

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203313Orig1s000**

**203314Orig1s000**

**CROSS DISCIPLINE TEAM LEADER REVIEW**

## Cross-Discipline Team Leader Review

<b>Date</b>	20 Sep 2015
<b>From</b>	Lisa Yanoff, M.D.
<b>Subject</b>	Cross-Discipline Team Leader Review
<b>NDA #</b>	203314/203313
<b>Applicant</b>	Novo Nordisk
<b>Date of Submission</b>	26 Mar 2015
<b>PDUFA Goal Date</b>	26 Sep 2015
<b>Proprietary Name / Established (USAN) names</b>	Tresiba/Ryzodeg 70/30 Insulin degludec injection/insulin degludec insulin aspart injection
<b>Dosage forms / Strength</b>	solution for sc injection U100 and U200 (Tresiba) U100 (Ryzodeg 70/30)
<b>Proposed Indication</b>	Indicated to improve glycemic control in adults with diabetes mellitus
<b>Recommended Action</b>	Approval

## Cross Discipline Team Leader Review

### 1. Introduction

This document contains the summary review written by the Division of Metabolism and Endocrinology Products cross-discipline team leader for the second cycle resubmission of NDA 203314 for insulin degludec injection and NDA 203313 for insulin degludec insulin aspart injection, both combination products of insulin and a disposable pen injector device.

The reader is referred to the multiple discipline reviews for a more comprehensive review and detailed discussion of the development programs for insulin degudec and insulin degludec insulin aspart. Because this is a second cycle resubmission, some disciplines did not have new data to review for this cycle; in these cases, the reader is referred to the original NDA reviews for those disciplines. Further, information to address several of the section headings in this memo were previously provided in the original summary memo(s) from the original NDA review.

This memo references the following documents/sources:

Subject	Author	Date	Cycle
<b>Office Director Memo</b>	Dr. Curtis Rosebraugh	8 Feb 2013	1
<b>Divisional Summary memo</b>	Drs. Mary Parks and Jean-Marc Guettier	1 Feb 2013	1
<b>Clinical Efficacy review</b>	Dr. Jean-Marc Guettier	26 Jan 2013	1
<b>Clinical Safety review</b>	Dr. Karim Calis	18 Dec 2012	1
<b>Clinical Efficacy and Safety Review</b>	Dr. Tania Condarco	31 Aug 2015	2
<b>Statistical review (DBII)</b>	Dr. Jiwei He and Mark Rothmann	2 Sep 2015	2
<b>Statistical review (DBII) Tresiba only</b>	Dr. Cynthia Liu	14 Nov 2012	1
<b>Statistical review (DBII) Ryzodeg 70/30 only</b>	Dr. Dongmei Liu	16 Nov 2012	1
<b>Statistical review (DBVII)</b>	Drs. Bo Li, Eugenio Andraca-Carrera and Mat Soukup	28 Aug 2015	2
<b>Clinical Pharmacology (OCP) review</b>	Drs. Manoj Khurana and Jayabharathi Vaidyanathan	15 Jun 2012 with addendum 26 Jun 2012	1
<b>Nonclinical Pharmacology Toxicology review</b>	Dr. Miyun Tsai-Turton and Dr. Karen Davis-Bruno	1 Jun and 4 Jun 2012	1
<b>OBP review</b>	Drs. Fred Mills and Daniela Verthelyi	31 May 2012 with addendum 14 Jun 2012	1
<b>DMEPA labeling review</b>	Dr. Sarah Vee	17 Jul and 7 Aug 2015	2
<b>Product Quality review*</b>	Dr. Muthukumar Ramaswamy	3 Sep 2015	2
<b>CDRH consult review</b>	Dr. Lana Shiu	9 Sep 2015	2
<b>PeRC meeting minutes</b>	PeRC members	27 Jun 2012	1

<b>Complete Response Letter (CRL) for NDAs 203314 and 203313</b>	DMEP	8 Feb 2013	1
<b>End of Review Meeting Minutes</b>	DMEP	1 May 2013	1
<b>Type C Meeting Responses</b>	DMEP	20 Mar 2015	N/A
<b>Email from ORP</b>	Janice Weiner	11 Sep 2015	2
<p><b>*Product quality includes reviews from ONDP (drug substance, drug product, process, and environmental assessment) and consults from CDRH (device) and OPF (microbiology, facility)</b>  <b>DBII: Division of Biometrics 2; DBVII: Division of Biometrics 7, OBP: Office of Biotechnology Products; DMEPA: Division of Medication Error and Prevention; CDRH: Center for Devices and Radiologic Health; PeRC: Pediatric Review Committee; DMEP: Division of Metabolism and Endocrinology Products; ORP: Office of Regulatory Policy</b></p>			

## 2. Background

### ***Product Information***

The active ingredient in Tresiba is insulin degludec. The drug substance insulin degludec is an analogue of human insulin which is considered ‘long-acting’ in that it is intended for use as basal insulin. The fixed ratio product Ryzodeg 70/30 contains two active drug substances: insulin degludec and the approved insulin analogue, insulin aspart (trade name NovoLog approved under NDA 020986 on 7 Jun 2000). Insulin aspart is a ‘rapid-acting’ insulin analogue intended for use as a mealtime (or bolus) insulin. Fixed ratio insulin products allow for the basal and bolus insulin to be administered with one injection, but they limit individualized titration of basal and bolus dosing. Please see Dr. Guettier’s original NDA clinical efficacy review for details.

### ***Regulatory History***

Please refer to Dr. Guettier’s original NDA clinical efficacy review for a table of presubmission regulatory activity pertinent to the original NDA submission. Please also refer to Dr. Condarco’s second cycle clinical efficacy and safety review for a summary of presubmission regulatory activity pertinent to the second cycle resubmission.

The key element to note here is the original review findings that led to the Complete Response (CR), and the agreements made between FDA and the Sponsor regarding information needed to resolve the deficiencies outlined in the Complete Response Letter (CRL).

During review of the original NDA submissions for insulin degludec and insulin degludec/insulin aspart, 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. The meta-analysis results suggested an increase in CV risk of insulin degludec or insulin degludec insulin aspart relative to the pooled comparator arm, using both the prespecified primary major adverse cardiovascular event (MACE+: composite

of CV death, myocardial infarction, stroke and unstable angina pectoris) and a strict MACE endpoint which excluded the unstable angina component from MACE+.’ The MACE evaluation using the totality of the data showed a point estimate of 1.67 and statistical significance [95% CI (1.01, 2.75)].

This concerning CV risk finding could not simply be concluded to be due to chance for a number of reasons. As noted in Dr. Rosebraugh’s Office Director memo, ‘while not designed to explicitly exclude CV risk, the insulin degludec program did have prespecified CV evaluations, an adequate number of events, and was performed in a manner consistent with agency guidance in the development of type 2 diabetes mellitus (T2DM) agents.’

He notes that ‘insulin products were not addressed regarding excluding a pre-specified margin of CV risk as noted in the 2008 draft guidance for industry: Diabetes mellitus-Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 diabetes.’ However, ‘companies developing insulin products are advised to prospectively collect and adjudicate CV events.’ The clinical development program for insulin degludec and insulin degludec insulin aspart did appear to follow this advice, as outlined in Dr. Li’s statistical review the CV risk assessment ‘was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. Of the 17 trials, 7 included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the statistical analysis plan (SAP).’

