CLINICAL PHARMACOLOGY REVIEW

NDA	203313/S-02 Serial 0069
Link to EDR	\\CDSESUB1\evsprod\NDA203313\0069
Submission Date(s)	February 16, 2016
Brand Name	Ryzodeg®70/30
Generic Name	Insulin degludec/Insulin Aspart
OND Division	Metabolism and Endocrinology Products
Sponsor	Novo Nordisk Inc.
Formulation; Strength	Solution for Injection for subcutaneous injection, 100 Units of 70% insulin degludec/30% insulin aspart per mL (U-100)
Relevant IND	IND 073198
Indication	*Use of Ryzodeg in pediatric patients with diabetes mellitus from 1 to* (b) (4) (b) (4)
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Table of Contents

List of Tables

List of Figures

1 Executive Summary

The applicant, Novo Nordisk Inc., has submitted a pediatric efficacy supplement (Supplement 2, Serial 0069) for NDA 203313- Ryzodeg® (insulin degludec/insulin aspart) is a premix consisting of 70% insulin degludec (IDeg) and 30% insulin aspart (IAsp). The dose strengths proposed are the same as that approved for adults -100 Units/mL (U-100). The proposed revised indication is to improve glycemic control in adults and children with diabetes mellitus.

NDA 203313 for Ryzodeg® 70/30- Insulin degludec/insulin aspart (IDegAsp), 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:

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

Novo Nordisk has completed the PMR study and is submitting this as an Efficacy Supplement for a new indication - *'Use of Ryzodeg in pediatric patients with diabetes mellitus from 1 to* (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 203313, Supplement 2. The clinical pharmacology data is acceptable to support the 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 203313 included the following studies:

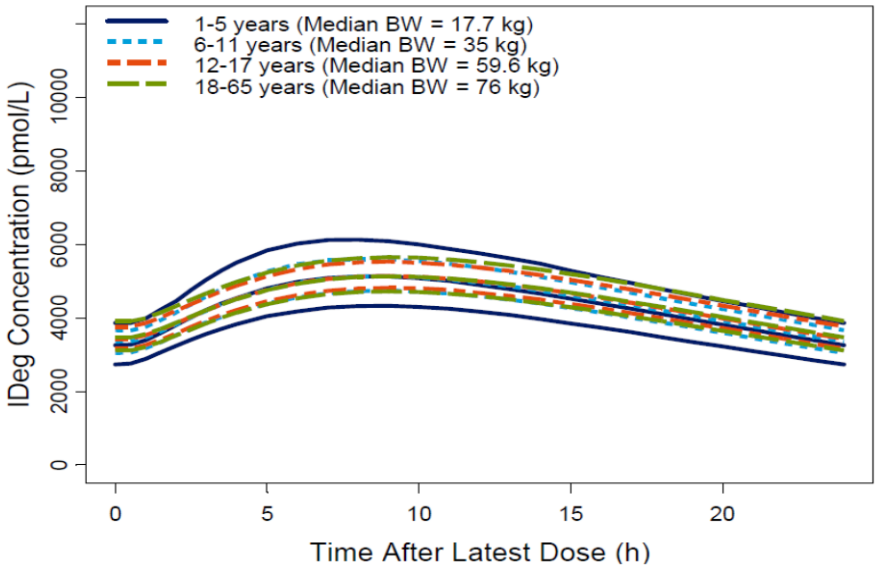
- A single-center, randomized, double-blind, two-period cross-over, single-dose trial investigating the pharmacokinetics (PK) properties of IDeg and IGlar in children (6−11 years), adolescents (12−17 years) and adults (18−65 years) with type 1 diabetes mellitus (T1DM) (Trial 1995)
- A single-center, single-dose, open-label trial investigating the PK and pharmacodynamics (PD) properties of IDegAsp in children (6−11 years), adolescents (12−17 years) and adults (18−65 years) with T1DM (Trial 1982)
- A 16-week multinational, multi-center, randomized, 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 (Trial 3816)
- A 26-week multinational, multi-center, randomized, 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 (Trial 3561)

The sponsor submitted a PK/PD modeling report (NDA 203313, Module 5.3.3.5, Modeling Report for Ryzodeg) where the PK data of Trial 1982, Trial 1995 and Trial 3561 were combined to perform population PK modeling for IDeg.

The results of single dose PK Trial 1982 were reviewed at the time of original NDA 203313 submission (see review by Dr. Ritesh Jain 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): 1.42 [95% CI: 0.94-2.16], AUC ratio (adolescents/adults): 1.23 [95% CI: 0.96-1.58], C_{max} ratio (children/adults) 1.38 [95% CI: 1.09-1.76], C_{max} ratio (adolescents/adults) 1.16 [95% CI: 0.95-1.42]). 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 13 adults). Nevertheless, it is worth noting that the magnitude of increase in AUC is modest i.e. 23 to 42%. These results were similar to that observed with IDeg PK in Trial 1995 (see Clinical Pharmacology review for Tresiba (NDA 203314/S-03) in DARRTS).

In the population PK analysis this rich single dose PK data (Trial 1982 and 1995) from 75 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 a 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 adjusted for, age was not correlated to the variability in the parameters. Using the final population PK model the sponsor conducted simulation to predict the steady state concentration 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 203313, Modelling Report for Ryzodeg, Section 5.3.3.5, Page 8

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

In Trial 3816 the primary objective was to compare the glycemic control, as measured by change in HbA1c after 16 weeks of treatment of IDegAsp + meal-time IAsp for the remaining meals and IDet + meal-time IAsp to a non-inferiority limit of 0.4%. Both treatment regimens improved glycemic control over 16 weeks. Analysis of HbA1c after 16 weeks showed that IDegAsp OD + IAsp effectively maintained glycemic control and was non-inferior to IDet + IAsp in terms of change from baseline in HbA1c, with an estimated mean treatment difference (IDegAsp OD − IDet) of −0.04% points [−0.23; 0.15]95% CI (refer to the Statistical review for further details).

Combined results of the population PK modeling and Trial 3816 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 2 of NDA 203313 is acceptable to support the pediatric approval.

2. Question-Based Review

2.1. Background

IDegAsp is a co-formulation of the long-acting IDeg and the rapid-acting IAsp in a ratio of 70% IDeg to 30% IAsp. The formulation of IDegAsp has been optimized such that the individual components do not interact, with IAsp present as soluble and stable hexamers and IDeg as soluble and stable di-hexamers. Once injected into the subcutaneous (s.c.) tissue the IAsp hexamers immediately form monomers which are rapidly absorbed into the capillaries while the IDeg di-hexamers form soluble multi-hexamers which in themselves are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. To a lesser extent, binding of IDeg to circulating albumin also contributes to the protraction mechanism. In this manner, it has been possible to obtain a clear distinction between the effects of the prandial (IAsp) and basal (IDeg) components of IDegAsp. At the target tissues, IDeg and IAsp monomers bind to and activate insulin receptors, triggering the same cellular effects as human insulin such as promoting glucose uptake. Thus, IDegAsp combines the benefits of a long-acting basal insulin with that of a rapid-acting insulin in one product intended for dosing with a meal in subjects with diabetes mellitus.

IAsp PK properties in adults:

- The rapid absorption characteristics of IAsp are preserved in IDegAsp; after injection, IAsp monomers are released rapidly into the circulation. The onset of appearance of IAsp from IDegAsp is within 14–21 minutes of injection reaching maximum concentration after 72−102 minutes. The rapid absorption characteristics translate into a rapid onset of action of the IAsp component of IDegAsp, hence providing mealtime coverage.
- IAsp total exposure from IDegAsp increases essentially proportionally in adults and maximum exposure increases proportionally with increasing dose.
- The maximum glucose-lowering effect increases with increasing IDegAsp dose (proportionally in subjects with T1DM and linearly in subjects with type 2 diabetes mellitus (T2DM)). The glucose-lowering effect of the IAsp component of IDegAsp declines from its maximum until the end of prandial coverage.

