Cross-Discipline Team Leader Review

Date	Electronic stamp
From	Lisa Yanoff, M.D.
Subject	Cross-Discipline Team Leader Review
NDA #s	203314 203313
Applicant	Novo Nordisk
Date of Submission	16 Feb 2016
PDUFA Goal Date	16 Dec 2016
Proprietary Name / Established (USAN) names	Tresiba/insulin degludec injection Ryzodeg 70/30/insulin degludec insulin aspart injection
Dosage forms / Strength	solution for subcutaneous injection U100 and U200 (Tresiba) U100 (Ryzodeg 70/30)
Proposed Indication	Indicated to improve glycemic control in pediatric patients with diabetes mellitus from 1 to (b) (4) (b) (4)
Recommended Action	Approval

Cross Discipline Team Leader Review

1. Introduction

This document contains the summary review written by the Division of Metabolism and Endocrinology Products (DMEP) Cross-Discipline Team Leader for Efficacy Supplement 002 for NDA 203313 (Ryzodeg 70/30; insulin degludec/insulin aspart) and Efficacy Supplement 003 for NDA 203314 (Tresiba; insulin degludec) each containing new clinical data to support an expanded indication for pediatric patients with diabetes mellitus ages 1 to (b) (4) (b) (4). The clinical studies submitted are also intended to fulfill Postmarketing Requirements required under the Pediatric Research Equity Act (PREA) for the two aforementioned NDAs. In these submissions the Applicant has also proposed language to update labeling to conform to the Pregnancy and Lactation Labeling Rule (PLLR).

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of the issues. Both Tresiba and Ryzodeg 70/30 are drug-device combination products, and the Center for Devices and Radiologic Health (CDRH) provided consultative review regarding the device constituent.

This memo references the following documents/sources:

Subject	Author	Date
Clinical Efficacy and Safety Review	Dr. Tania Condarco	4 Nov 2016
Statistical review (DBII)	Dr. Shuxian Sinks	10 Nov 2016
Clinical Pharmacology (OCP) review	Dr. Renu Singh	13 Nov 2016
DPMH labeling review	Dr. Jane Liedtka	14 Nov 2016
DMEPA labeling reviews	Dr. Sarah Vee	15 Aug, 12 Sep 2016
Product Quality review	Dr. Suong Tran	18 Feb 2016
CDRH consult review	Dr. Lana Shiu	14 Jul 2016
PeRC meeting minutes	PeRC members	9 Nov 2016
DBII=Division of Biometrics II; OCP=Office of Clinical Pharmacology; DPMH=Division of Pediatric and Maternal Health; DMEPA=Division of Medication Error Prevention and Analysis; CDRH=Center for Devices and Radiologic Health; PeRC=Pediatric Review Committee		

2. Background

Product Information

Tresiba

Tresiba (insulin degludec) is a long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. The product is intended for use as basal insulin. Tresiba is available in two different strengths: 100 units/mL (U-100) and 200 units/mL (U-200) both in a prefilled pen device (FlexTouch) to be administered by subcutaneous injection. U-200 and U-100 strengths are bridged to each other in adults based on both PK/PD and Phase 3 trials; therefore, if these supplements are approved, both of these formulations will be applicable for pediatrics.

Ryzodeg 70/30

Ryzodeg 70/30 is a mixture of insulin degludec, and insulin aspart (trade name NovoLog approved under NDA 020986 on 7 Jun 2000), a rapid-acting human insulin analog, indicated to improve glycemic control in adults with diabetes mellitus. Ryzodeg 70/30 contains 70% insulin degludec and 30% insulin aspart. Fixed-ratio insulin products such as Ryzodeg 70/30 allow for the basal and bolus insulin to be administered with one injection, but they limit individualized titration of basal and bolus dosing. Ryzodeg 70/30 is available in a 100 unit/mL (U-100) strength in the FlexTouch device to be administered by subcutaneous injection.

Regulatory History

Adult Approval

Both Tresiba and Ryzodeg 70/30 were approved 25 Sep 2015 after two review cycles. During review of the original NDA submissions a potential adverse cardiovascular (CV) signal was observed in the phase 3 development program, based upon a pre-specified meta-analysis to assess the CV risk associated with these drugs. For the resubmission the Sponsor provided the interim results from DEVOTE (a cardiovascular outcomes trial) which adequately addressed the deficiencies related to cardiovascular safety of insulin degludec and insulin degludec insulin aspart for approval.

PREA (Pediatric Research Equity Act)

Tresiba and Ryzodeg 70/30 were reviewed prior to approval in adults by the Pediatric Review Committee (PeRC) on June 27, 2012 and at the time the plan for pediatric patients was as follows:

> Waivers: T1DM <1yr; T2DM 0yrs 0mos – 16yrs 11mos
> Deferral: T1DM 1yr to 16yrs 11mos

The PeRC agreed to this plan with the caveat that the Division should reconsider the planned full waiver for T2DM and instead grant partial waiver and deferral (i.e., partial waiver for ageless than 10 and deferral for ages 10 to less than 18) similar to other products indicated for T2DM in pediatrics. The Division agreed because insulin degludec and perhaps insulin degludec insulin aspart have the potential to be used by T2DM pediatric patients and therefore,

labeling these products for pediatric T2DM would be appropriate. The Division amended the product specific waivers and deferrals as recommended by PeRC to the following:

Waivers: T1DM <1yr; T2DM 0yrs 0mos to < 10 yrs
Deferral: T1DM 1yr to 16yrs 11mos; T2DM 10 yrs to 17 yrs 11 mos

The pivotal safety and efficacy study for Tresiba is an open-label, 26-week, randomized, controlled trial comparing Tresiba 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. A separate trial in pediatric T2DM is not required as the aforementioned trial can be leveraged to support labeling Tresiba for T2DM pediatric patients, provided that there are no unexpected findings or problematic trial conduct issues.

The pivotal safety and efficacy study for Ryzodeg 70/30 is an open-label, 16-week, randomized, controlled 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). Similar to Tresiba, a separate trial in pediatric T2DM is not required as the aforementioned trial can be leveraged to support labeling Ryzodeg 70/30 for T2DM pediatric patients, provided that there are no unexpected findings or problematic trial conduct issues.

Please see Dr. Condarco's Clinical review for a detailed discussion of interaction between the Applicant and the Agency with regard to design elements and statistical considerations for the pediatric studies.

BPCA (Best Pharmaceuticals in Children Act)

The Sponsor submitted a Proposed Pediatric Study Request (PPSR) on December 2013 (prior to approval in adults) for a trial in children and adolescents with type 1 diabetes. A Written Request was not issued because the PPSR did not include individuals with type 2 diabetes, thereby omitting meaningful safety and efficacy information for an important segment of the pediatric population. The requirements for BPCA and PREA are distinct and, as discussed subsequently in this review, while the trials are adequate to support labeling Tresiba and Ryzodeg 70/30 for T2DM pediatric patients based on leveraging of data from T1DM to T2DM, under BPCA all potential indications should be studied.

3. CMC/Device

CMC

Please see Dr. Suong Tran's CMC review in DARRTS dated 18 Feb 2016. The CMC recommendation is for approval of both supplements because there is no change in the currently approved CMC information (including facility and device information), and the Environmental Assessment (EA) categorical exclusion request is acceptable.

Device

DMEPA completed the review for the supplements (see DARRTS 15 Aug 2016) and concluded that pediatric patients can safely and effectively use the Tresiba and Ryzodeg 70/30 U-100 FlexTouch prefilled pens. However, an information request (IR) was sent to the Applicant requesting that they submit a comprehensive risk analysis and justification or rationale that Tresiba *U-200* FlexTouch pen can be used safely and effectively in pediatric patients. DMEPA reviewed the response to IR and found it acceptable. I agree with the basis for DMEPA's conclusion (discussed below).

Ryzodeg 70/30 and Tresiba were approved as prefilled pens (FlexTouch); however, the Phase 3 trials for the pediatric indication were conducted with the NovoPen Junior and NovoPen Echo reusable pen injectors using the 3 mL cartridges of Ryzodeg 70/30 and Tresiba. These pens deliver insulin in 0.5 unit dose increments in contrast to the FlexTouch which delivers in 1 unit increments (and 2 unit increments for the U-200 Tresiba formulation). DMEPA noted that the overall design of the three pens is similar in terms of user interface and user steps with two additional exceptions other than dose increment: cartridge type (integrated for FlexTouch vs. replaceable for NovoPen Echo/Junior), and dose button extension (none for FlexTouch vs. extend for NovoPen Echo/Junior). Since the FlexTouch platform has an integrated cartridge, the step to insert a cartridge is eliminated compared to NovoPen Echo/Junior thereby eliminating the possibility of a use error associated with this step. In addition the FlexTouch may be easier to use for pediatric patients who would, in general, have smaller hands compared to adult patients, since the dose button does not extend. DMEPA also stated that Applicant's rationale that adult use data can be extrapolated to pediatric use is reasonable since other insulins (e.g. Novolog, Levemir) that are manufactured by the Applicant with the FlexTouch prefilled pen platform are indicated for use by both adults and children. In addition, the Applicant submitted a Human factors study for the original Ryzodeg 70/30 and Tresiba NDAs that included 15 pediatric users (all trained, participated in U-100 study) with no use errors reported.

Because of the difference in dose increment between the device used in the pediatric Phase 3 studies and the U.S. marketed pen, Dr. Condarco is recommending that a limitation of use for pediatric patients be included in Tresiba and Ryzodeg 70/30 labeling as follows: *Not recommended for pediatric patients requiring less than 5 units daily* because in the clinical trials, subjects using less than 5 units would be experiencing large percentage changes in dose with a 1 unit incremental change which could in theory result in a higher risk of hyper- or hypoglycemia. Also, dosing instructions in the trials required 0.5 unit dose changes if subjects were using less than 5 units daily. I agree with Dr. Condarco's recommendation. Due to lack of availability of a delivery device that delivers in 0.5 unit increments, patients using less than 5 units daily should not use these products.

A CDRH consult was requested to review the device constituent of the Tresiba and Ryzodeg 70/30 combination products. Refer to Lana Shiu, M.D.'s review in DARRTS dated 14 Jul 2016. Performance aspects of the delivery device, the PDS290/FlexTouch injector, were reviewed during the original NDA reviews for these two products. As such there are no approvability issues from an engineering standpoint for the current supplements.

