CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

SUMMARY REVIEW

Division Director Summary Review for Regulatory Action

Date	(electronic stamp)
From	Jean-Marc Guettier, MD
Subject	Division Director Summary Review
NDA/BLA # **Supplement #**	203314 and 203313
Applicant	Novo Nordisk
Date of Submission	26 March, 2015
PDUFA Goal Date	26 September, 2015
Proprietary Name / **Non-Proprietary Name**	NDA 203314-Tresiba (insulin degludec injection) NDA 203313-Ryzodeg 70/30 (insulin degludec and insulin aspart injection)
Dosage Form(s) / Strength(s)	Tresiba Dosage Form-Injection Tresiba Strengths- 100 U/mL (600 nmol/mL of insulin degludec) or 200 U/mL (1200 nmol/mL of insulin degludec) Ryzodeg 70/30 Dosage From-Injection Ryzodeg Strength- 100 U/mL (420 nmol/mL of insulin degludec and 180 nmol/L of insulin aspart)
Applicant Proposed Indication(s)/Population(s)	Tresiba is indicated to improve glycemic control in adults with diabetes mellitus. Ryzodeg 70/30 is indicated to improve glycemic control in adults with diabetes mellitus.
Action/Recommended Action for NME:	(Approval)
Approved/Recommended Indication/Population(s)	Identical to applicant proposed

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	**CONDARCO, TANIA A; CALIS, KARIM A.**
Statistical Review	**LI, BO; LIU, CYNTHIA Y.**
Pharmacology Toxicology Review	**TSAI-TURTON, MIYUN M.**
OPQ Review	**RAMASWAMY, MUTHUKUMAR; LEGINUS, JOSEPH**
Microbiology Review	**VINAYAK, PAWAR**
Clinical Pharmacology Review	**KHURANA, MANOJ**
OPDP	**KALOLA, ANKUR S.**
OSI	**MULINDE, JEAN**
CDTL Review	**YANOFF, LISA**
OSE/DEPI	**BRIGHT, PATRICIA L.**
OSE/DMEPA	**VEE, SARAH K.**
OSE/DRISK	**PATEL, MONA**

OND=Office of New Drugs
OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion

OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

Benefit-Risk Assessment

APPEARS THIS WAY ON ORIGINAL

Benefit-Risk Summary and Assessment

The applicant has demonstrated that insulin degludec administered as Tresiba or pre-mixed with insulin aspart as Ryzodeg 70/30 improved glycemic control in patients with type 1 and 2 diabetes mellitus who were not optimally controlled at trial entry. Effectiveness was established by comparing the glucose lowering effect of Tresiba and Ryzodeg 70/30 to the glucose lowering effect of currently marketed insulin comparators in treat to target trials where doses of the new drug and comparator drug were adjusted to achieve pre-defined glycemic goals. Non-inferiority comparisons as well as responder analyses shows a trend that suggests Tresiba provides slightly less effective glucose lowering than glargine U-100 (i.e., the most widely prescribed and arguably the current standard of car, once daily, long acting insulin). The safety and effectiveness of TRESIBA and Ryzodeg 70/30 was established when used in combination with a mealtime insulin in both diabetes types and when used in combination with common oral anti-diabetic agents in type 2 diabetes. The applicant has also demonstrated that administering Tresiba at <u>any time</u> each day resulted in a treatment effect that was, from a clinical standpoint, not unacceptably worse than administering Tresiba at <u>the same time</u> each day in both patients with type 1 and type 2 diabetes in two pivotal trials evaluating a worst-case scenario dosing schedule [i.e., an injection schedule that alternated between long (40 hours) and short (8 hours) dosing intervals]. Risk of hypoglycemia was clinically comparable between the <u>same time</u> each day and <u>any time</u> each day regimens in these two trials. This is the first long-acting insulin to establish the safety and effectiveness of <u>an</u> <u>any time a day</u> dosing regimen in two clinical trials. The option to inject a long acting insulin at any a day may provide added convenience to patients. Finally, the applicant demonstrated the safety and effectiveness of the U200 formulation in a clinical trial. The twice concentrated insulin will be useful to patients requiring more than 80 units of insulin degludec per day by minimizing the number of daily injections of long-acting insulin required to meet demands.

The applicant hypothesized that Tresiba's unique PD profile would confer the insulin with a lower inherent risk of hypoglycemia compared to glargine U-100. Testing this hypothesis was a secondary objective in some trials and the primary objective of a meta-analysis of glargine comparator trials in the Tresiba NDA. (b) (4)

In the meta-analysis, for example, the reduction in risk; did not extend to type 1 diabetes (a population particularly at risk for hypoglycemia and that stands to benefit the most from risk reduction in absolute terms), was only seen when considering one endpoint (event rate and not incidence rate) and one definition of hypoglycemia (a non-specific definition which includes mostly non-severe events and events in part attributable to point of care measurement errors). As was stated earlier, glycemic control was on average better on glargine U-100 than Tresiba and differences in glycemic control alone could have contributed to slight differences in observed hypoglycemia event rate. When considering the most susceptible population, and the most severe and clinically meaningful hypoglycemia definition no trend of benefit was apparent.

Approval of the applications was refused on the first review cycle because cardiovascular (CV) risk was identified as a potential product related risk and suggested insulin degludec was not safe under the conditions of use recommended. Although the analysis relied on agreed upon event definitions, proactive and prospective data capture, and independent event adjudication, the analysis of CV-risk was not derived from a single trial enrolling patients at high baseline cardiovascular risk but rather from a meta-analysis of all available cardiovascular events accrued in 17 glycemic efficacy trials. The data in the resubmission is more reliable than the data in the original CV-risk meta-analysis in that it is derived from a single trial specifically designed to address CV-risk. The analysis in the resubmission is also based on ~1.7 times the number of major adverse cardiovascular events (non-fatal MI, non-fatal strokes and CV-death) than the number of events in the meta-analysis. The analysis in the resubmission has definitely excluded the possibility that insulin degludec is associated with an excess in CV-risk of 80% over a comparator with no known CV-risk. Tresiba and Ryzodeg 70/30 product-related risks, other than CV-risk, were found to be comparable to risks associated with other approved long-acting insulin analog products.

I recommend approval. As laid out in the first Complete Response letter, the applicant will be required to complete their ongoing cardiovascular outcomes trial with the objective of definitively excluding the possibility that use of degludec is associated with an excess CV-risk of 30% or more over a comparator with no known CV-risk in the post-marketing setting.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• *29. 1 million ndividuals in the US have diabetes* • *Type 1 and Type 2 diabetes mellitus are diseases associated with abnormal glucose metabolism that result in elevation of blood glucose. Acute elevation in blood glucose can lead to symptoms and chronic elevation of glucose over years can cause blindness, kidney failure, and nerve damage. Diabetes is also associated with serious heath complications including an increased risk of atherosclerotic cardiovascular disease. Diabetes is the leading cause of blindness, lower extremity amputations and end stage renal disease in the United States. It is also a leading cause of premature death in the United States.* • *Type 1 diabetes is caused by insulin deficiency and patients require insulin for survival*	• *Lowering of blood glucose over many years (~10 years) with glucose lowering drugs (insulin, sulfonylurea and metformin) has been shown to reduce the incidence and progression of microvascular disease complications (eye, kidney and never damage) in prospective studies of patients with Type 1 diabetes (Diabetes Control and Complications Trial) and Type 2 (United Kingdom Prospective Diabetes Study) diabetes mellitus. Changes to HbA1c (hemoglobin A1c) were used as a measure of glucose lowering in these trials. HbA1c level and likelihood of new or progressive microvascular disease were highly correlated in these studies* • *Effectiveness of new anti-diabetic products is established through their effect on HbA1c over ~6 months. Although not directly captured, the intended clinical benefits are acute symptomatic control of high glucose and reduction in long-term diabetes complications tied to high glucose. HbA1c is thus a surrogate used for full approval and*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• *Type 2 diabetes is caused by an insufficient response of the body to insulin and to inadequate insulin secretion* •	*long term studies documenting an effect on microvascular are not required.* • *Safety and effectiveness of new agents are typically characterized across various common clinical use settings (i.e., monotherapy setting or as an add-on therapy to commonly use drugs)*
Current Treatment Options	• *Twelve classes of drugs, including insulins, are approved to improve glycemic control in patients type 2 diabetes* • *Insulins and amylin are available to improve glycemic control in patients with type 1 diabetes mellitus*	• *In type 2 diabetes insulin is generally avoided by caregiver and patients until the disease is fairly advanced because of its side effect profile (hypoglycemia, weight gain, need for injection and monitoring) but remains the most effective glucose lowering agent available.* • *In type 1 diabetes insulin is required to normalize macronutrient metabolism and prevent life-threatening complications of keto-acidosis, extreme elevation in blood glucose and starvation.*
Benefit	• *Reduces HbA1c from baseline in patients with type 1 and 2 diabetes mellitus not adequately controlled at baseline over 26 to 52 weeks* • *Provides background insulin in the form of a once daily injection that can be administered at any time of day.* • *Provides a twice concentrated background insulin preparation with PK/PD characteristics similar to those of the U100 preparation.*	• *Improvement in glucose control acutely in patients with very high glucose improves signs and symptoms associated with hyperglycemia. Improvement in glucose control over years should reduce the incidence and progression of eye, kidney and nerve disease* • *Reduces the number of injections needed and may provide more convenience to patients.* • *Availability of a twice-concentrated insulin allows delivery of a larger dose of insulin in ½ the volume. May be beneficial to patients resistant to insulin's action who require high doses by in effect reducing the number of injections needed per day. The maximum dose of insulin U100 that can be delivered in a single injection with standard pen device or syringe is ~80-100 units.*
Risk	• *Hypoglycemia* • *Medication Errors* • *Weight gain* • *Fluid retention* • *Injection Site Reaction/Lipodystrophy* • *Allergic Reactions* • *Immunogenicity* • *Potential CV-risk*	• *All Tresiba and Ryzodeg 70/30 product-related risks, except for potential CV-risk, are similar to the risks for other approved long-acting insulin analog products.*

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk Management	• *The risks of Tresiba and Ryzodeg 70/30 will be communicated and mitigated through labeling. Risks, other than CV-risk and immunogenicity, will be followed through routine pharmacovigilance in the post-marketing setting.* • *CV-risk will be evaluated at the completion of the DEVOTE safety trial.* • *Risks associated with dosing errors that may result from introduction of a twice concentrated long acting insulin product in the marketplace (i.e., Tresiba U200) will be mitigated through labeling to ensure adequate product differentiation and by restricting the U200 product presentation to a dedicated, relatively tamper-proof, delivery device specifically calibrated to deliver insulin in Units with no requirement for patients or caregivers to perform conversions for appropriate dosing. Routine pharmacovigilance will be used to monitor for this risk.* • *Immunogenicity will be further evaluated through use of post-marketing commitments.*	• *The current available data suggest the risks associated with Tresiba and Ryzodeg are similar to the risks of other approved long-acting insulin analog products which do not require Risk Evaluation and Mitigation Strategies to ensure the benefits outweigh the risks for the proposed indication.* • *An interim analysis from a dedicated cardiovascular outcomes trial performed after accrual of 25% of the events needed for the final analysis, does not suggest that insulin degludec use, in type 2 DM patients at high risk of a new or recurrent CV event, causes an 80% excess in CV-risk when compared to insulin glargine. Although results of the interim analysis are reassuring and reliably exclude a large excess risk, estimates based on partial or incomplete data (i.e., interim data) are subject to change with accrual of additional data and may ultimately prove unreliable for the purpose of definitively excluding a smaller, yet clinically meaningful, risk increase. The most reliable and robust estimate of degludec associated CV-risk will be derived from the final analysis of the DEVOTE trial.* • *Risk of dosing errors with U500, another concentrated insulin, has been attributed in part to lack of both adequate product differentiation and availability of a dedicated and specifically calibrated delivery device.* • *The anti-drug antibody assay developed by the applicant is insufficiently sensitive and the applicant has committed to developing an improved assay. While analyses performed with the current assay do no suggest an obvious effect of anti-drug antibodies on product efficacy or safety, conclusions based on these analyses are subject to the limitations of the assay. Immunogenicity data with a newer more sensitive assay will be obtained post-marketing.*

1. Background

On 29 September, 2011 Novo Nordisk submitted two new drug applications (NDA), for Tresiba and Ryzodeg respectively, under section 505(b)(1) of the Federal Food Drug and Cosmetic Act. The applicant is seeking to market Tresiba and Ryzodeg 70/30 to improve glycemic control in adults with diabetes mellitus. Tresiba and Ryzodeg 70/30 are injections containing insulin degludec in solution. Insulin degludec is a new, long-acting, insulin dosed according to an individual's metabolic needs and administered subcutaneously once daily to cover background (i.e., basal) insulin requirements in patients with type 1 and type 2 diabetes mellitus. Two strengths of Tresiba and one strength of Ryzodeg 70/30 have been proposed for marketing. A full summary of the issues identified in the first cycle of review can be found in the Division Decisional Memorandum entered in the Document Archiving Reporting and Regulatory Tracking System (DARRTS) under NDA 203314 and NDA 203313 on 1 February 2013.

On 8 February 2013 the two applications received a Complete Response for manufacturing deficiencies noted by the Office of Compliance on inspection of the Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark, manufacturing facility and because results of a meta-analysis comparing cardiovascular risk (CV-risk) between insulin degludec and comparators (mostly other insulins and predominantly insulin glargine) suggested CV-risk was higher in patients randomized to insulin degludec.[1] The meta-analysis was pre-planned, stratified by trial and was based on all cardiovascular events data accrued across all completed and ongoing Tresiba and Ryzodeg phase-3 glycemic efficacy trials (17 trials in all). Cardiovascular events across the Tresiba and Ryzodeg programs had been prospectively collected and adjudicated using agreed-upon endpoint definitions. In the analysis based on 132 first events of; CV-death, non-fatal myocardial infarction, non-fatal stroke or unstable angina (i.e., MACE+), CV-risk was estimated to be 30% and up to 93%[2] higher on degludec than on comparators. In a secondary analysis based on 91 first events of; CV-death, non-fatal myocardial infarction and non-fatal stroke (MACE), CV-risk was estimated to be 67% and up to 175%[3] higher on degludec than on comparators. In light of the CV-risk meta-analysis results which suggested insulin degludec was not safe under the conditions recommended, approval of the applications was refused.

In the two applications, Novo Nordisk had demonstrated across fourteen 26 and 52 week trials that the glucose lowering effect afforded by insulin degludec containing products, captured using the change in Hemoglobin A1c (HbA1c) from baseline, was not unacceptably worse than the glucose lowering effect afforded by available, marketed, basal insulin comparators in patients with type-1 and type-2 diabetes[4]. Although the glucose lowering

[1] Refer to Complete Response communication entered in the DARRTS by Rachel Hartford on 8 February 2013.
[2] Based on the corresponding upper 95% confidence margin around the point estimate.

difference between treatment and comparator fell within the bounds of the pre-specified non-inferiority margins, a trend for Tresiba providing marginally less glucose lowering benefit was observed in the majority of trials when examining point estimates of the difference in mean change from baseline in HbA1c and proportions of subject achieving optimal HbA1c control (i.e., <7%) at trial end. Specific risks, other than CV-risk, identified in the safety review, and attributed to degludec containing products, were consistent with the drug class and included; hypoglycemia, injection site reactions, fluid retention, weight gain, hypersensitivity and allergic reactions. (b) (4) , the Agency did not agree that this claim was justified or supported by the data for multiple reasons identified in the review which were summarized in the aforementioned Divisional Decisional Memorandum and the Efficacy Review documents.

In the Complete Response letter, the Agency asked the applicant to exclude the possibility that insulin degludec was associated with excess CV-risk by comparing degludec to glargine[5] in a dedicated, double-blind, cardiovascular outcomes trial. The letter specified that a three components composite MACE endpoint was the outcome of interest for this trial. At an End-of-Review meeting held on 4 April 2013[6], the Agency defined excess CV-risk as a risk of 30% or higher[7] compared to glargine and advised the applicant to adequately power the trial to exclude this level of risk. At that meeting, the Agency agreed that a trial restricted to patients with type-2 diabetes, enriched for prevalent co-morbid CV disease or CV-disease risk factors could be used for this purpose and provided guidance aimed at enhancing generalizability of the results and minimizing the potential for bias. Issues regarding specific glucose targets, minimal dosing requirements, appropriateness of other comparators and general approach to the analyses were also discussed.

In both the Complete Response letter and at the End-of-Review meeting, the Agency agreed to review, and potentially approve the applications, based on an interim analysis of CV-risk if the point estimate and corresponding upper risk margin for the results of this interim analysis were reassuring. The Agency also agreed that the interim analysis should be powered to, at minimum, definitively exclude the possibility that insulin degludec caused an 80% excess CV-risk compared to glargine. This in effect meant that the interim analysis, and potential approval of the applications, would occur after accrual of ~25% of the total cardiovascular events needed to fulfill the dedicated cardiovascular outcomes trial's primary objective.
A risk incurred with an approach that relies on use of an interim analysis relates to disclosure of interim results (i.e., results from a partially completed trial). Disclosure of interim clinical

[4] Refer to Efficacy Review entered in DARRTS by Jean-Marc Guettier on 26 January 2013.
[5] Glargine was the most common comparator used across degludec glucose lowering efficacy trials, has the same physical appearance and dosing schedule as degludec and is the only basal insulin with a robustly established, neutral, CV-risk profile. Refer to the result of the ORIGIN trial for details (N Engl J Med 2012; 367:319-328).