IDeg PK properties in adults:

- The terminal half-life (t½) of IDeg after s.c. administration is estimated to be 25 hours in subjects with either T1DM or 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).

Between injections of IDegAsp, the glucose-lowering effect of the basal component remains at a stable rate, providing basal coverage due to the slow, continuous release of IDeg.

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

The pediatric clinical pharmacology program for Ryzodeg (Table 1) consisted of the following:

- A single-center, randomized, 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 (Trial 1995)
- A single-center, 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 (Trial 1982)
- A 16-week multinational, multi-center, randomized, 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 (Trial 3816)
- A 26-week multinational, multi-center, randomized, 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. Sparse PK and PD measurements were collected during the main 26-week treatment period of the pediatric trial of IDeg (Trial 3561)
- A PK/PD modeling report 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

In addition, this supplemental NDA (sNDA) 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 [redacted] (b) (4)) 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 IDegAsp 100 U/mL and the NovoPen® Junior/NovoPen® Echo pen-injectors used in the phase 3 pediatric clinical Trial 3816 including extrapolation from adult use of the PDS290 pen-injector for IDegAsp 100 U/mL as well as Human factors/usability validation conducted for the PDS290 pen-injector in the pediatric population demonstrating safe and effective use.

Table 1. Summary of pediatric clinical pharmacology development program.

Trial ID	Trial Design	Trial Objectives	Treatment
Clinical pharmacology trial of IDegAsp			
NN5401-1982	Open-label, single-dose	PK, PD and safety profile in children (6−11 years), adolescents (12−17 years) and adults (18−65 years) with T1DM	IDegAsp: single dose of 0.5 units/kg
Clinical pharmacology trial of IDeg			
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 of IDeg 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, IDegAsp: insulin degludec/insulin aspart, IDet: insulin determir, IGlar: insulin glargine, OD: once daily, PD: pharmacodynamic(s), PK: pharmacokinetic(s), T1DM: type 1 diabetes mellitus

Source: NDA 203313 - Summary of Clinical Pharmacology Studies - Pediatric Indication, section 2.7.2, page 10

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 3816-

- IDegAsp 100 U/mL, 3 mL Penfill® cartridge using Novopen Junior® (green pen) in the US and Novopen Echo® (green pen) in other countries
- IAsp 100 U/mL, 3 mL Penfill® cartridge (NovoRapid®/ NovoLog®) using Novopen Junior® (yellow pen) in the US and Novopen Echo® (orange pen) in other countries

Trial 3561-

- IDeg 100 U/mL, Penfill® 3 mL 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 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

Trial 1982 -

- IDegAsp (F) in 3 mL Penfill® cartridges, 100 U/mL
- IAsp - NovoRapid®, 100 U/mL in 3 mL FlexPen® and 10 mL vials

The primary difference between the device approved for adults (PDS290 pen-injector) for IDegAsp 100 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 Trial 3816 and the PDS290 pen-injector for IDegAsp 100 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 Trial 3816 for IDegAsp 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 IDegAsp 100 U/mL, which has the same operating principle. Extrapolation from adult use of the PDS290 pen-injector for IDegAsp 100 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?

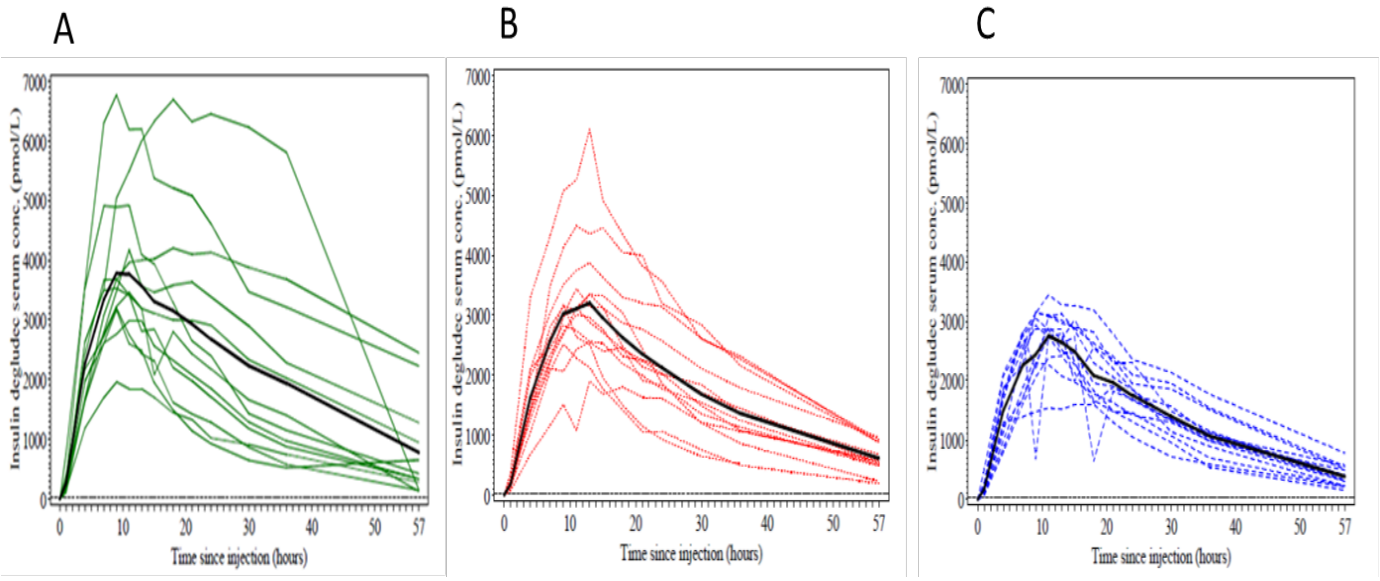
Yes, the total steady state exposures in the pediatric and adult population were similar.

Single dose PK data for IDegAsp in children, adolescents and adults with T1DM were evaluated in Trial 1982 and the results of this study were reviewed previously by Dr. Ritesh Jain during original NDA 203313 submission (DARRTS date 06/15/2012). Data from Trial 1982 suggested that exposure appeared to be higher in children and adolescents than in adults (AUC ratio (children/adults): 1.42 [95% CI: 0.94-2.16], AUC ratio (adolescents/adults): 1.23 [95% CI: 0.96-1.58], C_{max} ratio (children/adults) 1.38 [95% CI: 1.09-1.76], C_{max} ratio (adolescents/adults) 1.16 [95% CI: 0.95-1.42]). These results were similar to that observed with IDeg PK in Trial 1995 (see Clinical Pharmacology review for Tresiba (NDA 203314/S-03) in DARRTS)

While the exposures following subcutaneous dose were, on an average, higher in pediatric population compared to 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 slightly 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 1982. 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 of IDeg after single dose of 0.5 U/kg IDegAsp in children (A), adolescents (B) and adults (C).



Source: NDA 203313, module 5.3.3.3, study report NN5401-1982, page 87

Additional sparse PK data for IDeg 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. No PK was collected in Trial 3816. To further evaluate relation between age and exposure of IDeg the sponsor performed population PK modeling by combining the data from Trials 1995, 1982 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 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 included as a covariate in the model, age was not found to be a significant covariate affecting IDeg PK. After accounting for body weight, race was also identified as a significant covariate with Asian Non-Indians showing 53% higher CL/F than White pediatric patients. However, race effect was not considered important because of the following reasons:

- Asian Non-Indian population for the analysis was coming from only one study (Trial 3561) whereas White population was coming from Trials 1982, 1995 and 3561 and study effect could be a confounding factor.
- No effect of race on exposure was observed with Tresiba pediatric population PK modeling.
- Currently no race based dose adjustment for IDeg is suggested for adults.