4. Nonclinical Pharmacology/Toxicology

Nonclinical Pharmacology/Toxicology data were reviewed during the original NDA review, and there is no new nonclinical Pharmacology/Toxicology information in the resubmission. Juvenile toxicity studies were not necessary based on the already available animal data with insulin degludec and insulin aspart.

The Nonclinical Pharmacology/Toxicology review team has reviewed and agreed upon the revised labeling language to be compliant with PLLR (along with DPMH).

5. Clinical Pharmacology/Biopharmaceutics

Dr. Renu Singh recommends approval of these supplements. See her review in DARRTS dated 13 Nov 2016.

Insulin and its analogs lower blood glucose by stimulating peripheral glucose uptake, especially by skeletal muscle and fat, and by inhibiting hepatic glucose production. IDeg is a long-acting insulin analog. The protracted time action profile of IDeg is predominantly due to its delayed absorption from the subcutaneous tissue to the systemic circulation and to a lesser extent due to binding of insulin-degludec to circulating albumin. IAsp is a rapid-acting insulin analog. Once injected into the subcutaneous tissue the IAsp hexamers immediately form monomers which are absorbed into the capillaries. The rapid absorption characteristics of IAsp are preserved in IDegAsp.

The clinical pharmacology program consisted of:

- A single-dose Phase 1 study of IDeg and insulin glargine in children/adolescents/adults with T1DM (Trial 1995)
- A single-dose Phase 1 study of IDegAsp in children/adolescents/adults with T1DM (Trial 1982)
- Sparse PK and PD measurements during Phase 3 trials 3561 and 3816. PK/PD modelling analysis to develop a population PK model for IDeg in children younger than 6 years and conduct an exposure-response analysis focusing on this age group. IDeg PK data from Trials 1982, 1995, and 3561 were combined for the population PK analysis and data from Trial 3561 were used for the exposure-response analysis.

The results of single dose PK Trials 1995 and 1982 were reviewed at the time of original NDA submissions for IDeg and IDegAsp, respectively. Bioanalytical methods were determined to be acceptable. Overall, data show higher total and peak exposures of IDeg (when administered alone and as IDegAsp) for and IAsp (when administered as IDegAsp) for children and adolescents as compared to adults. Between-subject variability is also higher for children and somewhat for adolescents. Because insulin is dosed individually based on glycemic targets, the PK differences between pediatric patients and adult patients are not necessarily of clinical

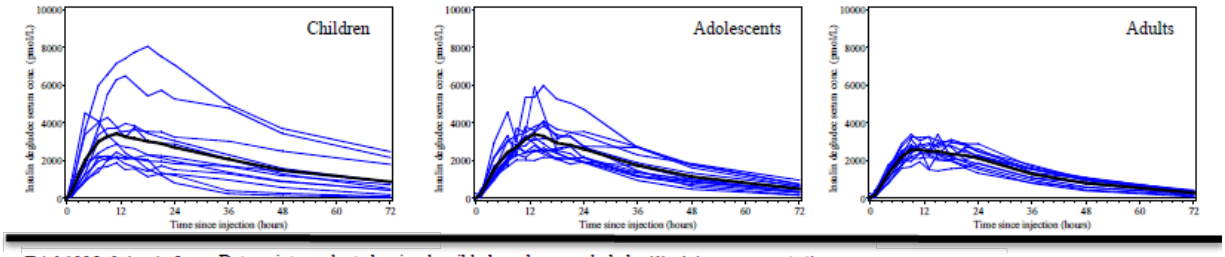
concern. However, as will be discussed later in this review, some differences in the dosing and administration regimens applied in the Phase 3 pediatric trials warrant different dosing and administration instructions in labeling for pediatrics.

Trial 1995

Trial 1995 was a randomized, double-blind, two-period cross-over study comparing PK of a single dose of 0.4 units/kg IDeg with a single dose of 0.4 units/kg insulin glargine in children (6-11 years), adolescents (12-17 years) and adults (18-65 years). This trial was reviewed in the original NDA for IDeg.

Total and peak exposures of IDeg were higher in children and adolescents than in adults, but differences were not consistently statistical significant. The magnitude of increase in AUC is modest. However, the OCP reviewer stated that the difference may have been lost in the greater variability of IDeg PK observed in children. PK behavior of IDeg is less predictable or highly variable in children (73% and 51% CV for AUC0-inf and Cmax, respectively) than that in adults (21% and 17% CV for AUC0-inf and Cmax, respectively). Median time to maximum concentration (tmax) was within the same range (11-15 hours) across age groups. The prolonged PK profile of IDeg in adults was preserved in children and adolescents.

Study 1995- mean and compiled individual concentration-time profiles for IDeg after single dose in children (6-11 years), adolescents (12-17 years), and adults (18-65 years)



Trial 1995: 0.4 units/kg Data points evaluated as implausible have been excluded. Black line represents the mean.
Horizontal dashed line represents the lower limit of quantification for IDeg (20 pmol/L).

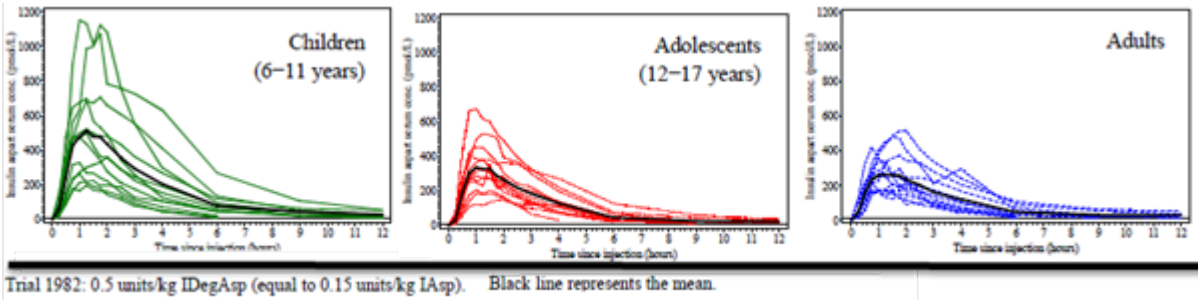
Trial 1982

Trial 1982 was an open-label single dose PK/PD study of the administration of 0.5 units/kg IDegAsp. IDeg and IAsp exposures were measured in in children (6-11 years), adolescents (12-17 years) and adults (18-65 years). This trial was reviewed in the original NDA for IDegAsp.

Consistent with Trial 1995, IDeg single dose exposure was 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], Cmax ratio (children/adults) 1.38 [95% CI: 1.09-1.76], Cmax ratio (adolescents/adults) 1.16 [95% CI: 0.95-1.42]). However, higher variability was again observed in the pediatric population as compared to the adults in the trial. The prolonged PK profile of IDeg from IDegAsp in adults was preserved in children and adolescents.

For IAsp, total exposure and peak concentration of IAsp in IDegAsp were statistically significantly higher in children than in adults, but more similar in adolescents and adults. Overall the individual variability was higher in children (6-11 years) than in adolescents or adults.

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



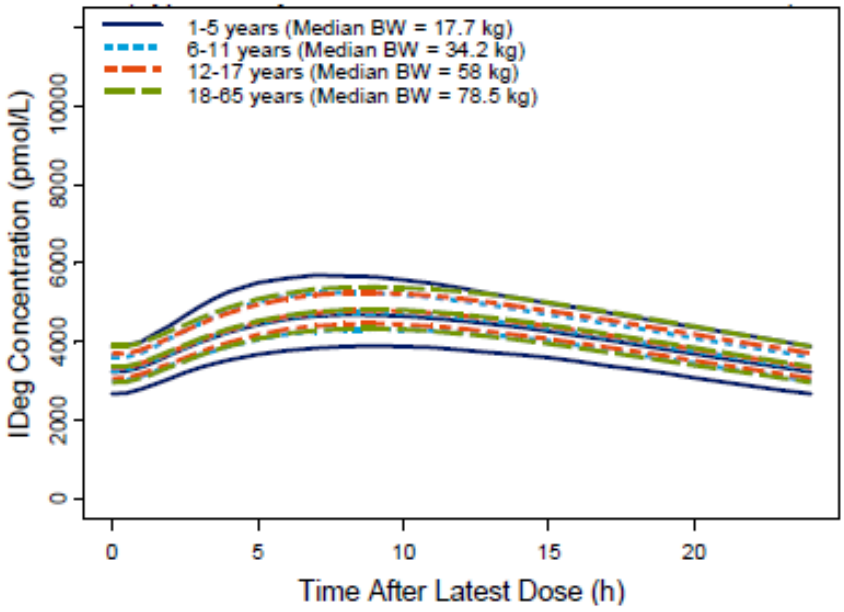
Trial 1982: 0.5 units/kg IDegAsp (equal to 0.15 units/kg IAsp). Black line represents the mean.
Horizontal dashed line represents the lower limit of quantification for IAsp (10 pmol/L).

In the standardized meal challenge part of the study, mean plasma glucose profiles were evaluated by age groups after administration of IDegAsp and a standard meal. The glucose lowering effect of IDegAsp after a standard meal was comparable across age groups.

Population PK and modelling

The population PK analysis showed that the IDeg concentration-time profile at steady state in children 1-5 years was similar to the concentration-time profiles in children 6-11 years, adolescents (12-17 years) and adults (18-65 years) when IDeg is dosed per body weight (kg). Body weight was the most important covariate. Age group was highly correlated with body weight, but was not significant by itself when body weight was included; age was also not a significant covariate in the final exposure-response model (data shown in OCP review and Dr. Condarco's clinical review).

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



Data are medians with 95% CI obtained from the final population PK model.
BW: Body weight

6. Clinical Microbiology

There is no new Clinical Microbiology information in the resubmission.

7. Clinical/Statistical- Efficacy

Drs. Sinks (Biostatistics) and Condarco (Clinical) have reviewed the submissions in detail, and both recommend approval of these two supplements. Please see their reviews in DARRTS dated 10 Nov 2016 and 4 Nov 2016, respectively. This section summarizes the efficacy review findings. There was one pivotal trial submitted to each NDA. Each was a randomized, open-label, parallel-group, active-controlled study.

