transferred from trial product to a marketed product and information on the new product was not captured by the Sponsor.

Reference ID: 4009596

Figure 13- Study 3816- Study Design



Source: CSR trial 3816, figure 9-1 page 48

The following investigational products were used in this trial:

- Insulin degludec/ insulin aspart (IDegAsp) 100 U/ml, Penfill 3 ml cartridge
- Insulin aspart (IAsp) 100 U/mL, 3 mL Penfill cartridge
- Insulin detemir (Levemir) 100 U/ml, Penfill 3 ml cartridge

Devices which permit 0.5 Unit dosing increments were used. For specific pen devices used with these cartridges refer to **Table 2 .**

Insulin dosing and Titration:

Dose selection:

All subjects received therapy with:

- IDegAsp once daily (QD) with one of the main meals + meal time IAsp
- IDet once daily or twice daily (BID)[34] + mealtime IAsp

IAsp was to be given with the main meals, 2-4 times daily in subjects randomized to IDet and 1-3 times daily for subjects randomized to IDegAsp.

Reviewer's labeling comment: The approved Ryzodeg 70/30 PI dosing administration is different from the dosing used in the Phase 3 pediatric trial. The approved Ryzodeg 70/30 PI states: "inject RYZODEG 70/30 subcutaneously once or twice daily with any meal", while the phase 3 pediatric trial evaluated use of Ryzodeg 70/30 administered once a day. Given the findings of the increased risk of hypoglycemia for IDegAsp (when compared to IDet), see section 7.3.4Significant Adverse Events*; the reviewer does not believe that there is sufficient evidence to support the use of IDegAsp twice a day in pediatric patients.*

Dose selection:

At randomization (Visit 2), the Investigator was to *reduce* the total daily insulin dose by 20 percent and adjust the basal-to bolus ratio to either 50:50 or 70:30. The total daily basal and bolus doses are shown

[34] Subjects on a twice daily regimen were to dose at breakfast and in the evening either at main evening meal or at bedtime

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Table 47 (in the appendix) for subjects randomized to IDegAsp and **Table 48** (in the appendix) for subjects randomized to IDet.

At randomization (Visit 2), the subjects were switched to IDet from previous basal insulin dose(s) and dosed according to **Table 48**. The dose could be administered once daily or divided into two daily doses according to labeling.

Subjects on IDet QD were changed to BID if the mean pre-breakfast plasma glucose (PG) reached 90-145 mg/dL and mean pre-dinner PG >145 mg/dL. The start of the second dose of detemir was to be 2-4 U with further adjustments as per **Table 7**.

At randomization the subject switched to IAsp from previous bolus insulin. The dose of IAsp was as per **Table 8.**

Reviewer's labeling comment: in an information request, the Sponsor was asked to justify the starting dose in the pediatric trials, since the instructions for the starting dose in the approved PI states that RYZODEG 70/30 should be started at the same unit dose as premix or self-mix insulin or as the same unit dose as basal insulin.

In an information request, dated August 18, 2016, the Sponsor stated that the trial-specific dosing guidelines are described in section 14 of the proposed label. The rationale for not including these trial-specific dosing guidelines in section 2 is that:

"The PK, PD and exposure−response results indicate no need for age-specific considerations when developing dosing recommendations for IDegAsp for children and adolescents aged 1 to less than 18 years
- Trial 3816 was conducted based on a treat-to-target principle. The insulin dose was adjusted for each individual subject with the aim of achieving similar pre-breakfast SMPG targets for each treatment group. The ultimate decision regarding dosing of basal and bolus insulin was at the discretion of the investigator.
-The investigators did not consistently apply a 20%reduction in the pre-trial total insulin dose at randomization and there was large variation in the magnitude of change applied
- For subjects randomized to IDegAsp, a reduction in total insulin dose of approximately 20% (i.e. from 15% to 25%) was implemented for 22% of subjects. A dose reduction of any magnitude was implemented for 73% of subjects."

In order to better understand the changes in dose from the screening basal insulin dose to the starting IDegAsp dose the reviewer evaluated the relationship between the IDegAsp dose at baseline when compared to the screening dose as shown in Figure 14.

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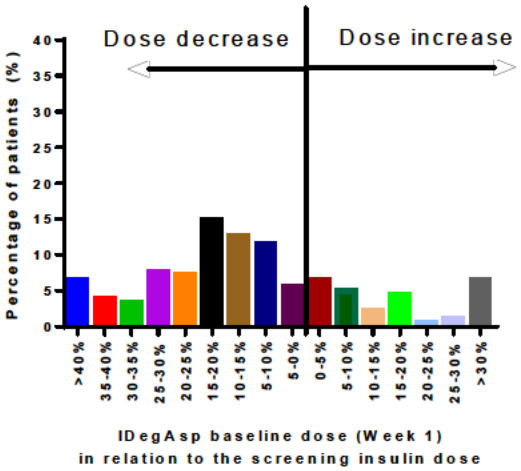
Figure 14 – Trial 3816 – Changes to the baseline (week 1) IDegAsp dose in relation to the screening basal insulin dose -safety analysis set



Source: Information request dated 17 August 2016, IR \\CDSESUB1\evsprod\NDA203314\0093\m1\us, reviewer generated graph of Table 5

Although the reviewer agrees with the fact that the investigators did not strictly adhere to the 20% reduction from screening to IDegAsp dose, section 2 in the approved label recommends converting to the same dose of IDegAsp, which may be misleading to health care providers of pediatric patients and may result in overdosing.

Therefore the reviewer recommends adding language in Section 2 regarding a lower starting dose in pediatric patients.

Titration and assessment of compliance
See section **Common elements.**

Definitions of analysis sets
Refer to section **Common elements** for definition of the FAS and SAS. The PP analysis set is shown below.

The Per-Protocol analysis set will consist of all subjects in the Full Analysis Set who fulfill the following criteria:

a) Have not violated any inclusion criteria
b) Have not fulfilled any exclusion criteria
c) Have a non-missing HbA1c at screening or randomization
d) Have at least one non-missing HbA1c after 12 weeks of exposure
e) Have at least 12 weeks of exposure

Endpoints:
Only endpoints derived after 16 weeks of treatment were analyzed statistically. The mixed model for repeated measurements (MMRM) data was used to account for missing data in the statistical analysis.

Analyses of all endpoints were based on the Full Analysis Set (FAS). The primary efficacy analysis was repeated on the Per Protocol (PP) analysis set

Secondary efficacy endpoints were summarized using the FAS. Safety endpoints were summarized using the Safety Analysis Set (SAS).

Primary efficacy endpoint:
The primary endpoint was the change from baseline in centrally measured HbA1c (%) after 16 weeks of treatment.

All observed HbA1c measurements available post-randomization were analyzed using MMRM with an unstructured covariate matrix. The model included treatment, sex, region and age group and visit as factors and baseline HbA1c as covariate. Interactions between visit and all factors and covariates were included in the model.

Region was a factor with three levels: 1. Europe (including Russia and Israel), 2.North America, 3. Other

Age group was a factor with the following three levels:

- 1 to less than 6 years of age
- 6 to less than 12 years of age
- 12 to less than 18 years of age

The primary objective was the demonstration of non-inferiority of IDegAsp +meal time IAsp vs. IDet + mealtime IAsp.

- Non-inferiority was confirmed if the upper bound of the two-sided 95% confidence interval was below or equal to 0.4% or equivalent if the p-value for the one-sided test of H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$, was less than or equal to 2.5%, where D is the mean treatment difference (IDegAsp + mealtime IAsp minus IDet + mealtime IAsp).

If non-inferiority was confirmed, the superiority of IDegAsp +mealtime IAsp over IDet + mealtime IAsp was investigated. Superiority was confirmed if the upper bound of the two-sided 95% confidence interval, which is calculated using the FAS, and a threshold of below 0%.

Of note, the Sponsor justifies use of the non-inferiority margin of 0.4% (absolute) was chosen in accordance with the Food and Drug Administration (FDA) guidance.

All subjects withdrawing from the trial were asked to attend an end-to trial visit, to assess HbA1c.

Sensitivity analyses
The primary efficacy analysis was repeated using the PP analysis set and the set of all completed subjects. Other sensitivity analyses included:

- ANCOVA method with treatment sex, region and age group as fixed factors and baseline HbA1c as covariate, with missing values imputed by Last Observation Carried Forward (LOCF) method
- MMRM with an unstructured covariance matrix where the only factors are treatment and visit and baseline HbA1c as a covariate. The two interactions between visit and treatment and visit and baseline HbA1c was also included

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Secondary efficacy endpoints:
The following were secondary endpoints were analyzed after 16 weeks of treatment:

- Change from baseline in centrally measured Fasting Plasma Glucose (FPG)[35]
- SMPG measurements (4-point profiles) obtained throughout the trial for dose adjustments
  - Mean plasma glucose (PG) before meals and before bedtime[36]
  - Within-subject variability as measured by the CV%[37]
- SMPG measurements (8-point profiles)[38]
  - 8-point profiles
  - Mean of the 8-point profiles
  - Fluctuation in the 8-point profiles
  - Prandial PG increment from 8-point profiles

Nocturnal increments of 8-point SMPG were summarized descriptively.

Safety endpoints:
See **Table 11** for safety endpoints assessed at baseline and at 16 weeks.

Table 11 – Safety endpoints for trial 3816

Safety endpoints	**Details**
Incidence of treatment emergent adverse events	
^Hypoglycemia Number of the following TEAEs:	• confirmed hypoglycemic episodes (<56 mg/dL) or severe hypoglycemia • *nocturnal* [11 p.m. – 7 a.m. inclusively]confirmed hypoglycemic episodes (<56 mg/dL) or severe hypoglycemia • hypoglycemic episodes, in accordance with ISPAD/ADA definitions • *nocturnal* [11 p.m. – 7 a.m. inclusively]c hypoglycemic episodes, in accordance with ISPAD/ADA definitions
Hyperglycemia Number of:	• hyperglycemic episodes (>250 mg/dL) where subject looks/feels ill • hyperglycemic episodes (>250 mg/dL) where subject looks/feels ill *with ketosis* (blood ketones > 1.5 mmol/L) $^{\sigma}$
Change from baseline in **central laboratory assessments**	• Hematology $^{\sim}$ • Biochemistry$^{\$}$ • Lipid profile$^{€}$ • Insulin doses $^{\Omega}$ • Body weight and BMI

[35] Analyzed with a MMRM with an unstructured covariance matrix, the model includes treatment, sex, region, age-group and visit as factors and baseline FPG as covariate. Interactions between visit and all factors and covariates are also included in the model
[36] All observed mean of before meals and all observed before bedtime PG values available post randomization at scheduled measurement times were analyzed separately with a MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age-group and visit as factors and baseline response value as covariate. Interactions between visit and all factors and covariates are also included in the model.
[37] Within-subject variability as measured by CV% for a treatment can be calculated from the corresponding residual variance σ^2 as $CV\% = 100\sqrt{(\exp(\sigma^2 - 1))}$. The confidence interval for the CV ratio between treatments will be calculated using the delta method.
[38] All observed mean and fluctuation in the 8-point profile and prandial PG increments available post randomization at scheduled measurements times were to be analyzed with a MMRM with an unstructured covariance matrix. The model includes treatment, sex, region, age-group and visit as factors and baseline values of the response as covariate. Interactions between visit and all factors and covariates were also included in the model. Fluctuation in the 8-point profile will be logarithmically transferred before analysis.

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	• Vital signs

^ refer to section **7.3.4 Significant Adverse Events** for definitions of hypoglycemia
[σ] all ketone measurements were self-measured
[~]hemoglobin, hematocrit, erythrocytes, thrombocytes and leucocytes
[$]creatinine, ALAT, ASAT, alkaline phosphatase, sodium, potassium, albumin and total bilirubin)
[€]cholesterol, HDL and LDL
[Ω]Units/day and Units/kg/day both for total, basal and bolus

Reviewer's comment: the threshold of hyperglycemic safety endpoints were higher for this trial (at>250 mg/dL) than for trial 3561, where the threshold was >200 mg/dL.

Of note, *before* data base lock, the following analyses were changed from the original protocol:

- Evaluation of the standard deviation scores for body weight (SD scores) in order to compare the body weight in the various age groups.[39] The SD scores were derived from the age and sex of the subjects and the body weight together with growth curves defined for reference population of each country. For countries with no reference values, the reference values for the US were used[40].

Exploratory analysis included evaluation of observed 8-point profile (SMPG) measurements available post randomization.

Sample size calculation:
Sample size was determined using a t-statistic under the assumption of a one-sided test of size 2.5% and a zero mean treatment difference (i.e. D=0%). Based on experience from previous phase 3 trials in children and adolescents with T1DM treated with insulin a conservative estimate for the SD of 1.25% for HbA1c was used in the sample size calculation.[41]

The total number of randomized subjects was to be at least 346 subjects in order to have at least 80% power in the evaluation of the PP analysis set. [42]

6 Review of Efficacy

Efficacy Summary

Insulin degludec (IDeg) efficacy summary

[39] All SD score (based on observed weight) measurements available post-randomization at scheduled measurement times were analyzed with a MMRM with an unstructured covariance matrix. The model included treatment, sex, region, age-group and visit as factors and baseline SD score as covariate. Interactions between visit and all factors and covariates were also included in the model.
[40] Brazil, Canada, Croatia, Israel, Macedonia, Poland, Russian Federation, Serbia, Slovenia and South Africa
[41] The SD of 1.25% used in the sample size calculation was based on results from two previous pediatric trials with IDet (Trials NN304-1379 and NN304-1689). In NN304-1379 the SD was 0.88 % for HbA1c (%) after 18 weeks of treatment in children with age ranging from 6 to less than 18 years. In NN304-1689, the SD was 1.09% for HbA1c (%) after 26 weeks in children with age ranging from 2 to 16 years.
[42] In previous phase 3 trials, in insulin treated children and adolescents with T1DM, less than 9% of the randomized subjects were excluded from the PP analysis set. In this trial, an estimate of 10% was used and sample size was capped in the FAS to have integer sample size for each group that adheres exactly to the group allocation weights (1:1).

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Overall the Sponsor has demonstrated the efficacy of insulin degludec U100 in pediatric patients with type-1 diabetes at ages 1 to 18, in a randomized, open label, 26 week treat to target trial with a 26 week safety extension (trial NN1250-3561). Baseline characteristics were balanced. At 26 weeks, retention rate were high for both intervention groups (>94%).

Using an analysis of variance (ANOVA) with the last observation carried forward (LOCF) to account for missing data, insulin degludec, administered once daily was shown to not be unacceptably worse than insulin detemir administered once or twice daily. Both treatment arms had co-administration of insulin aspart with meals. The mean adjusted baseline reduction in HbA1c achieved using insulin degludec (-0.15) was smaller than the mean adjusted baseline reduction in HbA1c achieved using insulin detemir (-0.30); this treatment difference (+0.15) met the pre-specified non-inferiority margin because the upper bound of the 95% confidence interval (0.32) was less than the pre-specified 0.4% margin. The glycemic findings were similar when evaluated by pre-specified age subgroups (1-5, 6-11 and 12-17 years).

The secondary endpoints were not adjusted for multiplicity and included glycemic measures at 26 weeks and 52 weeks of treatment. The 52 week data was also affected by a larger proportion of missing data, with a 17.5% greater retention for insulin degludec than insulin detemir (detemir retention: 69.3%).The 52 week HbA1c adjusted mean difference of insulin degludec-insulin detemir was -0.01%, with slightly worsened glycemic control seen in 12-17 year olds randomized to insulin degludec. The trends for fasting plasma glucose at 26 and 52 weeks overall and by subgroups, showed either similar or slightly better glycemic control for insulin degludec than insulin detemir.

At the end of 26 weeks, patients randomized to insulin degludec used less total insulin per day than insulin detemir (~5 units less or 0.14 U/kg less), with similar trends at 52 weeks (~7 units less or 0.2 U/kg less), with 62.3% of patients randomized to insulin detemir on a twice a day regimen at week 52.

Insulin degludec/insulin aspart (IDegAsp) efficacy summary

Overall the Sponsor has demonstrated the efficacy of insulin degludec/insulin aspart in pediatric patients with type-1 diabetes at ages 1 to 18, in a randomized, open label, 16 week treat to target trial (trial NN5401-3816). Baseline characteristics were balanced and at 16 weeks, retention rate were high for both intervention groups (>93%).

Using an analysis of a mixed model for repeated measurements, insulin degludec/insulin aspart, administered once daily was shown to not be unacceptably worse than insulin detemir administered once or twice daily. Both treatment arms had co-administration of insulin aspart with meals. The mean adjusted baseline reduction in HbA1c achieved using insulin degludec/insulin aspart (-0.27) was slightly larger than the mean adjusted baseline reduction in HbA1c achieved using insulin detemir (-0.23); this treatment difference (-0.04) met the pre-specified non-inferiority margin because the upper bound of the 95% confidence interval (0.15) was less than the pre-specified 0.4% margin. The glycemic findings were similar when evaluated by pre-specified age subgroups (1-5, 6-11 and 12-17 years).

The secondary endpoints were not adjusted for multiplicity. The trends for fasting plasma glucose at 16 weeks overall and by subgroups, showed either similar or slightly better glycemic control for insulin degludec/aspart than insulin detemir.

At the end of 16 weeks, patients randomized to insulin degludec/aspart used less total insulin per day than insulin detemir (~8 units less or 0.13 U/kg less), with ~54% of patients randomized to insulin detemir on a twice a day regimen at week 16.

6.1 Indication

In this supplemental NDA the Sponsor seeks to update the Tresiba and Ryzodeg 70/30 labels to include the clinical safety and efficacy data from the pediatric studies in T1DM patients in the 26-week data of study NN1250-3561 and the 16-week data of study NN5401-3816.

6.1.1 Methods

Clinical efficacy data from both the 26-week and 52 week period of trial NN1250-3561 (for IDeg) and 16-week period for trial NN5401-3816 (for IDegAsp) were used to support the proposed indication/labeling changes.

Because children vary in physiology by age, the reviewer evaluated efficacy parameters for the following subset of ages: 1-5 years, 6-11 years and 12-17 years. Differences noted in these age groups are noted as pertinent.

6.1.2 Demographics

6.1.2.1 Demographics NN1250-3561(IDeg)

The baseline characteristics and demographics of NN1250-3561 (for IDeg) are shown below. Overall, the treatment groups were well matched with respect to baseline demographic characteristics. There were slight numerical imbalances in the number of patients assigned to treatment groups by country of residence, and race. The baseline HbA1c and FPG was also slightly higher for IDeg OD than IDet (HbA1c: 8.2% vs. 8%; FPG: 162 vs. 151 mg/dL respectively).

Consistent with entry criteria, patients' age ranged from 1.5 to less than 18 years[43]. Patients enrolled had a mean age of 10 years with a quarter of patients at age 1- 5; 39% were patients ages 6-11; and 36% patients were ages 12-17. Overall the mean duration of diabetes was 4 years. 55% were male. 75% were White, 3% Black or African American. 3% were Hispanic or Latino. Approximately 29% of subjects were from the U.S (which enrolled the largest percentage of subjects). Across treatment groups, the average HbA1c was 8.1%.

There were only 4 patients with diabetic complications at screening (1 in the IDeg OD[44] group and 3 in the IDet group[45]).

[43] One subject (704005) in the IDeg arm was randomized prior to his 18th birthday, but due to local regulations (Germany) only the birth year was recorded, and the birth date set to 1st June by default. The subject therefore appears as being aged 18.4 years in the table below.
[44] Complication of diabetic ketoacidosis
[45] Complication of diabetic neuropathy

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Table 12 – Trial 3561- Demographics and baseline characteristics- summary- FAS

	IDeg OD		IDet		Total	
AGE GROUP	**N**	**%**	**N**	**%**	**N**	**%**
12-17 years	61	35.1%	66	37.5%	127	36.3%
1-5 years	43	24.7%	42	23.9%	85	24.3%
6-11 years	70	40.2%	68	38.6%	138	39.4%
All	174	100.0%	176	100.0%	350	100.0%
SEX						
Female	78	44.8%	78	44.3%	156	44.6%
Male	96	55.2%	98	55.7%	194	55.4%
All	174	100.0%	176	100.0%	350	100.0%
RACE						
Asian non-Indian	23	13.2%	32	18.2%	55	15.7%
Black	5	2.9%	5	2.8%	10	2.9%
Not Applicable	2	1.1%	7	4.0%	9	2.6%
Other	7	4.0%	7	4.0%	14	4.0%
Pacific Islander	1	0.6%	0	0.0%	1	0.3%
White	136	78.2%	125	71.0%	261	74.6%
All	174	100.0%	176	100.0%	350	100.0%
ETHNIC						
Hispanic	7	4.0%	3	1.7%	10	2.9%
Not Hispanic	167	96.0%	173	98.3%	340	97.1%
All	174	100.0%	176	100.0%	350	100.0%
REGION						
Europe	89	51.1%	93	52.8%	182	52.0%
Japan	23	13.2%	32	18.2%	55	15.7%
North America*	57	32.8%	44	25.0%	101	28.9%
South Africa	5	2.9%	7	4.0%	12	3.4%
All	174	100.0%	176	100.0%	350	100.0%

*all the patients from North America came from USA
Source: Reviewer generated table from S. Dataset, numbers match CSR 3561, table 10-5, page 99

The subjects were randomized based on measurements performed on Visit 1 and baseline values were recorded 1 week later (at Visit 2). Since some subjects had an increase in HbA1c from Visit 1 to Visit 2, the maximum value of HbA1c is shown in **Table 13**.

Reviewer's comment: In previous correspondence, the Sponsor was encouraged to enroll a population that is representative of the pediatric population in the United States who will use these products. The Sponsor was asked to ensure that some patients (e.g., ~20-25% of those enrolled in these trials) come from sites in the United States.

Table 13 – Trial 3561- baseline and diabetes characteristics – descriptive statistics- FAS

	IDeg OD	IDet	Total
Number of Subjects	174	176	350
Age (years)			
N	174	176	350
Mean (SD)	10.0 (4.4)	10.0 (4.4)	10.0 (4.4)
Median	10.2	10.3	10.3
Min ; Max	1.5 ; 18.4[$]	1.8 ; 17.7	1.5 ; 18.4[$]
Height (m)			
N	174	176	350
Mean (SD)	1.37 (0.25)	1.38 (0.25)	1.38 (0.25)
Median	1.39	1.38	1.39
Min ; Max	0.80 ; 1.86	0.82 ; 1.89	0.80 ; 1.89
Body Weight (kg)			
N	174	176	350
Mean (SD)	38.0 (18.7)	37.8 (18.9)	37.9 (18.8)
Median	35.0	32.7	34.8
Min ; Max	11.2 ; 102.2	10.8 ; 95.3	10.8 ; 102.2
BMI (kg/m^2)			
N	174	176	350
Mean (SD)	18.7 (3.6)	18.5 (3.6)	18.6 (3.6)
Median	17.9	17.4	17.6
Min ; Max	12.9 ; 34.5	10.0 ; 30.4	10.0 ; 34.5
Duration of Diabetes (years)			
N	174	176	350
Mean (SD)	3.9 (3.6)	4.0 (3.4)	4.0 (3.5)
Median	2.5	2.9	2.7
Min ; Max	0.3 ; 15.8	0.0 ; 15.0	0.0 ; 15.8
HbA1c (%)			
N	174	176	350
Mean (SD)	8.2 (1.1)	8.0 (1.1)	8.1 (1.1)
Median	8.2	8.0	8.1
Min ; Max	5.5 ; 10.7	5.4 ; 11.1	5.4 ; 11.1
FPG (mmol/L)			
N	157	160	317
Mean (SD)	9.0 (5.2)	8.4 (4.9)	8.7 (5.1)
Median	8.4	7.6	8.2
Min ; Max	0.8 ; 34.4	0.4 ; 25.6	0.4 ; 34.4
FPG (mg/dL)			
N	157	160	317
Mean (SD)	162.1 (94.4)	151.0 (87.7)	156.5 (91.1)
Median	152.1	137.5	147.0
Min ; Max	14.1 ; 620.0	7.0 ; 462.0	7.0 ; 620.0

BMI: Body mass index, N: Number of subjects, SD: Standard deviation
FPG: Fasting plasma glucose [$]All subjects were within the age range 1-<18 years at screening.

Source: CSR 3561, Table 10-6, page 101

Evaluation of demographic characteristics by age group, were mostly similar between treatment groups. Slight imbalances between treatment arms were seen for the following (data not shown):

- Slightly higher baseline FPG for IDeg OD than IDet for ages 6-11 (mean: 167 mg/dL vs. 148 mg/dL)
- Slightly higher baseline HbA1c for IDeg OD than IDet for ages 12-17 (mean: 8.3% vs. 8% respectively)

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- Slightly higher FPG for IDeg OD than IDet for ages 12-17 (mean 154 mg/dL vs. 145 mg/dL respectively)
- Slightly longer duration of diabetes for IDeg OD than IDet for ages 12-17 (mean 6.4 vs. 5.7 years)

Insulin used at screening

At screening the majority of subjects (335, 95.7%) were using basal/bolus therapy; 5 (1.4%) were using basal/bolus + premix; 15 (4.3%) were using 'other' regimens, i.e. basal, bolus, premix alone or premix in combination.

Table 14 shows the types of insulin used at screening. IDet was the most common basal insulin used in about 46% of patients, insulin glargine (IGlar) was used in about 40% of patients. More than 60% of patients used insulin aspart as bolus insulin.

Table 14 – Study 3561- Insulin type at screening- summary -FAS

	IDeg OD		IDet		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	174		176		350	
Basal insulin	169	(97.1)	168	(95.5)	337	(96.3)
IDet	82	(47.1)	80	(45.5)	162	(46.3)
IDet + Insulin NPH	3	(1.7)	3	(1.7)	6	(1.7)
IGlar	70	(40.2)	75	(42.6)	145	(41.4)
IGlar + Insulin NPH	1	(0.6)	1	(0.6)	2	(0.6)
Insulin NPH	13	(7.5)	9	(5.1)	22	(6.3)
Bolus insulin	172	(98.9)	170	(96.6)	342	(97.7)
HI	14	(8.0)	14	(8.0)	28	(8.0)
HI + IAsp	8	(4.6)	1	(0.6)	9	(2.6)
HI + ILis	1	(0.6)			1	(0.3)
IAsp	107	(61.5)	120	(68.2)	227	(64.9)
IAsp + IGlu			2	(1.1)	2	(0.6)
IGlu	2	(1.1)	4	(2.3)	6	(1.7)
ILis	40	(23.0)	29	(16.5)	69	(19.7)
Premix insulin	6	(3.4)	8	(4.5)	14	(4.0)
BHI	3	(1.7)	3	(1.7)	6	(1.7)
BIAsp	2	(1.1)	3	(1.7)	5	(1.4)
Lispro Mix	1	(0.6)	2	(1.1)	3	(0.9)

N: Number of subjects
%: Proportion of subjects
Subjects can use more than one type of insulin within each group.
BHI: Biphasic Human Insulin, BIAsp: Biphasic Insulin Aspart, HI: Human Insulin
IAsp: Insulin Aspart, IDet: Insulin Detemir, IGlar: Insulin Glargine
IGlu: Insulin Glulisine, ILis: Insulin Lispro
Insulin NPH: Neutral Protamine Hagedorn

Source: CSR 3561, Table 10-7, page 103

6.1.2.2 Demographics Trial NN5401-3816 (IDegAsp)

The baseline characteristics and demographics of NN1250-3816 (for IDegAsp) are shown below. Overall, the treatment groups were well matched with respect to baseline demographic characteristics. There were slight numerical imbalances in the number of patients assigned to treatment groups by region of residence with slightly more patients randomized to IDegAsp from North America than IDet. The baseline FPG was also slightly higher for IDegAsp than IDet (mean FPG: 156 vs. 147 mg/dL respectively).
Consistent with entry criteria, patients' age ranged from 1.9 to less than 17.9 years. Patients enrolled had a mean age of 11 years with 23% of patients ages 1- 5; 34% were patients ages 6-11; and 44% patients were ages 12-17. Overall the mean duration of diabetes was 3 years. 48% were male. 93% were White, 3%

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Black or African American. 8% were Hispanic or Latino. Approximately 32% of subjects were from the U.S. across treatment groups, the average HbA1c was 8.0%.

There were 14 patients with diabetic complications at screening (5 patients in the IDegAsp[46] group; 9 patients in the IDet group[47]).

