

FDA Briefing Document

NDA 203313 and NDA 203314

Insulin Degludec and Insulin Degludec/Aspart

Applicant: Novo Nordisk, Inc.

**Endocrinologic and Metabolic Drugs
Advisory Committee Meeting**

November 8, 2012

Table of Content

1. Purpose
2. Discussion Points
3. Clinical Review
4. Clinical Safety Review
5. Degludec Efficacy: Statistical Review
6. Degludec/Aspart Efficacy: Statistical Review
7. Cardiovascular Meta-Analysis: Statistical Review
8. Hypoglycemia Meta-Analysis: Statistical Review
9. Appendix

Degludec Advisory Committee Meeting Purpose

FDA has convened an advisory committee meeting on November 8th, 2012, to discuss the pending new drug applications for insulin degludec and insulin degludec/aspart. Both applications are seeking an indication for the treatment of type 1 (T1DM) and type 2 diabetes mellitus (T2DM) in adults. The goal of the advisory committee meeting is to discuss the cardiovascular safety findings in these two applications and to weigh these findings in light of the benefits afforded by these two drug products.

At the time of NDA filing, a meta-analysis of sixteen Phase 3 trials in the degludec and degludec/aspart programs estimated that use of degludec products could increase the composite risk of cardiovascular death, non-fatal MI, non-fatal stroke and unstable angina by 10%¹ relative to active comparators. This estimate was based on 80 cases and approximately 5444 patient years of exposure. The uncertainty (i.e., 95% confidence interval) around the estimate of hazard was large and demonstrated that the true risk could be as high as 77% or alternatively that degludec products could lower cardiovascular risk by 32%.

The applicant had six ongoing long-term controlled extensions of parent Phase 3 trials at the time of NDA filing. On April 27th 2012, the Agency asked Novo Nordisk to update the original analysis with data from ongoing Phase 3 trials. An updated analysis based on 142 cases and approximately 7716 patient-years of exposure was received. In the analysis containing the additional follow-up data degludec, products were estimated to confer a 30%² increased risk of cardiovascular death, non-fatal MI, non-fatal stroke and unstable angina relative to comparators. The uncertainty around the estimate showed that the increase in risk could be as high as 93% or alternatively that degludec products reduced the risk by 12% relative to comparator. The Cardiovascular Meta-Analysis: Statistical Review by Dr. Bo Li presents the results of this analysis in detail as well as the results of additional FDA analyses related to cardiovascular safety.

The degludec development program was large. The breadth of the program can be attributed to the fact that two new insulin products were developed in parallel (i.e., single product and a fixed-ratio combination product), that both T1DM and T2DM populations were studied, and that indications for novel basal insulin strengths (i.e., U100 and U200) and administration schedules (i.e., thrice weekly and flexible daily) were sought. The Clinical Review document summarizes the Phase 3 clinical development program in detail. This document also describes key regulatory considerations in the development of injectable insulin products and provides background regarding the two drug products. Finally a detailed account of the baseline characteristics of the population used in the efficacy

¹ Source: Table 4 Cardiovascular Meta-analysis: Statistical Review

² Source: Ibid.

analyses are provided, and disposition of patients across the degludec and degludec/aspart parent trials is reviewed.

The degludec program was primarily designed to confirm the efficacy of degludec or degludec/aspart with respect to glucose control. The benefits of degludec and degludec/aspart in terms of glucose control are presented in detail in the Degludec and Degludec/aspart Efficacy: Statistical Reviews provided by Drs. Cynthia Liu (degludec) and Dongmei Liu (degludec/aspart), respectively. These documents also contain results of inferential testing for hypoglycemia data across individual trials.

Another goal of the degludec program was to evaluate the safety of the two products for their intended use. In the Clinical Safety Review document, Dr. Calis reviews the characteristics of the population in the safety database and the major safety findings in the program. A particular emphasis is placed on review of safety parameters related to cardiovascular disease. Another focus of Dr. Calis' review is a description of the methodology behind the pre-planned meta-analysis of cardiovascular safety. In this section of the document, details related to cardiovascular event definitions, cardiovascular event capture, adjudication procedures and other issues of relevance to cardiovascular data quality/reliability can be found.

Finally, the applicant sought to demonstrate a unique benefit of degludec over the comparator glargine on the risk of developing hypoglycemia. To demonstrate this unique benefit, the applicant performed a pre-planned meta-analysis of glargine comparator trials across the degludec program. Dr. Andraca-Carrera reviews the results of this meta-analysis in detail in the Hypoglycemia Meta-Analysis: Statistical Review and provides a number of additional analyses. Definitions and capture of hypoglycemia data across the program are reviewed in the Clinical Review Document. The Clinical Review and Degludec Efficacy: Statistical Review document also include a review of descriptive hypoglycemia data and results of inferential testing of these data across individual trials and across alternative hypoglycemia definitions. A discussion related to factors with the potential to impact the reliability and generalizability of hypoglycemia data in the degludec program is provided in the Clinical Review Document.

Draft Discussion Points:

Cardiovascular Safety Assessment

As agreed with the FDA, the degludec and degludec/aspart programs were not designed to rule out a pre-specified margin of cardiovascular (CV) risk. However, at the End-of-Phase 2 meeting, FDA informed the applicant that this program was still required to collect and analyze CV data from clinical trials as outlined in the December 2008 Guidance for Industry. Based on the information provided in the briefing package and the presentations at today's meeting, please comment on the reliability of the CV risk assessment with respect to:

- The CV endpoints included in the primary analysis for CV risk
- The definition of the endpoints and the adjudication process
- The patient population included in the CV risk assessment
- The design of the clinical program (e.g., open-label nature, parent trial versus controlled extensions) and the impact if any this may have had on reporting, collecting and interpreting the results of the CV meta-analysis

Please discuss the clinical relevance of the CV safety signal identified in the degludec and degludec/aspart program with respect to the use of these two insulin products in the treatment of T1 and T2DM.

Hypoglycemia Risk Assessment

The applicant performed several pre-specified secondary analyses of hypoglycemia data across several trials in the degludec and degludec/aspart programs and a pre-planned meta-analysis to compare the risk of "confirmed hypoglycemic events" between insulin degludec and insulin glargine.

In these analyses "confirmed hypoglycemic episodes," represent the sum of "severe episodes" and "Novo Nordisk minor episodes."

- A severe episode was defined as an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions.
- A Novo Nordisk minor episode was defined as an episode not requiring third party assistance where a plasma glucose < 56 mg/dL or whole blood glucose <50 mg/dL was recorded (i.e., with or without presence of hypoglycemic symptoms).

Other definitions for hypoglycemia and their rates have been presented.

Based on the information provided in the briefing package and the presentations at today's meeting, please discuss the following:

- The clinical relevance of the results of the pre-planned meta-analysis of hypoglycemia relying on the Novo Nordisk definition of “confirmed” hypoglycemic episodes.
- The clinical relevance of differences in hypoglycemic risk between types of diabetes (T1DM vs. T2DM) observed in the meta-analysis of hypoglycemia
- The clinical relevance of differences in hypoglycemic risk between geographic regions (U.S. versus non-U.S.) observed in the meta-analysis of hypoglycemia
- In the overall program, comment on the clinical relevance of the hypoglycemic event findings. Please consider in your discussion the following:
 - The relative importance of “confirmed” nocturnal episodes versus “confirmed” episodes over the entire 24-hour period
 - The time frame used to define the nocturnal period
 - The differences between degludec and comparator in regards to timing of injection as well as insulin pharmacokinetic and pharmacodynamic properties
 - How the primary findings demonstrating glycemic non-inferiority, and how the insulin dose differences between groups observed at end of trial, influence interpretation of the hypoglycemia results.

Clinical Review Document

Endocrinologic and Metabolic Drug Advisory Committee Meeting

November 8th 2012

NDAs 203313 and 203314: Degludec and Degludec/aspart

Applicant: Novo Nordisk Inc.,

Prepared by

Jean-Marc Guettier, MDCM

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II, Office of New Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

Table of Contents

1. INJECTABLE INSULIN PRODUCT DEVELOPMENT:	7
1.1. General Considerations Regarding Insulins as a Class of Anti-diabetic Agent.....	8
1.2. Benefits Associated with Glycemic Control Intensification Using Insulin in Type 1 and 2 DM.....	9
1.3. Risks Associated with Glycemic Control Intensification using Insulin in Type 1 and 2 DM.....	9
1.4. Insulin and Cardiovascular Disease in Type 1 and 2 DM:.....	10
1.5. Hypoglycemia and Cardiovascular Disease Risk in T2DM	11
2. DRUG PRODUCTS	12
2.1. INSULIN DEGLUDEC	12
2.2. INSULIN DEGLUDEC/ASPART	12
3. DEGLUDEC INSULIN IN-VITRO PHARMACOLOGY SUMMARY	13
4. CLINICAL PHARMACOLOGY SUMMARY	14
5. CLINICAL DATA	15
5.1. CLINICAL DATA DEGLUDEC NDA	15
5.2. CLINICAL DATA DEGLUDEC/ASPART NDA.....	16
5.3. TRIALS AND DATA CUTOFF DATES FOR FDA ANALYSES	16
5.4. THERAPEUTIC CONFIRMATORY TRIALS INSULIN DEGLUDEC NDA.....	19
5.5. THERAPEUTIC CONFIRMATORY TRIALS INSULIN DEGLUDEC/ASPART NDA	21
5.5.1. Primary Objective	22
5.5.2. Secondary Objectives:.....	22
5.5.3. Design	22
5.5.4. Randomization.....	23
5.5.5. Blinding.....	23
5.5.6. Representative Trial Time Line	23
5.5.7. Controlled Interventions: Degludec Program	24
5.5.8. Controlled Interventions: Degludec/aspart Program	28
5.5.9. Basal or Premix Insulin Doses.....	30
5.5.10. Concomitant Glucose Lowering Medications	31
5.5.11. Study Population.....	32
5.5.12. Key Withdrawal Criteria	34
5.5.13. Statistical Considerations	35
6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS	39
6.1. Type 1 DM Trials: Degludec Program:	39
6.2. Type 2 DM Trials: Degludec Program, Once Daily Indication:	41
6.3. Type 1 DM (Trial 5401-3594): Degludec/aspart; Once Daily Indication	45
6.4. Type 2 DM Trials: Degludec/aspart Program; Once daily or Twice daily indication.....	47

7. SUBJECT DISPOSITION.....	50
7.1. Disposition Type 1 DM Trials Degludec Program.....	50
7.2. Disposition Type-2 DM Trials Degludec Program	56
7.3. Disposition Type 1 DM Trials Degludec/aspart Program.....	61
7.4. Disposition Type-2 DM Trials Degludec/aspart Program	66
8. EFFICACY FINDINGS:	69
8.1. Primary Analyses	69
8.2. Secondary Analyses: Weight Change.....	71
9. RELIABILITY AND GENERALIZABILITY OF THE HYPOGLYCEMIA DERIVED DATA.....	73
9.1. Issues related to the design of phase 3 trials:	74
9.2. Issues related to endpoints selected for analyses.....	75
9.3. Issues related to analytical accuracy of point of care glucose meter devices.....	76
9.4. Issues related to pooling multiple trials for the purpose of a meta-analysis of hypoglycemia data.	77
10. HYPOGLYCEMIA	78
10.1. Capture of Hypoglycemia	78
10.2. Definitions of Hypoglycemia	78
10.3. Hypoglycemia Descriptive Data: Degludec Program.....	79
10.3.1. Severe Hypoglycemia Type 1 DM	80
10.3.2. Hypoglycemia Broad Definitions Type 1 DM	80
10.3.3. Nocturnal Hypoglycemia Type 1 DM Degludec Program.....	84
10.3.4. Inferential Testing: Hypoglycemia Type 1 DM	84
10.3.5. Severe Hypoglycemia Type 2 DM	88
10.3.6. Hypoglycemia Broad Definitions Type 2 DM	88
10.4. Hypoglycemia Descriptive Data Degludec/Aspart Program	92
10.4.1. Hypoglycemia Type 1 DM.....	92
10.4.2. Hypoglycemia Type 2 DM.....	92

Table of Tables

Table 1: List and Pharmacokinetic Profiles of Currently Available Insulins Indicated for the Treatment of Type 1 and 2 Diabetes. (Table Created by Author of Document)	8
Table 2: Trials Included in FDA CV-metanalysis.....	18
Table 3: Overview of Therapeutic Confirmatory Trials for Degludec Once Daily in Type 1 Diabetes.....	19
Table 4: Overview of Therapeutic Confirmatory Trials for Degludec Once Daily or Thrice Weekly in T2DM.....	20
Table 5: Overview of Therapeutic Confirmatory Trials for Degludec/aspart.....	21
Table 6: Intervention Arm, Type 1 DM, Degludec Trials	26
Table 7: Intervention Arm, Type 2 DM, Degludec Trials	27
Table 8: Randomized Interventions in Degludec/aspart Program.....	29
Table 9: Basal Insulin Dose Adjustment Type 1 DM trials 3583 and 3585*	30
Table 10: Basal Insulin Dose Adjustment Type 2 DM trials	31
Table 11: Key Inclusion Criteria in the Degludec Program.....	32
Table 12: Inclusion Criteria Degludec/aspart Program.....	33
Table 13: Key Exclusion Criteria in the Degludec and Degludec Program	33
Table 14: Exclusion Criterion Specific to Degludec/aspart Program	34
Table 15: Hierarchical Testing Order for Confirmatory Secondary Endpoints in Type 1 DM trials.....	36
Table 16: Hierarchical Testing Order for Confirmatory Secondary Endpoint in Type 2 DM trials.....	37
Table 17: Hierarchical Testing Order for Confirmatory Secondary Endpoint Degludec/aspart.....	38
Table 18: Other Analyses Datasets Used	39
Table 19: Baseline Characteristics, Type 1 DM, Degludec Program	40
Table 20: Baseline Characteristics, Type 2 DM, Degludec, Once Daily, Trials...43	
Table 21: Types of Insulin Used at Baseline in Basal Bolus Type 2 DM Degludec OD trial.....	45
Table 22: Baseline Characteristics, Type 1 DM Trial (5401-3594), Degludec/aspart Program	46
Table 23: Baseline Characteristics, Type 2 DM, Degludec/aspart Program	48
Table 24: Subject Disposition, Pooled Type 1 DM trials, Degludec Program.....	51
Table 25: Categorization of Withdrawal Events Classified as “Others”, Pooled Type 1 DM trials, Degludec Program	51
Table 26: Withdrawals Due to Hypoglycemia Across All Categories of Withdrawal, Pooled Type 1 DM Trials, Degludec Program	52
Table 27: Withdrawals due to Withdrawal Criteria, Degludec, Type 1 DM.....	55
Table 28: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 1 DM.....	56
Table 29: Subject Disposition, Pooled Type 2 DM, Degludec Once Daily trials*	57
Table 30: Categorization of Withdrawal Events Classified as “Others”, Pooled Type 2 DM trials, Degludec Program	58