The NDAs were discussed at an Endocrine and Metabolic Drug Advisory Committee meeting on 8 Nov 2012. As summarized by Dr. Rosebraugh “The panel voted yes-12, no-0 that a cardiovascular outcomes trial should be conducted for degludec. Panel members voted yes-8, no-4 in support of marketing of the two NDAs...and any potential adverse CV effect could be further explored post-approval.”

The Sponsor had argued for various unique clinical benefits of insulin degludec that were reviewed by the Agency and discussed at the Advisory Committee meeting. One of the most extensively reviewed potential benefits was a hypoglycemia advantage. The review of this topic was complex and the reader should refer to Dr. Guettier’s efficacy review for details. In brief, the Agency’s conclusion was that the Sponsor had not been able to demonstrate a hypoglycemia advantage for insulin degludec over insulin glargine.

Based on the totality of the data, the Agency reviewers and signatory authority felt that these products should not be approved because there was no evidence of a clinical benefit of insulin degludec or insulin degludec insulin aspart to offset the uncertainty of the CV risk. In other words, there was no unmet need that these drugs would meet for diabetes patients that could not be met by marketed products such that further investigating the potential CV risk should not occur pre-marketing.

The CRL was issued on 8 Feb 2012. The CRL is quite detailed and nicely summarizes the Agency's viewpoint on why the products could not be approved at that time. The path forward outlined in the letter states that

'To address the above cardiovascular safety deficiencies, you will need to submit additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial using glargine as the comparator. The trial should be powered to exclude an excess cardiovascular risk based on a composite of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke (MACE), not MACE+. The risk margin to exclude that is necessary for approval should be discussed with the Agency at an End-of-Review meeting. At a minimum, the resubmission must include enough MACE events to definitively exclude a hazard of 80% with a reassuring point estimate. We encourage you to seek Agency feedback regarding trial design and statistical analysis plan before trial initiation.

[REDACTED] (b) (4)

As is standard Agency policy, the CRL also asked for a general safety update to be included in a resubmission of the NDA.

An End of Review meeting was held between the Agency and the Sponsor on 4 Apr 2013 during which discussion occurred and agreement was reached regarding the CVOT the Sponsor would need to conduct to address the deficiency related to CV safety. In particular, the risk margin that the Sponsor was told would need to be excluded in an interim analysis in order to resubmit the NDAs was 1.8 assuming a reassuring point estimate; however, the overall objective of the trial should be exclude the 1.3 risk margin. In subsequent communications between the Agency and the Sponsor, the design elements for the CVOT were agreed upon, including the study population, primary endpoint, glycemic targets, and the number of MACE events needed to conduct an interim analysis.

On 2 Jan 2015 the Sponsor submitted a Type C meeting request to discuss the interim CV data obtained from the dedicated CV outcome trial (named DEVOTE) and determine if these data would be sufficient to support resubmission of the NDAs. Written responses were issued which stated that the Sponsor appeared to have addressed the deficiencies in the CRL to justify resubmission.

### **3. CMC/Device**

#### **CMC**

Tresiba and Ryzodeg 70/30 are drug device combination products. Therefore, both the drug and device constituents are discussed in this section.





In his review for the second cycle resubmission, Dr. Ramaswamy recommends approval for both NDAs from a CMC perspective for both NDAs. There are no outstanding deficiencies related to chemistry, microbiology, and manufacturing facilities.

CMC review for drug substance, drug product, and microbiological controls in the manufacturing process was completed during first review cycle. Product quality Review was conducted as a team review with Joseph Leginus reviewing the Drug Substance and Muthukumar Ramaswamy reviewing the Drug Product. Dr. V. Pawar reviewed product quality microbiology information (provided in the NDAs) and sterilization validation information provided under DMF (b) (4). Dr. Guettier's original NDA clinical efficacy review contains a useful summary of these reviews.

An assessment of the drug substance and drug product manufacturing facilities was completed by Juandria Williams in consultation with CDRH reviewer, Crystal Lewis and an Approve recommendation was provided by the facility reviewer in Panorama (see also *CDRH Compliance* section below).

## **Device**

### CDRH Device Review

A CDRH consult was requested to review the device constituent of the Tresiba and Ryzodeg 70/30 combination products. Performance aspects of the delivery device were reviewed by Lana Shiu, M.D. (General Hospital Devices Branch, DAGRID, ODE, CDRH). Refer to her review in DARRTS dated 9/2/15.

The proposed device constituent is the Novo Nordisk FlexTouch (PDS290) which is a pen-shaped, prefilled device containing a non-replaceable, fixed, 3 ml cartridge with insulin, i.e. a disposable insulin delivery device with the insulin cartridge irreversibly integrated into the device. The FlexTouch pen has no push-button extension, and instead uses a unique spring-loading dosing mechanism. On their previous pen, the higher the dose, the more the push-button will extend out of the pen, making it more difficult to push to inject. On the FlexTouch, no matter what the dose, the button does not extend, making it easier to push.

There are already multiple approved and marketed products that use the FlexTouch platform injector. Two of these are insulin products (insulin aspart and insulin detemir, both approved 31 Oct 2013) approved under supplemental NDAs after the original NDA submissions for insulin degludec/insulin degludec insulin aspart. Therefore, in contrast to the original NDA review for insulin degludec/insulin degludec insulin aspart there is now clinical experience with the FlexTouch device and insulin products.

Dr. Shiu concluded that there are no device or engineering issues that would preclude approval. Of particular clinical relevance is dose accuracy data and the reader should refer to her review for detailed information. The dose accuracy was investigated at the three dose sizes; minimum dose 1 U, midpoint dose 40 U and maximum dose 80 U. The tests were carried out with the to-be-marketed versions of the dedicated PDS290 pen-injector for each insulin, i.e. degludec U100, degludec U200 and degludec aspart U100. Dose accuracy was



tested under variable conditions such as cold and hot temperature, preconditioning by free fall, among others. Overall the results were acceptable. However, Dr. Shiu pointed out that the deviation in accuracy was larger with the 1 U dose than with the higher two doses. For the 1U dialed dose the testing showed the injector can express a mean of 1U of insulin with a deviation ranging from +/-0.3 to +/- 0.7. This means that dialing the pen injector to deliver a 1 U dose could actually deliver a dose ranging from 0.3 U to 1.7 U. For the 40U and 80U doses the deviation from the mean is smaller - less than 1% for both 40U (0.4% to 0.6%) and 80U (0.39% to 0.46%). This means that dialing the pen injector to deliver a 40 U dose could actually deliver a dose ranging from 39.6 U to 40.4 U. Therefore, the relative dose accuracy is worst with the lowest, i.e. 1U, dose tested. This finding was similar for all three devices. Dr. Shiu noted that this result was expected due to the spring assisted design of the PDS 290 pen-injector and was similar to testing done for other drugs including other insulin products. The clinical review team concluded that the larger deviation observed with the 1U dose is still within an acceptable range from a clinical standpoint.

#### CDRH Compliance Review

The Office of Compliance at CDRH was consulted by CDER to evaluate the applicant's compliance with applicable Quality System Requirements for the approvability of the combination products and the need for an inspection of the involved sites. Per the consult report these NDAs are approvable from the perspective of the applicable Quality System Requirements.

## **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.

The Pharmacology/Toxicology review discipline recommended approval with no postmarketing requirements. Please see reviews of Drs. Miyun Tsai-Turton and Karen Davis-Bruno dated 1 Jun and 4 Jun 2012, respectively.