- The sponsor has not proposed any labeling recommendations for dose adjustment in the pediatric population based on race.

Overall, because of the above reasons and that insulin products are titrated to effect, a dosage adjustment for starting dose in Asian Non-Indians was not considered necessary.

Addition of covariates explained 28.5% variability in CL/F and 21.4 % 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 of IDeg was similar in the adult and pediatric population.

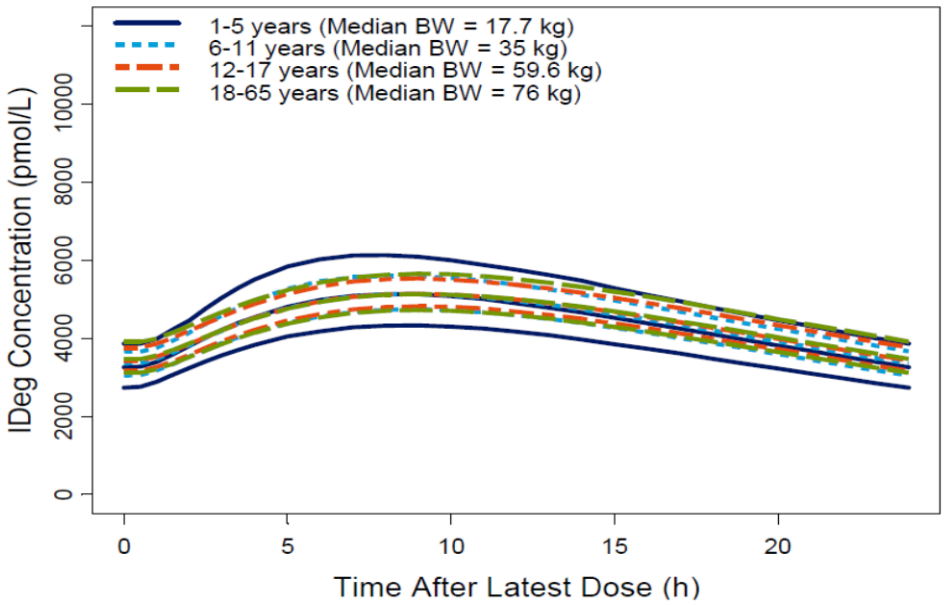
Using the final model from the covariate analysis, simulations of IDeg concentration profiles at steady-state following multiple dosing were performed and presented graphically for each of the four age groups (Figure 3). The sponsor concluded that the concentration-time profile in small children (1-5 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).

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 3. 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 203313, Modelling Report for Ryzodeg, 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 Ryzodeg.

2.3.2. Considering the results of the systemic exposures discussed above, what are the relevant aspects of the efficacy and safety results of IDegAsp in Trial 3816 from clinical pharmacology perspective?

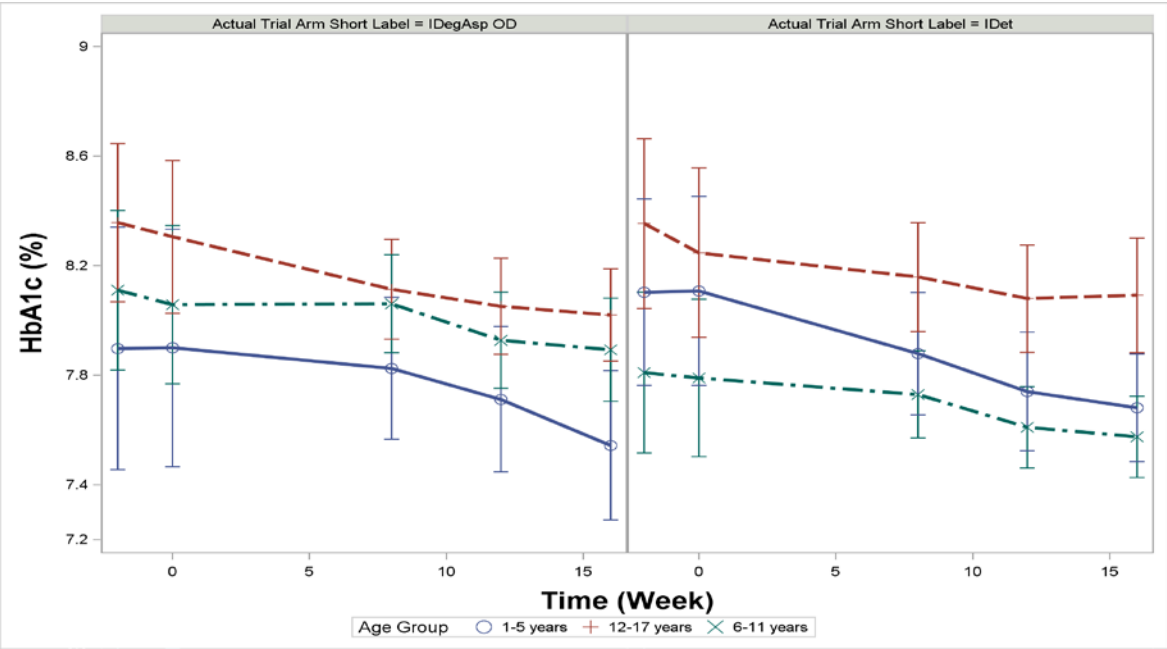
In the 16-week efficacy and safety Trial 3816 where the difference in change in HbA1c were compared between IDegAsp OD + IAsp and IDet + IAsp, a non-inferiority limit of 0.4% was met in T1DM subjects between 1 and less than 18 years of age (refer to Statistical review and Clinical review for further details). The HbA1c % in different age groups is shown in Figure 4 below where both treatment regimens improved glycemic control over 16 weeks.

The mean daily basal dose of IDeg at week 16 was 0.31 U/kg, 0.33 U/kg and 0.41 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively (Figure 5). The mean daily basal dose of IDet at week 16 was 0.40 U/kg, 0.49 U/kg and 0.53 U/kg in 1-5 years, 6-11 years and 12-17 years age groups, respectively. The mean daily bolus dose in the IDegAsp arm at week 16 was 0.48 U/kg, 0.51 U/kg and 0.55 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 16 was 0.51 U/kg, 0.50 U/kg and 0.55 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 IDegAsp remained slightly lower than IDet. However, numerically higher severe and nocturnal hypoglycemia events were observed in the IDegAsp arm versus the IDet arm. Key safety observations from Trial 3816 are summarized below (refer to the Clinical Review by Dr. Tania Condarco for comprehensive review of safety data).

- The rate for adverse events (AEs) was 915 events per 100 patient years of exposure (PYE) in the IDegAsp treatment group and 853 events per 100 PYE in the IDet treatment group. The rate of AEs considered possibly or probably related to trial drug by the investigator was numerically higher with IDegAsp compared to IDet (47 vs. 37 events per 100 PYE, respectively). The rates of serious adverse events (SAEs) were generally low, however, numerically higher with IDegAsp compared to IDet (26 vs. 13 events per 100 PYE, respectively).
- The observed rates of confirmed hypoglycemic episodes were 4623 and 4955 episodes per 100 PYE for IDegAsp and IDet, respectively, and there was no statistically significant difference between treatment arms (IDegAsp OD/IDet: 0.95 [0.76; 1.17]95%CI).
- In the IDegAsp treatment group, 6.1% reported and 1.7% reported severe hypoglycemic in IDeg and IDet group, respectively. There was no statistically significant difference in severe hypoglycemia between treatment groups (IDegAsp OD/IDet: 3.20 [0.88; 11.66]95%CI).
- The observed rates of nocturnal confirmed hypoglycemic episodes were 577 and 540 episodes per 100 PYE for IDegAsp and IDet, respectively, and there was no statistically significant difference between treatment groups (IDegAsp OD/IDet: 1.09 [0.81; 1.48]95%CI).
- There was no statistically significant difference between IDegAsp and IDet with respect to the rate of hyperglycemic episodes (1.08 [0.64; 1.81]95%CI). Overall, although numerically higher adverse events were observed with IDegAsp versus IDet, these differences were not statistically significant.