Table 15 – Study 3816 – Demographics and baseline characteristics- summary - FAS

	IDegAsp OD		IDet		Total	
AGE GROUP	**N**	**%**	**N**	**%**	**N**	**%**
12-17 years	80	44.0%	78	43.3%	158	43.6%
6-11 years	61	33.5%	61	33.9%	122	33.7%
1-5 years	41	22.5%	41	22.8%	82	22.7%
All	182	100.0%	180	100.0%	362	100.0%
SEX						
Female	93	51.1%	94	52.2%	187	51.7%
Male	89	48.9%	86	47.8%	175	48.3%
All	182	100.0%	180	100.0%	362	100.0%
RACE						
White	169	92.9%	168	93.3%	337	93.1%
Black	8	4.4%	4	2.2%	12	3.3%
Other	5	2.7%	7	3.9%	12	3.3%
Asian Indian	0	0.0%	1	0.6%	1	0.3%
All	182	100.0%	180	100.0%	362	100.0%
ETHNIC						
Not Hispanic	167	91.8%	167	92.8%	334	92.3%
Hispanic	15	8.2%	13	7.2%	28	7.7%
All	182	100.0%	180	100.0%	362	100.0%
REGION						
Europe	99	54.4%	119	66.1%	218	60.2%
North America	72	39.6%	53	29.4%	125	34.5%
USA	64	35.2%	50	27.8%	114	31.5%
Other	11	6.0%	8	4.4%	19	5.2%
All	182	100.0%	180	100.0%	362	100.0%

Source: reviewer generated table from S. dataset, numbers match CSR 3816, table 10-5, page 95.

[46] 4 patients had diabetic neuropathy and 1 patient had microalbuminuria
[47] 5 patients had diabetic neuropathy and 3 patients had microalbuminuria ad 1 patient had diabetic cataract

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Table 16 – Study 3816- Baseline and diabetes characteristics- descriptive statistics- FAS

	IDegAsp OD	IDet	Total
Number of Subjects	182	180	362
Age (years)			
N	182	180	362
Mean (SD)	10.5 (4.3)	10.8 (4.6)	10.6 (4.5)
Median	11.0	11.4	11.2
Min ; Max	2.2 ; 17.8	1.9 ; 17.9	1.9 ; 17.9
Height (m)			
N	180	179	359
Mean (SD)	1.41 (0.24)	1.42 (0.27)	1.42 (0.25)
Median	1.44	1.48	1.46
Min ; Max	0.90 ; 1.87	0.83 ; 1.91	0.83 ; 1.91
Body Weight (kg)			
N	182	180	362
Mean (SD)	41.1 (20.7)	42.9 (21.2)	42.0 (20.9)
Median	39.4	39.9	39.7
Min ; Max	12.1 ; 117.1	9.4 ; 104.4	9.4 ; 117.1
Duration of Diabetes (years)			
N	182	180	362
Mean (SD)	4.4 (3.7)	3.8 (3.2)	4.1 (3.5)
Median	3.1	2.8	3.0
Min ; Max	0.3 ; 14.6	0.3 ; 13.9	0.3 ; 14.6
BMI (kg/m^2)			
N	180	179	359
Mean (SD)	19.2 (4.2)	19.6 (4.0)	19.4 (4.1)
Median	18.4	18.6	18.5
Min ; Max	11.0 ; 35.1	12.8 ; 31.9	11.0 ; 35.1
HbA1c (%)			
N	182	180	362
Mean (SD)	8.1 (1.2)	8.1 (1.2)	8.1 (1.2)
Median	8.0	8.0	8.0
Min ; Max	5.1 ; 11.1	5.4 ; 10.9	5.1 ; 11.1
FPG (mg/dL)			
N	172	166	338
Mean (SD)	155.6 (80.2)	146.5 (74.9)	151.1 (77.6)
Median	139.0	130.1	133.0
Min ; Max	9.0 ; 373.0	35.0 ; 452.1	9.0 ; 452.1

BMI: Body mass index, N: Number of subjects, SD: Standard deviation
FPG: Fasting plasma glucose

Source: CSR 3816, table 10-6, page 97

Evaluation of demographic characteristics by age group, were mostly similar between treatment groups. Slight imbalances between treatment arms were seen for the following (data not shown):

- Slightly longer duration of diabetes for IDegAsp than IDet for ages 12-17 (mean: 6.4 vs. vs. 5.6 years)
- Slightly higher baseline FPG for IDegAsp than IDet for ages 12-17 (mean: 162.4mg/dL vs. 146.1 mg/dL respectively)

Reference ID: 4009596

Insulin used at screening

At screening the majority of subjects (92%) were using basal/bolus therapy; 5 (1.4%) were using basal/bolus + premix; 24 (6.6%) were using 'other' regimens, i.e. basal, bolus, premix alone or premix in combination.

Table 17 shows the types of insulin used at screening. IDet was the most common basal insulin, which was used in about 46% of patients followed by insulin glargine (IGlar), which was used in about 41% of patients. In regards to bolus insulin, more than 58% of patients used insulin aspart as bolus insulin.

Table 17 – Trial 3816 – Insulin type at screening – summary - FAS

	IDegAsp OD		IDet		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	182		180		362	
Basal insulin	171	(94.0)	171	(95.0)	342	(94.5)
IDet	72	(39.6)	92	(51.1)	164	(45.3)
IDet + Insulin NPH	3	(1.6)	3	(1.7)	6	(1.7)
IGlar	77	(42.3)	70	(38.9)	147	(40.6)
Insulin NPH	19	(10.4)	6	(3.3)	25	(6.9)
Bolus insulin	176	(96.7)	177	(98.3)	353	(97.5)
HI	21	(11.5)	19	(10.6)	40	(11.0)
HI + IAsp	3	(1.6)	5	(2.8)	8	(2.2)
HI + ILis	1	(0.5)	1	(0.6)	2	(0.6)
IAsp	104	(57.1)	108	(60.0)	212	(58.6)
IGlu	6	(3.3)	8	(4.4)	14	(3.9)
ILis	41	(22.5)	36	(20.0)	77	(21.3)
Premix insulin	7	(3.8)	7	(3.9)	14	(3.9)
BHI			2	(1.1)	2	(0.6)
BIAsp	6	(3.3)	3	(1.7)	9	(2.5)
Lispro mix	1	(0.5)	2	(1.1)	3	(0.8)

N: Number of subjects, %: Proportion of subjects
IGlar: Insulin glargine, ILis: Insulin lispro
IAsp: Insulin aspart, NPH: Neutral protamine hagedorn
BHI: Biphasic human insulin, BIAsp: Biphasic insulin aspart
IDet: Insulin detemir, HI: Human insulin, IGlu: Insulin glulistin

Source: CSR 3816, table 10-7, page 99

6.1.3 Subject Disposition

This section evaluates the patient's disposition by considering the impact it may have on the efficacy evaluation. Discontinuation due to adverse events is discussed in detail in section 7.3.3 Dropouts and/or Discontinuations. For discontinuation due to other reasons, the Reviewer has manually included the reason in the Sponsor tables below.

6.1.3.1 Subject disposition- NN1250-3561(IDeg)

Overall the patient disposition was similar between treatment groups, with minor numerical differences.

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A total of 363 patients were screened, of whom 350 were randomized (with 13 screen failures[48]). During the 26 week treatment period the percentage of patients who discontinued treatment was 4.3%, with a numerically lower percentage for IDeg than IDet (2.3% vs. 6.3% respectively). The most common reason for withdrawal was meeting withdrawal criteria. [49] There were no withdrawals in the IDeg group due to adverse events, while IDet had 2 withdrawals due to this reason.

The reviewer also evaluated the disposition of the additional 26 week safety period by using the Sponsor's provided datasets (which matched the Sponsor's results shown in **Table 18**). A larger proportion of patients randomized to IDeg (87.4%) continued into the extension period, than those randomized to IDet (72.7%). During the extension period, there was 1 additional withdrawal in the IDeg group (meeting withdrawal criteria) and 6 additional withdrawals in the IDet group (5 due to withdrawal criteria, 1 due to adverse event).

Reviewer's comment: the extent of missing data during the main 26 week period is low overall for IDeg (2.3%) and IDet (6.3%). This percentage is higher when considering the 52-week extension period, with a drop out of 13.2% for IDeg and 30.7% for IDet. This reviewer defers to the statistical reviewer to evaluate the impact of missing data on the primary outcome.

[48] 5 did not meet HbA1c criteria, 2 could not perform 4 and 8 point profiles (inclusion criteria), 1 failed having 3 months of insulin use, 5 withdrew consent.
[49] Most of the subjects withdrew due to withdrawing consent.

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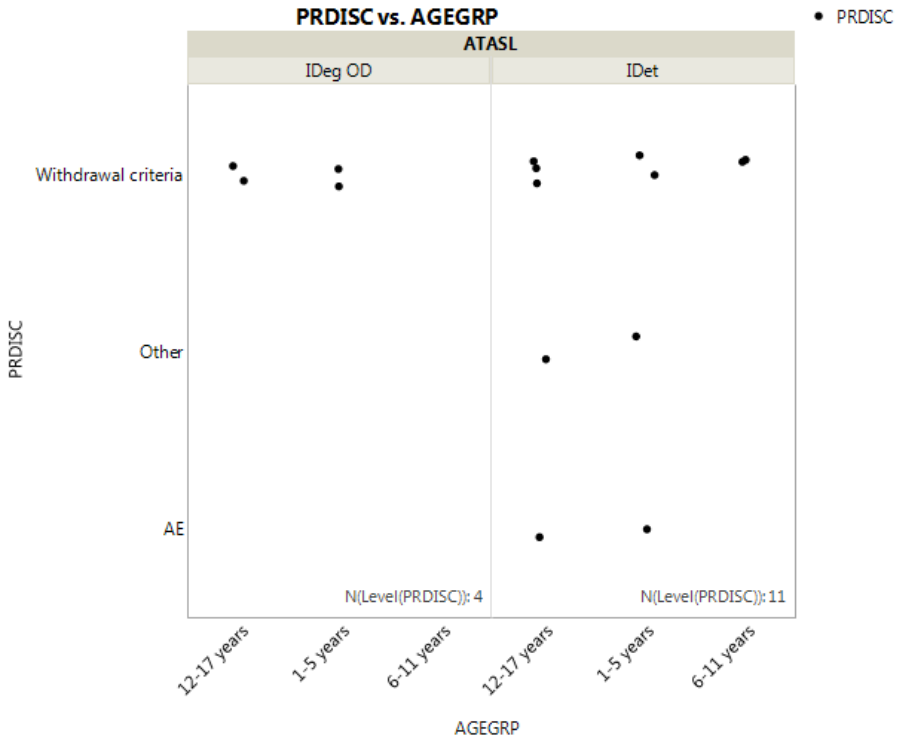
Table 18 – Trial 3561 - Subject disposition (26 and 52 week period) – Summary

		IDeg		IDet		Total	
		N	%	N	%	N	%
MAIN 26-week period	screened					363	
	Screening failure					13	
	Withdrawn before randomization					0	
	Randomized	174	100%	176	100%	350	100%
	Exposed	174	100%	175	99.4%	349	99.7%
	Withdrawn after/at randomization	4	2.3%	11	6.3%	15	4.3%
	Adverse event	0	0	2	1.1%	2	0.6%
	Other	0	0	2	1.1%	2	0.6%
	Subject wants to return to pump	0	0	1	0.6%	1	0.3%
	Poor glucose control, no trust pen	0	0	1	0.6%	1	0.3%
	Withdrawal criteria	4	2.3%	7	4%	11	3.1%
	Completed 26 week main period	**170**	**97.7%**	**165**	**93.8%**	**335**	**95.7%**
26 week Extension period	Completed main trial. Did not consent to participate in extension	18	10.3%	37	21%	55	15.7%
	Included in extension	152	87.4%	128	72.7%	280	80%
	Withdrawal during extension	1	0.6%	6	3.4%	7	2%
	Adverse event	0	0	1	0.6%	1	0.3%
	Withdrawal criteria	1	0.6%	5	2.8%	6	1.7%
	Completed extension	**151**	**86.8%**	**122**	**69.3%**	**273**	**78%**
Analysis sets	FAS	174	100%	176	100%	350	100%
	PP analysis set	171	98.3%	167	94.9%	338	96.6%
	SAS	174	100%	175	99.4	349	99.7%

Source: CSR 3561-extension - table 10-1, page 95, modified by reviewer

Figure 15 shows the subject disposition by age subgroups. Across age groups, there were slight numerical imbalances between treatment groups regarding reasons for withdrawal, without clear treatment-specific trend in any age group.

Figure 15 - Trial 3561- Subject disposition (26 week period) by age subgroups



6.1.3.2 Subject disposition - Trial NN5401-3816(IDegAsp)

Overall the patient disposition was similar between treatment groups, with minor differences.

A total of 387 patients were screened, of whom 362 were randomized (with 25 screen failures[50]). During the 16 week treatment period, the percentage of patients who discontinued treatment was 5.5%, with a numerically lower percentage for IDegAsp (4.4% for IDegAsp and 6.7% for IDet). Withdrawals seen in the IDegAsp group included 2 patients (one withdrawing for an adverse event and another withdrawing for non-compliance), while the IDet group had a higher number of patients withdrawing due to meeting withdrawal criteria (5.6% for IDet vs. 3.3% for IDegAsp)[51].

[50] 17 did not meet HbA1c criteria, 1 patient used oral antidiabetic agents, and 1 patient met the exclusion criteria of mental incapacity to participate and 6 subjects withdrew consent.
[51] Most of the subjects withdrew due to withdrawing consent.

Table 19 – Trial 3816 - Subject disposition – Summary

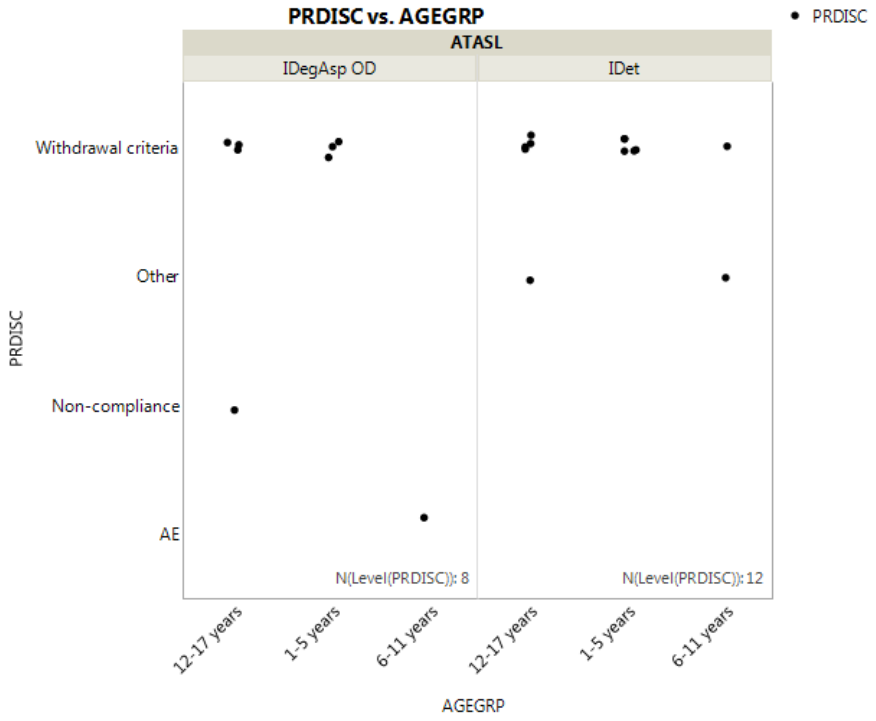
	IDegAsp		IDet		Total	
	N	%	N	%	N	%
screened					387	
Screening failure					25	
Withdrawn before randomization					0	
Randomized	182	100%	180	100%	362	100%
Exposed	181	99.5%	179	99.4%	360	99.4%
Withdrawn after/at randomization	8	4.4%	12	6.7%	20	5.5%
Adverse event	1	0.5%	1	0.05%	2	0.6%
Non-compliance	1	0.5%	0	0.00%	1	0.3%
Other	0	0.00%	1	0.6%	1	0.3%
Patient expected to be in IDegAsp arm	0	0.00%	1	0.6%	1	0.3%
Withdrawal criteria	6	3.3%	10	5.6%	16	4.4%
completed	174	95.6%	168	93.3%	342	94.5%
FAS	182	100%	180	100%	362	100%
PP analysis set	174	95.6%	171	95%	345	95.3%
SAS	181	99.5%	179	99.4%	360	99.4%

Highlighted text notes differences in the reviewer and the Sponsor's categorization of events. Patient #904003 withdrew due to intermittent but recurrent hypoglycemia attributable to trial product and was categorized as "other" by the Sponsor; the reviewer considers this reason as an adverse event, thus this patient is counted in the Adverse event category, and not the "other" category in this table.

Source: CSR 3816- table 10-1, page 90, modified by reviewer to add reasons for the 'Other' category

Figure 16 shows the subject disposition by age subgroups. Across age groups, the main reason for withdrawal was meeting withdrawal criteria.

Figure 16 – Trial 3816- Subject disposition by age subgroups



Source: Reviewer generated figure using S.xpt dataset, selecting variable PRDSC and AGEGRP, usign JMP generate graph, date 7/19/16.

Reviewer's comment: age subgroup analyses show that the there were small numerical imbalances across treatment arms in regards to reasons for withdrawal. However these imbalances do not suggest a withdrawal trend for any particular age sub group that may have resulted from exposure to the investigational product.

6.1.4 Analysis of Primary Endpoint(s)

As discussed by the 2008 Draft Guidance for industry[52], HbA1c is considered a "well-validated surrogate for the short term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus." As discussed previously, the primary endpoint for each study was to evaluate the change in HbA1c from baseline to week 26 for study 3561 and to week 16 for study 3816.

6.1.4.1 Primary Endpoint - NN1250-3561(IDeg)

Please see the Statistical review by Dr. Susie Sinks for the FDA's statistical analysis.

As stated previously, the primary endpoint was the change from baseline (week 1, visit 2) in HbA1c (%) after 26 weeks of treatment. For the overall trial, the mean baseline HbA1c was 8.2% for IDeg and 8.0% for IDet. The adjusted mean change from baseline in HbA1c at 26 weeks was -0.15 for IDeg and -0.30 for IDet (see **Table 20**). For the full analysis set population, following the intention-to-treat-principle, with last-

[52] Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

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observation-carried-forward, the adjusted mean difference (IDeg-IDet) was +0.15% with a corresponding 95% confidence interval of (-0.03; 0.32). These findings support the conclusion of non-inferiority of IDeg vs. IDet because the upper bound of the 95% confidence interval for the treatment difference is less than 0.4%, the pre-specified non-inferiority margin (see **Table 20**).

Table 20 - Trial 3561 - HbA1c (%) after 26 weeks of treatment - primary statistical analysis - FAS

	FAS	estimate	SE	95% CI
HbA1c				
LS means				
IDeg	174	7.95	0.09	
IDet	176	7.80	0.08	
Change from baseline				
LSMeans				
IDeg	174	-0.15	0.09	
IDet	176	-0.30	0.08	
Treatment contrast				
IDeg-IDet		0.15		[-0.03; 0.32]

N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of the mean The response and change from baseline in the response after 26 weeks of treatment is analysed using an ANOVA method with treatment, sex, region and age group as fixed effects and baseline response as a covariate. Missing data is imputed using last observation carried forward

Source CSR 3561, Figure 11-1, page 113

Reviewer's comment:Although IDeg meets the pre-specified non-inferiority margin, the average change from baseline in HbA1c for IDeg is numerically worse than IDet; the treatment difference (IDeg- IDet) therefore favored IDet at 26 weeks.

Evaluation of HbA1c by treatment week is shown in **Figure 17**. Overall the HbA1c trends were similar for IDeg and IDet from randomization (week 0) to week 26, there was a decrease in HbA1c in both treatment arms. The biggest HbA1c drop occurred at week 12, followed by an increase in HbA1c by week 26. When evaluating by age groups, the trends were similar across age groups; overall The HbA1c for IDeg was slightly higher than IDet at baseline and for the duration of the trial.

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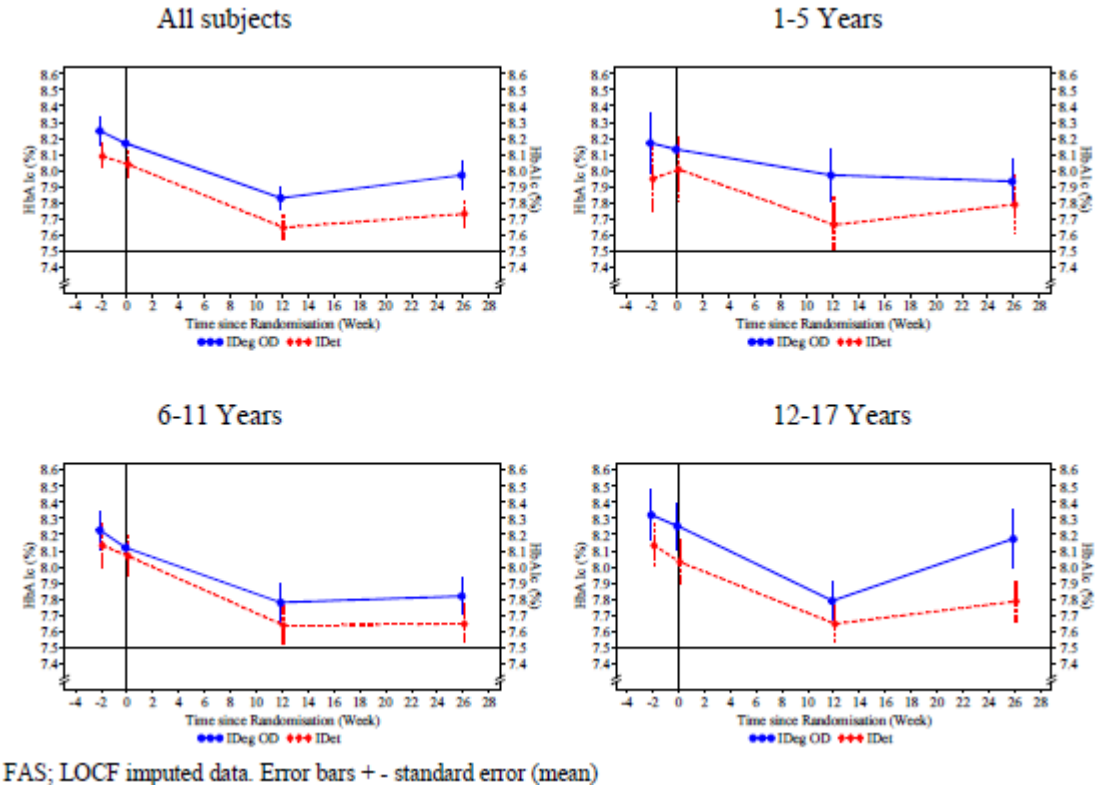
Figure 17 – Trial 3561 – HbA1c (%) by treatment week – mean plot –by ages - FAS



Source: Trial 3561- Figure 11-1, page 115

As described previously, the Sponsor performed sensitivity analyses using the per protocol analysis set[53], completer analysis set[54], and the full analysis set using a simple model[55] and the repeated measurement model[56]. The post hoc sensitivity analysis using multiple imputations[57] and the tipping point analysis were also consistent with the primary analysis and supported the non-inferiority of IDeg as compared to IDet, using the upper limit of the CI below 0.4%. Of these sensitivity analyses the highest upper bound for the 95% confidence interval for the treatment difference was 0.37.

Trial 3561 – Mean daily insulin dosage (basal, prandial, and total)

In order to interpret the primary efficacy results, the reviewer also evaluated the mean daily insulin dosage as well as the titration of insulin during the duration of the study period. As mentioned previously, the protocol did not make any specific recommendations regarding adjustment of the total insulin dose upon switching to trial drug treatment.

Table 21 shows the insulin dose at randomization and at week 26, while **Figure 18** shows the total insulin dose by study week. Both **Table 21** and **Figure 18** show that the total insulin dose across age groups was

[53] Per protocol sensitivity analysis treatment difference: IDeg OD- IDet (%-points) = 0.19 [0.01 ; 0.37]95%CI.
[54] Completer sensitivity analysis treatment difference: IDeg OD- IDet = 0.19%-points [0.01 ; 0.37]95%CI
[55] Simple model sensitivity analysis treatment difference: IDegOD- IDet = 0.16%-points [-0.02 ; 0.33]95%CI
[56] Repeated measurement model treatment difference IDeg OD- IDet = 0.18%-points [0.00; 0.36]95%CI
[57] Multiple imputations- jump to reference, treatment difference IDegOD- IDet = 0.19 [0.01 ; 0.36] 05% CI and Multiple imputations- copy reference, treatment difference IDeg OD – IDet = 0.18 [0.01 ; 0.36]95% CI

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lower for the IDeg group than the IDet group at baseline, week 26, and week 52; although overtime the total insulin dose increased in both treatment groups. Total insulin trends were consistent between different age subgroups.

At Week 26, the total insulin dose remained lower for IDeg than IDet.

Table 21 – Trial 3561 – Insulin dose at randomization, week 26 and week 52

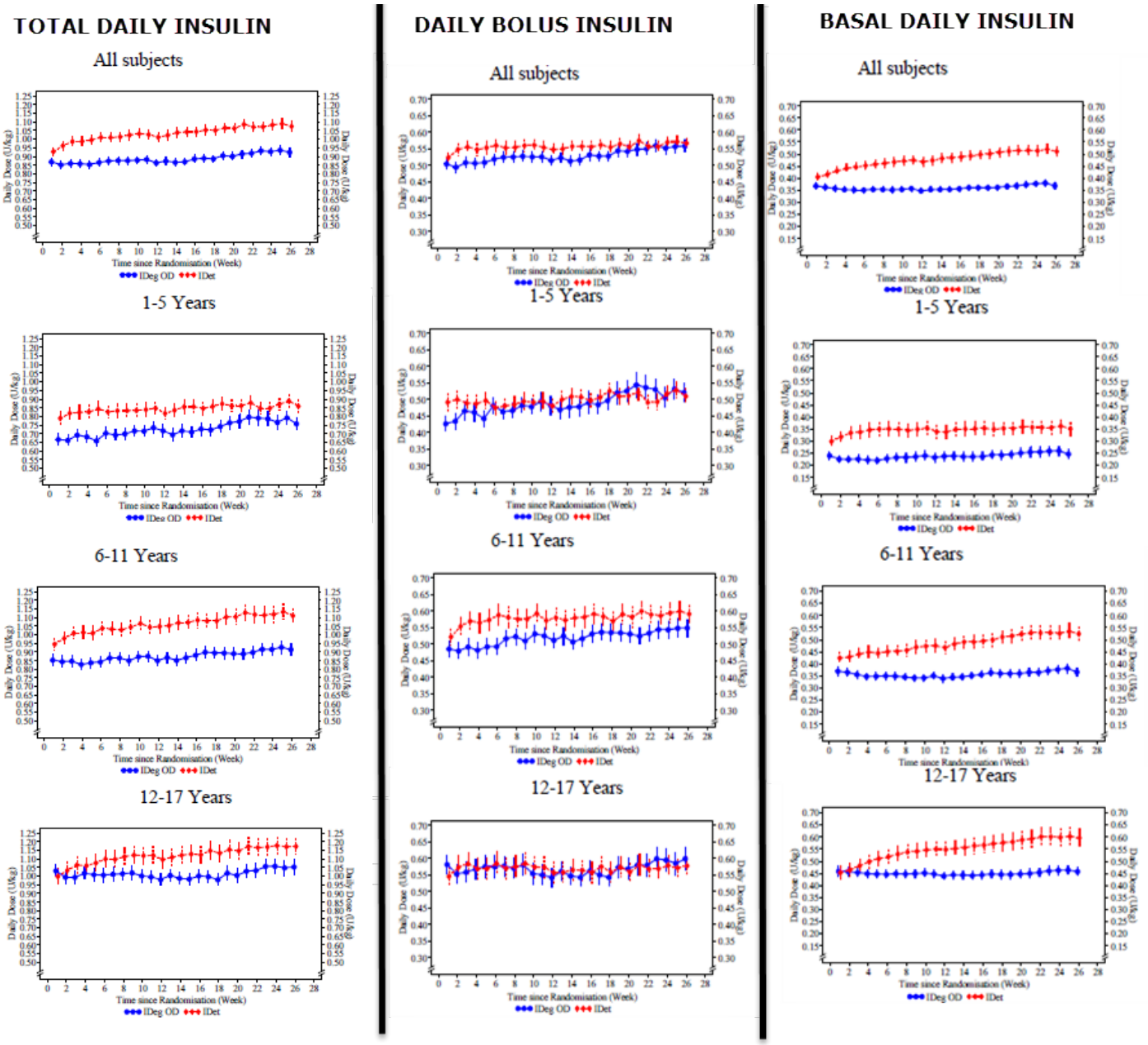
	IDeg			**IDet**		
	At randomization (week 1)	Week 26	Week 52	At randomization (week 1)	Week 26	Week 52*
All age groups combined						
Basal	**15 U** 0.37 U/kg	**16 U** 0.37 U/kg	**17 U** 0.38	**16 U** 0.41 U/kg	**22 U** 0.51 U/kg	**24** U 0.55 U/kg
Bolus	**20 U** 0.5 U/kg	**23 U** 0.56 U/kg	**24 U** 0.55 U/kg	**20 U** 0.52 U/kg	**22 U** 0.57 U/kg	**24** U 0.58 U/kg
Total	35U 0.87 U/kg	39 U 0.93 U/kg	41 U 0.93 U/kg	36 U 0.93 U/kg	44 U 1.07 U/kg	48 1.13 U/kg
1-5 years of age						
Basal	4 U 0.24	5 U 0.25	5 U 0.27 U/kg	6 U 0.30	6 U 0.34	7 U 0.37 U/kg
Bolus	8 U 0.43 U/kg	10 U 0.52 U/kg	10 U 0.47 U/kg	9 U 0.49 U/kg	9 U 0.51 U/kg	10 0.51 U/kg
Total	12 U 0.67 U/kg	15 U 0.76 U/kg	15 U 0.72 U/kg	14 U 0.79 U/kg	16 U 0.85 U/kg	17 U 0.88 U/kg
6-11 years of age						
Basal	12 U 0.37 U/kg	13 U 0.37 U/kg	15 U 0.38 U/kg	13 U 0.42 U/kg	18 U 0.52 U/kg	20 U 0.56 U/kg
Bolus	16 U 0.49 U/kg	19 U 0.55 U/kg	20 U 0.53 U/kg	16 U 0.52 U/kg	20 U 0.59 U/kg	21 0.60 U/kg
Total	28 U 0.85U/kg	33 U 0.91U/kg	35 U 0.91 U/kg	29 U 0.95U/kg	37 U 1.11U/kg	41 U 1.16 U/kg
12-17 years of age						
Basal	26 U 0.46 U/kg	27 U 0.46 U/kg	29 U 0.47 U/kg	25 U 0.45 U/kg	34 U 0.60 U/kg	38 U 0.64 U/kg
Bolus	34 U 0.58 U/kg	35 U 0.61 U/kg	38 U 0.62 U/kg	31 U 0.55 U/kg	33 U 0.58 U/kg	36 U 0.61 U/kg
Total	59 U 1.03 U/kg	62 U 1.06 U/kg	66 U 1.08 U/kg	56 U 1.0 U/kg	67 U 1.17 U/kg	75 U 1.25 U/kg

source: 3561CSR, 14.2.8-11, CSR, 14.2.39-46, CSR, 14.2.65-72, \\CDSESUB1\evsprod\NDA203314\0092
In bold are the values that the Sponsor is proposing to include in the PI
After 52 weeks of treatment, more than 60% of subjects in the insulin detemir arm were dosed BID.