The reader may also refer also to Dr. Guettier's original NDA clinical efficacy review for a summary of the Pharmacology/Toxicology findings.

## **5. Clinical Pharmacology/Biopharmaceutics**

Clinical Pharmacology data were reviewed during the original NDA review, and there is no new Clinical Pharmacology information in the resubmission.

The recommendation from the Clinical Pharmacology discipline is approval with no recommended postmarketing requirements. Please see reviews of Drs. Manoj Khurana and Jayabharathi Vaidyanathan dated 15 Jun 2012.

The reader may also refer also to Dr. Guettier's original NDA clinical efficacy review for a summary of the Clinical Pharmacology findings.

## **6. Clinical Microbiology**

Please see section 3 (CMC). There were no Clinical Microbiology deficiencies that would preclude approval. Clinical Microbiology data were reviewed during the original NDA review, and there is no new Clinical Microbiology information in the resubmission.

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## 7. Clinical/Statistical- Efficacy

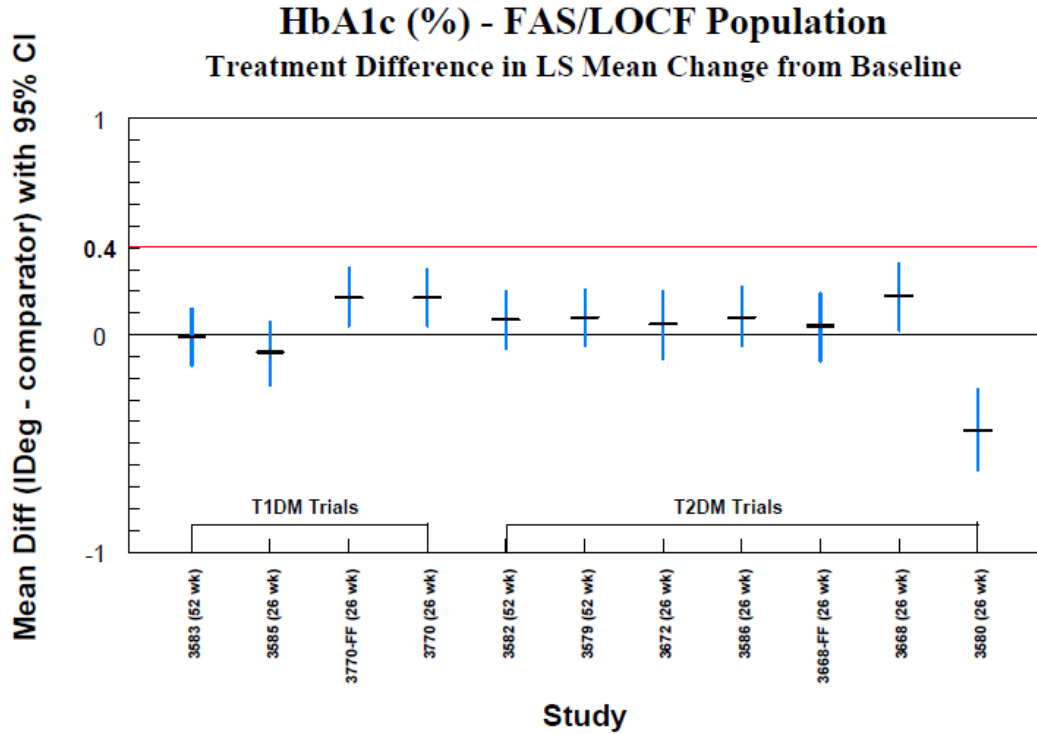
Clinical and statistical efficacy was clearly established during the original NDA review of insulin degludec and insulin degludec insulin aspart. Please refer to Dr. Guettier's original clinical efficacy review (both NDAs) and Dr. Cynthia Liu's (Tresiba) and Dr. Dongmei Liu's (Ryzodeg 70/30) original statistical reviews.

The Divisional summary memo from the original NDA review states that "Novo Nordisk has conducted a comprehensive program for its two insulin products, degludec and degludec-aspart. The program clearly establishes the glycemic efficacy of these two products and their ability to lower HbA1c in both T1 and T2DM patients." As such, there were no deficiencies related to efficacy in the CRL.

For the reader's convenience a very brief overview of the efficacy review findings from the original NDA review is included below.

### *Tresiba*

This figure from Dr. Cynthia Liu's statistical review of Tresiba depicts the totality of the phase 3 trial results. Her figure summarizes the treatment differences between degludec and insulin control (the far right data point compares degludec to sitagliptin in a superiority trial). For each trial, the horizontal black lines represent the point estimate for each trial and the blue vertical lines the confidence intervals. The red line running horizontally marks the non-inferiority margin prespecified for all of the non-inferiority trials. Confidence intervals that have the upper bound below the red line represent trials for which the non-inferiority margin was met. All of the trials met their primary endpoint and support the conclusion of effectiveness of Tresiba for glycemic lowering. At the same time, however, for the non-inferiority trials point estimates above the zero line indicate that the glycemic lowering effect of insulin degludec was numerically worse than insulin comparator. This finding proved to be important in the risk/benefit assessment in the original NDA review which identified the CV risk signal from the meta-analysis. However, in terms of the evaluation of efficacy alone, i.e. out of context of the safety concerns, efficacy of Tresiba was clearly established.



Note 1: Except that 3770-FF, 3668-FF, and 3580 were IDeg flexible dosing, all others were fixed dosing.  
 Note 2: Except for 3580 a superiority trial, all others were NI trials.  
 Note 3: Treatment difference above 0 favored the comparator.

*Ryzodeg*

For Ryzodeg, there was one pivotal trial in T1DM subjects. In this trial Ryzodeg was non-inferior to insulin detemir with the LS mean treatment difference of -0.05 with accompanying 95% CI of (-0.18, 0.08). Ryzodeg resulted in an average 1% reduction in HbA1c from baseline.

There were four pivotal trials in T2DM subjects, and the statistical reviewer presented the T2DM data in table format. This summary table from Dr. Dongmei Liu is shown below.

Study #	Treatment Group	Baseline Mean (SD)	LS Mean Chg from Baseline	LS Mean Treatment Difference (Degludec-Control)	95% CI
3590	1. Deg-Asp (266) 2. Glargine (263)	8.86 (1.0) 8.91 (0.9)	-1.72 -1.75	+0.03 --	(-0.14, 0.20)
3593	1. Deg-Asp (230) 2. Glargine (233)	8.29 (0.8) 8.36 (1.0)	-1.00 -0.97	-0.03 --	(-0.20, 0.14)
3592	1. Deg-Asp (224) 2. Biphasic Aspart (222)	8.33 (0.8) 8.40 (0.9)	-1.31 -1.29	-0.03 --	(-0.18, 0.13)
3597	1. Deg-Aspart (280) 2. Biphasic Aspart (142)	8.45 (0.8) 8.44 (0.9)	-1.39 -1.44	+0.05 --	(-0.10, 0.20)

Ryzodeg was non-inferior to its comparator across all four T2DM trials as the upper bound of the 95% CI was below 0.4. The average change in HbA1c from baseline ranged from -1.0 to -1.7 with no consistent pattern relative to comparator.