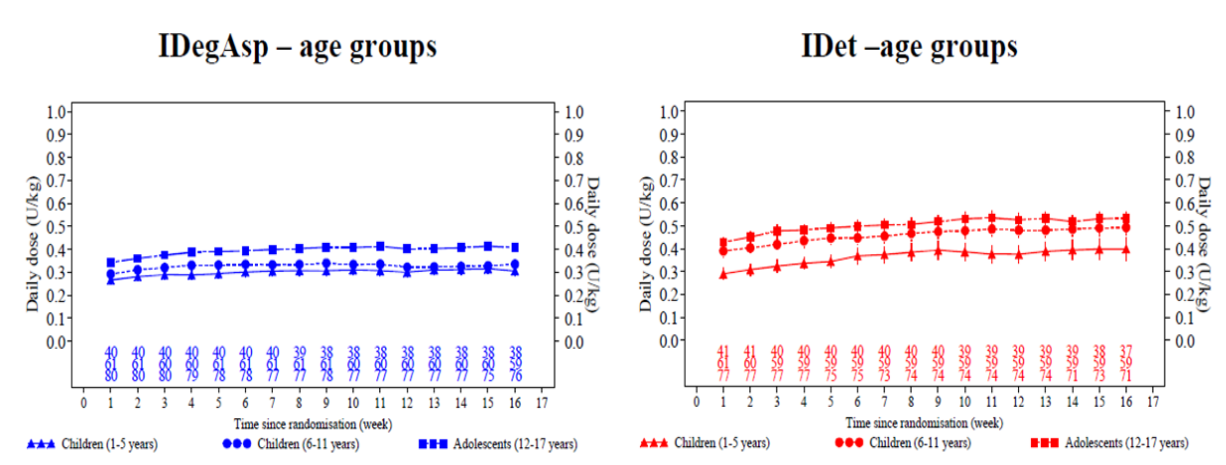
Figure 4. HbA1c (%) over time by age groups – mean plot (FAS dataset).



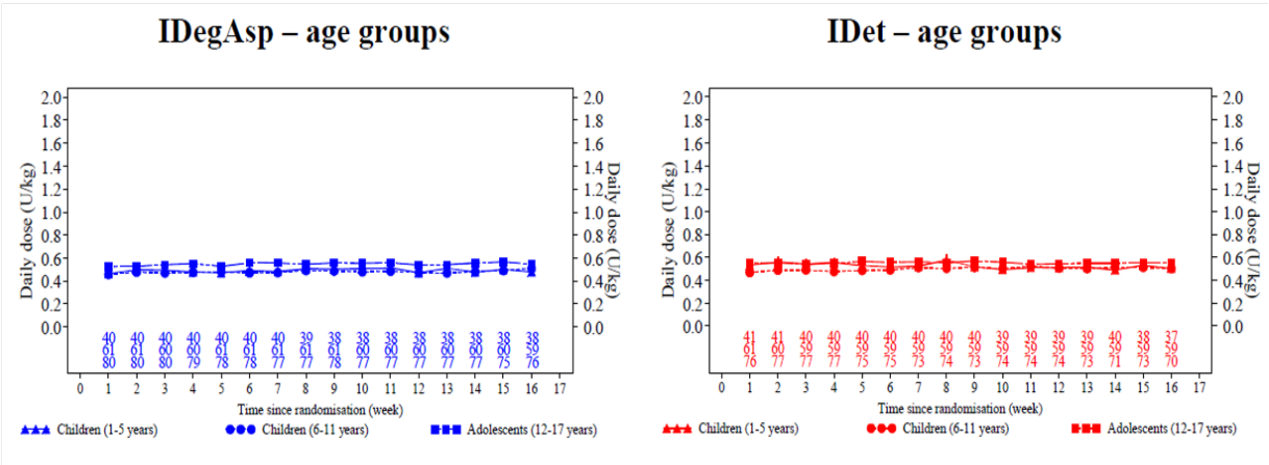
Source: NDA 203313 - Re-plotted from study report NN1250-3816 page 111

Figure 5. 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 203313 - Study report NN1250-3816 page 128-131

2.4. Bioanalytical

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

Yes, the methods of bioanalysis for the trials included in this application were the same as in the original NDA 203313.

IAsp was quantified by a specific sandwich enzyme-linked immuno sorbent assay (ELISA). The capture antibody coated on the microtitre plate was a monoclonal mouse antibody specific for human insulin (HUI-018), and the detection antibody, labelled with biotin, was an IAsp specific monoclonal mouse antibody (X14-6-F34). In samples, the IAsp concentration was determined by interpolation from a series of calibrators included in each analysis set. These calibrators were made by spiking of the reference material into the same matrix as the samples.

IDeg was quantified by a specific sandwich ELISA. 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 validation and analysis of samples were performed in accordance with current practice and were reviewed previously in the following reviews:

- Trial 1982 - Dr. Ritesh Jain review in DARRTS dated 06/15/2012
- Trial 1995 - Dr. Manoj Khurana review in DARRTS dated 06/15/2012
- Trial 3561 - Clinical Pharmacology review for Tresiba (NDA 203314/S-03) in DARRTS

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, RYZODEG 70/30 should always be titrated according to individual requirements.

Pediatrics-

(b) (4)

(b) (4) Population pharmacokinetic analysis conducted for insulin degludec in RYZODEG 70/30 using data from (b) (4) 224 pediatrics patients (1 - <18 years) (b) (4) with type 1 diabetes obtained from studies utilizing single and multiple subcutaneous administration showed body weight as a significant covariate affecting clearance of insulin degludec. After adjusting for body weight, the (b) (4) total insulin exposure of insulin degludec 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)
- A single-dose trial of IDegAsp with rich PK in children/adolescents/adults (Trial 1982)
- 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 1982 all subjects received a single dose of 0.5 U/kg of IDegAsp, containing 0.35 U/kg of IDeg and 0.15 U/kg of IAsp, 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. In Trial 1982 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, 30h, 36h, and finally at 57h 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. 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, no covariates were excluded, and the final model was thus identical to the full model and consisted of the base model with body weight as a covariate for both CL/F and V/F and race as a covariate for CL/F (mainly driven by lower exposure in Asian subjects). 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 1.68 L/h and 10.6 L, respectively, and were determined with good precision (relative standard errors (RSEs) of 4.7% and 13.4%, respectively). As seen in Table 5, the estimated allometric exponents for CL/F and V/F in the final model were close to 1 (0.982 [95% CI: 0.840-1.12] for CL/F and 1.13 [95% CI: 0.705-1.56] for V/F). The goodness of fit plots and visual predictive check plot are shown in Figure 6 and 7.

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 -75.7% was seen for the coefficient for the other race category – a parameter for which the 95% CI included 0 in both the primary and the sensitivity analysis. 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 -10.4% was seen for the allometric exponent for V/F.