Reviewer's labeling comment: in the proposed PI, the Sponsor proposes to label the mean basal and bolus doses of IDeg and IDet at 26 and 52 weeks. This labeling is consistent with the pre-existing label, where baseline basal and bolus insulin doses are already labeled. However given the range of ages in the pediatric population, the reviewer suggests that the information be presented by units/kg in addition to showing insulin units.

Figure 18 shows the trends of insulin by time and subgroup. Across age groups, similar trends were observed to the overall group. Overall, the total insulin IDeg dose was lower than the IDet at baseline and at week 26. The bolus insulin remained similar across treatment groups, which suggests that the difference in total insulin was mainly due to the basal daily insulin.

Figure 18– Trial 3561 – Total, daily bolus, and basal daily insulin doses (actual) in units/kg by treatment week– mean plot and by age groups– safety analysis set

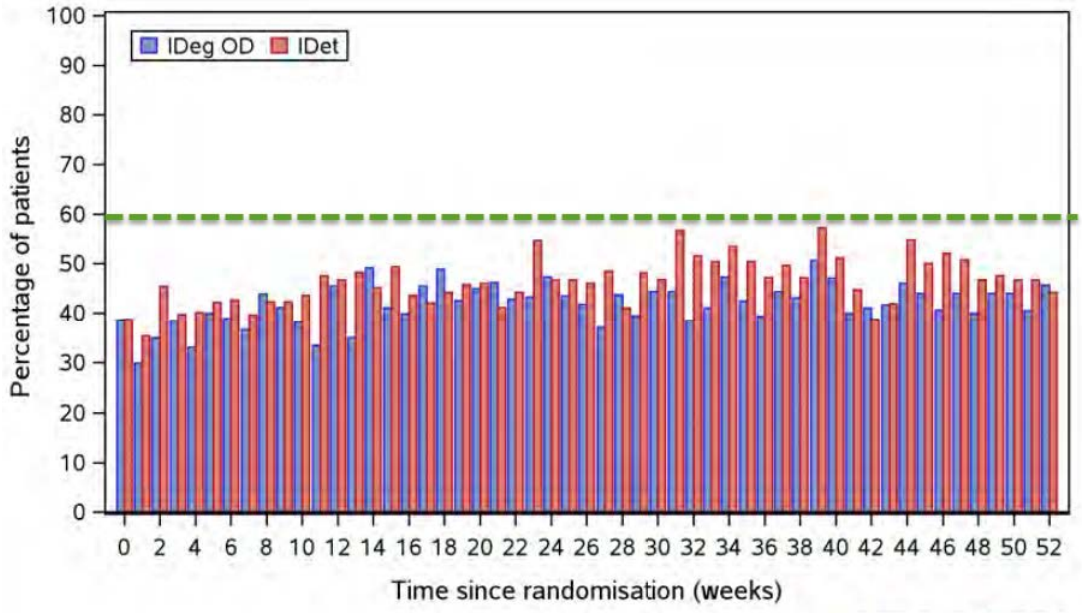


Source: CSR 3561, figure 12-1, 12-2 and 12-3

Reviewer's comment: the information on insulin doses suggests that there was minimal titration during the study period for both the IDeg and IDet arms. Perhaps some factors that contributed to the minimal titration were that there was no requirement to lower the starting dose of basal drug product at trial start or that investigators may have been conservative with titration (perhaps due to fear of hypoglycemia).

In order to explore any differences in titration between treatment arms, the reviewer sent an information request to the Sponsor to evaluate the percentage of subjects achieving SMPG titration targets by week of study. The Sponsor responded on August 18, 2016 providing the requested information (see **Figure 19**). Overall, there was a *slight* trend for higher proportion of patients randomized to IDet who reached titration goals, than patients randomized to IDeg (particularly later in the trial). These trends were maintained when evaluating by the following age groups: 1-5 years, 6-11 years and 12-17 years of age (the sub-group analysis is not show in the review).

Figure 19 – Trial 3561 main and extension- proportion of subjects reaching SMPG before breakfast target of 90-145 mg/dL by visit – full analysis set



Source: information request, \\CDSESUB1\evsprod\NDA203314\0093\m1\us, green line added to show that all values were blow 60%.

Reviewer's comment: The proportion of patients meeting titration goals was between 40% and 70%. Although there were slight differences in the percentage of patients that met glycemic goals (being slightly higher in the IDet group), there did not appear to be any systemic issues with titration identified with this analysis.

Treatment compliance

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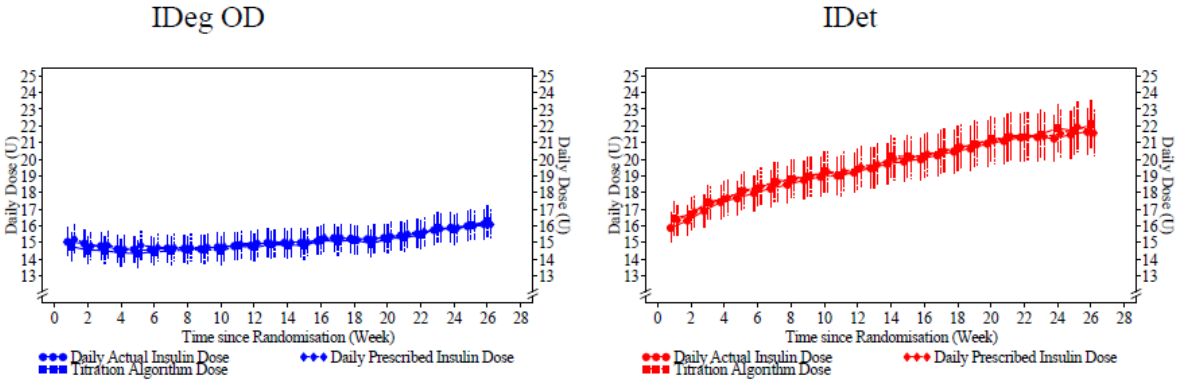
The Investigator assessed the compliance of the subject at each visit based on a review of glycemic control, adherence of the visit schedule, completion of the subject's diary including the SMPG profiles. Titration was to be performed according to the Insulin Titration Guideline in the protocol.

Drug accountability was performed at Visits 6, 10, 14, 18, 23, 28 (investigational product) and 29 (NPH). **Figure 20** shows the daily prescribed, actual and titration doses of the basal insulin.

Figure 20 – Trial 3561- Daily IDeg and daily IDet insulin dose in units by treatment week – prescribed, actual and titration algorithm dose – mean plot – safety analysis set



SAFETY; LOCF imputed data. Error bars + - standard error (mean)

Source: CSR3561, Figure 10-1, page 105

6.1.2.2 Primary Endpoint - Trial NN5401-3816 (IDegAsp)

Please see the Statistical review by Dr. Susie Sinks for the FDA's statistical analysis.

As stated previously, the primary endpoint was the change from baseline (week 1, visit 2) in HbA1c (%) after 16 weeks of treatment. Per the Sponsor's analysis, the mean baseline HbA1c was 8.1% for IDegAsp and IDet. The adjusted mean change from baseline in HbA1c at 16 weeks was -0.27 for IDegAsp and -0.23 for IDet (**Table 22**). For the full analysis set population, following the intention-to-treat-principle, using a mixed model for repeated measurements, the adjusted mean difference (IDegAsp- IDet) was -0.04 with a corresponding 95% confidence interval of (-0.23; 0.15). These findings support the conclusion of non-inferiority of IDegAsp vs. IDet because the upper bound of the 95% confidence interval for the treatment difference is less than 0.4%, the pre-specified non-inferiority margin (see **Table 22**).

Table 22 – Trial 3816 – HbA1c after 16 weeks of treatment – primary statistical analysis - FAS

	FAS	estimate	SE	95% CI

Reference ID: 4009596

HbA1c				
LS means				
IDegAsp	182	7.79	0.07	
IDet	180	7.83	0.07	
Change from baseline				
LSMeans				
IDegAsp	182	-0.27	0.07	
IDet	180	-0.23	0.07	
Treatment contrast				
IDegAsp-IDet		-0.04		[-0.23; 0.15]

FAS: Full analysis set, N: number of sugjects contributing to the analysis, CI: confidence interval, SE: Standard error of the mean, All observed HbA1c measurements available post-randomization at the scheduled measuremetn times is analyzied with a MMRM with an unstructured covariance matrix. The model includes treatment, sex, region, age-group and visit as factors and baseline HbA2c as covariate. Interactions between visit and all factors and covariates are also included in the model.

Source: CSR 3816, Table 11-1, page 109

Reviewer's comment: There was a relatively low percentage for missing HbA1c data in this study (2.7% for IDegAsp, and 3.9% for IDet), which is less likely to have affected the overall efficacy findings. Refer to the statistical review for further comments regarding missing data.

Evaluation of HbA1c by treatment week is shown in **Figure 21**. Overall the HbA1c trends were similar for IDegAsp and IDet from randomization (week 0) to week 16; there was a slight decrease in HbA1c in both treatment arms. When evaluating by age groups, patients ages 6-11 randomized to IDegAsp tended to have higher HbA1c when compared to IDet for the duration of the trial; in all other age groups HbA1c measures between treatments arms tended to be more similar.

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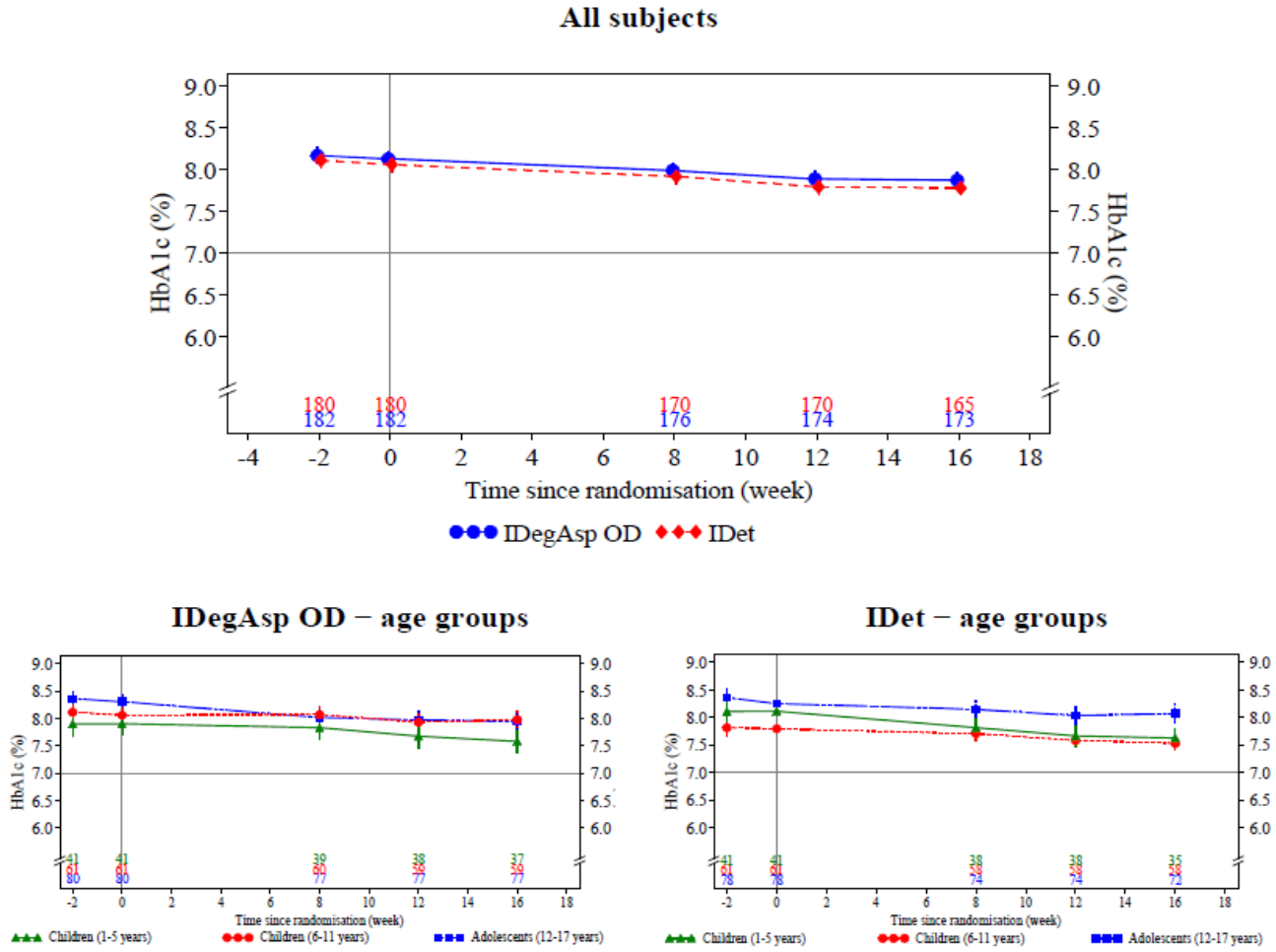
Figure 21 – Trial 3816 – HbA1c (%) by treatment week – mean plot – and subgroup by ages- FAS



Source: CSR 3816 Summary of clinical efficacy page 43, figure 3-2

Reviewer's comment: The HbA1c trends reflect a slight decrease from baseline to week 16 for both treatment arms, while the age subgroup analysis shows slight differences in HbA1c trends by age.

The Sponsor's sensitivity analyses using the per protocol analysis set[58], completer analysis set[59], ANOVA using LOCF, [60] simple model[61] were consistent with the primary analysis and supported the non-inferiority of IDegAsp compared to IDet. Of these sensitivity analyses, the highest upper bound for the 95% confidence interval for the treatment difference was 0.19.

[58] Per protocol sensitivity analysis treatment difference: IDegAsp OD- IDet (%-points) = -0.04 [-0.23 ; 0.15] 95%CI.
[59] Completer sensitivity analysis treatment difference: IDegAsp OD- IDet =-0.03 -0.22 ; 0.16]
[60] ANOVA model treatment difference: IDegAsp OD- IDet (%-points) = -0.04 [-0.22 ; 0.15] 95%CI.
[61] Simple model: IDegAsp OD- IDet (%-points) = -0.00 [-0.19 ; 0.19] 95%CI.

Reference ID: 4009596

Trial 3816 – Mean daily insulin dosage (basal, prandial, and total)

In order to interpret the primary efficacy results, the reviewer also evaluated the mean daily insulin dosage as well as the titration of insulin during the duration of the study period. As per the protocol, each subject's total daily insulin dose was to be decreased by 20% at randomization, although the ultimate decision regarding dosing was at the discretion of the investigator.

Table 23 shows the insulin dose at randomization and at week 16, while **Figure 22** shows the total insulin dose by study week.

Both **Table 23** and **Figure 22** show that the total insulin dose across age groups was lower for the IDegAsp group than the IDet group at baseline and at Week 16. When evaluating by bolus insulin. Overtime the total insulin dose increased in both treatment groups. Total insulin trends were consistent between different age subgroups.

When evaluating the overall (all ages) insulin dose, at baseline, the total insulin dose was lower for IDegAsp + meal time IAsp than for IDet + meal time IAsp. Both the basal and bolus doses were lower for IDegAsp than IDet at baseline. At Week 16, the total insulin dose remained lower for IDegAsp + meal time IAsp than IDet + meal time IAsp. Most of the difference of the total insulin dose was made up by the lower basal insulin dose for IDegAsp than IDet (the bolus insulin dose was the same in both treatment groups).

Table 23 – Trial 3816 – Insulin dose at randomization and at week 16

	IDegAsp		**IDet***	
	At randomization (week 1)	Week 16	At randomization (week 1)	Week 16
All age groups combined				
Basal	13 U 0.31 U/kg	16 U 0.36 U/kg	17 U 0.38 U/kg	22 U 0.49 U/kg
Bolus	20 U 0.49 U/kg	22 U 0.52 U/kg	23 U 0.52 U/kg	23 U 0.52 U/kg
Total	**33 U** 0.79 U/kg	**38 U** 0.88 U/kg	**40 U** 0.89 U/kg	**46 U** 1.01 U/kg
1-5 years of age				
Basal	5 U 0.27 U/kg	6 U 0.31 U/kg	5 U 0.29 U/kg	7 U 0.40 U/kg
Bolus	9 U 0.46 U/kg	10 U 0.48 U/kg	9 U 0.53 U/kg	9 U 0.51 U/kg
Total	14 U 0.73 U/kg	16 U 0.78 U/kg	14 U 0.82 U/kg	16 U 0.9 U/kg
6-11 years of age				
Basal	10 U 0.29 U/kg	12 U 0.33 U/kg	14 U 0.39 U/kg	18 U 0.49 U/Kg
Bolus	14 U 0.46 U/kg	17 U 0.51 U/kg	17 U 0.47 U/kg	18 U 0.50 U/kg
Total	24 U 0.75 U/kg	28U 0.84 U/kg	30U 0.85 U/kg	37 U 1.0 U/kg

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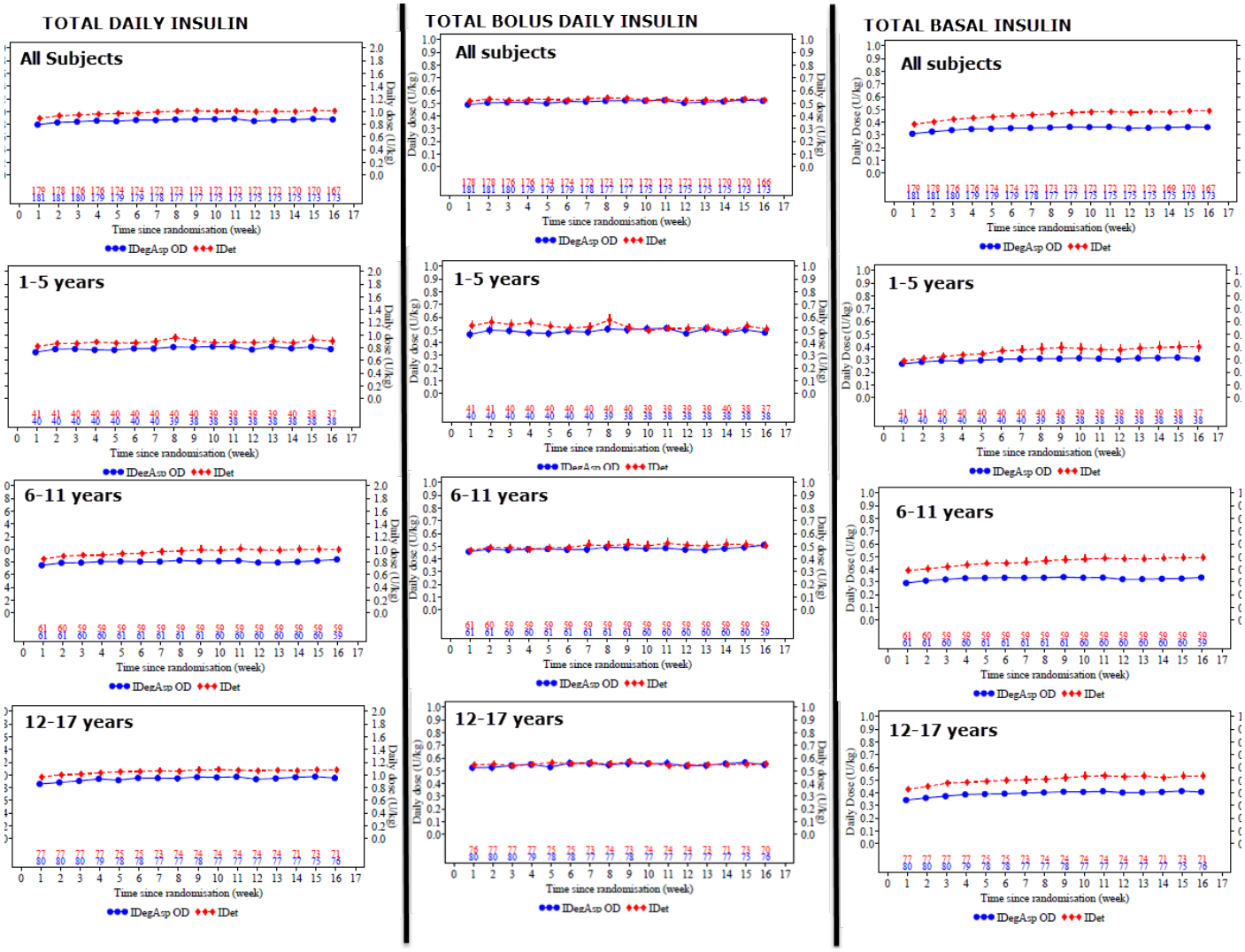
12-17 years of age				
Basal	20 U 0.34 U/kg	25 U 0.41 U/kg	26 U 0.43 U/kg	33 U 0.53 U/kg
Bolus	31 U 0.53 U/kg	33 U 0.55 U/kg	34 U 0.55 U/kg	35 U 0.55 U/kg
Total	50 U 0.86 U/kg	57 U 0.95 U/kg	60U 0.97 U/kg	68 U 1.08 U/kg
Bolded numbers are included in the proposed PI *53.9% of patients randomized to IDet were taking IDet BID at week 16.				

Reviewer's labeling comment: In the proposed PI, the Sponsor proposes to label the total daily insulin dose (including the basal and bolus insulin doses) of IDegAsp and IDet at 16 weeks. This labeling is consistent with the pre-existing label, where baseline and mean dose after end of trial are labeled. However given the range of ages in the pediatric population, the reviewer suggests that the information be presented by units/kg in addition to showing insulin units.

Across age groups, similar trends were observed to the overall group. With minor differences, the total insulin IDegAsp + meal time IAsp dose was lower than the IDet + mealtime IAsp at baseline and at week 16. Most of the difference in the total insulin dose was due to the higher basal insulin doses.

Figure 22 – Trial 3816 – actual total insulin dose (basal + bolus) [top graph], with subsets of total insulin dose by age subgroups [bottom graphs] – safety analysis set



Source: CSR 3816, figures 14.2.126 -129 and 14.2.70-14.2.73

Reviewer's comments: Similar to study 3561, there was minimal titration in this study, despite the recommended total daily dose decrease of 20% before starting of investigational trial drug.

In order to explore any differences in titration between treatment arms, the reviewer sent an information request to the Sponsor to evaluate the percentage of subjects achieving SMPG titration targets by week of study. The Sponsor responded on August 18, 2016 providing the requested graphs. Overall, there were no convincing differences between treatment groups with regards to proportion of patients reaching titration goals. When evaluating by the following age groups: 1-5 years, 6-11 years and 12-17 years of age, there was a slight trend favoring IDeg in

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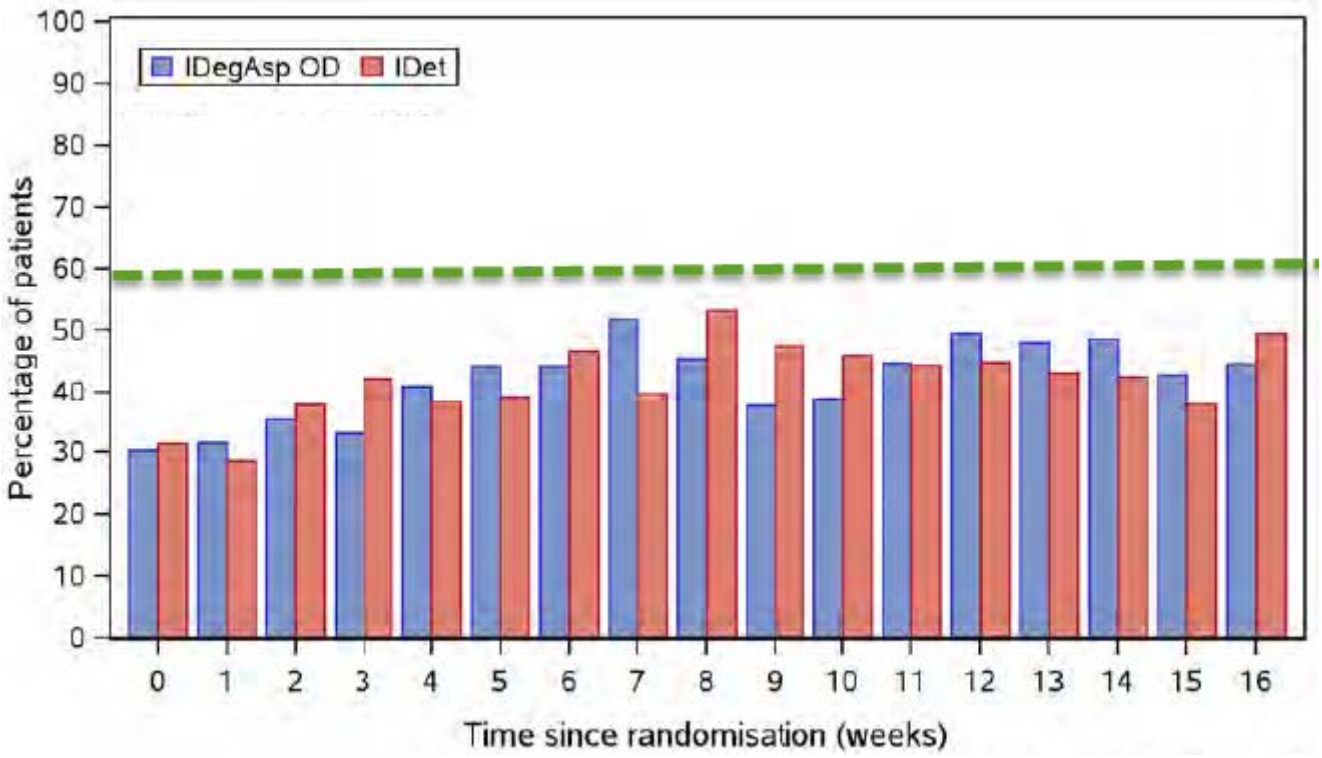
patients ages 1-5 years of age. **Figure 23** shows the overall proportion of patients reaching titration targets by study week.

Figure 23 – Trial 3816- proportion of subjects reaching SMPG before breakfast target of 90-145 mg/dL by visit – full analysis set



Source: information request, \\CDSESUB1\evsprod\NDA203314\0093\m1\us, green line added by reviewer to show that all values were blow 60%.

Reviewer's comment: Similar to the observations for trial 3561, the slight differences noted in the percentage of patients that met glycemic goals did not appear to suggest any systemic issues with titration.

Treatment compliance

The Investigator assessed the compliance of the subject at each visit based on a review of glycemic control, adherence of the visit schedule, completion of the subject's diary including the SMPG profiles. Titration was to be performed according to the Insulin Titration Guideline in the protocol.

Drug accountability was performed at Visits 4, 8, 12, and 16 (visits 6, 10, 14 and 18). **Figure 24** shows the daily prescribed, actual and titration doses of the basal insulin.