[7] This is the same risk level as that established in the; *Guidance for Industry-Diabetes Mellitus Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes.*

trial data or interim trial results by any party while the clinical trial is still ongoing has the potential to impact behavior of the sponsor, investigators and participants through pre-judgment and to influence trial conduct for the remaining portion of the clinical trial. These changes in turn could jeopardize the integrity of the trial, render the overall trial results uninterpretable and lead to failure of the trial's primary objective. With loss of trial integrity, the benefit that individual participants and the general public stand to gain from availability of a timely and reliable evaluation of the trial's main scientific question would also be lost and with it the trial's ethical underpinnings.

To mitigate against this, the applicant was asked to submit a data access plan prior to interim data unblinding that would define procedures to be put in place to limit access of interim information to those individuals within and outside the company considered essential to the regulatory submission of the applications. This plan, along with a list of names of individuals within and outside Novo Nordisk who would have access to interim data, interim results or both was submitted to the IND on 10 November 2014, was reviewed and deemed acceptable by the Agency. To date; the data monitoring committee (5 individuals), the independent statistical support group (12 individuals), Novo Nordisk personnel with clinical development, clinical safety, regulatory affairs, medical writing, and publishing responsibilities (15 individuals) and external consultants also supporting regulatory submission (5 individuals) have had access to interim data or interim results or both. Novo Nordisk has put in place an adequate environment that includes electronic and physical firewalls to minimize the extent of unblinding so as to ensure trial integrity is not compromised and final analysis of insulin degludec's CV-risk is timely and reliable (refer to Table 44 in Dr. Condarco's review for an overview of Committees and blinding status of each of these committees in the ongoing trial).

Novo Nordisk filed Class 2 re-submissions for the Tresiba and Ryzodeg 70/30 applications on 26 March 2015 with interim results from their dedicated cardiovascular outcomes trial (DEVOTE trial) comparing CV-risk in adults with type 2 diabetes using degludec versus glargine to support safety of the two products. In addition, the applicant provides updated integrated safety analyses with safety data accrued from ongoing extensions of previously reviewed Phase 3 glycemic control trials or from altogether new and completed short term trials.

2. Product Quality

Chemistry, manufacturing and controls (CMC) data related to the drug substance and drug products (Tresiba and Ryzodeg 70/30) manufacturing processes were reviewed during the first cycle and are detailed in Drs. Leginus' and Ramaswamy's reviews of the two applications. Drs. Vinayak and Metcalfe reviewed manufacturing processes and controls to ensure product quality from a microbiology/sterility perspective. Dr. Shiu from the Center for Devices and Radiological Health (CDRH) reviewed the engineering and biocompatibility aspects of the delivery device and recommends approval. The Office of Compliance within CDRH has

reviewed manufacturing and assembly of the finished drug/device combination products, including in-process and final controls and recommends approval. Deficiencies found by the Office of Compliance on inspection of the Novo Nordisk A/S, Novo Alle, DK-2880 Bagsvaerd, Denmark, commercial manufacturing and testing facilities during the first review cycle have been addressed. There are no outstanding CMC review issues that preclude approval.

A shelf life of (b) (4) months will be granted for the insulin degludec drug substance when stored at (b) (4). This is based on acceptable long-term stability results from real-time studies obtained for the drug substance from primary stability batches at production scale. The Tresiba product shelf-life will be 30 months at 2°C - 8°C, protected from light. Tresiba in-use shelf-life period will be 56 days at temperatures not exceeding 30°C. Ryzodeg 70/30 product shelf-life will be 24 months at 2° - 8°C, protected from light. Ryzodeg 70/30 in-use shelf life will be 28 days at temperatures not exceeding 30°C.

The product presentations for Tresiba and Ryzodeg 70/30 are multiple-dose, disposable pen injectors[8] containing a 3 mL cartridge pre-filled with an insulin degludec solution. The 100 U/mL products [i.e., Tresiba (100 U/mL) and Ryzodeg 70/30 (100 U/mL)] will deliver up to 80 units of insulin and the 200 U/mL product (Tresiba 200 U/mL)] will deliver up to 160 units of insulin. Usability studies (i.e., a user handling studies and a product differentiation studies) with the final product presentations were reviewed by the Division of Medication Error Prevention and Analysis during the first review cycle and demonstrated that, from a medication errors perspective, the PDS290 pen injector presentations could be used safely by the intended users. No medication error issues that would preclude approval were identified.

3. Nonclinical Pharmacology/Toxicology

The nonclinical reviewers recommend approval of the two NDAs. Dr. Tsai-Turton in her review has not identified issues that would require additional post-marketing studies. Please refer to the reviews by Drs. Tsai-Turton and to the summary review by Paul Brown for a detailed review of the nonclinical pharmacology and toxicology program in these two applications.

4. Clinical Pharmacology

The clinical pharmacology of Tresiba and Ryzodeg 70/30 were reviewed previously. Please refer to reviews by Dr. Khurana for Tresiba and Jain for Ryzodeg 70/30, respectively. The clinical pharmacology review team recommends approval of the two NDAs.

[8] Relying on Novo Nordisk's proprietary PDS290 pen-injector platform used and approved for delivery of insulin Levemir and Novolog.

5. Clinical Microbiology

Not applicable.

6. Clinical/Statistical-Efficacy

The efficacy of Tresiba and Ryzodeg 70/30 respectively was reviewed during the first submission cycle. Refer to Division Decisional Memorandum and Clinical Efficacy Review documents for details. In all Tresiba and Ryzodeg trials, the primary efficacy objectives were met and no efficacy issues that would preclude approval were identified. Dr. Yanoff's CDTL memorandum provides a high level summary of previously reviewed efficacy data.

7. Safety

The safety of Tresiba and Ryzodeg 70/30 respectively was reviewed during the first submission cycle. Refer to the Clinical Safety Review document by Dr. Karim Calis for details and to the Clinical Efficacy Review document for a review of the hypoglycemia findings in the application. Other than the issues surrounding CV-risk discussed in the Background section of this document, Dr. Calis did not identify another specific safety issue that would have precluded approval of Tresiba or Ryzodeg 70/30 products in the original data supporting filing and 120-day safety update of the NDA's. In these re-submissions, Dr. Tania Condarco reviewed updated safety information that includes clinical safety data accrued since the time of original database lock (i.e., 31 January 2011) and Dr. Li reviewed data and results of the interim CV-risk analysis specifically. No safety issues that would preclude approval were identified in the re-submissions. Refer to Dr. Condarco and Li's reviews for a detailed account of the review findings. My memorandum will summarize key elements of the safety update and interim CV-risk assessment.

Updated integrated safety analyses capture data accrued in glycemic efficacy trials until 30 September 2014. Data from 5 extensions of parent trials, six new phase-3 trials, and 1 pediatric trial were not available in the original NDA submissions and have since been integrated for the purpose of updated safety analyses. The integrated summary of safety pools all subjects exposed to Tresiba and Ryzodega 70/30 products in the phase 3 glycemic efficacy trials (i.e., does not include data from the ongoing CVOT). As Dr. Condarco shows in Tables 3 and 4 of her review, the updated integrated safety information includes an additional 1931 and 1022 subjects exposed to Tresiba and Ryzodeg 70/30 products respectively. Exposure duration to Tresiba and Ryzodeg 70/30 has in turn increased by 2517 and 590 subject years of exposure respectively since the date of the original integrated safety database lock (31 January 2011). This brings the total number of subjects exposed to Tresiba and Ryzodeg 70/30 in glycemic efficacy trials to 6206 and 2382 respectively and the total exposure to 5345 and 1340 patients-years respectively as of 30 September 2014, including 1419 and 0 subjects on Tresiba and Ryzodeg 70/30 respectively who have been followed for eighteen months or greater.

Dr. Condarco reviewed updated information on the following major safety findings across the Tresiba and Ryzodeg 70/30 phase 3 trials according to diabetes type; deaths, non-fatal serious adverse events, adverse events leading to product discontinuation, injection site reactions adverse events, immunogenicity reactions adverse events, medication-errors related adverse events, neoplasm related adverse events, lipodystrophy adverse events and common adverse events. In her review, she identified no imbalance across any of the above listed events that would preclude product approval. (b) (4) it is notable[9] that in the most susceptible individuals (i.e., subjects with type 1 diabetes) numerically more subjects on Tresiba experienced at least one serious adverse event coded to the term hypoglycemia (4.3 % versus 3.4% for Tresiba versus other long-acting comparators respectively) and hypoglycemia coma (0.6% versus 0.2% for Tresiba versus other long-acting comparators respectively).

DEVOTE Trial Interim Analysis

The DEVOTE trial is an ongoing randomized, double-blind, active-controlled, multi-center, multi-national trial comparing the cardiovascular risk of insulin degludec to the cardiovascular risk of insulin glargine. The trial is a time to event trial and 633 major adverse cardiovascular events[10] (i.e., a three components composite of CV-deaths, non-fatal myocardial infarction, non-fatal stroke) are needed to fulfill the trial's primary objective of excluding a 30% excess CV-risk of insulin degludec over that of glargine.

Patients with a diagnosis of type-2 diabetes inadequately controlled (HbA1c ≥ 7%) on insulin and on at least one oral medication or adequately controlled (≤7 %) but on at least 20 units of insulin per day and on at least one oral medication were eligible to participate. All eligible patients were to also have either a history of a past cardiovascular event or risk factors for CV-risk. Patients were ineligible if they had any one of the following; a recent CV-event within the past 60 days, a planned future revascularization procedure, New York Heart Association class IV heart failure, severe renal impairment or end-stage liver disease.

Trial procedure includes a 2-week screening phase followed by randomized assignment to intervention for up to 59 months if required. During the intervention phase, patients return for site visits on Weeks 1, 2, and 4 then monthly for the first six months and then every three months for up to 59 months if required. Subjects are followed for 30 days after treatment is discontinued. Dose of intervention therapies are titrated based on results of self-blood glucose monitoring to ensure that the lowest of three self-measure blood glucose three days before titration visits falls between 71 to 90 mg/dL.

[9] Refer to Table 10 in Dr. Condarco's Clinical Review.

[10] Major Adverse Cardiovascular Events-MACE

In planning the trial the applicant had assumed that the rate of first MACE event would be 2.1 event per 100 patient year of exposure, that trial recruitment would be uniform over 18 months, that the last patient last visit would occur five years after first randomization, and a loss to follow-up of 1 %. Based on these assumptions 3750 subjects would need to be randomized to each treatment group to accrue 633 events.

The trial was fully recruited 13 months after first randomization (29 October 2013) and this rapid enrollment has been in part attributed to a lower than expected screening failure rate due the trial's simple design. At interim, the rate of first MACE event appears to be twice as rapid (~4.0 first MACE event per 100 PYE) as originally anticipated and the projected date for trial completion has been revised down by 2.5 years with a last patient last visit now planned for August 2016 instead of late 2018.

The date of first patient first visit was 29 October 2013, the date of last patient first visit for the interim analysis was 28 November 2014 and the data cut-off for the interim analysis was 19 January 2015.

In total, 7638 participants have been randomized and baseline characteristics were balanced. The average age (SD) of the trial population is 65 (7.4) years, and is composed mostly of White (~76%), males (~63%) recruited predominantly from North America (~69%). The average BMI of participants is in the obese range, the average duration of diabetes was 16 years at baseline, and most participants were recruited on the basis of a prior history of CV disease (86%) as opposed to CV risks factor only (14.6%). At the interim data cutoff date, 50% of the randomized individuals had been followed for 6 months or less (median days of follow-up; 174 days).

Dr. Yanoff in her CDTL memorandum and Dr. Li in her review have reviewed attributes of trial performance (target population enrolled, enrollment rate, retention rate, MACE event rate, exposure by duration and dose, dose titration, overall levels of HbA1c reduction) available to date and conclude that the trial appears to have been well conducted and in accordance with Agency recommendations made at the End of Review meeting and through several guidance meetings held to reach agreement on a final trial protocol. Review of the DMC minutes from closed and open sessions are consistent with this assessment and I concur that no trial performance issues susceptible to influencing the trials intended primary objective have been identified to date.

The primary analysis of the interim data was an "on-study" analysis based on initial treatment assignment (i.e., "as randomized") and followed an intent-to-treat principle. At interim, study withdrawal was low (<0.2%), and 95% of individuals remained on randomized intervention. In the remaining participants, treatment had either been "paused" or participants had died. All first MACE events that had been confirmed through adjudication from the date of the first subject randomized to the date of last direct contact (on-site visit or phone contact with subject) before the cut-off date were included in the interim analysis.

Dr. Li analyzed the interim results and was able to confirm the applicant's finding. Results of the primary analysis are shown in Table 8 of her review. Dr. Li, in exploratory analyses, analyzed the results for individual components of MACE using the same model as the one used in the primary analysis. The robustness of primary analysis results was also tested, in seven, applicant and FDA generated, "on-treatment" sensitivity analyses. Finally subgroup analyses by Age, Gender, Race and Disease characteristics were repeated using the same Cox proportional hazard model as the one used in the main analysis. Supportive analyses were consistent with the primary analysis.

The results of the interim analysis performed after accrual of 24% of the events needed for the final analysis, does not suggest that insulin degludec use, in type 2 DM patients at high risk of a new or recurrent CV event, causes an 80% excess in CV-risk when compared to insulin glargine. Although results of the interim analysis are reassuring and reliably exclude a large excess risk, estimates based on partial or incomplete data (i.e., interim data) are subject to change with accrual of additional data and may ultimately prove unreliable for the purpose of definitively excluding a smaller, yet clinically meaningful, risk increase. As has been pointed out by Dr. Li and Yanoff, the current estimate of risk is based on ¼ of the overall data and on relatively short median exposure to Tresiba. The most reliable and robust estimate of degludec associated CV-risk will be derived from the final analysis of the DEVOTE trial. Based on the interim analyses of the Devote trial, I conclude that the Applicant has demonstrated that insulin degludec is not associated with an excess CV-risk increase 80% that of glargine.

8. Advisory Committee Meeting

An advisory committee meeting was not convened for the second cycle resubmission because the applications did not raise questions requiring input from external advisors. Please refer to the original NDA reviews for information regarding the Advisory Committee meeting convened for these applications during the original review cycle.

9. Pediatrics

Dr. Yanoff has summarized the relevant pediatric issues in her CDTL memorandum. Refer to her review for details.

10. Other Relevant Regulatory Issues

Dr. Yanoff has summarized the other relevant regulatory issues in her CDTL memorandum. Refer to her review for details.

11. Labeling

Dr. Yanoff has summarized the relevant labeling issues in her CDTL memorandum. Refer to her review for details.

12. Postmarketing

Dr. Yanoff has summarized the post-marketing studies that will be required under the Pediatric Research Equity Act (PREA) and Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA). Completion of the ongoing DEVOTE trial is a postmarketing requirement (PMR 2954-2) under Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) with the following mandated timelines for completion and submission.

- Trial Completion: December 2016
- Final Report Submission: September 2017

Two post-marketing commitments

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/s/

JEAN-MARC P GUETTIER
09/24/2015

Division Decisional Memo

Date	January 31, 2013
From	Jean-Marc Guettier, M.D.C.M. Mary H. Parks, M.D.
Subject	Summary Review
NDA/BLA # **Supplement #**	203314 and 203313
Applicant Name	Novo Nordisk Inc.
Date of Submission	September 29, 2011
Proprietary Name / **Established (USAN) Name**	Tresiba and Ryzodeg (Insulin degludec and insulin degludec/insulin aspart)
Dosage Forms / Strength	solution for sc injection U100 and U200 (Tresiba) U100 (Ryzodeg)
Proposed Indication(s)	Improvement of glycemic control in adults with diabetes mellitus
Action/Recommended Action for NME:	Complete Response

1. Introduction

This memo serves as the division decisional memo on the two NDAs for insulin degludec and insulin degludec/aspart. It will focus only on the key safety and efficacy issues shaping the final recommendation for non-approval. At issue is a finding of excess cardiovascular (CV) risk associated with these two products; hence, this memo spends an extensive amount of time describing the CV findings in this program. The reader is referred to the multiple discipline reviews and the advisory committee background materials for a more comprehensive review and discussion of other aspects in the development program for both these products.

2. Background

Development of injectable insulin therapies for T1DM and T2DM presents unique challenges not evident in other classes of anti-diabetic therapies. Insulin is the only anti-diabetic therapy available for which there is no maximal dose for efficacy. Given in sufficient quantities, one can normalize plasma glucose and reduce HbA1c levels to targeted goals. However, achievement of these goals is countered by the risk of hypoglycemia and the fear of hypoglycemia often serves as the barrier for tight glycemic control with the most effective anti-diabetic agent available. This risk alongside with weight gain and subcutaneous route of administration often lead to

insulin being relegated to late-option therapy in T2DM. In T1DM insulin is an absolute requirement.

The number of clinical trials submitted with NDAs 203314 (degludec) and 203313 (degludec-aspart) was extensive. At filing there were 41 and 21 Phase 1 through 3 trials submitted in support of approval for degludec and degludec-aspart. Dr. Guettier has thoroughly summarized the extent of the clinical program and the additional studies relied upon by FDA to address a cardiovascular safety signal identified in the course of our review of these two NDAs. For purposes of this memo, we will be focusing primarily on the Phase 3 trials because these were all controlled studies of the longest duration (24 to 104 weeks, including the extension periods). Please see Dr. Guettier's briefing document for the advisory committee meeting, efficacy review and the reviews of specific disciplines for a detailed description of trials not addressed in this memo.