Pivotal Phase 3 Trials Submitted				
Trial	**Subjects**	**Duration**	**Treatment and Control**	**Design**
Tresiba – Trial 3561	Ages 1 to <18 with T1DM HbA1c ≤ 11%, using total daily insulin ≤ 2.0 U/kg (any regimen) for at least 3 months prior to Visit 1.	26 weeks + 26 week extension	IDeg + IAsp vs. IDet + IAsp	Randomized 1:1, Open-label NI
Ryzodeg 70/30 – Trial 3816		16 weeks	Ryzodeg 70/30 + IAsp vs. IDet + IAsp	
IDeg=insulin degludec; IAsp=insulin aspart; NI=noninferiority hypothesis test				

Tresiba – Trial 3561

Trial 3561 evaluated the safety and efficacy of Tresiba compared with insulin detemir (IDet) in combination with insulin aspart in children and adolescents with T1DM. Pediatric subjects ages 1 to less than 18 were randomized in 1:1 ratio to IDeg + IAsp or IDet + IAsp both as basal-bolus insulin therapy. Eligible subjects were diagnosed with T1DM (based on clinical judgment and supported by laboratory analysis as per local guidelines), HbA1c ≤ 11%, using total daily insulin ≤ 2.0 U/kg (any regimen) for at least 3 months prior to Visit 1. No oral anti-diabetic drugs (OADs) were allowed. Known hypoglycemic unawareness or recurrent severe hypoglycemic events as judged by the Investigator was an exclusion criterion. The trial was multinational and included 72 sites in 12 countries.

Insulin dosing and titration– Trial 3561

Dosing regimen– *Trial 3561*

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

IDeg was administered via a durable pen device and supplied in the Penfill 3mL cartridge. This product presentation is not marketed in the U.S. (In the U.S. Tresiba is approved with a disposable FlexTouch pen device). IDet was also given via the durable pen product presentation in this trial. These devices permit 0.5 Unit dosing increments.

Starting dose– *Trial 3561*

After randomization subjects were switched to their assigned treatment, and based on the Investigators choice, used a basal bolus ratio of either 50:50 or 70:30. There were no specific recommendations regarding adjustments of the total insulin doses upon switching to trial product (i.e. there was no decrease in dose recommended). Dr. Condarco asked the Applicant to justify the starting dose in the pediatric trials, since the instructions for the starting dose in the approved PI for patients already on insulin are to "Start TRESIBA at the same unit dose as the total daily long or intermediate-acting insulin unit dose." In the trial, only 1/3 of patients started IDeg at the same unit dose as the pre-randomization total daily basal insulin dose, whereas a majority had an increase of 0-5% in IDeg starting dose at baseline in relation to the screening basal insulin dose. It is unclear if the observed higher rate of hypoglycemia early (first month) in this trial could be related to the starting dose of basal insulin. Dr. Condarco recommends modifying the Dosage and Administration instructions in the product label for pediatrics to decrease the dose by 20% when initiating therapy with IDeg. As discussed later in this review, a dose reduction of 20% was used in the Ryzodeg 70/30 pediatric trial, which did not show a similar early bump in hypoglycemia events. For simplicity/parity it would make sense to have the same dose initiation instructions for Tresiba and Ryzodeg 70/30. Further, a decrease in dose with expedient titration to glycemic target is not expected to compromise the clinical outcomes of patients. For these reasons, I agree with Dr. Condarco's recommendation.

Titration– *Trial 3561*

Titration of basal insulins was based on an algorithm as shown below based on a fasting glycemic goal of 90-145 mg/dL. Note that titration was done by ½ units for doses less than 5 units. Investigators were to contact subjects 'at least once weekly' for insulin dose adjustments. A blinded titration committee provided oversight to help ensure adequate titration.

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

Titration of bolus IAsp was done weekly using the algorithm below or by carbohydrate counting. Carbohydrate counting was allowed for subjects and care takers who had prior experience with this method. Please see Dr. Condarco's review for details of the carbohydrate counting methodology.

Bolus Insulin Titration Algorithm		
Current bolus dose	**≤ 5U**	**> 5U**

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

Study results– Trial 3561

Subject disposition– *Trial 3561*

The table below from Dr. Sinks' review shows subject disposition for Trial 3561. The percentage of missing data at week 26 was about 5% with the IDet group having more missing data compared with the IDeg group. One subject in IDet group was withdrawn before being exposed to the medication. Four subjects in IDeg group withdrew due to fulfillment of withdrawal criteria (i.e. subject consent). 2 subjects in IDet group withdrew due to adverse event, and 7 subjects withdrew due to fulfillment of withdrawal criteria, and 2 subjects withdrew due to other reasons. Dr. Condarco reviewed the reasons for dropout in detail, and did not identify any problems with coding. She noted no clustering of dropouts among any age subgroup (i.e. 1-5, 6-11, or 12-17 years).

	IDeg	**IDet**	**Total**
Randomized	174	176	350
Exposed	174	175	349
Withdrawn at/after randomization			
Adverse Event	0	2	2
Withdrawal Criteria	4	7	11
Other	0	2	2
Completed	170	165	335

Source: FDA statistical review

Subject demographics and baseline characteristics– *Trial 3561*

The trial population was 44.6% female, mean age was 10 years, 24.3% were aged 1-5 years, 39.4% were aged 6-11 years, and 36.3% were aged 12-17 years. Regarding geographic region, 52.0% were from Europe, 28.9% were from North America, and 15.7% were from Japan. The majority (74.6%) were White and non-Hispanic (97.1%), and 15.7% were Asian non-Indian. The mean HbA1c was 8.1%. Demographic and baseline characteristics were reasonably balanced across treatment groups. A sufficient number of subjects were enrolled in each age subgroup. Mean duration of diabetes was 4 years. The majority of subjects (335, 95.7%) were using basal/bolus therapy; 5 (1.4%) were using basal/bolus + premix; 15 (4.3%) were using 'other' regimens, i.e. basal, bolus, premix alone or premix in combination. IDet was the most

common basal insulin used in about 46% of patients, and insulin glargine was used in about 40% of patients.

Analysis of the primary endpoint– *Trial 3561*

Methods

The primary efficacy endpoint was change from baseline in HbA1c after 26 weeks of treatment. The 26-week extension period was intended to evaluate longer-term safety. Analyses of efficacy endpoints were performed on the full analysis set i.e. included all randomized subjects. Treatment difference of treatment group and active comparator was estimated based on an ITT population, including all randomized subjects regardless of adherence to treatment or use rescue therapy.

The applicant used an analysis of variance (ANCOVA) to assess the efficacy of IDeg compared with IDet. The ANCOVA model included treatment, sex, region and age group as fixed factors and baseline HbA1c as covariate. Missing data were imputed using last observation carried forward (LOCF) approach.

The hypothesis test (for both studies) was non-inferiority. The applicant did not provide justifications for the choice of the non-inferiority margins 0.4% in both studies. An IR was sent to the applicant on 27 September 2016 and requested that the applicant provide justification for the choice of 0.4% margin. The Applicant essentially justified the margin based on precedent as non-inferiority margin of 0.4% has been used in other trials comparing insulin that have been part of NDA submissions. I agree with the Biostatistics reviewer that this is acceptable.

Results

In the Applicant's analysis, the LS mean HbA1c at baseline was 7.95 in the IDeg group and 7.80 in the IDet group. The LS mean change from baseline was -0.15% in the IDeg group and -0.30% in the IDet group with an estimated treatment difference of 0.15%, 95% CI [-0.03; 0.32]. The non-inferiority of IDeg versus IDet was established in the Applicant's analysis, as the upper limit of the 95% CIs was below the prespecified non-inferiority margin 0.4%. The estimated treatment effect of IDeg was, however, numerically less than that of IDet.

Trial 3561 - HbA1c (%) after 26 weeks – Applicant's primary analysis - FAS

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

FAS: full analysis set, CI: Confidence interval, SE: Standard error of the mean, *=LS means. The response and change from baseline in the response after 26 weeks of

treatment is analyzed using an ANOVA method with treatment, sex, region and age group as fixed effects and baseline response as a covariate. Missing data is imputed using last observation carried forward.
Source: Adapted from Dr. Condarco's review

Adequacy of insulin dosing

In a non-inferiority trial, adequate dosing of comparator is important for trial interpretation, i.e. the validity of trial results assumes that the comparator dosing was adequate and that the within-trial comparator effect size was similar to the historical effect size for trials similarly designed.

Dr. Condarco's review discusses insulin dosing in detail and by age subgroup. She found no clinically important differences in these assessments by age subgroup; therefore, the trial population as a whole is discussed here.

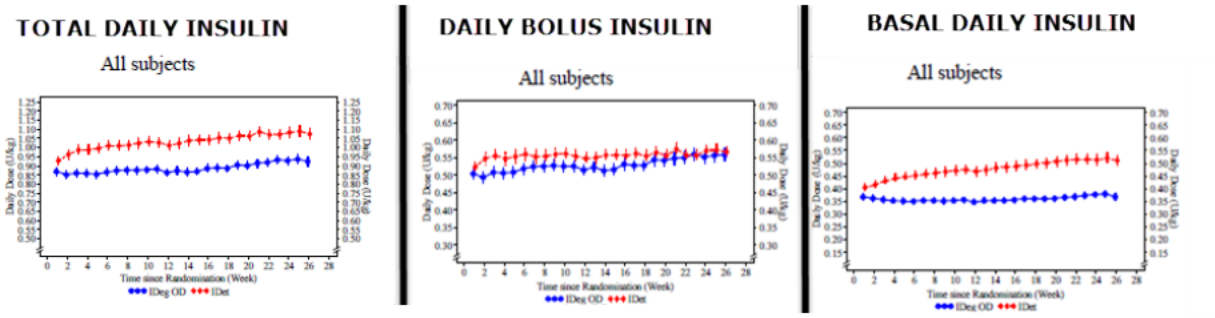
It appears that minimal titration of both bolus and basal insulin occurred in the IDeg group (mean of 1 unit) while the IDet group increased basal insulin by a mean of 6 units. The mean basal insulin dose was similar at baseline between treatment arms; after 26 weeks the mean basal insulin dose in the IDeg group was 16 units (0.37 units/kg) and in the IDet group was 22 units (0.51 units/kg). Bolus insulin dosing was similar between treatment arms, but increased slightly from baseline to Week 26; therefore, some of the reduction in HbA1c is likely due to the bolus insulin (rather than the basal insulin). It is difficult to discern the contribution of the basal insulin specifically in the IDeg group because of the lack of dose increase. As discussed above the average baseline dose of IDeg increased by 0-5% as compared to the screening basal insulin dose. This increase in the baseline IDeg dose could have been the cause of the apparent lack of titration of basal insulin in the IDeg arm, but yet still a reduction in HbA1c (albeit modest) of -0.15%.

