CLINICAL PHARMACOLOGY REVIEW

NDA	203314/S-03 Serial 0075
Link to EDR	\\CDSESUB1\evsprod\NDA203314\0075
Submission Date(s)	February 16, 2016
Brand Name	Tresiba®
Generic Name	Insulin degludec
OND Division	Metabolism and Endocrinology Products
Sponsor	Novo Nordisk Inc.
Formulation; Strength	Solution for Injection for subcutaneous injection, 100 Units/mL and 200 Units/mL
Relevant IND	IND 076496
Indication	*Use of Tresiba in pediatric patients with diabetes mellitus from 1 to* [redacted]
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1 Executive Summary

The applicant, Novo Nordisk Inc., has submitted a pediatric efficacy supplement (Supplement 3, Serial 0075) for NDA 203314- Tresiba® (insulin degludec injection), a long-acting basal soluble insulin analogue. The dose strengths proposed are the same as that approved for adults -100 Units/mL (U-100) and 200 Units/mL (U-200). The proposed revised indication is to improve glycemic control in adults and children with diabetes mellitus.

NDA 203314 for Tresiba® (insulin degludec injection (IDeg)), a long-acting basal soluble insulin analog, was approved on September 25, 2015, for the treatment of adults with diabetes mellitus for the control of hyperglycemia. Following PMR was issued at the time of approval:

> 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.

Novo Nordisk has completed the PMR study and is submitting this as an efficacy supplement for a new indication - *'Use of Tresiba in pediatric patients with diabetes mellitus from 1* (b) (4) (b) (4).

1.1. Recommendations

The Office of Clinical Pharmacology/Divisions of Clinical Pharmacology 2 (OCP/DCP2) and Pharmacometrics (OCP/DPM) have reviewed the information submitted under NDA 203314, Supplement 3. The clinical pharmacology data is acceptable to support approval of this supplement. Preliminary labeling recommendations are provided on page 14.

1.2. Post Marketing Requirement

None.

1.3. Summary of Important Clinical Pharmacology Findings

The applicant's pediatric development program for NDA 203314 included the following studies:

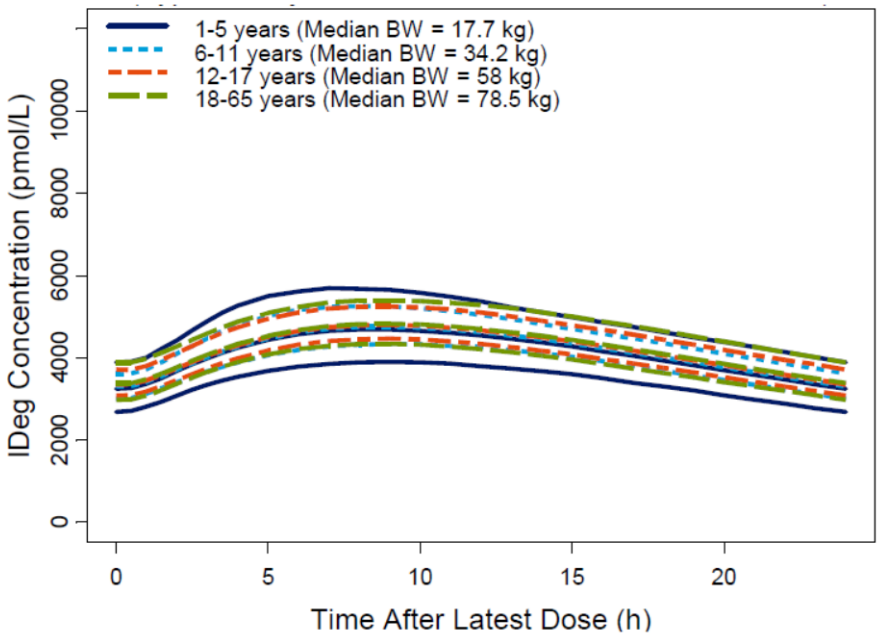
- NN1250-1995 - A single-center, randomized, double-blind, two-period cross-over, single-dose trial investigating the pharmacokinetic (PK) properties of IDeg and insulin glargine (IGlar) in children (6−11 years), adolescents (12−17 years) and adults (18−65 years) with type 1 diabetes mellitus (T1DM) with rich PK sampling. (Trial NN1250-1995, hereafter referred to as Trial 1995)
- NN1250-3561- A 26-week multinational, multi-center, randomized, open-label, two-arm, parallel group, efficacy and safety comparison of IDeg and insulin detemir (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. Sparse PK and pharmacodynamic (PD) measurements were collected during the main 26-week treatment period of this pediatric trial of IDeg (Trial NN1250-3561, hereafter referred to as Trial 3561)

The sponsor submitted a PK/PD modeling report (NDA 203314, Module 5.3.3.5, Modeling Report for Tresiba) where the PK data of Trial 1995 and Trial 3561 were combined to perform population PK modeling for IDeg.

The results of single dose PK Trial 1995 were reviewed at the time of original NDA submission (see review by Dr. Manoj Khurana, NDA 203314, dated 06/15/2012 in DARRTS). In this trial IDeg single dose exposure appeared to be higher in children and adolescents than in adults (AUC ratio (children/adults): 1.48 [95% CI: 0.98-2.24], AUC ratio (adolescents/adults): 1.33 [95% CI: 1.08-1.64], C_{max} ratio (children/adults) 1.20 [95% CI: 0.90-1.60], C_{max} ratio (adolescents/adults) 1.23 [95% CI: 1.00-1.51]). However, higher variability was observed in the pediatric population as compared to the adults in the trial with lower number of subjects (12 children, 13 adolescents, and 12 adults). Nevertheless, it is worth noting that the magnitude of increase in AUC is modest i.e. 33 to 48%.

In the population PK analysis, rich single dose PK data (Trial 1995) from 37 subjects was combined with the sparse steady state PK from Trial 3561 from 174 subjects. Using a one-compartment PK model, body weight was identified as the only significant covariate explaining the variability in apparent clearance (CL/F) and apparent volume of distribution (V/F). Because body weight and age are highly correlated in the pediatric population, once body weight was included in the model, age was not found to a significant covariate. Addition of body weight as a covariate explained 26% variability in CL/F and 17.4 % variability in V/F. Using the final population PK model, the sponsor conducted simulations to predict the steady state IDeg concentrations for different age groups. The results for a typical subject in the age group are shown in Figure 1.

Figure 1. Model-derived concentration-time profiles over a 24 hour dosing internal at steady-state following once-daily dosing of 0.4 U of IDeg per kg body weight to a typical subject (based on median body weight) in four different age groups.



Data are medians with 95% CI obtained from the final population PK model.
Source: NDA 203314, Modelling Report for Tresiba, Section 5.3.3.5, Page 8

The overall variability in the pediatric population appeared to be greater than adult population; however there was significant overlap in the steady state exposures of the adult and pediatric population.

In Trial 3561 the primary objective was to compare the glycemic control, as measured by change in HbA1c after 26 weeks of treatment, of IDeg once daily (OD) with that of IDet administered OD or twice-

daily (BID) plus mealtime IAsp with the non-inferiority margin set as 0.4%. Both treatment regimens improved glycemic control over 26 weeks. Analysis of HbA1c after 26 weeks showed that IDeg was non-inferior to IDet (IDeg – IDet: 0.15 [-0.03; 0.32]95%CI) (refer to the Statistical review for further details).

Combined results of the population PK modeling and Trial 3561 led to the conclusion that no dosage adjustment is needed in the pediatric population based on age. Independent analysis conducted by the reviewer showed that the population PK modeling and conclusions were appropriate and acceptable (see Appendix 4.1 and 4.2).

Overall, Clinical Pharmacology data submitted for supplement 3 of NDA 203314 is acceptable to support pediatric approval and labeling.

2. Question-Based Review

2.1. Background

IDeg is a long-acting basal insulin modified such that the amino acid residue threonine in position B30 of human insulin has been omitted, and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. This structure allows IDeg to form soluble and stable multi-hexamers resulting in a depot in the subcutaneous (s.c.) tissue after injection. The gradual separation of IDeg monomers from the multi-hexamers results in a slow and continuous delivery of IDeg from the s.c. injection region into the circulation. Furthermore, binding of the fatty acid moiety of IDeg to albumin contributes to some extent to the protraction mechanism. 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.

Based on the clinical pharmacology program conducted for the NDA for IDeg in adults (NDA 203314, module 2.7.2, section 3), the following conclusions of PK and PD properties of IDeg were made:

- The terminal half-life (t½) of IDeg after s.c. administration is estimated to be 25 hours in subjects with either T1DM or type 2 diabetes mellitus (T2DM). The long t½ of IDeg after s.c. administration primarily reflects the protracted absorption process of IDeg, implying that the rate at which IDeg is eliminated after s.c. administration is determined by the absorption rate.
- Steady state for the basal component is achieved following 3−4 days of once-daily (OD) dosing with no further increase in exposure thereafter.
- Due to the long t½ of IDeg, the glucose-lowering effect of IDeg extends beyond 24 hours.
- The day-to-day variability in glucose-lowering effect for IDeg is low.
- Total exposure of IDeg increases proportionally with increasing dose and total glucose-lowering effect of IDeg increases with increasing dose (proportionally in subjects with T1DM and linearly in subjects with T2DM).

2.1.1. What are the Clinical Pharmacology and Biopharmaceutics studies submitted in this NDA?

The pediatric clinical pharmacology program for Tresiba consisted of the following:

- A single-dose, randomized, double-blind, two period crossover trial investigating PK properties of IDeg in children, adolescents and adults with T1DM with rich PK sampling (Trial 1995) (see summary in Table 1)
- A 26-week, multinational, multi-center, open-labelled, randomized, parallel, efficacy and safety comparison of IDeg and IDet in children and adolescents 1 to less than 18 years with T1DM on a basal-bolus regimen with IAsp as bolus insulin. Sparse PK and PD measurements were collected

during the main 26-week treatment period of the pediatric trial of IDeg (Trial 3561) (see summary in Table 1)

- A PK/PD modeling analysis using Trial 1995 and 3561 data 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.