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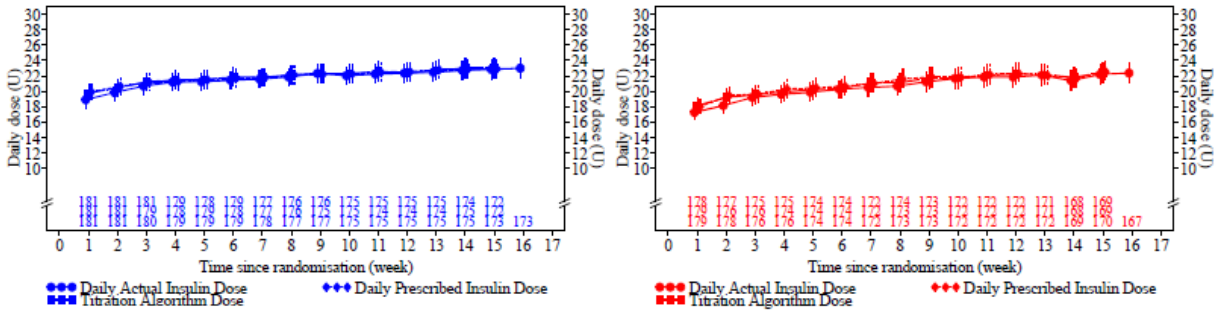
Figure 24 – Trial 3816 - Daily IDegAsp (left plot) and Daily IDet (right plot) insulin dose in units by treatment week - prescribed, actual and titration algorithm dose- mean plot- safety analysis set



Source: CSR 3816, Figure 10-1 page 101

6.1.5 Analysis of Secondary Endpoints(s)

Neither trial had confirmatory secondary endpoints that were adjusted for multiplicity. See section **5.3 Discussion of Individual Studies/Clinical** Trials, for a description of secondary endpoints in these trials. The reviewer will focus the review of secondary endpoints which the Sponsor proposes to label and for which the statistical analysis plan pre-specified a statistical analysis.

The remaining secondary endpoints are not discussed in detail due to inherent problems with bias (i.e, 8 point SMPG measurement requires home measurements), because they are considered exploratory and because they are not being proposed in labeling.

6.1.5.1 Secondary Endpoints - NN1250-3561(IDeg)

Change from baseline to week 52 in HbA1c
Change in HbA1c at 52 weeks was a secondary endpoint in this trial. **Table 24** shows that the change from baseline HbA1c at the end of 52- weeks was similar between treatment arms. The adjusted mean change from baseline in HbA1c was -0.2 for IDeg and -0.19 for IDet (see **Table 20**). For the full analysis set population with last-observation-carried-forward, the adjusted mean difference (IDeg-IDet) was -0.01% with a corresponding 95% confidence interval of (-0.2; 0.19). In the 52 week data the missing data was 13.2% for IDeg, and 30.7% for IDet. There was no pre-specified statistical testing in the protocol, nor adjustment for multiplicity.

Table 24 - Trial 3561 - HbA1c (%) after 52 weeks of treatment - primary statistical analysis - FAS

	FAS	estimate	SE	95% CI
HbA1c				
LS means				
IDeg	174	7.91	0.09	
IDet	176	7.91	0.08	
Change from baseline				
LSMeans				
IDeg	174	-0.2	0.09	
IDet	176	-0.19	0.09	
Ttreatment contrast				
IDeg-IDet		-0.01		[-0.2; 0.19]

FAS: Full analysis set, N: Number of subjects contributing to analysis, CI: Confidence interval, SE: Standard error of the mean
The response and change from baseline in the response after 52 weeks of treatment was analyzed using an ANOVA method with treatment, sex, region and age group as fixed effects and baseline response as a covariate. Missing data are imputed using last observation carried forward

Source- CSR 3561- extension period, table 11-1

Reviewer's labeling comments: The current proposed Prescriber's information (PI) includes the HbA1c at 52 weeks with the adjusted mean change from baseline (as listed in the table above). The clinical reviewer defers to the statistical reviewer to evaluate the impact of missing data in the 52 week results.

As shown in **Figure 25**, the trends of HbA1c were similar between treatment arms and across 1-5 and 6-11 age groups. For the 12-17 age group there was worse glycemic control for IDeg than IDet at week 52.

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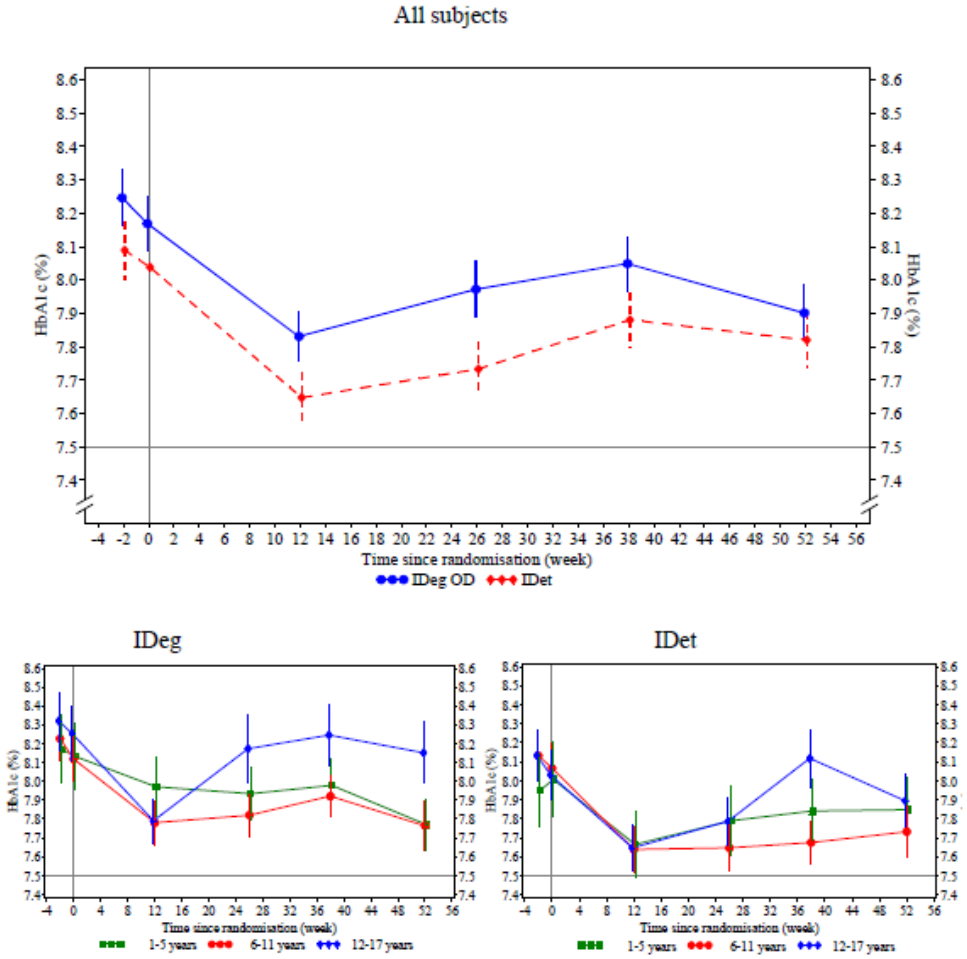
Figure 25 – Trial 3561- 52 weeks- HbA1c by treatment week- mean plots (all subjects- upper panel and age groups- lower panel) –FAS-LOCF



Source: Trial 3561 extension CSR , Figure 11-1 page 136

Change in fasting plasma glucose (FPG) at 26 weeks

Figure 26 shows the FPG values up to 26 weeks, by age groups. The overall trends for IDeg showed a decrease of -12.1 mg/dL in FPG from a baseline of 162 mg/dL to 149.4 mg/dL; while for IDet there was an increase of +9 mg/dL in FPG from a baseline mean of 151.2 mg/dL to 160.2 mg/dL. Trends based on age groups showed that for IDeg, FPG decreased or remained somewhat stable for all age groups; while for IDet, FPG remained relatively constant for ages 12-17, and increased for ages 1-5 and 6-11.

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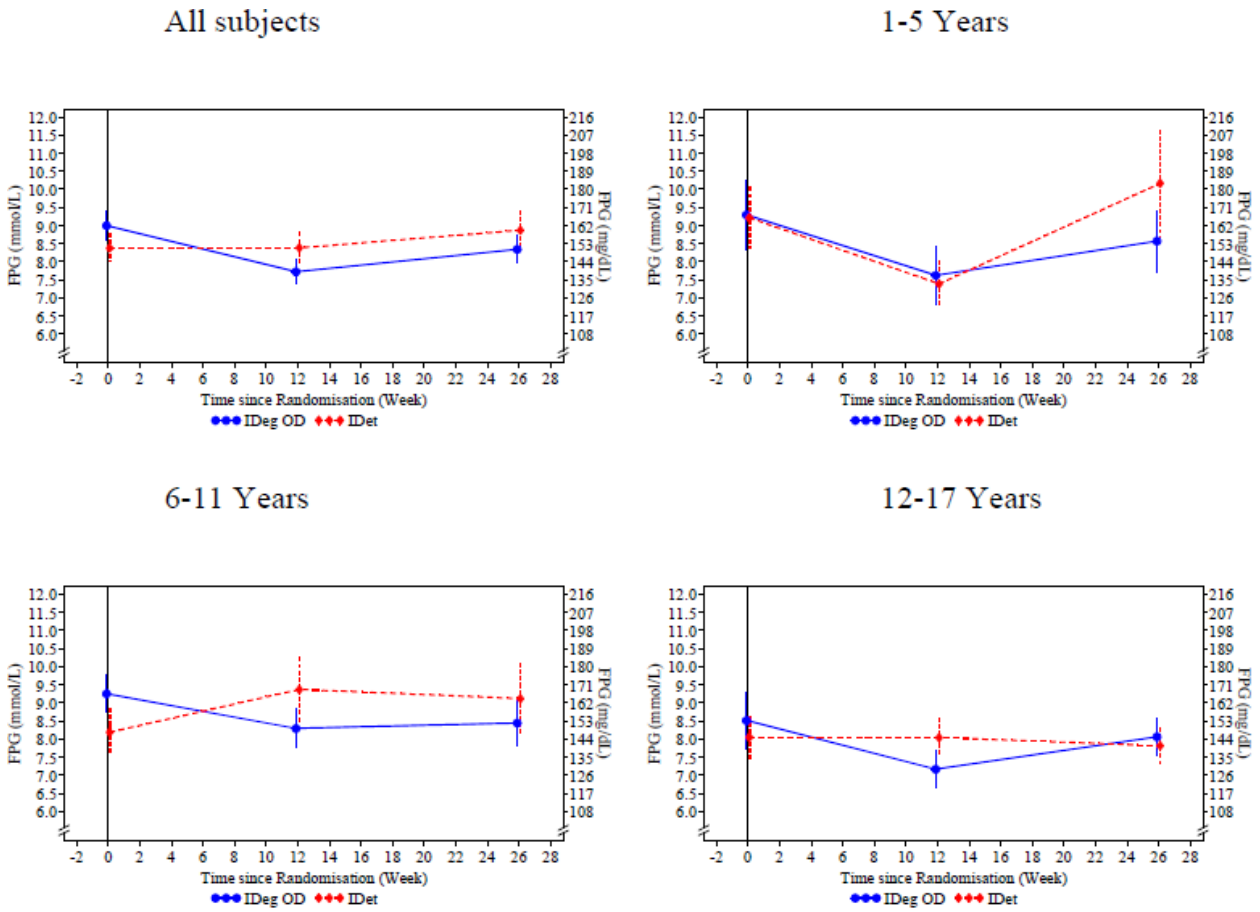
Figure 26 – Trial 3816- FPG by treatment week – mean plots (all subjects - top; by age groups - bottom)



Source: CSR 3816, figure 11-2, page 117

Reviewer's comment: The 26 week-FPG trends show an overall better glycemic control at week 26 by IDeg than by IDet, these trends are in contrast to the HbA1c trends, which show overall better control with IDet than IDeg. Because multiple factors (preceding: meal, physical activity, insulin dose) affect FPG; FPG is considered to be more variable, than with HbA1c which measures the average 120 days of glycemia.

Change in fasting plasma glucose (FPG) at 52 weeks

Figure 27 shows the FPG values to 52 weeks by age groups; in general the glycemic trends observed in the initial 26 weeks, continued until week 52. IDeg showed a decrease of 23.22 mg/dL in FPG from a baseline of 162 mg/dL to 140.4 mg/dL; for IDet there was an increase of 19.8 mg/dL in FPG from a baseline mean of 151.2 mg/dL to 171 mg/dL. Trends based on age groups showed that for IDeg, FPG decreased or remained somewhat stable from baseline for all age groups, while for IDet, FPG increased for all age groups, but more so for ages 1-5 years.

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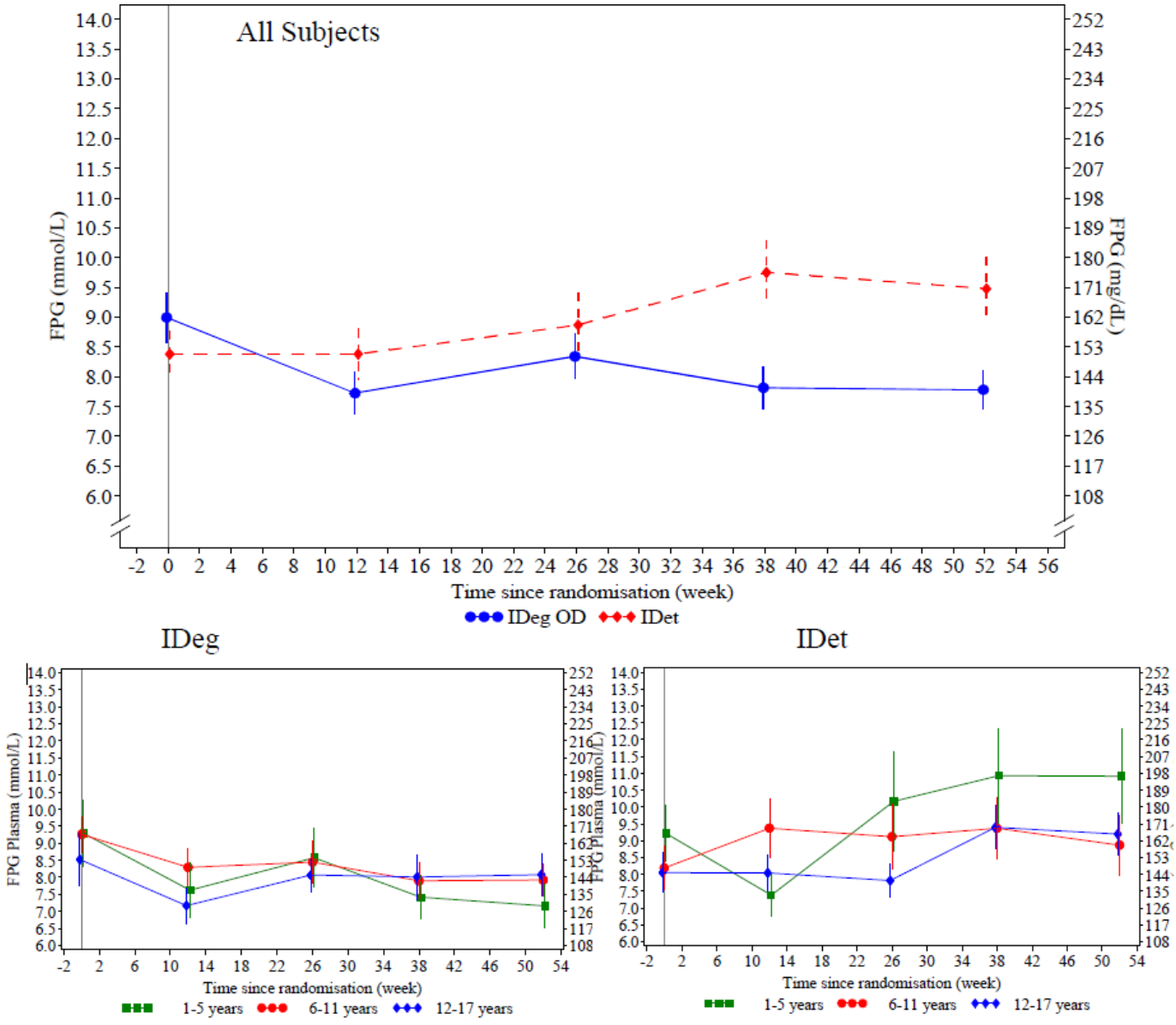
Figure 27 – Trial 3561- 52 week data- Fasting plasma glucose by treatment week – mean plots (upper panel: all subjects; lower panel: age groups)



AS: LOCF imputed data. Error bars + - standard error (mean)

Source: CSR 3561-ext, Figure 11-2, page 138

6.1.5.2 Secondary Endpoint - Trial NN5401-3816 (IDegAsp)

Change in fasting plasma glucose (FPG) at 16 weeks

Figure 28 shows the FPG values throughout the trial by age groups. The overall trends for IDegAsp showed a decrease of 5.4 mg/dL in FPG, while for IDet there was a decrease of 1.8 mg/dL. Trends based on age groups showed that for IDegAsp, FPG remained relatively stable or

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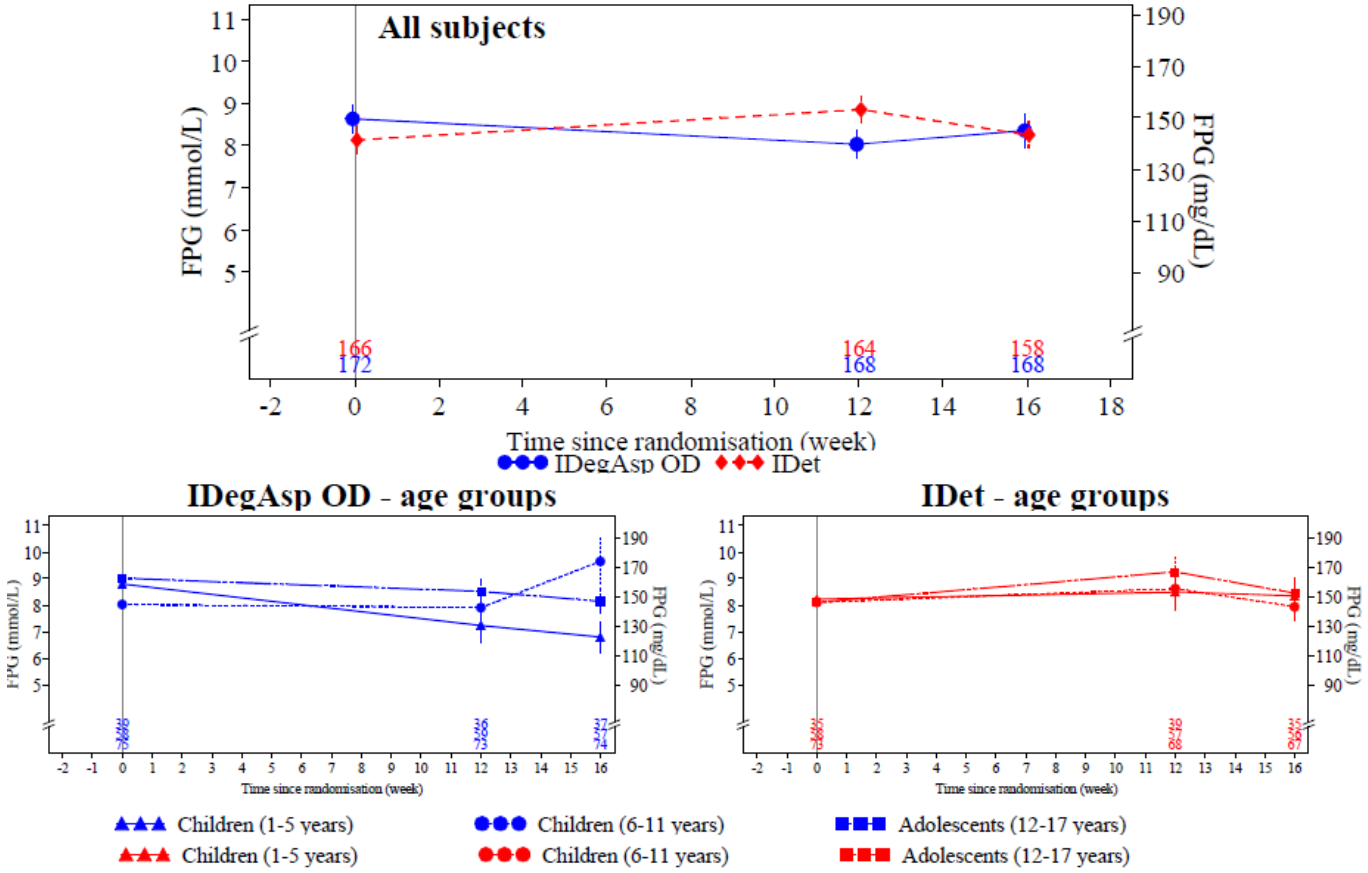
declined in both treatment groups, with the exception of patients ages 6-11 randomized to IDegAsp, who had an increase in FPG from week 12 to week 16.

Figure 28 – Trial 3816 - Fasting plasma glucose by treatment week – mean plots (upper panel: all subjects; lower panel: age groups)



FAS; Observed data. Error bars + - standard error (mean). Numbers of subjects contributing to the data points are provided in the bottom section of each plot. In the lower panel, the age groups are presented from top to bottom: children 1-5 years, children 6-11 years, adolescents 12-17 years.
Source: CSR 3816, modified Figure 11-2, page 114

Reviewer's comment: Overall the FPG trends are similar to the HbA1c trends.

6.1.6 Other Endpoints

No other endpoints are proposed for labeling

6.1.7 Subpopulations

No statistical subgroup analyses have been performed.

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6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Analysis of clinical information relevant to dosing is discussed throughout this review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Not applicable.

6.1.10 Additional Efficacy Issues/Analyses

As previously discussed, the Division agreed that clinical studies in pediatric patients with type 2 diabetes mellitus would not be required under PREA, if data from pediatric patients with type 1 diabetes mellitus was adequate to support use of IDeg or IDegAsp in pediatric patients with type 2 diabetes mellitus. The efficacy results in this submission support the indication for pediatric T2DM patients for both IDeg and IDegAsp.

7 Review of Safety

Safety Summary

Insulin degludec (IDeg) safety

The evaluation of safety of insulin degludec includes the 26 week efficacy period and the 26-week safety extension.

There were no deaths reported in the 52 week treatment period. When comparing across treatment groups, there were small numerical differences between serious adverse events, without clear trends. Most adverse events occurred in single individuals, without notable differences when examining by age subgroups (1-5, 6-11 and 12-17 years).

Dropouts and discontinuations due to adverse events were few and only seen in the insulin detemir group. An analysis of adverse events resulting in dose reduction, however, showed a numerical imbalance favoring insulin detemir. This imbalance was due to a larger proportion of subjects undergoing a dose reduction due to hypoglycemia in the insulin degludec group. The evaluation of hypoglycemia, as defined by International Society for Pediatric and Adolescent Diabetes (ISPAD) for severe hypoglycemia and documented symptomatic hypoglycemia showed a numerical imbalance favoring insulin detemir for hypoglycemia (severe hypoglycemia: adjusted event rate of 51 events per 100 patient year exposure for insulin degludec vs. 40 events per 100 year exposure for insulin detemir), particularly in the first month of starting insulin degludec. The FDA's statistical analyses of hypoglycemia however did not reveal a pattern showing a higher rate of hypoglycemia for insulin degludec compared to insulin detemir.

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There was no noted increased risk, over what has been labeled for adult patients, due to medication errors, injection site reactions or immunogenicity.

The adjusted event rate of common adverse events was similar between treatment groups and included more categories related to the system organ class of Infections and Manifestations than what is already labeled for the adult trials.

Insulin degludec/insulin aspart (IDegAsp) safety summary

The evaluation of safety of insulin degludec/insulin aspart includes the 16 week duration of the study.

There were no deaths reported. When comparing serious adverse events across treatment groups, there was a higher patient event rate exposure per 100 years (PYE) for the IDegAsp vs. IDet group (26 event rate PYE vs 13 event rate per 100 PYE). This difference was mostly accounted by the preferred terms related to hypoglycemia. Dropouts and discontinuations due to adverse events were few (one patient in each treatment arm). An analysis of adverse events resulting in dose reduction, however, showed a numerical imbalance favoring insulin detemir. This imbalance was due to a larger proportion of subjects undergoing a dose reduction due to hypoglycemia in the insulin degludec/insulin aspart group. The evaluation of hypoglycemia, as defined by International Society for Pediatric and Adolescent Diabetes (ISPAD) for severe hypoglycemia showed a numerical imbalance favoring insulin detemir (event rate of 26 events per 100 patient years for insulin degludec/aspart versus 7 events per 100 patient years for insulin detemir). The rate of documented symptomatic hypoglycemia was reversed, favoring insulin degludec/insulin aspart (the finding was driven by a larger number of events in fewer patients randomized to insulin detemir). The FDA's statistical analyses of hypoglycemia however did not reveal a pattern showing a higher rate of hypoglycemia for IDegAsp compared to IDet.

There was no noted increased risk over what has been labeled due to medication errors or injection site reactions.

The adjusted event rate of common adverse events was similar between treatment groups and included more categories related to the system organ class of Infections and Manifestations than what is already labeled for the adult trials.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Since this application contained one study in support of IDeg and one study in support of IDegAsp, there is no integrated (pooled) summary of safety provided in this efficacy supplement. Therefore, the reviewer evaluated safety from the individual study reports: study 3561 (for IDeg) and for study 3816 (for IDegAsp). Because study 3561 had an additional 26 week safety

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extension, the entire 52 week period is considered for safety purposes[62]. The safety findings for each study will be discussed separately within each subheading in the safety review.

7.1.2 Categorization of Adverse Events

Adverse events were coded using different MedDRA versions, for Trial 3561, all adverse events were coded using the MedDRA version 16; for trial 3816, all adverse events were coded using MedDRA version 17. There were no events adjudicated in either trial. The MedDRA hierarchy that will be used in this review will include preferred terms (PT) and system organ class terms (SOC).

For both trials, an adverse event (AE) is defined as any untoward medical occurrence in a subject administered a product and which does not necessarily have a causal relationship with this treatment. An AE can include abnormal laboratory finding, symptoms, disease associated with use of the product, a clinically worsening of a concomitant illness and hypo- and hyperglycemic episodes. For trial 3816, any episode of self-measured blood ketones>1.5mmol/L was also considered an AE; ketones were not specified as an AE for trial 3561.

In both trials, serious adverse events (SAEs) were defined as[63] AEs that result in any of the following: death; a life-threatening experience; in-patient hospitalization, or prolongation of exiting hospitalization; persistent or significant incapacity; and congenital anomaly or birth defect.

The following medical events of special interest (MESI) were identified in both trials:
- Medication errors concerning trial products[64]
- Severe hypoglycemia, as defined by the ISPAD[65]
- Neoplasms
- (For trial 3561 only) elevated blood ketones >1.5 mmol/L
- (For trial 3561 only) adverse events leading to withdrawal

All AEs were reported spontaneously by the subject and recorded by the investigator at each contact.

[62] Safety information for the 52 week period was obtained from the Study report for "Trial ID NN1250-3561-main-ext

[63] All SAEs were to be followed up until the outcome of the event was "recovered", "recovered with sequelae" or "fatal", and until all queries had been resolved. Cases of chronic conditions, cancer or AEs ongoing at time of death (where death was due to another AE) could be closed with the outcome "recovering" or "not recovered", when the subject had completed the follow up period.

[64] This included administration of wrong drug, wrong route of administration, administration of a high dose with intention to cause harm, administration in an accidental overdose.

[65] Child with altered mental status and cannot assist in their own care, is semiconscious or unconscious or in a coma with or without convulsions and may require parenteral therapy (glucagon or IV glucose)

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A treatment emergent adverse event (TEAE) was defined as an event with onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day on randomized treatment.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Pooling was not applicable for the evaluation of safety since each study in the submission was evaluated individually.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

This section discusses the exposure to IDeg and IDegAsp separately. Exposure is also evaluated by subgroups in the population of each trial.

Reviewer's comment: In previous communications on March 21, 2011, the FDA agreed that clinical data from pediatric populations outside of the United States could be used in support of FDA approval provided the data demonstrate safety and effectiveness in pediatric patients and the trials were conducted in a manner relevant to how the product will be used in the United States.

7.2.1.1 Exposure Trial NN1250-3561(IDeg)

When considering the main and extension period, 174 subjects, had a mean exposure to IDeg of 0.93 years; while 175 subjects had a mean exposure to IDet of 0.84 years. At 26 weeks (the main trial), exposure was similar between treatment groups, with 96% of IDeg participants and 91.4% of IDet participants[66] having a duration of exposure between 25-28 weeks. Approximately, 87% of subjects in the IDeg arm and 70% of subjects in the IDet arm were exposed for at least 49 weeks. The exposure trends continued to show higher exposure to IDeg then IDet, when evaluating across age groups, as shown in **Figure 29**.