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

	IDeg			**IDet**		
	Baseline	Week 26	Week 52	Baseline	Week 26	Week 52*
Basal	15 U 0.37 U/kg	16 U 0.37 U/kg	17 U 0.38	16 U 0.41 U/kg	22 U 0.51 U/kg	24 U 0.55 U/kg
Bolus	20 U 0.5 U/kg	23 U 0.56 U/kg	24 U 0.55 U/kg	20 U 0.52 U/kg	22 U 0.57 U/kg	24 U 0.58 U/kg
Total	35 U 0.87 U/kg	39 U 0.93 U/kg	41 U 0.93 U/kg	36 U 0.93 U/kg	44 U 1.07 U/kg	48 U 1.13 U/kg

source: adapted from Dr. Condarco's review
*After 52 weeks of treatment, more than 60% of subjects in the insulin detemir arm were dosed BID.

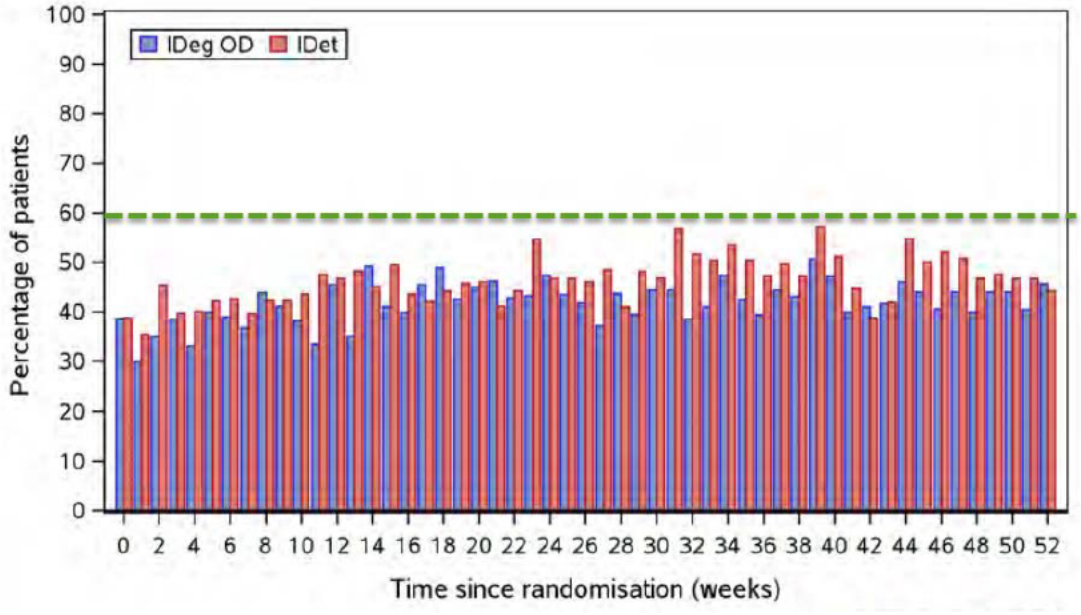
Trial 3561 – Total, daily bolus, and basal daily insulin doses (actual) in units/kg body weight by treatment week–safety analysis set



Source: Figure 18 in Dr. Condarco's review

Since the trial was a treat-to-target design, dosing was based on reaching self-measured fasting plasma glucose (SMPG) goals. Dr. Condarco shows in Figure 19 in her review (reproduced here) that roughly 40 to 60% of subjects reached SMPG breakfast target of 90-145 mg/dL. I agree with Dr. Condarco that there is no clear evidence of bias favoring one treatment group over the other for the 26-week efficacy endpoint, although it appears that a slightly higher proportion of patients randomized to IDet reached titration goals than patients randomized to IDeg particularly in the extension phase of the trial. More notable is that the proportion meeting SMPG goals by the end of the trial doesn't appear to have increased substantially from baseline. It should be noted that the finding of 40 to 60% reaching SMPG goals is not necessarily the major concern here, as this range is consistent with other active comparator insulin trials in adults recently reviewed by the Division. The concern is that there was not much movement from baseline to 26 weeks *in either group* calling into question adequacy of dosing of the active comparator in the NI design.

Trial 3561 - Proportion of subjects reaching SMPG pre-breakfast target of 90-145 mg/dL by visit – full analysis set



Source: Figure 18 in Dr. Condarco's review

Figure 20 in Dr. Condarco's review shows that the prescribed dose, actual dose, and titration algorithm dose were virtually identical to each other throughout the trial suggesting good treatment adherence to the algorithm by Investigators, and by study subjects to prescribed dosing. In sum, the reason for the lack of significant dose increases throughout the trial remains uncertain, but is likely largely due to the 'switch study' design in which subjects are switched from pretrial insulin doses with no dose reduction.

Overall, I believe the trial results still provide adequate evidence of effectiveness of IDeg in pediatric patients for the following reasons. The results of Trial 3816 (Ryzodeg 70/30 trial) provide supportive evidence of the effectiveness of IDeg; there is no physiologic reason or Clinical Pharmacology data to expect that IDeg would not be effective in children; the IDet comparator group used overall more insulin than did the IDeg group; given the natural history of type 1 diabetes if IDeg were not reasonably effective the HbA1c would surely increase throughout the trial, and the bolus insulin administered is not expected to be sufficient to lower HbA1c without contribution of IDeg.

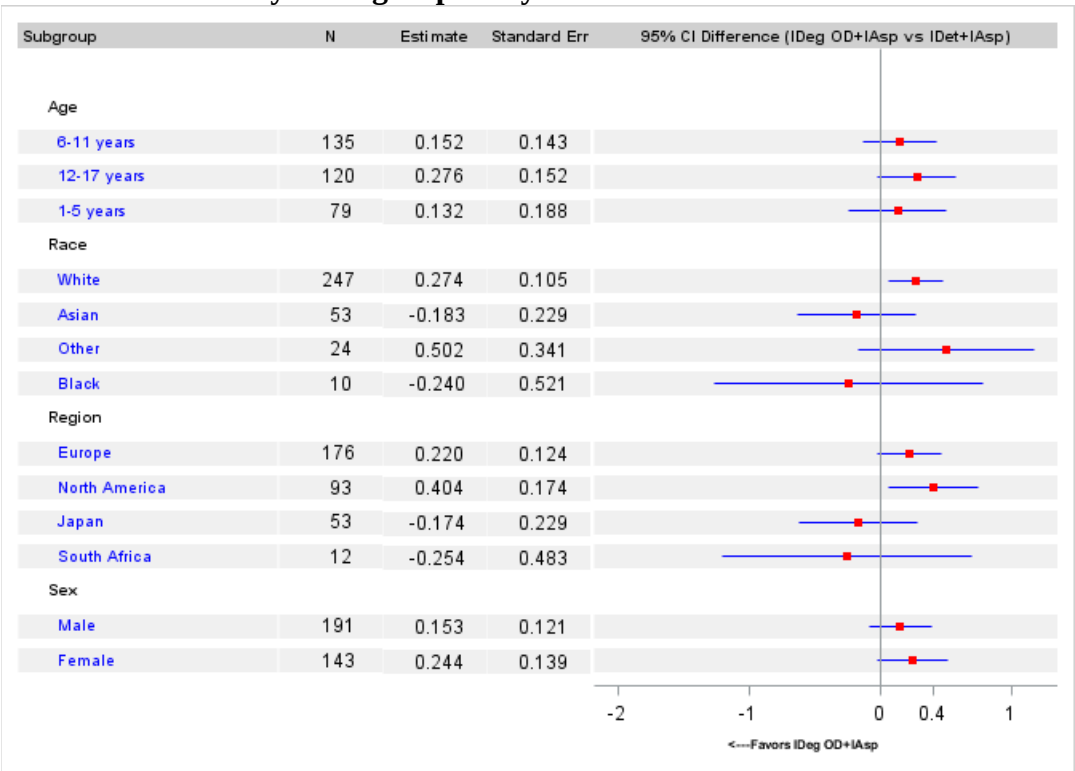
I requested that Dr. Sinks preform a subgroup analysis of efficacy results by baseline HbA1c (≤8% or >8%). For this exploratory analysis, she used an ANCOVA model and did not consider missing data in the analysis. The results, shown below, suggest that with a sufficiently high baseline HbA1c, subjects treated with IDeg experienced a clinically meaningful reduction in HbA1c that was similar to the comparator.

				95% Confidence interval	
Treatment group	**Baseline HbA1c**	**Estimate**	**Standard Error**	**Lower**	**Upper**
IDeg	<=8	0.2416	0.1188	0.007929	0.4752
IDeg	**>8**	-0.5495	0.1058	-0.7577	-0.3413
IDet	<=8	-0.03235	0.1050	-0.2388	0.1741
IDet	**>8**	-0.6408	0.1173	-0.8715	-0.4100

Subgroup analysis

Due to the limitations associated with multiplicity and low power, subgroup analysis results were considered as supportive and exploratory. No significant interaction between defined subgroups and treatment were observed.

Trial 3561 – Efficacy – Subgroup analyses



Source: Dr. Sinks' statistical review

Missing data considerations– *Trial 3561*

The Applicant used multiple imputation approach to assess the impact of missing data on efficacy conclusions. Methods used included Jump to Reference, Copy to Reference, and Tipping Point. Neither study was designed to continuing collect data from subject discontinued treatment early; a "retrieved dropouts" approach for handling missing data was not applicable.