Table 1. Summary of pediatric clinical pharmacology development program.

Trial ID	Trial Design	Trial Objectives	Treatment
Clinical pharmacology trial			
NN1250-1995	Randomised, double-blind, two-period crossover, single-dose	PK and safety profile in children (6−11 years), adolescents (12−17 years) and adults (18−65 years) with T1DM	IDeg: single dose of 0.4 units/kg IGlar: single dose of 0.4 units/kg
Therapeutic confirmatory trial with PK assessments			
NN1250-3561	Randomised, open-label, two-arm parallel group	Efficacy, safety and PK in children and adolescents with T1DM (1−17 years)	IDeg OD versus IDet OD/BID as basal insulin; both with IAsp as bolus insulin; 26 weeks of treatment

BID: twice daily, IAsp: insulin aspart, IDeg: insulin degludec, IDet: insulin determir, IGlar: insulin glargine, OD: once daily, PD: pharmacodynamic(s), PK: pharmacokinetic(s), T1DM: type 1 diabetes mellitus

Source: NDA 203314 - Summary of Clinical Pharmacology Studies - Pediatric Indication, section 2.7.2, page 7

In addition, this supplemental NDA provides for the following:

- The current approved physician insert (PI) has been updated to include pediatric information in Section 1 Indications and Usage, Section 6 Adverse Reactions, Section 8.4 Pediatric Use, Section 12.3 Pharmacokinetics (Special Populations) and Section 14 Clinical Studies.

- Revisions have also been made to Section 8 Use In Special Populations (Section 8.1 Pregnancy, Section 8.2 Lactation and Section 8.3 Females and Males of Reproductive Potential) of the PI to be compliant with the Pregnancy and Lactation Labeling Rule and consistent with *Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential; Labeling for Human Prescription Drug and Biological Products – Content and Format.*

- Comparison of the design features of the PDS290 pen-injector for IDeg 100 U/ml and 200 U/mL and the NovoPen® Junior/NovoPen® Echo pen-injectors used in the phase 3 pediatric clinical Trial 3561 including extrapolation from adult use of the PDS290 pen-injector for IDeg 100 U/ml and 200 U/ml as well as Human factors/usability validation conducted for the PDS290 pen-injector in the pediatric population demonstrating safe and effective use.

2.2. General Attributes

2.2.1. What were the devices/formulations used in the pediatric clinical studies?

The following products for subcutaneous injection were used in the clinical trials:

Trial 3561-

- IDeg 100 U/mL, in 3 mL Penfill® cartridge. The basal insulin was to be administered with NovoPen® Echo (blue for basal) and in Japan NovoPen® 300 Demi Lime and in the US NovoPen® Junior. In Finland and the UK only, NovoPen® 4 (blue/silver) was used for administration of higher basal insulin doses.

- IAsp (NovoRapid®/Novolog®) 100 U/mL, in 3 mL Penfill® cartridge. The bolus insulin was to be administered with NovoPen® Echo (red for bolus), in Japan NovoPen® 300 Demi Apricot and in the US NovoPen® Junior.

Trial 1995 -

- IDeg (100 U/mL) in 3 mL Penfill® cartridges.
- IAsp (NovoRapid®, NovoLog®) 100 U/mL, in 3 mL FlexPen® and in 10 mL vials.

The primary difference between the device approved for adults (PDS290 pen-injector) for IDeg 100 U/mL and 200 U/mL and the NovoPen® Junior/NovoPen® Echo pen-injectors is the elimination of the protruding dose button for the PDS290 pen-injector. The sponsor claims that this difference does not raise any significant issues of safety and effectiveness. The NovoPen® Junior and NovoPen® Echo pen-injectors used in the clinical Trial 3561 and the PDS290 pen-injector for IDeg 100 U/mL and 200 U/mL all fulfill ISO 11608-1 for dose accuracy.

The sponsor mentions that previous clinical use showed that ISO 11608-1 compliant pen-injector devices can deliver the drug product subcutaneously to achieve similar safety and effectiveness. Therefore, the sponsor claims that clinical benefits seen in the clinical Trial 3561 for IDeg that used NovoPen® Junior and NovoPen® Echo pen-injectors would be expected to be the same with no clinically meaningful difference for the PDS290 pen-injector for IDeg 100 U/mL and 200 U/mL which has the same operating principle. Extrapolation from adult use of the PDS290 pen-injector for IDeg 100 U/mL and 200 U/mL also support use in pediatric patients. The extrapolation evaluation is appropriately supported in that the PDS290 pen-injector is approved by the FDA for adults, there is significant knowledge of the disease (diabetes mellitus) in pediatrics, the HbA1c endpoint can be directly borrowed from adults, and human factors did not affect the safety in pediatric patients.

2.3. General Clinical Pharmacology

2.3.1. Are the systemic exposures of IDeg comparable between pediatric and adult population?

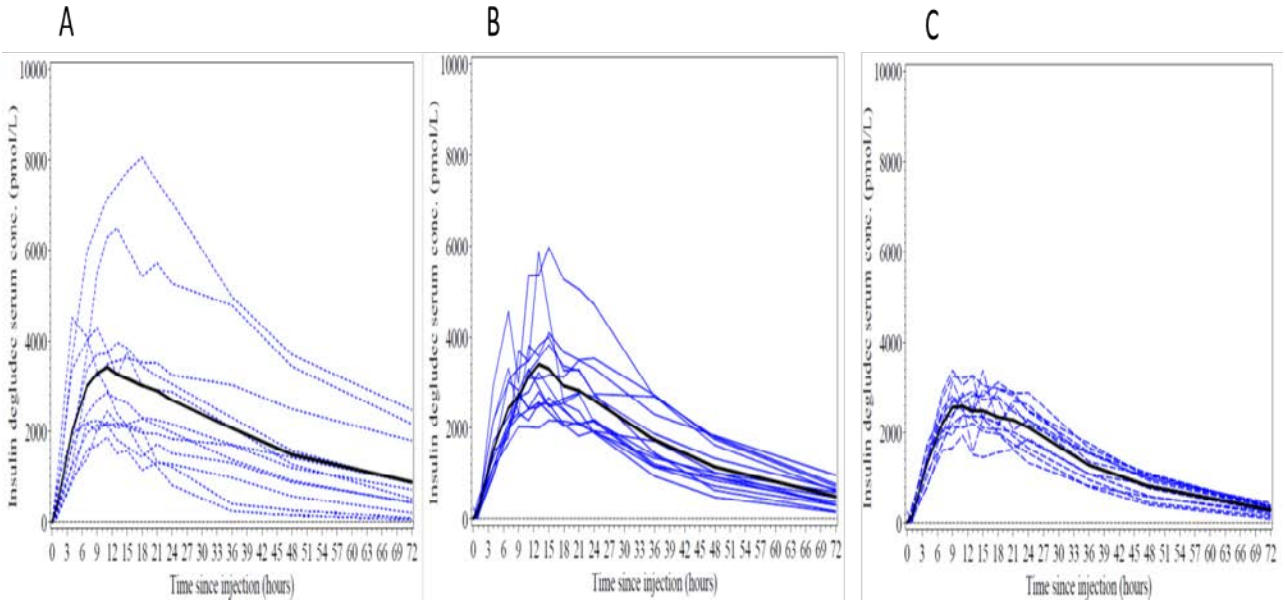
Yes, the total steady state IDeg exposures in the pediatric and adult population were similar.

Single dose PK data for IDeg in children, adolescents and adults with T1DM were evaluated in Trial 1995 and the results of this study were reviewed previously by Dr. Manoj Khurana during original NDA 203314 submission (DARRTS date 06/15/2012). Data from Trial 1995 suggested that exposure appeared to be higher in children and adolescents than in adults (AUC ratio (children/adults): 1.48 [95% CI: 0.98-2.24], AUC ratio (adolescents/adults): 1.33 [95% CI: 1.08-1.64], C_{max} ratio (children/adults) 1.20 [95% CI: 0.90-1.60], C_{max} ratio (adolescents/adults) 1.23 [95% CI: 1.00-1.51]).

While the exposures following single subcutaneous dose were, on an average, higher in pediatric population than adults, higher variability in the PK was noted in the pediatric population as compared to the adults (Figure 2). As shown in Figure 2 the mean concentrations were higher in the children and adolescents versus adults, however, there was a significant overlap in the distribution of IDeg exposure

for the three age groups evaluated in Trial 1995. Demographics characteristics (BMI, age, race, gender) of individuals with higher concentrations were compared to that of the population; however, none of the demographic variables were noted as different in these individuals.

Figure 2. Individual (blue) and mean (black) concentration-time profiles for IDeg after single dose of 0.4 U/kg in children (A), adolescents (B) and adults (C).