Both these clinical development programs were specifically designed to establish not only glycemic efficacy of degludec and degludec-aspart, but also to evaluate cardiovascular and hypoglycemic safety. Even within the confines of efficacy evaluation, the two programs were evaluating efficacy with respect to different dosing regimens (fixed or flexible dosing), basal versus basal plus bolus insulin regimens (degludec only or degludec + aspart), types of diabetes (T1 or T2DM), and concentrations (U100 or U200). And while all the Phase 3 trials were active-controlled in design, different comparators were used (glargine, detemir, biphasic insulin aspart, and sitagliptin). Consequently, the efficacy and safety reviews are complex and different grouping of trials are considered for different purposes. For these reasons, the reader should anticipate a brief summary of what trials are considered under different sections of this memo with an understanding that those trials were selected because their designs were specific to the matter under discussion.

Finally, the applicant also evaluated a very novel dosing regimen for a basal insulin – three times weekly (3TW) dosing. There were two trials of degludec U200 formulation which compared this 3TW dosing to once-daily dosing of glargine in T2DM. The primary objective of these two trials was to establish non-inferiority between the two insulin therapies. (b) (4) These two trials will not be discussed to any extent in this memo but it does serve to remind us that pharmacokinetic and pharmacodynamic profiles of insulin alone do not always establish the best dosing regimen for T1 and T2DM treatment.

In December 2008, FDA issued a Guidance for Industry titled, *Evaluating CV Risk in New Anti-diabetic Therapies to Treat T2DM (see hyperlink)*

(http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/%20Guidances/UCM071627.pdf)

after a 2-day advisory committee in July 2008 wherein the majority of panel members from 3 committees (Metabolism and Endocrinology, Cardiorenal, and Drug Safety and Risk Management) recommended all new therapies for T2DM provide a prospective assessment of CV risk. FDA's guidance defined this recommendation in the context of a two-stage approach to evaluating risk in which an 80% excess risk should be excluded prior to marketing followed by a more conservative 30% excess risk excluded post-marketing. Although insulin therapies are used in T2DM, the complexity of trial design (e.g., open-label) and necessity to conduct an active-controlled trial presented challenges to implementation of the guidance for these therapies. As such, these products were not required to conduct clinical programs to exclude a pre-specified margin of CV risk but they were required to prospectively collect and adjudicate CV events to enable a thorough assessment of risk in their marketing applications.

The role of insulin in promoting CV disease in diabetes is controversial. As described by Dr. Guettier in his AC briefing document, much of the evidence for increased risk derives from data of excess endogenous insulin in the insulin-resistant state. Trials in which exogenous insulin therapy is evaluated in Type 1 and Type 2 diabetes patients, including the landmark Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS), have not established an excess risk with exogenous insulin therapy. In a recently published trial titled Outcome Reduction with Initial Glargine Intervention (ORIGIN), insulin glargine was compared to placebo in a population of patients with pre-diabetes or T2DM to determine if glargine would reduce the risk of two co-primary endpoints. The first being the composite of CV death, nonfatal MI, or nonfatal stroke and the second being the composite of the first plus a revascularization procedure or hospitalization for heart failure. Glargine did not lower CV risk; instead, in this study population, glargine had a neutral effect on CV risk. This finding is of relevance as the degludec program primarily compared itself to glargine for both CV safety and hypoglycemic risk.

3. CMC/Device

The overall recommendation from CMC is complete response as a result of a Withhold recommendation from the Office of Compliance dated 26 October 2012. The deficiencies from the OC inspection are specific to the manufacturing facility A/S located at Novo Alle, Bagsvaerd, Denmark. Please see reviews of Drs. Leginus, Ramaswamy, Ryan and Nguyen for details on the drug substance, product, and pen injector device.

Insulin degludec is an analog of human insulin, produced through recombinant DNA technology and chemically modified. The expression system for production of the

peptide precursor is in the yeast, *Saccharomyces cerevisiae*. This peptide differs from human insulin through omission of threonine at position 30 of the B-chain (B30) and chemical attachment of a C-16 fatty acid at position B29. This chemical modification confers the extended PK/PD characteristics of insulin degludec.

The drug product is a sterile, clear, colorless solution to be available in two different concentrations of insulin degludec: 100 U/mL (U-100) or 200 U/mL (U-200). The 100 U/mL strength contains 600 nmol of insulin degludec and the 200 U/mL strength contains 1200 nmol of insulin degludec. The same excipients and preservatives are present in both presentations with a higher amount of zinc present in the 200 U/mL presentation.

The 100 U/mL strength product is to be available as (b) (4) pre-filled disposable pen ((b) (4) pre-assembled in a PDS290 pen-injector). The 200 U/mL strength product is to be available only as a prefilled disposable pen (PDS290 pen-injector). (b) (4) The PDS290 pen-injector is not approved for use with any insulin product and at present is still undergoing review by CDRH and DMEPA. A deficiency review letter was issued on 9 July 2012 outlining ongoing concerns over user errors associated with this presentation. Insulin degludec in 200 U/l mL concentration strengths is a benefit for patients with insulin resistance requiring high doses of insulin. The higher concentration strength would allow for fewer injections in these patients; however, should the deficiencies of the (b) (4) device for this dosage strength not be resolved, it is unlikely to preclude the approval of insulin degludec 100 U/mL, notwithstanding other approvability issues with this NDA.

The drug product is light sensitive and will require secondary packaging to maintain product stability. A shelf-life of 30 months at refrigerated temperature ($5^{o}C \pm 3^{o}C$) is recommended and an in-use period of 56 days at temperatures up to $30^{o}C$ is recommended for both dosage strength products.

4. Nonclinical Pharmacology/Toxicology

Please see review of Drs. Miyun Tsai-Turton and Karen Davis-Bruno dated 1 June and 4 June 2012, respectively. Pharmacology/toxicology review discipline recommends approval with no postmarketing requirements.

Because of the CV safety concerns noted in the clinical program, this memo will only highlight that the CV safety pharmacology study in dogs did not identify any significant effect of degludec on blood pressure, heart rate or ECG findings. Similarly, an assessment of QT effect on rabbit-isolated Purkinje fibers did not identify any notable effect on the QRS complex or QT interval. However, the absence of a nonclinical finding does not eliminate the clinical concerns.

5. Clinical Pharmacology/Biopharmaceutics

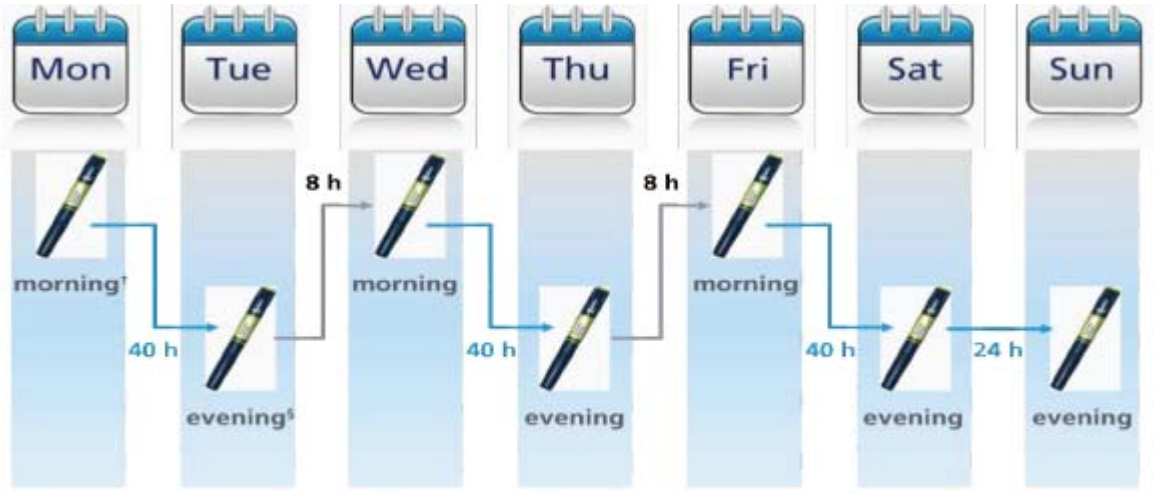
Please see review of Drs. Manoj Khurana and Jaya Vaidyanathan dated 15 June 2012 for insulin degludec and also review of Drs. Ritesh Jain and Jaya Vaidyanathan dated 15 June 2012 for insulin degludec/aspart. Clinical pharmacology/biopharmaceutics review discipline recommends approval with no postmarketing requirements.

Phase 1, single sc dose in PK/PD studies in healthy, T1 and T2 patients demonstrated the long half-life of degludec, exceeding 24 hrs. Multiple dose PK/PD studies in T1 and T2 patients demonstrate that steady state was achieved at approximately 72 hrs. In the T2 study, PK sampling continued for 5 days after 6 days of daily dosing at three different doses (0.4, 0.6, or 0.8 U/kg). Clamp study was also conducted after the 6th dose at steady state. PK profile was dose-proportional and PK/PD assessment after 6th dose suggest that the duration of action for IDeg could extend beyond 24 hrs for doses exceeding 0.4 U/kg. All in all, degludec has a protracted time-action profile that is relatively flat at steady state which was considered a unique attribute of a basal insulin that might enable true once-daily coverage with a lower risk of hypoglycemia. This also led to Novo Nordisk's evaluation of three dosing regimens: once-daily and flexible once-daily in both T1 and T2DM; and three times a week (3TW) dosing in T2DM. As noted in the *Introduction*, 3TW dosing is not being pursued by Novo Nordisk (b) (4)

The flexible once-daily dosing regimen warrants some discussion because this would be a different recommendation over other basal insulin analogues. The FDA-approved labels for the two other marketed basal insulin analogues state the following:

- Levemir®: Administer subcutaneously once daily or in divided doses twice daily.
- Lantus®: Administer subcutaneously once daily at any time of day, but at the same time every day.

In other words, when Levemir or Lantus are dosed, they are given at fixed times every day. The flexible dosing regimen studied for degludec included allowing the patient to administer degludec at any time of the day provided the consecutive doses were no sooner than 8 hrs apart or longer than 40 hrs apart or in an alternating morning/evening regimen as illustrated below:



†Morning defined as time period from waking up to first meal of the day.
§Evening defined as time period from start of main evening meal to bedtime.
Dosing schedule provided for a maximum dosing interval of 40 h and a minimum dosing interval of 8 h

The applicant argues that a flexible dosing schedule, without compromising safety or efficacy, is a benefit over the other approved basal insulins since a patient might forget to take his/her basal insulin on a fixed daily regimen and taking a missed dose might lead to alterations in efficacy/safety profile. The impact of flexible dosing schedule on efficacy/safety is discussed in Sections 7 and 8 below.

Degludec is highly bound to serum albumin; therefore, in vitro studies were conducted to assess the effect of other common protein-bound drugs on displacement of degludec. In addition, the effects of selected anti-diabetic drugs (sitagliptin, glimepiride, metformin, and liraglutide) as well as long-chain fatty acid were also evaluated. There was negligible effect on the binding of degludec to serum albumin in the presence of any of these compounds tested.

Among the many Phase 1 studies in the IDeg-Asp program, only the findings from Trial 1959 are mentioned here. Trial 1959 evaluated the PK/PD of IDeg-Asp to the separate, simultaneous administration of insulin degludec and insulin aspart. The PK profile of degludec was similar when administered as a separate injection with aspart or as the pre-mix IDeg-Asp. The PK profile of aspart was 30% lower (both Cmax and AUC) when administered in the pre-mix compared to its separate co-administration with degludec. However, the PD profile was not impacted by this difference in PK.

6. Clinical Microbiology

Please see the Product Quality Microbiology Review by Drs. Vinayak Pawar and John Metcalfe, dated 13 June 2012, for degluldec, and 7 June 2012, for degludec-aspart. Both reviews identified no outstanding issues at this time and approval was recommended.

7. Clinical/Statistical-Efficacy

7.1. Efficacy of Degludec

7.1.1. Overview of Efficacy Assessment

Please see Dr. Cynthia Liu's review for a thorough description of the glycemic efficacy for degludec.

Degludec was evaluated as part of a basal-bolus regimen in 3 T1DM trials. There were 8 trials investigating degludec in T2DM; however, we will exclude any discussion on two of these as they were for the 3TW dosing regimen not being pursued for marketing by Novo Nordisk. Of the remaining 6 trials in T2DM, only one evaluated degludec as part of a basal-bolus regimen. **Five of the 6 trials investigated degludec as a once-daily basal- only regimen**. The relevance of this point will be revisited in our discussion of hypoglycemic risk associated with degludec.

The applicant has emphasized the advantages of the longer duration of action of degludec and its relatively flat pharmacokinetic profile at steady state over other basal insulin analogues. They assert that these characteristics lend to a once-daily flexible dosing regimen wherein degludec can be administered daily but the timing can vary from day to day. Two trials, one each in T1 and T2DM, included a treatment arm which compared a predefined flexible dosing schedule to the fixed-daily schedule of degludec and the once-daily dosing of glargine. One T2DM trial allowed for variable dosing of degludec, provided that interval between doses remained within an 8 to 40 hour window. Except in these three trials where there was a treatment arm allowing for a flexible dosing regimen of degludec (referred to as degludec flex hereafter), degludec was always administered at a fixed 24-hr interval either with the evening meal or in between the evening meal and bedtime. The dosing interval of the comparator basal insulin was as per the approved product label. For all trials using glargine as the comparator, glargine was administered once-daily at any time of day but that time could not vary from day to day. For the trial using detemir as the comparator, detemir was administered once-daily between start of the evening meal and bedtime up until Week 8. After Week 8, an additional dose of detemir could be prescribed at the discretion of the investigator to achieve optimal glycemic control as per dosing algorithm. In effect, all trials comparing basal degludec to basal glargine were once-daily-only treatment regimens. We will revisit the relevance of this issue later in this memo.

All the trials were open-label and active-controlled. Except for one superiority trial comparing degludec to the oral dipeptidyl-peptidase-IV (DPP4) inhibitor, sitagliptin, all these trials were designed to establish non-inferiority to another insulin regimen at a pre-specified non-inferiority margin of 0.4. Glargine was the predominant active comparator in these non-inferiority trials except in one T1DM trial where detemir served as the comparator. When degludec was evaluated in a basal-bolus regimen

(all T1DMtr ials and one T2DM trial), the prandial insulin used in all treatment groups was insulin aspart.

One trial evaluated the more concentrated formulation of degludec U200 (200 units/mL) to glargine. This was the only trial from which efficacy data in this formulation are being relied upon for its approval.

The following table summarizes the trials discussed under this section.

Table 7.1.1a Table of Studies in Degludec Phase 3 Program

Study #	Treatment Groups (N)	Objective	Background Therapy	Timepoint of Efficacy Analysis
Type 1 Diabetes Mellitus				
3583	1. Degludec (472) 2. Glargine (157)	non-inferiority	Insulin Aspart as prandial insulin	Week 52
3585	1. Degludec (303) 2. Detemir (153)	non-inferiority	Insulin Aspart as prandial insulin	Week 26
3770	1. Degludec flex (164) 2. Degludec (165) 3. Glargine (164)	non-inferiority	Insulin Aspart as prandial insulin	Week 26
Type 2 Diabetes Mellitus				
3582	1. Degludec (755) 2. Glargine (251)	non-inferiority	Insulin Aspart +/- OADs	Week 52
3579	1. Degludec (773) 2. Glargine (257)	non-inferiority	OADs	Week 52
3672	1. Degludec U200 (230) 2. Glargine (230)	non-inferiority	OADs	Week 26
3586	1. Degludec (289) 2. Glargine (146)	non-inferiority	OADs	Week 26
3668	1. Degludec flex (229) 2. Degludec (228) 3. Glargine (230)	non-inferiority	OADs	Week 26
3580	1. Degludec flex (229) 2. Sitagliptin (229)	superiority	OADs	Week 26

7.1.2. Efficacy of Degludec in T1DM

Table 7.1.2a. summarizes the primary efficacy findings of degludec in the three T1DM trials.

Table 7.1.2a Effect on HbA1c Endpoint in T1DM Trials

Study #	Treatment Group	Baseline Mean (SD)	LS Mean Chg from Baseline	LS Mean Treatment Difference (Degludec-Control)	95% CI
3583	1. Degludec (472) 2. Glargine (154)	7.69 (0.94) 7.73 (0.99)	-0.36 -0.35	-0.01 --	(-0.14, 0.12)
3585	1. Degludec (301) 2. Detemir (152)	7.98 (0.98) 7.99 (0.87)	-0.70 -0.62	-0.08 --	(-0.23, 0.06)
3770	1. Degludec flex (164)* 2. Degludec (165) 3. Glargine (161)	7.69 (1.00) 7.70 (0.94) 7.74 (0.90)	-0.40 -0.41 -0.59	+0.17 +0.17 --	(0.04, 0.31) (0.04, 0.30)

*primary comparison in 3770 was degludec flex to glargine; additional analyses compared degludec to glargine

Degludec was non-inferior to detemir and glargine as the upper bound of the 95% CI in all trials was below 0.4. Degludec treatment in T1DM resulted in an average change from baseline in HbA1c of -0.36 to -0.70 in these three trials. Relative to comparators, degludec achieved greater HbA1c reduction over detemir (Study 3585) but was not statistically superior as the upper bound of the 95% CI did not exclude zero. Less HbA1c reduction over glargine was observed in Study 3770 which included a flexible dosing regimen. In Study 3770 the lower bound of the 95% CI excluded zero so while degludec flexible and fixed dosing regimens met the non-inferiority criterion, these two treatment arms were also statistically inferior to glargine.

7.1.3. Efficacy of Degludec in T2DM

Table 7.1.3a summarizes the primary efficacy findings of degludec in the six T2DM trials.