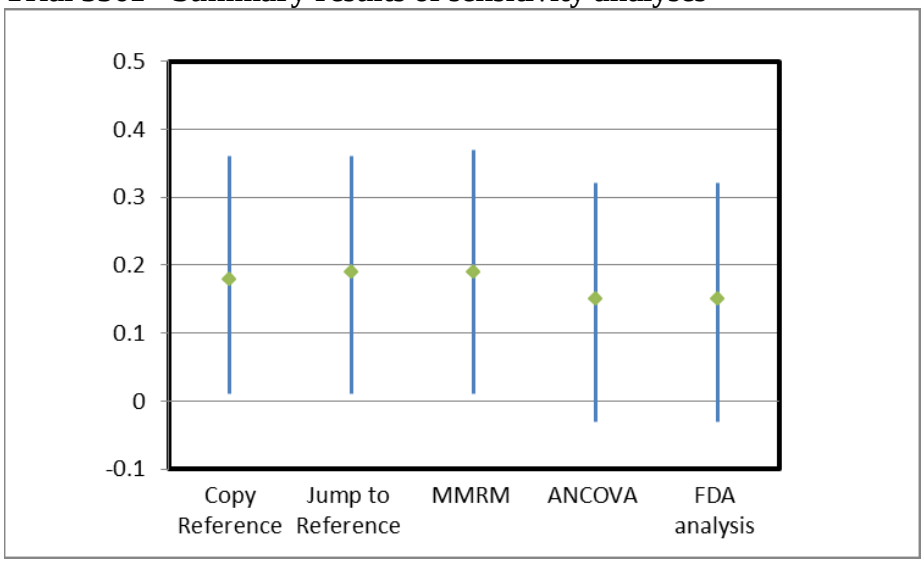
Jump to Reference assumes that withdrawn subjects in the IDeg group are 'switched' to the IDet group. Copy to Reference assumes that withdrawn subjects in the IDeg group are the same as subjects in the IDet group during the entire trial. For both methods, the imputed value for the IDeg group is penalized by adding the NI margin, whereas the imputed value for the IDet group is not penalized. The applicant also performed a tipping point analysis to explore the sensitivity of the conclusion supported by the efficacy data. Copy reference method was utilized to impute the missing data when conducting the tipping point analysis.

The FDA statistician additionally conducted a 'Return to Baseline' analysis; subjects with missing data known or believed to have discontinued protocol therapy were assumed to have a washout ("return to baseline") of any potential treatment effect.

-on the control arm impute their week 16 or 26 HbA1c measurement equal to their baseline measurement plus an error and
-on the experimental arms impute their week 16 or 26 HbA1c measurement equal to their baseline measurement plus 0.4% plus an error.

The conclusion of non-inferiority is supported by all sensitivity analyses. Dr. Sinks recommends that the FDA analysis should be used for labeling Section 14 of the PI.

Trial 3561 - Summary results of sensitivity analyses



Source: FDA statistical review

Secondary endpoints– *Trial 3561*

There were no secondary efficacy endpoints that were adjusted for multiplicity. In the trial, analysis of secondary endpoints supported the conclusion of effectiveness of IDeg.

HbA1c difference at 52 weeks

The adjusted mean change from baseline in HbA1c was -0.2 for IDeg and -0.19 for IDet. For the full analysis set population with last-observation-carried-forward, the adjusted mean difference (IDeg-IDet) was -0.01% with a corresponding 95% confidence interval of (-0.2; 0.19). At 52 weeks, the proportion of missing data was 13.2% for IDeg and 30.7% for IDet.

Fasting plasma glucose (FPG)

Based on the non-adjusted data, at Week 26 the IDeg group had a mean decrease of -12.1 mg/dL in FPG from a baseline of 162 mg/dL to Week 26 value of 149.4 mg/dL; the IDet group had an increase of 9 mg/dL in FPG from a baseline mean of 151.2 mg/dL to Week 26 value of 160.2 mg/dL. At Week 52, the IDeg group had a mean decrease of 23.22 mg/dL in FPG from a baseline of 162 mg/dL to 140.4 mg/dL; while for the IDet group there was a mean increase of 19.8 mg/dL in FPG from a baseline of 151.2 mg/dL to 171 mg/dL.

Dr. Sinks performed an MMRM analysis of FPG at Week 26 with treatment, sex, and region, age group, visit, interaction between visit and treatment as fixed effects and baseline response

as a covariate. The estimated mean change from baseline in FPG was -3.9 mg/dL for the IDeg group and was 1.3 mg/dL for the IDet group. The estimated treatment difference between IDeg and IDet and corresponding 95% confidence interval was -5.2 mg/dL 95%CI (-28.6 - 18.2).

Ryzodeg 70/30 – Trial 3816

Trial 3816 evaluated the safety and efficacy of Ryzodeg 70/30 compared with IDet in combination with insulin aspart in children and adolescents with T1DM. Eligibility criteria were similar to Trial 3561.

Insulin dosing and Titration – Trial 3816

Dosing regimen – *Trial 3816*

Subjects were randomized to receive IDegAsp once daily (QD) with one of the main meals + meal time IAsp or IDet once daily or twice daily (BID) + mealtime IAsp. IAsp was to be given with the main meals, 2-4 times daily in subjects randomized to IDet and 1-3 times daily for subjects randomized to IDegAsp. Dr. Condarco notes that the approved Ryzodeg 70/30 dosing regimen for adults is different from the dosing used in the Phase 3 pediatric trial in that the approved Ryzodeg 70/30 allows for once or twice daily administration. Therefore, a once daily dosing regimen for pediatrics is recommended for labeling.

Starting dose– *Trial 3816*

At randomization (Visit 2), the Investigator was to *reduce* the total daily insulin dose by 20 percent and adjust the basal-to bolus ratio to either 50:50 or 70:30. As noted by Dr. Condarco investigators did not consistently apply a 20% reduction in the pre-trial total insulin dose at randomization, and there was large variation in the magnitude of change applied. For subjects randomized to IDegAsp, a reduction in total insulin dose of approximately 20% (i.e. from 15% to 25%) was implemented for 22% of subjects. A dose reduction of any magnitude was implemented for 73% of subjects.

While I agree with the Applicant's assertion that the PK, PD and exposure−response results indicate no need for age-specific considerations when developing dosing recommendations for IDegAsp for children and adolescents aged 1 to less than 18 years, the 20% reduction in total insulin dose used in the Phase 3 study 3816 appeared to be more successful at mitigating the risk of early hypoglycemia as compared to the IDeg trial 3561. Dosing and administration language in the Ryzodeg 70/30 label, therefore, should recommend a 20% total daily insulin dose reduction.

Titration– *Trial 3816*

Insulin titration also used the same algorithms (Ryzodeg 70/30 was titrated according to the 'basal insulin titration algorithm').

Study results– Trial 3816

Subject disposition– *Trial 3816*

The table below from Dr. Sinks' review shows subject disposition for Trial 3816. The percentage of missing data was 6.7% at week 16 with the IDet group having more missing data compared with IDegAsp group. A majority of subjects withdrawn from the study were due to withdrew consent. One subject in the IDegAsp group withdrew due to adverse event. One subject in the IDegAsp group withdrew due to non-compliance with the protocol. Two subjects in the IDet group withdrew due to other reasons. Dr. Condarco reviewed the reasons for dropout in detail, and did not identify any problems with coding. She noted no clustering of dropouts among any age subgroup (i.e. 1-5, 6-11, or 12-17 years).

	IDegAsp	IDet	Total
Randomized	182	180	362
Exposed	181	179	360
Withdrawn at/after randomization	8	12	20
Adverse Event	1	0	1
Non-compliance with Protocol	1	0	1
Withdrawal Criteria	6	10	16
Other	0	2	2
Completed	174	168	342

Source: FDA statistical review

Subject demographics and baseline characteristics– *Trial 3816*

The trial population was 51.7% female, mean age was 11 years, 22.7% were aged 1-5 years, 33.7% were aged 6-11 years, and 43.6% were aged 12-17 years. Regarding geographic region, 60% were from Europe and 34.5% were from North America. The majority (93.1%) were White and non-Hispanic (92.3%). The mean HbA1c was 8.1%. Demographic and baseline characteristics were reasonably balanced across treatment groups. A sufficient number of subjects were enrolled in each age subgroup. Mean duration of diabetes was 4.1 years, and the majority of subjects (92%) were using basal/bolus therapy; 5 (1.4%) were using basal/bolus + premix; 24 (6.6%) were using 'other' regimens, i.e. basal, bolus, premix alone or premix in combination.

Analysis of the primary endpoint– *Trial 3816*

Methods

The primary efficacy endpoint was change from baseline in HbA1c after 16 weeks of treatment. Similar to trial 3561, analyses of efficacy endpoints were performed on the full analysis set i.e. included all randomized subjects, and treatment difference of treatment group and active comparator was estimated based on an ITT population, including all randomized subjects regardless of adherence to treatment or use rescue therapy.

The applicant used a mixed effect model for repeated measure (MMRM) to assess the efficacy of IDegAsp compared with IDet. The MMRM model included treatment, sex, region, age group and visits as factors and baseline as covariate, and interactions between visits and all factors and covariate. An unstructured covariance matrix was utilized for model fitting.

The hypothesis test (for both studies) was non-inferiority (NI). See discussion above regarding the selection of the NI margin.

Results

In the Applicant's analysis, the LS mean HbA1c at baseline was 7.79 in the IDegAsp group and 7.83 in the IDet group. The LS mean change from baseline was -0.27% in the IDegAsp group and -0.23% in the IDet group with an estimated treatment difference of -0.04%, 95% CI [-0.23; 0.15]. The non-inferiority of IDegAsp versus IDet was established in the Applicant's analysis, as the upper limit of the 95% CIs was below the prespecified non-inferiority margin 0.4%. Superiority of IDegAsp over IDet was not confirmed.

Trial 3816 – HbA1c after 16 weeks of treatment – Applicant's primary analysis - FAS				
	FAS	estimate	SE	95% CI
HbA1c*				
IDegAsp	182	7.79	0.07	
IDet	180	7.83	0.07	
Change from baseline*				
IDegAsp	182	-0.27	0.07	
IDet	180	-0.23	0.07	
Treatment difference				

IDegAsp-IDet		-0.04		[-0.23; 0.15]

FAS: Full analysis set, N: number of sugjects contributing to the analysis, CI: confidence interval, SE: Standard error of the mean, *=LS Means. All observed HbA1c measurements available post-randomization at the scheduled measurement times is analyzied with a MMRM with an unstructured covariance matrix. The model includes treatment, sex, region, age-group and visit as factors and baseline HbA1c as covariate. Interactions between visit and all factors and covariates are also included in the model.
Source: adapted from Dr. Condarco's review, table 22