#### Resubmission

Reviews for the resubmission were completed by Dr. Jiwei He (statistics) and Dr. Tania Condarco (clinical). Dr. He stated that no new efficacy data or results were submitted and that she concurs with the conclusions in the previous statistical reviews. Dr. Condarco also did not have any additional comments regarding the efficacy data for the resubmission and noted that the reader should refer to Dr. Guettier's review and the Divisional summary memo for the Agency's review of the efficacy findings for these NDAs.

Since the original NDA the Sponsor has conducted additional clinical trials (some ongoing) including controlled extensions of trials submitted with the original NDAs; these are outlined in Dr. Condarco's clinical efficacy and safety review for the resubmission. However, the efficacy results for the completed trials were not submitted for Agency review. Hence, there was no new clinical efficacy information in the resubmission that was reviewed by Dr. Condarco to inform the current risk/benefit assessment for either product. This is appropriate because resubmissions should generally provide information only to address the deficiencies outlined in the CRL. In fact, in the written responses to the 20 Mar 2015 Type C meeting request the Sponsor was advised not to submit any new efficacy results for labeling claims. However, these additional trials resulted in a large increase in the overall safety exposure and safety data from these trials were reviewed by Dr. Condarco as discussed in Section 8 (Safety).

## **8. Safety**

### **Cardiovascular Safety**

The primary reason for the Complete Response action for the original submissions was a concerning CV risk signal. The interim results from DEVOTE (the dedicated CVOT) were the basis for the resubmission and will be summarized in this section. The review of the DEVOTE data was conducted by a team from the Office of Biostatistics VII. Please see their review in DARRTS for full information.

The concept of DEVOTE was briefly described in section 2 of this memo. Specifically, as summarized in the statistical review, ‘DEVOTE is a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled, event-driven trial which was designed and powered with a primary objective to confirm cardiovascular safety of insulin degludec (IDeg) compared to that of insulin glargine (IGlar) when added to standard of care in male and female subjects with T2DM at high risk of cardiovascular events. The study objective is to be supported by a non-excessive risk analysis to demonstrate that the hazard ratio (HR) of a primary MACE composite endpoint (3-component: CV death including deaths of unknown cause, non-fatal myocardial infarction, or non-fatal stroke) for IDeg versus IGlar is no greater than 1.8 before resubmission of IDeg/insulin degludec insulin aspart (IDegAsp) NDAs, assessed by a pre-planned single interim analysis when 150 adjudicated primary MACEs have been accrued. The study will continue until the planned trial conclusion when 633 MACE events have been collected and confirmed. A final analysis will then be performed to further demonstrate non-excessive risk of MACE against a risk margin of 1.3. All potential MACE events are to be adjudicated by an independent and blinded event adjudication committee (EAC).’

#### **DEVOTE interim results:**

On November 28, 2014, DEVOTE reached its full enrollment of 7638 subjects, with 3818 subjects randomized to receive IDeg and 3820 subjects randomized to receive IGlar; they comprise the full analysis set (FAS) population which was used for all analyses of cardiovascular endpoints performed by the safety statistical reviewer. A total of 29 subjects had not been exposed to trial products at the time of cut-off for the interim analysis. In total, 3807 subjects were exposed to IDeg and 3802 subjects were exposed to IGlar.

The IDeg and IGlar treatment arms were well-balanced with regard to baseline demographics and disease characteristics (see Table 3 in Dr. Li’s review). In the FAS population, there were more male subjects than female subjects (63% versus 37%). Approximately 76% of subjects were White, 11% were Black, 10% were Asian and 3% belong to other race categories. Nearly 70% of the total population were recruited from sites in the U.S. Approximately 15% of the subjects in the FAS population were Hispanic or of Latino ethnicity. Approximately half of the subjects in the FAS were between 60 and 69 years of age, with a mean age of 65 years. The average body mass index (BMI) was 33.6 kg/m<sup>2</sup>. The mean duration of T2DM at baseline was 16 years. Overall, about 85% of the FAS population had established CV disease (CVD) prior to randomization. More than 90% of the FAS subjects received anti-hypertensive therapy at baseline. The majority of the subjects were non-smokers: 45% had never smoked and 44% were previous smokers, while only 11% were current smokers at baseline.

As of the date of interim data cut-off on January 19, 2015, i.e., when a total of 150 adjudicated first MACEs had been collected, a total of 9 subjects had withdrawn from the study, (b) (4) subjects had died, and 98.5% of randomized subjects remained in the trial for primary CV events follow-up. 95.7% of subjects on IDeg and 94.7% of subjects on IGlár were on study treatment. The total patient-years of follow-up were 3709 years, corresponding to a mean length of approximately 6 months of follow-up per subject. The total patient-years of exposure to treatment at the interim were 3654 years excluding all periods of treatment pauses (see Dr. Li's review for description of treatment pauses). The median treatment exposure time was 174 days for both treatment groups. Both the follow-up and exposure time were distributed evenly between the two comparison groups. Figure 2 in Dr. Li's review shows the distribution of the time of follow-up until either first MACE or the date of last direct contact before interim data cut-off for both treatment arms of DEVOTE. The two curves are virtually overlapping. Overall, the distribution of treatment exposure time was similar across both arms either including all intermittent treatment pauses or excluding the pauses. (See table 6 in Dr. Li's review).

(b) (4) out of 3818 subjects randomized to IDeg (b) (4) % and (b) (4) out of 3820 randomized to IGlár (b) (4) % experienced MACE during the trial through the cut-off date of interim data. The incidence rate of first MACE (b) (4) (w) (4) Among the 150 first MACE events, a total of (b) (4) first events were adjudicated as CV death (including death with unknown or undetermined cause), non-fatal MI, and non-fatal stroke, respectively. The number of subjects who experienced CV death and non-fatal stroke as their first MACE (b) (4) two treatment arms. (b) (4) subjects randomized to IGlár than IDeg (b) (4) experienced non-fatal MI as their first MACE.

Per the statistical analysis plan, for the interim analysis, the pre-specified primary endpoint was the time from randomization to first EAC-confirmed occurrence of a 3-component MACE: CV death (including unknown cause of death), non-fatal MI, or non-fatal stroke. Note that the primary analysis was based upon time-to-event methods for MACE. If a subject experienced multiple events of interest, only the first event was to be included in the analysis. The agreed upon primary analysis method for MACE was a Cox proportional hazards regression model with a fixed effect for treatment to estimate the hazard ratio, and corresponding two-sided 95% confidence interval, of IDeg versus IGlár. This analysis was not adjusted for covariates.

The estimated hazard ratio of MACE associated with insulin degludec relative to insulin glargine was (b) (4) with a 95% confidence interval of (b) (4) The upper bound of the 95% confidence interval for the hazard ratio of MACE was (b) (4) thus the CV risk margin of 1.8 was successfully ruled out. A Kaplan-Meier plot showed that cumulative probability of developing MACE for the two treatment arms (b) (4) (see Figure 3 in Dr. Li's review). An exploratory analysis of the components of the primary composite endpoint showed that the estimated hazard ratios for CV death, non-fatal MI and non-fatal stroke were (b) (4) respectively. Confidence intervals for each component include (b) (4)



For the primary analysis of MACE, an “on-study” censoring scheme was utilized for event ascertainment. However, order to evaluate the robustness of the primary analysis to alternative censoring schemes, four “on-treatment” sensitivity analyses were conducted by the Sponsor considering a temporary treatment pause between two treatment periods as “off-treatment”. Sensitivity analyses conducted by the Sponsor used the same Cox model as the one used in the primary analysis. The statistical reviewer noted that a typical “on-treatment” censoring scheme is slightly different from what the Sponsor utilized, regarding the intermittent off-treatment pause between two treatment periods. The typical “on-treatment” period refers to the time from the first dose of study drug to the last dose of study drug before the end of a trial (or before the database lock for an interim analysis); the intermittent off-treatment pauses are not considered. Therefore the Agency statisticians conducted additional post-hoc sensitivity analyses based on this different definition of “on-treatment”. All sensitivity analysis results were in line with the result of the pre-specified primary analysis for MACE, i.e., these results are consistent with the conclusion that the risk margin of 1.8 was ruled out for primary MACE (see section 3.2.4.1.2 in Dr. Li’s review).