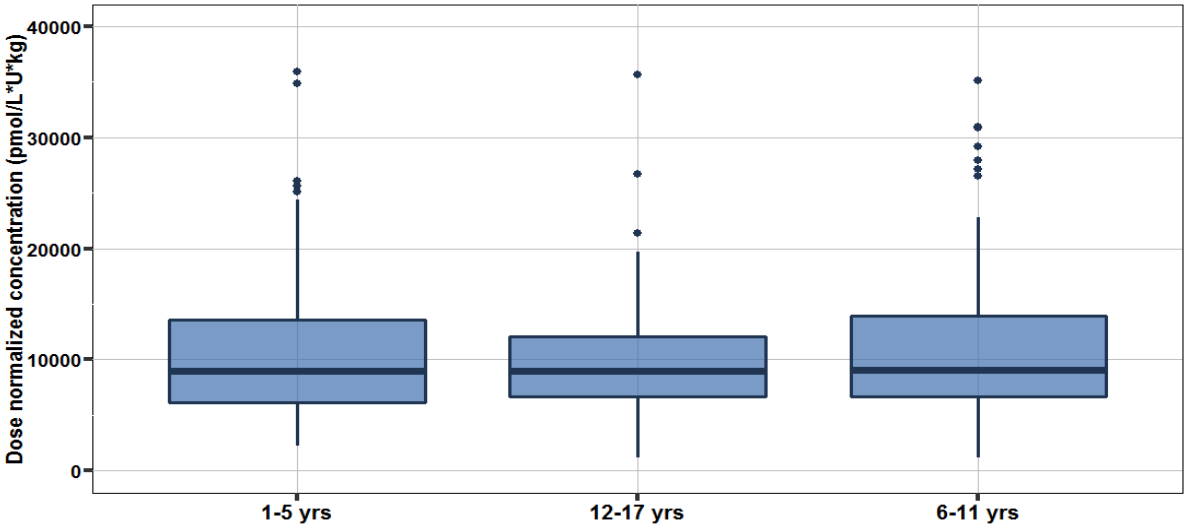
Source: NDA 203314, module 5.3.3.3, study report NN1250-1995, page 67-69

Additional sparse PK data was collected by the sponsor in the efficacy and safety Trial 3561. Sampling schedule in Trial 3561 included 3 samples at steady state collected at week 2, 12 and 26. Boxplot in Figure 3 shows that the distribution of concentrations in the three pediatric age groups was similar in Trial 3561, however the variability was high. To further evaluate relation between age and exposure the sponsor performed population PK modeling by combining the data from Trials 1995 and 3561. The details of the population PK modeling are entailed in Appendix 4.1 and 4.2. Body weight, age group, BMI z-score category, gender and race were evaluated as covariates.

After a step-wise inclusion/elimination process only body weight was identified as a significant covariate on both CL/F and V/F. Because body weight and age are highly correlated in the pediatric population (correlation coefficient > 0.5), once body weight was adjusted for, age was not found to be a significant covariate on IDeg PK. Addition of body weight explained 26% variability in CL/F and 17.4 % variability in V/F. The final parameter estimates of the sponsor's population PK analysis in pediatrics were similar to that obtained from population PK analysis in adult population in Trials 1996 and 3586 (Table 2) suggesting that the PK behavior was similar in the adult and pediatric population.

Using the final model from the covariate analysis, simulations of IDeg concentration profiles at steady-state following multiple dosing were performed and presented graphically for each of the four age groups (Figure 4). The sponsor concluded that the concentration-time profile in small children (1-5 years) is 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 kg body weight. The sponsor's analysis was confirmed by the reviewer and found to be acceptable (See Appendix 4.1 and 4.2).

Figure 3. Boxplot for dose and body weight normalized concentration of IDeg in various age groups in Trial 3561.



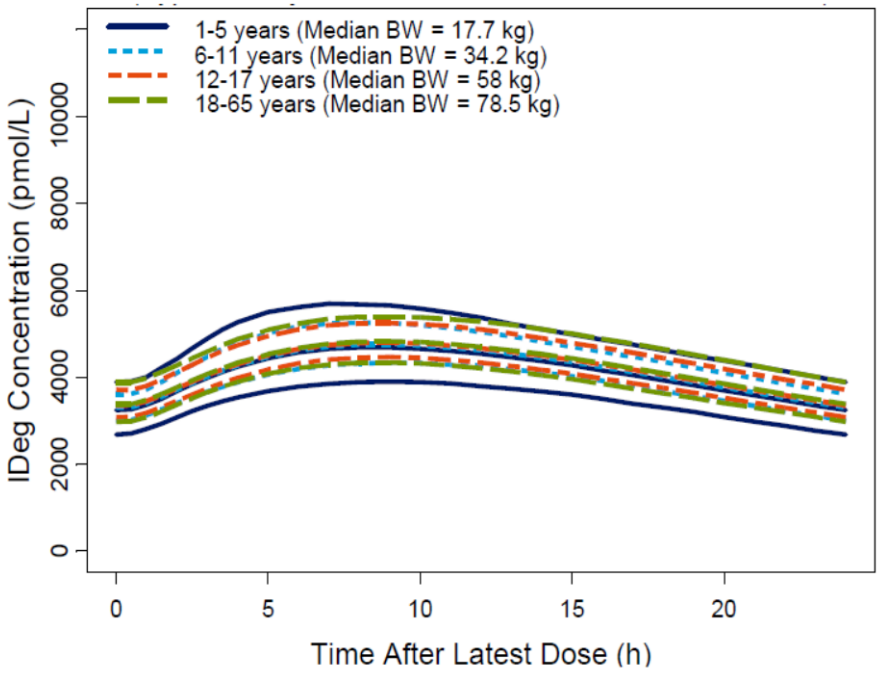
Boundaries of boxes indicate the 25th and the 75th percentiles. Lines within boxes mark the median. Whiskers indicate minimum and maximum values. Black solid circles indicate outlier data points.
Steady state PK samples in these three age groups were collected at week 2, 12 and 26. Data was pooled across timepoints for these age groups for this analysis.
Source: Reviewer's analysis for data submitted in module 5.3.5.1 study report NN1250-3561

Table 2. Summary of population PK parameters across patient population from various clinical studies

Parameters	Description	Units	Pop PK Pediatrics Ryzodeg	Pop PK Pediatrics Tresiba	Pop PK Adults Tresiba (Trial 3586)	Pop PK Adults Tresiba (Trial 1996)
K_A	Absorption rate constant	1/h	0.045	0.038	0.054 (fixed)	0.054
K_T	Transit rate constant	1/h	0.819	0.923	-	-
CL/F	Apparent clearance	L/h	1.68	1.77	1.61	1.65
V/F	Apparent volume of distribution	L	10.6	10.4	13.9 (fixed)	13.9
$\Theta_{wt,CL}$	Allometric exponent on CL	NA	0.98	0.98	0.76	-
$\Theta_{wt,V}$	Allometric exponent on V	NA	1.13	1.01	-	-
$\Theta_{AsianNI}$	Race coeff on CL	NA	0.424	-	-	-
Θ_{Other}	Race coeff on CL	NA	-0.133	-	-	-
BSV CL/F	Between subject variability on CL/F	%CV	51.4	55.2	15	30.3
BSV V/F	Between subject variability on V/F	%CV	45.3	38.3	-	49
BSV K_A	Between subject variability on K_A	%CV	-	-	-	38.9

Source: Reviewer's compilation of final PK parameters reported in Module 5.3.5.1 –Pop PK analysis NN1250-3586, page 54 (NDA 203314), Module 5.3.3.5 – Modelling Report for Ryzodeg, page 49 (NDA 203313) and Module 5.3.3.5 – Modelling Report for Tresiba, page 47 (NDA 203314).

Figure 4. Model-derived concentration-time profiles over a 24 hour dosing internal at steady-state following once-daily dosing of 0.4 U of IDeg per kg body weight to a typical subject (based on median body weight) in four different age groups.



Data are medians with 95% CI obtained from the final population PK model.
Source: NDA 203314, Modelling Report for Tresiba, Module 5.3.3.5, Page 8

The sponsor also conducted additional analysis where IDeg efficacy exposure-response relationship was compared between children younger than 6 years of age and other age groups. In this analysis a linear model between pre-breakfast self-measured plasma glucose (SMPG) and 24 hour steady-state AUC for IDeg was used and the sponsor concluded that the exposure-response relationship in small children (1-5 years) appeared to be similar to that for children (6-11 years) and adolescents (12-17 years). These analyses are not discussed in the review because of the empirical nature of evaluation, the large variability in pre-breakfast SMPG and the lack of any labeling impact for IDeg.

2.3.2. Considering the results of the systemic exposures discussed above, what are the relevant aspects of the efficacy and safety results of IDeg in Trial 3561 from clinical pharmacology perspective?

In the 26-week efficacy and safety Trial 3561 where the difference in change in HbA1c were compared between IDeg + IAsp and IDet + IAsp, a non-inferiority limit of 0.4% was met in T1DM subjects between 1 and less than 18 years of age (refer to Statistical review and Clinical review for further details). The HbA1c % in different age groups is shown in Figure 5 below where both treatment regimens improved glycemic control over 26 weeks.

The mean daily basal dose of IDeg at week 26 was 0.25 U/kg, 0.37 U/kg and 0.46 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively (Figure 6). The mean daily basal dose of IDet at week 26 was 0.35 U/kg, 0.52 U/kg and 0.60 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively. The mean total daily bolus dose in the IDeg arm at week 26 was 0.52 U/kg, 0.55 U/kg and