Shrinkage for CL/F and V/F were estimated at 2.45% and 46.2%, 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 (continuous variables)

	Trial 3561 Mean (SD) [Range]	**Trial 1995** Mean (SD) [Range]	**Trial 1982** Mean (SD) [Range]	**Total** Mean (SD) [Range]
N	169	36	38	243
Age (years)	10.0 (4.4)	16.8 (9.4)	16.9 (9.0)	12.1 (7.0)
	[1.5-18.4]	[8.0-57.0]	[8.0-57.0]	[1.5-57.0]
Body Weight (kg)	37.9 (18.6)	61.0 (16.0)	62.2 (17.5)	45.1 (21.1)
	[11.2-102]	[30.0-92.8]	[30.1-95.7]	[11.2-102.0]
BMI (kg/m^2)	18.7 (3.6)	21.8 (3.4)	21.9 (3.2)	19.7 (3.8)
	[12.9-34.5]	[16.2-29.9]	[15.4-29.2]	[12.9-34.5]
BMI z-score (-)	0.50 (1.11)	0.77 (0.71)	0.78 (0.69)	0.59 (1.01)
	[-2.97-3.51]	[-0.42-2.04]	[-0.66-2.04]	[-2.97-3.51]

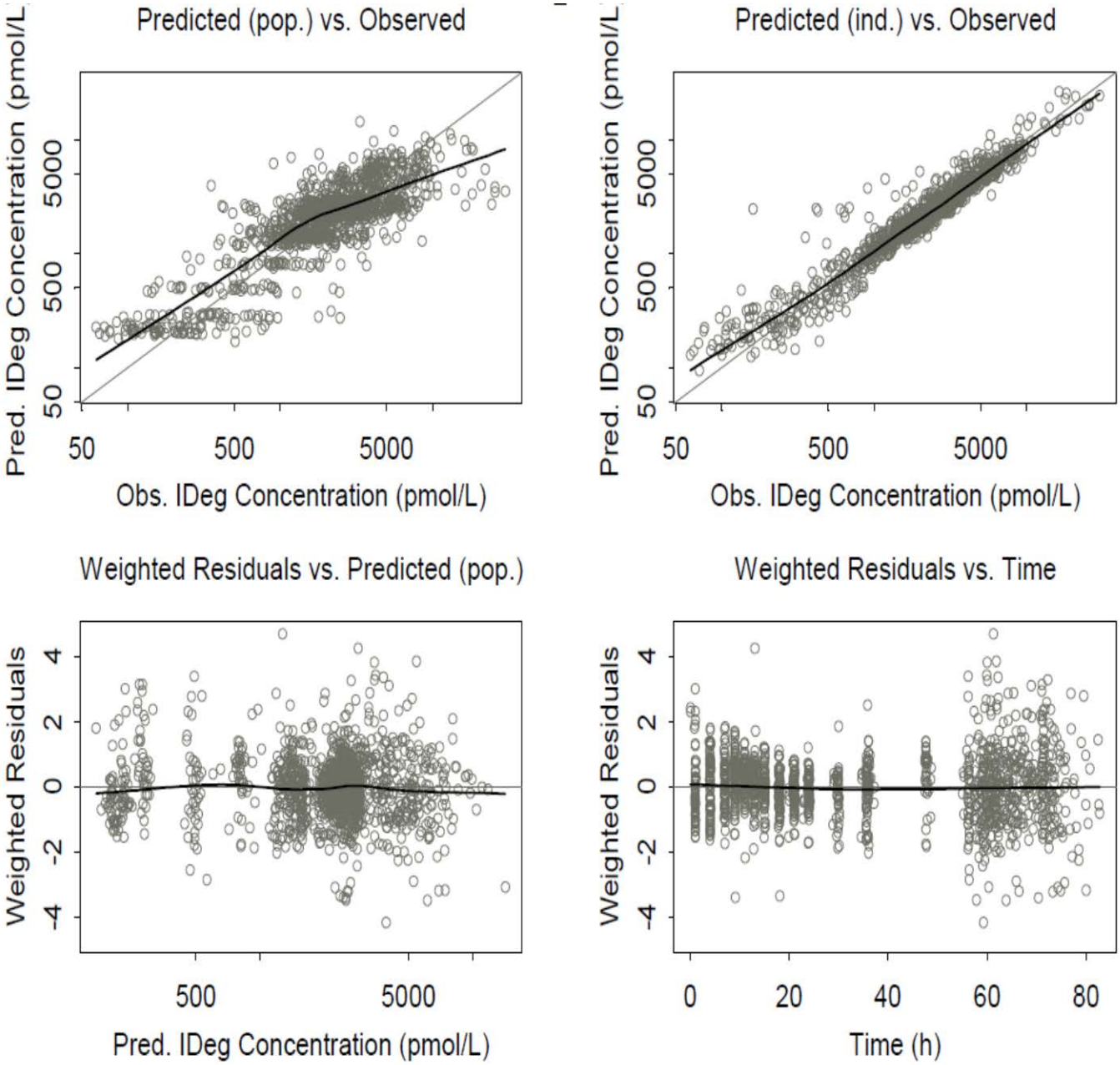
For German subjects, date of birth was set to January 1st for protection of subject anonymity. For one subject in Trial 3561 this led to a derived age of 18.4 years. In reality, this subject was less than 18 years of age at screening.
Source: ND NDA 203313, Modelling Report for Ryzodeg, Module 5.3.3.5, Page 23

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

Covariate	Category	Trial 3561 N (%)	Trial 1995 N (%)	Trial 1982 N (%)	Total N (%)
Gender	Female	76 (45)	17 (47)	15 (39)	108 (44)
	Male	93 (55)	19 (53)	23 (61)	135 (56)
Race	Asian Non-Indian	22 (13)	-	-	22 (9)
	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)	2 (5)	10 (4)
	White	132 (78)	35 (97)	36 (95)	203 (84)
Ethnicity	Hispanic or Latino	7 (4)	-	-	7 (3)
	Not Hispanic or Latino	162 (96)	36 (100)	38 (100)	236 (97)
Country	Bulgaria	14 (8)	-	-	14 (6)
	Germany	5 (3)	36 (100)	38 (100)	79 (33)
	Finland	9 (5)	-	-	9 (4)
	France	2 (1)	-	-	2 (1)
	Great Britain	8 (5)	-	-	8 (3)
	Italy	7 (4)	-	-	7 (3)
	Japan	22 (13)	-	-	22 (9)
	Macedonia	8 (5)	-	-	8 (3)
	Netherlands	11 (7)	-	-	11 (5)
	Russia	23 (14)	-	-	23 (9)
	South Africa	5 (3)	-	-	5 (2)
	USA	55 (33)	-	-	55 (23)
Total		169 (70)	36 (15)	38 (15)	243 (100)

Source: NDA 203313, Modelling Report for Ryzodeg, Module 5.3.3.5, Page 22

Figure 6. Goodness-of-fit plots for the final model.