Time to all-cause deaths was pre-specified as a secondary endpoint and was assessed by the statistical reviewer as relevant to CV safety evaluation. In total, (b) (4) randomized subjects had died by the time of database lock for the interim analysis, (b) (4) deaths for IDeg arm and (b) (4) deaths for IGlar arm. The “on-study” analysis for time to all-cause deaths resulted in a hazard ratio estimate of (b) (4) with an associated 95% confidence interval of (b) (4).

In a post-hoc analyses of MACE+ the observed number of subjects reporting EAC-confirmed non-fatal unstable angina pectoris requiring hospitalization (b) (4) with IDeg (b) (4) than with IGlar (b) (4)). However, (b) (4) the subjects with EAC-confirmed unstable angina pectoris events later reported EAC-confirmed MACE. The data of adjudicated hospitalizations of unstable angina pectoris were incorporated into the calculation of time to first MACE+ endpoint. The results of this post-hoc analysis were supportive of the results for primary MACE, (b) (4).

Analysis results for the CV safety endpoint MACE (FAS, on-study) were also conducted by subgroups including gender, age (<60, 60 to <70, and ≥ 70), race (White, Black, Asian, other), region (US vs. non-US), baseline CV disease (established CVD vs. risk factor only), baseline renal function (normal renal function to mild renal impairment, moderate renal impairment, and severe renal impairment), baseline BMI ( $\leq 30 \text{ kg/m}^2$  vs.  $>30 \text{ kg/m}^2$ ), duration of diabetes at baseline ( $\leq 10$  yrs vs.  $> 10$  yrs). It should be noted that these analyses are exploratory in nature to assess general trends, and there were no protocol-defined multiplicity corrections for subgroup analyses. (b) (4)

#### **Discussion of interim analysis results:**

In order to be able to rely on the interim results from DEVOTE for regulatory action, one should consider whether, based on what is known at this time, the trial has been conducted adequately. Trial design was agreed upon with the Agency previously, so the focus of this discussion is on trial conduct and interim analysis results. The statistical review noted that ‘by the date of interim data cut-off, the trial was generally well-conducted and there were no significant statistical issues about trial design, conduct or analysis’ and concluded that ‘with no reason for statistical concern indicated in these analyses, it can be concluded that the analysis of MACE in DEVOTE met the 1.8 risk margin and the deficiency of the cardiovascular safety listed in the FDA Complete Response Letter was successfully addressed from a statistical perspective. In conclusion, DEVOTE demonstrated that the cardiovascular safety of IDeg lies within acceptable bounds for marketing approval.’ I agree that the results of the interim analysis of DEVOTE support approval of insulin degludec and insulin degludec insulin aspart. Specific aspects are explored below.

*Study subjects and MACE event rate:*

The trial population of DEVOTE, which enrolled T2DM patients enriched for higher CV risk, consists of subjects with existing, or high risk of CV disease in an effort to ensure a population such that the MACE event rate would be sufficiently high. DEVOTE planned to randomize a total of 7,500 male and female subjects with T2DM at elevated risk for cardiovascular events based on the following two categories: subjects aged  $\geq 50$  years with established CV diseases, e.g. prior myocardial infarction; and, subjects aged  $\geq 60$  years with risk factors for CV diseases such as microalbuminuria or hypertension. Subject enrollment from this second category was limited to 1,500 to secure a study population with sufficient overall cardiovascular risk. Approximately 14.6% of the population (1114 subjects) was enrolled based solely on risk factors for CV disease, fulfilling the pre-defined criteria of a maximum of 1,500 subjects in this group in order to secure a study population with sufficiently high overall CV risk to accrue 633 first MACEs in a timely manner. (b) (4)

the observed event rate in DEVOTE at the time of the interim database lock is what would be expected (IDeg 1.9% and IGlax 2.0%). The sponsor’s enrichment strategy which was agreed upon with the Agency appears adequate to have generated the requisite number of MACE events within a reasonable time period.

In addition, at the End of Review meeting the Agency specified that a minimum of one-third of the study population should be derived from study sites within the United States, and that trial participants should be representative of the U.S. type 2 diabetes population with cardiovascular disease. This also appears to have successfully occurred with nearly 70% of the total population recruited from sites in the U.S. Overall, the statistical reviewer did not identify any issues related to subject selection that would affect the generalizability of the interim results.

*Reasonable follow up of study subjects and minimization of missing data:*

The protocol states that efforts will be made to follow all randomized subjects and collect outcome data for the complete duration of the trial. Subjects are scheduled to attend the study site once every month during the first 6 months and every third month during the rest of the

trial, and to have monthly phone contacts with the investigator between the site visits. Given that the subject retention rate was very high, these and any other specific mechanisms to enhance subject retention appear to have been successful. In fact, monthly contact is relatively frequent for a trial of this size and duration and is likely to have positively impacted the high subject retention. The statistical review states ‘by the time of the interim data cut-off, the disposition of subjects suggested that DEVOTE was well-conducted.’

*Active comparator design:*

The CV safety of Lantus was evaluated in a CVOT named the ‘ORIGIN’ study, where subjects with pre-diabetes and new onset T2DM were treated with Lantus versus standard of care. This trial showed no difference in MACE observed between the treatment groups. In addition, insulin glargine was the predominant comparator in the degludec Phase 3 experience, accounting for more than 70% of all active comparators. As a result, the CV signal identified was in large part based on the comparison of degludec to glargine. For these reasons, the Sponsor was told that the only active comparator that would be acceptable would be insulin glargine. The DEVOTE trial was designed with Lantus as the active comparator, and therefore, the interim results support the conclusion that the risk signal identified in the meta-analysis of the phase 3 efficacy trials is not likely represent a true excess in CV risk due to degludec.

*Trial blinding:*

In the CRL, the Agency requested a double-blind trial conducted to assess the cardiovascular safety of insulin degludec. In DEVOTE, IDeg and IGlar was supplied and administered using indistinguishable vials and syringes to allow a double-blind design of the CVOT. At the End of Review meeting the Sponsor had stated that blinding using this approach, i.e. as opposed to using insulin pen devices, may imperil the integrity of the final analysis due to anticipated higher drop-out rate, and that using vial and syringe may also affect the in-trial medication adherence. At this time the data suggest that the drop-out rate was not compromised by the use of vial and syringe as noted above, roughly 95% of subjects remained on treatment. A blinded trial addresses inherent biases that affect open-label trial designs and is more reassuring that the interim data analysis of DEVOTE should be relied upon for a regulatory decision over the meta-analysis which included many open-label trials.