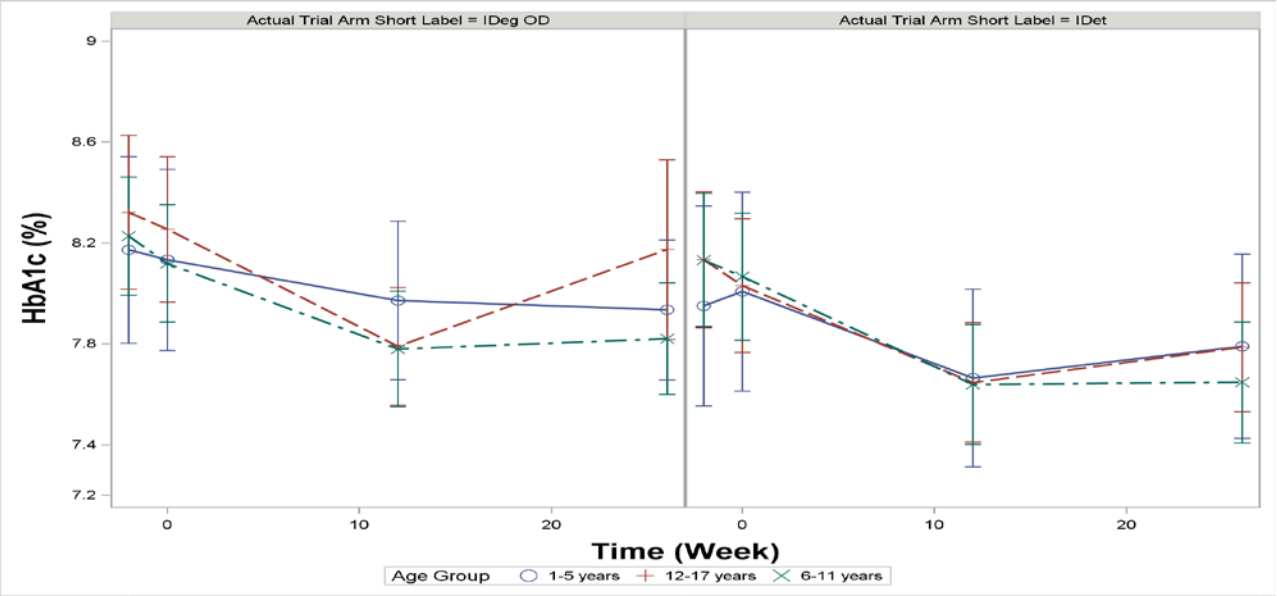
0.61 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively. The mean daily bolus dose in the IDet arm at week 26 was 0.51 U/kg, 0.59 U/kg and 0.58 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively. Considering that age was not a significant covariate affecting the IDeg exposure, the systematic trend for lower U/kg insulin dose observed between different age cohort is more reflective of the cautious approach in insulin dosing in clinical practice for pediatrics to avoid hypoglycemia.

The trend in basal and bolus dose with age groups did not correlate to HbA1c reduction in the age groups. Further, throughout the trial the daily dose of IDeg remained slightly lower than IDet. However, numerically higher hypoglycemia events were observed in the IDeg arm versus the IDet arm. Key safety observations are listed below (refer to the Clinical Review by Dr. Tania Condarco for a comprehensive review of safety data).

- A similar percentage of subjects reported adverse events in the IDeg and IDet treatment arms (83.3% and 81.1%, respectively). The observed rate of all adverse events was similar for the IDeg and IDet groups (944 and 899 events per 100 patient years of exposure (PYE), respectively).
- Less than 10% of subjects in either treatment arm reported severe treatment emergent adverse events (TEAEs), which were mostly related to hypoglycemia. The observed rate of severe TEAEs was numerically higher with IDeg than IDet (27 vs 17 events per 100 PYE, respectively). The rate of all TEAEs considered possibly or probably related to trial product was similar with IDeg and IDet. More than 80% of subjects in either treatment arm recovered from the events
- The observed rates of confirmed hypoglycemic episodes were 5812 and 5579 episodes per 100 PYE for IDeg and IDet, respectively, and there was no statistically significant difference between treatment arms (IDeg/Det: 1.13 [0.90; 1.41]95% CI). There was no apparent clustering of confirmed hypoglycemic episodes for any specific age groups.
- The observed rates of severe hypoglycemic episodes were 51 and 40 episodes per 100 PYE for IDeg and IDet, respectively, but there was no statistically significant difference between treatment arms (1.22 [0.57; 2.62]95% CI).
- The observed rates of nocturnal confirmed hypoglycemic episodes were 604 vs 714 episodes per 100 PYE with IDeg and IDet, respectively with no statistically significant difference between IDeg and IDet (0.96 [0.70;1.34]95% CI).

In reviewer's analysis, the median post-hoc CL/F of IDeg for subjects experiencing severe hypoglycemia (external classified treatment emergent severe hypoglycemic episodes – Safety Analysis Set) versus the subjects who didn't experience hypoglycemia was slightly lower (0.73L/h versus 0.94 L/h, respectively), however the number of subjects with severe hypoglycemia was small (N=22) to make any reliable conclusion. Additionally, these results should be interpreted with caution since individual level time matched data to correlate hypoglycemia events to systemic exposure were not available.

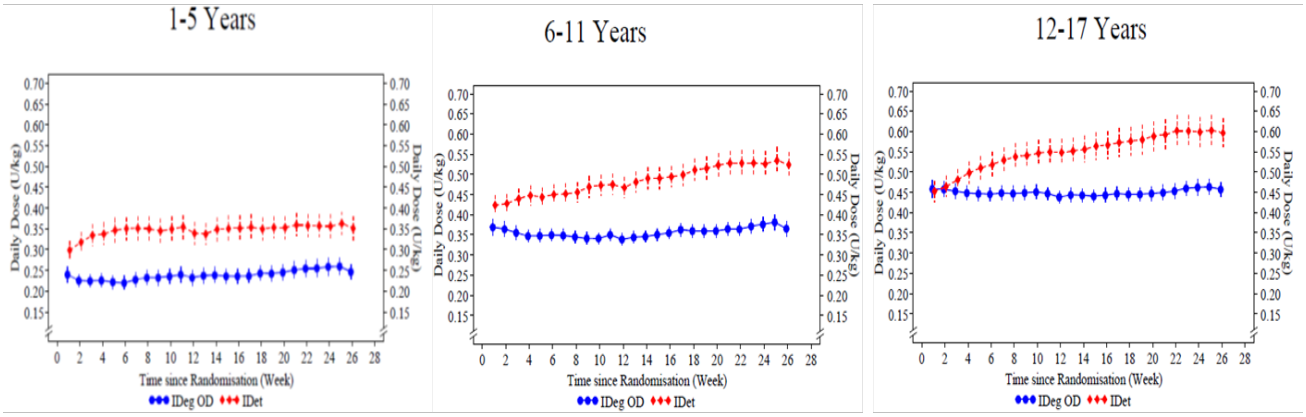
Figure 5. HbA1c (%) over time by age groups – mean plot (FAS dataset).



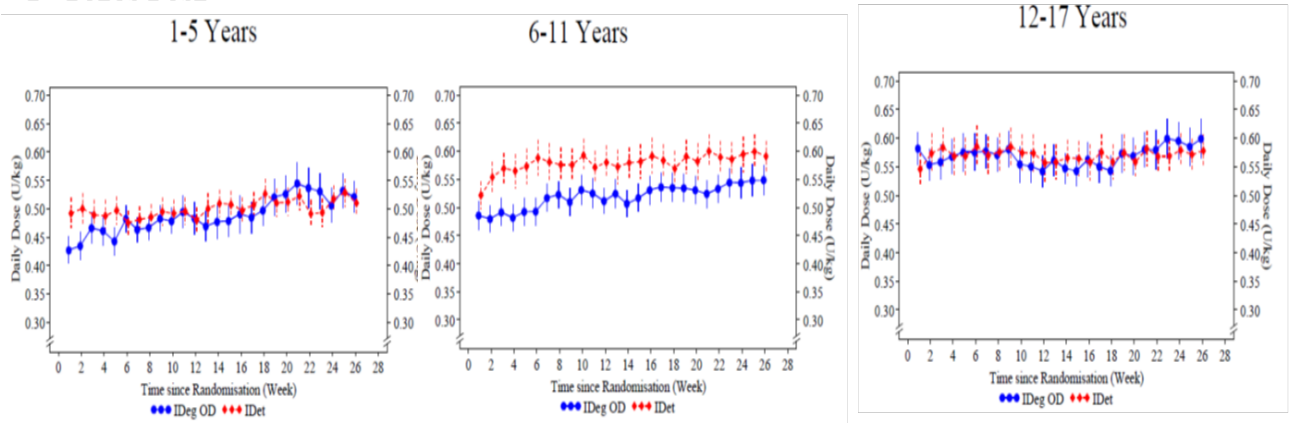
Source: NDA 203314 - Re-plotted from study report NN1250-3561 page 115

Figure 6. Mean daily basal (panel A) and bolus (panel B) insulin dose in U/kg by treatment week.

A – BASAL DOSE



B – BOLUS DOSE



LOCF imputed data. Error bars +/- standard error
Source: NDA 203314 -study report NN1250-3561 page 126-128

2.4. Bioanalytical

2.4.1. Are the bioanalytical methods properly validated to measure IDeg in plasma samples?

Yes, the methods of bioanalysis for the trials included in this application were the same as in the original NDA. IDeg was quantified by a specific sandwich enzyme-linked immunosorbent assay (ELISA) used in the clinical trials. The capture antibody was a mouse monoclonal antibody specific for human insulin (HUI 001) and the detection antibody was a biotin-labelled monoclonal mouse antibody (NN-454-1 F31) specific for IDeg.

The assay method and validation were performed in accordance with current practice and were reviewed at the time of original NDA 203314 submission (Dr. Manoj Khurana review dated 06/15/2012). In brief, the assay lower limit of quantitation (LLOQ) was determined to be 20 pmol/L and upper limit of quantitation (ULOQ) to be 750 pmol/L. The samples are stable for 9 months and 2 weeks at -20°C, and can undergo up to 5 freeze/thaw cycles (NDA 203314, module 5.3.1.4, study NN209383). There was no cross-reactivity from IGlar, IDet, IAsp and human insulin. The presence of severe hemolysis in the samples generates invalid results for determination of IDeg concentration (NDA 203314, module 5.3.1.4, studies NN205289 and NN205498). Further assessments of the hemolysis interference showed that more than 5% hemolysis in the samples generated invalid results for IDeg concentrations (NDA 203314, module 5.3.1.4, study AA81207). Consequently, samples with more than 5% hemolysis were not reported.

The samples from Trial 3561 were received frozen and stored at -20°C from first sample receipt (03/15/2012) to the end of sample analysis (26/02/2013). All samples were analyzed successively with regard to shipment arrival and did not exceeding long-term stability (272 days at -20°C). Short-term and freeze-thaw stabilities were also not exceeded.