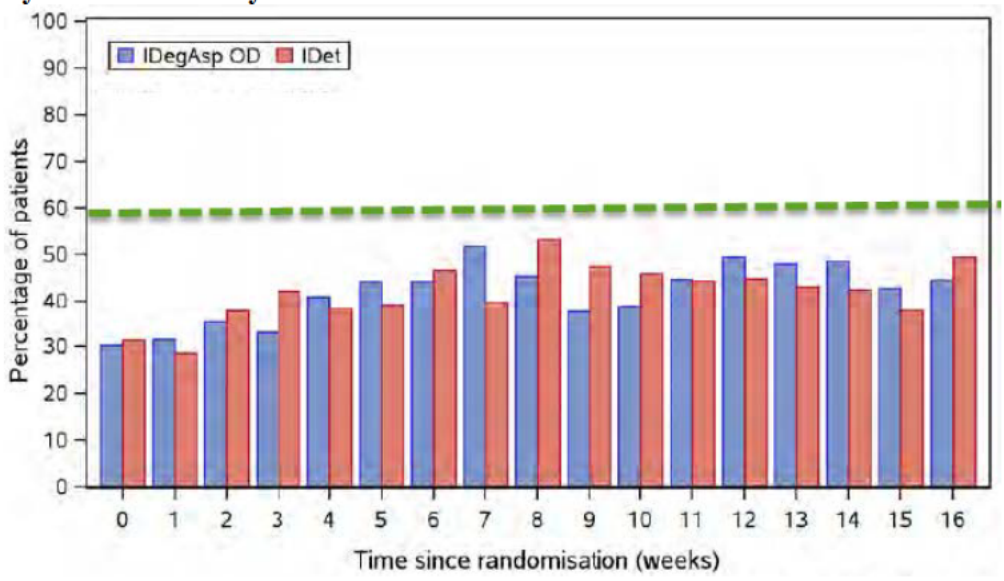
Adequacy of insulin dosing

Similar to Trial 3561, Dr. Condarco found no clinically important differences in these assessments by age subgroup; therefore, the trial population as a whole is discussed here. In contrast to Trial 3561, it appears a dose increase for basal insulin was observed from baseline to Week 16 in both treatment groups. Recall that in this trial the baseline dose was reduced by 20% from the pre-trial screening insulin dose. The IDet group used overall more insulin per kg of body weight than did the IDegAsp group. Most of the difference in the total insulin dose was due to the basal insulin, validating the conclusion of effectiveness of IDegAsp.

Trial 3816 – Insulin dose at baseline and at week 16				
	IDegAsp		**IDet***	
	Baseline	Week 16	Baseline	Week 16
Basal	13 U 0.31 U/kg	16 U 0.36 U/kg	17 U 0.38 U/kg	22 U 0.49 U/kg
Bolus	20 U 0.49 U/kg	22 U 0.52 U/kg	23 U 0.52 U/kg	23 U 0.52 U/kg
Total	33 U 0.79 U/kg	38 U 0.88 U/kg	40 U 0.89 U/kg	46 U 1.01 U/kg
*53.9% of patients randomized to IDet were taking IDet BID at week 16. Source: adapted from Table 23 in Dr. Condarco's review				

Analysis of the proportion of subjects reaching SMPG pre-breakfast targets shows an increase during the first 8 weeks of the trial with stabilization from Week 8 to Week 16 with about half the subjects reaching the glycemic target. The prescribed dose, actual dose, and titration algorithm dose were virtually identical to each other throughout the trial suggesting good treatment adherence to the algorithm by Investigators, and by study subjects to prescribed dosing (see Figure 24 in Dr. Condarco's review).

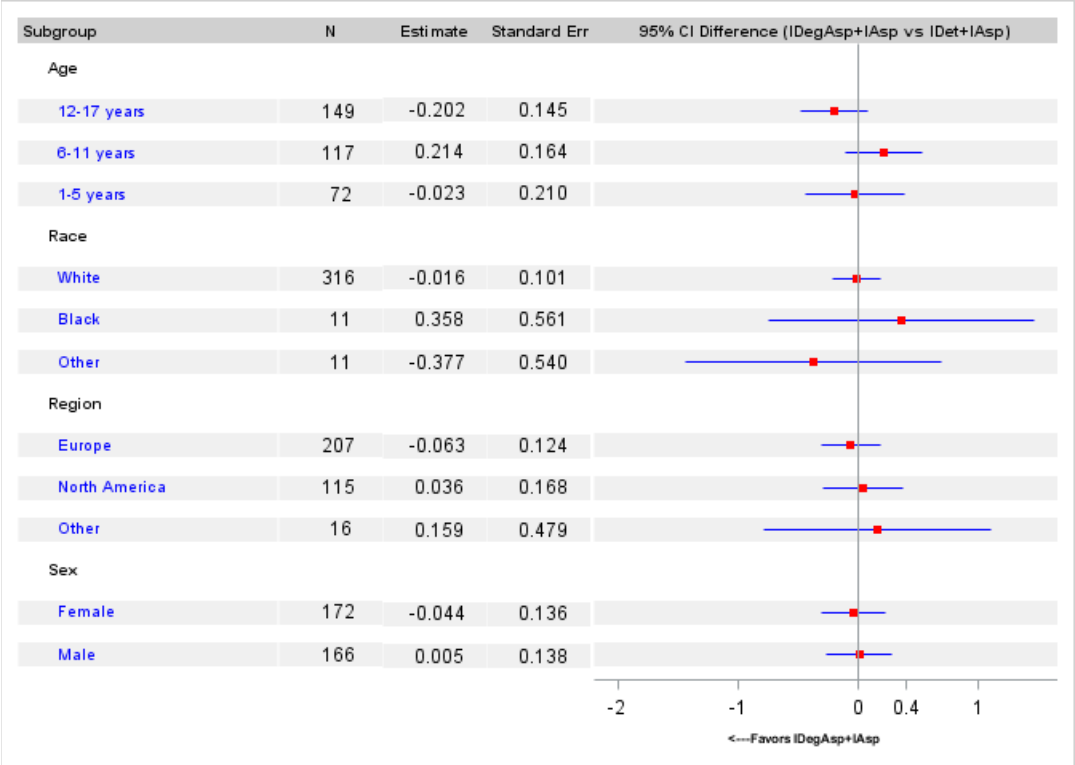
Trial 3816- Proportion of subjects reaching SMPG pre-breakfast target of 90-145 mg/dL by visit – full analysis set



In sum, for Trial 3816 it appears that reasonable adequate titration of the insulin comparator occurred as to allow valid conclusion of non-inferiority of IDegAsp.

Subgroup analysis

Due to the limitations associated with multiplicity and low power, subgroup analysis results were considered as supportive and exploratory. No significant interaction between defined subgroups and treatment were observed.



Source: Dr. Sinks' statistical review

Missing data considerations– *Trial 3816*

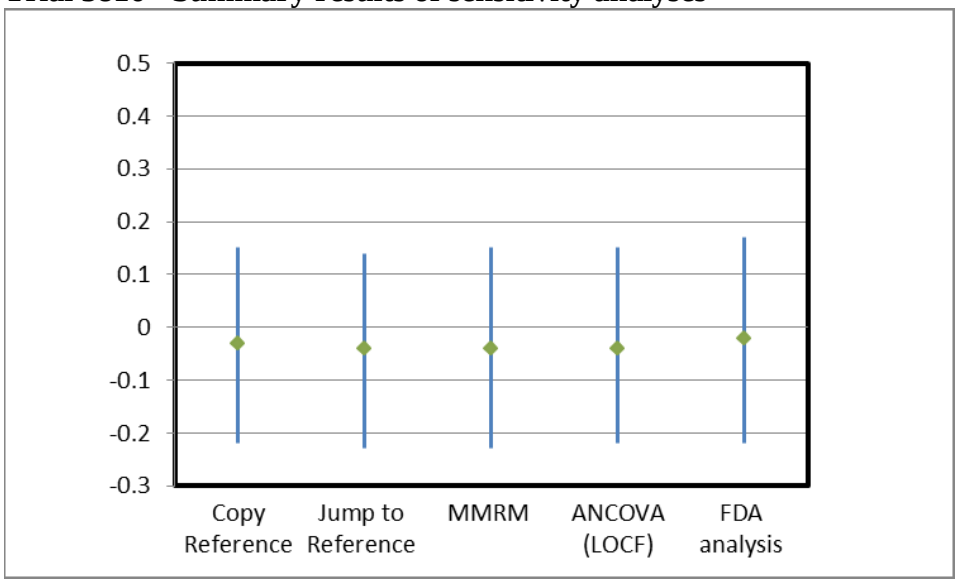
The Applicant used multiple imputation approach to assess the impact of missing data on efficacy conclusions. Methods used included Jump to Reference, Copy to Reference, and Tipping Point. Neither study was designed to continuing collect data from subject discontinued treatment early; a "retrieved dropouts" approach for handling missing data was not applicable.

Jump to Reference assumes that withdrawn subjects in the IDegAsp group are 'switched' to the IDet group. Copy to Reference assumes that withdrawn subjects in the IDegAsp group are the same as subjects in the IDet group during the entire trial. For both methods, the imputed value for the IDegAsp group is penalized by adding the NI margin, whereas the imputed value for the IDet group is not penalized. The applicant also performed a tipping point analysis similar to that described above for Trial 3561.

The FDA statistician additionally conducted a 'Return to Baseline' analysis; see description of this method above, in review of Trial 3561.

The conclusion of non-inferiority is supported by all sensitivity analyses. Dr. Sinks recommends that the FDA analysis should be used for labeling Section 14 of the PI.

Trial 3816 - Summary results of sensitivity analyses



Source: FDA statistical review

Secondary endpoints– *Trial 3816*

There were no secondary efficacy endpoints that were adjusted for multiplicity.

FPG

Unadjusted data showed a baseline FPG of 172 mg/dL in the IDegAsp group decreasing to 168 mg/dL at Week 16, and a baseline FPG of 168 mg/dL in the IDet group decreasing to 158 mg/dL at Week 16

Dr. Sinks performed an MMRM analysis of FPG at Week 16 with treatment, sex, and region, age group, visit, interaction between visit and treatment as fixed effects and baseline response as a covariate. The estimated mean change from baseline in FPG was -0.7 mg/dL for the IDegAsp group and -6.4 mg/dL for the IDet group. The estimated treatment difference between IDegAsp and IDet and corresponding 95% confidence interval was 5.6 mg/dL 95%CI (-12.7 - 24.0).

8. Safety

The safety profile for IDeg and IDegAsp has been established in adults. The pediatric trials are intended to provide additional safety data specific to pediatrics, and exposure to investigational product is less than compared to what was required in adults. In Trial 3561, when considering the main and extension period, 174 subjects, had a mean exposure to IDeg of 0.93 years; while 175 subjects had a mean exposure to IDet of 0.84 years. In Trial 3816, about 180 subjects had mean exposure of 0.3 years in each arm. Known important risks with insulin products in

general include hypoglycemia and weight gain. Immunogenicity/allergic and injection site reactions are also safety issues of concern. Aside from hypoglycemia, Dr. Condarco did not identify any safety concerns that specifically affected the risk/benefit assessment for the pediatric indication. Please see her review for details. The overall safety findings for the two trials are summarized below.