*Adequate exposure to study drug:*

In order to believe that the MACE analyses estimate true CV risk related to treatment, it is important that subjects are exposed to an adequate dose of insulins in each study arm. Agreements were reached between the Agency and the Sponsor in order to help improve the likelihood that adequate exposure would occur, such as a target for fasting self-monitored blood glucose level of 90 mg/dL for dose titration, ensuring subjects with a prior history of insulin use who are receiving > 20 units are adequately represented in the study, ensuring that insulin-naïve individuals not constitute more than 1/3 of the total planned enrollees, and incorporating a plan to monitor the adequacy of dose titration in your study.

In addition to adequate exposure, similar exposure between study arms is also an important consideration. A “treat-to-target” concept was applied targeting similar glycemic control for all subjects in both arms with titration aiming for an HbA1c < 7%. Insulins are titratable drugs

with doses individualized to achieve certain glycemic targets. Following this insulin treatment scheme would be important for ensuring similar exposure to insulin products between the two study arms so that effects of the drugs on CV risk can be fairly compared. At the time of the interim analysis insulin dose data is still blinded to treatment allocation, and baseline HbA1c was reported only for the combined population. Therefore, whether or not the treat-to-target design was actually successfully followed and treatment groups had similar HbA1c at the time of the interim analysis is unknown. Ideally, verification that insulin dose titration and glucose control were roughly equivalent between study arms for the interim analysis would be done. However, these data are not necessarily required for the critical question that the interim analysis is intended to answer, and unblinding glycemic and dose data would lead to additional Sponsor personnel being unblinded to these data, potentially compromising overall trial integrity. Therefore, in my view maintaining trial integrity outweighs concerns about potential unequal dosing and glycemic control between study arms, which is unlikely to have occurred in a large, blinded trial.

Of note, in contrast to insulin therapies for diabetes, oral antihyperglycemic therapies usually have fixed doses and thus far the majority of CVOTs for oral drugs have been placebo controlled trials where the trial design specifies that the placebo group should be treated to standard of care. This design in theory should allow for similar HbA1c between study groups at the end of the trial, but with the recent completion of the CVOTs for saxagliptin, alogliptin, and sitagliptin it appears that the placebo arm generally does not reach the same level of glycemic control as the treatment arm, introducing potential bias in study results based on non-comparable glycemic control. DEVOTE hopefully will be successful in the treat-to-target design and CV risk in the final analysis will be able to be compared without concern for the potential bias of glycemic control itself on CV risk.

**Data quality:**

Data and reports in this submission were submitted electronically in support of these NDAs. The format, content and documentation of the submitted data were determined by the statistical reviewers to be adequate to conduct a statistical evaluation of the CV risk associated with insulin degludec. No data quality issues were identified.

**Limitations of interim trial results:**

DEVOTE was designed and initiated as a dedicated CVOT to provide definitive evidence of the CV safety profile of IDeg. The final confirmation of the CV safety of IDeg versus IGlax in terms of excluding the risk margin of 1.3 will be evaluated when at least 633 first MACE events have been accrued in DEVOTE. However, the Agency agreed that the Sponsor could base their NDA resubmissions on an interim analysis of the trial data to satisfy the 1.8 risk margin.

In accepting an interim analysis to resolve the deficiencies we need to acknowledge that there are limitations to the data. First, the interim data of DEVOTE provided only 24% of the total anticipated primary events in the trial with limited length of follow-up and drug exposure. As stated in the statistical review approximately 46% of the subjects had at least 6 months of follow-up, 21% had follow-up longer than 9 months, and only 5% of the FAS population had follow-up longer than one year. As such, the interim data of DEVOTE provides limited

information on the cardiovascular risk beyond 9 months of follow-up and almost no information beyond one year of follow-up. Further, based on the best assessment possible at this time there do not appear to be any trial conduct problems that would be expected to affect the interim data analysis; however, it remains possible that trial conduct issues that would not be apparent based on interim results, could be identified upon review of the final study results, such as unequal treatment of study groups in terms of glycemic control.

There are also well-recognized limitations of interim analyses in general, i.e. issues not necessarily specific to degludec. Some of these include accepting potentially misleading early results from fitting of noise that could lead to random over- or underestimates in the estimate of treatment effect. Further, interim data may be subject to less rigorous quality assurance and quality control processes than a completed trial. However, based on the review of the degludec resubmission, these concerns are theoretical at this time.

**Trial integrity:**

Any information that has the potential to unblind the ongoing DEVOTE trial could potentially bias study investigators and /or study subjects such as effects on subject enrollment or retention based on release of interim results and inability to complete trials and perhaps in ways that may not even be foreseeable. This could result in compromise of the final trial results. Therefore, measures to protect trial integrity are of the utmost importance. Indeed, confidentiality of interim results in cardiovascular outcomes trials was the subject of a public hearing at FDA on 11 Aug 2014.<sup>1</sup>

The statistical reviewers note that for DEVOTE the Sponsor established operational processes and procedures to preserve confidentiality and blinding of the trial and thereby ensure that the integrity of the ongoing trial is maintained after the interim analysis is conducted, submitted, and acted upon by the Agency. These processes were described in detail in a Data Access Management Plan (DAMP) developed by the applicant, which was shared with the Agency before the data base lock of the interim analysis (refer to Section 3.2.1.2 in the statistical review for a summary and discussion of this plan). Importantly, the DAMP specifies that to avoid unblinding of the results and to protect the integrity of the ongoing trial, none of the results or conclusions made based on unblinded interim data will be communicated publically, unless a critical safety concern is identified. The interim analysis for the purposes of ruling out the 1.8 risk margin was performed solely for regulatory purposes with no impact on the continuation of the trial (no early stopping). Further, no changes to the trial design and trial conduct will be made based on the results of the interim analysis. The statistical reviewer states that ‘The data access management plan (DAMP) was shared with the Agency and was considered acceptable.’

Dr. Condarco’s clinical review (section 7.7) contains a very detailed description of the procedures implemented to maintain data integrity. She also concluded that these were overall in agreement with Agency advice, including procedures for what should be unblinded vs. remain blinded, firewalls, and who had access to certain data. Her review also includes

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<sup>1</sup> Transcript of Part 15 - PUBLIC HEARING BEFORE THE COMMISSIONER Confidentiality of Interim Results in Cardiovascular (CV) Outcomes Safety Trials;  
<http://www.fda.gov/downloads/Drugs/NewsEvents/UCM436369.pdf>

additional information that was not included in the resubmission that were submitted upon her request to better understand the communication between the blinded and unblinded parties and their contact with the Data Monitoring Committee.

Although data integrity and maintenance of confidentiality is ongoing challenge, at the time of this review I am as confident as possible that all measures reasonably conceivable to maintain confidentiality in DEVOTE have been planned and/or implemented.

### **General Safety Update:**

As noted above, the CRL specified that an overall safety update with the additional exposure from their completed extension studies and other completed studies be part of the resubmission. The intention of this safety update was to ensure that no new safety signal became evident since the original NDA review that would affect the overall risk benefit assessment. Therefore, the focus of the clinical review was on the additional safety data accumulated since the application was last reviewed. Dr. Condarco compared the additional exposure data in the resubmission with Dr. Karim Calis' original safety review and looked for any changes in major safety findings.