A total number of 516 human serum samples were received and analyzed for the concentration of IDeg and 511 samples were received and analyzed for the concentration of IDet. All analyzed samples yielded reportable results, except for four samples which were not reportable due to hemolysis levels and three samples which were left ambient at the central lab.
An analytical run was acceptable if all of the following criteria were met:

- at least 75%, representing 6 for IDeg and 7 for IDet, of non-zero calibration standards (non-anchor points) were within their acceptance criteria (CV of duplicate responses was ≤ 20% / ≤ 25% at LLOQ and ULOQ and mean back-calculated concentration was within ± 20% / ± 25% at LLOQ and ULOQ of the nominal concentration) and no two consecutive nonzero standards were out of acceptance,
- at least two-thirds of the quality control (QC) samples and at least 50% at each concentration level were within their acceptance criteria (CV of duplicate calculated concentrations was ≤ 20% and mean back - calculated concentration was within ±20% of the nominal concentration).

The accuracy of study sample dilution was verified by additional diluted QC samples diluted in the same way as the study samples. At least 50% of the diluted QC samples had to be within their acceptance criteria (CV of duplicate calculated concentrations was ≤20% and mean back –calculated concentration was within ±20% of the nominal concentration) for the respective dilution factor to be accepted. For both IDeg and IDet all samples were first analyzed after a 10-fold dilution. Where required, further dilutions or reanalysis with no dilution, were done following initial analysis.

In order to assess the reproducibility and accuracy of the analytical methods at least 10% of the study samples were reassayed for each analyte and compared with the original result for incurred assay reproducibility (ISR). The % difference was calculated for each pair of original and repeat analyses. A pair was considered as matching if the % difference was less than or equal to 30%. A total of 51 of 56 ISR result pairs (91.1%) for IDeg and 53 of 55 ISR result pairs (96.4%) for IDet were reproducible within 30% difference. The analytical method was considered reproducible as more than 75% of the result pairs matched fulfilling the ISR criteria. In no cases was the % difference greater than 66.7%.

The % bias for QC samples was -7.7% to 4.2% and CV% was 9.6 to 11.7%. The overall performance of the ELISA method met the acceptance criteria and the results obtained were of the required integrity and quality. Therefore the bioanalytical data can be used for further interpretation.

3. Label Recommendations

Preliminary comments on relevant label sections are shown below. Red strikethrough text means deletion of the sponsor's proposed text. Blue underscored text means recommended addition.

12.3 Pharmacokinetics

Specific Populations

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

Pediatrics-
Pediatrics-

(b) (4)

Population pharmacokinetic analysis conducted using data from 199 pediatric patients (1- <18 years) (b) (4) (b) (4) (b) (4) with type 1 diabetes obtained from studies utilizing single and multiple subcutaneous administration of TRESIBA showed body weight as a significant covariate affecting the clearance of TRESIBA. After adjusting for body weight, the (b) (4) total exposure of TRESIBA at steady state was independent of age.

4. Appendix

4.1. Review of Sponsor's Population PK Analysis

Objective: The objective of population PK modeling was to compare the steady-state IDeg exposure between children younger than 6 years of age and other age groups. Additionally, the sponsor investigated the impact of body weight, age, BMI, gender and race as covariates.

Data: PK data collected from the following two trials was used in the population PK analysis:

- A single-dose trial of IDeg with rich PK in children/adolescents/adults (Trial 1995)
- Sparse PK and PD measurements during the main 26-week treatment period of the pediatric efficacy and safety trial of IDeg (Trial 3561)

In Trial 3561 the subjects administered IDeg OD at approximately the same time of the day every day. During the trial, titration of the IDeg dose was performed once-weekly according to a titration guideline. In Trial 1995 all subjects received a single dose of 0.4 U/kg of IDeg on a single occasion.

In Trial 3561 blood samples were drawn to measure the serum concentration of IDeg after 2, 12 and 26 weeks of treatment. In Trial 1995 blood samples were drawn to measure the serum concentration of IDeg at 0 h (predose), 1h, 4h, 7h, 9h, 11h, 13h, 15h, 18h, 21h, 24h, 36h, 48h, and finally at 72h after administration.

Model: The first order conditional estimation method with interaction (FOCE+I) in NONMEM was used for the population PK analysis. A one-compartment model with first-order absorption through a single transit compartment and with first-order elimination was used to describe the PK. One-compartment model has previously been found to adequately describe the PK of IDeg in adult trials (NDA 203314, Sequence 0000, Pop PK analysis NN1250-3586).

The covariates investigated on CL/F were body weight, age group (small children: 1 to 5 years of age, children: 6 to11 years of age, adolescents: 12 to17 years of age, adults: 18 to 65 years of age), BMI category (BMI z-score was treated as a categorical covariate (less than -1/-1 to +1/greater than +1), gender, and race (White, Asian Non-Indian, Other). For V/F, only the effect of body weight was investigated. Exponential model was used to evaluate the impact of continuous and categorical covariates on PK parameters.

Using the final model from the covariate analysis, simulations of IDeg concentration profiles at steady-state following multiple dosing were performed and presented graphically for each of the four age groups. The simulations were performed using the estimated population mean parameters from the final model by simulating a profile for a typical individual within each age group.

All missing data (dosing history, PK, pre-breakfast SMPG) were assumed to be missing at random and not confounded with exposure and/or response levels.

During the forward inclusion procedure, body weight and race were identified as covariates for CL/F and body weight was identified as a covariate for V/F, and these three covariate effects were included in the full model. Age group, BMI category and gender were not significant covariates for CL/F and were therefore not included in the full model. During the backward elimination procedure, race was excluded as a covariate for CL/F, whereas body weight was retained for both CL/F and V/F. The final model thus

consisted of the base model with body weight as a covariate for both CL/F and V/F. Sensitivity analyses for outliers were also performed.

Result: Subject characteristics for the data included in the population PK analysis are shown in Table 3 and 4. Parameter estimates from the final model are shown in Table 5. The CL/F and V/F estimates for a typical subject were 1.77 L/h and 10.4 L, respectively, and were determined with good precision (relative standard errors (RSEs) of 5.56% and 16%, respectively). As seen in Table 5, the estimated allometric exponents for CL/F and V/F in the final model were close to 1 (0.977 [95% CI: 0.815-1.14] for CL/F and 1.01 [95% CI: 0.493-1.52] for V/F). The goodness of fit plots and visual predictive check plot are shown in Figure 7 and 8.

The sensitivity of the model towards outliers identified in the graphical data analysis was investigated by excluding these values and re-estimating the model. Exclusion of outliers had a relatively small influence on parameter estimates. The numerically highest percentage change of -8.24% was seen for the allometric exponent for CL/F. The sensitivity of the model towards influential observations not identified in the graphical data analysis were investigated by excluding all records giving rise to an absolute conditional weighted residual above 4 or an absolute weighted residual above 4, and re-estimating the model. The model was relatively robust towards exclusion of data with high residuals. The numerically highest percentage change of -12.7% was seen for the allometric exponent for V/F. Shrinkage for CL/F and V/F were estimated at 2.79% and 60%, respectively, indicating that the individual estimates of V/F (but not the estimates of CL/F) were biased towards the mean estimate.

Table 3. Summary of subject characteristics for the data included in the population PK analysis (categorical variables)

Covariate	Category	Trial 3561 N (%)	Trial 1995 N (%)	Total N (%)
Gender	Female	76 (45)	17 (47)	93 (45)
	Male	93 (55)	19 (53)	112 (55)
Race	Asian Non-Indian	22 (13)	-	22 (11)
	Black or African American	5 (3)	-	5 (2)
	Missing	2 (1)	-	2 (1)
	Native Hawaiian or other Pacific Islander	1 (1)	-	1 (0)
	Other	7 (4)	1 (3)	8 (4)
	White	132 (78)	35 (97)	167 (81)
Ethnicity	Hispanic or Latino	7 (4)	-	7 (3)
	Not Hispanic or Latino	162 (96)	36 (100)	198 (97)
Country	Bulgaria	14 (8)	-	14 (7)
	Germany	5 (3)	36 (100)	41 (20)
	Finland	9 (5)	-	9 (4)
	France	2 (1)	-	2 (1)
	Great Britain	8 (5)	-	8 (4)
	Italy	7 (4)	-	7 (3)
	Japan	22 (13)	-	22 (11)
	Macedonia	8 (5)	-	8 (4)
	Netherlands	11 (7)	-	11 (5)
	Russia	23 (14)	-	23 (11)
	South Africa	5 (3)	-	5 (2)
	USA	55 (33)	-	55 (27)
Total		169 (82)	36 (18)	205 (100)