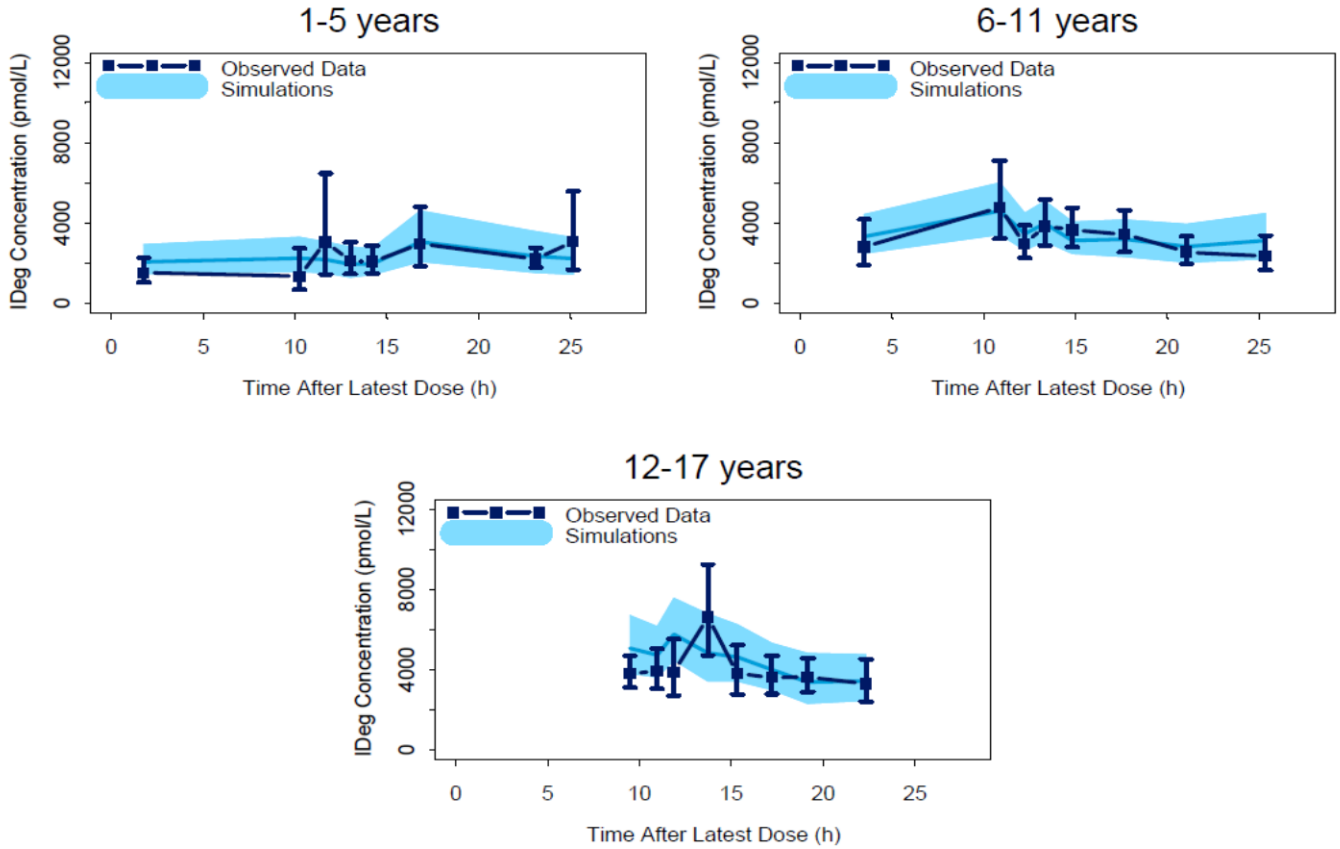
Source: NDA 203313, module 5.3.3.5, Modelling report for Ryzodeg, page 53

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	0.0450	8.20	[0.0378;0.0522]	[0.0413;0.0488]
K_T	Transit rate constant	1/h	0.818	12.0	[0.626;1.01]	[0.672;0.997]
CL/F	Apparent clearance	L/h	1.68	4.73	[1.52;1.84]	[1.52;1.86]
V/F	Apparent volume of distribution	L	10.6	13.4	[7.79;13.4]	[8.62;12.9]
$\theta_{wt,CL}$	Allometric exponent on clearance	NA	0.982	7.38	[0.840;1.12]	[0.858;1.11]
$\theta_{wt,V}$	Allometric exponent on volume	NA	1.13	19.3	[0.705;1.56]	[0.793;1.47]
$\theta_{Asian\ Non\text{-}Indian}$	Race coefficient on clearance	NA	0.424	18.5	[0.270;0.578]	[0.203;0.645]
θ_{Other}	Race coefficient on clearance	NA	-0.133	153	[-0.532;0.266]	[-0.402;0.132]
Random-effects parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**		
IIV – CL/F	Between-subject variability on CL/F	% CV	51.4	2.45		
IIV – V/F	Between-subject variability on V/F	% CV	45.3	46.2		
Residual error parameters	**Description**	**Unit**	**Estimate**	**% Shrinkage**		
$Sigma_1$	Residual error (proportional, % CV)	% CV	18.9	11.2		
$Sigma_2$	Residual error (additive, SD)	pmol/L	107	10.8		

Source: NDA 203313, module 5.3.3.5, Modelling report for Ryzodeg, page 49

Figure 7. 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 203313, module 5.3.3.5, Modelling report for Ryzodeg, page 55

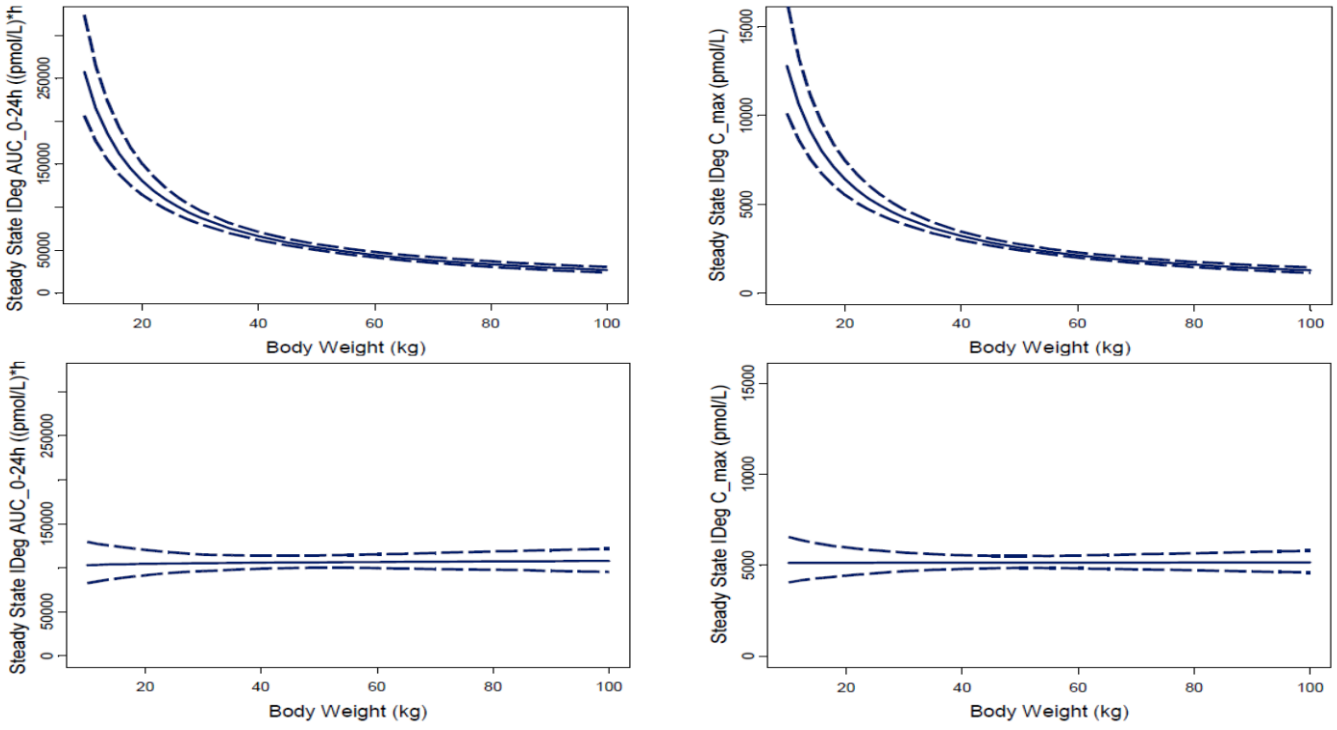
Sponsor's Conclusion:

- 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 most important covariate.
- Age group was highly correlated with body weight, but was not significant, when body weight was included. Race was also a significant covariate – mainly driven by lower exposure in Asian subjects. BMI z-score and gender 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). Race effect was not considered important for reasons described in section 2.3.1 of this review.
- 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 8. 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 weight. When dosed per kg body weight, the exposure becomes independent of body weight, as shown in Figure 8 for a dose of 0.4 U of IDeg per kg body weight administered to a typical subject.