From the cut-off date of the integrated summary of safety (ISS) which was the safety dataset submitted in the original NDA (31 January 2011) to the cut-off date for the Safety Update (30 September 2014), the following 18 additional trials were completed with IDeg:

- 12 phase 3 trials
  - 5 extension periods to phase 3a trials (Trials 3644, 3725, 3770 EX, 3667, 3643)
  - 6 phase 3 trials (Trial 3587, 3923, 3948, 4060, 3846, 3944)
  - 1 pediatric trial with a main and an extension period (Trial 3561 main + extension)
- 4 clinical pharmacology trials (Trials 1999, 4000, 3999, 3763)
- 2 other therapeutic trials (Trials 3874, 3943)

For insulin degludec insulin aspart 10 trials have been completed since the ISS (including one extension trial and two trials with exploratory formulations).

- 7 phase 3 trials (all in T2DM)
  - 1 extension part
  - 6 phase 3 trials
- 3 clinical pharmacology trials

Overall, the additional data from the completed extensions and other completed trials added an additional 3263 subjects exposed to any form of insulin degludec (IDeg or IDegAsp). For IDeg this resulted in an increase in total exposure in subject-years by almost double – from 2826 to 5344 subject-years. The increased subject –year exposure was represented across both type 1 and type 2 diabetes populations and included increased exposure for both insulin naïve and insulin-treated type 2 diabetes subjects. Therefore, the safety database in the Safety Update appears to be reasonably similar from a disease/demographic perspective to the safety database reviewed by Dr. Calis in the original application. For IDegAsp all of the increased exposure occurred in type 2 diabetes subjects. Further, Dr. Condarco points out that much of

the additional exposure reported in the Safety Update still occurred in the first 6 months of therapy as a result of trial design.

Data from DEVOTE were not included in the Safety Update. Datasets from DEVOTE were submitted separately from the Safety Update datasets. Data other than those needed for the interim analysis to exclude the 1.8 CV risk margin were not reviewed in this review cycle as they are considered incomplete and will be reviewed upon submission of the final study report for DEVOTE. Further, the majority of safety data from DEVOTE remains blinded. Although the datasets for SAEs and deaths were unblinded, the narratives for these events remained blinded. Severe hypoglycemic episodes that were positively adjudicated were also unblinded for the interim analysis. However, again, the Agency's previous review of hypoglycemia (a known safety issue with all insulins) concluded that degludec appeared to confer a reasonable hypoglycemia risk that was generally in line with the active comparator insulin glargine, but no new analyses of a potential hypoglycemia benefit would be considered until DEVOTE was complete.

This approach of not reviewing general safety data from the ongoing CVOT is in contrast to some recently approved products, e.g. empagliflozin. The advantage of including data from an ongoing CVOT is that this approach enriches the safety pool with data from subjects who are generally older with more advanced diabetes than those subjects in the typical diabetes phase 3 development programs. Such enrichment could enhance the ability to detect safety signals that may occur more commonly in older patients such as renal impairment and could be missed in a safety database made up of primarily younger subjects. On the other hand, the use of general safety data from an ongoing CVOT in order to approve or label a product has the potential to bias the ongoing trial and compromise the final results of the CVOT. Given that the overall safety profile of degludec was deemed acceptable during the original NDA review both in terms of the overall findings and the adequacy of the demographics and baseline disease characteristics of the exposed population, I do not believe that reviewing unblinded general safety data from DEVOTE is warranted, and the potential for compromise of trial integrity outweighs any need for these data at this time. It is acceptable to review these data with submission of the final study report for the degludec NDAs.

In sum, review of the Safety Update in the resubmission showed no important differences in the safety profile for degludec and degludec aspart compared to the safety findings at the time of the original NDA review. Therefore, there are no new safety issues of concern that should be considered in the overall risk benefit assessment for degludec and degludec aspart. Please see Dr. Condarco's clinical review for details of the Safety Update.

## **9. Advisory Committee Meeting**

An advisory committee meeting was *not* convened for the second cycle resubmission. Please refer to the original NDA reviews for information regarding the Advisory Committee meeting convened for these applications during the original review cycle.



## 10. Pediatrics

Tresiba and Ryzodeg 70/30 were reviewed 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 – (b) (4)  
Deferral: T1DM 1yr to (b) (4)

The PeRC agreed to this plan with the caveat that the Division should reconsider the planned (b) (4) 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. PeRC stated that if the Division changed the waiver and deferral plan along these lines, the NDAs would not need to be re-presented at a PeRC meeting. The Division's view is that insulin degludec and perhaps insulin degludec insulin aspart have the potential to be used by T2DM pediatric patients (b) (4). The Division will amend 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 (b) (4); (b) (4)

(b) (4)  
The trial for Tresiba is an open-label, 26-week, randomized, controlled efficacy and safety 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. At (b) (4)

(b) (4) This study will be a Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR) and the final report submission will be due June 2016.

(b) (4). The trial (b) (4) 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). This study will be a Pediatric Research Equity Act (PREA) Postmarketing Requirement (PMR). Final report submission will be due June 2016. (b) (4)

As a historical note, at the time of the original NDA submissions, different procedures were in place to review pediatric protocols, e.g. the requirement to submit an initial Pediatric Study

Plan (iPSP) had not yet been established. Therefore, there are no ‘agreed iPSPs’ for these applications.

## 11. Other Relevant Regulatory Issues

### *Use of proprietary name ‘Lantus’ in Tresiba/Ryzodeg 70/30 labeling*

The Division sought input from the Office of Regulatory Policy regarding use of the proprietary name Lantus in the labeling for these products. There is precedent (Toujeo, Humalog, Novolog, and Bydureon) for use of the comparator trade name in approved labeling by the same sponsor. However, it was unclear to the Division whether this would be acceptable in approved labeling by a different sponsor.

Based on Division experience, U-100 insulin glargine products approved under the 505(b)(2) pathway should not be considered the ‘same’ as the listed drug. Given that Basaglar (insulin glargine) is only tentatively approved, a modified approach to labeling is not necessary at this time. Therefore, the Office of Regulatory Policy has recommended the PI describe the comparator as “Lantus (insulin glargine)” the first time it is referenced in labeling, and subsequently describe the comparator as insulin glargine. They also recommend that Novo Nordisk use this approach (trade name in the initial reference, and subsequently refer to the nonproprietary name) for references to comparator insulin products owned by Novo Nordisk instead of solely referring to the other comparator products by trade name.

## 12. Labeling

DMEPA conducted a carton and container labeling review and found that the carton and container labeling are acceptable from a medication error perspective. Refer to reviews dated 17 Jul 2015 and 7 Aug 2015. Updated carton and container labeling based on the recommended change to the trade name (i.e. (b) (4) to Ryzodeg 70/30) is pending at the time of this memo.

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.

### High Level Labeling issues:



(b) (4)  
Single arm data showing the incidence of hypoglycemia in Tresiba and Ryzodeg arms is recommended. A statement that there were no clinically important differences between Tresiba/Ryzodeg and active comparator is also recommended for the following reasons: the statement is adequate to inform prescribers of the relative risk of hypoglycemia vs. active comparator without being misleading; this statement is acceptable because it refers to the currently available data only and is written in past tense. A similar approach was taken for the recently approved insulin product Toujeo (insulin glargine U-300).