Source: NDA 203314, Modelling Report for Tresiba, Module 5.3.3.5, Page 21

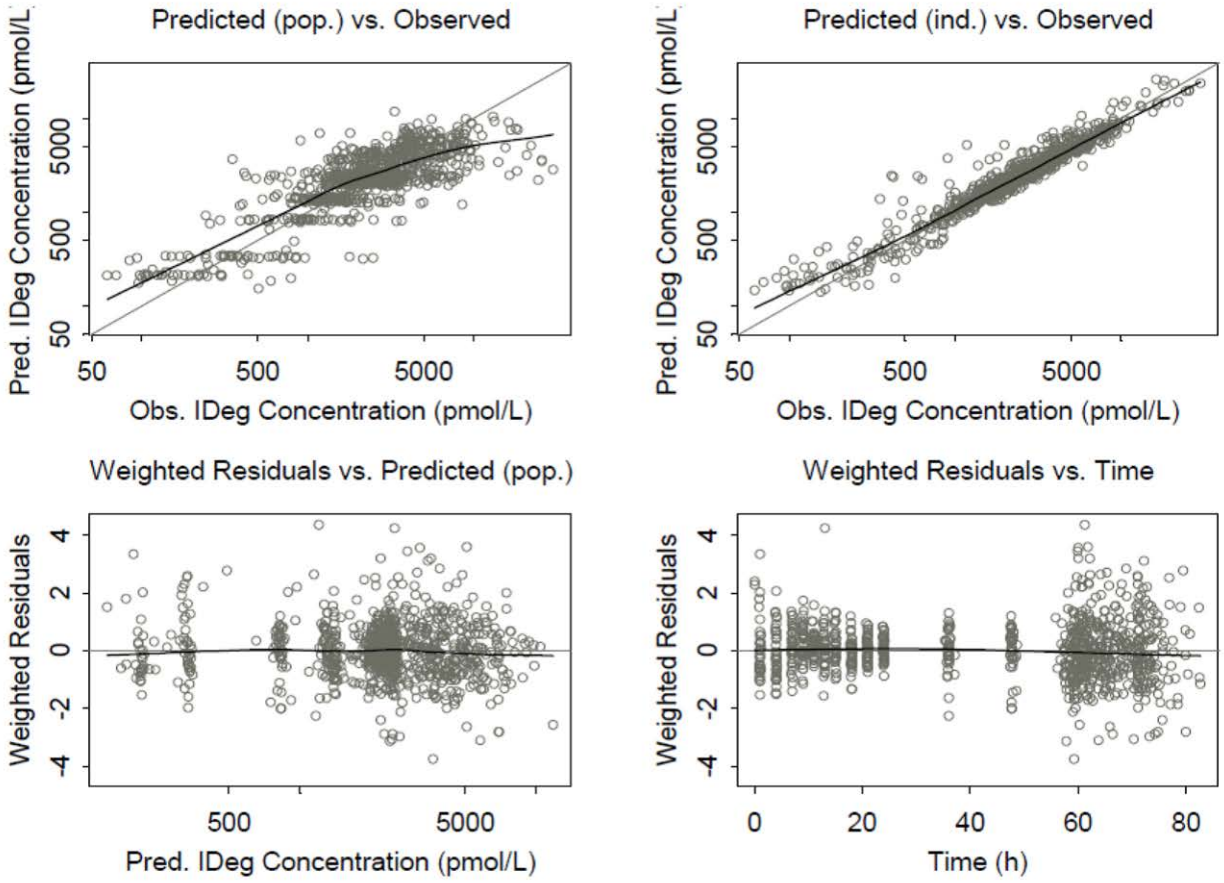
Table 4. Summary of subject characteristics for the data included in the population PK analysis (continuous variables)

	Trial 3561 Mean (SD) [Range]	Trial 1995 Mean (SD) [Range]	Total Mean (SD) [Range]
N	169	36	205
Age (years)	10.0 (4.4)	16.8 (9.4)	11.2 (6.1)
	[1.5-18.4]	[8.0-57.0]	[1.5-57.0]
Body Weight (kg)	37.9 (18.6)	61.0 (16)	42.0 (20.2)
	[11.2-102]	[30.0-92.8]	[11.2-102.0]
BMI (kg/m^2)	18.7 (3.6)	21.8 (3.4)	19.3 (3.8)
	[12.9-34.5]	[16.2-29.9]	[12.9-34.5]
BMI z-score (-)	0.50 (1.11)	0.77 (0.71)	0.55 (1.06)
	[-2.97-3.51]	[-0.42-2.04]	[-2.97-3.51]

For German subjects, date of birth was set to January 1st for protection of subject anonymity. For one subject in Trial 3561 this led to a derived age of 18.4 years. In reality, this subject was less than 18 years of age at screening.

Source: ND NDA 203314, Modelling Report for Tresiba, Module 5.3.3.5, Page 22

Figure 7. Goodness-of-fit plots for the final model.



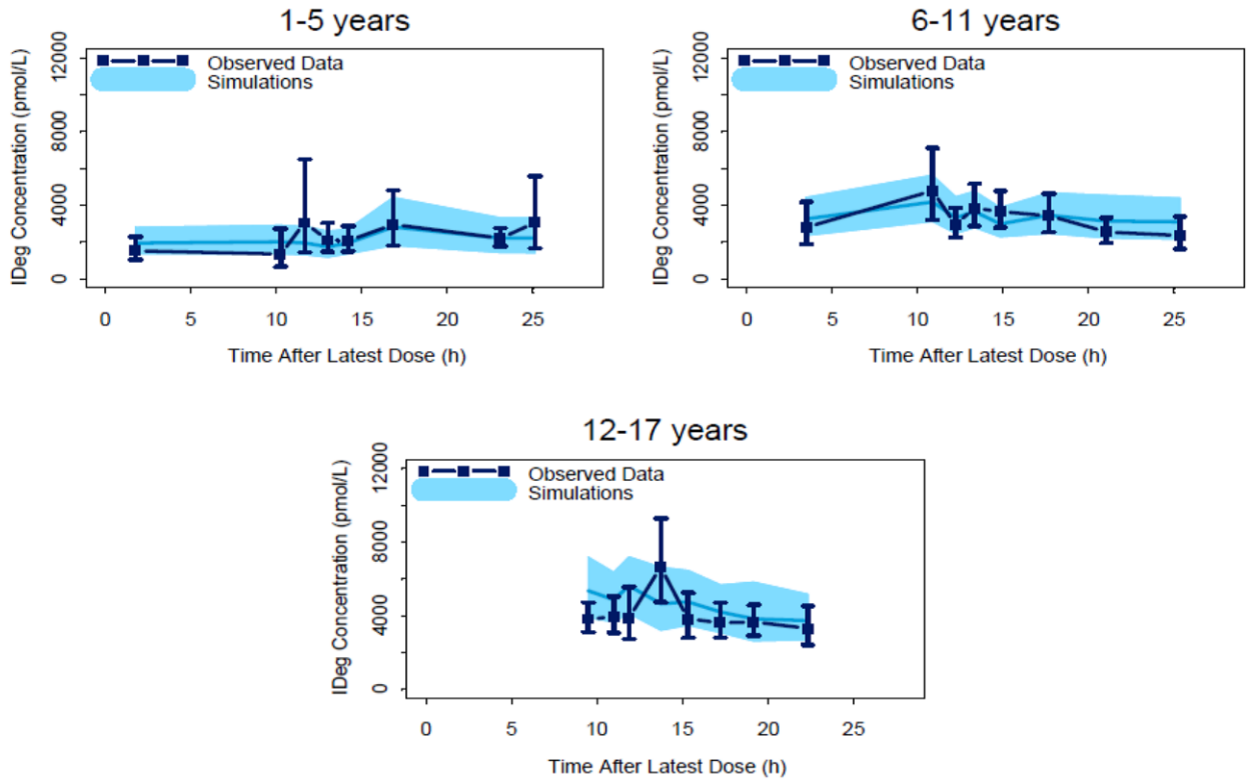
Source: NDA 203314, module 5.3.3.5, modelling report for Tresiba, page 51

Table 5. Parameter estimates for the final PK model.

Fixed-effects parameters	Description	Unit	Estimate	% RSE	95% CI from Covariance Matrix	95% CI based on Likelihood Profiling
K_A	Absorption rate constant	1/h	0.0386	8.86	[0.0319;0.0453]	[0.0347;0.0432]
K_T	Transit rate constant	1/h	0.923	20.2	[0.557;1.29]	[0.641;1.3]
CL/F	Apparent clearance	L/h	1.77	5.56	[1.58;1.96]	[1.56;2.01]
V/F	Apparent volume of distribution	L	10.4	16	[7.16;13.7]	[7.83;13.6]
$\theta_{wt,CL}$	Allometric exponent on clearance	NA	0.977	8.44	[0.815;1.14]	[0.833;1.12]
$\theta_{wt,V}$	Allometric exponent on volume	NA	1.01	26	[0.493;1.52]	[0.58;1.44]
Random-effects parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**		
IIV – CL/F	Between-subject variability on CL/F	% CV	55.2	2.79		
IIV – V/F	Between-subject variability on V/F	% CV	38.3	60		
Residual error parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**		
$Sigma_1$	Residual error (proportional, % CV)	% CV	21	13.1		
$Sigma_2$	Residual error (additive, SD)	pmol/L	108	12.5		

Source: NDA 203314, module 5.3.3.5, modelling report for Tresiba, page 47

Figure 8. Simplified visual predictive check for the final population PK model.



Data are geometric mean with 95% CI for the observed data, and median and 95% range for the geometric mean across 1000 replicates for the simulated data.
Source: NDA 203314, module 5.3.3.5, modelling report for Tresiba, page 53