Figure 8. 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 203313, module 5.3.3.5, Modelling report for Ryzodeg, page 25

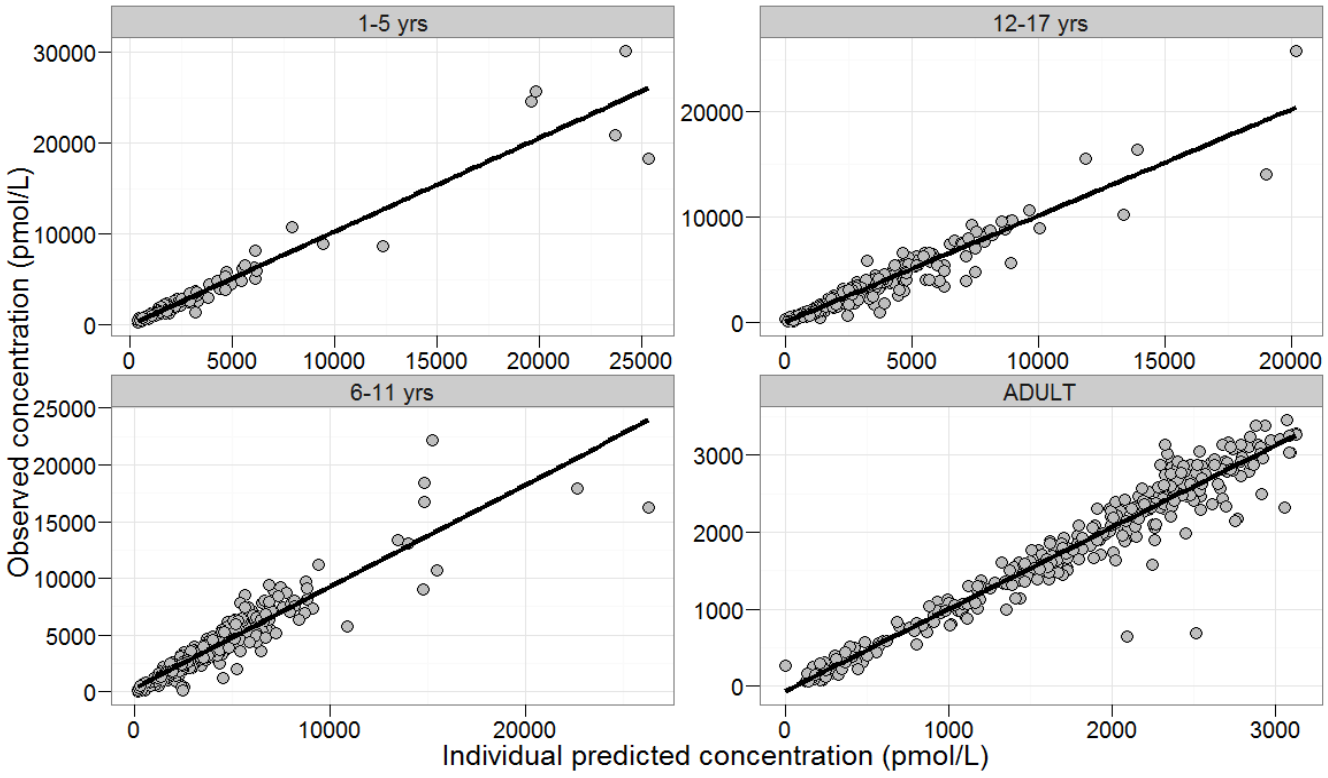
4.2. Reviewer's analysis

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 was evaluated in these age groups. As shown in Figure 9 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 and Trial 1982 was higher in pediatrics model diagnostics were plotted by trial to evaluate the model predictions from single dose PK Trial 1995 and Trial 1982 versus Trial 3561. As shown in Figure 10 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 11 and 12). After inclusion of body weight as a covariate in sponsor's final model, no systematic trend between inter-individual variability on CL/F and V/F versus body weight was observed (Figure 11 and 12).

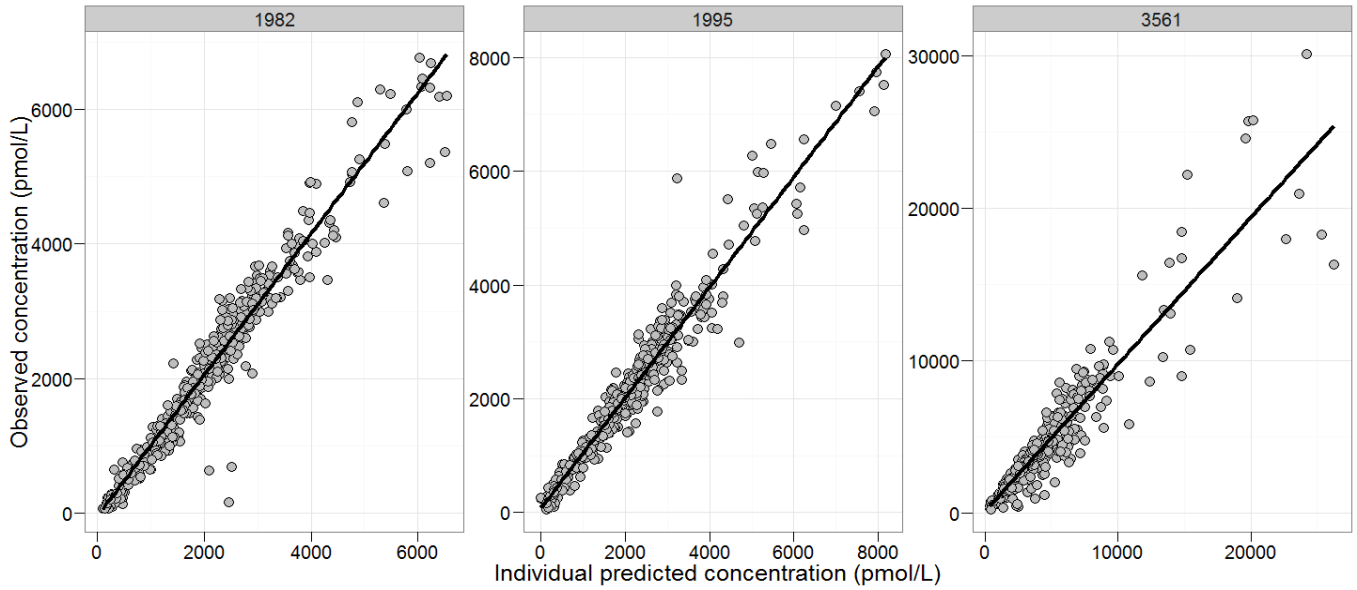
A trend for increasing inter-individual variability of CL/F with increase in age was also noted (Figure 13A). However, age was found to be highly correlated to body weight (correlation coefficient > 0.5) and thus inclusion of body weight as a covariate in the final model resulted in no systematic trend between inter-individual variability on CL/F and age as shown in Figure 13B.

Figure 9. Observed versus individual predicted concentration stratified by age group.