[66] Based on the FAS, the N for IDeg was 174 (100%) and 175 for IDet (100%)

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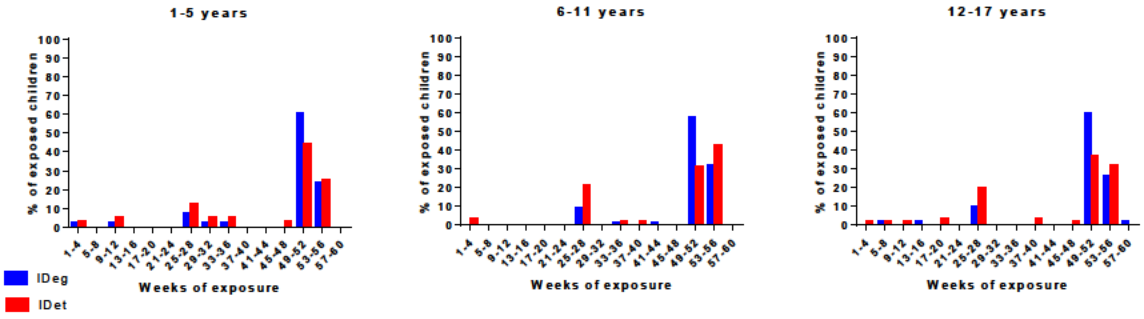
Figure 29 – Trial 3561- exposure by age group and treatment week- summary- safety analysis set



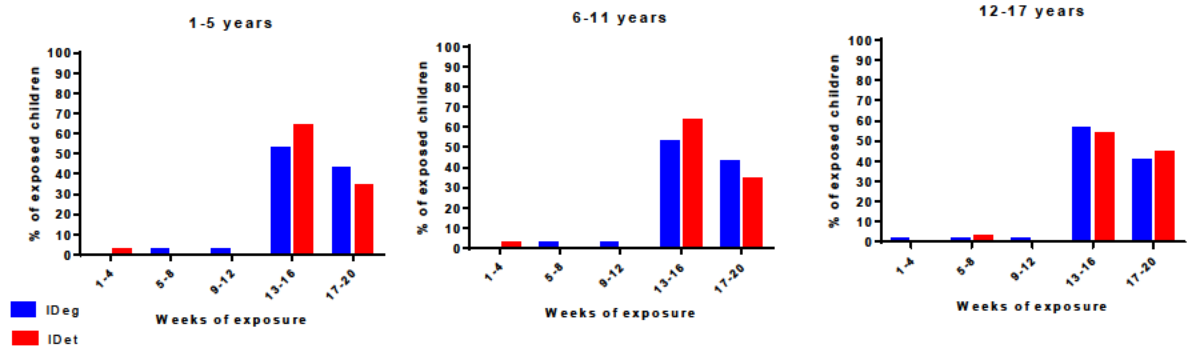
Source: reviewer graphed the exposure summary data in CSR 3561-ext, table 14.2.8, page 339.

Reviewer's comment: the exposure to IDeg in this trial was adequate

7.2.1.2 Exposure Trial NN5401-3816 (IDegAsp)

The mean exposure was similar between treatment groups, approximately 97% of subjects had at least 13 weeks of treatment (96.7% of patients randomized to IDegAsp and 97.2% of subjects randomized to IDet). The mean exposure was 0.3 mean years in each arm. Exposure by subgroups was similar throughout the duration of the study for either treatment group, see **Figure 30**.

Figure 30 – Trial 3816- exposure by age group and treatment week- summary- safety analysis set



Source: reviewer graphed the exposure summary data in CSR 3816, table 14.2.6, page260.

Reviewer's comment: As mentioned previously, the trial duration was agreed upon between the Sponsor and the Division. However, when compared to other trials (in the adult population), 16

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weeks duration is relatively short in evaluating safety in glycemic control trials, and may result in underestimation of safety signals that occur with longer exposure.

7.2.2 Explorations for Dose Response

Both IDeg and IDegAsp were titrated to glycemic goals; explorations of dose response are not applicable.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable to this efficacy supplement. In prior correspondence with the Sponsor on March 21, 2011, the FDA stated that the juvenile toxicity study was not necessary based on the animal data with IDeg and the approved product for insulin aspart.

7.2.4 Routine Clinical Testing

Safety assessments in both trials included monitoring and collection of adverse events, physical examinations, vital signs, body weight, and clinical laboratory testing as shown in **Table 25**.

Table 25 – Laboratory testing (centrally and non-centrally measured)

	Trial 3561	**Trial 3816**
Centrally measured laboratories	HbA1c Fasting plasma glucose [a] Safety laboratory assessments: hematology; biochemistry; lipids; serum β-HCG pregnancy tests [b] Antibodies Pharmacokinetics	HbA1c Fasting plasma glucose [a] Safety laboratory assessments: hematology; biochemistry; lipids; serum β-HCG pregnancy tests [b]
Laboratories not centrally measured	SMPG [c] Ketones [c]	SMPG [c] Ketones [c]

[a] A home blood sampling kit was provided to collect the FPG sample at home if preferred. All FPG samples, whether collected at home and at the clinic, were analyzed at a central laboratory.
[b] Additional pregnancy tests could be conducted locally if a menstrual period was missed or if pregnancy was suspected.
[c] SMPG and ketone measurements were made using a dual function glucose/ketone meter (b) (4) (b) (4) plasma-calibrated glucose test strips and ketone strips supplied by Novo Nordisk.

7.2.5 Metabolic, Clearance, and Interaction Workup

Please refer to the original NDA review for IDeg and IDegAsp.

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7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Please refer to the original NDA for IDeg and IDegAsp for a discussion of these issues in the original review. Hypoglycemia, immunogenicity and injection site reactions are adverse events that are associated with insulin use. These adverse events will be discussed in a separate section of the review: hypoglycemia and injection site reactions, section **7.3.4 Significant Adverse Events** and immunogenicity, section **7.4.6 Immunogenicity.**

7.3 Major Safety Results

7.3.1 Deaths

There were no deaths reported in either trial.

7.3.2 Nonfatal Serious Adverse Events

In this section the reviewer evaluates the incidence of non-hypoglycemia-associated nonfatal SAEs. Hypoglycemia-associated SAEs and severe hypoglycemia are discussed in section **7.3.4 Significant Adverse Events**. Because the physiology of children varies by age, the reviewer also evaluated SAEs by age groups.

7.3.2.1 Nonfatal Serious Adverse events- Trial NN1250-3561 (IDeg)

Table 26 shows the SAEs by SOC and PT during the 52 week trial period. In total there were 34 patients that experienced 49 SAEs. Both Infections and Infestations and Metabolism and Nutrition disorders SOCs had the highest event rate with 4 events per 100 patient year exposure (PYE) for each SOC.

When comparing across treatment groups by SOC or single PT's, there were small numerical differences between SAEs, without clear trends; with most PT categories occurring in single individuals.

Review of the trends of PT terms in **Table 26** suggests some splitting for the categories of hypoglycemia[67] and hyperglycemia. The hypoglycemia trends will be discussed in section **7.3.4 Significant Adverse Events**; the hyperglycemia trends are evaluated further below.

67 As shown in **Table 26,** the PT terms "loss of consciousness" and "convulsion," do not suggest a hypoglycemia cause; while the PT terms "hypoglycemia," "hypoglycemic seizure," "hypoglycemic unconsciousness" and "accidental overdose" **do** suggest a hypoglycemic cause.

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Table 26 – Trial 3561- Serious adverse events by SOC and PT- treatment emergent- summary - safety analysis set

	IDEG				IDET				TOTAL			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	174				175				349			
Events	18	10.3	25	15	16	9.1	24	16	34	9.7	49	16
Infections and infestations	**5**	**2.9**	**5**	**3**	**7**	**4**	**7**	**5**	**12**	**3.4**	**12**	**4**
Appendicitis	1	0.6	1	1	2	1.1	2	1	3	0.9	3	1
Gastroenteritis	1	0.6	1	1	2	1.1	2	1	3	0.9	3	1
Gastroenteritis viral					2	1.1	2	1	2	0.6	2	1
Bronchitis	1	0.6	1	1					1	0.3	1	0
Pharyngitis					1	0.6	1	1	1	0.3	1	0
Respiratory tract infection viral	1	0.6	1	1					1	0.3	1	0
Urinary tract infection	1	0.6	1	1					1	0.3	1	0
Metabolism and nutrition disorders	**6**	**3.4**	**9**	**6**	**4**	**2.3**	**4**	**3**	**10**	**2.9**	**13**	**4**
Hypoglycemia	5	2.9	7	4	2	1.1	2	1	7	2	9	3
Ketosis	1	0.6	1	1	1	0.6	1	1	2	0.6	2	1
Dehydration					1	0.6	1	1	1	0.3	1	0
Diabetic ketoacidosis	1	0.6	1	1					1	0.3	1	0
Nervous system disorders	**4**	**2.3**	**4**	**2**	**5**	**2.9**	**6**	**4**	**9**	**2.6**	**10**	**3**
Hypoglycemic seizure	1	0.6	1	1	3	1.7	4	3	4	1.1	5	2
Hypoglycemic unconsciousness	1	0.6	1	1	1	0.6	1	1	2	0.6	2	1
Convulsion^	1	0.6	1	1					1	0.3	1	0
Headache	1	0.6	1	1					1	0.3	1	0
Loss of consciousness*					1	0.6	1	1	1	0.3	1	0
Investigations	**2**	**1.1**	**3**	**2**	**2**	**1.1**	**4**	**3**	**4**	**1.1**	**7**	**2**
Blood ketone body increased	1	0.6	2	1	2	1.1	4	3	3	0.9	6	2
Body temperature increased	1	0.6	1	1					1	0.3	1	0
Injury, poisoning and procedural complications	**3**	**1.7**	**3**	**2**					**3**	**0.9**	**3**	**1**
Accidental overdose~	1	0.6	1	1					1	0.3	1	0
Toxicity to various agents	1	0.6	1	1					1	0.3	1	0
Wrong drug administered	1	0.6	1	1					1	0.3	1	0
Gastrointestinal disorders	**1**	**0.6**	**1**	**1**	**1**	**0.6**	**1**	**1**	**2**	**0.6**	**2**	**1**
Fecaloma	1	0.6	1	1					1	0.3	1	0
Vomiting					1	0.6	1	1	1	0.3	1	0
Psychiatric disorders					**1**	**0.6**	**1**	**1**	**1**	**0.3**	**1**	**0**
Anxiety disorder					1	0.6	1	1	1	0.3	1	0
Respiratory, thoracic and mediastinal disorders					**1**	**0.6**	**1**	**1**	**1**	**0.3**	**1**	**0**
Cough					1	0.6	1	1	1	0.3	1	0

N= number of subjects, %= percentage of subjects, E= number of events, R=event rate per 100 exposure years
*Narrative of subject # 904001 suggests that the 17 year old patient had "too much alcohol" and lost consciousness, blood glucose was 252 mg/dL at the hospital, there were no ketones measured.
^Narrative of subject # 124007 suggests that the 6 year old patient who had a seizure. Blood glucose at the time of the event was 204 mg/dL and was "never lowered" per the report.
~Narrative of subject#102012 of an 11 year old male took 16 units of detemir at bed time and whose mother also gave him an additional dose of 16 units, blood glucose in the morning was 63 mg/dL and patient was asymptomatic

Source: Trial 3561- ext, table 12-15, page 172

The PT terms "Ketosis" and "blood ketone body increased" can be grouped (and to minimize confusion, call "high ketones") for an evaluation of overall events of serious ketosis. By

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grouping these PT terms, the event rate of "high ketones" is 2 events per 100 PYE for IDeg and 4 events per 100 PYE for IDet. Of note, other non-SAE events of ketosis will be discussed in section **7.3.4 Significant Adverse Events.**

Reviewer's comment: The SAEs in the T1DM pediatric population is consistent with the adverse events that would be expected in this age group (as compared to SAEs in the adult T1DM population which had more events of macrovascular disease). All insulins, including insulin degludec, are labeled for the risk of hyper-and hypoglycemia. The SAEs, as identified by the Sponsor in the pediatric population, do not change the already labeled safety profile for IDeg.

Figure 31 shows an exploratory analysis that the reviewer created using the Sponsor provided adverse event dataset. Please note that there are slight differences in the counts provided by the Sponsor (shown in **Table 26**) and those shown in the reviewer-generated figures. Because the purpose of the reviewer-generated figure is to evaluate trends, these differences do not drastically alter the conclusions drawn.

In **Figure 31**, the dotted green rectangle highlights PT terms associated with hypoglycemia. And the "*" groups the terms associated with "hyperglycemia." When comparing IDeg and IDet by age groups, the trends for hypoglycemia and hyperglycemia are similar. It is worth noting, however that regardless of treatment group, patients ages 5 or below are more predisposed to have events associated with hyperglycemia (as noted by the "*"). Given that the numbers are overall small; this observation may be a numerical imbalance.

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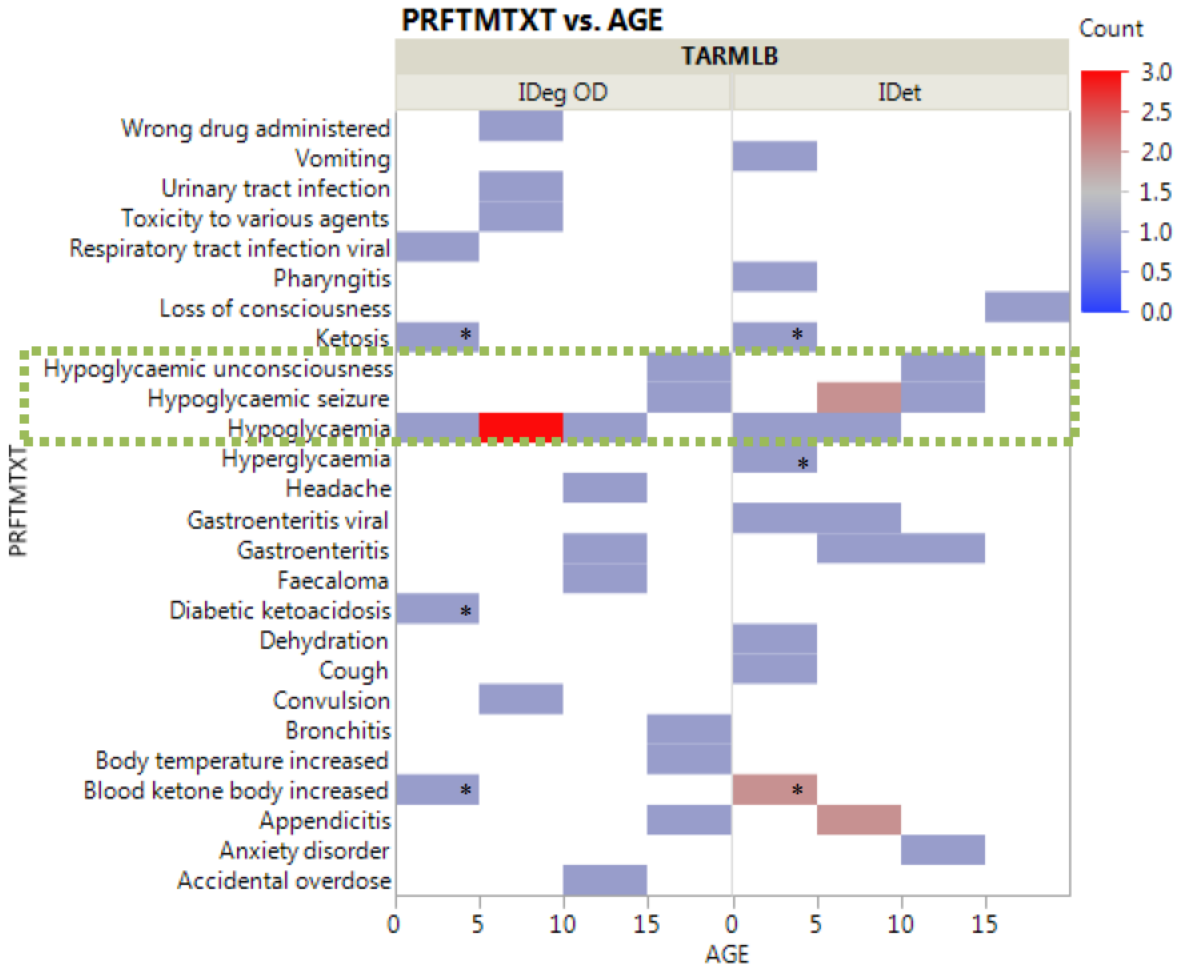
Figure 31- Trial 3561 – treatment emergent serious adverse events by preferred terms (PRFTMTXT) and Age- treatment emergent - SAS



Source: Reviewer generated figure using SAE.xpt, selecting for treatment emergent flag and safety set, usign JMP to generate graph, date 7/18/16. The "counts" refers to the number of patients experiencing the PT. Green dotted line outlines the PT terms that are associated with hypoglycemia. * refers to PT events grouped to evaluate hyperglycemia.

Reviewer's comment: The data do not suggest any clear trends of SAEs by age group. that differ between treatment groups.

7.3.2.2 Nonfatal Serious Adverse events- Trial NN1250-3816 (IDegAsp)

Table 27 shows the serious adverse events for trial 3816. There were 18 patients who experienced 21 events serious adverse events. When evaluated by treatment group, there was a higher patient event rate exposure per 100 years (PYE) for the IDegAsp vs. IDet group (26 event rate PYE vs. 13 event rate per 100 PYE). This difference was mostly accounted by the preferred term (PT) of "hypoglycemia." Review of the trends of PT terms in **Table 27** suggests some

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splitting for the categories of hypoglycemia[68] and hyperglycemia. The hypoglycemia trends will be discussed in section **7.3.4 Significant Adverse Events**; the hyperglycemia trends are evaluated further below.

Most PT terms were seen in single patients (with the exception of 2 patients who had multiple events)[69] with no notable difference between treatment arms.

[68] Based on the narrative review, the PT terms: fall, fibula fracture, and tibia fracture (in **Table 27) do not** suggest a hypoglycemia etiology, while the PT of "loss of consciousness", "hypoglycemic seizure" and "hypoglycemia" all suggest a hypoglycemic etiology.
[69] Subject ID 451007- had PT of Viral infection and hypoglycemia; Subject ID 910001- had fibula fracture, tibia fracture and compartment syndrome.

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Table 27 – Trial 3816- Serious adverse events by system organ class and preferred term - treatment emergent- summary - safety analysis set

	IDEGASP				IDET				TOTAL			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	181				179				360			
Events	11	6.1	14	26	7	3.9	7	13	18	5	21	19
Metabolism and nutrition disorders	**6**	**3.3**	**6**	**11**	**3**	**1.7**	**3**	**6**	**9**	**2.5**	**9**	**8**
Hypoglycemia	5	2.8	5	9	1	0.6	1	2	6	1.7	6	6
Diabetic ketoacidosis	1	0.6	1	2	1	0.6	1	2	2	0.6	2	2
Hyperglycemia					1	0.6	1	2	1	0.3	1	1
Infections and infestations	1	0.6	1	2	2	1.1	2	4	**3**	**0.8**	**3**	**3**
Viral infection	1	0.6	1	2	1	0.6	1	2	2	0.6	2	2
Laryngitis					1	0.6	1	2	1	0.3	1	1
Gastrointestinal disorders	**2**	**1.1**	**2**	**4**					**2**	**0.6**	**2**	**2**
Constipation	1	0.6	1	2					1	0.3	1	1
Gastritis	1	0.6	1	2					1	0.3	1	1
Injury, poisoning and procedural complications	1	0.6	2	4	1	0.6	1	2	**2**	**0.6**	**3**	**3**
Fall*					1	0.6	1	2	1	0.3	1	1
Fibula fracture^	1	0.6	1	2					1	0.3	1	1
Tibia fracture^	1	0.6	1	2					1	0.3	1	1
Nervous system disorders	1	0.6	1	2	1	0.6	1	2	**2**	**0.6**	**2**	**2**
Hypoglycemic seizure	1	0.6	1	2					1	0.3	1	1
Loss of consciousness~					1	0.6	1	2	1	0.3	1	1
Congenital, familial and genetic disorders	1	0.6	1	2					1	0.3	1	1
Developmental glaucoma	1	0.6	1	2					1	0.3	1	1
Musculoskeletal and connective tissue disorders	1	0.6	1	2					1	0.3	1	1
Compartment syndrome	1	0.6	1	2					1	0.3	1	1

N= number of subjects, %= percentage of subjects, E= number of events, R=event rate per 100 exposure years
*Narrative of subject ID #903011 describes a 17 year old male who was jumping on a trampoline in the evening and jumped off and landed on his leg resulting in a tibial plateau fracture requiring surgery
^narrative of subject ID #910001 describes a 12 year old male who was riding a motorized bike, when he fell. The report states that "there was no hypoglycemia related to the events." Blood sugar in the emergency room was 193 mg/dL.
~narrative of subject ID#803005 describes a 14 year old female who lost consciousness and fell down. After some minutes she regained consciousness. Glucose before the event was 105 mg/dL and was 68 mg/dL during the transport to the hospital. At admission blood sugar was 105 mg/dL.

Source: CSR 3816- Table 12-11, page 145

The PT terms "hyperglycemia" and "diabetic ketoacidosis" can be grouped for an evaluation of an overall serious hypoglycemia. By grouping these PT terms, there is a slight numerical imbalance favoring IDeg (IDeg event rate of 2 events per 100 PYE vs. IDet event rate of 4 events per 100 PYE).

Reviewer's comments: the SAEs in this trial are similar to the findings of trial 3561. Overall, there are no unexpected SAEs in the pediatric population that would change the labeled safety profile of IDegAsp.

Figure 32 shows the exploratory analysis of subjects with SAEs by age groups and treatment arms. In **Figure 32**, the dotted green rectangle highlights PT terms associated with

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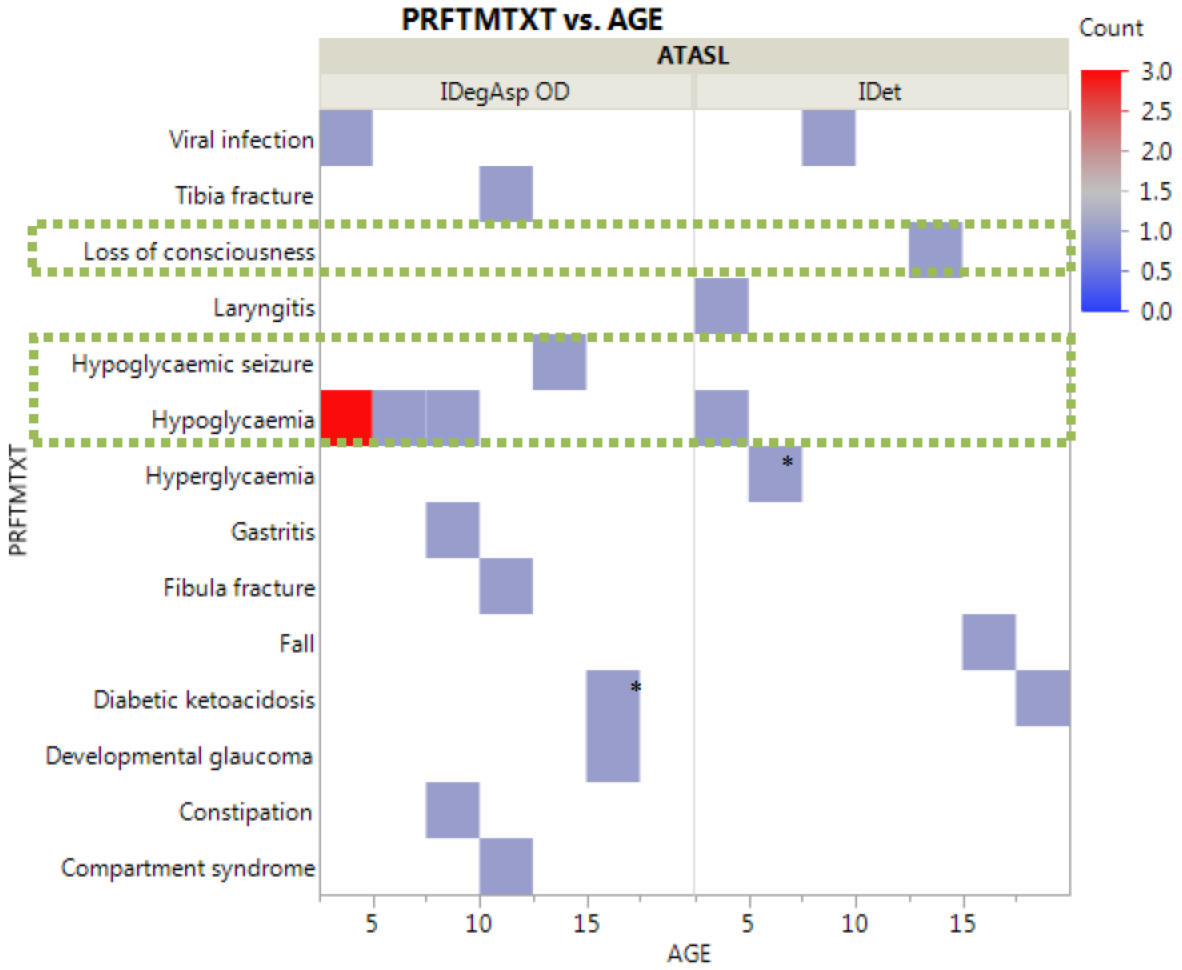
hypoglycemia. And the "*" groups the terms associated with "hyperglycemia." When evaluating serious adverse events by age, it appears that there was a slight numerical imbalance favoring IDet for patients under the age of 5 years of age. There were no clear differences between treatment groups when evaluating for hyperglycemia.

Figure 32- Trial 3816 – serious adverse events by preferred terms (PRFTMTXT) and Age



Source: Reviewer generated figure using SAE.xpt, selecting for treatment emergent flag and safety set, usign JMP to generate graph, date 7/15/16. The "counts" refer to the number of patients experiencing the PT. Green dotted line outlines the PT terms that are associated with hypoglycemia. The * refers to PT terms associated with hyperglycemia.

Reviewer's comment: The slight imbalance in hypoglycemia not favoring IDegAsp will be further evaluated in section 7.3.4 Significant Adverse Events .

7.3.3 Dropouts and/or Discontinuations

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This section discusses the dropouts and/or discontinuations in each trial due to adverse events and the adverse events resulting in dose reduction of trial product. The latter category is also discussed to further evaluate trends in drop outs due to hypoglycemia (given the findings in section **7.3.4 Significant Adverse Events**).

7.3.2.1 Dropouts and/or Discontinuations - Trial NN1250-3561 (IDeg)

There were a total of three subjects (all in the IDet group), who withdrew due adverse events in the 52 week period (2 of these patients withdrew in the 26 week period of the trial). The narratives for these events are provided below.

Subject #119002- (wrong drug administered)-13 year old female that accidentally administered 28 units of insulin aspart instead of 28 units of insulin detemir. The patient did not experience hypoglycemia; this was the second time the patient made this mistake (as the pens are similar). The patient decided to withdraw from the study due to this event.

Reviewer's comment: medication errors were MESI's that were evaluated by the Sponsor, these events are discussed in **7.3.5 Submission Specific Primary Safety Concerns.** *These medication errors highlight a previous concern with the Penfill devices—see section* **Common elements** *for comments regarding Penfill devices.*

Subject #601003 – (hypoglycemic seizure) -5 year old female treated with IDet experienced hypoglycemic seizure 70 days after drug start. The patient ate a 50 gram carbohydrate meal at 20:00 with blood sugar of 324 mg/dL and had 4 units of aspart administered. Two hours later blood sugar was 265 mg/dL and 7 units of detemir were administered. Two hours after detemir administration, the patient's blood sugar was 23 mg/dL.

Subject# 405003 – (anxiety disorder –after 26 weeks) - 11 year old male treated with IDet was diagnosed with 'anxiety disorder' with fears that limited his normal life. The patient had a previous episode of hypoglycemia which resulted in the patient being afraid to sleep in his own bed and increased fear of darkness.

Adverse events resulting in dose reduction – Trial 3561

Table 28 shows the adverse events leading to dose reduction. The event rate per 100 exposure years was slightly higher for IDeg than IDet (41 vs. 35 events per 100 exposure years, respectively). Categories which suggest a hypoglycemia etiology are highlighted in the table.