Table 31: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 2 DM Trials, Degludec Program	59
Table 32: Withdrawals Due To Withdrawal Criteria, Degludec, Type 2 DM	60
Table 33: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 2 DM	60
Table 34: Subject Disposition, Type 1 DM trial NN5401-3594, Degludec/aspart Program	61
Table 35: Disposition, Type 1 DM trial, Parent (3594) and Extension trial (3645)	62
Table 36: Withdrawals Events Classified as “Others”, Type 1 DM, Degludec/aspart Parent and Extension Trial (N5401-3594/3645).....	62
Table 37: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 1 DM Trials, Degludec/aspart Program	63
Table 38: Withdrawals Due to Withdrawal Criteria, Type 1 DM, Degludec/aspart Parent and Extension Trial (N5401-3594/3645).....	65
Table 39: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 1 DM, Degludec/aspart Program	65
Table 40: Subject Disposition, Pooled Type 2 DM Trials, Degludec/aspart Program	66
Table 41: Categorization of Withdrawal Events Classified as “Others”, Pooled Type 2 DM trials, Degludec/aspart Program	67
Table 42: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 2 DM Trials, Degludec/aspart Program	68
Table 43: Withdrawals Due To Withdrawal Criteria, Degludec/aspart, Type 2 DM	68
Table 44: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 2 DM	69
Table 45: Primary Efficacy Findings, Type 1 DM, Insulin Degludec Program	69
Table 46: Primary Efficacy Findings, Type 2 DM, Insulin Degludec Program	70
Table 47: Primary Efficacy Findings, Type 1 and 2 DM, Degludec/aspart Program	70
Table 48: Change in Body Weight (Kg), Type 1 DM, Degludec Program	71
Table 49: Change in Body Weight (Kg), Type 2 DM, Degludec Program	72
Table 50: Body Weight Changes, Type 1 and 2 DM, Degludec/Aspart.....	72
Table 51: Hypoglycemia, Type 1 DM, Degludec Program, Across Definitions...	79
Table 52: Hypoglycemia Reported as Serious Adverse Events, Type 1 DM, Degludec.....	82
Table 53: Novo Nordisk Nocturnal Hypoglycemia, Type 1 DM, Degludec Program, Across Definitions	83
Table 54: Hypoglycemia, Type 2 DM, Degludec Program, Across Definitions....	87
Table 55: Hypoglycemia Reported as Serious Adverse Events, Type 2 DM, Degludec.....	90
Table 56: Nocturnal Hypoglycemia, Type 2 DM, Degludec Program, Across Definitions	91
Table 57: Hypoglycemia, IDegAsp Program, Across Three Definitions	93

Table 58: Hypoglycemia Reported as a Serious Adverse Event, Type 1 DM, Trial NN5401-3594/3465.....	94
Table 59: Hypoglycemia Reported as Serious Adverse Events, Type 2 DM, Degludec/Aspart	95

1. INJECTABLE INSULIN PRODUCT DEVELOPMENT:

Sponsors developing novel injectable insulin products are required to carry out studies to establish the clinical safety and efficacy of the new product. The purpose of these studies is to demonstrate that the proposed method of use (e.g., injection schedule), the novel drug substance and/or specifics related to the formulation (e.g., strength) leads to effective diabetes management and that the treatment is not associated with undue hypoglycemia and/or immunogenicity risk. (See appended “**Guidance for Industry Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention**”)

The confirmatory studies should demonstrate actual reductions in glycemia (i.e., as opposed to simple maintenance of pretrial levels of control) from baseline to end of study for the indicated method of use in the population(s) in whom the drug is indicated. The test and comparator groups should be treated to similar glycemic goals in a non-inferiority trial design in order that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.

Confirmatory studies for insulin products are usually open label and active-controlled in design. Inability to adequately blind insulin preparations (due to differences in turbidity, due to proprietary drug delivery systems, or due to distinct methods of use), ethical issues (i.e., unacceptable number of daily injections) and issues of compliance (i.e., number of daily injections) have been invoked to explain the difficulty associated with designing, blinded, double-dummy insulin trials.

In December 2008, FDA issued a Guidance for Industry outlining a prescribed assessment of cardiovascular (CV) safety for all new anti-diabetic therapies developed for T2DM (refer to appended: “**Guidance for Industry Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes**”). The Guidance specified two thresholds of excess risk that needed to be excluded by applicants – a pre-marketing threshold of 80% and a post-marketing threshold of 30%. The Guidance was issued in recognition that patients with diabetes are at increased risk of developing cardiovascular disease and while no anti-diabetic therapy or glucose-lowering regimen has yet shown definitive evidence of CV risk reduction, the therapies themselves should not counterbalance the benefit of glycemic control with an unacceptable risk for CV harm. In contrast to non-insulin products for the treatment of type 2 diabetes, FDA has not required sponsors of injectable insulin products to plan their Phase 2/3 development program to exclude the aforementioned margins of excess CV risk. This has, in part, been due to the challenges of the trial designs for insulin products. Even though exclusion of a specific level of cardiovascular risk has not been required, sponsors are still asked to collect, in a prospective manner, reliable cardiovascular data where CV events are adjudicated by a blinded

endpoints committee in their Phase 2/3 program and include pre-specified cardiovascular analyses in their marketing application.

1.1. General Considerations Regarding Insulins as a Class of Anti-diabetic Agent

Insulin corrects all the metabolic disturbances associated with type 1 DM and is regarded as a lifesaving therapy for these patients. In subjects with type 2 DM, insulin is often the last effective form of therapy when patients are no longer controlled on maximum effective doses of non-insulin products or when presence of co-morbid conditions (e.g., renal impairment, heart failure) preclude the use of specific non-insulin product classes.

Table 1: List and Pharmacokinetic Profiles of Currently Available Insulins Indicated for the Treatment of Type 1 and 2 Diabetes. (Table Created by Author of Document)

Insulin preparations (100 U/mL) <i>Biosynthetic process</i>		Half-life (hrs)	Onset (hrs)	Peak (hrs)	Duration (hrs)	Compatible mixed** with
Rapid Acting	Drug Substance; rDNA Insulin Human*					
	Insulin regular (HumuLIN R®) <i>E.coli based</i>	—	0.5 to 1	3 to 4	8 to 12	NPH
	Insulin regular (NovoLIN R®) <i>S. cerevisiae based</i>	—	0.5 to 1	3 to 4	8 to 12	NPH
	Drug Substance; rDNA Insulin Analog Human					
	Insulin lispro (HumaLog®) <i>E.coli based</i>	1	0.25	0.5 to 1.5	2 to 5	NPH
	Insulin aspart (NovoLog®) <i>S. cerevisiae based</i>	1.5	0.25	1 to 3	3 to 5	^a
	Insulin glulisine (Apidra®) <i>E.coli based</i>	0.7	—	0.5 to 1.5	1 to 2.5	NPH
Intermediate Acting	Drug Substance; rDNA Insulin Human*					
	Insulin Isophane or Neutral Protamine Hagedorn (NPH) Humulin N® <i>E.coli based</i>	—	1 to 1.5	4 to 12	24	Regular
	Insulin Isophane or Neutral Protamine Hagedorn (NPH) Novolin N® <i>S.cerevisiae based</i>	—	1 to 1.5	4 to 12	24	Regular
Long Acting	Drug Substance; rDNA Insulin Analog Human					
	Insulin glargine (Lantus®) <i>E.coli based</i>	—	1.1	No pronounced peak	24	None
	Insulin detemir (Levemir®) <i>S.cerevisiae based</i>	—	0.8 to 2	No pronounced peak	up to 24	—

<p>*Over the counter schedule all others require a prescription **Marketed pre-mixed insulin preparations containing various proportions (denoted as a percentage) of insulin isophane and insulin regular: HumuLIN 70/30 ® NovoLIN 70/30® **Marketed pre-mixed insulin preparations containing various proportions (denoted as a percentage) of insulin analog isophane and insulin analog: HumaLOG mix 50/50 ®, HumaLOG mix 75/25 ®, NovLOG mix ® 70/30.</p>
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1.2. Benefits Associated with Glycemic Control Intensification Using Insulin in Type 1 and 2 DM

Insulin, used as a means to normalize glycemia, has been shown to reduce damage to the microvasculature caused by chronically elevated blood glucose levels in type 1 and 2 DM.

Intensive glucose control with insulin in subjects with T1DM was shown to delay the onset and slow the progression of retinopathy, nephropathy, and neuropathy in the Diabetes Control and Complications Trial (DCCT)(1).

A reduction in the onset and progression of retinopathy, nephropathy and neuropathy was also observed in T2DM subjects treated with intensive insulin therapy in a small Japanese study(2).

The United Kingdom Prospective Diabetes Study (UKPDS) study(3) demonstrated that intensive glucose control achieved using either sulfonylurea (N=1573), insulin (N=1156) or metformin (N=342 overweight) led to a significant reduction in the risk of microvascular disease complications compared to conventional glucose control in subjects newly diagnosed with T2DM. The effect was consistent across these three therapy subgroups.

1.3. Risks Associated with Glycemic Control Intensification using Insulin in Type 1 and 2 DM.

Insulin, used as a means to normalize glycemia, has been shown to increase the risk of hypoglycemia and to cause weight gain.

Hypoglycemia: The risk of hypoglycemia in the Diabetes Control and Complications Trial (DCCT) was three-fold higher in subjects randomized to intensive glucose control. In the UKPDS study, subjects randomized to intensive control with insulin were also more likely to experience a hypoglycemic event compared to subjects randomized to conventional therapy (i.e., 1.8-fold increase).

Weight Gain: In the DCCT subjects randomized to intensive insulin therapy gained significantly more weight than individuals randomized to conventional insulin treatment. A similar effect was observed in subjects randomized to insulin the UKPDS study.

1.4. Insulin and Cardiovascular Disease in Type 1 and 2 DM:

Insulin, used as a means to achieve tight glucose control, has not been associated with adverse clinical cardiovascular outcomes in large clinical trials¹.

In DCCT intensification of glycemic control with insulin for an average of 6.5 years was associated with a non-significant reduction in the incidence of 'major macrovascular' events (14 versus 3 events in the conventional versus intensive arm) and a beneficial effect on mean total serum cholesterol, calculated low-density lipoprotein cholesterol, and triglycerides(4). The cumulative incidence of hypertension between the intensive and conventional arm was similar.

The Epidemiology of Diabetes Interventions and Complications study (EDIC)(5) followed 93% of DCCT participants for 10 additional years after intervention had ceased to prospectively evaluate incident cardiovascular disease. In this study, cardiovascular disease was defined as: nonfatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina, or the need for coronary-artery revascularization. After a mean follow-up of 17 years, subjects who had been randomized to intensive treatment during the intervention phase were reported to have a 42% reduction (95 percent confidence interval, 9 to 63 percent; P=0.02) in the risk of any cardiovascular disease event and a 57% percent reduction (95 percent confidence interval, 12 to 79 percent; P=0.02) in the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease.

The Diabetes Mellitus Insulin Glucose Infusion in Acute Myocardial Infarction study (DIGAMI)(6) suggested that intensification of diabetes management initiated within the first 24-hours post-myocardial infarction through the use of insulin (intravenous followed by subcutaneous delivery) reduced mortality compared to standard treatment in patients with T2DM. A second, similarly designed, study (DIGAMI-2)(7) did not confirm a mortality advantage associated with intensification of insulin therapy immediately post myocardial infarction in patients with type 2 diabetes.

The impact of an intervention aimed at normalizing fasting plasma glucose, by using a basal insulin analogue, on cardiovascular outcomes in subjects with established Type-2 DM or patients with glucose abnormalities at high risk for cardiovascular events was studied in the recently published ORIGIN study(8). In this study, 12,537 individuals were randomized to receive insulin glargine at a dose individualized to target a fasting plasma glucose of ≤ 95 mg/dL or to standard of care therapy where treatment was based on investigator judgment and local guidelines. The investigators report that after a median of 6.5 years, glucose control achieved through the use of glargine was not associated with a favorable or harmful effect on cardiovascular outcomes (hazard ratio for the

¹ Note: Insulin type and preparation differed between trials: DCCT: Bovine, porcine and human rapid and basal insulin. DIGAMI: human rapid and basal insulin. ORIGIN: Analog basal insulin.

composite of: cardiovascular death, non-fatal myocardial infarction and non-fatal strokes, 1.02; 95% confidence interval [CI], 0.94 to 1.11; P = 0.63) . The intervention was associated with significant increases in weight and risk of hypoglycemia compared to standard of care therapy.

1.5. Hypoglycemia and Cardiovascular Disease Risk in T2DM

An association between severe hypoglycemia and cardiovascular morbidity and overall mortality has been suggested in large clinical trials of patients with T2DM.

The ACCORD(9) (Action to Control Cardiovascular Risk in Diabetes), VADT(10) (Veterans Affairs Diabetes Trial) and ADVANCE(11) (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) trials evaluated the impact of intensive glucose control (HbA1c target < 7%) compared to standard glucose control on cardiovascular outcomes in patients with T2DM at risk of cardiovascular events.

In the three trials, more intensive glycemic control was not associated with a beneficial effect on CV events or mortality. In the ACCORD study, subjects randomized to intensive control were more likely to die from all (5.0 vs. 4.0%; HR 1.22; 95% CI 1.01–1.46; P = 0.04) and CV-related (2.6 vs. 1.8%; HR 1.35; 95% CI 1.04–1.76; P = 0.02) causes.

In these three trials, the risk of severe hypoglycemia was significantly higher in the intensive compared with the standard arms. Post-hoc analyses from these three² studies suggest that hypoglycemia was a predictor of adverse clinical outcomes including deaths, CV-deaths and/or other cardiovascular outcomes (11;12). Even though subjects who suffered a fatal outcome in ACCORD were more likely to have had experienced a severe hypoglycemic event, severe hypoglycemia per se did not explain the excess mortality observed in intensively treated patients.

² Post-hoc hypoglycemia analyses of VADT data were presented by Dr. William Duckworth at the American Diabetes Association 69th Scientific Sessions in 2009.

2. DRUG PRODUCTS

2.1. INSULIN DEGLUDEC

The insulin degludec drug product is a solution for subcutaneous injection. The drug is intended to cover basal insulin requirements in patients with T1DM and T2DM.

The drug substance in insulin degludec is an analogue of human insulin produced using yeast recombinant DNA technology and chemical modification. Insulin degludec differs from human insulin by omission of a threonine residue at the amino terminal B-chain (B30) and by attachment of a 16 carbon fatty acid to the epsilon-amino group of the lysine residue at position 29 of the B-chain through a gamma-glutamic acid spacer. The structural formula for insulin degludec is shown in Figure 1.