Table 7.1.3a Effect on HbA1c Endpoint in T2DM Trials

Study #	Treatment Group	Baseline Mean (SD)	LS Mean Chg from Baseline	LS Mean Treatment Difference (Degludec-Control)	95% CI
3582	1. Degludec (742) 2. Glargine (248)	8.26 (0.80) 8.36 (0.89)	-1.11 -1.18	+0.07 --	(-0.06, 0.20)
3579	1. Degludec (766) 2. Glargine (257)	8.16 (0.83) 8.21 (0.78)	-1.07 -1.15	+0.08 --	(-0.05, 0.21)
3672	1. Degludec U200 (228) 2. Glargine (228)	8.29 (0.98) 8.24 (0.86)	-1.18 -1.22	+0.05 --	(-0.11, 0.20)
3586	1. Degludec (284) 2. Glargine (146)	8.45 (0.79) 8.46 (0.76)	-1.44 -1.53	+0.08 --	(-0.5, 0.22)
3668	1. Degludec flex (228)* 2. Degludec (228) 3. Glargine (229)	8.49 (0.95) 8.38 (0.94) 8.41 (0.93)	-1.17 -1.03 -1.21	+0.04 +0.18 --	(-0.12, 0.19) (0.02, 0.33)
3580	1. Degludec flex (222) 2. Sitagliptin (221)	8.78 (1.01) 8.97 (1.01)	-1.53 -1.09	-0.44 --	(-0.62, -0.25)

*primary comparison in 3668 was degludec flex to glargine; additional analyses compared degludec to glargine

Study 3580 was the only superiority trial in this program; it compared degludec administered in a flexible dosing regimen to the oral DPP4-inhibitor, sitagliptin. Treatment of patients with T2DM who were on background OADs with basal flexible dosing of degludec resulted in greater glycemic control than the addition of sitagliptin. The results from this trial are not surprising as insulin is the only anti-diabetic therapy that can be dosed to meet any targeted goal; there is no maximal effective dose.

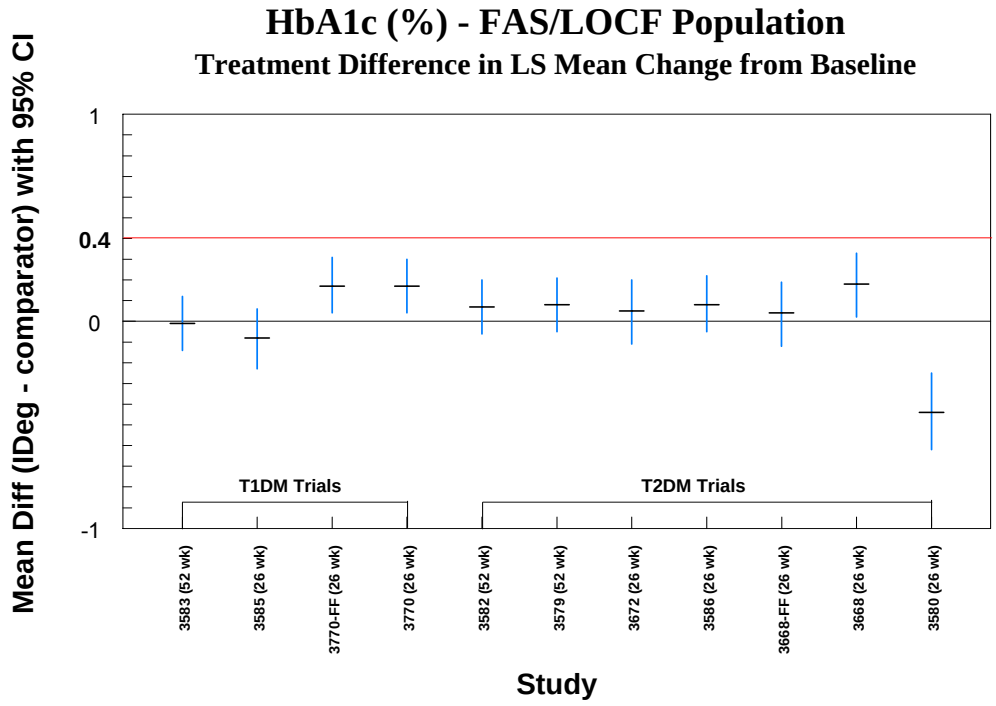
In the non-inferiority trials, degludec was non-inferior to glargine as the upper bound of the 95% CI in all these trials was below 0.4. The average change from baseline in HbA1c ranged from -1.07 to -1.53 with the larger reduction in T2DM as compared to the T1DM population being attributed to the higher baseline HbA1c levels. However, in contrast to the T1DM trials, degludec was consistently numerically worse than its comparator glargine as the treatment difference (Degludec – Glargine) always favored glargine.

7.1.4. Conclusions on Glycemic Efficacy of Degludec

Degludec was effective at lowering HbA1c across all trials in T1 and T2DM.

To depict the totality of the effect of degludec on HbA1c in both T1 and T2DM trials relative to its comparators, Dr. Liu created the following plot which provides an excellent visual display of the treatment differences between degludec and control (far right data point compares degludec to sitagliptin in a superiority trial).

Figure 7.1.4a. Plot of HbA1c Treatment Effect Across All Phase 3 Degludec Trials (from FDA statistician, Cynthia Liu)



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.

From this plot the following conclusions can be made about degludec as a basal insulin regimen in T1 and T2DM over the other two available basal analogues, glargine and detemir.

- Degludec is non-inferior to these other basal insulin analogues with regard to HbA1c reduction
- The point estimate of the treatment difference between degludec and glargine suggest a consistent pattern of degludec affording numerically worse glucose control compared to glargine once-daily. In one study (3770), the difference was found to be statistically significant.
- Only one trial compared degludec to detemir and that was in the T1DM population. This trial showed degludec to be numerically better than detemir.

Degludec has been reported in publications and at scientific meetings as a true once-daily basal insulin obviating the need for any split dosing to achieve full 24-hr coverage [1-3]. Glargine, the most widely prescribed basal insulin analogue and the predominant comparator in the Phase 3 trials, is labeled for once-daily use but reports[4, 5] of patients requiring additional coverage resulting in split dosing (a.m. and p.m.) has led some to view this insulin as not being a true 24-hr basal insulin. This difference in PK profile was lauded by advisory committee member, Ellen Seely, as an advantage of degludec over currently available insulin analogues where patients sometimes had to take a second injection of detemir or glargine. However, not evident in Figure 7.1.4a and not appreciated by any member of the advisory committee panel, is the fact that all glargine comparator trials dictated that glargine be dosed once-daily as per its label. In other words, these trials dictated the use of glargine to display its full effect over a 24 hour period with only one daily injection. In a clinical development program comparing a once-daily regimen of degludec to glargine, it can be concluded that there were no clinically meaningful difference between these two basal insulins on glycemic control.

7.2. Efficacy of Degludec-Aspart

7.2.1. Overview of Efficacy Assessment

Please see Dr. Dongmei Liu's review for a thorough description of the glycemic efficacy for degludec-aspart.

There were a total of five Phase 3 clinical trials conducted in support of the approval of degludec-aspart: one in T1DM and four in T2DM. All trials were non-inferiority in design with a pre-specified non-inferiority margin of 0.4. The comparator basal insulins were detemir or glargine. The comparator prandial insulin was always insulin aspart, administered as a separate injection from the basal comparator or as part of the biphasic approved insulin mix of Novolog 70:30 (referred to as biphasic aspart or BIAsp). Two trials did not employ a prandial insulin in the comparator group; these two trials were glargine-controlled trials. Similar to the degludec program, when glargine was used as a control, its dosing regimen was strictly defined as a once-daily regimen. Detemir was allowed to be dose once- or twice-daily.

The following table summarizes the trials discussed under this section.

Table 7.2.1a Pivotal Studies for Insulin Degludec-Aspart

Study #	Treatment Groups (N)	Objective	Background Therapy	Timepoint of Efficacy Analysis
Type 1 Diabetes Mellitus				
3594	1. Deg-Asp (366) 2. Detemir (182)	non-inferiority	Insulin aspart provided prandial coverage	Week 26
Type 2 Diabetes Mellitus				
3590	1. Deg-Asp (266) 2. Glargine (263)	non-inferiority	OADs	Week 26
3593	1. Deg-Asp (230) 2. Glargine (233)	non-inferiority	metformin	Week 26
3592	1. Deg-Asp (224) 2. Biphasic Aspart (222)	non-inferiority	OADs +/- insulin	Week 26
3597	1. Deg-Aspart (280) 2. Biphasic Aspart (142)	non-inferiority	OADs +- insulin	Week 26

7.2.2. Efficacy of Degludec-Aspart in T1DM

Degludec-aspart was studied in only one T1DM trial in which detemir served as the comparator basal insulin where it could be administered once- or twice-daily. Degludec-aspart was non-inferior to detemir with the LS mean treatment difference of -0.05 with accompanying 95% CI of (-0.18, 0.08). Degludec-aspart resulted in an average 1% reduction in HbA1c from baseline. The mean baseline HbA1c in the T1DM trial for the degludec-aspart program (~8.3) was higher than that in the degludec program (~7.7-8.0).

7.2.3. Efficacy of Degludec-Aspart in T2DM

Table 7.2.3a summarizes the primary efficacy findings of degludec in the six T2DM trials.

Table 7.2.3a Effect on HbA1c Endpoint in T2DM Trials

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)

Degludec-aspart 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.

7.2.4. Conclusions on Glycemic Efficacy of Degludec-Aspart

Degludec-aspart was effective at lowering HbA1c across all trials in T1 and T2DM and its efficacy is comparable to that of the different insulin comparators, including the approved biphasic insulin Novolog 70/30 which also allows for the convenience of a pre-mixed long and short-acting insulin.

8. Safety

Please see Dr. Karim Calis's clinical review for the details of overall safety for these two insulin products. This memo will only focus on cardiovascular safety and hypoglycemic risk as these two issues are pivotal to the benefit-risk decision for these two applications.

8.1 Cardiovascular Safety

As has already been described by Dr. Guettier in his advisory committee background package, injectable insulin products have not been required to exclude a pre-specified margin of CV risk as per the 2008 diabetes guidance. However, FDA recognized that insulin is used in patients with elevated background risk for cardiovascular disease,

especially in T2DM patients. And for that reason, companies are advised to prospectively collect and adjudicate CV events to enable a robust assessment and review of CV safety for these products. Novo Nordisk was given this advice at its End-of-Phase 2 meeting on 24 February 2009.

> **FDA Response: At the present time, we are not holding inhaled or injectable insulins to the 95% confidence interval upper bound values of 1.8 and 1.3 described in the December 2008 guidance document. Nonetheless, you should still collect and analyze the cardiovascular data from your clinical trials as outlined in that guidance document, perform statistical testing on your cardiovascular data, and report the values in your NDA submission. We recommend that you submit with your phase 3 protocols, a detailed plan describing how you will capture and analyze cardiovascular adverse events of interest in each trial and across your development programs.**

Novo Nordisk submitted its statistical analysis plan (SAP) for evaluating CV risk on 19 February 2010 to both INDs. In its SAP the applicant referred FDA to the following table which lists the trials to be included in the CV meta-analysis:

Table 4–2 IDeg and IDegAsp – Planned/Ongoing Confirmatory Phase 3a Trials

Trial	Comparator	Comment	Population	IDeg/ IDegAsp Regimen	Duration (Weeks)	Rando-misation Scheme	Total Randomised Subjects (plan)	FPFV (plan)
NN1250-3579	IGlar	---	T2, insulin-naïve	OD	52	3:1	1030	01SEP2009
NN1250-3580	DDP-IV	---	T2, insulin-naïve	OD	26	1:1	446	11JAN2010
NN1250-3582	IGlar	---	T2, insulin-users	OD	52	3:1	1006	01SEP2009
NN1250-3583	IGlar	---	T1	OD	52	3:1	629	01SEP2009
NN1250-3585	IDet	Japanese population	T1	OD	26	2:1	426	03MAR2010
NN1250-3586	IGlar	Japanese population	T2, insulin-naïve	OD	26	2:1	426	03MAR2010
NN1250-3668	IGlar	2 IDeg arms	T2, insulin-users	OD	26	1:1:1	675	30NOV2009[2]
NN1250-3672	IGlar	---	T2, insulin-naïve	OD	26	1:1	450	03MAR2010
NN1250-3718	IGlar	---	T2, insulin-naïve	3TW	26	1:1	450	03MAR2010
NN1250-3724	IGlar	---	T2, insulin-naïve	3TW	26	1:1	450	03MAR2010
NN1250-3770	IGlar	2 IDeg arms	T1	OD	26	1:1:1	486	03MAR2010
NN5401-3590	IGlar	---	T2, insulin-naïve	OD	26	1:1	526	11JAN2010
NN5401-3592	BIAsp	---	T2, insulin-naïve	BID	26	1:1	450	05NOV2009
NN5401-3593	IGlar	---	T2, insulin-users	OD	26	3:1	450	11JAN2010
NN5401-3594	IDet	---	T1	OD	26	2:1	548	25AUG2009
NN5401-3597	BIAsp	Japanese population	T2, insulin-users	BID	26	2:1	426	03MAR2010

T1: type 1 diabetes, T2: type 2 diabetes, BID: twice daily dosing, DPP-IV: sitagliptin, FPFV: First Patient First Visit, IDet: insulin detemir, IGlar: insulin glargine OD: once daily dosing, 3TW: three times weekly dosing. , BIAsp: biphasic insulin aspart

Importantly, the SAP included several planned extensions to the Phase 3a trials. These planned extensions are summarized in the following table:

Table 4–3 IDeg and IDegAsp – Planned Extensions to Confirmatory Phase 3a Trials

Trial	Extension of Trial	FPFV (Expected Date)	LPFV (Expected Date)	Duration (Weeks)
NN1250-3643	3579	01SEP2010	01DEC2011	52
NN1250-3667	3582	01SEP2010	01JUN2011	26
NN1250-3644	3583	01SEP2010	01DEC2011	52
NN1250-3725	3585	01SEP2010	01JUN2011	26
NN1250-3829	3770	03SEP2010	25APR2011	26
NN5401-3645	3594	16MAR2010	24JAN2011	26
NN5401-3726	3590	26JUL2010	25APR2011	26

FPFV: First Patient First Visit, LPLV: Last Patient Last Visit

The following paragraph in the SAP made it very clear that analysis of these planned extensions was part of the CV meta-analysis and not a post-hoc analysis, as Novo Nordisk repeatedly describes in its advisory committee briefing materials.

4.2.2 Handling of Extension Trials

An extension trial will be included in the across trial analysis by joining the extension data with its respective main trial data and thereafter consider the joined data as one trial using the trial id from the main trial as identifier. The combined data set will be the basis for summaries, analyses and presentation of MACE. Baseline will be defined at the randomisation visit in the main trial.

8.1.1 Effect of IDeg/IDeg-Asp on MACE+ in Original Meta-analysis

At the time of NDA submission, the CV meta-analysis did not include data from these planned extensions, with the exception of Study 3645, because studies were still ongoing and database lock for these had not yet occurred. The primary composite endpoint in the meta-analysis included adjudicated CV death, nonfatal MI, stroke and unstable angina requiring hospitalization (MACE+). The applicant limited their analysis to treatment-emergent events occurring on or after the first day of treatment to no later than 7 days after the last day of randomized treatment, even though this was not pre-specified in the SAP. Based on these criteria the applicant's primary analysis revealed an estimated hazard ratio (95% CI) for MACE+ of 1.10 (0.68-1.77). FDA statistician, Dr. Xiao Ding included 3 more events in his review of the original CV meta-analysis. These 3 events occurred 9, 11, and 18 days after the last day of treatment. His rationale for including these three additional incident cases was based on the fact that the sponsor had not prospectively defined the treatment-emergent time period in the SAP and that most other development programs consider CV events occurring up until 30 days after the last day of randomized treatment as treatment emergent events. His analysis yielded an estimated HR (95% CI) for MACE+ of 1.17 (0.73-1.87).

Upon completion of Dr. Ding's review (dated 16 April 2012), FDA inquired on the status of ongoing clinical trials and learned of the completion of the remaining 6 planned extension trials. In addition, a new Phase 3 trial of degludec-aspart conducted in T2DM patients in Japan was recently completed (Study 3896). This was a 26-week non-inferiority trial between degludec-aspart and glargine in patients on a variety of background oral anti-diabetic therapies. As the 6 planned extension trials were to be included in the CV meta-analysis as per original SAP and Study 3896 prospectively collected and adjudicated CV events similarly to the originally planned meta-analysis, FDA conducted an updated meta-analysis of the 16 original trials plus their planned extensions and one new trial.

Table 8.1 summarizes all the trials contributing to this updated meta-analysis. The planned extension trials are listed along side its parent trial in the same rows.