Table 28 - Trial 3561 – Adverse events leading to dose reduction by SOC and PT- treatment emergent- safety analysis set

	IDEG				IDET				TOTAL			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	174				175				349			
Events	33	19	67	41	33	18.9	52	35	66	18.9	119	39
Metabolism and nutrition disorders	14	8	26	16	5	2.9	8	5	19	5.4	34	11
Hypoglycemia	13	7.5	25	15	4	2.3	7	5	17	4.9	32	10
Decreased appetite	1	0.6	1	1	1	0.6	1	1	2	0.6	2	1
Injury, poisoning and procedural complications	4	2.3	4	2	5	2.9	5	3	9	2.6	9	3
Wrong drug administered	3	1.7	3	2	3	1.7	3	2	6	1.7	6	2
Accidental overdose	1	0.6	1	1	2	1.1	2	1	3	0.9	3	1
Nervous system disorders	5	2.9	5	3	5	2.9	5	3	10	2.9	10	3
Hypoglycemic seizure	2	1.1	2	1	2	1.1	2	1	4	1.1	4	1
Hypoglycemic unconsciousness	3	1.7	3	2					3	0.9	3	1
Dizziness					2	1.1	2	1	2	0.6	2	1
Headache					1	0.6	1	1	1	0.3	1	0
Infections and infestations	14	8	15	9	17	9.7	21	14	31	8.9	36	12
Gastroenteritis	4	2.3	4	2	10	5.7	11	7	14	4	15	5
Gastrointestinal infection	1	0.6	1	1	3	1.7	3	2	4	1.1	4	1
Gastroenteritis viral	2	1.1	2	1	1	0.6	1	1	3	0.9	3	1
Nasopharyngitis URI	2	1.1	2	1					2	0.6	2	1
Viral infection	1	0.6	1	1	1	0.6	2	1	2	0.6	3	1
Bronchitis	1	0.6	1	1					1	0.3	1	0
Ear infection					1	0.6	1	1	1	0.3	1	0
Gastrointestinal viral infection	1	0.6	1	1					1	0.3	1	0
Influenza					1	0.6	1	1	1	0.3	1	0
Pharyngitis	1	0.6	1	1					1	0.3	1	0
Pneumonia mycoplasmal					1	0.6	1	1	1	0.3	1	0
Sinusitis					1	0.6	1	1	1	0.3	1	0
Gastrointestinal disorders	5	2.9	10	6	8	4.6	9	6	13	3.7	19	6
Diarrhea	3	1.7	5	3	3	1.7	3	2	6	1.7	8	3
Vomiting	3	1.7	3	2	3	1.7	3	2	6	1.7	6	2
Abdominal pain upper					1	0.6	1	1	1	0.3	1	0
Gastric disorder	1	0.6	1	1					1	0.3	1	0
Gastritis					1	0.6	1	1	1	0.3	1	0
Gastrointestinal disorder					1	0.6	1	1	1	0.3	1	0
Nausea	1	0.6	1	1					1	0.3	1	0
General disorders and administration site conditions	2	1.1	3	2	1	0.6	1	1	3	0.9	4	1
Pyrexia	2	1.1	3	2	1	0.6	1	1	3	0.9	4	1
Investigations	1	0.6	1	1	2	1.1	2	1	3	0.9	3	1
Blood ketone body increased	1	0.6	1	1	2	1.1	2	1	3	0.9	3	1
Respiratory, thoracic and mediastinal disorders	2	1.1	2	1	1	0.6	1	1	3	0.9	3	1
Cough	1	0.6	1	1	1	0.6	1	1	2	0.6	2	1
Oropharyngeal pain	1	0.6	1	1					1	0.3	1	0
Eye disorders	1	0.6	1	1					1	0.3	1	0
conjunctivitis	1	0.6	1	1					1	0.3	1	0

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N= number of subjects, %= percentage of subjects, E= number of events, R=event rate per 100 exposure years
Source: CSR 3561-ext, table 14.3.1.36, page 1620 and 1621

Reviewer's comment: Despite the fact that there were no withdrawals in the IDeg group due to adverse events, the analysis of adverse events resulting in dose reduction suggests an imbalance in hypoglycemia favoring IDet.

7.3.2.2 Dropouts and/or Discontinuations - Trial NN1250-3816 (IDegAsp)

One patient in the IDegAsp treatment group and one patient in the IDet group were withdrawn from the trial due to an adverse event.

Subject #904010 – (hypoglycemic seizure) – An 11 year old female treated with IDegAsp had a hypoglycemic seizure on day 67 after drug start. Before dinner at 11 PM the blood sugar was above 501 mg/dL and was given 46 U of IDegAsp and had a carbohydrate rich meal. At 6 AM the next morning she started "twitching" and had a tonic-clonic seizure. The patient was treated with oral glucose and blood sugar was 76 mg/dL.

Subject #904003 – (intermittent but recurrent hypoglycemia)- Patient was randomized to IDet. There was no narrative provided for this patient since he was withdrawn due to "Other" criteria with the comments specifying that it was due to recurrent hypoglycemia.

Adverse events resulting in dose reduction/temporary withdrawal of drug product – Trial 3816

Table 29 shows the adverse events leading to dose reduction. From this table, it can be seen that the event rate per 100 exposure years was higher for IDegAsp than IDet (38 vs. 28 events per 100 exposure years, respectively). Categories which suggest a hypoglycemia etiology or an increased risk for hypoglycemia (such as overdose) are highlighted below. From this analysis, it appears that more patients treated with IDegAsp had dose reduction related to hypoglycemia than patients randomized to IDet.

Table 29 – Trial 3816 – Adverse events leading to dose reduction by SOC and PT- treatment emergent- safety analysis set

	IDEGASP				IDET				TOTAL			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	181				179				360			
Events	15	8.3	21	38	8	4.5	9	17	23	6.4	30	28
Metabolism and nutrition disorders	5	2.8	5	9					5	1.4	5	5
Hypoglycemia	4	2.2	4	7					4	1.1	4	4
Decreased appetite	1	0.6	1	2					1	0.3	1	1
Injury, poisoning and procedural complications	2	1.1	2	4	1	0.6	1	2	3	0.8	3	3
Accidental overdose					1	0.6	1	2	1	0.3	1	1
Overdose	1	0.6	1	2					1	0.3	1	1
Wrong drug administered	1	0.6	1	2					1	0.3	1	1
Nervous system disorders	2	1.1	2	4					2	0.6	2	2
Headache	1	0.6	1	2					1	0.3	1	1
Hypoglycemic seizure	1	0.6	1	2					1	0.3	1	1
Infections and infestations	5	2.8	6	11	6	3.4	6	11	11	3.1	12	11
Gastroenteritis viral	1	0.6	1	2	3	1.7	3	6	4	1.1	4	4
Nasopharyngitis	1	0.6	1	2	2	1.1	2	4	3	0.8	3	3
Gastroenteritis	2	1.1	2	4					2	0.6	2	2
influenza					1	0.6	1	2	1	0.3	1	1
Upper resp. tract infection	1	0.6	1	2					1	0.3	1	1
Viral infection	1	0.6	1	2					1	0.3	1	1
Gastrointestinal disorders	3	1.7	5	9	2	1.1	2	4	5	1.4	7	6
Gastritits	2	1.1	3	5					2	0.6	3	3
vomiting					2	1.1	2	4	2	0.6	3	3
Enterocolitis	1	0.6	1	2					1	0.3	1	1
Toothache	1	0.6	1	2					1	0.3	1	1
Respiratory, thoracic and mediastinal disorders	1	0.6	1	2					1	0.3	1	1
Oropharyngeal pain	1	0.6	1	2					1	0.3	1	1

N= number of subjects, %= percentage of subjects, E= number of events, R=event rate per 100 exposure years
Source: CSR 3816, table 14.3.1.36, page 1001 and 1002

Reviewer's comment: Although the actual withdrawal rate due to adverse event does not reveal an imbalance between treatment groups, the analysis of adverse events leading to dose reduction suggests that there is an imbalance for higher hypoglycemia risk associated with IDegAsp than IDet. Refer to section 7.3.4.2 Hypoglycemia - Trial NN1250-3816 (IDegAsp) *for further analysis related to hypoglycemia.*

7.3.4 Significant Adverse Events

Hypoglycemia is considered a significant adverse event that is labeled for all insulin drug products. In this section, the method of capture and hypoglycemia definitions will be discussed first, followed by the hypoglycemia findings in each individual study.

Reference ID: 4009596

Hypoglycemia methods of capture and definitions

Capturing of hypoglycemia:

Plasma glucose was to be measured and the value recorded in a provided diary, when there was suspicion of a hypoglycemic episode. All recorded values were to be transcribed into the electronic case report form (eCRF) throughout the trial from screening visit to follow up visit.

The following information was to be recorded: date and time of episode, time and type of last insulin dose prior to episode, time of last main meal prior to episode, symptoms related to episode, if episode was in relation to exercise, if the patient had altered mental status and could not assist in their care (is semiconscious, unconscious, in a coma or having convulsions), and the plasma glucose before the treating episode (if available).

The investigator was to fill out a hypoglycemic episode form for all hypoglycemic episodes. If the hypoglycemic episode fulfilled criteria for an SAE, an AE form and safety information was to be filled out by the investigator.

Investigators were instructed that FPG values ≤70mg/dL analyzed by central laboratory should not be recorded as hypoglycemic events in the subject's diary nor transcribed into the eCRF.

Of note, both studies had a centralized external classification of severe hypoglycemia events. Severe hypoglycemia events were reviewed by an expert who performed a blinded classification of these events in accordance with ISPAD and based on the provided narratives. However, because the data did not undergo a formal adjudication process, the reviewer presents the data as captured by the Sponsor, (and not the classification by the external expert).

Reviewer's comment: The centralized external classification of the events as severe hypoglycemia differed from a formal adjudication process in that there was only one expert that classified all the severe hypoglycemia events based on provided narratives and "paraclinical findings" (the meaning of "paraclinical findings" is not clarified in the submission.)

Hypoglycemia classification

Both protocols defined hypoglycemia episodes based on the International Society for Pediatric and Adolescent Diabetes (ISPAD) and the American Diabetes Association (ADA) guidelines.

- **Severe hypoglycemia**: The child is having altered mental status and cannot assist in their care, is semiconscious or unconscious, or in coma ± convulsions and may require parenteral therapy (glucagon or i.v. glucose).
- **Documented symptomatic hypoglycemia:** The child or parent is aware of, responds to, and treats the hypoglycemia orally after documenting a BG level of ≤ 70 mg/dL.
- **Asymptomatic hypoglycemia:** The child is not symptomatic with hypoglycemia but the BG is documented to be ≤ 70 mg/dL.
- **Probable symptomatic hypoglycemia:** An episode during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination (but that was presumably caused by a plasma glucose concentration ≤ 70 mg/dL.

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- **Relative hypoglycemia:** An episode during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets those as indicative of hypoglycemia, but with a measured plasma glucose concentration > 70 mg/dL.

The Sponsor also used a Novo Nordisk created definition, hereto referred as "Novo Nordisk Confirmed." This definition combines elements of asymptomatic hypoglycemia and documented symptomatic hypoglycemia as described below:

- **Novo Nordisk confirmed hypoglycemia:** An episode with symptoms consistent with hypoglycemia with confirmation by plasma glucose < 56 mg/dL, or full blood glucose < 50 mg/dL and which does not fulfill the requirements for being classified as a severe hypoglycemia, or any asymptomatic plasma glucose value < 56 mg/dL or full blood glucose value < 50 mg/dL AND severe hypoglycemia (as defined above).

Reviewer's comments: The Sponsor's definitions of hypoglycemia are overall similar to the definitions used in the adult diabetes trials included in the product label. The reviewer will focus on the hypoglycemia results for severe, documented symptomatic, and Novo Nordisk Confirmed hypoglycemia since these definitions have precedence for labeling and because of their clinical relevance.

For context, in the interpretation of the severe hypoglycemia results for either trial, it is worth noting that the incidence of severe hypoglycemia (from studies) in pediatrics is estimated to range from 5 to 20 per 100 patient years[70]. It is also important to remember that the hypoglycemia findings in both trials apply to a population at lower risk of hypoglycemia, since the exclusion criteria excluded patients with hypoglycemic unawareness or recurrent severe hypoglycemic events, as judged by the investigator.

Dr. Sinks' review addresses the statistical comparisons between treatment groups for each trial. Per her analysis, there was no clear statistical difference between treatment groups for confirmed, documented symptomatic or severe hypoglycemia in either trial. The statistical analysis for hypoglycemia is shown in **Table 30** *for incidence rate (defined as percent of patients with at least 1 hypoglycemic episode) and* **Table 31** *for event rate. Although these analyses were post-hoc analyses, they do not suggest that the numerical imbalances in hypoglycemia rates (discussed below) were as a result of robust statistical findings; there was no consistent pattern to suggest a higher rate of hypoglycemia for either IDegAsp or IDeg compared to IDet.*

[70] Ly TT, Maahs DM, Rewers A, Dunger D, Oduwole A, Jones TW, et al. ISPAD Clinical Practice Consensus Guidelines 2014. Assessment and management of hypoglycemia in children and adolescents with diabetes. Pediatr Diabetes. 2014;15 Suppl 20:180-92.

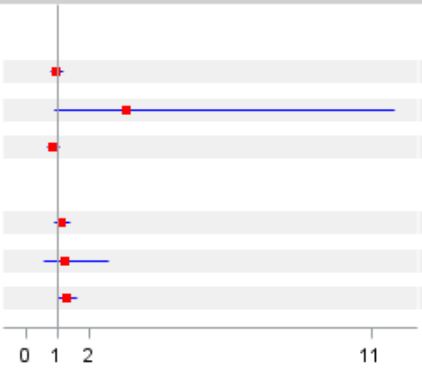
Table 30 – FDA- Summary of Fisher's Exact Test Results for Hypoglycemia Incidence

Hypoglycemia	IDegAsp or IDeg N (%)	IDet N(%)	P-value
Trial 3816			
	182	180	
Confirmed	168 (92%)	164 (91%)	0.70
Severe	11(6%)	3 (2%)	0.05
Documented Sympt.	167 (92%)	160 (89%)	0.38
Trial 3561			
	174	176	
Confirmed	169 (97%)	161 (91%)	0.04*
Severe	24 (14%)	17 (10%)	0.25
Documented Sympt.	12 (7%)	9 (5%)	0.57

*Analysis was not adjusted for multiplicity

Table 31 – FDA -Summary of Analysis Results for Hypoglycemic Events

Type	IDegAsp or IDeg Events #	IDet Events #	Risk Ratio(95% CI)	Risk Ratio (95% CI)	P-value
Ryzodeg-16 weeks					
Confirmed	2532	2672		0.94 (0.76,1.17)	0.58
Severe	14	4		3.21 (0.88,11.7)	0.08
Documented sympt.	3005	3648		0.82 (0.65,1.05)	0.12
Tresiba-26 weeks					
Confirmed	5020	4748		1.13 (0.90,1.41)	0.29
Severe	44	34		1.21 (0.56,2.62)	0.62
Documented sympt.	5914	4904		1.28 (1.00,1.64)	0.05



*analysis was not adjusted for multiplicity. Negative binomial model was used for analyzing hypoglycemic events. The model included treatment, age group, region and sex.

7.3.4.1 Hypoglycemia - Trial NN1250-3561(IDeg)

Table 30 shows the hypoglycemia findings for the 26 week and 52 week for trial 3561. Overall trends across hypoglycemic definitions favored IDet; there was a higher event rate of hypoglycemia for IDeg.

The for both the 26 and 52 week period, the rate of severe, documented symptomatic and Novo Nordisk confirmed hypoglycemia was higher for IDeg when compared to IDet. For these

definitions, the number of patients and number of events were higher for IDeg when compared to IDet.

Table 32– Trial 3561 – Summary of ISPAD hypoglycemia definitions for the 26 and 52 week period –safety analysis set

	IDeg N= 174			IDet N=175		
	N (%)	E	R	N (%)	E	R
26 week period						
ISPAD	174 (100)	11835	13791	175 (100)	11051	13058
Severe	24 (13.8)	44	51	17 (9.7)	34	40
Documented symptomatic	161 (92.5)	5914	6892	159 (90.9)	4904	5794
Asymptomatic	170 (97.7)	5754	6705	165 (94.3)	6053	7152
Probably symptomatic	12 (6.9)	70	82	9 (5.1)	21	25
Relative	14 (8)	53	62	20(11.4)	39	46
Unclassifiable	45 (25.9)	233	272	32 (18.3)	151	178
Novo Nordisk Confirmed	169 (97.1)	4988	5812	161 (92%)	4722	5579
52 week period						
ISPAD	174 (100)	21784	13492	175 (100)	18489	12543
Severe	31 (17.8)	82	51	24 (13.7)	48	33
Documented symptomatic	166 (95.4)	10887	6743	163 (93.1)	8614	5844
Asymptomatic	171 (98.3)	10591	6560	165 (94.3)	9711	6588
Probably symptomatic	13 (7.5)	97	60	11 (6.3)	38	26
Relative	20 (11.5)	127	79	25 (14.3)	78	53
Unclassifiable	52 (29.9)	410	254	41 (23.4)	233	158
Novo Nordisk Confirmed	171 (98.3)	9317	5771	168 (96)	7967	5405

Source: CSR Trial 3561 and 3561-ext. Table 12-14 and Table 12-18; N: Number of Subjects; %: Percentage of Subjects with the Event; E: Number of Events; R: Event Rate per 100 Patient Year(s) of Exposure
Highlighted cells were added by the reviewer to better evaluate trends when the event rate of hypoglycemia of IDeg was higher than IDet.

In an information request[71] the sponsor clarified that although the observed incidences and rates of confirmed and severe hypoglycemia "were higher across the 26-week treatment period for IDeg and IDet, the blinded external classification of severe hypoglycemia were categorized as severe based on most subjective component of the ISPAD definition (altered mental status and cannot assist in his care). The number of episodes associated with (semi)unconsciousness (6 episodes in 6 subjects on IDeg; 6 episodes in 4 subjects on IDet) or coma ± convulsions (2 episodes in 2 subjects on IDeg; 7 episodes in 4 subjects on IDet) were either numerically similar or lower with IDeg than IDet."

[71] Information request received on September 12, 2016: *\\CDSESUB1\evsprod\NDA203314\0098\m1\us*

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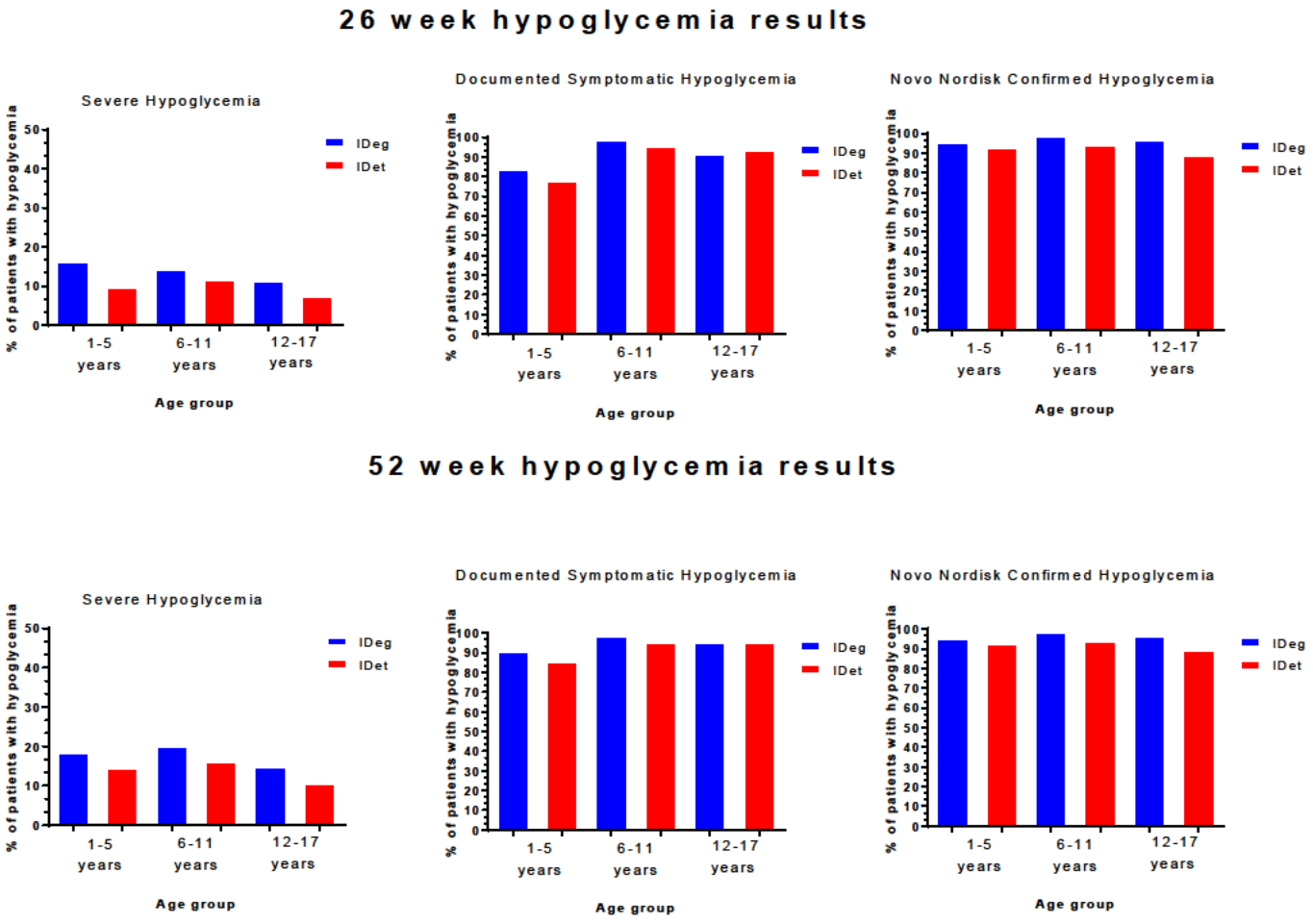
Reviewer's comment: the reviewer does not agree with the Sponsor's rationale. The reviewer feels that the ISPAD definition for severe hypoglycemia is clinically relevant and appropriate in identifying cases of severe hypoglycemia, without need to "split" the cases by mental status.

In order to understand the severe hypoglycemia trends by age groups, the reviewer graphed the Sponsor reported percentage of subjects with severe, documented symptomatic and Novo Nordisk confirmed hypoglycemia in **Figure 33**.

When evaluating by age subgroups, it is clear that the hypoglycemia findings were not driven by a particular age group. Across age groups, the proportion of patients experiencing either severe, documented symptomatic or confirmed hypoglycemia favored IDet.

Figure 33 - Trial 3561- Percent of patients with hypoglycemia -- age subgroup analysis of hypoglycemia

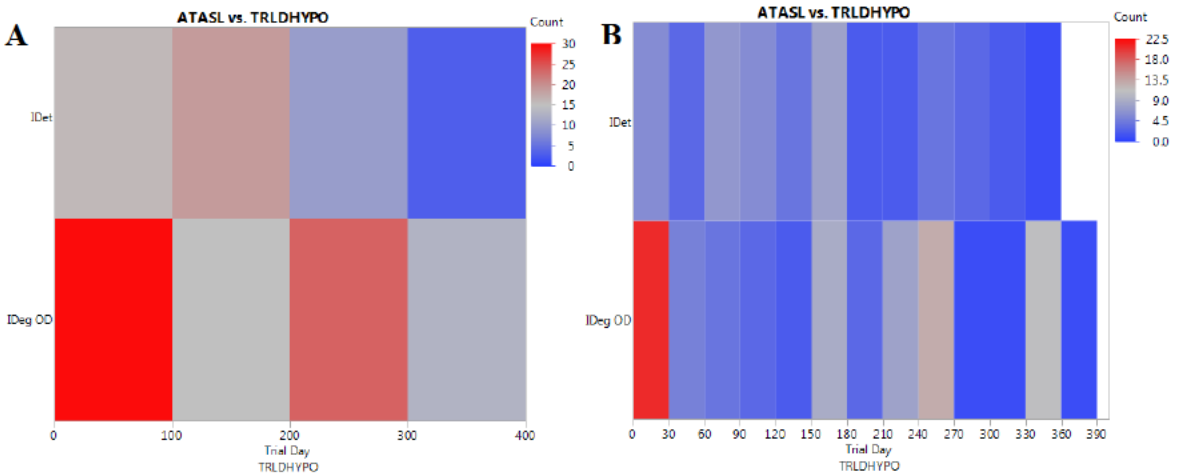


Source: Table 12-21 from CSR 3561-ext, and Table12-17 from CSR 3561

For the 52 week period, the reviewer also performed an evaluation of event frequency of severe hypoglycemia by study day; see **Figure 34.**

This exploratory analysis shows that most of the 130 events of severe hypoglycemia (as defined by ISPAD, shown in **Table 30**) occurred early in the trial for IDeg group. The analysis shows the trends by 100 day increments and 30 day increments. More granular analysis (by 7 days), that is not shown in the review shows that most of the episodes of severe hypoglycemia occurred within the first 2 weeks. A second period with increased severe hypoglycemia is also seen after 26 weeks (after day 182).

Figure 34 – Trial 3561- Events of severe hypoglycemia by trial day- safety analysis set (A. by 100 day increments, and B. 30 day increments)



Source: Exploratory analysis using SHE.xpt dataset, selecting HYPISPAD (ISPAD Classification) column for "severe" and graphing by ATASL (actual treatment arm)

Overall Reviewer's hypoglycemia comment:
*The FDA statistical analysis of hypoglycemia did not identify a clear difference in hypoglycemia between IDeg and IDet. There were numerical imbalances in the incidence of hypoglycemia, which were higher for IDeg when compared to IDet, across age groups, and across hypoglycemia definitions (particularly for severe and the documented symptomatic definitions). The numerical imbalances were seen early in the trial (first 2 weeks to first month), and suggests that these episodes may be related to transitioning to a new basal insulin for patients randomized to IDeg (as **Table 14** shows, ~50% of patients were on IDet prior to trial start, therefore patients re-randomized to IDet would be less likely to experience hypoglycemia, than those switched from IDet to IDeg).*

7.3.4.2 Hypoglycemia - Trial NN1250-3816 (IDegAsp)

Table 31 shows the hypoglycemia findings for the 16 week period of trial 3816. The severe, asymptomatic and relative hypoglycemia trends of the events per 100 patient years of exposure

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favored IDet; while the documented symptomatic, probably symptomatic and the Novo Nordisk Confirmed definition favored IDeg.

Of note, although IDegAsp had a lower event rate per 100 patient years than IDet for the documented symptomatic definition and the Novo Nordisk Confirmed hypoglycemia, there were more patients in the IDegAsp group than in the IDet group with hypoglycemia with a higher number of events in the IDet group. Therefore, the event rate per 100 patient years in the documented symptomatic and Novo Nordisk Confirmed hypoglycemia was driven by patients who had more events.

Table 33– Trial 3816 – Summary of ISPAD hypoglycemia definitions –safety analysis set

	IDegAsp N= 181			IDet N=179		
	N (%)	E	R	N (%)	E	R
16 week period						
ISPAD	178 (98.3)	5833	10651	170 (95)	5922	10982
Severe	11 (6.1)	14	26	3 (1.7)	4	7
Documented symptomatic	167 (92.3)	3005	5487	160 (89.4)	3648	6765
Asymptomatic	158 (87.3)	2763	5045	145 (81)	2226	4128
Probably symptomatic	2 (1.1)	2	4	4(2.2)	5	9
Relative	16 (8.8)	49	89	11 (6.1)	39	72
Unclassifiable	28 (15.5)	120	219	31 (17.3)	168	312
Novo Nordisk Confirmed	168 (92.8)	2532	4623	164 (91.6)	2672	4955

Source: CSR Trial 3816 Table 12-14; N: Number of Subjects; %: Percentage of Subjects with the Event; E: Number of Events; R: Event Rate per 100 Patient Year(s) of Exposure

In an information request[72] the sponsor clarified that in a blinded external classification of severe hypoglycemia, "7 of the episodes (in 6 subjects) in the IDegAsp group were categorized as severe based on the most subjective component of the ISPAD definition (*altered mental status and cannot assist in his care*), whereas no episodes in the IDet group met this criterion. For the remaining severe events, 6 episodes (in 5 subjects) in the IDegAsp group and 4 episodes (in 3 subjects) in the IDet group involved the child being *semiconscious or unconscious* or in a *coma ± convulsions*, and 1 episode in the IDegAsp group was not confirmed as severe."

Reviewer's comment: as mentioned previously, the reviewer disagrees with the splitting of cases in the severe hypoglycemia definition.

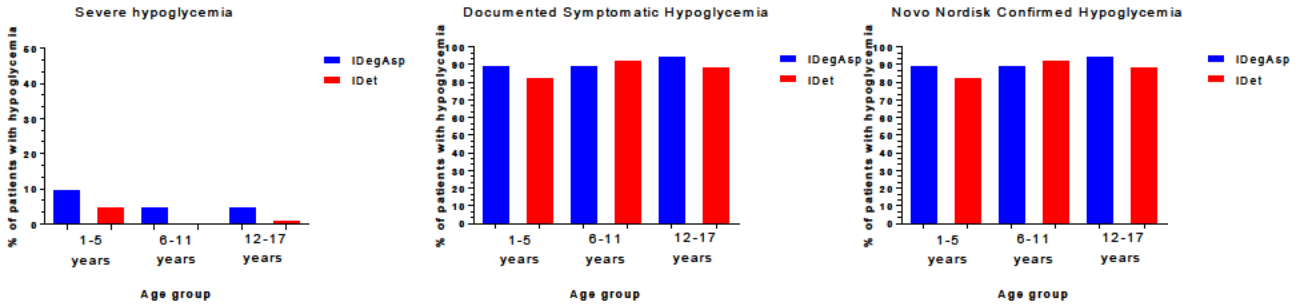
In order to understand the severe hypoglycemia trends by age groups, the reviewer graphed the Sponsor reported percentage of subjects with severe, documented symptomatic and Novo Nordisk confirmed hypoglycemia, in **Figure 35**.

[72] Information request received on September 12, 2016: \\CDSESUB1\evsprod\NDA203314\0098\m1\us

Reference ID: 4009596

When evaluating by age subgroups, it is clear that the hypoglycemia findings were not driven by a particular age group. Across age groups, the proportion of patients experiencing severe hypoglycemia favored IDet. The incidence of documented symptomatic and Novo Nordisk confirmed hypoglycemia generally favored IDet, except for patients ages 6-11 years old.