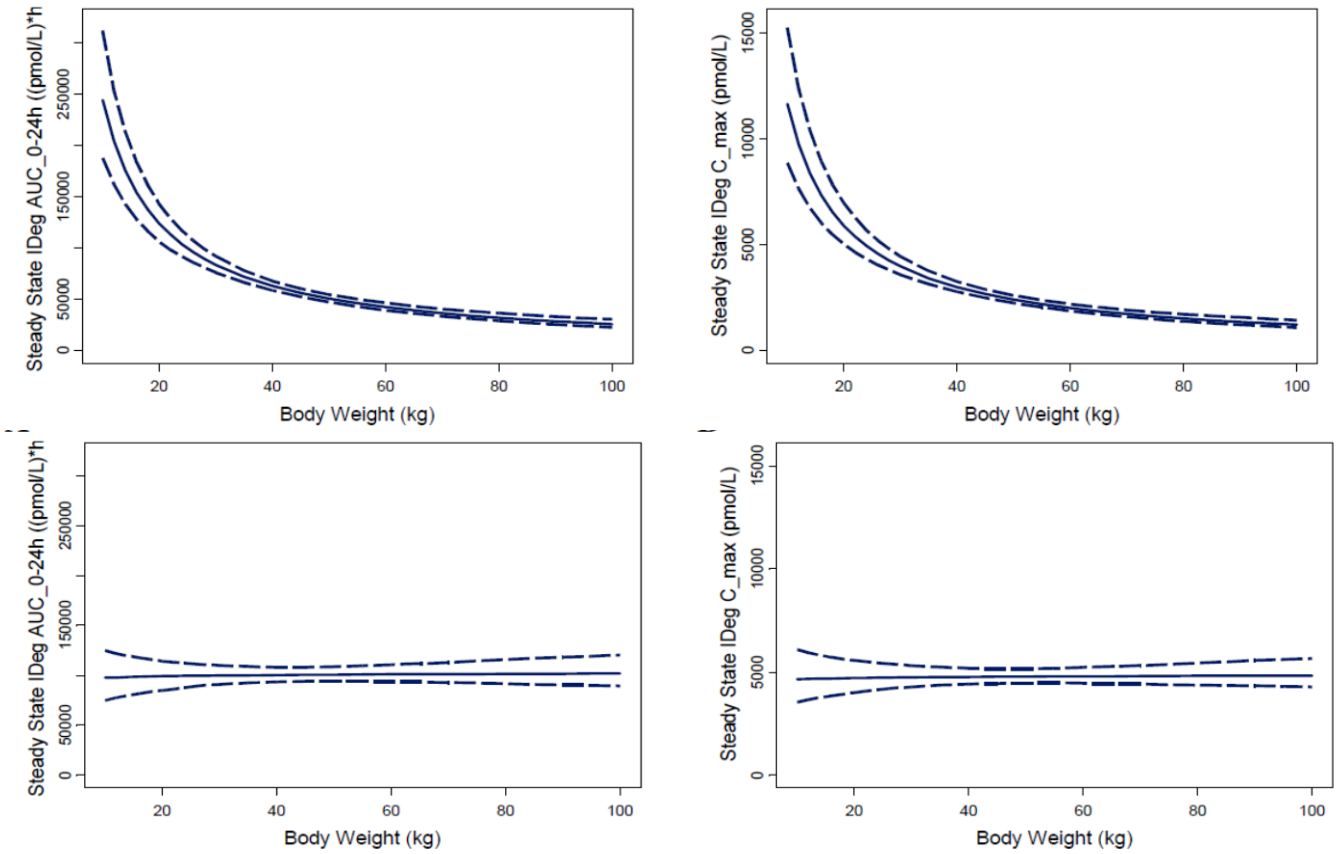
Sponsor's Conclusion:

- The population PK analysis showed that the concentration-time profile in small children (1-5 years) is 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 kg body weight.
- As expected, and as observed for other insulins and for IDeg in other populations, body weight was the only significant covariate.
- Age group was highly correlated with body weight, but was not significant, when body weight was included. BMI z-score, gender and race did not significantly affect exposure.

Reviewer's comment on Sponsor's analysis:

- Overall the population PK modeling analysis method was reasonable and acceptable.
- Sponsor's conclusion that no dose adjustment is needed based on age is acceptable (see reviewer's analysis in section 4.2).
- Body weight was identified as a significant covariate. Steady state AUC and C_{max} relationship with body weight for 0.4 U/kg and 10 U IDeg are shown in Figure 9. Incidence of T2DM is not common in less than 10 years (<body weight 40 kg) of children. Hence, in majority of T2DM pediatric population the steady state exposure from 10 U of IDeg is not likely to change by body weight. When dosed per kg body weight, the exposure becomes independent of body weight, as shown in Figure 9 for a dose of 0.4 U of IDeg per kg body weight administered to a typical subject.

Figure 9. AUC and C_{max} at steady-state vs. body weight for typical subjects in the weight range 10-100 kg dosed with 10 U of IDeg (top panel) and 0.4 U of IDeg per kg body weight (bottom panel).



Data are medians with 95% CI obtained from the final population PK model.

Source: NDA 203314, module 5.3.3.5, modelling report for Tresiba, page 24

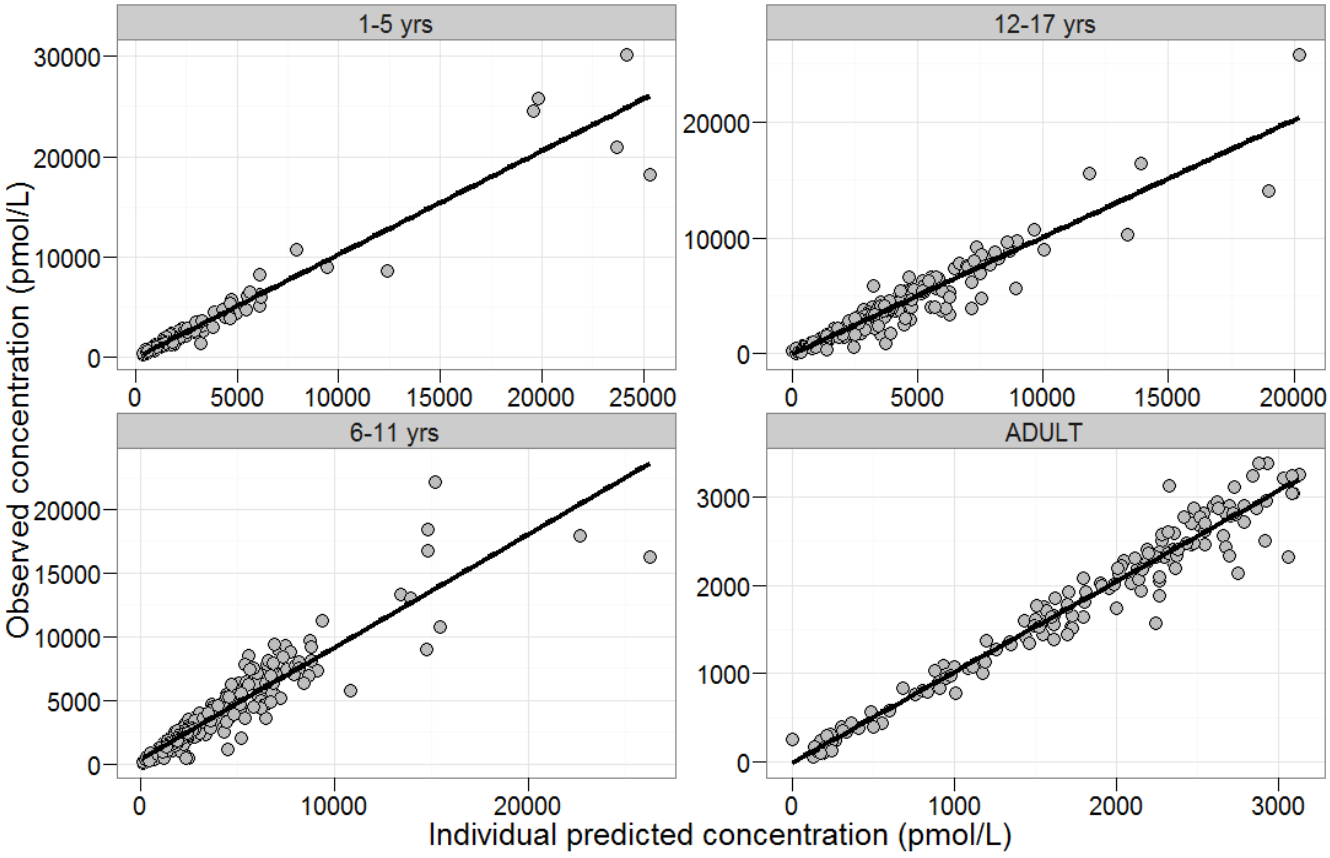
4.2. Reviewer's analysis

The sponsor's analysis was confirmed by the reviewer using NONMEM 7.3. Additionally, in order to investigate population PK model performance for different age groups, the trend of observed versus prediction concentrations from the final model was evaluated in these age groups. As shown in Figure 10 the individual predicted concentrations were correlated to the observed values for all age groups similarly and no bias was observed. Since the exposure from single dose PK study Trial 1995 was higher in pediatrics model diagnostics were plotted by trial to evaluate the model predictions from single dose PK Trial 1995 versus Trial 3561. As shown in Figure 11 the individual predicted concentrations were correlated to the observed concentrations showing that the final model described the single dose data reasonably.

There was an increasing trend in inter-individual variability of CL/F and V/F with increasing body weight (Figures 12 and 13). After inclusion of body weight as a covariate in the final model, no systematic trend between inter-individual variability of CL/F and V/F versus body weight was observed (Figure 12 and 13).

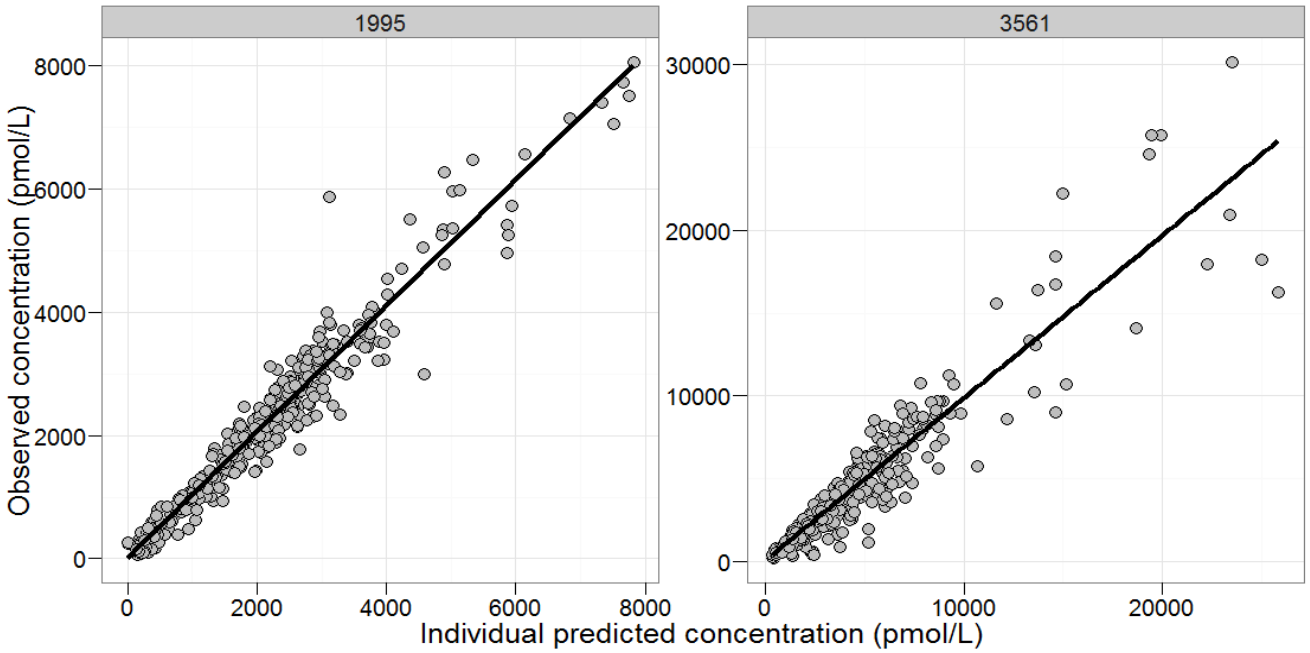
There was a trend for increasing inter-individual variability of CL/F with increase in age (Figure 14A). However, age was found to be highly correlated to body weight (correlation coefficient > 0.5) and thus inclusion of body weight in the final model resulted in no systematic trend between inter-individual variability on CL/F and age as shown in Figure 14B.