Table 8.1.1a All Trials Included in Updated CV Meta-analysis

Study #	Treatment Group	N	Patient Population	Duration (wks)
3579 + 3643	degludec glargine	773 257	T2DM	52 + 52
3580	degludec sitagliptin	225 222	T2DM	26
3582 + 3667	degludec glargine	744 248	T2DM	52 + 26
3583 + 3644	degludec glargine	472 157	T1DM	52 +52
3585 + 3725	degludec detemir	302 153	T1DM	26 +36
3586	degludec glargine	289 146	T2DM	26
3668	degludec degludec flex glargine	 230	T2DM	26
3672	degludec glargine	228 229	T2DM	26
3718	degludec glargine	233 234	T2DM	26
3724	degludec glargine	229 230	T2DM	26
3770 + 3829	degludec degludec flex glargine	 164	T1DM	26 + 26
3590 +3726	degludec-aspart glargine	266 263	T2DM	26 + 26
3592	degludec-aspart BIAsp	224 222	T2DM	26
3593	degludec-aspart glargine	230 233	T2DM	26
3594 + 3645	degludec-aspart detemir	366 182	T1DM	26 + 26
3597	degludec-aspart BIAsp	280 142	T2DM	26
3896	degludec-aspart	147	T2DM	26

	glargine	149		

There is disagreement between Novo Nordisk and the FDA review team on the appropriate meta-analysis for describing CV risk of degludec. Novo Nordisk argues that a benefit-risk assessment for this NDA should be based on findings submitted with its original NDA. The applicant argues that consideration of the extension phases introduces marked imbalance in pt-years of follow-up between degludec/degludec-aspart and comparators because three of the trials in which these extensioin phases occurred had a 3:1 randomization. However, Dr. Bo Li carefully evaluated the characteristics of the patients in the original meta-analysis versus the characteristics of the patients who continued into the extension trials and noted the following:

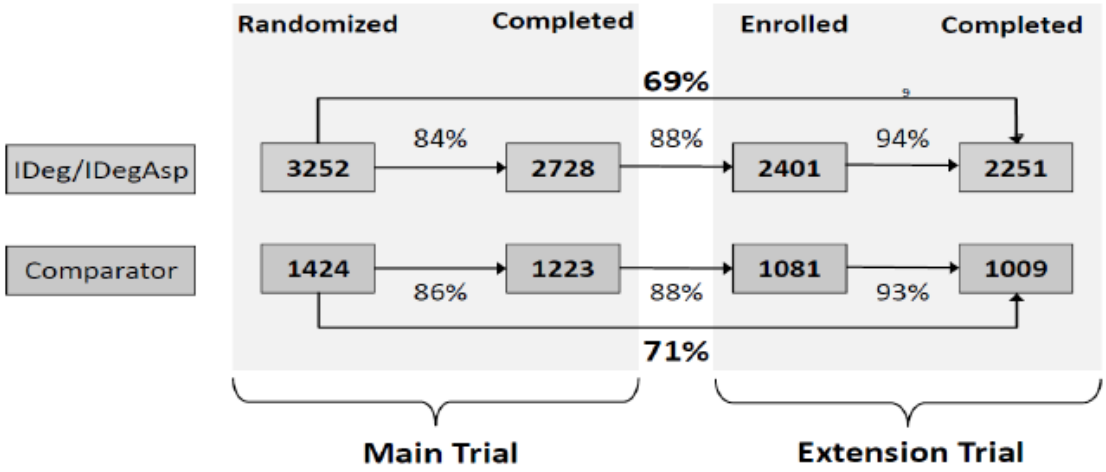
- No difference in demographics and baseline characteristics in those patients at time of randomization to those who enrolled in extension phases (See Table 3 in Dr. Bo Li's review). The following table adapted from Tables 3 and 4 of Dr. Li's review shows the similarity among the patient population, both at time of randomization and at time of extension. The updated database had a slightly higher percentage of patients with HTN, prior CVD and renal impairment but these characteristics were balanced between IDeg/IDeg-Asp and Comparator.

Table 8.1.1b Characteristics of Patients at Time of Study Randomization, Extension, and Updated Database

	Original Randomized Cohort of 16 trials		**Extension Cohort from 6 extension phases**		**Updated Database Cohort**	
	IDeg/Deg-Asp N=3252	**Comparator N=1424**	**IDeg/Deg-Asp N=2401**	**Comparator N=1081**	**IDeg/Deg-Asp N=5794**	**Comparator N=3461**
Age, yrs	51±14	51±14	51±14	51±13	54±13	55±12
Female	44.2%	45.1%	42.8%	44.2%	43.9%	44.8%
BMI, kg/m2	29.0±5.2	28.8±5.2	29±5.2	28.9±5.1	29.0±5.3	29.5±5.4
Duration of diabetes, yrs	13.9±10	13.6±9.7	13.8±9.8	13.3±9.3	12.6±9	11.8±8.4
Baseline HbA1c, %	8.1±0.9	8.2±0.9	8.1±0.9	8.2±1.0	8.2±0.9	8.3±0.9
HTN	54%	52.5%	54.6%	53%	60%	62%
Prior CVD	14.3%	12.5%	14.6%	12.9%	16.2%	15.3%
Renal Impairment	11.3%	11.2%	10.9%	11.2%	16.5%	16.6%

- The percentages of patients completing the main trials, enrolling into the extension, and completing the extension phases were similar between the degludec/degludec-aspart and comparator group (see Figure below from Dr. Bo Li's review)

Figure 1: Patient Retention in Trials with Extensions (FAS)



Although the extension phases were voluntary, Dr. Li found no evidence of selection bias for continued participation in either treatment groups. She carefully evaluated the discontinuation rates and reasons for discontinuation and found no difference in rate or reason for discontinuation between the treatment groups or across the 17 trials in the updated database (See Table 5 and Figures 2 through 4 of Dr. Li's review). Furthermore, the collection and adjudication process for CV events remained the same for the main and extension trials. Finally, the extension trials contributed an additional 60% of CV events. Consequently, the review staff has determined that the updated meta-analysis should be considered in the overall benefit-risk assessment of this NDA because the data derived from these extension trials are robust and relevant to further evaluate the safety signal that arose from the original meta-analysis. Please see Dr. Bo Li's statistical review dated 13 December 2012 for details of this updated meta-analysis from which I will highlight some key findings.

8.1.2. Effect of IDeg/IDeg-Asp on MACE+ and MACE in Updated Meta-analysis

The pre-specified composite endpoint for CV safety assessment was MACE+ (the applicant refers to this as MACE in its NDA) which is comprised of CV death, stroke, acute coronary syndrome (NSTEMI or STEMI), and unstable angina pectoris (UAP). FDA performed additional analyses restricting events to only CV death, stroke, and ACS, referred to as MACE throughout this memo. All components were identified using well-established definitions and adjudicated by an independent endpoints committee. The applicant's original NDA only analyzed treatment-emergent events (within 7 days of treatment discontinuation) even though this was not pre-specified in the SAP. For the updated meta-analysis, Dr. Li presented analyses using censoring

time points of 7 and 30-day. This memo will only present analyses based on treatment-emergent events defined using the applicant's original definition (i.e., up to 7 days after cessation of randomized treatment) because the cardiovascular safety concerns are similar for either censoring time point considered.

The following table adapted from Tables 8 and 9 of Dr. Li's review summarizes the time-to-event analysis based on the Cox proportional hazards (CPH) model stratified by trial with treatment as a fixed effect. Results for both MACE+ and MACE from the original meta-analysis and updated meta-analysis are presented.

Table 8.1.2a CV Meta-analysis in Original and Update Database for MACE+ and MACE

	Original Database		**Updated Database**	
	IDeg/IDeg-Asp N=5647 (PYE 3569.9)	**Comparator N=3312 (PYE 1873.9)**	**IDeg/IDeg-Asp N=5794 (PYE 5153.6)**	**Comparator N=3461 (PYE 2562.7)**
MACE+ MI Stroke CV Death UAP	53 (14.8) 20 (5.6) 11 (3.1) 8 (2.2) 14 (3.9)	27 (14.4) 7 (3.7) 4 (2.1) 4 (2.1) 12 (6.4)	95 (18.4) 34 (6.6) 24 (4.6) 12 (2.3) 25 (4.8)	37 (14.4) 9 (3.5) 6 (2.3) 6 (2.3) 16 (6.2)
MACE+ HR (95% CI)	1.10 (0.68, 1.77)		1.30 (0.88, 1.93)	
MACE MI Stroke CV Death	39 (10.9) 20 (5.6) 11 (3.1) 8 (2.2)	15 (8.0) 7 (3.7) 4 (2.1) 4 (2.1)	70 (13.5) 34 (6.6) 24 (4.7) 12 (2.3)	21 (8.2) 9 (3.5) 6 (2.3) 6 (2.3)
MACE HR (95% CI)	1.39 (0.76, 2.57)		1.67 (1.01, 2.75)	

In all 4 analyses there is an increase in CV risk associated with degludec use over comparator, reaching statistical significance only for the MACE component in the updated meta-analysis. The Kaplan-Meier (K-M) curves for MACE+ and MACE analyses are presented below:

Figure 8.1.2a Kaplan-Meier Plot of MACE+ (from Dr. Bo Li's FDA AC presentation)

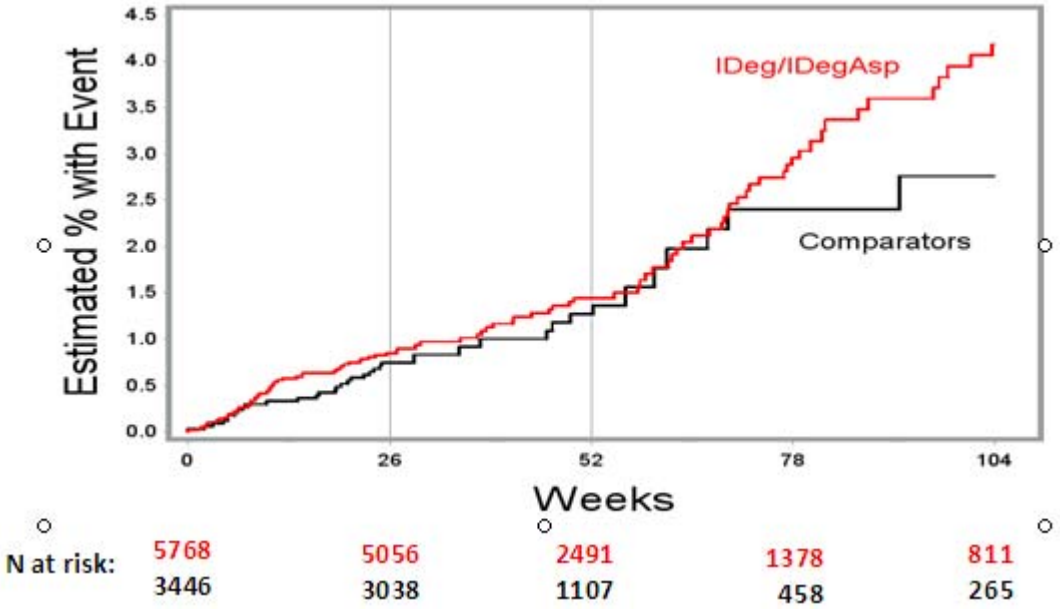
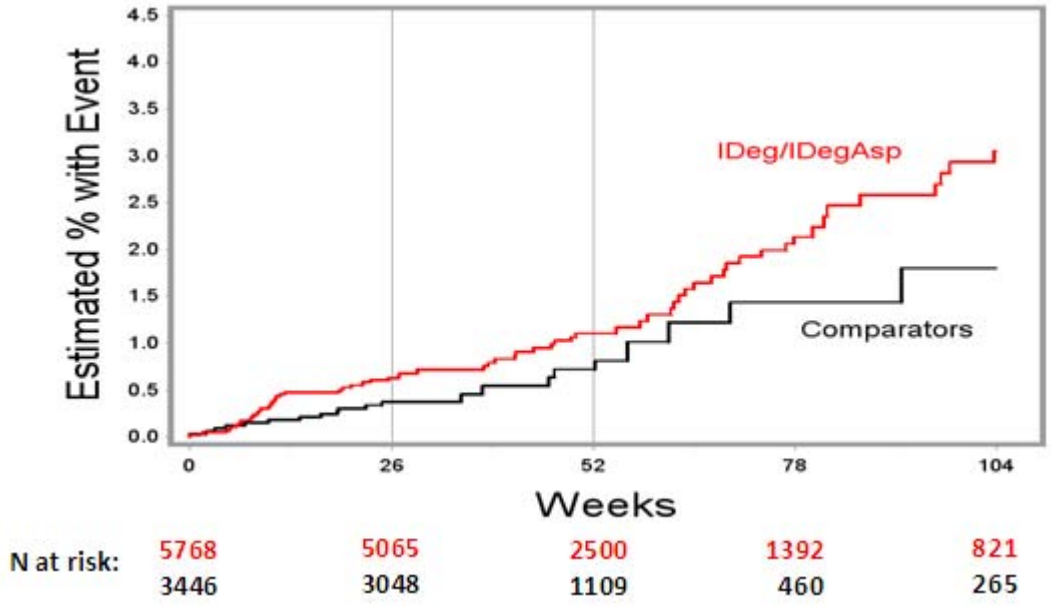


Figure 8.1.2b Kaplain-Meier Plot of MACE (from Dr. Bo Li's FDA AC presentation)

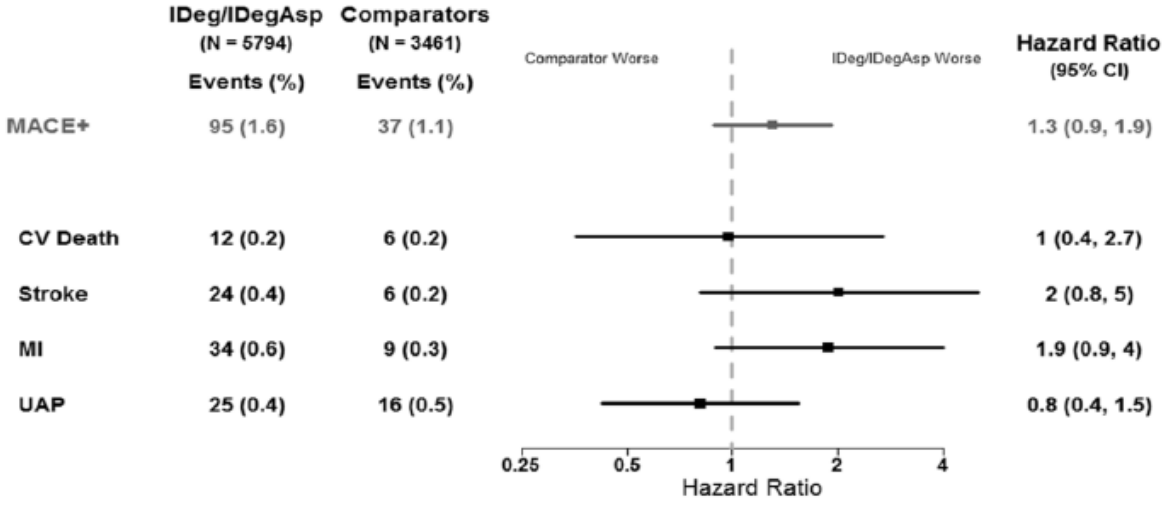


In both K-M plots there is continued accrual of events in the IDeg/IDeg-Asp arm whereas event rates appear to have plateaued in the comparator arm between Weeks 52 and 78. Novo Nordisk argues against conclusions on CV risks based on time

points beyond Weeks 52 because of the decreasing sample size and unexplained change in hazard rates. There was speculation that the open-label nature of the trial might have resulted in biased reporting of events by investigator but no concrete evidence for intentional or unintentional under-reporting for the comparator arm was produced by the applicant.

Even if one were to consider results after Week 52 to be unreliable, the K-M plot for MACE up to Week 52 reveals an early between-group separation in incident MACE events not favoring degludec. The separation occurs before issues affecting data reliability can be invoked (i.e., loss of randomization due to drop-outs or differential handling of events in trial extensions). The applicant argues that focusing only on strict MACE events reduces the total number of CV events and may be therefore less reliable than an estimate based on MACE+. In our view, an endpoint based on strict MACE events (i.e., CV death, nonfatal MI, nonfatal stroke) is more objective and less susceptible to interpretation than an endpoint based on MACE+ (i.e., definition for hospitalization for unstable angina lacks robust objective criteria). The addition of a component that lacks specificity (i.e., hospitalization for unstable angina) to the strict MACE endpoint would be expected to add "noise" to the estimate and could therefore bias the results towards the null. Point in fact, Table 8.1.2a reveals that the original meta-analysis of MACE+ shows a numerically higher rate of MI and stroke with IDeg/IDeg-Asp compared to control and it is only the unstable angina component that trends in favor of IDeg/IDeg-Asp. This is further illustrated in the following forest plot created by Dr. Li in which she presents the HRs for the individual components of MACE+ in the updated meta-analysis.

Figure 8.1.2c Forest Plot of MACE+ Analysis in Updated Meta-Analysis (From Dr. Li's review)



Regardless of what analysis one wants to place emphasis on, none of the analyses show a reduced HR for IDeg/IDeg-Asp. In fact, if we were to evaluate the CV safety

of degludec as Novo Nordisk set out to do in its statistical analysis plan, we would have observed the following risk estimates.

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Table 8.1.2b CV Meta-analysis Based on ALL TRIALS as prespecified in the SAP (excluded one new trial 3896):

	Degludec/Deg-Asp	Comparator
MACE+ Events	93	36
HR (95% CI)	1.29 (0.87, 1.91)	
MACE Events	68	20
HR (95% CI)	1.65 (0.99, 2.75)	

8.1.3. Subgroup Analyses

Dr. Li performed several analyses in specific subgroups. As noted by her, these analyses are exploratory without prespecified adjustments for multiplicity. These results are presented here as a basis to inform us on the conduct of future trials. In other words, their findings should be viewed as hypothesis-generating and where appropriate, additional studies can be conducted to further test these hypotheses.

Of interest was the analysis restricted only to glargine-comparator trials which comprised 12 of the 17 trials in the updated meta-analysis. Reflecting the larger contribution of these trials to the overall cohort, 114/129 (88.3%) of the MACE+ and 78/91 (85.7%) of the MACE occurred in these trials. The HRs and accompanying 95% CIs for both MACE+ and MACE in the glargine-controlled trials showed a higher risk of developing a MACE+ or MACE with degludec/degludec-aspart than glargine, on par with what was observed in the overall cohort.