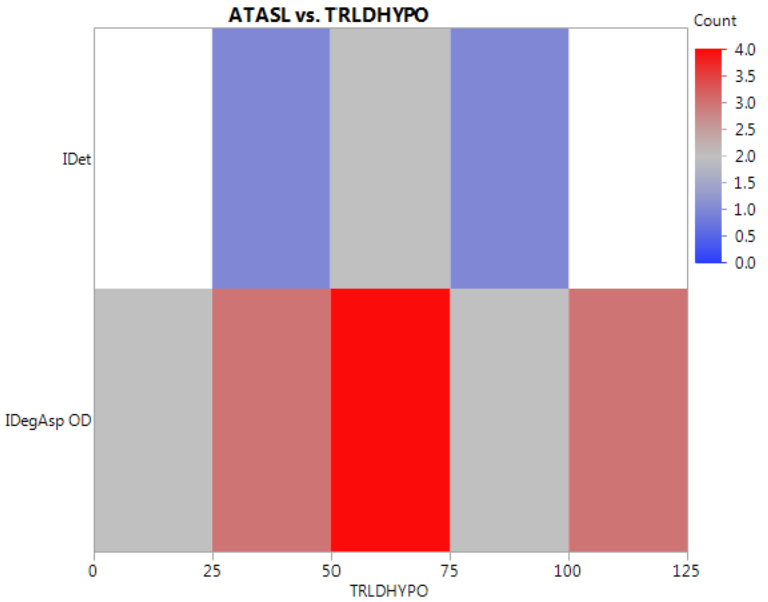
Figure 35 - Trial 3816- Percent of patients with hypoglycemia -- age subgroup analysis of hypoglycemia



Source: CSR Trial 3816, Table 12-16, page 158

The reviewer also performed an evaluation of event frequency of severe hypoglycemia by study day; see **Figure 36.**
This exploratory analysis shows the 18 events of severe hypoglycemia (as defined by ISPAD, shown in **Table 31**) do not show a clear pattern of severe hypoglycemia for IDegAsp group.

Figure 36 - Trial 3816- Events of severe hypoglycemia by trial day- safety analysis set



Source: Exploratory analysis using SHE.xpt dataset, selecting HYPISPAD (ISPAD Classification) column for "severe" and graphing by ATASL (actual treatment arm)

Overall Reviewer's hypoglycemia comment:
The FDA statistical analysis of hypoglycemia did not identify a clear difference in hypoglycemia between IDegAsp and IDet. There were numerical imbalances in the incidence of hypoglycemia, which were higher for IDegAsp when compared to IDet, across age groups and across hypoglycemia definitions (particularly for severe hypoglycemia). In order to decrease the risk of hypoglycemia in pediatric patients, the reviewer suggests pediatric-specific dosing that recommends a decrease in insulin dose upon converting to IDegAsp.

7.3.5 Submission Specific Primary Safety Concerns

The following safety concerns will be examined in this section: medication errors, injection site reactions and episodes of hyperglycemia.

Medication errors

Medication errors are labeled for all insulin products. The reviewer was particularly interested in medication errors in this supplement, because the pen devices used in this application are different from the pen devices already labeled for either Tresiba or Ryzodeg 70/30 (as discussed in section **Pen devices**). Because during the review cycle there was discussion regarding the possible utility of these half-unit pen devices, the reviewer evaluated the medication errors in these trials to see if there was any additional risk associated with the half-unit pen devices that would preclude their use in the indicated population.

Medication errors - Trial NN1250-3561(IDeg)
The event rate of medication errors was similar between IDeg and IDet (8 and 9 events per 100 PYE respectively). Two of these events were reported as SAEs in the IDeg group only (narratives below):

Subject # 401002 - 12 year old female randomized to IDeg from Finland, injected 21 units of insulin degludec twice, because she had forgotten that she already had injected the first dose. The patient went to the hospital where she was monitored with hourly blood sugars, no IV glucose was needed and the patient was discharged from the hospital the next morning.

Subject #117007- 9 year old male randomized to IDeg from the USA, received an accidental administration of 3.5 units of insulin degludec instead of insulin aspart after lunch. There were no adverse events noted and blood sugar was 498 mg/dL with normal ketones.

Table 34 – Trial 3561- Medication errors

	IDeg OD				IDet				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**				**349**			

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Events	12	6.9	13	8	11	6.3	14	9	23	6.6	27	9
Serious events	2	1.1	2	1	0	0	0	0	2	0.6	2	1
Accidental overdose	1	0.6	1	1	5	2.9	5	3	6	1.7	6	2
Drug dispensing error	1	0.6	1	1	0	0	0	0	1	0.3	1	0
Incorrect dose administered	1	0.6	1	1	0	0	0	0	1	0.2	1	0
Incorrect route of drug administration	1	0.6	1	1	0	0	0	0	1	0.3	1	0
Wrong drug administered	9	5.2	9	6	6	3.4	9	6	15	4.3	18	6

The table was modified by the reviewer. The reviewer removed rows which cited investigator's causality determination from the table.
Source: CSR Trial 3561-ext, Table 14.3.1.42

The majority of medication errors were due to the wrong drug being administered (i.e. basal being administered instead of bolus or vice versa) in 9 subjects with 9 events in the IDeg group and 6 subjects with 9 events in the IDet group. [73] In 5 of these cases, (2 cases for IDeg and 3 cases for IDet), there was hypoglycemia reported. The Sponsor states that most of the mix-ups were reported from the US[74] during the initial part of the trial, "possibly due to the similarity of the NovoPen Junior pens used at the US sites. Few mix-up cases were reported after introduction of different color NovoPen Junior pens to be used for basal and bolus insulin." As **Table 2** shows, initially, the same colored pen was used for the basal and prandial insulin (yellow pen) in the United States.

A notable difference between the two treatment arms in the report of accidental overdose, which was lower for IDeg than IDet (1 vs. 3 events per 100 PYE respectively).

Reviewer's comment: the medication errors do not reveal any drug specific differences between treatment groups; this finding is not surprising, since the same pens were used to administer IDeg and IDet in this trial. A notable medication error for either treatment arm was the "wrong drug administered" which may have resulted from the similar appearance of the basal and prandial pens used in the USA sites.

Medication errors- Trial NN1250-3816 (IDegAsp)

The event rate of medication errors was similar between IDegAsp and IDet (15 and 11 events per 100 PYE respectively). There were no SAEs related to medication errors.

Table 35 – Trial 3816- Medication errors

	IDegAsp OD				**IDet**				**Total**			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of subjects	**181**				**179**				**360**			
Events	7	3.9	8	15	6	3.4	6	11	13	3.6	14	13

[73] In the IDeg group 5 subjects administered IDeg instead of IAsp while 3 subjects administered IAsp instead of IDeg. 1 subject administered her brothers basal insulin (IDet) rather than her own (IDeg). In the IDet group, 2 subjects administered IDet instead of IAsp and in 7 cases IAsp was administered instead of IDet.
[74] The reviewer's exploratory analysis using the datasets submitted, by the reviewer showed that in the US there were 13 of the 18 events reported as PT "wrong drug administered," with 6 events reported in the IDeg group and 7 events reported in the IDet group.

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	IDegAsp OD				IDet				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	**181**				**179**				**360**			
Events	7	3.9	8	15	6	3.4	6	11	13	3.6	14	13
Accidental overdose	0	0	0	0	2	1.1	2	4	2	0.6	2	2
Drug dispensing error	0	0	0	0	1	0.6	1	2	1	0.3	1	1
Overdose	1	0.6	1	2	0	0	0	0	1	0.3	1	1
Wrong drug administered	6	3.3	7	13	3	1.7	3	6	9	2.5	10	9

The table was modified by the reviewer. The reviewer removed rows which cited investigator's causality determination from the table.
Source: CSR Trial 3816-ext, Table 14.3.1.41 , page 1007

The majority of medication errors were due to the wrong drug being administered: 6 subjects with 13 events in the IDegAsp group and 3 subjects with 3 events in the IDet group. [75]

Reviewer's comment: The small numerical imbalances noted between treatment arms should be interpreted in light of the fact that both arms used the same pen devices for administration of basal insulin and same pen device for administration of the prandial component. Overall, there are no clear drug specific differences between treatment groups. The medication errors in this trial do not clearly suggest any additional trends, than what is already labeled, for this product.

The pen devices used in each trial raise some concern regarding the external differentiation and the risk for medication error. These same concerns resulted in the Sponsor's removal of the penfill pens during the second review cycle; refer to section **Pen devices.**

Injection Site Reactions
Injection site reactions- Trial NN1250-3561(IDeg)

Injection site reactions were more commonly reported for IDeg than IDet, with 22 patients reporting 33 events for IDeg and 11 patients reporting 14 events for IDet, with an event rate for IDeg twice that of IDet (20 vs 9 events per 100 PYE respectively). Most of the events with an event rate greater than 1, in the IDeg group, included the following PT terms: "injection site reaction", "injection site pain," injection site bruising and "lipohypertrophy"; see **Table 34**.

Table 36 - Trial 3561 - injection site reactions by SOC and PT- summary - safety analysis set

	IDeg OD				IDet			
	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**			
General Disorders and Administration Site Conditions	22	12.6	33	20	11	6.3	14	9
Injection site reaction	7	4	14	9	3	1.7	3	2

[75] In the IDegAsp treatment group, 5 out of the 7 'wrong drug administered' events were due to mix-up between the two trial products, and 2 events (both in subject 911008) were due to mix-up between the trial product and the pre-trial insulin. In the IDet treatment group, out of the 3 'wrong drug administered' events, 1 was due to mix-up between the two trial insulins, and 2 were due to mix-up with the pre-trial insulin product.

Reference ID: 4009596

	IDeg OD				IDet			
	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**			
General Disorders and Administration Site Conditions	22	12.6	33	20	11	6.3	14	9
Injection site pain	4	2.3	4	2				
Injection site bruising	3	1.7	3	2				
Injection site erythema	1	0.6	1	1	1	0.6	1	1
Application site irritation	1	0.6	1	1				
Injection site hemorrhage	1	0.6	1	1				
Injection site mass					1	0.6	1	1
Injection site rash	1	0.6	1	1				
Injection site swelling					1	0.6	1	1
Vessel puncture site bruise	1	0.6	1	1				
Vessel puncture site pain	1	0.6	1	1				
Vessel puncture site swelling	1	0.6	1	1				
Skin and Subcutaneous Tissue Disorders								
Lipohypertrophy	4	2.3	4	2	2	1.1	2	1
Lipodystrophy acquired	1	0.6	1	1	3	1.7	5	3

Source: CSR-Trial 3561-ext, Table 12-11, page 165

The Sponsor's analysis of injection site reactions possibly related to the basal insulin (rather than the aspart insulin) was 10 patients with 15 events for IDeg and 7 patients with 9 events for IDet (an event rate of 9 vs. 6 events per 100 PYE respectively).

Reviewer's comment: despite the higher event rate of injection site reactions for IDeg than IDet, the analysis by relationship to basal insulin reveals that most of the injection site reactions may have been due to the bolus insulin, therefore making the difference between treatment groups smaller when analyzing by basal insulin. Overall, as with other insulins, there is a concern with injection site reactions, but the signal does not appear to be worse for IDeg than for other basal insulins.

Injection site reactions- Trial NN1250-3816 (IDegAsp)

There were few injection site reactions reported in this trial; with an event rate of 2 vs. 6 per 100 PYE for IDegAsp vs. IDet respectively, see **Table 35**.

Table 37 - Trial 3816 - injection site reactions by SOC and PT- summary - safety analysis set

	IDegAsp OD				IDet			
	N	%	E	R	N	%	E	R
Number of subjects	**181**				**179**			
General Disorders and Administration Site Conditions	1	0.6	1	2	3	1.7	3	6
Injection hypertrophy	1	0.6	1	2	2	1.1	2	4
Injection site swelling					1	0.6	1	2

Source: CSR-Trial 3816, Table 14.3.1.37, page 1003

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Reviewer's comment: there were too few patients/events in this trial to determine any trends regarding injection site reactions.

Hyperglycemia

The ISPAD guidelines[76] recommend monitoring ketones during episodes of uncontrolled hyperglycemia (persistent blood glucose>250 mg/dL), state of insulinopenia, and illness. Ketone levels may help guide treatment to prevent severe ketoacidosis. Therefore the findings in this section may be interpreted in light of the SAE findings for hyperglycemia, see section **7.3.2 Nonfatal Serious Adverse Events.** For both trials, the measurement of ketones required an additional blood stick; refer to section **5.3 Discussion of Individual Studies/Clinical Trials** for protocol violations related to ketone measurements.

Hyperglycemia- Trial NN1250-3561(IDeg)

According to the protocol, patients were to report hyperglycemia with a glucose≥ 200 mg/dL, and if the blood glucose measurements exceeded 250 mg/dL the patient was to measure capillary blood ketones. Ketosis was considered present if blood ketones were ≥1.5 mmol/L. The CSR states that there were protocol deviations related to missing ketones.

Overall there were was a numerically lower number of episodes of hyperglycemia with ketosis for IDeg than for IDet (16.7% of patients experienced 109 events for IDeg and 25.7% of patients experienced 161 events for IDet).

Table 38 – Trial 3561- Hyperglycemic episodes and episodes of ketosis- treatment emergent- summary - safety analysis set

	IDeg OD				IDet			
	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**			
Hyperglycemic episodes	174	100	58679	36344	175	100	52831	35840
Hyperglycemia>250mg/dL	173	99.4	33689	20866	174	99.4	29627	20099
Hyperglycemia with ketones measured	172	98.9	28148	17434	174	99.4	24780	16811
Episodes of ketosis	29	16.7	109	68	45	25.7	161	109

Source: CSR 3561-ext, table 12-30, page 203

Reviewer's comment: the exploratory trends of hyperglycemia did not suggest worsened hyperglycemia with use of IDeg. These findings are supported by the findings of only 1 case of diabetic ketoacidosis reported as an SAE (in the IDeg group).

Reviewer's labeling comments: Because of the extent of missing data and potential bias, the reviewer does not recommend the comparative labeling of the hyperglycemia with ketosis findings as proposed by the Sponsor:

[76] Rewers MJ, Pillay K, de Beufort C, Craig ME, Hanas R, Acerini CL. ISPAD Clinical Practice Consensus Guidelines 2014 Compendium, Assessment and monitoring of glycemic control in children and adolescents with diabetes. Pediatr Diabetes 2014; 15(Suppl 20):102-114

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(b) (4)

Hyperglycemia- Trial NN1250-3816 (IDegAsp)
According to the protocol, patients were to report hyperglycemia with a glucose measure ≥250 mg/dL and the subject looked/felt ill. Patients were then to measure ketone bodies, which involved an additional finger prick. Ketosis was considered present if blood ketones were ≥1.5 mmol/L.

As mentioned previously, there were multiple protocol deviations related to missing ketones when experiencing hypoglycemia. [77] Overall there were a similar number of patients who experienced hyperglycemic episodes (72 vs. 73 patients for IDegAsp vs. IDet respectively); with more events in the IDegAsp than the IDet group (599 vs. 449 events for IDegAsp vs. IDet respectively).

The number of hyperglycemic episodes with ketosis (>1.5 mmol/L) was low overall, and numerically favored IDegAsp.

Table 39 – Trial 3816- Hyperglycemic episodes and episodes of ketosis- treatment emergent- summary - safety analysis set

	IDegAsp OD				IDet			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of subjects	**181**				**179**			
Hyperglycemic episodes	72	39.8	599	1094	73	40.8	449	833
Hyperglycemia with ketones measured	57	31.5	441	805	60	33.5	301	558
Hyperglycemia with ketones>1.5 mmol/L	4	2.2	6	11	8	4.5	12	22

Source: CSR 3816, table 12-23, page 170

Reviewer's comments: The interpretation of the hyperglycemia findings in both trials should be interpreted in light of measurement bias (i.e. some patients could have missed episodes of hyperglycemia because they did not measure their blood sugar, or alternatively, a patient measures blood sugars frequently and likely to capture more episodes of hyperglycemia).

In addition, patients with hyperglycemia may not experience "symptoms" and thus may be missing from the analysis shown. The evaluation of SAEs for both trials (Trial 3651 and 3816) did not reveal any trends suggesting a risk of DKA favoring any treatment group.

[77] Ketone bodies were not measured for approximately 26% of hyperglycemic episodes in the IDegAsp group and for 33% in the IDet treatment group

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7.4 Supportive Safety Results

7.4.1 Common Adverse Events

7.4.1.1 Common Adverse events- Trial NN1250-3561 (IDeg)

Table 38 shows the Sponsor's adverse events ≥5% by PT terms, which has been modified by the reviewer by excluding the SOCs and grouping categories related to abdominal pain.[78] Overall the event rate of adverse events, by PT term, was similar between treatment groups. Notable differences between treatment arms included the following PT terms: "Blood ketone body" which was lower for IDeg than IDet (50 vs 92 events per 100 PYE) and "hypoglycemia," which is higher for IDeg vs. IDet (43 vs.22 events per 100 PYE).

Table 40 – Trial 3561- AEs by SOC and PT – most frequent (>=5%) – treatment emergent –SAS

	IDeg OD				IDet				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**				**349**			
Events	146	83.9	962	596	143	81.7	918	623	289	82.8	1880	609
Nasopharyngitis	72	41.4	177	110	67	38.3	141	96	139	39.8	318	103
Headache	46	26.4	107	66	54	29.1	121	82	97	27.8	228	74
Abdominal pain	40	23	58	36	25	14.3	42	28	65	18.6	100	32
Upper respiratory tract infection	34	19.5	56	35	24	13.7	58	39	58	16.6	114	37
Blood ketone body increased	31	17.8	80	50	46	26.3	135	92	77	22.1	215	70
Cough	31	17.8	52	32	29	16.6	42	28	60	17.2	94	30
Pyrexia	30	17.2	59	37	28	16	45	31	58	16.6	104	34
Oropharyngeal pain	29	16.7	45	28	34	19.4	50	34	63	18.1	95	31
Hypoglycemia*	28	16.1	69	43	19	10.9	33	22	47	13.5	102	33
Vomiting	26	14.9	38	24	23	13.1	36	24	49	14	74	24
Diarrhea	22	12.6	26	16	17	9.7	25	17	39	11.2	51	17
Influenza	16	9.2	19	12	18	10.3	21	14	34	9.7	40	13
Gastroenteritis	16	9.2	20	12	23	13.1	27	18	39	11.2	47	15
Nasal congestion	13	7.5	17	11	7	4	13	9	20	5.7	30	10
Nausea	13	7.5	18	11	9	5.1	12	8	22	6.3	30	10
Rhinitis	12	6.9	19	12	14	8	23	16	26	7.4	42	14
Pain in extremity	11	6.3	16	10	5	2.9	5	3	16	4.6	21	7
Gastroenteritis viral	10	5.7	15	9	10	5.7	15	10	20	5.7	30	10
Ear pain	10	5.7	12	7	5	2.9	5	3	15	4.3	17	6
Sinusitis	9	5.2	13	8	6	3.4	6	4	15	4.3	19	6
Bronchitis*	9	5.2	11	7	8	4.6	11	7	17	4.9	22	7
Ear infection	9	5.2	11	7	11	6.3	11	7	20	5.7	22	7
Wrong drug administered*	9	5.2	9	6	6	3.4	9	6	15	4.3	18	6
The table was modified by combining abdominal pain upper with abdominal pain and the category is called												

[78] The PT term "Abdominal pain" also includes the category "abdominal pain upper", which was a separate PT term included in the Sponsor's table in the CSR.

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	IDeg OD				IDet				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
Number of subjects	**174**				**175**				**349**			
Events	146	83.9	962	596	143	81.7	918	623	289	82.8	1880	609
"abdominal pain" in the table. * refers to PT terms that are not included in the common adverse reaction in the proposed section 6.												

Source: CSR 3561-ext, table 12-9, page 161 modified by reviewer.

The reviewer evaluated the Sponsor's table of common adverse events in proposed PI, and noted that although the proposed table lists most of the PT in **Table 38**, with the exception of the PT terms marked with "*".

Reviewer's comment: The common adverse events in the pediatric trial includes additional preferred terms in the Infectious and Infestations system organ class than the already labeled common adverse reactions in the adult type 1 diabetes trials, as shown in **Table 39**. *The exclusion of hypoglycemia from the common adverse event table is in accordance with the labeling of other anti-diabetic products, as hypoglycemia is usually addressed in other sections of the label. The clinical importance of labeling additional preferred terms which may not be drug related will need to be further discussed within the Division.*

Table 41- already labeled adverse reactions occurring in≥5% of Tresiba- adult treated patients with type 1 diabetes mellitus

Adverse Reaction	TRESIBA (n=1102)
Nasopharyngitis	23.9 %
Upper respiratory tract infection	11.9 %
Headache	11.8 %
Sinusitis	5.1 %
Gastroenteritis	5.1 %

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203314lbl.pdf

7.4.1.2 Common Adverse events- Trial NN1250-3816 (IDegAsp)

Table 40 shows the Sponsor's adverse events ≥5% by PT terms. The reviewer modified the table in the study CSR by removing the SOCs and grouping categories related to abdominal pain.[79] Overall the event rate of adverse events, by PT term, was similar between treatment groups. Notable differences between treatment arms included the following PT terms favoring IDegAsp "headaches", "upper respiratory tract infection" and "pharyngitis;" while the PT terms

[79] The PT term "Abdominal pain" also includes the category "abdominal pain upper", which was a separate PT term included in the Sponsor's table in the CSR.

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"pyrexia" and "hypoglycemia" favored IDet (note that hypoglycemia is discussed further in section **7.3.4.2 Hypoglycemia - Trial NN1250-3816 (IDegAsp).**

Table 42- Trial 3816- common adverse events occurring in ≥5%

	IDegAsp				IDet				All			
Preferred term	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Number of subjects	181				179				360			
Events	100	55.2	242	442	97	54.2	243	451	197	54.7	485	446
Abdominal pain	24	13.2	35	64	24	13.4	39	72	48	13.3	74	68
Headache	23	12.7	47	86	32	17.9	64	119	55	15.3	111	102
Nasopharyngitis	36	19.9	43	79	32	17.9	42	78	68	18.9	85	78
Pyrexia	17	9.4	26	47	10	5.6	15	28	27	7.5	41	38
Vomiting	22	12.2	25	46	12	6.7	13	24	34	9.4	38	35
Cough	13	7.2	16	29	9	5	9	17	22	6.1	25	23
Oropharyngeal pain	9	5	13	24	13	7.3	14	26	22	6.1	27	25
Hypoglycemia	11	6.1	12	22	3	1.7	4	7	14	3.9	16	15
Upper respiratory tract infection	11	6.1	12	22	17	9.5	18	33	28	7.8	30	28
Influenza	9	5	10	18	10	5.6	12	22	19	5.3	22	20
Pharyngitis	3	1.7	3	5	10	5.6	13	24	13	3.6	16	15

Source: Trial 3816, modified CSR, table 12-6

Reviewer's comment: The common adverse events in the pediatric trials include additional preferred terms in the Infectious and Infestations system organ class than the already labeled common adverse reactions in the adult type 1 diabetes trials, as shown in **Table 41**.

Table 43- already labeled adverse reactions occurring in≥5% of Ryzodeg 70/30- adult treated patients with type 1 diabetes mellitus

Adverse Reaction	RYZODEG 70/30 (N=362)
Nasopharyngitis	24.6 %
Headache	9.7 %
Upper respiratory tract infection	9.1 %
Influenza	6.9 %

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/203313lbl.pdf

7.4.2 Laboratory Findings

Table 25 shows the centrally and non-centrally measured laboratories for each trial. For both trials, (b) (4) was responsible for analysis of all blood and urine samples taken during the trial and sending the data electronically to the Sponsor and sending laboratory results to the investigator on an ongoing basis.

For both trials, the Sponsor provided summary tables showing the change from baseline by visit and shift tables from baseline. Evaluation of the Sponsor provided biochemistry and hematology

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laboratories did not reveal any clinically relevant change from baseline to end-of treatment for the treatment arms of trial 3561 or trial 3816.

7.4.3 Vital Signs

In both the IDeg (trial 3561)[80] and IDegAsp trial (3618)[81], there were no relevant changes in mean blood pressure (systolic and diastolic) and mean HR from baseline to the end of trial (Week 52 for trial 3561 and week 16 for trial 3816). There were no important differences between treatment groups in either trial. Refer to section **7.6.3 Pediatrics and Assessment of Effects on Growth** for a discussion on height and weight.

7.4.4 Electrocardiograms (ECGs)

ECGs were not performed in either trial.

7.4.5 Special Safety Studies/Clinical Trials

Not applicable to this efficacy supplement, refer to the original NDA review.

7.4.6 Immunogenicity

As per the FDA Guidance for Industry[82], immune response to therapeutic protein products may affect the safety and/or efficacy of the product. However, because the immune response varies in clinical relevance (i.e., antibody response with no visible clinical findings to a life-threatening reaction), the interpretation of the antibody findings may be limited if no/or few clinical findings are seen.

The Sponsor submitted the final report to fulfill the PMC 2955-2 "to develop and validate an assay to assess for the presence of anti-degludec antibodies"[83] to NDA 203313 and NDA203314 during the review of the current supplement. This PMC is currently under review by the Office of Biotechnology Products and will not be discussed further in this review.

In this section the reviewer evaluates the trends in cross reactivity antibody status and level of insulin antibodies in affecting efficacy (antibody relationship to HbA1c) and safety in patients randomized to IDeg vs. IDet; there was no specific immunogenicity assessment for trial 3816.

The following antibodies were measured in trial 3561: insulin 454 (what is that?) specific antibodies, detemir specific antibodies, aspart specific antibodies and antibodies cross-reacting to

[80] Pulse, systolic and diastolic blood pressure were measured at Visit 1 (screening), Week 26, week 52
[81] Pulse, systolic and diastolic blood pressure were measured at Visit 1 (screening), Week 16, end of trial visit
[82] http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm338856.pdf, Guidance for Industry Immunogenicity Assessment for Therapeutic Protein Products, August 2014.
[83] Submission submitted on September 8, 2016 to NDA 203313 and 203314 (sequence 97)

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human insulin. Antibodies were measured at randomization, week 12, 26, 38, 52, and 53 by the test facility, (b) (4).

Of note, cross-reactive antibodies at week 53 were measured one week after discontinuation of study drug. The method of analysis was a radioimmunoprecipitation (RIP) assay using [^{125}I]-labelled tracers in the presence or absence of unlabelled antigen. After incubation overnight, the total amount of antibodies was precipitated together with any antigen that may have bound to the antibodies. The precipitate was counted in a gamma counter and the amount of radioactivity was expressed in percent of the total amount of added radioactivity (%B/T). The %B/T value is a measure of antibodies in the sample (i.e. antibody titer).

Cross reactive antibody analysis

Figure 37 shows the cross reacting antibodies to human insulin by treatment group. Over the course of the study, the mean level of insulin antibodies cross-reacting between insulin analogues and human insulin slightly decreased with IDeg and increased slightly with IDet; with similar trends in age subgroups.

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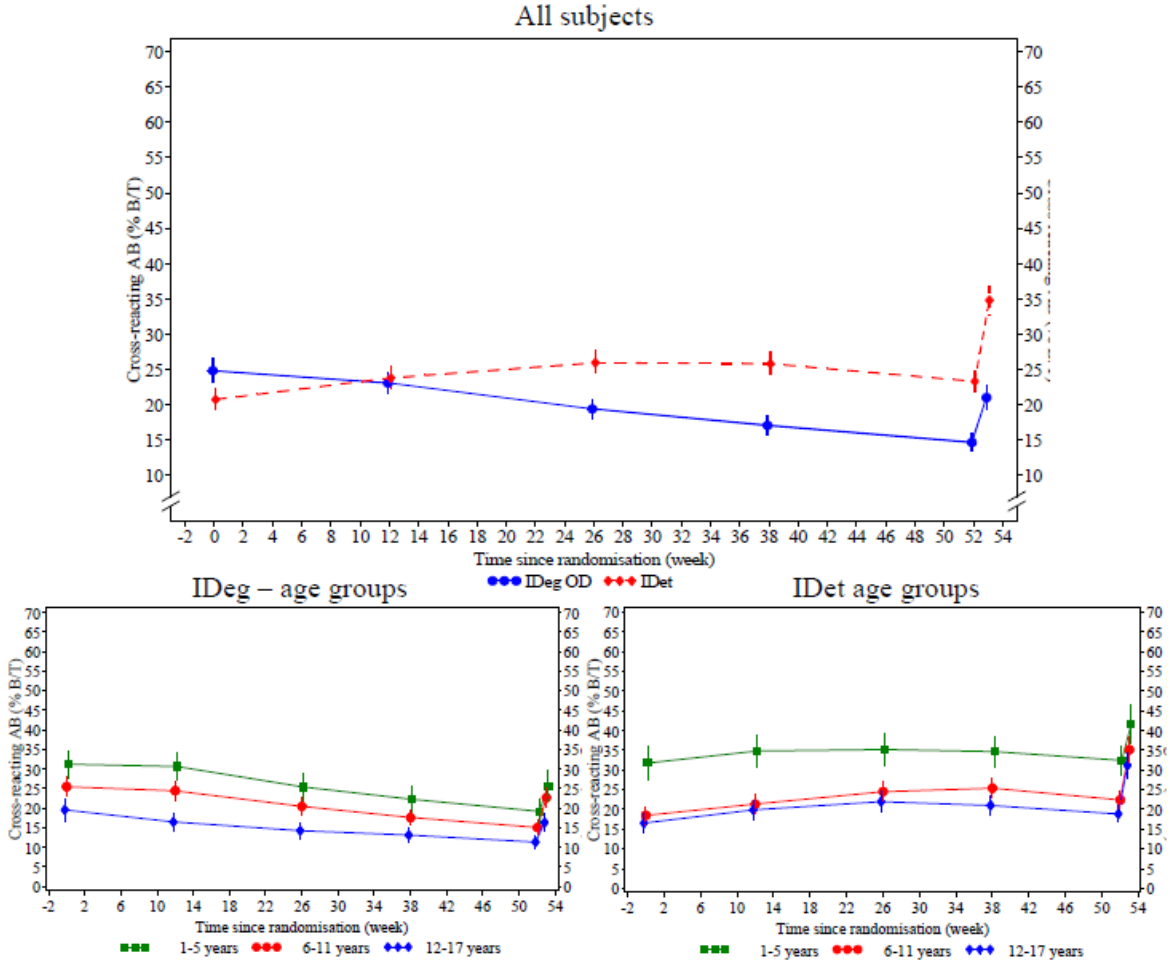
Figure 37 - Cross-reacting antibodies to human insulin (% B/T) – mean plot (upper panel: all subjects; lower panel: age groups) – ETS



Ext: LOCF imputed data. Error bars ± standard error (mean). AB: antibodies, LOCF: last observation carried forward

Source: CSR 3561- ext, Figure 12-8,page 210

The interpretation of **Figure 37** should take into account that there was no washout period preceding the study start. The Sponsor explains the increase in cross reacting antibodies from week 52 and 53 due to more radiolabelled insulin in the assay binding the insulin antibodies since the binding sites were not already occupied by exogenous insulin in the blood stream.