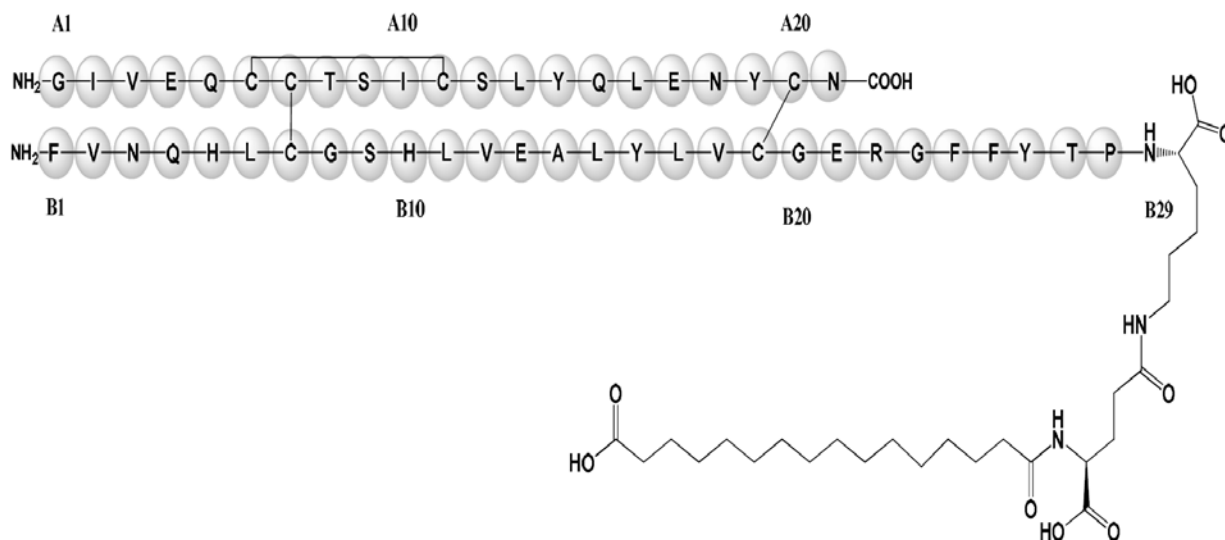


Figure 1: Degludec Insulin, Structural Formula. Source NDA 203314. Module 2.3.I.

Two formulation strengths are proposed in the degludec application: one containing 100 units of analogue insulin per milliliter (600 nmol/mL) and a twice concentrated formulation containing 200 units of analogue insulin per milliliter (1200 nmol/mL). The product formulation was optimized using standard excipients to delay systemic absorption of the drug substance from the subcutaneous depot in order to prolong the time action profile of the insulin. The fatty acid moiety of degludec insulin binds to albumin and further contributes to the protracted time action profile.

2.2. INSULIN DEGLUDEC/ASPART

The insulin degludec/aspart fixed ratio drug product is a solution for subcutaneous injection. The drug is intended to cover basal insulin requirements

and prandial insulin requirements for one meal of the day in patients with T1DM and T2DM.

The drug substances in insulin degludec/aspart are two insulin analogues: degludec insulin and the approved analogue, aspart insulin. The drug product formulation strength is 100 units per milliliter (600 nmol/mL) and contains 70% degludec weight (i.e., 420 nmol of degludec insulin in 1 mL) and 30% aspart weight by volume (i.e., 180 nmol of aspart insulin in 1 mL).

3. DEGLUDEC INSULIN IN-VITRO PHARMACOLOGY SUMMARY

The degludec drug product was optimized to delay systemic absorption of the drug substance from the subcutaneous depot in order to prolong the time action profile of the insulin. Once absorbed, the pharmacological effect of degludec results from binding to insulin receptors expressed on the surface of specific cells.

Insulin degludec was found to be selective for the insulin receptor (IR) and the structurally similar insulin like growth factor receptor (IGF-1R) in assays of standard receptors and transporters.

Insulin degludec was shown to bind the two insulin receptor isoforms (IR-A and IR-B) with similar affinity. Degludec insulin binds human insulin receptors with less affinity than regular human insulin (relative affinity of degludec was 13 and 15% that of regular insulin for IR-A and IR-B isoforms respectively). Presence of albumin in experimental conditions lowered the binding affinity of degludec for the human insulin receptor further (comparative affinity to regular insulin: 4.3% for the IR-A and 3.2% for the IR-B isoforms). This finding is not unexpected as degludec insulin binds to proteins (i.e., a property of its fatty acid moiety) and in the presence of protein, less free degludec insulin is available to bind receptors.

The binding affinity of degludec for the human insulin-like growth factor 1 receptor (IGF-1R) was ~ 2% and 0.4% that of human insulin in the absence and presence of albumin respectively.

In functional studies, degludec insulin was observed to be less potent than human insulin. This observation was consistent with the observed lower binding affinity of degludec insulin for the insulin receptor. The maximal functional response elicited by degludec insulin and regular human insulin were, however, similar suggesting degludec insulin acts as a full agonist at the insulin receptor.

In vivo, insulin degludec is expected to have similar efficacy to human insulin despite observed differences in *in-vitro* potency. Steady-state insulin concentrations *in vivo* depend on insulin clearance which is determined primarily by insulin receptor binding/internalization. Analogue insulins with lower binding affinity, such as degludec, are expected to reach higher insulin concentration at

steady-state compared to human insulin concentration *in vivo* thereby minimizing efficacy/potency differences observed *in-vitro*.

Levels of total (i.e., bound and unbound) circulating insulin degludec are high after single or repeat injections *in-vivo* (i.e., >10X the levels of non-acylated insulins). This is in part due to the receptor binding affinity and insulin clearance issues discussed above but more likely related to the fact that the fatty acid moiety of insulin degludec allows it to bind strongly to circulating albumin.

Common protein-bound drugs like ibuprofen, warfarin, acetylsalicylate, salicylate and frequently used antidiabetic agents glimepiride, metformin, sitagliptin and liraglutide as well as palmitate, oleate and linoleate did not affect insulin degludec binding to human serum albumin at therapeutically/physiologically relevant drug concentrations.

The potential of insulin degludec to competitively displace albumin-bound drugs is considered to be very low, as the concentration of insulin degludec is significantly lower in human plasma (<10 nmol/L) compared to the albumin concentration (0.6 mmol/L ~ 600 000 nmol/L); and insulin degludec will occupy less than 0.01% of the circulating albumin molecules. Based on these findings, protein binding interaction is considered unlikely.

No or only minor effect on individual cytochrome P-450 (CYP) expression (less than 2-fold induction) was observed following insulin degludec treatment in rats. All effects of insulin degludec were similar to those elicited by human insulin.

Degludec was not found to influence ECG parameters or hemodynamic parameters in anesthetized, mechanically ventilated, glucose clamped, male beagle dogs after single intravenous doses up to 12 nmol/kg. No effect of degludec on the action potential recorded from Rabbit Purkinje fibers was observed following incubation with 1000 nmol/L of insulin degludec. Insulin degludec was not found to bind hERG channels.

No significant effects on blood pressure, ECG or heart rate were noted in conscious female beagle dogs dosed with single subcutaneous doses up to 24 nmol/kg or with repeated daily dosing up to 26 weeks at > 8 nmol/kg/day.

4. CLINICAL PHARMACOLOGY SUMMARY

Steady state serum concentrations of degludec insulin are reached after 2–3 days of once daily subcutaneous dosing.

Total exposure, at steady state after subcutaneous administration, is dose proportional within the therapeutic dose range in subjects with T1DM and T2DM.

Degludec insulin was detectable in serum for at least 120 hours (5 days) after the last steady state subcutaneous dose of degludec was administered. The $\frac{1}{2}$ life in this setting was approximately 25 hours.

The duration of action of degludec insulin was demonstrated to last beyond 42 hours. Because of this prolonged half-life, the applicant also investigated flexible dosing regimens of degludec in its clinical development program.

Advance age (i.e., ≥ 65 years of age), sex (i.e., male, female), race and ethnicity did not impact total exposure at steady state.

Renal function and hepatic function did not impact the pharmacokinetic properties after a single dose.

The steady state pharmacokinetic profile of degludec insulin was not affected by co-formulation with aspart insulin.

Some differences in the pharmacokinetic profile of aspart insulin when co-formulated with degludec insulin were observed. However these did not translate into statistically and/or clinically significant effects on the pharmacodynamic properties of the aspart insulin.

5. CLINICAL DATA

5.1. CLINICAL DATA DEGLUDEC NDA

At the time of NDA 203314 filing, 41 studies evaluating the insulin degludec (i.e., IDeg) drug product were completed and submitted to FDA. Efficacy and safety evaluation for these completed studies have a cutoff date of January 31st 2011. The 41 studies can be subdivided into the following trial types;

- 25 clinical pharmacology trials
- 3 therapeutic exploratory trials
- 11 therapeutic confirmatory trials
- 2 trials that do not fit in the above categories

At the time of NDA filing, 6 insulin degludec studies were ongoing. Five of these studies were extension of completed therapeutic confirmatory trials (TCT) and one study was a 26-week trial comparing the efficacy and safety of two IDeg titration algorithms (**NN1250-3846**). In the original submission, efficacy and safety evaluation for these ongoing studies had a cutoff date of March 31st 2011.

At the 120-day safety update (i.e., January 27th 2012), three of the five TCT extension studies were completed (i.e., extensions of parent trials 3585, 3770, 3582). Four studies were newly initiated and three studies were still ongoing studies. The 120 day safety update has a data cutoff date of October 6th 2011.

5.2. CLINICAL DATA DEGLUDEC/ASPART NDA

At the time of NDA 203313 filing, 21 studies evaluating the insulin degludec/aspart fixed ratio combination drug product were completed and submitted to FDA. Efficacy and safety evaluation for these completed studies have a cutoff date of January 31st 2011. The 21 studies can be subdivided into the following trial types;

- 13 clinical pharmacology trials
- 3 Therapeutic exploratory trials
- 5 Therapeutic confirmatory trials

At the time of NDA filing, 2 degludec/aspart studies were ongoing. Efficacy and safety evaluation for these ongoing studies had a cutoff date of March 31st 2011. Study **3726** is an extension of a completed therapeutic confirmatory study (i.e., 3590). Trial **3896** was a therapeutic confirmatory trial conducted in Japan (not included in efficacy analyses).

At the time of the 120-day safety update (i.e., January 27th 2012) the two studies that had been ongoing were completed. The 120-day safety update has a data cutoff date of October 6th 2011. There is one ongoing bioequivalence trial comparing degludec/aspart 100 units/mL to degludec/aspart 200 units/mL and data up until November 11th 2011 for this study is included in the updated safety database.

5.3. TRIALS AND DATA CUTOFF DATES FOR FDA ANALYSES

Note: The prefix 'NN1250' denotes trials in the degludec program. The prefix 'NN5401' denotes trials in the degludec/aspart program.

Efficacy analyses for degludec (Dr. Cynthia Liu) were performed on completed therapeutic confirmatory trials **NN1250-3583, NN1250-3585, NN1250-3770, NN1250-3582, NN1250-3579, NN1250-3672, NN1250-3586, NN1250-3580 and NN1250-3668** with a data cutoff date of January 21, 2011.

Efficacy analyses for degludec/aspart (Dr. Dongmei Liu) were performed on completed therapeutic confirmatory trials **NN5401-3594, NN5401-3590, NN5401-3593, NN5401-3592, and NN5401-3597** with a data cutoff date of January 21, 2011.

The clinical safety review for degludec (Dr. Karim Calis) was based on the 41 clinical studies completed as of January 31, 2011. The focus of the safety review was based on the 11 therapeutic confirmatory trials because these were randomized, controlled, were of long duration and evaluated the to-be commercialized formulation.

The clinical safety review for degludec/aspart (Dr. Karim Calis) was based on the 21 clinical studies completed as of January 31, 2011. The focus of the safety review was based on the 5 therapeutic confirmatory trials because these were randomized, controlled, were of long duration and evaluated the to-be commercialized formulation.

Statistical safety analyses of hypoglycemia (Dr. Eugenio Andraca-Carrera) were based on a meta-analysis of the following seven completed degludec therapeutic confirmatory trials: **NN1250-3583, NN1250-3770, NN1250-3582, NN1250-3579, NN1250-3672, NN1250-3586, NN1250-3668** (i.e., all glargine comparator trials in degludec program). Data cutoff January 31, 2011.

Statistical analyses related to cardiovascular safety (Dr. Bo Li) were based on a meta-analysis of all Phase 3 trials that were complete on the cutoff date of May 1st 2012 and contained a non degludec comparator arm. The meta-analysis encompassed the parent trials and controlled extensions of parent trials highlighted in the table below as well as one additional trial (**NN5401-3896**) initiated after NDA filing and not shown in the table.

Table 2: Trials Included in FDA CV-metanalysis.

Parent Trial	Controlled Extensions of Parent Trials
Degludec Type 1 DM	
NN1250-3583*	NN1250-3644 (ext 3583)
NN1250-3585*	NN1250-3725 (ext 3585)
NN1250-3770*	NN1250-3770 extension
Degludec Type 2 DM	
NN1250-3582*	NN1250-3667 (ext 3582)
NN1250-3579*	NN1250-3643 (ext 3579)
NN1250-3672*	
NN1250-3586*	
NN1250-3580*	
NN1250-3668*	
NN1250-3718*	
NN1250-3724*	
Degludec/aspart Type 1 DM	
NN5401-3594*	NN5401-3645 (ext 3594)*
Degludec/aspart Type 2 DM	
NN5401-3590*	NN5401-3726 (ext 3590)
NN5401-3593*	
NN5401-3592*	
NN5401-3597*	
*Included in original CV-meta-analysis with data cutoff date of January 31, 2011. CV data for trials not designated by the asterisk were not included in the original NDA and were obtained between January 31 st 2011 and May 2 nd 2012.	

Two additional trials that were complete (i.e., **NN1250-3846** and **NN1250-3923**) did not have a non degludec comparator and were not included in the CV-meta-analysis. **Trial NN5401-3896** was initiated after filing NDA 203313. This trial compares degludec/aspart to glargine in a population of insulin naïve patients with T2DM. Efficacy data for this trial were not reviewed or submitted in the original NDA.

5.4. THERAPEUTIC CONFIRMATORY TRIALS INSULIN DEGLUDEC NDA

Reviewer Note: This section focuses on key design aspects of therapeutic confirmatory trials in NDA 203314. The trial prefix, NN1250, used in the degludec program, is omitted in this section for the sake of simplicity.

Eleven therapeutic confirmatory, 26—52 weeks, phase III trials evaluated the efficacy and safety of different degludec dose strengths and administration schedules in Type 1 (i.e., Trials; 3583, 3585 and 3770) and T2DM (Trials; 3582, 3579, 3672, 3586, 3580, 3668, 3718, 3724). Table 3 summarizes key attributes of trials performed in patients with T1DM.

Table 4 summarizes key attributes of clinical trials performed in patients with T2DM. The presentation is arranged according to clinical use scenarios.