Table 16: Analysis Results for MACE+/MACE in IGlar-controlled Trials (FAS, 7 Day Censoring)

	MACE+		MACE	
	IDeg/IDegAsp	IGlar	IDeg/IDegAsp	IGlar
N	4397	2540	4397	2540
Events (IR*)	87 (20.4)	27 (13.3)	62 (14.6)	16 (7.9)
HR (95% CI)	1.54 (0.99, 2.40)		1.82 (1.03, 3.19)	
RD (%) (95% CI)	0.59 (0.01, 1.17)		0.54 (0.07, 1.01)	

Source: Created by reviewer. *: Per 1,000 PYE

Dr. Li also analyzed CV risk excluding all trials where a prandial insulin (i.e., aspart) was co-administered with degludec or its comparator. This analysis isolates CV risk attributable to basal insulin use alone in the overall meta-analysis. The results of this

analysis were consistent with the overall analysis suggesting an increased risk of developing a CV event with degludec over comparator.

Finally, a subgroup analysis was performed by type of diabetes. In T1DM, the HR (95% CI) for MACE+ and MACE were 0.96 (0.30-3.09) and 1.30 (0.27-6.29), respectively. In contrast, in T2DM, the HRs (95% CI) for MACE+ and MACE were larger at 1.35 (0.89-2.04) and 1.71 (1.01-2.90), respectively. Because 77.0 % (7130/9255) of patients in the program had T2DM, it is not surprising that the findings in the T2DM population yield results close to those of the overall analysis. Patients with T2DM were at higher risk for experiencing a CV event as illustrated by the fact that 89 % (118/132) of all MACE and MACE+ occurred in the T2DM population. This was expected based on baseline demographic and disease characteristics. Only 14 MACE+ and 9 MACE occurred in patients with T1DM, severely limiting any conclusions one can make on the CV effects of degludec in T1DM. Although limited, these subgroup analyses do not suggest that risk of CV events in degludec treated patients differs drastically by type of diabetes studied.

8.1.4. Conclusions on CV Safety of Degludec and Degludec-Aspart

The insulin degludec program (including degludec-aspart) was not explicitly designed to exclude a specific excess CV-risk margin, as required of non-insulin based therapies for T2DM. However, the sponsor prospectively defined, collected and adjudicated CV events in Phase III with the intention of enabling a robust assessment of CV risk in the overall program. Several AC panel members noted that there were insufficient CV events in this program to adequately assess CV safety While the trial did not enroll a population of high CV risk patients as one might expect in a CVOT, the demographics and event rates from this program reflect a higher CV risk population requiring insulin. As such, the number of events observed in these two NDAs is comparable to what FDA has observed in the past few years from non-insulin-based programs designed to exclude a CV risk margin as per the 2008 Guidance. The following table summarizes the number of MACE and MACE+ observed in the dapagliflozin and alogliptin programs at the time of their NDA submission.[1] Both these NDAs designed their Phase 2/3 trials and/or dedicated CV outcomes trial to have sufficient power to exclude an 80% excess CV risk relative to comparators under the assumption that the true HR is 1.0. The updated meta-analysis for degludec/deg-aspart program had 132 MACE+ and 91 MACE, exceeding the number of events observed in these two programs.

[1] Alogliptin submitted their prespecified CV meta-analysis in a 2nd submission

Table 8.1.4a MACE and MACE+ Analyses for Dapagliflozin and Alogliptin*

	n(%) MACE	n(%) MACE+	MACE analysis	MACE+ analysis
Dapagliflozin Comparator	39/3616 (1.1%) 22/1225 (1.8%)	48/4344 (1.1%) 30/1849 (1.6%)	0.60 (0.32, 1.10)**	0.67 (0.38, 1.18)**
Ttl # of events	61	78		
Alogliptin Comparator	36/1015 (3.5%) 46/1029 (4.5%)	41/1058 (3.9%) 55/1079 (5.1%)	0.81 (0.44, 1.50)	0.74 (0.42,1.32)
Ttl # of events	82	96		

*data presented here are from initial NDA submission specific to address diabetes guidance requirements and are ONLY for comparative purposes to degludec/deg-aspart on number of CV events necessary to evaluate risk in a pre-marketing application. FDA has performed more CV analyses on dapagliflozin and alogliptin and reader is referred to those separate reviews for a complete discussion of the CV risk assessment for these two NDAs.
** Risk estimate in dapagliflozin calculated a 98% CI

In conclusion, these two NDAs have CV risks assessments that are of sufficient quality to raise serious concern over the CV safety of degludec. Across multiple analyses, a consistent trend of CV risk not favoring degludec is noted. In fact, one could conclude that while Novo Nordisk did not design its CV risk assessment to specifically exclude a risk margin of 1.8 like dapagliflozin and alogliptin, all other aspects of its program are comparable to these other NDAs and if we were to apply the CV guidance to degludec, Novo Nordisk failed to rule out an unacceptable level of CV risk to permit marketing of degludec and degludec-aspart.

At the advisory committee, panel members were asked to discus the CV safety assessment program and vote on whether a CVOT should be conducted. All twelve members voted in favor of a dedicated CVOT be conducted to further investigate the signal arising from the meta-analysis.

8.2 Hypoglycemic Risk

All insulin products carry a risk of hypoglycemia which may be influenced by a variety of factors including, but not limited to, the timing of insulin administration in relation to a meal and its macronutrient contents, the amount/dose of insulin administered, PK/PD characteristics of the insulin, and individual patient characteristics. Just as these factors might exacerbate or mitigate hypoglycemic risk, the actual characterization of risk is also affected by how hypoglycemia is defined, captured, perceived and reported.

8.2.1 Definitions of Hypoglycemia

Before delving further into the findings on hypoglycemic risks in this program, the reader should become familiar with the different definitions used to capture hypoglycemia in this program. Each definition has a different degree of specificity and clinical relevance. Definitions capturing the more serious/severe events are generally more specific (i.e., more likely to reflect a true hypoglycemic event) and clinically

relevant (i.e., impacts patient well-being or outcome). However, the more serious/severe events are rare in clinical trials and more often drug development programs attempt to characterize risk of hypoglycemia using broader and less specific definitions. While this approach might lend feasibility to a clinical program to collect sufficient events to assess hypoglycemic risk, it includes many nonserious events and some may not even represent true hypoglycemia. Reliance on such data obfuscates the benefit-risk calculus. For example, it is difficult to make a conclusion that Drug A has a lower risk of hypoglycemia than Drug B if the key clinical difference between the two products is accounted for by more events of 'dizziness and lightheadedness' with Drug B than Drug A.

The primary endpoint for the meta-analysis was the total number of 'confirmed' hypoglycemic events identified if the event met one of the following two criteria:

1. An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or resuscitative measures. (also referred to as a severe episode)
2. An episode with or without symptoms of hypoglycemia confirmed by a low blood glucose < 3.1 mmol/L (56 mg/dL).

Note: Although requiring confirmation with a low blood glucose level in criterion 2 would appear to increase specificity, values were obtained from self-blood glucose monitors which measure whole blood in contrast to plasma samples in laboratory tests. In general, whole blood glucose measures are lower than those obtained from plasma blood samples and can therefore overestimate hypoglycemia, especially in the absence of any symptoms.

Confirmed Nocturnal Hypoglycemia – these events were a subset of those identified in the primary endpoint used for the meta-analysis except limited to the timeframe of 00:01 to 06:00 hrs.

American Diabetes Association (ADA)-Definitions
Probable – symptoms and no plasma glucose measurement
Asymptomatic – no symptoms and low plasma glucose measurement (< 70 mg/dL)
Documented symptomatic – symptoms and low plasma glucose measurement (< 70 mg/dL)
Severe – third party assistance required to actively administer carbohydrate, glucagons, or other resuscitative actions

8.2.2. Meta-analysis of Glargine-controlled Trials in Degludec Program

As noted above, the PK/PD characteristics of degludec led Novo Nordisk to believe its product would have a lower risk of hypoglycemia over other insulin products, particularly glargine. (b) (4) [redacted]. It is

beyond the scope of this memo to summarize the communications with Novo Nordisk on its proposal but the reader is referred to an advice letter sent to the company on 8 October 2010 under IND 73198 reflecting FDA's concerns over the methods proposed by Novo Nordisk for evaluating hypoglycemic risk. Among these concerns included the following:

- Trial design introducing bias on how hypoglycemia would be reported (e.g., open-label design, reliance on self-reports recorded in patient diaries)
- Reliance on less specific definitions or less clinically relevant definitions for hypoglycemia
- Variable presentations of hypoglycemia by patient population (e.g., Type 1 and Type 2) or skewed results driven by a few patients in the overall patient population

In all of its communications, including the preNDA meeting minutes issued on 15 July 2011, (b) (4) .

With these two NDA submissions, FDA reviewed a planned meta-analysis to compare hypoglycemic risk in trials involving only degludec and glargine as well as hypoglycemic findings across the entire development program. Please see the review conducted by Dr. Eugenio Andraca-Carrera dated 4 June 2012 for a statistical critique of the meta-analysis. In addition, please refer to Dr. Jean-Marc Guettier's clinical briefing document to the advisory committee and his presentation which provides clinical context to the interpretation of hypoglycemic risks in this program.

The statistical analysis plan for the meta-analysis evaluating risk for hypoglycemia included seven trials in which degludec administered once-daily was compared to glargine administered once-daily. Two of these trials were in patients with T1DM (3583 and 3770) and five were in T2DM (3582, 3579, 3672, 3586 and 3668). Please note that the flexible-dosing arms in trials 3770 and 3668 were not included in this meta-analysis. Of the 5 trials in T2DM, only Study 3582 employed a basal-bolus regimen; the remaining 4 trials evaluated insulin as a basal-only therapy.

As stated under Section 8.2.2, the primary endpoint for the meta-analysis was the total number of 'confirmed' hypoglycemic events identified if the event met one of the following two criteria:

- An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or resuscitative measures. (also referred to as severe episode)
- An episode with or without symptoms of hypoglycemia confirmed by a low blood glucose < 3.1 mmol/L (56 mg/dL).

There was significant heterogeneity in the rate of confirmed hypoglycemia by trial and type of diabetes. In his review, Dr. Andraca-Carrera presented the overall findings

and by Type 1 and Type 2 diabetes as summarized in the following table adapted from his review.

Table 8.2.2a Primary Findings from Meta-analysis of Hypoglycemic Risk and by T1/T2DM

	IDeg Once-Daily	Glargine Once-Daily
Primary Analysis of Confirmed Hypoglycemia (Full Cohort)		
Total subjects randomized Subjects used in analysis	2899 2886	1431 1421
Rate Ratio (95% CI)	0.91 (0.83, 0.99)	
Type 1 Diabetes Cohort		
Total subjects randomized Subjects used in analysis	637 637	321 316
Rate Ratio (95% CI)	1.11 (0.94, 1.31)	
Type 2 Diabetes Cohort		
Total subjects randomized Subjects used in analysis	2262 2249	1110 1105
Rate Ratio (95% CI)	0.84 (0.76, 0.93)	

The overall results revealed a reduced rate of 'confirmed hypoglycemia' associated with degludec use. When analyzed by type of diabetes, there was a non-significant increase in rate of confirmed hypoglycemia in the Type 1 population and a significant decrease in the Type 2 population.

Disparate findings between T1 and T2DM were not entirely surprising as it was conveyed to Novo Nordisk in the 8 October 2010 advice letter *that differences in trial characteristics and patient populations will affect the risk of hypoglycemia (e.g., patients with T1DM are expected to have more hypoglycemia than patients with T2DM)*. This was indeed observed in the meta-analysis as approximately 43-47% of patients with T2DM experienced zero confirmed hypoglycemic event whereas more than half of patients with T1DM experience 29 or more events annually; only 3-4% of patients with T1DM reported no events. This information is summarized in the following table from Dr. Andraca-Carrera's review.

Table 7. Distribution of observed rate of confirmed hypoglycemia by type of diabetes

T1DM			T2DM		
Events / year	IDeg	IGlar	Events / year	IDeg	IGlar
0	3.5%	4.0%	0	43.3%	47.0%
(0-12]	17.0%	19.0%	(0-2]	20.1%	17.8%
(12-29]	20.9%	15.9%	(2-10]	22.9%	21.4%
(29-51]	20.1%	18.7%	(10-20]	7.9%	8.0%
(51-93]	20.2%	19.9%	(20-222)	5.8%	5.8%
(93-354)	18.4%	22.4%			

Datasets: hypo.xpt

Novo Nordisk attributes the higher rate of hypoglycemia with degludec in some trials to the use of bolus insulin. Basal-bolus insulin therapy is a more complex regimen with overlapping PK/PD profiles for the different types of concomittant insulins used and overdosing or inaccurate timing for meal coverage potentially exacerbating the risk for hypoglycemia. For T1DM, all patients require basal-bolus insulin therapy; however, only one T2DM trial evaluated basal-bolus insulin therapy. In this one trial (3582), the annualized rate of confirmed hypoglycemia was higher than the other four T2DM trials.

Table 8.2.2b Observed Annual Rate (SE) of Confirmed Hypoglycemia by Basal-Bolus or Basal Only Regimen in T2DM Trials

	IDeg	**Glargine**
T2DM Basal-Bolus		
3582	11 (17)	13 (17)
T2DM Basal-Only		
3579	1.4 (2.5)	1.7 (4.1)
3672	1.2 (2.7)	1.3 (3.1)
3586	3.2 (5.8)	3.9 (6.1)
3668	4.1 (15.8)	3.5 (6.9)

Notable observations from Table 8.2.2b include the low rate of hypoglycemia with basal-only insulin use in T2DM and the small numerical differences in the annual rate of confirmed hypoglycemia between degludec and glargine. The rate ratio and accompanying 95% CI for confirmed hypoglycemia based on the four basal-only trials were calculated by Dr. Andraca-Carrera and found to be similar to the overall results. Basal-only use of degludec in T2DM patients was associated with a lower rate of events defined as confirmed hypoglycemic episodes compared to glargine – 0.85 (0.73, 0.99).

To further appreciate whether these small differences favoring degludec in the T2DM trials represent events of clinical relevance, Drs. Guettier and Andraca-Carrera conducted detailed reviews of the types of events contributing to the overall observed finding under 'confirmed hypoglycemia' and noted that the majority of these events were asymptomatic events. In Dr. Guettier's advisory committee presentation he displayed the following table (8.2.2c) which shows that more than half of the patients with T2DM (53.4%) experienced an asymptomatic event that was captured based only on a glucose level ≤ 70 mg/dL (note that glucose values used in analyses could be derived from: interstitial space, whole blood or plasma).

Table 8.2.2c Proportion of Total Hypoglycemic Events by ADA Definitions in Degludec Program (From Dr. Guettier's AC presentation)

	T1DM	T2DM
Probable	1.1%	1.6%
Asymptomatic	32.3%	53.4%
Documented	65.8%	39.4%
Severe	0.27%	0.08%

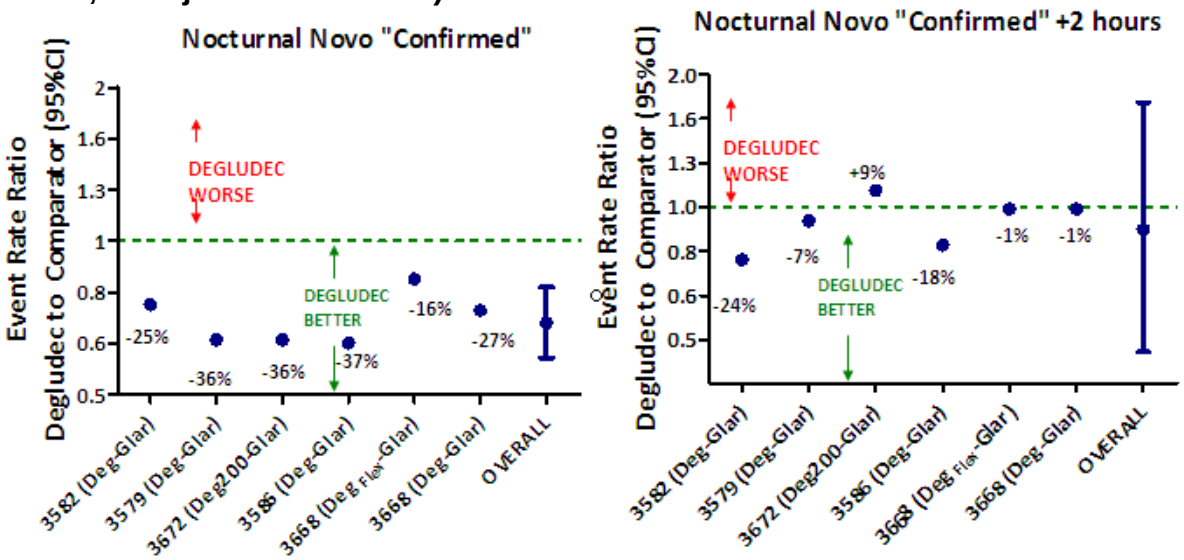
Data are calculated from NDA203314: Module 5.3.5.3: ISE: Appendix 6.2 Tables 260-262. Total % of events do not add up to 100% because there were episodes not classifiable under the four above-listed categories. These events represent the remaining episodes of hypoglycemia (e.g., relative hypoglycemia: symptoms present but measured glucose value > 70 mg/dL).