An evaluation of cross-reacting insulin antibodies at week 52 when compared to HbA1c (see **Figure 38**) did not reveal any apparent correlation between cross-reacting antibodies and HbA1c.

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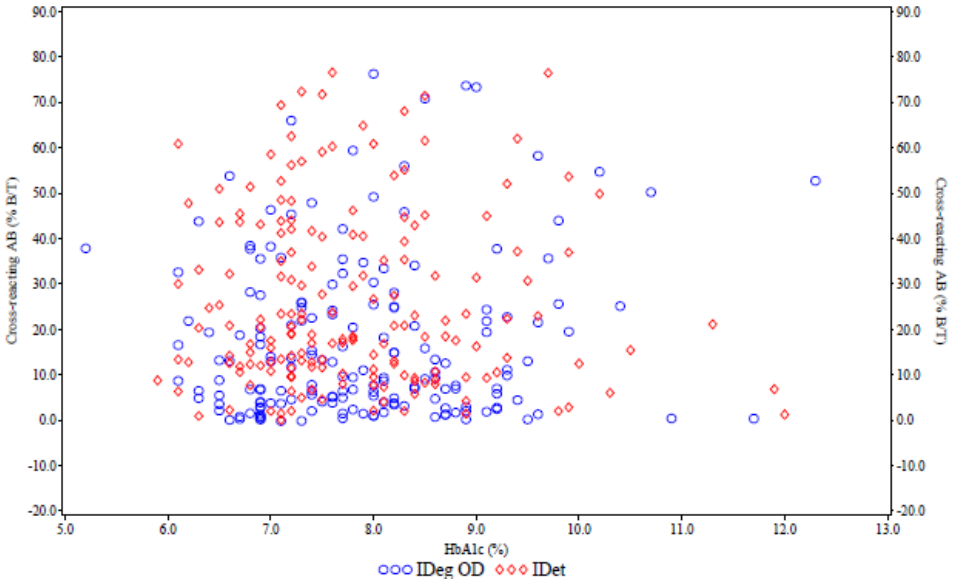
Figure 38 – Trial 3561 – Cross-reacting antibodies to human insulin (%B/T) against HbA1c (%) after 52 weeks of treatment – LOCF -safety analysis set-



Source: CTR 3561-ext, figure 14.3.6.165, page 2673

Insulin antibody levels

Specific antibody levels for IDeg and IDet remained low during the trial. **Figure 39** shows levels of anti-IDeg and anti-IDet antibody binding. Overall, there was a slightly lower insulin antibodies with IDeg, when compared to IDet (mean levels of IDeg vs. IDet: 0% B/T and 4% B/T, respectively). In addition, the Sponsor evaluated the anti-aspart antibodies in both treatment arms. There was not notable difference between anti-aspart antibodies between treatment groups (data not shown in review).

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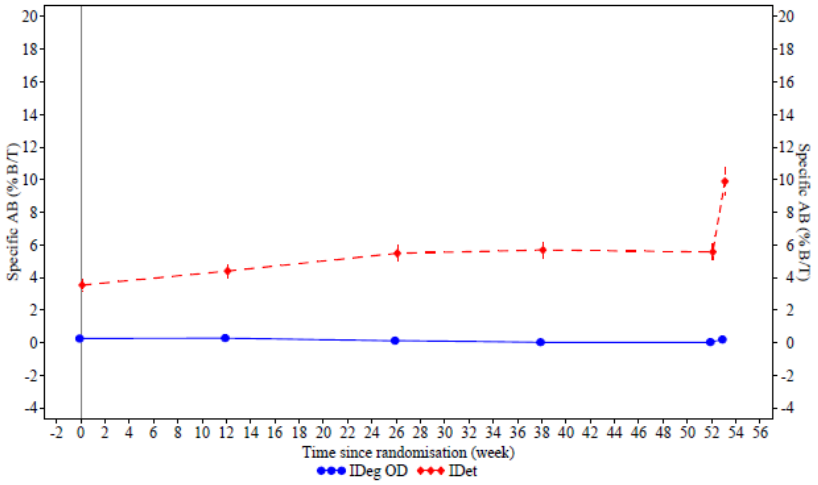
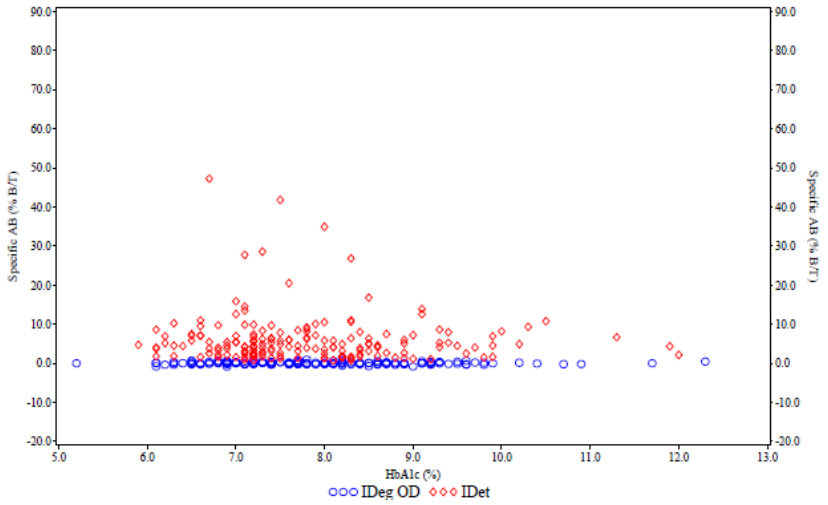
Figure 39 – Trial 3561- Insulin degludec/IDet specific antibodies (% B/T) – LOCF- mean plot extension trial set



Source: CTR 3561- ext, 14.3.6.89, page 2597

There was no clear association of insulin antibodies to IDeg or IDet at week 52 and HbA1c or total daily insulin dose (**Figure 40**).

Figure 40 – Trial 3561 – Insulin degludec/comparator specific antibodies (%B/T) against HbA1c (%) after 52 weeks of treatment-LOCF- safety analysis set



Source: CTR 2561-ext, 14.3.6.149, page 257

Evaluation of adverse events vs. antibody positivity

In order to evaluate the relationship of adverse events to immune status, the reviewer requested an analysis of adverse events by specific antibody status. In an information request dated September 20, 2016, the Sponsor clarified that cut-points for determination of antibody positivity based on antibody levels measured at baseline in the current trial are not recommended. The cut

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point for determination of antibody positivity was determined from analysis of 150 samples from healthy, insulin naïve individuals during assay validation. The upper limit of the normal range was calculated as the 95% percentile. The cut-points for each antibody population are as follows: IDeg specific Ab: 0.6% B/T; IDet specific Ab: 1.3% B/T.

The safety analyses revealed that the antibody positivity for IDet was higher than for IDeg (56 out of the 174 patients had +IDeg antibodies; 174 out of the 175 patients had a +IDet antibody). These findings are not altogether surprising since the majority of patients prior to trial start were on insulin detemir.

An evaluation of injection site events and adverse events by system organ class and preferred terms, among subjects with and without at least one positive specific antibody status during the 52 week period did not reveal any clinically significant differences by antibody status[84] (data not shown in this review).

An evaluation of severe hypoglycemia by antibody status revealed that there was a slightly larger proportion of patients who were +IDeg than +IDet that experienced severe hypoglycemia at week 53 (see **Table 42**). Since most events of severe hypoglycemia occurred within the first month of treatment, and the first non-baseline antibody measurement occurred at week 12, a relationship between antibody status and hypoglycemia is difficult to determine.

[84] Refer to information request: \\CDSESUB1\evsprod\NDA203314\0099\m1\us

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Table 44 – Trial 3561- Severe hypoglycemia (as per ISPAD) in subjects with and without at least one positive specific antibody status during the trial- safety analysis set

	Negative				Positive			
	− IDeg Ab		− IDet Ab		+ IDeg Ab		+ IDet Ab	
	N	(%)	N	(%)	N	(%)	N	(%)
Number of subjects	118		1		56		174	
Severe hypoglycaemia	20	(16.9)	0	(0.0)	11	(19.6)	24	(13.8)

N: number of subjects, %: percentage of subjects.

+ IDeg Ab (+ IDet Ab): subjects in the IDeg (IDet) group with at least one positive measure of specific antibodies from baseline (week 0) to follow-up (week 53) inclusive.

− IDeg Ab (− IDet Ab): subjects in the IDeg (IDet) group with no positive measure of specific antibodies from baseline (week 0) to follow-up (week 53) inclusive.

Source: \\CDSESUB1\evsprod\NDA203314\0099\m1\us

Reviewer's comment: The overall antibody analyses do not reveal an effect of antibody response on efficacy or safety parameters.

7.5 Other Safety Explorations

Not applicable to this efficacy supplement, refer to the original NDA review.

7.5.1 Dose Dependency for Adverse Events

Not applicable to this efficacy supplement, refer to the original NDA review.

7.5.2 Time Dependency for Adverse Events

See section **7.3.4 Significant Adverse Events** for an evaluation of severe hypoglycemia events.

7.5.3 Drug-Demographic Interactions

Not applicable to this efficacy supplement, refer to the original NDA review.

7.5.4 Drug-Disease Interactions

Not applicable to this efficacy supplement, refer to the original NDA review.

7.5.5 Drug-Drug Interactions

Not applicable to this efficacy supplement, refer to the original NDA review.

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7.6 Additional Safety Evaluations

Not applicable to this efficacy supplement, refer to the original NDA review.

7.6.1 Human Carcinogenicity

For a full evaluation of human carcinogenicity, refer to the original NDA review. In trial 3561 there was only 1 event of "skin papilloma" reported with IDet and no events in the IDeg group. For trial 3816, there were no neoplasms identified for IDegAsp and 1 event for "skin papilloma" reported for IDet.

Reviewer's comment: the incidence of neoplasms was very small in either trial to determine any causality.

7.6.2 Human Reproduction and Pregnancy Data

The Sponsor submitted a PI with proposed changes to be compliant with the Pregnancy and Lactation labeling Rule. Refer to the review by the Division of Pediatric and Maternal Health for labeling recommendations to meet PLLR, regarding sections: 8.1 Pregnancy, 8.2 Lactation, 8.3 Females and Males of Reproductive Potential.

7.6.3 Pediatrics and Assessment of Effects on Growth

Although these studies assessed growth (height and weight) during the trial, the assessment of growth is limited by three main factors:

1. Because growth in the pediatric population is a process that occurs over long periods of time, the limited duration of the clinical trials in this submission may not provide a sufficient period of observation to assess the effects of drugs on growth.

2. Neither study was designed to decrease measurement errors or variability in the assessment of growth. As the Sponsor notes, "the instruments used to measure the child should be validated and checked regularly; consecutive height measurements should be standardized and performed at approximately the same time of the day (to avoid the influence of diurnal variation) by the same measuring device and preferably by the same trained observer; and height should be measured in replicate at each time point and the results averaged for analyses."

3. For the height analysis, although the Prader height velocity standards have been shown to be in good agreement with those of American and other European cohorts, it is unknown if these growth standards are representative of Japanese subjects (which were enrolled in trial 3561).

The limitations listed above should be kept in mind when interpreting the results in this section.

In both studies, growth was assessed by measurement of height and weight. Height was assessed without shoes in meters or inches at designated visits[85]. Body weight was to be measured in kilograms or pounds without coat and shoes and wearing only light clothing at designated visits.[86] The protocol for Trial 3816 specified that the same scale should be used throughout the trial.

No further instructions were provided to investigators for Trials 3561 or 3816 regarding the methods of measuring height or weight.

Neither trial evaluated patients for pubertal status.

Height analysis
In an information request the Sponsor was asked to provide information on of subjects who were below the 3rd, 10th and 25th percentiles of growth velocity for both trials. The Sponsor responded on September 27, 2016.[87]

Annualized height velocity for each subject was compared with the Prader velocity standards based on age and sex of the subject to determine if the subject's growth velocity was below the 3rd, 10th or 25th percentiles. Age at the time of the post-baseline height measurement was used to determine if the subject's growth velocity was below the specified cut points (the analysis is shown in **Table 43**). Because growth velocities in an individual child can have high variability in consecutive growth intervals, the Sponsor presented data from baseline to the last measurement in each trial.

Table 45 – Trial 3561 and Trial 3816 - Proportion of subjects with growth velocity below 3rd, 10th and 25th percentiles - full analysis set

All subjects	FAS	N	Below the 3rd percentile N (%)	Below the 10th percentile N (%)	Below the 25th percentile N (%)
Trial 3561					
IDeg	174	173	17 (9.8)	28 (16.2)	47 (27.2)

[85] For trial 3561: Visits: 1, 14, 28, 42 and 56 (screening, weeks 12, 26, 38 and 52); for trial 3816: Visits: 2, 14 and 18 (randomization, weeks 12 and 16).
[86] For trial 3561: Visits: 1, 2, 14, 28, 42 and 56 (screening, randomization, weeks 12, 26, 38 and 52); for trial 3816: Visits: 1, 2, 14 and 18 (screening, randomization, weeks 12 and 16).
[87] For details regarding this information request refer to: \\cdsesub1\evsprod\NDA203314\0101\m1\us
Growth velocity was assessed based on height of subjects in Trials 3561 and 3816 against height velocity reference data established by Prader and colleagues in a cohort of healthy European subjects who were followed from birth to maturity. The Prader reference data are well-established standards for assessing growth velocity as they cover the full pediatric age range from birth to 20 years of age. The Prader standards have previously been accepted by the FDA as a valid standard and are therefore used in the response below.
Annualized height velocity was calculated for each subject as follows:
Height velocity (cm/year) =(height at week 'x' visit - height at baseline)/(time from baseline to week 'x' visit in years).

Reference ID: 4009596

IDet	176	172	15 (8.7)	26 (15.1)	48 (27.9)
Trial 3816					
IDegAsp	182	178	22 (12.4)	36 (20.2)	56 (31.5)
IDet	180	176	19 (10.8)	33 (18.8)	60 (34.1)
Source: modified table 2 and table 3 from information request on September 27, 2016: \\cdsesub1\evsprod\NDA203314\0101\m1\us					

In general, in both trials the proportions of subjects who were below the 3rd, 10th and 25th percentiles for growth velocity were similar between the two treatment groups.

Weight analysis

In trial 3561after 52 weeks of treatment, the trends among age subgroups were similar: the SD score for body weight was higher for IDeg than IDet. Patients in the IDeg arm had a slightly higher weight SD score at baseline (0.33 vs. 0.32). After 52 weeks the mean weight SD score was 0.44 with IDeg and 0.25 with IDet.

In trial 3816[88], both treatment groups had similar weight SD scores at baseline (mean 0.4 vs. 0.47 for IDegAsp and IDeg respectively). After 16 weeks of therapy, patients in the IDegAsp group had an increase in SD score of +0.06 to an SD score of 0.44 while the IDet group had a decrease of SD score of -0.02 to an SD score of 0.46 with IDet.

Reviewer's comment: All insulins are labeled for weight increases. Although there was a slightly greater increase in weight in the IDeg (for trial 3561) or IDegAsp (in trial 3816) than the comparator IDet group, the clinical importance of this difference is unclear.

Evaluation of outliers was done by analysis of the proportions of subjects with body weight below the 5th percentile or above the 95th percentile[89]. In both trials, the number and percentage of subjects having body weight below the 5th or above the 95th percentiles were small with no clear treatment differences between arms.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Not applicable to this efficacy supplement, refer to the original NDA review.

7.7 Additional Submissions / Safety Issues

Not applicable to this efficacy supplement, refer to the original NDA review.

[88] Body weight was measured at Visit 1 (screening), week 0, week 12, and Week 16 for trial 3816.
[89] Data was derived from the age, sex and body weight of each subject compared to body weight curves defined by the US Center for Disease Control. Age at time of the body weight measurement was used to determine if the subject was above or below the specified cut points.

8 Postmarket Experience

The Periodic Safety Update Report/ Periodic Benefit-Risk Evaluation Report (covering the period of 01 October 2014 to 30 September 2015) for Tresiba and Ryzodeg was reviewed.

As of January 31, 2016, Tresiba is approved in the European Union and Japan for the treatment of diabetes mellitus in pediatric patients from age 1. The Sponsor submitted an application to the EMA to update the prescribing information of Ryzodeg in children and adolescents with T1DM, but was not approved at the time of the PSUR.

The potential off-label use of Tresiba in children and adolescents above the age of 1 revealed four cumulative SAEs associated with either hypoglycemia or DKA. There were 6 case reports of off-label use of Ryzodeg in children and adolescents with only 1 case reporting an AE ('blood glucose abnormal'), the remaining cases did not report an AE and noted that Ryzodeg was administered to a child.

Overall, since approval of IDeg and IDegAsp, no new safety concerns and no new information relevant to existing safety concerns were received.

9 Appendices

9.1 Literature Review/References

These are mentioned as pertinent throughout the review.

9.2 Labeling Recommendations

These recommendations are included throughout the review.

9.3 Advisory Committee Meeting

An advisory committee meeting is not recommended for this application.

Clinical investigator Financial Disclosure

Application Number: 203313
Submission Date(s): 15 February 2016
Applicant: Novo Nordisk
Product: Insulin degludec/Insulin aspart 70/30 (Ryzodeg 70/30)

Reviewer: Tania Condarco, M.D.
Date of Review: 11/4/2016
Covered Clinical Study (Name and/or Number): NN5401-3816- IDegAsp

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)

Reference ID: 4009596

Total number of investigators identified: 220		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Table 46 – Trial 3816 - Significant Payments of Other Sorts

Site no.	Investigator	Disclosable Financial Interests			Total	Patients Randomized to Site
		Explanation	Amount	Date		
(b) (4)	(b) (6)	Honoraria/Fees	$150,100	10/2013-8/2015	$150,100	(b) (4)
		Honoraria/Fees	$27,900	11/2013-4/2015	$27,900	

Source: Information request on June 2, 2016 \\CDSESUB1\evsprod\NDA203313\0079

Application Number: 203314
Submission Date(s): 15 February 2016
Applicant: Novo Nordisk
Product: Insulin degludec

Reviewer: Tania Condarco, M.D.
Date of Review: 11/4/2016
Covered Clinical Study (Name and/or Number): Study NN1250-3561

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: 276		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 26 (2 are from the United States, and 24 from outside the United States).		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

Table 47 – Trial 3561- Significant Payments of Other Sorts

Site no.	Investigator	Disclosable Financial Interests			Total	Number Randomized to Site
		Explanation	Amount	Date		
(b) (4)	(b) (6)	Honoraria/Fees	$165,740	11/2011-09/2014	$165,740	(b) (4)
		Honoraria/Fees	$26,250	12/2011-09/2014	$26,250	

Site no.	Investigator	Disclosable Financial Interests (NON-US SITES)			Total	Number Randomized to Site
		Explanation[A]	Amount[B]	Date		
(b) (4)	(b) (6)	Donation to hospital	$106,853.00	08/2012-11/2013	$106,853.00	(b) (4)
		Donation to hospital Honoraria	$106,853.00 $6,456.00	08/2012-11/2013 12/2011-05/2013	$113,309.00	
		Donation to hospital	$181,140.00	12/2011-12/2012	$181,140.00	
		Donation to hospitals Honoraria	$182,122.00 $1,106.00	12/2011-07/2013 12/2011-09/2013	$183,228.00	
		Donation to hospital	$181,140.00	12/2011-12/2012	$181,140.00	
		Donation to hospital Honoraria	$181,140.00 $45,366.00	12/2011-12/2012	$226,506.00	
		Donation to hospital	$154,267.00	12/2012-09/2013	$154,267.00	

(b) (4)	(b) (6)					(b) (4)
		Donation to hospital Honorarium	$154,647.00 $1,111.00	12/2012-09/2013 10/2012	$155,758.00	
		Donation to hospital Honorarium	$154,267.00 $18,009.00	12/2012-09/2013 01/2012-10/2013	$172,276.00	
		Donation to hospital	$30,700.00	12/2011-04/2013	$30,700.00	
		Donation to hospital Honorarium	$30,700.00 $1,542.00	12/2011-04/2013 04/2013-11/2013	$32, 242.00	
		Donation to hospital Honorarium	$30,700.00 $5,222.00	12/2011-04/2013 12/2011-07/2013	$35,923.00	
		Donation to hospital Honorarium	$62,500.00 $4,618.00	10/2012-12/2012 03/2012-09/2013	$67,117.00	
		Donation to hospital Honorarium	$36,288.00 $701.00	12/2011-03/2012 02/2013	$36,929.00	
		Donation to hospital	$36,228.00	12/2011-03/2012	$36,228.00	
		Donation to hospital Honorarium	$36,228.00 $5167.00	12/2011-03/2012 08/2012-08/2013	$41,395.00	
		Donation to hospital Honorarium	$30,700.00 $1,542.00	12/2011-04/2013 04/2013-11/2013	$32, 242.00	
		Donation to hospital Honorarium	$161,228.00 $701.00	12/2011-12/2012 06/2013	$161,929.00	
		Donation to hospital Honorarium	$161,228.00 $837.00	12/2011-12/2012 09/2012-09/2013	$162,065.00	
		Donation to hospital Honorarium	$161,228.00 $3,899.00	12/2011-12/2012 03/2012-07/2013	$165,127.00	
		Donation to hospital	$73,900.00	12/2011-11/2013	$73,900.00	
		Donation to hospital	$73,900.00	12/2011-11/2013	$73,900.00	

(b) (4)	(b) (6)	Research grant	$83,448.00	2010-2012	$83,448.00	(b) (4)
		Donation to hospital	$159,733.00	01/2012-12/2012	$159,733.00	
		Honorarium	$25,001.00	07/2013[C]	$25,001.00	

PI=principal investigator

[A] For sites with investigators reporting donations to the same hospital, this amount is counted only once per site in the BIMO dataset. The table reflects the amount as reported by each non-US investigator on the Novo Nordisk Certification: Financial Disclosure document in Module 1.3.4.

[B] Conversions used:

2010: 1 Euro = 7.45 Danish Krone (DKK); 1 DKK = 0.052 USD

2011: 1 Japanese Yen = 0.064 DKK; 1 DKK = 0.057 USD

1 Euro = 7.45 DKK

2012: 1 Japanese Yen = 0.065 DKK; 1 DKK = 0.052 USD

1 Euro = 7.45 DKK

2013: 1 Japanese Yen = 0.073 DKK; 1 DKK = 0.058 USD

[C] Dates of when (b) (6) received the honoraria were not disclosed. The date provided in the table reflects the signature date on the Novo Nordisk Certification: Financial Disclosure document in Module 1.3.4.

Source: \\CDSESUB1\evsprod\NDA203313\0069\m1\us\103-admin\1034-financial

Table 48 – Trial 3561-Start dose of total, bolus (Iasp) and basal insulin (IDeg and IDet)

Total daily insulin dose	Bolus:basal ratio 50:50		Bolus:basal ratio 70:30		Total daily insulin dose	Bolus:basal ratio 50:50		Bolus:basal ratio 70:30	
	Total bolus	Total basal	Total bolus	Total basal		Total bolus	Total basal	Total bolus	Total basal
4	2	2	3	1	**54**	27	27	38	16
6	3	3	4	2	**56**	28	28	39	17
8	4	4	6	2	**58**	29	29	41	17
10	5	5	7	3	**60**	30	30	42	18
12	6	6	8	4	**62**	31	31	43	19
14	7	7	10	4	**64**	32	32	45	19
16	8	8	11	5	**66**	33	33	46	20
18	9	9	13	5	**68**	34	34	48	20
20	10	10	14	6	**70**	35	35	49	21
22	11	11	15	7	**72**	36	36	50	22
24	12	12	17	7	**74**	37	37	52	22
26	13	13	18	8	**76**	38	38	53	23
28	14	14	20	8	**78**	39	39	55	23
30	15	15	21	9	**80**	40	40	56	24
32	16	16	22	10	**82**	41	41	57	25
34	17	17	24	10	**84**	42	42	59	25
36	18	18	25	11	**86**	43	43	60	26
38	19	19	27	11	**88**	44	44	62	26
40	20	20	28	12	**90**	45	45	63	27
42	21	21	29	13	**92**	46	46	64	28
44	22	22	31	13	**94**	47	47	66	28
46	23	23	32	14	**96**	48	48	67	29
48	24	24	34	14	**98**	49	49	69	29
50	25	25	35	15	**100**	50	50	70	30
52	26	26	36	16	**102**	51	51	71	31

Source: Trial 3561- Protocol Appendix C, page 6

Reference ID: 4009596

Table 49 – Trial 3816- Starting dose of IDegAsp and total IAsp

Total daily insulin dose - 20%	Basal:bolus ratio 50:50		Basal:bolus ratio 30:70	
	IDegAsp	Total IAsp	IDegAsp	Total IAsp
4	3	1	2	2
6	4	2	3	3
8	6	2	3	5
10	7	3	4	6
12	8	4	5	7
14	10	4	6	8
16	11	5	7	9
18	13	5	8	10
20	14	6	9	11
22	15	7	9	13
24	17	7	10	14
26	18	8	11	15
28	20	8	12	16
30	21	9	13	17
32	22	10	14	18
34	24	10	15	19
36	25	11	15	21
38	27	11	16	22
40	28	12	17	23
42	29	13	18	24
44	31	13	19	25
46	32	14	20	26
48	34	14	21	27
50	35	15	22	29
52	36	16	22	30
54	38	16	23	31
56	39	17	24	32
58	41	17	25	33
60	42	18	26	34
62	43	19	27	35
64	45	19	28	36
66	46	20	28	38
68	48	20	29	39
70	49	21	30	40
72	50	22	31	41
74	52	22	32	42
76	53	23	33	43
78	55	23	34	44
80	56	24	34	46

Source: Trial 3816, Protocol, Appendix A, page 5, table 2-1

Reference ID: 4009596

Table 50 - Trial 3816- Starting dose of IDet and total IAsp

Total daily insulin dose - 20%	Basal:bolus ratio 50:50		Basal:bolus ratio 30:70	
	Total IDet	Total IAsp	Total IDet	Total IAsp
4	2	2	1	3
6	3	3	2	4
8	4	4	2	6
10	5	5	3	7
12	6	6	4	8
14	7	7	4	10
16	8	8	5	11
18	9	9	5	13
20	10	10	6	14
22	11	11	7	15
24	12	12	7	17
26	13	13	8	18
28	14	14	8	20
30	15	15	9	21
32	16	16	10	22
34	17	17	10	24
36	18	18	11	25
38	19	19	11	27
40	20	20	12	28
42	21	21	13	29
44	22	22	13	31
46	23	23	14	32
48	24	24	14	34
50	25	25	15	35
52	26	26	16	36
54	27	27	16	38
56	28	28	17	39
58	29	29	17	41
60	30	30	18	42
62	31	31	19	43
64	32	32	19	45
66	33	33	20	46
68	34	34	20	48
70	35	35	21	49
72	36	36	22	50
74	37	37	22	52
76	38	38	23	53
78	39	39	23	55
80	40	40	24	56

Source: Trial 3816, Protocol, Appendix A, page 6, table 2-2

Reference ID: 4009596

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/s/

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11/04/2016

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