Trial 3561 - IDeg

Major safety results – *Trial 3561*

Deaths

There were no deaths in the trial.

Serious adverse events

Serious adverse events (SAEs) were reported by 10.3% of subjects in the IDeg group and 9.1% of subjects in the IDet group over the 52 week trial period. Exposure adjusted event rate was similar between arms (15 per 100 subject years for IDeg and 16 per 100 subject years for IDet). The majority of SAEs were in the Infections and infestations System Organ Class (SOC) with Preferred Terms (PTs) such as appendicitis (1 in IDeg and 2 in IDet) and bronchitis (1 in IDeg and 2 in IDet). No unusual infections were noted. Across SOCs, most PTs were not reported for more than one subject.

Dropouts and/or discontinuations

Evaluation of dropouts and/or discontinuations from trial 3561 showed no dropouts in the IDeg group due to adverse events. Three subjects in the IDet group dropped out of the trial (reasons: mixing up insulin aspart and IDet pens, hypoglycemic seizure, and anxiety disorder).

Common adverse events (AEs)

AEs were reported by 83.9% of subjects in the IDeg group and 81.7% in the IDet group over the 52 week trial period. The exposure adjusted event rate was 596 vs. 623 per 100 subject years for IDeg vs. IDet, respectively. The most commonly reported AE was nasopharyngitis (41.4% vs. 38.3% in IDeg vs. IDet, respectively) followed by headache (26.4% vs. 29.1% in IDeg vs. IDet, respectively) and abdominal pain (23% vs. 14.3% in IDeg vs. IDet, respectively). These are similar to AEs reported for adults likely because these are overall common adverse events experienced in general and are unlikely to be drug related. 'Blood ketone body increased' was commonly reported in the trial, and this differs from what was observed in adult trials. However, this finding is likely due to the fact that pediatric subjects were instructed to self-measure ketones during the trial. The reported rate of 'blood ketone body increased' was lower in the IDeg group than in the IDet group.

Vital signs and routine laboratory testing

There were no clinically important findings with regard to vital signs and routine laboratory testing in Trial 3561. Please see Dr. Condarco's review for details.

Trial 3816 – IDegAsp

Major safety results – *Trial 3816*

Deaths

There were no deaths in the trial.

Serious adverse events

SAEs were reported by 6.1% of subjects in the IDegAsp group and 3.9% in the IDet group in the 16 week trial period. Exposure adjusted event rate was higher in the IDegAsp group (26 per 100 subject years for IDegAsp and 13 per 100 subject years for IDet). Some of the observed imbalance was due to likely chance events unrelated to study drug, such as 'gastritis' and 'glaucoma'. However, there were 5 events of hypoglycemia in the IDegAsp arm and 1 in the IDet arm comprising part of the imbalance in overall SAEs.

Dropouts and/or discontinuations

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

Common AEs

AEs were reported by 55.2% of subjects in the IDegAsp group and 54.2% in the IDet group. The exposure adjusted event rate was 442 vs. 451 per 100 subject years for IDegAsp vs. IDet, respectively. The most commonly reported AE was abdominal pain (13.2% vs. 13.4% in IDegAsp vs. IDet, respectively) followed by headache (12.7% vs. 17.9% in IDegAsp vs. IDet, respectively) and nasopharyngitis (19.9% vs. 17.9% in IDegAsp vs. IDet, respectively). Again, these are similar to AEs reported for adults likely because these are overall common adverse events experienced in general and are unlikely to be drug related.

Vital signs and routine laboratory testing

There were no clinically important findings with regard to vital signs and routine laboratory testing in Trial 3816. Please see Dr. Condarco's review for details.

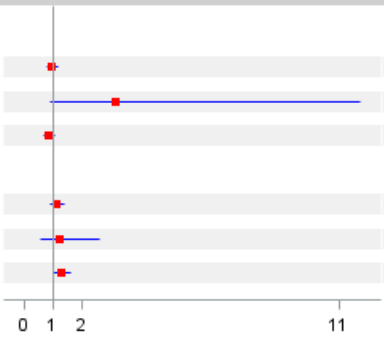
Submission specific safety concerns

Hypoglycemia – *both Trials 3561 and 3816*

Hypoglycemia is the most clinically important adverse reaction associated with insulin products. In the IDeg and IDegAsp pediatric trials, the methods to define and capture hypoglycemia as a safety endpoint appear adequate. Definitions of hypoglycemia used in the trials were based on both the American Diabetes Association definitions used for adults and International Society for Pediatric and Adolescent Diabetes (ISPAD) guidelines. Based on her review of the data, Dr. Condarco was concerned about the pattern of hypoglycemia incidence and events favoring comparator in both trials. Trends were unfavorable for most definitions of hypoglycemia in Trial 3561. In trial 3816, there was a notable numerical imbalance not favoring IDegAsp, but the number of events in the IDet arm was small, and may have been, by chance, below expected. It is important to note that about half of the subjects entering the trial were already using IDet; this factor could have biased the early transition period of the trial in favor of the comparator arm. The unfavorable trends in hypoglycemia were not dependent on age subgroup. See Dr. Condarco's review for details.

Dr. Sinks concluded that there is no strong evidence to indicate a higher rate of hypoglycemia with IDeg or IDegAsp compared to IDet. See her analysis below examining incidence rates of hypoglycemia using three difference definitions: severe[1], Novo Nordisk confirmed[2], and documented symptomatic hypoglycemia[3]. I agree that there is no clear evidence of a differential hypoglycemia risk between IDeg and IDegAsp vs. comparator.

Type	IDegAsp or IDeg Events #	IDet Events #	Risk Ratio(95% CI)	Risk Ratio (95% CI)	P-value
Trial 3816-16 weeks					
Confirmed	2532	2672		0.94 (0.76,1.17)	0.58
Severe	14	4		3.21 (0.88,11.7)	0.08
Documented sympt.	3005	3648		0.82 (0.65,1.05)	0.12
Trial 3561-26 weeks					
Confirmed	5020	4748		1.13 (0.90,1.41)	0.29
Severe	44	34		1.21 (0.56,2.62)	0.62
Documented sympt.	5914	4904		1.28 (1.00,1.64)	0.05



Source: Dr. Sinks' statistical review

Taking both clinical and statistical reviewers conclusions into consideration, I believe that there is insufficient evidence to include a statement in labeling that IDeg confers an overall higher risk of hypoglycemia than comparator. It is important to note that the analyzed definitions of hypoglycemia overlap somewhat and they are not necessarily independent confirmation of each other. It is likely that the unfavorable numerical imbalance observed, if not due to chance, stems from the process of dose conversion rather than an inherent characteristic of IDeg itself. For these reasons, I do not recommend labeling increased hypoglycemia risk for IDeg, but I agree with recommending a 20% dose reduction for IDeg for pediatric patients converting from other insulin therapies to mitigate any theoretical risk of hypoglycemia. This small dose reduction is not likely to lead to harm, i.e. underinsulinization/diabetic ketoacidosis to patients.

Weight gain

Body weight gain is a known adverse reaction of insulin products in adults and is related to insulin's mechanism of action. In the pediatric studies assessment of growth and development

[1] Severe hypoglycemia in pediatric patients: an episode with altered mental status, where the child could not assist in his own care, was semiconscious or unconscious, or in a coma ± convulsions and required parenteral therapy (glucagon or i.v. glucose).

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

[3] The child or parent is aware of, responds to, and treats the hypoglycemia orally after documenting a BG level of ≤ 70 mg/dL.

showed normal weight gain in children and no apparent inappropriate weight gain with IDeg or IDegAsp as compared to insulin detemir.

Immunogenicity

Antibody assessments were performed in Trial 3561 only and used the same assay for insulin degludec specific antibodies as was used in the clinical development program for the adult indication, i.e. radioimmunoprecipitation (RIP) assay using [$_{125}$I]- labelled tracers. However, at the time of approval of Tresiba the assay was determined to be not sufficiently sensitive.

For this reason there are two Postmarketing Commitments (PMCs) in the approval letter for Tresiba. These PMCs are as follows:

> 2955-2 (Tresiba): To develop and validate an assay to assess for the presence of anti-degludec antibodies that has a sensitivity consistent with FDA guidance. Your final report should include a summary of the validation exercise including supporting data, a summary of the development data supporting assay suitability for parameters not assessed in the validation exercise, and the assay standard operating procedure (SOP).
>
> PMC 2954-4 (Ryzodeg 70/30) and PMC 2955-3 (Tresiba): To assess the incidence and titers of anti-degludec antibodies in sera from patients treated with Tresiba (insulin degludec injection) in Tresiba (insulin degludec injection) clinical trials and determine whether they are associated with differences in pharmacokinetics parameters (e.g. exposure), efficacy (e.g. hemoglobin A1c, insulin dose), and safety (e.g. hypoglycemia and hypersensitivity). The clinical samples should not be tested until the results from the PMC for anti-degludec antibody assay development and validation have been submitted to and reviewed by the Agency.

The Sponsor has submitted the final report to fulfill PMC 2955-2 and the draft protocol for PMC 2954-4 (Ryzodeg 70/30) and PMC 2955-3 (Tresiba). Both are currently under Agency review. The draft protocol includes antibody evaluation for Trial 3561.

In her review for the current submissions, Dr. Condarco has summarized the Applicant's antibody assessments for Trial 3561 which include antibody titer summaries, and cross reactive antibody analyses of efficacy and safety endpoints. These data did not suggest any clinically important concerns regarding immunogenicity; however, given the inadequacy of the anti-insulin degludec assay, this safety issue will need to be explored further in the to-be-conducted protocol for PMC 2954-4 (Ryzodeg 70/30) and PMC 2955-3 (Tresiba). Labeling of specific antibody titer data is not recommended at this time because of the poor sensitivity of the assay.

9. Advisory Committee Meeting

An advisory committee meeting was *not* convened for these submissions.

10. Pediatrics

Pediatrics, as the focus of this review, has been discussed throughout this memo. The Division met with the Pediatric Review Committee (PeRC) on 9 Nov 2016 to discussion these submissions. The PeRC agreed with the Division's assessment of these submissions and that the PREA PMRs 2954-1 and 2955-1 are fulfilled.