Several secondary endpoints were also evaluated as part of the SAP for the meta-analysis including nocturnal confirmed, severe and ADA-documented hypoglycemia. Section 3.6.3 of Dr. Andraca-Carrera's review summarizes the results from these secondary analyses. These secondary analyses revealed no significant difference between degludec and glargine in T1DM for any of these different hypoglycemic definitions. For T2DM, a reduced risk reaching statistical significance was only observed for nocturnal confirmed hypoglycemia. Table 56 of Dr. Guettier's briefing document shows event rate for hypoglycemic episodes for three hypoglycemic episode categories including severe hypoglycemic episode. Severe nocturnal hypoglycemic episodes were rare in the T2DM basal-only trial (i.e., three events across the five Phase 3 trials all on degludec). Compared to patients using glargine, subjects using degludec as part of a basal-bolus regimen (trial 3582) had more severe episode events at night (i.e., 2.1 versus 1.3 events per 100 patient year of exposure). These findings are not consistent with findings based on the nocturnal confirmed hypoglycemic episode definition.

Novo Nordisk has emphasized the clinical significance of nocturnal hypoglycemia in its NDA submission. Indeed, having a hypoglycemic episode in one's sleep should not be dismissed as trivial. However, that degludec appears to reduce nocturnal hypoglycemic risk over glargine without any significant effect on other hypoglycemic episodes over the remainder of the day does require further investigation. Dr. Guettier noted differences in the PD profile between degludec and glargine (refer to Figure 2 in Dr. Guettier's briefing document) and questioned whether the timing of injection in the evening and the duration selected to identify nocturnal hypoglycemia could account for this difference.

Except for Study 3586, all five trials in T2DM considered in the meta-analysis specified that degludec be administered with the evening meal. For Study 3586, degludec was to be administered between start of the evening meal and bedtime. For glargine, there wasn't a fixed time of day for administration and all 5 trials specified 'at any time of the day, once daily". Based on steady-state PD profile of the two insulins, the time to maximal glucose infusion rate (T_{max} for glucose-lowering) was observed to be 12 hrs for degludec and 4 hrs for glargine. Recall that the applicant identified nocturnal events as only those occurring between midnight and 0600 hrs. Dr. Guettier questioned whether the prescribed dosing schedule for degludec (with evening meal or between evening meal and bedtime) might result in a peak PD effect and risk of hypoglycemia occurring outside of the time band for identifying nocturnal hypoglycemia. In contrast, the shorter T_{max} for glargine and the possibility that some patients might inject glargine in the evening (FDA inquired if Novo Nordisk captured when glargine was injected in trials and this information was not obtained) might result in an ascertainment bias against glargine. To explore his hypothesis, he requested analysis of nocturnal events in which the time band was extended by two hours (0000 hrs to 0800 hrs). Re-analysis for nocturnal hypoglycemia with this extended time band showed an attenuated reduction in risk associated with degludec.

Figure 8.2.2a Re-analysis of Nocturnal Hypoglycemia in T2DM Trials with Extension of Time Band by 2 hrs (from Dr. Guettier's AC presentation: trial based, unadjusted estimates)



The sponsor was asked to provide model based, patient-level, adjusted estimates (95% CI) for this analysis in an information request dated 11/14/2012 (results re-copied below for convenience). The results based on patient level data were consistent with trial-level based estimates and show that when two hours are added to the nocturnal time period the relative hypoglycemia benefit of degludec compared to glargine dissipates (i.e., all comparisons cross unity except one).

Table 3–1 Confirmed Hypoglycemia (Between 00:01 and 05:59 and Between 00:01 and 07:59 AM), Individual Trials, IDeg vs. IGlar, Phase 3, NDA

Trial (population, wks)	Time Interval 00:01 to 05:59			Time Interval 00:01 to 07:59		
	IDeg Rate	IGlar Rate	IDeg/IGlar Estimate [95% CI]	IDeg Rate	IGlar Rate	IDeg/IGlar Estimate [95% CI]
3583 (T1DM, 52 wks)	440.7	585.7	0.75 [0.59; 0.96]*	937.5	1036.3	0.89 [0.73; 1.09]
3770[§] (T1DM, 26 wks)	960.7	995.6	0.98 [0.72;1.34]	2447.8	2142.6	1.17 [0.92 ; 1.49]
3582 (T2DM, 52 wks)	138.7	184.4	0.75 [0.58; 0.99]*	209.6	276.6	0.77 [0.60; 0.97]*
3579 (T2DM, 52 wks)	25.3	38.5	0.64 [0.42; 0.98]*	73.1	78.5	0.89 [0.66; 1.20]
3672 (T2DM, 26 wks)	18.0	28.1	0.64 [0.30; 1.37]	62.4	57.0	1.09 [0.68; 1.74]
3586 (T2DM, 26 wks)	78.0	123.8	0.62 [0.38; 1.04]	170.9	207.7	0.83 [0.56; 1.21]
3668[§] (T2DM, 26 wks)	55.6	74.8	0.64 [0.37;1.10]	165.0	166.6	0.87 [0.56 ; 1.34]

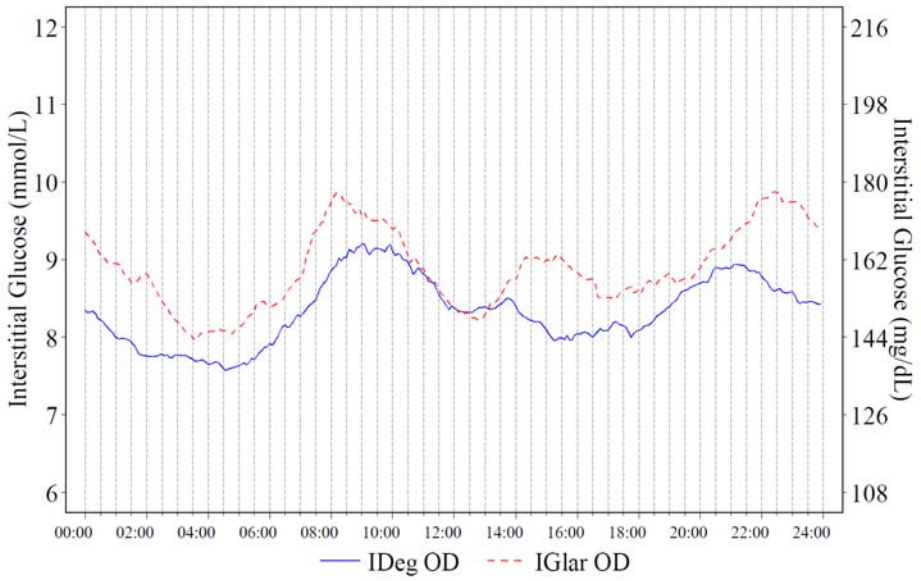
[§]IDeg fix arm, *p< 0.05, Observed rates per 100 PYE (SAS), Estimated rates and rate ratio (FAS)

Cross-reference: M2.7.3, App. 2 Tables 264-266 and Response to FDA 25 May 2012, Tables 1, 2, and 3

Several of the trials included continuous glucose monitoring (CGM) of interstitial glucoses in a subset of patients. These data are generated more for exploratory analyses; however, review of these profiles, particularly in the evening may lend some useful data for interpretation of the nocturnal hypoglycemic results.

For the subgroup of type 1 DM participants who underwent CGM measurements (n/N=119/472 vs. 38/114; degludec vs. glargine respectively) in trial 3583, the average interstitial glucose (mean of 72-hours of recording) at the end of 52 weeks at night and in the early morning was consistently lower on degludec compared to glargine (i.e., by ~ 15-30 mg/dL) and peak to trough variability was not different between the two insulins (data not shown refer to clinical trial report for variability analyses).

Figures 8.2.2b: 24-hour Plots of Interstitial Glucose Readings from Subset of Patients undergoing CGM in Studies 3583 (source – Applicant Response to FDA information request submitted on 30 Nov 2012)



FAS; LOCF imputed data

These data are inconsistent with the conclusion that fewer hypoglycemic episodes (25% fewer compared to glargine based on point estimate) occurred at night with degludec in type 1 DM compared to glargine. Lower mean nocturnal glucose on degludec as suggested by the interstitial glucose profile for this subgroup would be expected to place degludec treated patients at increased risk for events. Results based on nocturnal severe hypoglycemic episodes (the most specific definition) for this subgroup of participants in trial 3583 are consistent with this notion (7.1 vs. 2.7 events of severe hypoglycemia per 100 patient year of exposure; Table 2-1 response to information request dated 11/30/2012).

Furthermore, the profiles do not support the notion that hypoglycemic risk as defined by mean ambient glucose levels changes from favorable (at night) to neutral (during waking hours when patient is also injecting prandial insulin). In fact, ambient glucose profile in degludec treated patients track in parallel to profiles in glargine treated subjects and do not suggest that degludec treated patients are less at risk for any particular time segment of the day. This does not lend support to the sponsor's hypothesis that degludec benefit is best assessed at night because use of bolus insulin is mostly responsible for hypoglycemic episodes occurring during waking hours.

For the T2DM trials, 191 subjects from Study 3579 and 236 subjects from Study 3668 underwent CGM every 5 minutes for a period of 72 hrs before randomization and for 72 hrs after 26 and 52 weeks (Study 3579 only) of treatment.

In Study 3579, which evaluated a larger subset of patients for a longer duration of treatment, there was no statistically significant difference between the two treatment

groups in mean nocturnal interstitial glucose profiles (obtained between 2400 and 0600 hrs) after 52 weeks of treatment. No significant difference for nocturnal interstitial glucose profiles was observed between glargine and degludec flexible dosing regimen or the flexible dosing and once-daily dosing of degludec in Study 3668 (data not shown).

Table 11–23 Mean of Nocturnal Interstitial Glucose Profile after 52 Weeks of Treatment - Statistical Analysis - Full Analysis Set

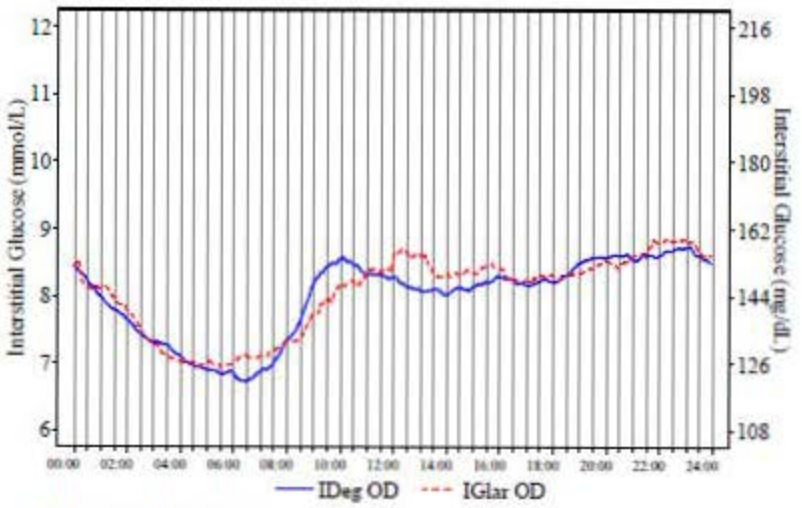
	FAS	N	Estimate	95% CI
Mean Nocturnal IG Profile				
LSMeans				
IDeg OD	773	139	7.60	
IGlar OD	257	47	7.71	
Treatment Contrast				
IDeg OD - IGlar OD			-0.11	[-0.95; 0.73]

N= Number of subjects contributing to analysis, CI= Confidence Interval
Mean nocturnal profile value is defined as the adjusted area under the profile and is calculated using the trapezoidal method using IG values from 00:01-05:59
The endpoint is analysed using a mixed model with treatment, sex, region and antidiabetic treatment at screening as fixed effects, and age and baseline response as covariates.
Missing data is imputed using last observation carried forward.

Source: Applicant's Clinical Study Report

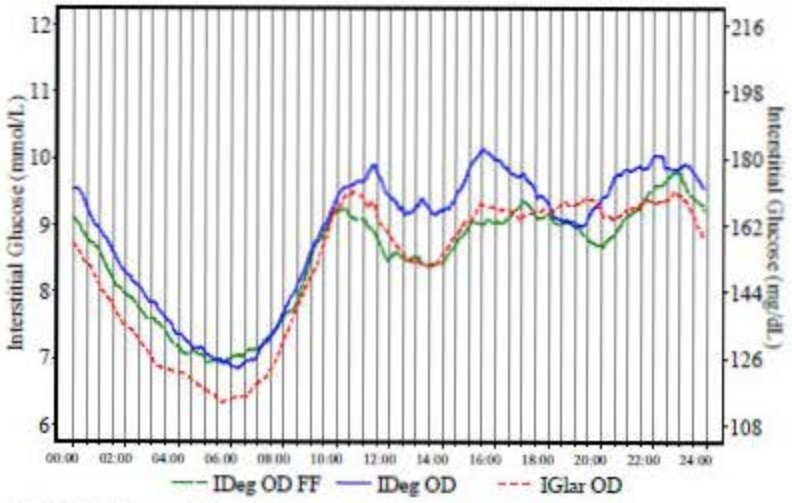
Dr. Guettier also requested plots of CGMS data over the entire 24 hr period for both Study 3579 and 3668. The following figures show a similar pattern of CGM readings during the nocturnal period for Study 3579 between degludec and glargine. The mean nocturnal (00:01-5:59) interstitial glucose value was 135 mg/dL at Week 52 in both groups and the minimum recorded glucose value was 49 and 68 mg/dL in the degludec and glargine group respectively (Source: individual clinical trial report for nn1250-3579 Table 14.2.132 page 488). In Study 3668, glargine-treated patients had lower mean nocturnal CGM values at Week 28 (146, 140 and 131 mg/dL for deg flex, deg fixed and glargine) but the mean recordings never fell below 108 mg/dL in any group and the minimum nocturnal values between groups were similar [40, 67 and 56 mg/dL for deg flex, deg fixed and glargine (Source: individual clinical trial report for nn1250-3668 Table 14.2.131 page 428)]. In addition, the figure shows that differences between groups were largely the result of baseline differences (i.e., lower glucose at midnight-the start of the nocturnal time period) rather than differences in the rate of nocturnal glucose drop (i.e., slopes are paralell) between groups. There were no severe hypoglycemic episodes reported by any patients in the CGM subset.

Figures 8.2.2c and d 24-hour Plots of Interstitial Glucose Readings from Subset of Patients undergoing CGM in Studies 3579 and 3668 (source – Applicant Response to FDA information request submitted on 30 Nov 2012)



FAS; LOCF imputed data

Figure 2–7 Interstitial Glucose Profile at Treatment Week 52 - Mean Plot - Trial 3579 - Full Analysis Set



FAS; LOCF imputed data

Figure 2–9 Interstitial Glucose Profile at Treatment Week 26 - Mean Plot - Trial 3668 - Full Analysis Set

The CGM data for the nocturnal time period are not entirely consistent with the observed reduced risk of nocturnal hypoglycemia in the overall T2 population. Novo

Nordisk cautions against making any conclusive statements based on these 24 hr CGM plots. They argue that meal times and daily activities known to affect CGM readings vary markedly; however, if the time point of interest is 00:00 to 0600 (nocturnal period), there should be less impact of meals and activities. It should be acknowledged though that CGM data are exploratory and have not been relied upon for labeling of hypoglycemic risks. Furthermore, these data are derived from a subset of patients in two trials and differences between patients who consented to take part in the CGMS substudy and the overall trial population may exist which contribute to differences in finding. And finally, these recordings represent the mean of several data points and infrequent individual low excursions that are still concerning may not be captured in these plots.

8.2.3. Conclusions on Hypoglycemic Risk

Hypoglycemia is a well-established risk associated with insulin therapy and while the patient and prescriber can take appropriate measures to mitigate this risk, the risk can never be reduced to zero, especially if the goal of insulin therapy is to improve glycemic control not achieved by other therapies. Insulin degludec is no exception as evidenced by more withdrawals due to hypoglycemia and several serious cases of hypoglycemia associated with degludec use in the T1DM population detailed in narratives provided by Dr. Guettier in his AC briefing material (See Section 7.1 of this document).

In this program, Novo Nordisk sought to demonstrate a lower risk of hypoglycemia associated with degludec use in both the T1 and T2DM population over glargine through a pre-planned meta-analysis of 7 trials capturing events meeting the applicant's definition of "confirmed hypoglycemia" which included rare (<< 1% of all events), severe events as well as more frequent, less specific events. The majority of the events fell into the latter category.

The overall results of the meta-analysis suggested a reduced risk of degludec over glargine but a significant interaction by type of diabetes led the FDA statistical reviewer to analyze these results by T1 and T2DM population. The perceived risk reduction was observed only in the T2DM population, again based on an endpoint that captures mostly patient reported, non-specific, low self-measured whole blood glucose, asymptomatic events. The magnitude of the observed relative risk reduction was small (~16% by point estimate). It is also concerning that no risk reduction was seen in the T1DM population, a population more susceptible to developing hypoglycemia and more likely to experience deleterious adverse outcomes from hypoglycemia. As pointed out in Dr. Guettier's AC presentation the Phase 3 program excluded subjects most at risk of hypoglycemia further limiting the generalizability of the finding. The one subgroup analysis which suggests a benefit of degludec over glargine was nocturnal hypoglycemia. Another perplexing finding in the T2DM population was the difference in risks observed between U.S. and non-U.S. trials.

Nocturnal hypoglycemia is a much feared complication of insulin therapy, especially among the T1DM population. As defined by Novo Nordisk, the rate of having a "confirmed hypoglycemic" event during midnight and 6 am was lower in the T2DM population but not in the T1DM population. Similar to other analyses suggestive of a risk reduction, this one was also comprised predominantly of the asymptomatic or less severe events. CGMS data in a subset of patients did not show a pattern consistent with the purported benefit of degludec over glargine and analyses which might account for differences in PD profile and timing of insulin administration attenuated the observed risk reduction.