Table 3: Overview of Therapeutic Confirmatory Trials for Degludec Once Daily in Type 1 Diabetes

Trial	Duration (weeks)	Intervention	Prandial Insulin	Population	Primary Hypothesis Tested	Randomization and Number of Subjects Randomized	Anti-diabetic at Screening	Randomization Strata
Basal Insulin Once Daily and Prandial Insulin with Meals								
3583* Ext. 3644	52	IDeg 100 OD vs. IGLar OD	IAsp	Insulin treated	Non-inferiority [§]	3:1 IDeg: 472 IGlar: 157	Basal-bolus insulin regimen	None
3585* Ext. 3725	26	IDeg 100 OD vs. IDet OD [†]	IAsp	Insulin treated	Non-inferiority [§]	2:1 IDeg: 303 IDet: 153	Basal-bolus insulin regimen	Region: 1. Europe 2. Japan 3. India 4. South Asia
Basal Insulin, Once Daily, “Flexible” Dosing Interval and Prandial Insulin with Meals								
3770* Ext. 3770	26	IDeg 100 FF vs. IGLar OD [°] and IDeg 100 FF vs. IDeg 100 OD	IAsp	Insulin treated	Non-inferiority [§]	1:1:1 IDeg FF: 164 IGlar: 164 IDeg: 165	Basal-bolus insulin regimen	None

Adapted from NDA203314; Tables 1-1 Summary of Clinical Efficacy;

*These trials were followed by pre-planned controlled safety extensions lasting 52 weeks (i.e., Trial #3644 extension of 3583) or 26 weeks (3725 extension of 3585 and Ext. 3770) which were ongoing at the time of filing. The data cutoff date for the efficacy findings in original NDA submission is January 31st 2011. Blinded safety data from these extension trials is included in the integrated summary of safety with a data cutoff date of March 31 2011. CV safety data from all trials including completed extension of parent trials are included in CV safety analysis data cutoff date of May 2nd 2012.

[°]Primary comparison

Basal-bolus insulin regimen: Basal insulin (OD or BID) + any bolus insulin (≥3 daily injections)

[§] The difference in HbA1c change from baseline between IDeg and comparator does not exceed 0.4%

[†]OD at start, with the option to intensify to BID IDet dosing after 8 weeks if glycemic control inadequate

OD = Once Daily; FF; fixed flexible rotating dosing interval once daily; IDeg = Insulin degludec; IDet = Insulin detemir; IGLar = Insulin glargine; IAsp = Insulin aspart.

Table 4: Overview of Therapeutic Confirmatory Trials for Degludec Once Daily or Thrice Weekly in T2DM

Trial	Duration (Weeks)	Intervention	Treatment Combination	Population	Primary Hypothesis Tested	Randomization and Number of Subjects Randomized	Anti-diabetic at Screening	Randomization Strata
Basal Insulin Once Daily and Prandial Insulin with Meals added to OADs								
3582* Ext. 3667	52	IDeg 100 OD vs. IGlax OD	+IAsp ±met ±pio	Insulin treated	Non-inferiority [§]	3:1 IDeg: 755 IGlar: 251	Any insulin regimen (with or without OADs): premix, self-mix, basal insulin only, basal-bolus (≥1 bolus), bolus only, CSII	Prior treatment: 1. basal-bolus 2. basal insulin only 3. other
Basal Insulin, Once Daily, Added to Combination OADs								
3579* Ext. 3643	52	IDeg 100 OD vs. IGlax OD	+met ±DPP-4i	Insulin-naïve	Non-inferiority [§]	3:1 IDeg: 773 IGlar: 257	metformin (mandatory) ±SU/glin, ±α-GI, ±DPP4i in any combination	Prior treatment: 1. No DPP4i at baseline 2. DPP4i at baseline
3672	26	IDeg 200 OD vs. IGlax OD	+met ±DPP-4i	Insulin-naïve	Non-inferiority [§]	1:1 IDeg: 230 IGlar: 230	metformin (mandatory) ±SU/glin, ±DPP-4i, ±α-GI (in any combination)	None
3586	26	IDeg 100 OD vs. IGlax OD	±met ±SU/glin ±α-GI	Insulin-naïve	Non-inferiority [§]	2:1 IDeg: 289 IGlar: 146	monotherapy or combination of SU/glin and met ±α-GI or DPP4i	Region 1. Japan 2. Rest of Asia
Basal Insulin, Once Daily, “Flexible” Dosing Interval, Added to Combination OADs;								
3580	26	IDeg 100 OD vs. Sita 100 mg OD	+1-2 OADs: met, SU/glin, pio	Insulin-naïve	Superiority	1:1 IDeg: 229 Sita: 229	±met, ±SU/glin, ±pio, 1–2 OADs in any combination	Prior treatment: 1. TZD Yes 2. TZD No
3668	26	IDeg 100 FF vs. IGlax OD^o and IDeg 100 FF vs. IDeg 100 OD	±met ±SU/glin ±pio	Insulin-naïve or Insulin treated	Non-inferiority [§]	1:1:1 IDeg FF: 229 IGlar: 230 IDeg: 228	OAD(s) only or basal insulin only or basal insulin + OAD(s) OADs could be any combination of met, SU/glin, pio	Prior treatment: 1. OADs only 2. basal insulin only 3. basal insulin + OADs
Basal Insulin, Three Times Weekly, Added to Combination OADs;								
3718	26	IDeg 200 3TW vs. IGlax OD	+met ±DPP-4i	Insulin-naïve	Non-inferiority [§]	1:1 IDeg : 233 IGlar: 234	metformin (mandatory) ±SU/glin, ±DPP-4i, ±α-GI (in any combination)	None
3724	26	IDeg 200 3TW vs. IGlax OD	+met ±DPP-4i	Insulin-naïve	Non-inferiority [§]	1:1 IDeg : 230 IGlar: 230	metformin (mandatory) ±SU/glin, ±DPP-4i, ±α-GI (in any combination)	None

Adapted from NDA203314; Tables 1-2 Summary of Clinical Efficacy;

*These trials were followed by additional controlled safety extensions for 52 weeks (i.e., Trial# **3643** ext. of 3579) or 26 weeks (**3667** ext. of 3582) which were ongoing at the time of filing. Data cutoff date for efficacy findings in original NDA submission is January 31st 2011. Blinded safety data for extension trials is included in the integrated summary of safety with a data cutoff date of March 31 2011. CV safety data from all trials including completed extension of parent trials are included in CV safety analysis data cutoff date of May 2nd 2012.

°Primary comparison

§ The difference in HbA1c change from baseline between Degludec/aspart and comparator does not exceed 0.4%

†OD at start, with the option to intensify to BID IDet dosing after 8 weeks if glycemic control inadequate

OD = Once Daily; IDeg 100 = Insulin degludec (100 U/mL); IDeg 200 = Insulin degludec (200 U/mL); IDet = Insulin detemir; IGlar = Insulin glargine. Oral Antidiabetic Drugs (OADs); Sita=Sitagliptin; met=metformin; pio=pioglitazone; DPP-4i=dipeptidyl peptidase-4 inhibitor; SU=sulphonylurea; α-GI=alpha-glucosidase inhibitor; TZD=thiazolidinedione; glin=glinide drug class; CSII: continuous subcutaneous insulin infusion

5.5. THERAPEUTIC CONFIRMATORY TRIALS INSULIN DEGLUDEC/ASPART NDA

Note: The prefix, NN5401, is used to distinguish trials in the degludec/aspart program from those in the degludec program.

Table 5 provides an overview of the five therapeutic confirmatory degludec/aspart arranged by clinical use scenario. One trial was carried out in patients with T1DM and four trials in patients with T2DM.

Table 5: Overview of Therapeutic Confirmatory Trials for Degludec/aspart

Trial	Duration (weeks)	Intervention	OAD Combination	Population	Primary Hypothesis Tested	Randomization and Number of Subjects Randomized	Anti-diabetic at Screening	Randomization Strata
T1DM								
Premix or Basal Insulin Once Daily, Prandial Insulin with Meals								
NN5401 3594*	26°	Degludec/aspart OD + IAsp vs. IDet† OD + IAsp	None	Insulin treated	Non-inferiority§	2:1 Degludec/aspart:366 IDet:182	Basal-bolus insulin regimen or other mixed insulin regimen	Prior treatment; 1. Basal-bolus insulin regimen 2. Other insulin regimen
T2DM								
Premix or Basal Insulin Once Daily, Added to OADs, Insulin Naïve and Insulin Treated								
NN5401 3590°	26°	Degludec/aspart OD vs. IGlar OD	metformin	Insulin naïve	Non-inferiority§	1:1 Degludec/aspart: 266 IGlar: 263	Metformin and ≥1 other OAD except TZD	None
NN5401 3593	26	Degludec/aspart OD vs. IGlar OD	metformin ± pioglitazone ± DPP-4 inhibitor	Insulin treated	Non-inferiority§	1:1 Degludec/aspart : 230 IGlar: 233	Basal insulin OD and metformin ± other OADs	Prior treatment: 1. TZD Yes 2. TZD No
Premix Insulin Twice Daily, Added to Combination of OADs, Insulin Treated								
NN5401 3592	26	Degludec/aspart BID vs. BIAsp 30 BID	± metformin ± pioglitazone ± DPP-4 inhibitor	Insulin treated	Non-inferiority§	1:1 Degludec/aspart: 224 BIAsp 30: 222	Premixed/self-mixed insulin OD or BID ± OADs	Prior treatment: 1. OD insulin regimen 2. BID insulin regimen
NN5401 3597	26	Degludec/aspart BID vs.	± metformin	Insulin treated	Non-inferiority§	2:1 Degludec/aspart:	Basal insulin OD or BID ±	Prior treatment: 1. basal without

		BIAsp 30 BID				280 BIAsp 30: 142	metformin or premixed/self- mixed insulin OD or BID ± metformin	2. metformin basal with metformin 3. premix without metformin 4. premix with metformin
<p>Adapted from NDA203313; Table 1-1 Summary of Clinical Efficacy</p> <p>*Trial Extended by an additional 26 weeks (Extension Trial #3645) completed and submitted with original NDA</p> <p>∞Trial Extended by an additional 26 weeks (Extension Trial #3726) ongoing and not submitted in original NDA</p> <p>§ The difference in change from baseline in HbA1c between Degludec/aspart and comparator does not exceed 0.4%</p> <p>†OD at start, with the option to intensify to BID IDet dosing after 8 weeks if glycemic control inadequate</p> <p>BIAsp: biphasic insulin aspart; BID: twice daily; DPP-4: di-peptidyl peptidase-4; IAsp: insulin aspart; IDet: insulin detemir; IGlar: insulin glargine; OAD: oral antidiabetic drug; OD: once daily; TZD: thiazolidinedione.</p> <p>NN5401-3597 Japan, Korea, Hong Kong, Malaysia and Taiwan (no US sites)</p>								

5.5.1. Primary Objective

The primary stated objective in all of the therapeutic confirmatory trials (TCT) was to confirm the efficacy of degludec or degludec/aspart with respect to glucose control. Glucose control was assessed by measuring the difference in HbA1c between baseline and trial end.

In all except **3580**, efficacy was established by comparing glucose control in degludec or degludec/aspart treated subjects to that observed in active comparator treated subjects and demonstrating that glucose control in the degludec arm was not unacceptably worst than that of the comparator arm (i.e., non-inferiority studies based on a non-inferiority margin for the between group difference in the change from baseline in HbA1c of 0.4%). Study 3580 was designed to demonstrate superiority of once-daily degludec over the DPP4-inhibitor, sitagliptin.

5.5.2. Secondary Objectives:

Secondary objectives were selected to provide support to the primary glycemic efficacy findings or to distinguish, based on efficacy or safety parameters, the new insulins from comparator products. Secondary endpoints of relevance to the overall benefit risk assessment and their analyses will be discussed in the description of efficacy findings. Specifically we will present findings related to endpoints related to hypoglycemia, body weight, and immunogenicity.

5.5.3. Design

All therapeutic confirmatory trials (TCT) were randomized, **open-label**, parallel-group, active comparator, multicenter, multinational trials.

In most TCT two intervention groups were used (refer to Table 6 and

Table 7). For studies **3770 and 3668** three intervention groups were used (i.e., 1 comparator arm and 2 degludec arms; fixed and flexible dosing schedule).

With exception for Study 3580 which was designed as a superiority trial, all trials followed a treat-to-target principle whereby all treatment groups targeted a pre-defined fasting plasma glucose of < 90 mg/dL. In trials evaluating the twice daily degludec/aspart administration schedule, all treatment groups targeted a fasting pre-breakfast and pre-dinner blood glucose target of < 90 mg/dL.

The treatment period was 26 weeks in duration in 14 studies and 52 weeks in duration in three studies (**3583, 3759, and 3582**). A follow-up visit was to be scheduled at least one week after completion of the treatment period in all trials.

In trials where presence of insulin auto-antibodies was ascertained, subjects were switched to twice daily injection of neutral protamine Hagedorn (NPH) insulin between the end of treatment and the follow-up visit.

Controlled safety extensions of 26 to 52 weeks in duration were planned for 5 of the TCT.

5.5.4. Randomization

Randomization to intervention was balanced in the following nine Phase III trials across the degludec and degludec/aspart programs (i.e., **3770, 3580, 3668, 3672, 3718, 3724, NN5401-3590, NN5401-3593, NN5401-3592**).

In seven trials more subjects were randomized to degludec or to degludec/aspart than to comparator [i.e., **3583** (3:1), **3585** (2:1), **3759** (3:1), **3582** (3:1), **3586** (2:1), **NN5401-3594** (2:1) and **NN5401-3597** (2:1)].

In some trials randomization was stratified according to prior diabetes treatment (i.e., **3579, 3580, 3668, 3582, NN5401-3593, NN5401-3592 NN5401-3594 NN5401-3597**) or geographical regions (i.e., **3585, and 3586**).

5.5.5. Blinding

All trials were open-label. Novo Nordisk personnel involved in trial conduct and insulin titration were blinded to drug assignment. Site monitors, investigators and participants were not blinded.

5.5.6. Representative Trial Time Line

Trials consisted of a screening visit [Week (-)1], a randomization visit (Week 0), follow-up visits at the investigator sites [Weeks 1, 2, 4, 6, 8, 10, 12, 16, 20, 24, 26 (for 26-week trials), 32, 36, 40, 44, 48, 52 for 52-week trials], telephone visits [Weeks 2, 3, 5, 7, 9, 11, 13, 14, 15, 17, 18, 19, 21, 22, 23, 25 (for 26-week trials),

28, 30, 34, 38, 42, 46, 50 (for 52-weeks trial)] and a termination visit scheduled seven days after the actual date of the last treatment visit (i.e., Week 26 or 52).

At weekly (up to Week 26) and biweekly (after Week 26) site and telephone follow-up visits; withdrawal criteria, concomitant medication, 1 point self-measured blood glucose, adverse events, hypoglycemic episode, dose of trial insulin(s) (mean of 3 days before visit), dose of oral anti-diabetic medications (OAD) (i.e., in type 2 DM trials) were reviewed and the new adjusted dose of trial insulin(s) was (were) recorded.

Key efficacy parameters including HbA1c (central laboratory), fasting plasma glucose (central laboratory), 9-point self-measured blood glucose profile were obtained on weeks 0, 12, 16, 26, (note; two additional assessments at weeks 40 and 52 were carried out in 52 weeks trial).

5.5.7. Controlled Interventions: Degludec Program

Degludec

5.5.7.1. Degludec

Formulations Studied: In most degludec trials subjects were randomized to the U100 (i.e., 600 nmol/L) degludec formulation (see Table 6 and

Table 7).