As a reminder, PREA related language in the approval letters for Tresiba and Ryzodeg 70/30 was as follows:

> We are waiving the pediatric studies requirement for type 1 diabetes mellitus in ages 0 to < 1 year and type 2 diabetes mellitus in ages 0 to < 10 years because necessary studies are impossible or highly impracticable. This is because there are too few children in this age range with diabetes mellitus to study.
>
> We are deferring submission of your pediatric study for ages 1 to 17 years (inclusive) for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Tresiba

> 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.

Ryzodeg 70/30

> 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).

11. Other Relevant Regulatory Issues

Data quality and integrity

A routine site inspection from the Office of Scientific Investigations was not requested. Dr. Condarco stated that the submission quality was acceptable. Dr. Condarco reviewed all protocol amendments and determined that none compromised data integrity.

Financial disclosures were reviewed by Dr. Condarco, and she notes no concerns regarding any financial conflict of interest compromising data integrity. I agree with her assessment. Please see her review for details.

12. Labeling

Carton and container labeling, Instructions for Use and Patient Package Insert

DMEPA conducted a carton and container labeling review and found that the carton and container labeling, IFU, and PPI, are acceptable from a medication error perspective.

Pregnancy and Lactation Labeling Rule (PLLR)

Revisions have also been made to Section 8 Use In Special Populations (Section 8.1 Pregnancy, Section 8.2 Lactation and (b) (4) (b) (4)) of the PI to be compliant with the and consistent with PLLR Guidance for Industry: Pregnancy, Lactation, and Reproductive Potential; Labeling for Human Prescription Drug and Biological Products – Content and Format. These revisions were reviewed by DMEP's Nonclinical Pharmacology/Toxicology team and by DPMH (see review in DARRTS dated 14 Nov 2016).

Pediatric-specific dosing and administration

Starting dose: a 20% dose reduction is recommended for both products as discussed previously. For Tresiba the dose reduction should be from the basal insulin component of the patients previous regimen, i.e. Start TRESIBA at 80% of the total daily long or intermediate-acting insulin unit dose to minimize the risk of hypoglycemia [*see Warnings and Precautions (5.2)*]. For Ryzodeg 70/30 dose reduction should be from the basal component of the mix.

Dosing regimen: The approved Tresiba PI states: "Inject TRESIBA subcutaneously once-daily at any time of day" and to "ensure that at least 8 hours have elapsed between consecutive TRESIBA injections." The recommended dosing regimen was based, in part, on adequate phase 3 data in the adult program studying 'flexible' administration of IDeg (see original NDA review for IDeg). In the Phase 3 pediatric trials, subjects were instructed to administer their dose approximately at the same time of day, i.e. 'flexible' dosing was not studied. There is insufficient data to recommend dosing at any time of day for pediatric patients. Therefore, the dosing regimen recommended for pediatrics is once daily at the same time every day for Tresiba and once daily with any main meal for Ryzodeg 70/30

As noted previously, a limitation of use for both products for pediatric patients will be included as follows: *Not recommended for pediatric patients requiring less than 5 units daily.*

Safety information; section 6

For labeling of section 6, there are no important adverse reactions (ARs) unique to pediatrics. A separate table showing ARs for pediatrics would not contribute meaningfully to the safe and effective use of the product. Section 6 can simply state that ARs in pediatrics were similar to those observed in adults. The tables showing incidence rates of hypoglycemia (both Severe and Novo Nordisk Confirmed) should be updated with incidence rates from the pediatric trials.

Pediatric information in Section 8.4: Specific populations/pediatrics and Section 12: clinical pharmacology

Sections 8.4 and 12 should be updated with relevant pediatric data. The OCP reviewers recommend including language in Section 12 informing that total exposure and glucose lowering effect did not show clinically relevant differences in children and adolescents compared to adults.

Labeling of efficacy results in Section 14 of the PI

The Biostatistics reviewer recommends that the best/most appropriate estimate of the treatment difference should be used for labeling Section 14 of the PI. As there was a lack of retrieved dropouts, the FDA Biostatistician recommends a multiple imputation analysis which "washes out" any potential treatment effect for those subjects who have missing data at week 26 or 16. Specifically, as this is an active-controlled trial, missing data at week 26 or 16 should be imputed based on a distribution centered at baseline HbA1c value, and with a subject-level prediction standard deviation equal to that from an ANCOVA model performed on observed cases at week 26 or 16. For this analysis, in Dr. Sinks' review, she penalized the IDeg group by adding 0.4% for patients with missing data to best assess the robustness of the NI conclusion. However, for the product label, it is not recommended to penalize the experimental group 0.4% for the missing data. Although similar results were obtained for the extension period of Trial 3561 Dr. Sinks does not recommend labeling these results in section 14.

A line-by-line labeling review is being completed separately and the Agency is currently working with the Sponsor to come to agreement on labeling.

13. Recommendations/Risk Benefit Assessment

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

The Applicant has shown in adequate and well-controlled trials (one for each product) that Tresiba and Ryzodeg 70/30 are safe and effective for pediatric patients with type 1 diabetes ages 1 to less than 18 yrs. The trials are adequate to support labeling Tresiba and Ryzodeg 70/30 for T2DM pediatric patients, i.e. separate trials in pediatric T2DM are not required. Therefore, both supplements can be approved with the requested indication, i.e. indicated to

improve glycemic control in patients 1 year of age and older with diabetes mellitus. In addition, with these submissions the PREA PMRs 2954-1 and 2955-1 are fulfilled.

In Trial 3561 comparing Tresiba to insulin detemir both with mealtime insulin aspart, in the Applicant's analysis, the change from baseline was -0.15% in the IDeg group and -0.30% in the IDet group with an estimated treatment difference of 0.15%, 95% CI [-0.03; 0.32]. The non-inferiority of IDeg versus IDet was established in the Applicant's analysis, although the estimated treatment effect of IDeg was numerically less than that of IDet. In Trial 3816, comparing Ryzodeg 70/30 plus insulin aspart at the remaining meals to insulin detemir plus insulin aspart at meals, in the Applicant's analysis the mean change from baseline was -0.27% in the IDegAsp group and -0.23% in the IDet group with an estimated treatment difference of -0.04%, 95% CI [-0.23; 0.15]. The non-inferiority of IDegAsp versus IDet was established in the Applicant's analysis; superiority of IDegAsp over IDet was not confirmed. The conclusions of non-inferiority were not sensitive to analysis method.

As discussed above, in a non-inferiority trial design the assessment of efficacy is based on 'implied' efficacy relative to a comparator that is assumed to also be effective, with a non-inferiority margin pre-specified based on historical data of how the comparator should perform. As Dr. Sinks notes non-inferiority would still be concluded for both studies even if smaller margins were used (0.2% for trial 3816 at week 16, 0.33% for trial 3561 at week 26). Clinical pharmacology assessments, including single dose PK/PD studies, and population PK analysis using Phase 3 data, showed no clinically important differences in exposure-response between pediatric and adult subjects that necessitate dose adjustment. An increased between subject variability in exposure, however, was noted especially for younger subjects. No unique safety concerns were identified for pediatrics. Rates of hypoglycemia trended towards a higher rate with IDeg, but analyses did not identify a statistically significant difference between IDeg and comparator and observed differences were likely due to the process of converting from previous insulin therapy. Theoretically, since IDeg takes longer than other basal insulins to reach steady state dose overshoot is possible if patients do not wait the recommended 4 days for dose titration.

Pediatric specific dosing and administration instructions are recommended as discussed throughout this review:

- Starting dose: a 20% dose reduction is recommended for both products for patients previously on insulin therapy. The rationale for the recommendation for Ryzodeg 70/30 is clear – a 20% dose reduction was employed in the clinical trial. The rationale for the recommendation for dose reduction for Tresiba is more nuanced involving a number of considerations as follows: (1) using the same starting dose recommendation for both products may lead to less prescriber confusion; (2) while there was no strong evidence for an increase in hypoglycemia risk observed in the trials, trends were less favorable in the Tresiba trial than in the Ryzodeg 70/30 trial. It is possible that the 20% dose reduction employed in the Ryzodeg 70/30 trial mitigated early hypoglycemia due to dose conversion to the novel therapy; (3) increased between subject variability in exposure was observed in children and adolescents as compared to adults. While no link between this observation and hypoglycemia risk has been established, intuitively lowering the starting dose upon

dose conversion from other insulin products may help mitigate the theoretical risk of hypoglycemia due to relatively increased exposure from the new insulin product.

- 'Flexible' dosing not recommended for pediatric patients as the clinical trials do not support this dosing regimen. It is not clear that this dosing regimen can be leveraged from adult trials to support pediatric dosing.
- Ryzodeg 70/30 should be used once daily in pediatrics in contrast to the option for twice daily dosing in adults, the primary reason being that this was the dosing regimen employed in the clinical trial.
- For pediatric patients with type 2 diabetes, there are no data to inform dosing. Using the same starting dose as for adults makes clinical sense as pediatric patients with type 2 diabetes are expected to be at least equally insulin resistant compared to their adult counterparts. For patients converting from other insulin therapies, similar to type 1 diabetes, a 20% dose reduction is recommended. Using the same dose recommendation may mitigate medication error due to too complex dosing instructions in labeling, and this small degree of a starting dose reduction is not expected to result in any harm to patients.

PMRs for Tresiba and Ryzodeg 70/30 pertaining to immunogenicity risk assessment include testing of retained samples from these two pediatric trials. Further labeling of antibody assessments is deferred until those samples have been analyzed with the newly developed assay.

Lastly, I recommend approval of the labeling language to update labeling to conform to PLLR.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None: Tresiba and Ryzodeg 70/30 do not have REMS, and I do not recommend a new REMS based on the current supplements.

- Recommendation for other Postmarketing Requirements and Commitments

After review of the Efficacy Supplements I conclude that Study NN1250-3561 fulfills Post Marketing Requirement #2954-1 for Tresiba (NDA203314), and Study NN5401-3816 fulfills Post Marketing Requirement #2955-1 for Ryzodeg 70/30 (NDA203313).

The draft protocol for PMC 2954-4 (Ryzodeg 70/30) and PMC 2955-3 (Tresiba) was submitted to the Agency on 1 Nov 2016. The draft protocol includes antibody evaluation for Trial 3561.

- Recommended Comments to Applicant

No comments are recommended to the applicant at this time.

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/s/

LISA B YANOFF
12/16/2016

JEAN-MARC P GUETTIER
12/16/2016

Dr. Yanoff's review serves as the Division's decisional memorandum for this supplemental application. I concur with her summary and agree with her decision to recommend approval.