Figure 10. Observed versus individual predicted concentration stratified by age group.



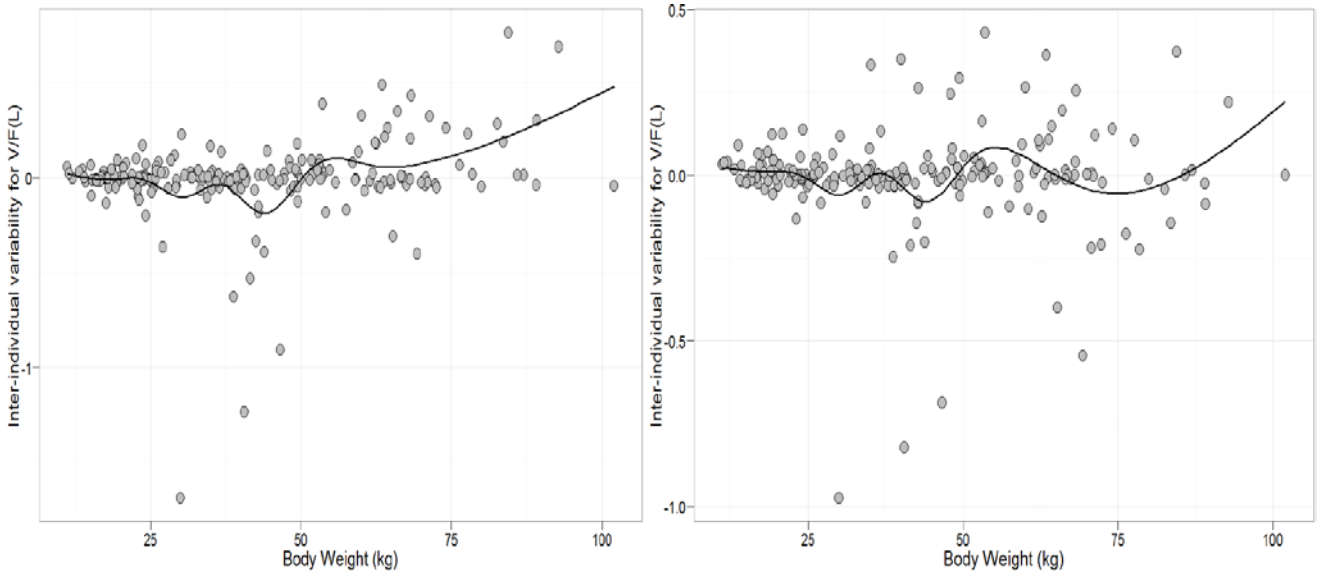
Source: Reviewer's analysis of data submitted in Modelling Report for Tresiba, Module 5.3.3.5

Figure 11. Observed versus individual predicted concentration stratified by trial.



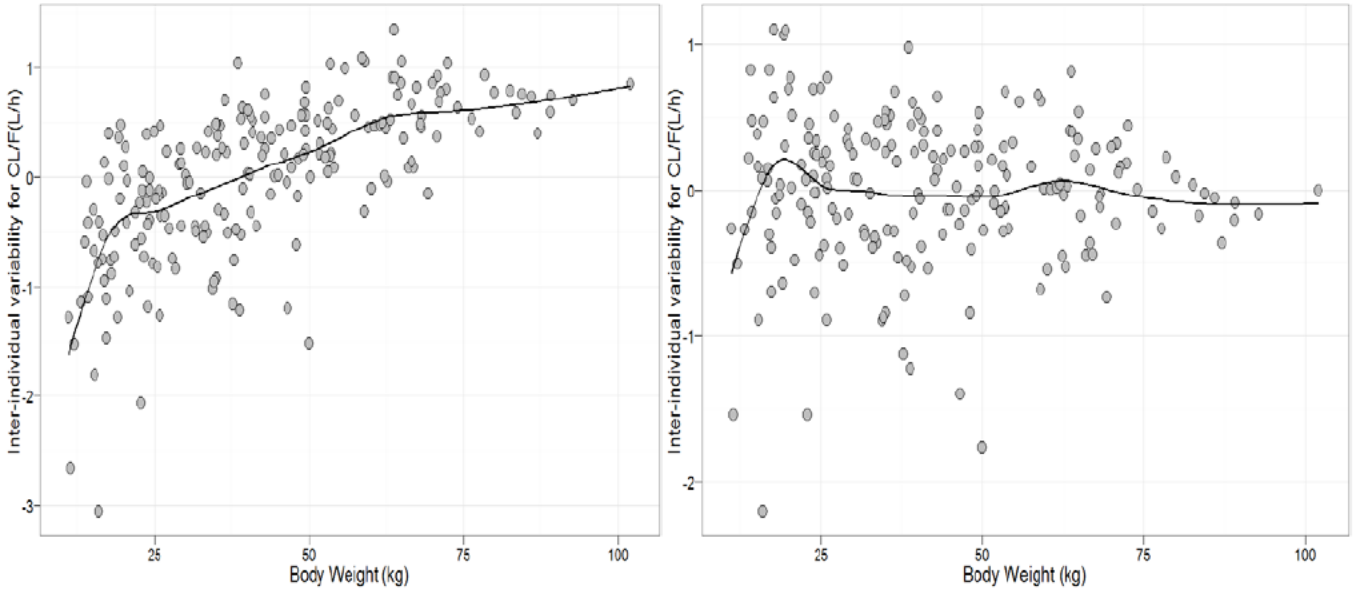
Source: Reviewer's analysis of data submitted in Modelling Report for Tresiba, Module 5.3.3.5

Figure 12. Scatter plot of inter-individual variability on V/F versus body weight using base model (left) and final model (right).



Source: Reviewer's analysis of data submitted in Modelling Report for Tresiba, Module 5.3.3.5

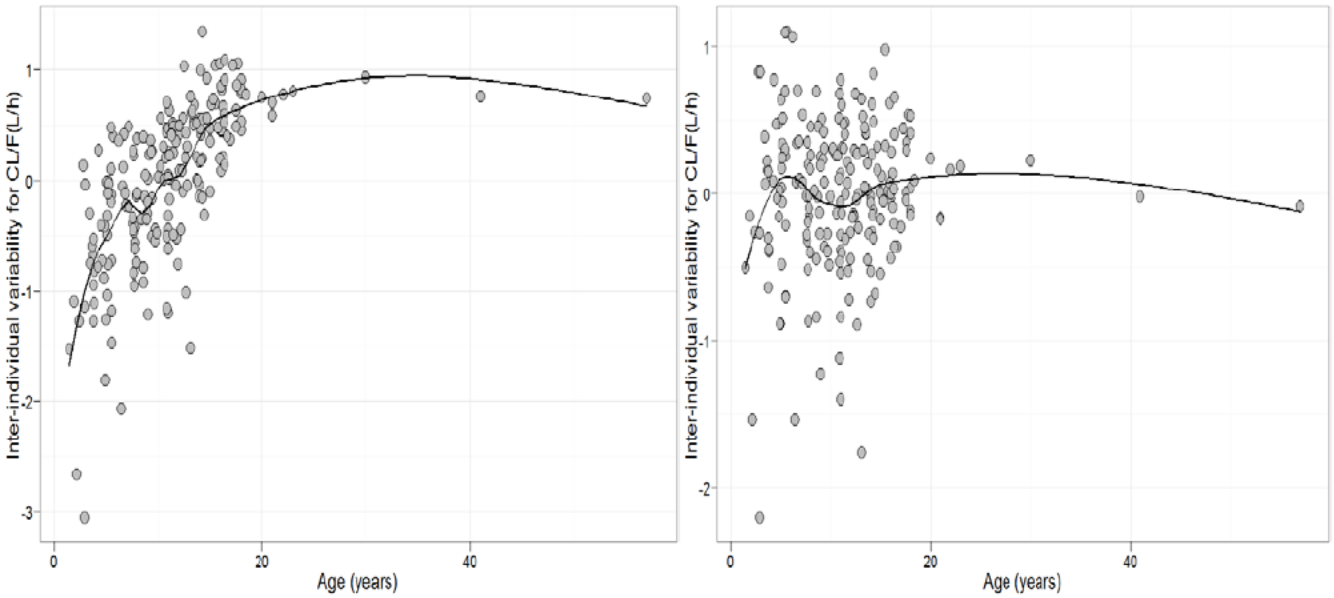
Figure 13. Scatter plot of interindividual variability on CL/F versus body weight using base model (left) and final model (right).



Source: Reviewer's analysis of data submitted in Modelling Report for Tresiba, Module 5.3.3.5

Figure 14. Scatter plot of interindividual variability on CL/F versus age using base model (left) and final model (right).

A B



Source: Reviewer's analysis of data submitted in Modelling Report for Tresiba, Module 5.3.3.5

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