The degludec U200 (i.e., 1200 nmol/mL) formulation was studied only in type 2 diabetes subjects. One trial evaluated once-daily, basal-only use of U200 and two trials evaluated thrice-weekly, basal-only use of U200 (refer to Table 4).

Dosing Interval Studied: Degludec was administered at fixed, 24-hour, dosing intervals in all studies (i.e., daily injection was injected at the same time each day) except 3770, 3668 and 3580.

In the three above-mentioned trials, degludec was administered using variable dosing intervals (i.e., 8-40 hours) between doses. This administration schedule is referred to as 'flexible' dosing. In trials 3770 and 3668 the impact of extreme (i.e., short and long), alternating, dosing intervals on efficacy and safety of degludec in type 1 and 2 DM were studied. Subjects were instructed to inject degludec in the morning on Monday, Wednesday, Friday and in the evening on Tuesday, Thursday Saturday and Sunday. In these trials, a 40-hour dosing interval (i.e., on days when a morning dose was followed by an evening dose) alternated with an 8-hour dosing interval (i.e., on days when an evening dose was followed by a morning dose). In trial 3580, subjects could vary the daily time of injection provided the time between the last injected dose and the dose to be administered was ≥ 8 but ≤ 40 hours.

Route and Site of Administration Studied: In all trials degludec was administered subcutaneously in either the deltoid, thigh or abdominal region. The choice of injection site was based on subject preference.

5.5.7.2. Comparators

Insulin glargine administered subcutaneously once daily by injection using the marketed pen device served as the comparator in all but two therapeutic confirmatory trials in the degludec program (i.e., **3585**, **3580**). In all but 4 of these trials (**3668**, **3770**, **3718** and **3724**) glargine administration was similar to degludec with regards to frequency, dosing intervals and site of injections. Insulin glargine differed from degludec with regards to the time of day the drug was administered. Glargine could be administered at anytime of the day but at the same time each day (e.g., a patient injecting glargine in the morning was to inject glargine in the morning for the entire study). The timing of degludec injection, in contrast, was restricted to specific time windows in all but trial **3580**. In trials **3585**; insulin detemir was used as the comparator. In trial **3580**; the oral DPP-IV inhibitor sitagliptin was used as the comparator.

Table 6 and

Table 7 highlight similarities and differences between intervention arms across therapeutic confirmatory trials in the degludec program.

Table 6: Intervention Arm, Type 1 DM, Degludec Trials

Trial	Degludec Arm	Comparator Arm
Basal Insulin Once Daily and Prandial^{ff} Insulin with Meals		
3583	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStarTM Subcutaneous Site: abdomen or deltoid or thigh
3585	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: between start of evening meal and bedtime Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin detemir <ul style="list-style-type: none"> Time of day: between start of evening meal and bedtime Frequency^o: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh
3770	Insulin degludec U100 Fixed Once Daily <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh Insulin degludec U100 “Worst-Case” Flexible <ul style="list-style-type: none"> Time of day: <ul style="list-style-type: none"> Morning on Mon., Wed., Fri.; Evening on Tues., Thurs., Sat., Sun. Frequency: once daily Dosing Interval: <ul style="list-style-type: none"> 8 hours; Evening to Morning sequence (e.g., Tues. dose to Wed. dose) 40 hours; Morning to evening sequence (e.g., Mon. dose to Tues. dose) Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStarTM Subcutaneous Site: abdomen or deltoid or thigh
Source: Adapted from NDA 203314; Table 1-12 Summary of Clinical Efficacy *Glargine was used in accordance with the US label ^o After 8 weeks of treatment, the frequency of detemir injections could be increased to twice daily at the investigator's discretion if adequate glucose control was not achieved ^{ff} Insulin aspart was used as the short acting insulin		

Table 7: Intervention Arm, Type 2 DM, Degludec Trials

Trial	Degludec Arm	Comparator Arm
Basal Insulin Once Daily and Prandial^{ff} Insulin with Meals added to OADs		
3582	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh
Basal Insulin, Once Daily, Added to Combination of OADs		
3579	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: PDS290 Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh
3672	Insulin degludec U200 <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: PDS290 Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh
3586	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: between start of evening meal and bedtime Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh
3580	Insulin degludec U100 <ul style="list-style-type: none"> Time of day: per patient preference (i.e., any time) Frequency: once daily Dosing Interval: whenever; as long as ≥ 8 hours and ≤40 hours between injections Device: PDS290 Subcutaneous site: abdomen or deltoid or thigh 	Sitagliptin 100 mg* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: N/A Subcutaneous Site: N/A
3668	Insulin degludec U100 Fixed Once Daily <ul style="list-style-type: none"> Time of day: with evening meal Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh Insulin degludec U100 Forced, “Worst-Case,” Flexible Once Daily <ul style="list-style-type: none"> Time of day: <ul style="list-style-type: none"> Morning on Mon., Wed., Fri.; Evening on Tues., Thurs., Sat., Sun. Frequency: once daily Dosing Interval: <ul style="list-style-type: none"> 8 hours; Evening followed by Morning dosing (e.g., Tues. dose to Wed. dose) 40 hours; Morning followed by Evening dosing (e.g., Mon. dose to Tues. dose) Device: FlexPen® 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh

Trial	Degludec Arm	Comparator Arm
	<ul style="list-style-type: none"> Subcutaneous site: abdomen or deltoid or thigh 	
Basal Insulin, Three Times Weekly, Added to Combination of OADs		
3718 and 3724	Insulin degludec U200 Fixed Three Times Per Week <ul style="list-style-type: none"> Time of day: with evening meal (3718), before breakfast (3724) Frequency: three times per week on Mon., Wed., and Fri. Dosing Interval: 48-72 hours depending on days of week Device: PDS290 Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStar™ Subcutaneous Site: abdomen or deltoid or thigh
Source: Adapted from NDA203314; Table 1-12 Summary of Clinical Efficacy *Glargine was used in accordance with the US label °After 8 weeks of treatment, the frequency of detemir injections could be increased to twice daily at the investigator's discretion if adequate glucose control was not achieved † Insulin aspart was used as the short acting insulin		

5.5.8. Controlled Interventions: Degludec/aspart Program

5.5.8.1. Degludec/aspart

Formulations Studied: The U100 degludec/aspart insulin formulation intended for commercial use was used in all therapeutic confirmatory trials.

Dosing Interval Studied: In the type 1 DM trial (**NN5401-3594**) degludec/aspart was administered once daily at the main meal. In type 2 diabetes trials degludec/aspart was administered either once daily with the evening or the largest meal or twice daily with breakfast and the main evening meal.

Route and Site of Administration Studied: Degludec/aspart was injected subcutaneously in the abdomen, deltoid or thigh.

5.5.8.2. Comparators

In the type 1 diabetes trial (**NN5401-3594**) insulin detemir was used as the comparator. In the once daily type 2 DM trials (**NN5401-3593**, **NN5401-3590**) insulin glargine was used as the comparator. In the two trials evaluating twice daily administration of pre-mixed insulin (**NN5401-3592** and **NN5401-3597**), the comparator insulin was biphasic insulin aspart (i.e., BIAsp 30: 30% insulin aspart, 70% protaminated aspart). All marketed products were used in a manner consistent with approved local labeling.

Table 8: Randomized Interventions in Degludec/aspart Program

Trial	Degludec/aspart (70/30)	Comparator
Premix or Basal Insulin Once Daily, Prandial^{jj} Insulin with Meals, Type 1 DM		
NN5401-3594	Insulin degludec/asp U100 <ul style="list-style-type: none"> Time of day: with any main meal Frequency: once daily Dosing Interval: 24 hours (with option to move to another meal at anytime) Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin Detemir^o <ul style="list-style-type: none"> Time of day: with evening meal or at bedtime Frequency: once daily Dosing interval: 24 hours Device: FlexPen® Subcutaneous Site: abdomen or deltoid or thigh
Premix or Basal Insulin Once Daily, Added to Metformin, Insulin Naïve, Type 2 DM		
NN5401-3593	Insulin degludec/asp U100 <ul style="list-style-type: none"> Time of day: with evening meal or largest meal Frequency: once daily Dosing Interval: 24 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStarTM Subcutaneous Site: abdomen or deltoid or thigh
Premix or Basal Insulin Once Daily, Added to Combination of OADs, Insulin Treated, Type 2 DM		
NN5401-3590	Insulin degludec/asp U100 <ul style="list-style-type: none"> Time of day: with breakfast Frequency: once daily Dosing Interval: 24 hours Device: PDS290 pen Subcutaneous site: abdomen or deltoid or thigh 	Insulin glargine* <ul style="list-style-type: none"> Time of day: at any time of the day Frequency: once daily Dosing interval: 24 hours Device: SoloStarTM Subcutaneous Site: abdomen or deltoid or thigh
Premix Insulin Twice Daily, Added to Combination of OADs, Insulin Treated, Type 2 DM		
NN5401-3592	Insulin degludec/asp U100 <ul style="list-style-type: none"> Time of day: with breakfast and main evening meal Frequency: twice daily Dosing Interval: ~12 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	BIAsp 30 (Novolog Mix 70/30) <ul style="list-style-type: none"> Time of day: with breakfast and main evening meal Frequency: once daily Dosing interval: ~12 hours Device: FlexPen® Subcutaneous Site: abdomen or deltoid or thigh
NN5401-3597	Insulin degludec/asp U100 <ul style="list-style-type: none"> Time of day: with breakfast and main evening meal Frequency: twice daily Dosing Interval: ~12 hours Device: FlexPen® Subcutaneous site: abdomen or deltoid or thigh 	BIAsp 30 (Novolog Mix 70/30) <ul style="list-style-type: none"> Time of day: with breakfast and main evening meal Frequency: once daily Dosing interval: ~12 hours Device: FlexPen® Subcutaneous Site: abdomen or deltoid or thigh
Source: Adapted from NDA 203313; Summary of Clinical Efficacy Table 1-8 ^{jj} Separate injections of insulin aspart were used for meals not covered by fixed ratio combination product (i.e., two meals in degludec/aspart arm and three meals in detemir arm) ^o After 8 weeks of treatment, the frequency of detemir injections could be increased to twice daily at the investigator's discretion if adequate glucose control was not achieved *Glargine was used in accordance with approved local labeling		

5.5.9. Basal or Premix Insulin Doses

5.5.9.1. Starting Dose

Insulin-naïve subjects with type 2 diabetes were to start basal insulin treatment at 10 U/day.

A 1:1 basal unit to basal unit transfer was recommended when switching between the pre-trial insulin regimen to the on-trial insulin regimen for subjects already on insulin.

5.5.9.2. Dose Adjustment

The degludec, degludec/aspart and comparator insulin doses were to be adjusted so as to target a fasting plasma glucose concentration of 90 mg/dL while avoiding hypoglycemia according to the algorithms in Table 9 and Table 10 respectively.

Within 24 hours of a site visit investigators were to document on the electronic case report form (eCRF), the pre-breakfast self monitored glucose values (three days worth), the insulin doses (three days worth), the new prescribed insulin dose and the reasons for deviating from the algorithm if a deviation occurred. These data were reviewed by Novo Nordisk personnel and could trigger a request for additional data if the reason for deviation was unclear or not justified.

Table 9: Basal Insulin Dose Adjustment Type 1 DM trials 3583 and 3585*

Mean Pre-Breakfast Self-Monitored Glucose		Dose Adjustment
<56 mg/dL	<3.1 mmol/L	Decrease by 4 U
<70 mg/dL	<3.9 mmol/L	Decrease by 2 U
<90 mg/dL	<5.0 mmol/L	No adjustment
<180 mg/dL	<10.0 mmol/L	Increase by 2 U
<270 mg/dL	<15.0 mmol/L	Increase by 4 U
≥270 mg/dL	≥15.0 mmol/L	Increase by 6 U
Adapted from Table 1-9 Summary of Clinical Efficacy (SCE) * Trial 3770 used the following simplified algorithm; (-) 2 units for FPG < 72 mg/dL; 0 units for FPG between 72 and 90 mg; and (+2) units for FPG >90 mg/dL		

Table 10: Basal Insulin Dose Adjustment Type 2 DM trials

Mean Pre-Breakfast Self-Monitored Glucose		Dose Adjustment
mg/dL	mmol/L	
<56	<3.1	Decrease by 4 U
<70	<3.9	Decrease by 2 U
<90	<5.0	No adjustment
<126	<7.0	Increase by 2 U
<144	<8.0	Increase by 4 U
<162	<9.0	Increase by 6 U
≥162	≥9.0	Increase by 8 U

Adapted from NDA203314; Table 1-10; IDeg Summary of Clinical Efficacy (SCE)

5.5.10. Concomitant Glucose Lowering Medications

5.5.10.1. Prandial Insulin:

In all basal-bolus trials (i.e., all Type 1 DM trials and Trial **3582** in type 2DM) insulin aspart (IAsp) was to be administered immediately before meals to cover meal-time requirements. Investigators were recommended to focus on basal insulin dose optimization for the first 8 weeks of the study and consider prandial insulin dose changes using a protocol specified algorithm once basal insulin dose had been optimized.

5.5.10.2. Oral Anti-diabetic Medications (OADs)

In confirmatory therapeutic trials enrolling patients with T2DM, the efficacy and safety of degludec and degludec aspart were studied in combination with various maximally effective, stable (i.e., 3 months), doses of one or up to three OADs.

The combined effect of degludec co-administered with metformin was studied in all therapeutic trials involving patients with T2DM. In trials **3579** and **3672** and **NN5401-3594** metformin use was mandatory.

The use of insulin secretagogues (i.e., sulfonylurea or glinides) was permitted in trials **3586**, **3668** and **3580** but not mandatory.

The use of thiazolidinediones (e.g., pioglitazone) was permitted in trials **3582**, **3580**, **3668** but not mandatory.

The use of dipeptidyl peptidase IV inhibitors was permitted in trials **3579** and **3672**.

The use of alpha-glucosidase inhibitors was studied in trials **3586**.

5.5.11. Study Population

Degludec and degludec/aspart were studied in subjects with established type 1 and 2 diabetes mellitus. Only adult subjects (i.e., ≥ 18 years of age) were studied. No upper age limit for participation was imposed to encourage participation of older subjects. The following two tables list key inclusion and exclusion criteria and highlights differences between trials across the degludec and degludec/aspart programs. Specific exclusionary criteria related to cardiovascular and hypoglycemic risk are underlined.