(b) (4)

a conclusion based on the data submitted is complicated by inconsistent findings and the questionable clinical relevance of the predominating events captured as summarized below:

- Inconsistencies between T1 versus T2DM - The higher rate of hypoglycemia in the T1DM population can not be dismissed as this population is at greater risk for severe/serious events and as already noted above, a higher frequency of hypoglycemia. Novo Nordisk argues that this higher risk was due to the bolus insulin but one cannot easily separate out the risk by the type of insulin given the overlapping PK/PD profiles. Furthermore, to attribute all excess risk in the T1DM population to the use of bolus insulin does present an unviable solution as these patients can not be managed with only basal use of degludec.

- Inconsistencies based on analyses using different definitions for hypoglycemia. For example, a risk reduction is observed with Novo Nordisk's composite definition for 'confirmed hypoglycemia' but is not seen using the American Diabetes Association-documented symptomatic episode definition.

- Inconsistencies based on data obtained from U.S. versus non-U.S.-sites.

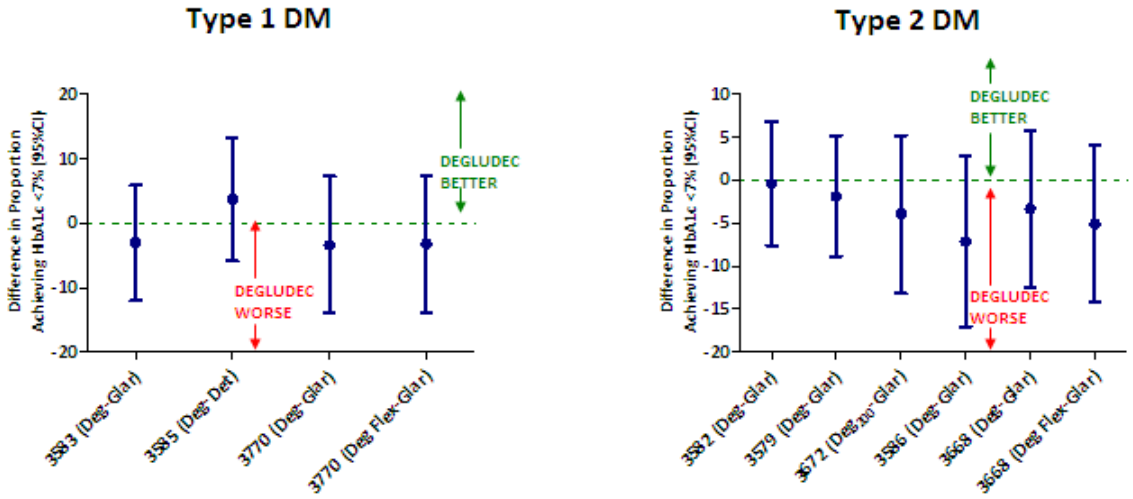
- Clinical significance of an observed risk reduction where the majority of the events were non-life-threatening and where close to 50% of the T2DM population did not even experience a single event.

The problems with characterizing hypoglycemic risk in this program were multiple and further compounded by the open-label trial design and reliance on self-reported symptoms and measures of events.

Finally, the risk of hypoglycemia should be considered in the context of glycemic efficacy. As noted under the Background section of this memo, insulin has no maximal effective dose and patients can achieve their targeted goals but at the risk of experiencing significant hypoglycemia. An insulin therapy that has a reduced risk for hypoglycemia over its comparator should enable better glycemic control than that comparator. Though robust data to support the theory is lacking, it is widely held that

hypoglycemia is an important factor limiting achievement of glycemic target goals. In this program, the presumed benefit of reduced hypoglycemic risk with degludec did not translate into more patients achieving ADA-target goals as noted in the following figures derived from data in Text Table-4 in Dr. Cynthia Liu's statistical efficacy review.

Figure 8.2.3a Proportion of Patients Achieving HbA1c < 7% in Degludec Trials



Overall, the data in support of a reduced risk of hypoglycemia for degludec are inconsistent and non-robust. They are also very much in contrast to the consistent and robust finding of excess cardiovascular risk associated with degludec and degludec-aspart use.

9. Advisory Committee Meetings

These two NDAs were presented at an Advisory Committee Meeting on Thursday, November 8, 2012. The outcome for the two voting questions to the panel members were:

Voting Questions

5. Based on the results from the CV meta-analysis, should a cardiovascular outcomes trial be conducted for degludec and degludec/aspart? (**Vote**)

12 yes to require a dedicated CVOT

6. Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of degludec and degludec/aspart for the treatment of Type 1 and Type 2 diabetes mellitus? (**Vote**)

8 yes, 4 no in support of marketing of these two NDAs

At present, the transcripts from this meeting are not available. Please see specific sections of this memo summarizing the thoughts of the panel members on the CV safety and hypoglycemic risk of degludec.

10. Pediatrics

A (b) (4) waiver was requested for (b) (4) type 1 diabetes ages 0-10 yrs. A deferral was requested for type 1 diabetes, ages (b) (4) yrs.

11. Other Relevant Regulatory Issues

These two NDAs were presented at a CDER Regulatory Briefing on 7 December 2012, chaired by OND Director, Dr. John Jenkins. A panel of CDER senior managers including Drs. Robert Temple, Sandy Kweder, Charles Ganley, Curtis Rosebraugh, and Julie Beitz were present. Other senior managers included OSE Director, Gerald DalPan. The panel members expressed concern that the CV safety signal was of sufficient evidence to support a requirement for a cardiovascular outcomes trial prior to approval.

12. Labeling

Labeling is deferred as a Complete Response action is recommended on both of these applications.

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action

Complete Response

- Benefit-Risk Assessment

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. The program also compared these two products to other approved basal insulins (glargine and detemir) and insulin mixtures (Novolog 70/30) in a diverse patient population such that we can conclude that degludec and degludec/aspart are non-inferior to currently available products. The clinical development program also

evaluated the cardiovascular safety of degludec and degludec-aspart through a well-designed, prospectively planned analysis that included broad collection of events subjected to rigorous blinded adjudication. A CV safety signal was detected from this robust program for which multiple analyses yield a consistent finding of elevated risk associated with degludec and degludec-aspart. The risk was of sufficient concern to consider whether a benefit exists for these two products to counterbalance the CV safety concern and allow marketing.

There are several benefits of these products which need to be considered in the overall benefit-risk assessment. This memo has already touched on the findings related to hypoglycemia. With regards to hypoglycemia, (b) (4)

However, there are unquestionable benefits of these two products that also need to be considered in the overall benefit-risk calculus. We discuss them below followed by arguments as to why each is not of a magnitude of gain or uniqueness to dismiss the CV safety signal and the need for a pre-market CV outcomes trial.

A True 24-hr Basal Insulin

The PK/PD profile and the trials in this program support a conclusion that degludec may be a true 24-hr basal insulin. This is an advantage over currently marketed basal insulin analogues as full day coverage isn't always provided by detemir (~12-24 hours) and glargine (~22 hours), especially detemir. In this program, degludec once-daily was predominantly compared to glargine and when glargine was used as the comparator it was also injected once-daily. Although there are reports of patients requiring twice daily administration of glargine in clinical practice, the efficacy and safety data comparing degludec to glargine in NDA 203314 is based on a once daily to once daily schedule comparison. This allows one to directly evaluate the incremental efficacy benefit gained by having a'true 24-hr basal insulin'. Efficacy results do not suggest that the novel PK/PD profile trends toward providing superior efficacy as might be expected. On the contrary, although degludec was shown to be non-inferior to glargine in 8 out 8 trials the point estimate consistently trended towards suggesting slightly worst glycemic control in degludec-treated patients (i.e., 7 out 8 trials). In two trials, the numerical difference in glycemic control between degludec and glargine reached statistical significance (see Figure 7.1.4a). This observation was consistent with efficacy results based on responder analyses (see Figure 8.2.3a).

Flexible dosing schedule

Two trials investigated a flexible dosing regimen for degludec and compared it to the once-daily dosing of degludec and glargine. A third trial compared the flexible dosing regimen of degludec to sitagliptin. Flexible dosing of degludec still allowed for effective lowering of HbA1c and did not appear to compromise safety. The advantage here is for the patient who forgets to take a dose of his/her basal insulin but can take that missed dose within a reasonable timeframe from the next scheduled dose with assurance of maintained efficacy and safety.

While this is an advantage, in terms of convenience, to some patients who might forget often or many patients who infrequently miss a dose, the currently available basal insulin products can still be used by these patients provided they monitor their blood glucose before and after taking their missed dose and adjust the next insulin dose or carbohydrate intake appropriately to maintain adequate glycemic control or reduce risk for hypoglycemia. In other words, withholding the availability of degludec to further investigate the CV safety signal is not denying patients the solution to treating diabetes because of missed insulin doses.

The only U-200 formulation for a basal insulin analogue
Currently marketed basal insulins are available only in a U-100 (i.e., 100 units/mL) dosage strength (note: regular insulin is available as a 500 units/mL strength and can be used for severely insulin resistant individual as a 'basal' insulin). For patients with extreme insulin resistance requiring large amounts of insulin at any one time, more than one injection is necessary. Novo Nordisk is proposing to market degludec in two dosage strengths, U-100 and U-200, the latter more concentrated formulation will allow for those patients requiring more than 80 units at any one time to receive degludec as a single injection. Patients likely requiring high doses of insulin include those with T2DM and marked obesity. Novo Nordisk estimates that 20-30% of the T2DM population will benefit from the availability of this U-200 formulation.

Reducing the number of injections in this patient population is an advantage but similar to the flexible dosing regimen, this is an option of convenience rather than necessity, as such coverage can be provided with currently available products. Even if one were to argue that such an advantage might support approval of degludec to this subset of patients, the insulin-resistant and obese patient with T2DM is also the population with greater baseline CV risks. It would not seem prudent to market degludec, given the residual CV safety concern, only to a subpopulation of diabetics at a high risk for CVD.

The only pre-mixed basal and prandial insulin analogue
The labels for both detemir and glargine warn against diluting or mixing of these basal insulin analogues with other insulins because the PK/PD profile of the insulins might be altered. In contrast, Novo Nordisk has formulated and evaluated the 70:30 fixed-ratio of its basal insulin, degludec, with the prandial insulin, aspart, and provided evidence that PK/PD characteristics are not significantly altered. NDA 203313, specifically studied this pre-mix formulation in T1 and T2DM patients and the data support its efficacy.

The availability of degludec-aspart is an advantage in that it reduces by one the number of injections necessary for those patients requiring basal-bolus insulin in which the basal insulin is an insulin analogue. Again, degludec-aspart's availability is not a necessity beyond this convenience as currently available basal analogues have been studied with short-acting insulins and can provide effective glycemic control, albeit with extra injections. Furthermore, different insulin pre-mixtures are approved

which contain a mix of longer acting insulin (i.e., protaminated insulins) and shorter acting insulins (regular human insulin or rapid acting insulin analogues) (e.g., Eli Lilly's Humulin or Humalog mixtures and Novo Nordisk's Novolin and NovoLog mixtures). In the clinical program, Novo Nordisk compared degludec-aspart pre-mix to the approved Novolog 70/30 in two trials (3592 and 3597) in T2DM. Novolog 70/30 is a biphasic insulin where the short-acting insulin aspart is formulated with protamine sulfate to produce a long-acting and short-acting profile similar to an insulin mixture. Degludec-aspart was found to be non-inferior to the NovoLog 70/30 mix (See Table 7.2.3a).

Finally, insulin mixtures provide convenience in the management of patients requiring basal-bolus insulin therapy but these mixtures are in fixed ratios and the gain in convenience is countered by a loss in dose flexibility and individualization. While a 70:30 ratio of basal:prandial insulin may approximate the usual ratio, not all patients may achieve optimal glycemic control with such a regimen and 75:25 or 60:50 may be desired. This is particularly important in the population for which basal:bolus insulin therapy is required – T1DM.

At the December 7th 2012 regulatory briefing for degludec and degludec/aspart, some panelists asked whether a patient population could be identified for which the benefits of degludec and degludec-aspart might still outweigh the CV safety concern. In particular, patients with type 1 diabetes was a consideration because the subgroup analyses for CV risk by diabetes type did not show the elevated risk observed in the overall meta-analysis or in the type 2 population. The absence of a signal likely reflects the low incidence of observed CV events (i.e., lack of power) in the T1DM population (only 14 MACE+ events observed) which does not allow for an adequate assessment of risk in this population. To accept this unknown CV risk should at least require some demonstration of unique benefit in the T1DM population to justify approval. In order to justify approval, the unknown CV risk in this population should ideally be counterbalanced by evidence that degludec offers a unique benefit over currently available therapies. In the T1DM population, such benefit does not exist both in terms of glycemic control or hypoglycemic risk reduction. Degludec and degludec-aspart were non-inferior for glycemic control relative to glargine and detemir and degludec resulted in a higher rate of hypoglycemia in the T1DM population than did glargine.

In conclusion, degludec and degludec-aspart products were associated with an increased CV risk relative to comparators for which a benefit could not be identified to offset this safety concern at present.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

None at this point as a CR action is recommended.

- Recommendation for other Postmarketing Requirements and Commitments

None at this point as a CR action is recommended.

- Recommendations to address CR deficiency

As recommended by all members of the AC committee and the senior CDER officials at the regulatory briefing, a cardiovascular outcomes trial is necessary to further investigate the signal arising from the cardiovascular safety meta-analysis. I am recommending that this trial be conducted as a pre-marketing study.

The objective of the trial should be to dispel the cardiovascular safety concern observed in the meta-analysis of Phase 3 trials. A non-inferiority trial comparing degludec to glargine would be appropriate for several reasons. No other safety concern has been identified necessitating that a CV benefit be shown with degludec to offset any additional risks. The CV safety signal from this program is concerning but not conclusive. To provide reasonable assurance that degludec is non-inferior to glargine, which has already been studied in a placebo-controlled CVOT and appears to carry a neutral CV risk profile, makes a non-inferiority trial to glargine a defensible requirement. Furthermore, glargine is used predominantly as a once daily basal insulin and was the the most frequent comparator used to establish efficacy and safety of degludec in the two Phase 3 programs. Hence, many of the hypotheses (e.g., hypoglycemia benefit) generated by the Phase 3 programs can be further evaluated in a large prospective head-to-head trial comparing these two insulins.

The non-inferiority margin requires further discussion. The margins of 1.8 and 1.3 proposed in the 2008 FDA guidance are based on feasibility, not on any identified CV risk of concern for an individual product or class of drugs. If we base our level of concern for degludec only on the hazard ratio (See Table 8.1.2a), the level of risk across different analyses for MACE would be 1.4 to 1.7 and 1.10 to 1.3 for MACE+. Dr. Mat Soukup has provided a table in his team leader memo dated 13 December 2012 providing different sample size estimates based on different risk margins for exclusion and estimated event rates of population studied, assuming 90% power, a type 1 error of 0.05 (2-sided) and a true HR of 1.0.

Table 13. Estimated Trial Size Based on Different Risk Margins and Background Rates of Study Population (from Dr. Mat Soukup's review)

Risk Margin	Events Needed	Max of Point Est.	Person Years		
			Rate=1.0%	Rate=1.5%	Rate=2.0%
1.2	1264	1.07	126400	84267	63200
1.3	610	1.11	61000	40667	30500
1.4	371	1.14	37100	24733	18550
1.5	255	1.17	25500	17000	12750
1.6	190	1.20	19000	12667	9500
1.7	149	1.23	14900	9933	7450
1.8	121	1.26	12100	8067	6050
1.9	102	1.29	10200	6800	5100
2.0	87	1.32	8700	5800	4350
2.2	67	1.37	6700	4467	3350
2.4	54	1.41	5400	3600	2700
2.6	46	1.46	4600	3067	2300
2.8	39	1.50	3900	2600	1950
3.0	34	1.54	3400	2267	1700
3.4	28	1.62	2800	1867	1400

Assuming 90% power, type 1 error = 0.05 (1-sided) and true HR 1.0

For example, if one were to place the most emphasis on the MACE analysis in the original meta-analysis because it is not impacted by excess non-specific terms of unstable angina or the extension period, the MACE finding for HR (95% CI) of 1.4 (0.76, 2.57) should require that we exclude a risk margin of 1.4 prior to marketing. As can be noted in Table 13, even with enrollment of a high-risk population whose background annualized event rate was 2.0%, a substantial number of patients would need to be enrolled for the targeted number of events necessary to exclude a 40% excess risk. However, such a trial might still be acceptable to Novo Nordisk wherein the agency is willing to accept an interim analysis to exclude a higher risk margin (e.g., 1.8 based on current standards) and assuming an acceptable point estimate at the interim analysis. The ongoing portion of this trial would have the objective of ruling out the lower risk margin, including the possibility of applying the current standard of 1.3 in the post-marketing setting.

All these scenarios assume a true HR of 1.0. If the true HR is below 1.0, lower pt-yrs of exposure than provided on this chart may achieve the stated objective. However, one should take note of the maximal point estimate in Table 13. Even for a risk margin of 1.3, there remains the possibility that the HR will be as high as 1.11 and internal discussions would need to be held on whether that is acceptable for a drug product wherein a CV safety signal has already been identified in a robust, prospective meta-analysis of planned trials.

None of these issues need to be relayed in the Complete Response letter and can be deferred for discussion at an End-of-Review meeting with Novo Nordisk.

Reference List

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/s/

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