#### *'Flexible' dosing claim*

In two of the clinical trials against the active comparator insulin glargine (one in type 1 diabetes patients and one in type 2 diabetes patients), insulin degludec was administered once daily using a dosing interval of 8 hours for the Monday, Wednesday, Friday injections and a dosing interval of 40 hours for the Tuesday, Thursday, Saturday and Sunday injections. Dosing with this 'flexible' regimen was shown to provide a level of glucose control at the end of 26 weeks that was not unacceptably worse than that provided by glargine administered once daily using a fixed 24-hour dosing schedule. There were no safety concerns, e.g. an excess of hypoglycemia events, with the 'flexible' regimen. In addition, the trials showed similar glycemic control between insulin degludec arms dosed with this 'flexible' schedule as compared to insulin degludec arms dosed with a fixed, i.e. once daily at the same time every day, dosing schedule, although the study did not include a prespecified endpoint for the degludec 'fixed' vs. degludec 'flexible' regimens. A third trial that compared the flexible dosing regimen of degludec to sitagliptin and also showed acceptable efficacy.

The Sponsor is proposing the language (b) (4), in the Tresiba label. In my view, this language is not acceptable because it is vague ( (b) (4) is not clear). Labeling guidances recommend against terminology that is vague and without established regulatory meaning. In addition, this language has a promotional tone. This reviewer could anticipate insulin competitors seeking labeling language stating (b) (4), similar to the sought after labeling claims that refer to the duration of action of insulin products. Indeed, Novo Nordisk has proposed to call insulin degludec an (b) (4) insulin. (This language is similarly not acceptable). I recommend that the dosing schedule for Tresiba be 'once daily at any time of day' with the instruction to ensure a minimum of eight hours between doses.

#### *Adverse reactions*

Studies with Tresiba/Ryzodeg were conducted entirely with active comparators; there are no placebo-controlled data to inform safety. While this is acceptable to support approval (insulins are difficult to blind because of injection volumes, delivery devices, etc. and it is unethical to conduct placebo controlled insulin trials in type 1 diabetes patients because these patients need insulin to survive) the Office of Prescription Drug Promotion has advised the Division to show single arm data only for common adverse events including hypoglycemia in section 6 of the full PI because this approach will help to prevent inappropriate safety claims, e.g.

hypoglycemia risk reduction, based on comparisons that the trials were not designed or powered to assess (see also discussion in Dr. Guettier's original NDA summary review).

### **13. Recommendations/Risk Benefit Assessment**

- Recommended Regulatory Action

Approval

- Risk Benefit Assessment

Approval is recommended for both products (insulin degludec and insulin degludec insulin aspart). My recommendation is aligned with the approval recommendations from all review disciplines.

There is substantial evidence of effectiveness from nine adequate and well-controlled pivotal phase 3 trials and five adequate and well-controlled pivotal phase 3 trials, for insulin degludec and insulin degludec insulin aspart, respectively, for the claimed indication (improvement in glycemic control in patients with diabetes mellitus). In these NDAs the determination of effectiveness is based on the surrogate endpoint of HbA1c which is consistent with the current approach to diabetes drug evaluation. The 2008 FDA draft guidance entitled Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention states, "For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control."

In the original NDA review a signal of cardiovascular risk associated with insulin degludec based upon a pre-specified meta-analysis of MACE+ observed in 17 efficacy clinical trials from the phase 3 development programs of insulin degludec and insulin degludec insulin aspart. Due to the inherent deficiencies associated with a meta-analysis of open-label efficacy trials, the CV signal was considered uncertain which warranted a further trial designed specifically for the evaluation of cardiovascular risk. The Agency agreed that an interim analysis from a dedicated CVOT to rule out a 1.8 risk margin could be the basis for a resubmission of the NDAs and if found acceptable the basis for approval of the NDAs. For this resubmission the Sponsor has provided the interim results from DEVOTE which have adequately addressed the deficiencies related to cardiovascular safety of insulin degludec and insulin degludec insulin aspart for approval. Further, the point estimate of the estimated hazard ratio is reassuring (b) (4)

The design and analysis of the DEVOTE trial were agreed upon with the Agency with incorporation of specific design elements to overcome deficiencies of the meta-analysis. The interim results from DEVOTE are based on a planned interim analysis and the results appear to be statistically robust with all sensitivity analyses supporting the primary analysis, consistency across subgroups, and no identifiable trial conduct problems. I believe that the

interim results of DEVOTE are a more reliable estimate of true CV risk than the meta-analysis and should support a conclusion of acceptable CV risk of degludec and degludec aspart sufficient for approval. This opinion assumes completion of DEVOTE as a postmarketing commitment.

As with most insulin products, the effectiveness of insulin degludec was established for the most part by non-inferiority studies against active comparator insulins. A study with non-inferiority hypothesis testing is designed to demonstrate that a new insulin is not unacceptably worse than a marketed insulin. For all of these studies insulin degludec met the non-inferiority criteria, but in no study did insulin degludec prove to be more effective than the insulin comparator. The Divisional summary memo from the original NDA review extensively discusses the relative benefit of insulin degludec, focusing on each potential benefit as proposed by the Sponsor, e.g. hypoglycemia advantage, longer duration of action, compared with other basal insulin products because the potential CV signal identified in the original review required a critical assessment of whether there were any potential benefits of insulin degludec that would outweigh the apparent CV safety risk and allow for approval at the time of the original application. As evidenced by the CR action, insulin degludec and insulin degludec insulin aspart products were concluded to be associated with an increased CV risk relative to comparators for which a benefit could not be identified to offset this safety concern at present. For the resubmission, which demonstrates that degludec is not associated with an unacceptable CV risk, these considerations of whether degludec offers any advantage from an efficacy perspective over existing therapies plays a lesser role in the risk/benefit assessment. The interim analysis of MACE in DEVOTE met the 1.8 risk margin and has satisfactorily addressed the CV safety-related deficiency cited in the CR letter. In addition, no new safety issues were identified based on an updated analysis of general safety data. In the absence of a concerning safety issue, the benefits of insulin degludec and insulin degludec insulin aspart outweigh the risks.

- Recommendation for Postmarketing Risk Evaluation and Management Strategies

None

- Recommendation for other Postmarketing Requirements and Commitments

At the time of this summary memo, the Postmarketing Requirements and Commitments (other than PREA PMRs which are discussed in Section 10) have been agreed upon between the Agency and Sponsor. There is one non-PREA PMR as follows:

Conduct a randomized, double-blind, active-controlled trial evaluating the effect of Tresiba (insulin degludec injection) on the incidence of major adverse cardiovascular events (MACE) in subjects with type 2 diabetes mellitus. The primary objective of the trial should be to demonstrate that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio comparing the incidence of adjudicated MACE (nonfatal myocardial infarction, non-fatal stroke, cardiovascular death) observed with Tresiba to that observed in the comparator group is less than 1.3.

Trial Completion: *December 2016*

Final Report Submission: *September 2017*

The above PMR is essentially a requirement for the Sponsor to complete and submit for review the DEVOTE trial.

There are two Postmarketing Commitments (PMCs). Both stem from the Office of Biotechnology Products (OBP) findings from the first review cycle that the Sponsor's assay to detect antibodies to insulin degludec was not sufficiently sensitive. (See OBP review in DARRTS) These PMCs are as follows:

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).

Final Report Submission: *September 2016*

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.

Final Protocol Submission: *January 2017*

Trial Completion: *July 2017*

Final Report Submission: *October 2017*

- Recommended Comments to Applicant

No comments are recommended to the applicant at this time.

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/s/  
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LISA B YANOFF  
09/21/2015

JEAN-MARC P GUETTIER  
09/22/2015