5.5.11.1. Inclusion Criteria

Table 11: Key Inclusion Criteria in the Degludec Program

1. Male and Female
2. ≥ 18 year of age (≥ 20 years in Japan)
3. Clinically diagnosed with diabetes mellitus
 - a. for ≥ 12 months for trials enrolling subjects with type 1 DM
 - b. for ≥ 6 months for trials enrolling subjects with type 2 DM
4. Pretrial Diabetes Treatment[#]:
 - a. Basal-bolus insulin therapy in trials enrolling subjects with type 1 DM
 - b. Oral anti-diabetic (monotherapy or combination therapy) on stable effective doses* for ≥ 3 months (exceptions were Trial **3668**: OADs and/or basal insulin and Trial **3582**: treated with any insulin treatment \pm OADs)
5. HbA1c (central laboratory determined value)
 - a. Less than 10% in trials enrolling subjects with type 1 DM
 - b. Between 7.0 and 10% inclusive in trials enrolling subjects with type 2 DM
 - c. Between 7.5 and 11% inclusive (in Trial **3580**)
 - d. Between 7.0 and 11% inclusive (for insulin naïve subjects enrolled in Trial **3668**)
6. BMI
 - a. ≤ 35 kg/m² (Type 1 DM and **3586**)
 - b. ≤ 40.0 kg/m² (Type 2 DM trials studying degludec U100)
 - c. ≤ 45 kg/m² (Type 2 DM trials studying degludec U200)

Source: Adapted from NDA 203314; Table 1-6; IDeg summary of Clinical Efficacy

[#]In trials enrolling insulin naïve subjects previous short term insulin treatment for up to 14 days during a hospitalization or for gestational diabetes was allowed.

* Effective dose was defined according to oral anti-hyperglycemic class in the following manner;

- Metformin: alone or in combination (including fixed dose combination) 1500 mg daily, or maximum tolerated dose (at least 1000 mg daily)
- Insulin secretagogue (sulfonylurea or meglitinide): $\geq 50\%$ of the daily maximal dose according to local labeling
- DPP-IV inhibitor (i.e., sitagliptin or vildagliptin): Minimum 100 mg daily or according to local labeling
- α -glucosidase-inhibitor (Acarbose): $\geq 50\%$ of the daily maximal dose or maximum tolerated dose
- Pioglitazone: $\geq 50\%$ of the daily maximal dose according to local labeling or maximum tolerated dose

[∞] In trials where OADs were discontinued at baseline a more conservative upper limit HbA1c cutoff was used

Table 12: Inclusion Criteria Degludec/aspart Program

1. Male and Female
2. ≥ 18 year of age (≥ 20 years in Japan)
3. Clinically diagnosed with diabetes mellitus <ul style="list-style-type: none"> d. for ≥ 12 months* for trials enrolling subjects with type 1 DM e. for ≥ 6 months for trials enrolling subjects with type 2 DM
4. Pretrial Diabetes Treatment: <ul style="list-style-type: none"> f. Type 1 DM: Basal and prandial insulin for 12 months g. Type 2 DM: Insulin naïve or insulin treated (basal or mixed insulin) and/or oral $> \text{or} =$ three months of mono or combination therapy with oral antidiabetic agents
5. HbA1c(central laboratory determined value) <ul style="list-style-type: none"> h. Between 7.0 and 10% i. Between 7.5 and 11% inclusive (in Trial NN5401-3590)
6. BMI <ul style="list-style-type: none"> j. $\leq 35 \text{ kg/m}^2$ (Type 1 DM trial and Asian type 2 DM trial NN5401-3597) k. $\leq 40.0 \text{ kg/m}^2$

NDA: 203313; Summary of Clinical Efficacy Table 1-3

5.5.11.2. Exclusion Criteria

Table 13: Key Exclusion Criteria in the Degludec and Degludec Program

1. Use within the last 3 months prior to screening of glucagon-like peptide 1 receptor agonists
2. Use within the last 3 months prior to screening of specific OADs: <ul style="list-style-type: none"> a. All thiazolidinediones (TZDs) in trials 3759, 3586, 3672 b. Rosiglitazone, specifically, in trials 3580, 3582, 3668 c. DPP4 inhibitors and α-glucosidase inhibitors in trials 3580 and 3668
3. Anticipated change in concomitant medication known to interfere significantly with glucose metabolism, such as systemic corticosteroids, beta-blockers, MAO inhibitors
4. Cardiovascular disease, within the last 6 months prior to visit 1 , defined as: stroke; decompensated heart failure New York Heart Association (NYHA) class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty
5. Uncontrolled treated/untreated severe hypertension (systolic blood pressure ≥ 180 millimeter (mm) mercury (Hg) and/or diastolic blood pressure ≥ 100 mmHg).
6. Impaired liver function, defined as ALAT ≥ 2.5 times upper limit of normal (one retest analyzed at the central laboratory within a week from receipt of the result is permitted with the result of the last sample being conclusive)
7. Impaired renal function defined as: <ul style="list-style-type: none"> a. Type 1 DM: serum creatinine $\geq 2.0 \text{ mg/dL}$ ($\geq 180 \text{ } \mu\text{mol/L}$) b. Type 2 DM: serum-creatinine $\geq 1.4 \text{ mg/dl}$ ($\geq 125 \text{ } \mu\text{mol/L}$) for males and $\geq 1.3 \text{ mg/dl}$ ($\geq 110 \text{ } \mu\text{mol/L}$) for females or according to local label for metformin [For France: glomerular filtration rate below 60 ml/min, calculated by the Cockcroft & Gault formula]; one retest within a week from receipt of the result is permitted with the result of the last sample being conclusive

8. **Recurrent severe hypoglycemia** (more than 1 severe hypoglycemic event during last 12 months) or hypoglycemic unawareness as judged by the Investigator or hospitalization for diabetic ketoacidosis during the previous 6 months
9. Proliferative retinopathy or maculopathy requiring treatment according to the Investigator.
10. Pregnancy, breast-feeding, or the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements [for Germany: implants, injectables, combined oral contraceptives, hormonal IUD, sexual abstinence or vasectomized partner
11. Medical history of cancer (except basal cell skin cancer or squamous cell skin cancer).
12. Any clinically significant disease or disorder, except for conditions associated with T2DM, which in the Investigator's opinion could interfere with the results of the trial
13. Mental incapacity, psychiatric disorder, unwillingness or language barriers precluding adequate understanding or co-operation, including subjects not able to read or write
14. Previous participation in this trial. Participation is defined as randomized. Re-screening of screening failures was allowed only once within the limits of the recruitment period
15. Known or suspected allergy to any of the trial products or related products.
16. Receipt of any investigational drug within one month prior to screening
17. Donation of blood or participation in other trials within one month prior to screening
18. Known or suspected abuse of alcohol, narcotics or illicit drugs

Source Document: Adapted from Table 1-7 Summary of Clinical Efficacy 203314 and 203313

Exclusion criteria in the degludec/aspart program were identical to the ones shown for degludec in Table 13 except for the one criterion below.

Table 14: Exclusion Criterion Specific to Degludec/aspart Program

Use within the last 3 months prior to screening visit (Visit 1) of glucagon-like peptide-1 (GLP-1) receptor agonists and/or rosiglitazone (additionally, no OADs allowed in Trial 3594 and no thiazolidinediones allowed in Trials 3597 or 3590)

5.5.12. Key Withdrawal Criteria

Subjects could be withdrawn;

1. If subjects no longer wanted to participate
2. For safety or non-compliance issues as judged by the investigator
3. If subjects were randomized in error
4. For pregnancy
5. For hypoglycemia during the treatment period posing a safety problem as judged by the investigator
6. For protocol deviation susceptible to affect efficacy or safety outcome as judged by the investigator
7. For initiation or significant change in systemic treatment which in the Investigator's opinion could interfere with glucose metabolism

(allowed exceptions; inhaled corticosteroids, interruption of metformin treatment for a planned radiographic procedure involving use of iodine containing contrast material)

8. For blood donation or participation in other trials
9. For lack of effect according to the following algorithm:

Lack of effect after 12 Weeks

- a. Subjects with no change from baseline in HbA1c and three consecutive self monitored pre-breakfast plasma glucose readings exceeding 240 mg/dL after 12 weeks of treatment were to follow-up with the investigator (i.e., within two weeks) to confirm lack of effect
- b. Lack of effect was confirmed by the investigator if a central lab determined fasting plasma glucose was > 240 mg/dL and a treatable cause for the hyperglycemia was absent.

5.5.13. Statistical Considerations

5.5.13.1. Primary Endpoint Variable

The primary endpoint variable was the change in HbA1c from baseline to end of treatment (analyzed by central laboratory).

Baseline was defined as the HbA1c at the baseline or randomization visit. Missing values (including intermittent missing values) were to be imputed using the Last Observation Carried Forward (LOCF) method. The “end of trial” for these subjects was defined as the subject’s last end of trial visit excluding the follow-up visit.

5.5.13.2. Primary Hypotheses Tested:

All Trials Except 3580 were non-inferiority trials

In each trial, non-inferiority was to be considered confirmed if the upper bound of the two-sided 95% confidence interval around the change from baseline in HbA1c difference between degludec (or degludec/aspart) and comparator was below or equal to 0.4% at the end of treatment. Otherwise stated as the null hypothesis for the one sided test [e.g., For a degludec trial; $H_0: (\text{Degludec } \Delta_{\text{baseline HbA1c}} - \text{Comparator } \Delta_{\text{baseline HbA1c}}) > 0.4\%$)] was rejected in favor of the alternative hypothesis [$H_A: (\text{Degludec } \Delta_{\text{baseline HbA1c}} - \text{Comparator } \Delta_{\text{baseline HbA1c}}) \leq 0.4\%$] if the p-value for the one-sided test was less than or equal to 2.5%.

Trial 3580 was a superiority trial and superiority was to be confirmed if the upper bound of the two-sided 95% confidence interval around the difference in HbA1c change from baseline between groups was below 0%.

Reviewer Comment: The rationale for the margins used to establish efficacy were discussed during development and found acceptable. The margin 0.4% has been used in other basal insulin development programs relying on NPH as the basal insulin comparator.

5.5.13.3. Pre-specified Primary Analysis Model(s)

The sponsor planned to analyze the change in HbA1c from baseline to the end of trial using an analysis of covariance (ANCOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline HbA1c as covariates in all trials. The number of levels for the anti-diabetic therapy and region factors varied across trials. In some trials, the numbers of pre-planned levels for some factors were altered in the final analyses due to insufficient number of patients in a pre-planned level. No other significant changes to the pre-planned primary analyses were made. For details regarding statistical consideration refer to Dr. Liu's statistical review.

5.5.13.4. Pre-specified Secondary Analyses:

The sponsor had planned to test between group differences for several, key, pre-specified, secondary endpoints in each trial. The family-wise type I error rate was to be controlled using a hierarchical (fixed sequence) testing procedure. This procedure was based on an *a priori* ordering of the null-hypotheses for each key secondary endpoint (see below) and on testing these hypotheses sequentially using the two-sided 95% confidence interval approach until a significant result appeared. Using this strategy, superiority would only be confirmed for endpoints where all previous null-hypotheses had been rejected. If the null hypothesis was not rejected, additional planned analyses were performed but formal hypothesis testing was not carried out (i.e., no p-value was calculated). Tables 9 and 10 summarize the hierarchical ordering of these endpoints by trial and denote the endpoints for which inferential testing was performed and found to be significant in the final analyses.

Reviewer Comment: The hierarchical testing procedure to control type-1 error rate were discussed during development and found to be acceptable.

Table 15: Hierarchical Testing Order for Confirmatory Secondary Endpoints in Type 1 DM trials

Trials (duration)	1st Priority	2nd Priority	3rd Priority	4th Priority
Basal Insulin Once Daily and Prandial Insulin with Meals, Type 1 DM				
3583 (52 wks)	Number of <u>nocturnal</u> confirmed hypoglycemic	Number of confirmed hypoglycemic episodes	<i>Change from baseline in FPG</i>	<i>Within subject variability in self-measured FPG</i>

Trials (duration)	1st Priority	2nd Priority	3rd Priority	4th Priority
	episodes*			
3585 (26 wks)	Number of nocturnal confirmed hypoglycemic episodes*	Number of confirmed hypoglycemic episodes	<i>Change from baseline in FPG</i>	<i>Within subject variability in self-measured FPG</i>
3770 (26 wks)	--	--	--	--
Source; Table 1-15 and Table 3-9; IDeg Summary of Clinical Efficacy *Bold formatting denotes a statistically significant difference between groups in final analyses. No inferential testing of the italicized endpoints was performed due to a preceding insignificant result. Descriptive statistics for these are provided.				

Table 16: Hierarchical Testing Order for Confirmatory Secondary Endpoint in Type 2 DM trials

Trials (duration)	1st Priority	2nd Priority	3rd Priority	4th Priority	5th Priority
Basal Insulin Once Daily and Prandial Insulin with Meals, added to OADs, Type 2 DM					
3582 (52 wks)	Number of confirmed hypoglycemic episodes*	Change from baseline in FPG	<i>Within subject variability in self-measured FPG</i>	<i>HbA1c <7% at end of trial without hypoglycemic episodes</i>	
Basal Insulin, Once Daily, Added to Combination of OADs, Type 2 DM					
3579 (52 wks)	Number of confirmed hypoglycemic episodes	<i>Change from baseline in FPG</i>	<i>Within subject variability in self-measured FPG</i>	<i>HbA1c <7% at end of trial without hypoglycemic episodes</i>	
3672 (26 wks)	Number of confirmed hypoglycemic episodes	<i>Change from baseline in FPG</i>	<i>Within subject variability in self-measured FPG</i>	<i>HbA1c <7% at end of trial without hypoglycemic episodes</i>	
3586 (26 wks)	Number of confirmed hypoglycemic episodes	<i>Number of nocturnal confirmed hypoglycemic episodes</i>	<i>Change from baseline in FPG</i>	<i>Within subject variability in self-measured FPG</i>	<i>HbA1c <7% at end of trial without hypoglycemic episodes</i>
3580 (26 wks)	Change from baseline in FPG*	HbA1c <7% at end of trial*	HbA1c <7% at end of trial without hypoglycemic episodes		
3668 (26 wks)	--	--	--	--	--
Source Data Table 1-16 IDeg Summary of Clinical Efficacy *Bold formatting denotes a statistically significant difference between groups in final analyses. No inferential testing of the italicized endpoints was performed due to a preceding insignificant result. Descriptive statistics for these are provided. FPG = central lab derived fasting plasma glucose.					