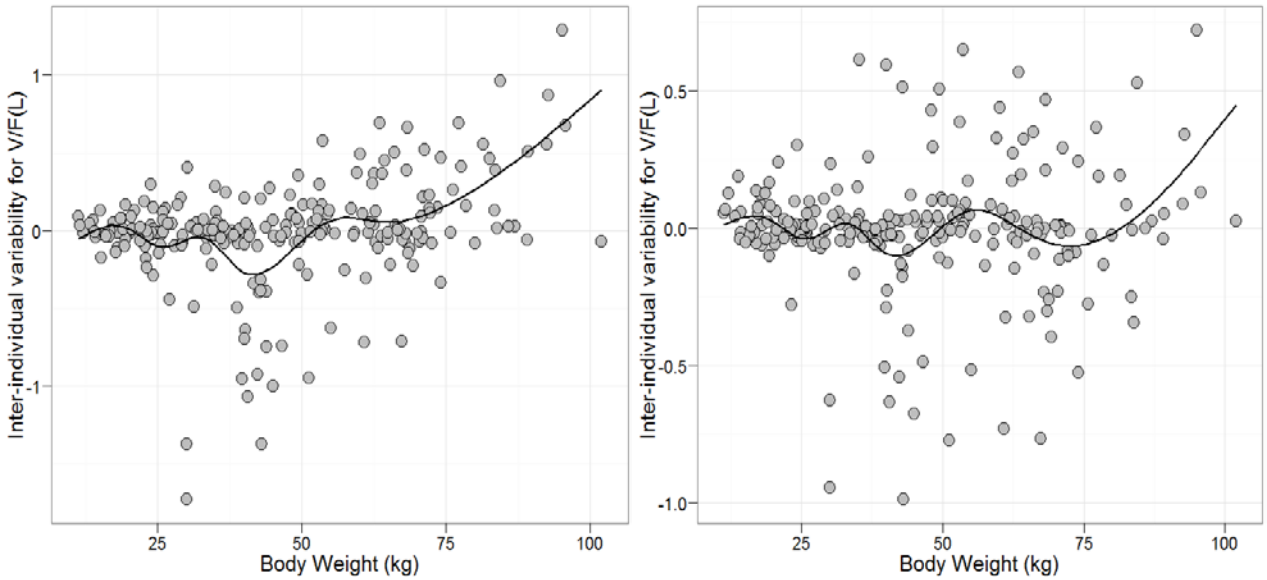
Source: Reviewer's analysis of data submitted in Modelling Report for Ryzodeg, Module 5.3.3.5

Figure 10. Observed versus individual predicted concentration stratified by trial.



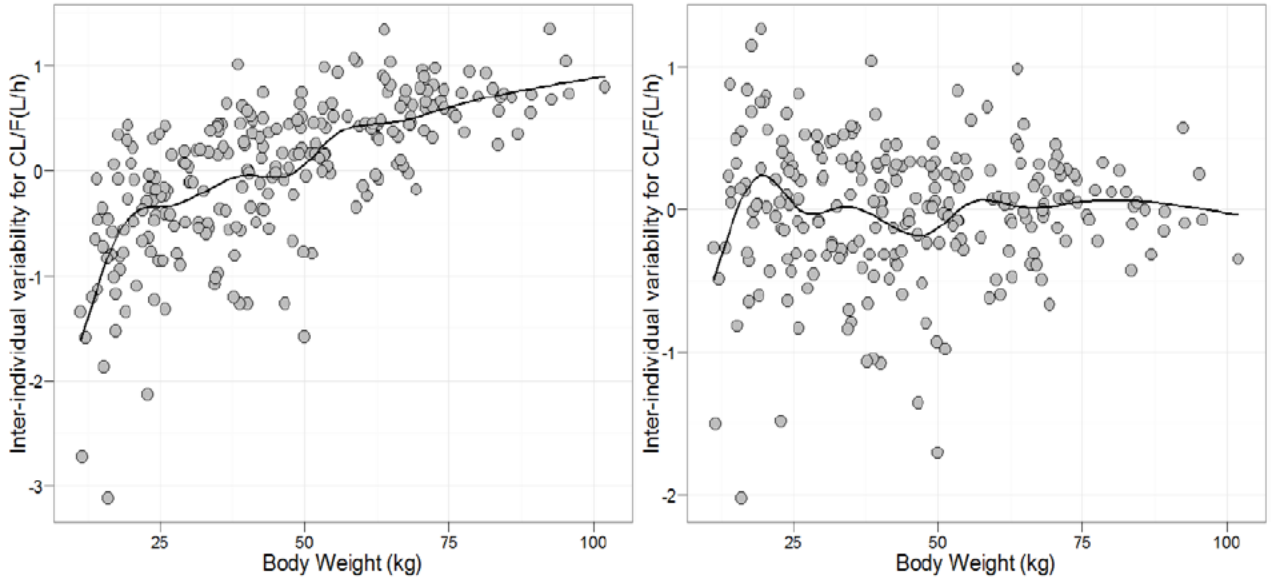
Source: Reviewer's analysis of data submitted in Modelling Report for Ryzodeg, Module 5.3.3.5

Figure 11. Scatter plot of inter-individual variability on V/F versus body weight using base model (left) and final model (right).



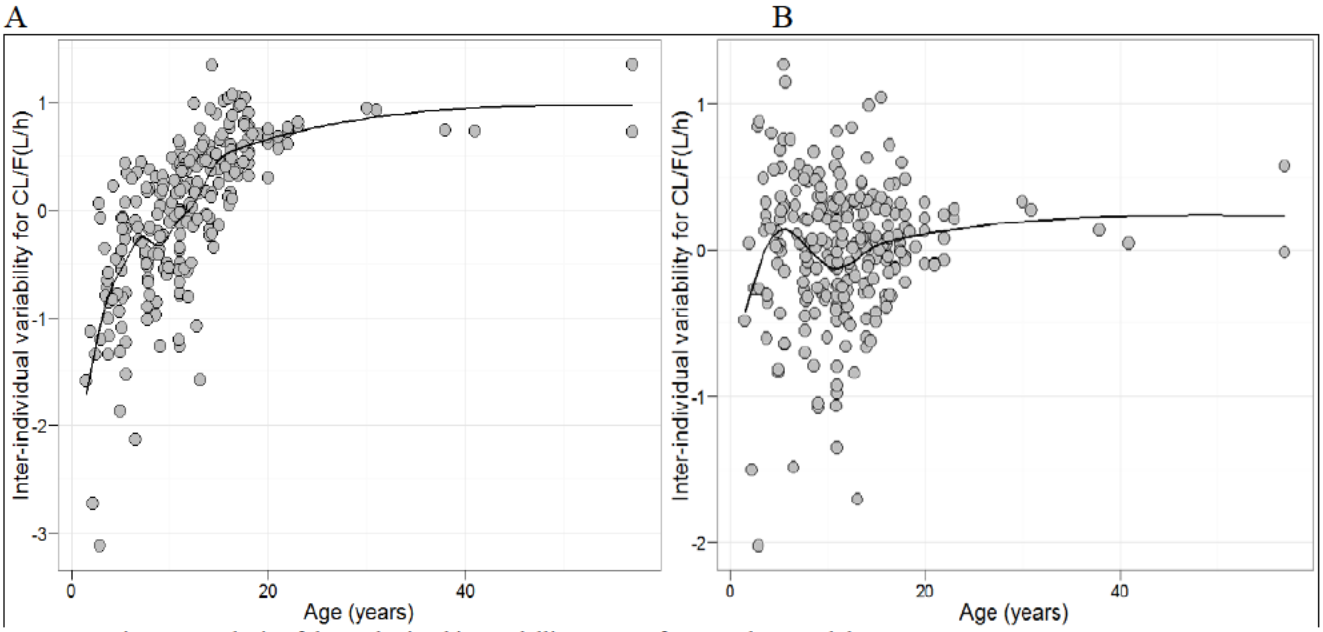
Source: Reviewer's analysis of data submitted in Modelling Report for Ryzodeg, Module 5.3.3.5

Figure 12. Scatter plot of inter-individual 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 Ryzodeg, Module 5.3.3.5

Figure 13. Scatter plot of inter-individual variability on CL/F versus age using base (left) and final (right) model.



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

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/s/

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