Table 17: Hierarchical Testing Order for Confirmatory Secondary Endpoint Degludec/aspart

Trials (duration)	1st Priority	2nd Priority	3rd Priority	4th Priority	5th Priority
Premix or Basal Insulin Once Daily, Prandial Insulin with Meals, Type 1 DM					
3594 (26 wks)	Change from baseline in FPG#	<i>HbA1c <7.0% at end-of-trial without <u>severe</u> hypoglycemic episodes</i>	<i>Number of <u>nocturnal</u> confirmed hypoglycemic episodes</i>		
Premix or Basal Once Daily, Added to Combination of OADs, Type 2 DM					
3592 (26 wks)	Change from baseline in FPG#	Number of confirmed hypoglycemic episodes	HbA1c <7.0% at end-of-trial without confirmed hypoglycemic episodes	<i>Change from baseline in body weight after 26 weeks</i>	<i>Number of <u>nocturnal</u> confirmed hypoglycemic episodes*</i>
3597 (26 wks)	Change from baseline in FPG#	Number of confirmed hypoglycemic episodes	<i>HbA1c <7.0% at end-of-trial without <u>confirmed</u> hypoglycemic episodes</i>	<i>Change from baseline in body weight after 26 weeks</i>	<i>Number of <u>nocturnal</u> confirmed hypoglycemic episodes*</i>
Premix or Basal Twice Daily, Added to Combination of OADs, Type 2 DM					
3593 (26 wks)	Prandial PG increment at main evening meal	HbA1c <7.0% at end-of-trial without <u>confirmed</u> hypoglycemic episodes*	<i>Fluctuation in nocturnal interstitial glucose as measured by CGM after 26 weeks (subpopulation only)</i>	<i>Number of <u>nocturnal</u> confirmed hypoglycemic episodes*</i>	<i>Change from baseline in body weight after 26 weeks</i>
3590 (26 wks)	Prandial PG increment at breakfast meal after 26 weeks	Fluctuation in nocturnal interstitial glucose as measured by CGM after 26 weeks (subpopulation only)	<i>HbA1c <7.0% at end-of-trial without <u>confirmed</u> hypoglycemic episodes*</i>	<i>Number of <u>nocturnal</u> confirmed hypoglycemic episodes*</i>	<i>Change from baseline in body weight after 26 weeks</i>
Source: 203313: 2.7.3: SCE: Table 1-10. Bold font indicates that the endpoint met superiority for the hierarchical testing procedure. Normal font indicates that the endpoint did not meet superiority and formal testing procedure was stopped. <i>Italicized</i> font indicates that these endpoints were not formally tested.					

5.5.13.5. Populations Used in Analyses:

Data from the full analysis dataset (i.e., Full Analysis Set or FAS) were used for the sponsor's primary efficacy analyses. This dataset comprised all randomized subjects. Statistical evaluation followed an intention to treat principle. Exclusion

of some randomized subjects was allowed and was the responsibility of the study group. Exclusion required adequate documentation justifying the reason for exclusion. Subjects lost to follow-up after randomization where exposure information was not available were excluded from the FAS.

Reviewer Comment: The population used in the primary analysis is usually comprised of all randomized subjects who received at least one dose of study. Although unclear from the sponsor's definition it appears that subjects who were randomized, lost to follow-up and had no exposure information were excluded from the FAS population.

Table 18: Other Analyses Datasets Used

Dataset Name	Population Defined by Dataset
Per Protocol Analysis Set	Includes all subjects in the Full Analysis Set who fulfill the following criteria: <ul style="list-style-type: none"> a. Have not violated any inclusion criteria b. Have not fulfilled any exclusion criteria c. Have a non-missing HbA1c at screening or randomization d. Have at least one non-missing HbA1c after 12 weeks of exposure e. Have at least 12 weeks of exposure
Safety Analysis Set	Includes all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set were to contribute to the evaluation "as treated".

6. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Note: Pooled analyses of the sponsor's defined FAS population, by disease type, are shown to facilitate data presentation. Notable differences between trials are highlighted in 'Reviewer Comments'.

6.1. Type 1 DM Trials: Degludec Program:

Baseline demographic characteristics, for the pool (N=1577) of patients with T1DM who were randomized to degludec once daily or comparator in the full analysis set population, were balanced between intervention groups (see **Table 19**). No imbalance was noted when characteristics were reviewed by individual study³. The mean (SD) age of participants was 43 (14) years [range: 18-82 years]. 93% of patients were 65 years old or younger and 0.9% of

³ Source Data NDA 203314: 5.3.5.3: Appendix 6.2: Tables 18, 30, 38 and 42

participants were older than 75 years (NDA 203314: 5.3.5.3: Appendix 6.2: Table 22). ~56% of participants were men. The study population consisted of ~81% Whites, ~16% Asians (i.e., Asian Indian and Asian non-Indian combined), and ~1.5% Blacks. In total, 69 subjects with T1DM were of Hispanic ethnicity (4%).

Other baseline characteristics were also balanced at baseline (see **Table 19**). On average the population was overweight per BMI criteria with a mean BMI of 26 kg/m² (range: 15-35). Participants had had diabetes for an average (SD) of 17 (12) years and had moderate glycemic control based on mean HbA1c [7.8 (1.0)]. 24% of participants had one or more diabetes complication at baseline. The most common diabetes related complications were ophthalmic (~16%) followed by neurologic (~9%). Hypertension (27%) and hyperlipidemia (18%) were the two most commonly associated co-morbid conditions reported at baseline.

Approximately, 99% of participants used a basal bolus regimen pre-trial. Glargine (62%) and aspart (53%) were the most frequently used basal and short acting insulins, respectively. Trials 3583 and 3585 allowed participants to enroll on any pre-trial basal-bolus regimen. Trial 3770 pre-specified that subjects had to be on at least 3 injections per day. At baseline the mean total daily insulin dose was balanced between intervention arms and ranged from 0.7-0.8 U/kg across the three trials (see

Table 19). This dose range reflects expected doses for this population.

The majority of trial participants in these trials were recruited from North America 45% (N=701), Europe 37% (N=576) and Japan 12% (N=186).⁴

Table 19: Baseline Characteristics, Type 1 DM, Degludec Program

Characteristic	Randomization	
	Degludec (N=1103) n (%) or mean (SD)	Comparator (N=474) n (%) or mean (SD)
Age (years)	42.6 (13.9)	43.2 (13.5)
Male	624 (56.6)	264 (55.7)
Body Weight (kg)	76.1 (15.9)	75.3 (16.3)
BMI (kg/m²)	25.8 (3.9)	25.7 (4.1)
Ethnicity		
Hispanic or Latino	46 (4.2)	23 (4.9)
Not Hispanic or Latino	1057 (95.8)	451 (95.1)
Race		
White	889 (80.6)	380 (80.2)
Black or African American	19 (1.7)	4 (0.8)
Asian Indian	41 (3.7)	20 (4.2)
Asian non-Indian	131 (11.9)	66 (13.9)
American Indian or Alaska Native	1 (0.1)	--
Native Hawaiian or Pacific Islander	--	1 (0.2)
Other	22 (2.0)	3 (0.6)
Duration of Diabetes (years)	17.5 (12.0)	16.9 (11.2)
HbA1c (%)	7.8 (1.0)	7.8 (0.9)
FPG (mg/dL)	171.7 (72.5)	173.4 (75.7)
Diabetes Complications		

⁴ Source Data NDA 203314: 5.3.5.3: Appendix 6.2: Table 47

Characteristic	Randomization	
	Degludec (N=1103) n (%) or mean (SD)	Comparator (N=474) n (%) or mean (SD)
All	268 (24.3)	103 (21.7)
Cardiovascular	5 (0.5)	2 (0.4)
Dermal	3 (0.3)	3 (0.6)
Gastrointestinal	1 (0.1)	1 (0.2)
Neurological	117 (10.6)	41 (8.6)
Ophthalmic	179 (16.2)	71 (15.0)
Renal	72 (6.5)	32 (6.8)
Other	5 (0.5)	1 (0.2)
Other Commonly Reported Concomitant Illnesses (i.e., >10%)		
Hyperlipidemia	200 (18.1)	84 (18.0)
Hypercholesterolemia	114 (10.3)	36 (7.7)
Hypertension	304 (27.6)	128 (27.4)
Hypothyroidism	135 (12.3)	56 (12.0)
Seasonal allergy	119 (10.8)	50 (10.7)
Depression	112 (10.2)	38 (8.1)
Pre-trial Anti-Diabetic Regimen 3583		
Basal Bolus	468 (99.2)	156 (99.4)
Other	4 (0.8)	1 (0.6)
Total Daily Insulin Dose (U/kg)	0.7 (0.4)	0.7 (0.3)
3585		
Basal Bolus	301 (99.7)	153 (100.0)
Other	1 (0.3)	--
Total Daily Insulin Dose (U/kg)	0.8 (0.3)	0.8 (0.3)
3770 FF		
Basal Bolus	163 (99.4)	164 (100.0)
Other	1 (0.6)	--
Total Daily Insulin Dose (U/kg)	0.7 (0.3)	0.7 (0.3)
Insulin		
Basal Insulin	1090 (98.8)	471 (99.4)
Insulin Glargine	690 (62.6)	289 (61.0)
Insulin Detemir	288 (26.1)	134 (28.3)
Insulin NPH	114 (10.3)	48 (10.1)
Insulin Regular Human	1 (0.1)	--
Bolus Insulin	1102 (99.9)	473 (99.8)
Insulin Regular Human	98 (8.9)	47 (9.9)
Insulin Aspart	581 (52.7)	259 (54.6)
Insulin Glulisine	44 (4.0)	16 (3.4)
Insulin Lispro	386 (35.0)	155 (32.7)
Premix Insulin	6 (0.5)	2 (0.4)
Basal Insulin Regular Human	2 (0.2)	--
Basal Insulin Aspart	4 (0.4)	2 (0.4)
Renal Function at Baseline		
eCreatinine Clearance > 80 mL/min	967 (87.7)	415 (87.7)
50 < eCreatinine Clearance < 80 mL/min	117 (10.6)	50 (10.5)
30 < eCreatinine Clearance < 50 mL/min	14 (1.3)	4 (0.8)
Alanine Amino Transferase (U/mL)	22.6 (12.1)	22.4 (11.5)

Source: 203314; section 2.7.3; Tables 3-3 to 3-7 and section 5.3.5.3 Tables; 62-64, 77-88, 99, 103, 111 Population: Full analysis set for all except for biochemical and hematological parameters (safety analysis set used). Diabetic CV complications groups the following preferred terms: diabetic vascular disorder, diabetic macroangiopathy cardiac autonomic neuropathy diabetic microangiopathy. Other Commonly Reported Concomitant Illnesses (i.e., >10%) derived from 5.3.5.3 Appendix 1.5 Table 3.
FF refers to fixed flexible arm Degludec OD not shown but overall similar FF arm.

6.2. Type 2 DM Trials: Degludec Program, Once Daily Indication:

Baseline demographic characteristics for the pool (N=4048) of patients with T2DM who were randomized to degludec once daily or comparator in the full

analysis set population were balanced between intervention groups (see Table 20).

The mean (SD) age of participants was 58 (9.8) years [range: 20-87 years]. 76% of patients were 65 years old or younger and 3.0% of participants were older than 75 years⁵. 56% of participants were men.

Approximately 70% of the participants were White, 21% were Asian (i.e., Asian Indian and Asian non-Indian) and 7% were Black. A total of 499 subjects with T2DM were of Hispanic ethnicity (12%). In the T2DM trials with U.S. participation (Trials 3582, 3579, 3672 and 3580), the proportion of Black subjects ranged from 7% to 14%, and the proportion Hispanic subjects ranged from 8% to 21%.

Other characteristics were matched at baseline between degludec and comparators overall (see Table 20) and for each individual studies. On average the population was obese per BMI criteria with a mean BMI of 31 kg/m² (range: 16-45). Comparison across trials showed that a greater proportion of individuals (i.e., ~30% versus 10-20%) had severe obesity (BMI > 35 kg/m²) in trials 3582 (Basal-bolus) and 3672 (Basal U200 + OAD). Trial 3586 (Asia) had the least (0.2%) number of individuals with severe obesity and the most with BMI <25 kg/m² (50 versus ~10% for all others) (NDA 203314: 5.3.5.3: Appendix 6.2: Table 36).

Participants had had diabetes for an average (range) of 11 (7) years and had inadequate baseline glycemic control with a mean HbA1c of 8.4 (0.9). The proportion of participants with any diabetes complications at baseline ranged from 11-39%. The most commonly reported diabetes-related complications in the pool of patients from the full analysis set enrolled in the five degludec once daily + OAD trials were neurologic (~11%) followed by ophthalmic (~8%) and renal (5%).

Hypertension (69.0%), hyperlipidemia (28.6%), dyslipidemia (20.7%), hypercholesterolemia (13.7%), obesity (10.8%), osteoarthritis (10.5%) and gastro esophageal reflux disease (10.5%) were the most commonly associated co-morbid conditions reported at baseline. The proportion of subjects on specific classes of oral anti-diabetic medication at baseline and mean dose is shown in Table 20. In Trial 3582 (Basal-bolus) ~ 40% of individuals were receiving glargine at baseline and 30% were receiving insulin aspart at baseline (see Table 21).

The majority of trial participants in these trials were recruited from North America 37% (N=1512), Europe 38% (N=1545) and Asia (Japan excluded) 15% (N=613)⁶.

⁵ NDA 203314: 5.3.5.3: ISE: Appendix 6.2: Table 52

⁶ Source Data NDA 203314: 5.3.5.3: ISE: Appendix 6.2: Tables 48 and 49

Table 20: Baseline Characteristics, Type 2 DM, Degludec, Once Daily, Trials

Characteristic	Randomization	
	Degludec (N=2716) n (%) or mean (SD)	Comparator (N=1332) n (%) or mean (SD)
Age (years)	58.3 (9.7)	57.3 (10.0)
Male	1148 (58.2)	598 (55.2)
Body Weight (kg)	86.1 (19.1)	86.7 (18.7)
BMI (kg/m²)	30.4 (5.2)	30.8 (5.1)
Ethnicity		
Hispanic or Latino	329 (12.1)	170 (12.8)
Not Hispanic or Latino	2349 (86.5)	1139 (85.5)
Not Applicable	38 (1.4)	23 (1.7)
Race		
White	1918 (70.6)	905 (67.9)
Black or African American	183 (6.7)	98 (7.4)
Asian Indian	187 (6.9)	120 (9.0)
Asian non-Indian	371 (12.7)	176 (13.2)
American Indian or Alaska Native	4 (0.1)	3 (0.2)
Native Hawaiian or Pacific Islander	3 (0.1)	3 (0.2)
Other	49 (1.8)	23 (1.7)
Duration of Diabetes (years)	10.8 (7.0)	9.9 (6.5)
HbA1c (%)	8.3 (0.8)	8.4 (0.9)
FPG (mg/dL)	166.5 (49.4)	169.3 (50.5)
Diabetes Complications#		
All	377 (19.1)	210 (19.4)
Cardiovascular	11 (0.6)	10 (0.9)
Dermal	4 (0.2)	--
Neurological	209 (10.6)	108 (10.0)
Ophthalmic	165 (8.4)	92 (8.5)
Renal	91 (4.6)	61 (5.6)
Other	1 (0.1)	--
Other Commonly Reported Concomitant Illnesses (i.e., >10%)		
Hypertension	69.0%	69.2%
Hyperlipidemia	29.3%	27.4%
Dyslipidemia	20.5%	21.1%
Hypercholesterolemia	13.4%	14.1%
Obesity	11.3%	9.8%
Osteoarthritis	10.3%	10.8%
GERD	9.7%	11.9%
Pre-trial Anti-Diabetic Regimen		
3582		
Basal Bolus insulin +/- OADs	362 (48.7)	124 (50)
Basal + Bolus insulin less than BID +/- OADs	19 (2.6)	3 (1.2)
Premix insulin +/- OADs	181 (24.3)	61 (24.6)
Basal +/- OADs	154 (20.7)	56 (22.6)
Bolus +/- OADs	28 (3.8)	4 (1.6)
Total Daily Insulin Dose (U/kg)	0.8 (0.4)	0.8 (0.5)
3579		
1 OAD	213 (27.6)	88 (34.2)
2 OADs	478 (61.8)	141 (54.9)
> 2 OADs	82 (10.6)	28 (10.9)
3672		
1 OAD	62 (27.2)	70 (30.6)
2 OADs	141 (61.8)	133 (58.1)
> 2 OADs	25 (11.0)	26 (11.4)
3586		
1 OAD	36 (12.5)	17 (11.6)
2 OADs	191 (66.1)	94 (64.4)
> 2 OADs	62 (21.5)	35 (24.0)
3580		
1 OAD	73 (32.4)	70 (31.5)
2 OADs	151 (67.1)	151 (68.0)
> 2 OADs	1 (0.4)	1 (0.5)
3668 FF		
OAD only	133 (58.1)	134 (58.3)
Basal insulin only	7 (3.1)	6 (2.6)

Characteristic	Randomization	
	Degludec (N=2716) n (%) or mean (SD)	Comparator (N=1332) n (%) or mean (SD)
Basal insulin + one OAD	89 (38.9)	89 (38.7)
Oral Antidiabetic Drug Class		
Alpha-Glucosidase Inhibitor n (%)	83 (3.1)	35 (2.6)
Acarbose n (%)	59 (2.2)	20 (1.5)
mean (SD) daily dose in mg	222.0 (76.7)	190.0 (80.5)
Miglitol n (%)	10 (0.4)	5 (0.4)
mean (SD) daily dose in mg	195.0 (38.7)	180.0 (41.1)
Voglibose n (%)	14 (0.5)	10 (0.8)
mean (SD) daily dose in mg	0.7 (0.2)	0.7 (0.2)
Biguanide n (%)	2310 (85.1)	1182 (88.7)
Metformin n (%)	2310 (85.1)	1182 (88.7)
mean (SD) daily dose in mg	1871.3 (547.1)	1872.5 (561.4)
DDP-4 inhibitor n (%)	205 (7.5)	106 (8.0)
Saxagliptin n (%)	--	1 (0.1)
mean (SD) daily dose in mg	--	5.0
Sitagliptin n (%)	187 (6.9)	97 (7.3)
mean (SD) daily dose in mg	98.4 (15.5)	98.7 (15.5)
Vildagliptin n (%)	18 (0.7)	8 (0.6)
mean (SD) daily dose in mg	100.0 (0.0)	100.0 (0.0)
Glinide n (%)	68 (2.5)	27 (2.0)
Mitiglinide n (%)	5 (0.2)	1 (0.1)
mean (SD) daily dose in mg	30.0 (0.0)	30.0
Nateglinide n (%)	3 (0.1)	2 (0.2)
mean (SD) daily dose in mg	330.0 (52.0)	360.0 (0.0)
Repaglinide n (%)	60 (2.2)	24 (1.8)
mean (SD) daily dose in mg	5.9 (3.6)	6.1 (2.4)
Sulphonylurea n (%)	1448 (53.3)	761 (57.1)
Glibenclamide n (%)	420 (15.5)	234 (17.6)
mean daily dose (mg)	13.0 (5.3)	13.6 (5.7)
Gliclazide n (%)	321 (11.8)	180 (13.5)
mean daily dose (mg)	131.0 (86.4)	148.9 (90.6)
Glimeperide n (%)	521 (19.2)	254 (19.1)
mean daily dose (mg)	4.8 (1.9)	4.7 (1.8)
Glipizide n (%)	177 (6.5)	91 (6.8)
mean daily dose (mg)	16.9 (10.3)	16.9 (7.8)
Gliquidone n (%)	2 (0.1)	--
mean daily dose (mg)	52.5 (10.6)	--
Glyburide n (%)	9 (0.3)	3 (0.2)
mean daily dose (mg)	13.3 (6.7)	20.0 (0.0)
Thiazolidinedione n (%)	94 (3.5)	44 (3.3)
Pioglitazone n (%)	93 (3.4)	43 (3.2)
mean daily dose (mg)	30.6 (9.4)	32.8 (10.0)
Rosiglitazone n (%)	1 (0.0)	1 (0.1)
mean daily dose (mg)	4.0	4.0
Renal Function at Baseline (estimated)		
creatinine clearance > 80 mL/min	2257 (83.1)	1140 (85.6)
creatinine clearance between 50 and up to 80 mL/min	428 (15.8)	172 (12.9)
creatinine clearance between 30 and < 50 mL/min	29 (1.0)	18 (1.3)
Alanine Amino Transferase (U/mL)#	30.2 (16.5)	31.3 (17.6)

Source: 203314; section 2.7.3; Tables 3-3 to 3-8 and section 5.3.5.3 Appendix 6.2 Tables 62-64, 78, 81, 83, 86, 89, 94, 98, 100 and 101.

Other Commonly Reported Concomitant Illnesses (i.e., >10%) are reported from the safety analysis set population (includes two additional three times a week trials) derived from 5.3.5.3 Appendix 1.5; Table 4. Proportions accurately reflect prevalence in full analysis set for once a day trials.

Values are mean (SD) or number (proportion in %)

FF refers to fixed flexible arm. Degludec OD not shown but overall similar FF arm.

#; trial 3582 not included but qualitatively similar results were found.

Table 21: Types of Insulin Used at Baseline in Basal Bolus Type 2 DM Degludec OD trial,

Characteristic	Degludec	Comparator
Basal Insulin	541 (72.7)	185 (74.6)
Insulin Glargine	322 (43.3)	104 (42.3)
Insulin Detemir	112 (15.1)	49 (19.8)
Insulin Neutral Protamine Hagedorn	105 (14.1)	23 (12.9)
Insulin Neutral Protamine Lispro	3 (0.4)	1 (0.4)
Bolus Insulin	430 (57.8)	137 (55.2)
Insulin Regular Human	88 (11.8)	25 (10.1)
Insulin Aspart	223 (30.0)	65 (26.2)
Insulin Glulisine	28 (3.8)	20 (8.1)
Insulin Lispro	97 (13.0)	27 (10.9)

6.3. Type 1 DM (Trial 5401-3594): Degludec/aspart; Once Daily Indication

Baseline demographic characteristics, for the 548 patients with T1DM who were randomized to Degludec/aspart and comparator, once daily, in the full analysis set population, are shown in **Table 22**. The mean (SD) age of participants was 41.3 (13) years [range: 18-80 years]. 95% of patients were 65 years old or younger and 1.1% (6 subjects) of participants were older than 75 years old (NDA 203313: 5.3.5.3: Appendix 6.2: Table 11). More subjects randomized to Degludec/aspart were younger than 65 years old (97% versus 92%). Overall, ~50% of participants were men but more subjects randomized to the Degludec/aspart arm were men. The study population consisted of ~90% Whites, ~2.9% Blacks and ~1.3% Asians (i.e., Asian Indian and Asian non-Indian combined). In total, 17 subjects with T1DM were of Hispanic ethnicity (3.1%).

Other characteristics were balanced at baseline. On average the population was overweight per BMI criteria with a mean BMI of 26 kg/m² (range: 16-36). Participants had had diabetes for an average (SD) of 17 (12) years and had poor glycemic control based on mean HbA1c [8.3 (0.8)]. 35% of participants had one or more diabetes complication at baseline. The most common diabetes related complications were ophthalmic (~27%) followed by neurologic (~18%).

There were imbalances in the associated co-morbid conditions between arms. 18% versus 11% of participants in the Degludec/aspart arm versus comparator arm had a diagnosis of hypothyroidism. 32% of participants in the Degludec/aspart arm versus 40% in the comparator arm had hypertension. These two conditions were also the two most prevalent co-morbidities.

Approximately 90% of participants used a basal-bolus regimen pre-trial. Glargine (66%) and aspart (50%) were the most frequently used basal and short acting insulins respectively. At baseline the mean total daily insulin dose was balanced between intervention arms (i.e., 0.7 U/kg).

Reviewer Comment: This average dose reflects expected dose for this population. There were small imbalances in characteristics noted at baseline. The influence of such imbalance is uncertain.

The majority of trial participants in this trial were recruited from Europe 58% (N=316), North America 30.5% (N=167) and Australia 12% (N=65).⁷

Table 22: Baseline Characteristics, Type 1 DM Trial (5401-3594), Degludec/aspart Program

Characteristic	Randomization	
	Degludec/aspart (N=366) n (%) or mean (SD)	Detemir (N=182) n (%) or mean (SD)
Age (years)	40.7 (12.8)	42.6 (13.2)
Males	190 (51.9)	82 (45.1)
Body Weight (kg)	76.7 (14.6)	76.0 (14.0)
BMI (kg/m²)	26.2 (4.0)	26.7 (2.9)
Hispanic or Latino	10 (2.7)	7 (3.8)
Not Hispanic or Latino	339 (92.6)	167 (91.8)
White	333 (91.0)	162 (89.0)
Black or African American	10 (2.7)	6 (3.3)
Asian Indian	1 (0.3)	--
Asian non-Indian	3 (0.3)	3 (1.6)
Native Hawaiian or Pacific Islander	1 (0.3)	1 (0.5)
Other	1 (0.3)	2 (1.1)
Not applicable	17 (4.6)	8 (4.4)
Duration of Diabetes (years)	17.2 (11.3)	17.9 (12.3)
HbA1c (%)	8.3 (0.8)	8.3 (0.7)
FPG (mg/dL)	185.6 (85.2)	198.1 (86.4)
All	119 (32.9)	70 (38.9)
Cardiovascular	14 (3.9)	2 (1.1)
Dermal	1 (0.3)	1 (0.6)
Gastrointestinal	1 (0.3)	1 (0.6)
Neurological	71 (19.6)	26 (14.4)
Ophthalmic	91 (25.1)	58 (32.2)
Renal	29 (8.0)	17 (9.4)
Other	1 (0.3)	1 (0.6)
Hypertension	116 (32.0)	72 (40.0)
Hypercholesterolemia	40 (11.0)	30 (16.7)
Hyperlipidemia	47 (13.0)	20 (11.1)
Dyslipidemia	34 (9.4)	22 (12.2)
Hypothyroidism	64 (17.7)	19 (10.6)
Depression	37 (10.2)	21 (11.7)
Basal Bolus	334 (91.3)	161 (88.5)
Other	32 (8.7)	21 (11.5)
Total Daily Insulin Dose (U/kg)	0.7 (0.3)	0.7 (0.3)
Insulin Glargine	238 (65.0)	125 (68.7)
Insulin Detemir	57 (15.6)	24 (13.2)
Insulin NPH	44 (12.0)	17 (9.3)
Insulin Regular Human	33 (9.0)	19 (10.4)
Insulin Aspart	180 (49.2)	91 (50.0)
Insulin Glulisine	22 (6.0)	13 (7.1)
Insulin Lispro	108 (29.5)	50 (27.5)
Basal Insulin Regular Human	12 (3.3)	7 (3.8)
Basal Insulin Aspart	16 (4.4)	10 (5.5)
Insulin Lispro Mix	5 (1.4)	2 (1.1)

Source: 203313; section 2.7.3; Tables 3-3 to 3-8 and section 5.3.5.3 Appendix 6.2 Tables; 40-43, 47. Appendix 1.5

⁷ Source Data NDA 203313: 5.3.5.3: Appendix 6.2: Table 24

Characteristic	Randomization	
	Degludec/aspart (N=366) n (%) or mean (SD)	Detemir (N=182) n (%) or mean (SD)

Table 1. Population: Full analysis set for except for concomitant illnesses (safety analysis set used).

6.4. Type 2 DM Trials: Degludec/aspart Program; Once daily or Twice daily indication

Baseline demographic characteristics for the pool (N=1860) of randomized patients with T2DM in the four confirmatory Degludec/aspart trials were balanced between intervention groups (see Table 23).

The mean (SD) age of participants was 58 (9.7) years [range: 20-89 years]. 74% of patients were 65 years old or younger (range: 68-92%) and 3% of participants were older than 75 years (range 2-5%)⁸. 54% of participants were men.

Approximately 47% of the participants were White, 48% were Asian (i.e., 18% Asian Indian and 31% Asian non-Indian) and 4% were Black. A total of 137 subjects with T2DM were of Hispanic or Latino ethnicity (7.4%).

Reviewer Comment: The pooled results reflect demographic characteristics for each of the individual studies⁹ except for race and ethnicity. Trial NN5401-3597 was carried out in Asia and >95% of participants were Asian non-Indian. The number of races and ethnic groups represented and the proportion of subjects in each do not accurately reflect the demographics of the United States population. Certain racial and ethnic groups (e.g., American Indians, Blacks and Hispanics) are underrepresented and Asians are overrepresented.

Other baseline characteristics were balanced between intervention arms in the overall pool of studies (see Table 23) and within each trial. The pooled population of type 2 DM patient was overweight to obese with a mean BMI of 29 kg/m² (range: 16-48). Comparison across trials showed that mean BMI was consistent with the overall population except for Trial NN5401-3597 (Asia) where the mean BMI was 25 kg/m² and the proportion of severely obese individuals was 0.5% (i.e., BMI > 35 kg/m²). In trials NN5401-3592, NN5401-3593 and NN5401-3590, 13-20% of individuals were severely obese (i.e., BMI > 35 kg/m²).

Participants had diabetes for an average (range) of 12 (9-16) years and had inadequate baseline glycemic control [mean HbA1c of 8.5 (0.9)]. The proportion of participants with any diabetes complications at baseline ranged from 15-69%. The most commonly reported diabetes related complications, at baseline, in the

⁸ NDA 203313: 5.3.5.3: ISE: Appendix 6.2: Table 12

⁹ NDA 203313: 5.3.5.3: ISE: Appendix 6.2: Tables 10, 12, 14, 16, 18, 20, 22

pool of type 2 DM patients enrolled in the four Degludec/aspart trials were ophthalmic (~17%) followed by neurologic (~15%) and renal (8%).

Reviewer Comment: Baseline characteristics were matched within trials. Differences in glucose control at baseline, diabetes duration and prevalence of diabetes related complications at baseline were seen between trials (Data not shown)¹⁰.

In trial NN5401-3590 baseline Hba1c was higher than in other trials (i.e., 8.9% versus ~ 8.4%).

In Trial NN5401-3597 (Asia) a larger proportion of participants had diabetes for > 10 years (77% versus 45%). This is consistent with the observation that mean diabetes duration was ~ 4 years longer compared to the pooled estimate (i.e., 16 years) and that more participants in this trial had diabetes related complications at baseline (i.e., 69% versus < 23% for other trials).

Participants in Trial NN5401-3590 (Degludec/aspart once daily versus glargine) had diabetes for the shortest duration (i.e., ~9 years) and had the fewest baseline complications from diabetes. Between trial differences may be important for the clinical interpretation of results linked to specific safety endpoints in the pooled analysis of safety.

Hypertension (68%), hyperlipidemia (28%), and dyslipidemia (24%), were the most commonly associated co-morbid conditions reported at baseline. The proportion of subjects on specific insulin regimens as well as type and dose of oral anti-diabetic medication at baseline is shown in Table 23. The most commonly used classes of OADs at baseline were biguanide and sulfonylurea.

The majority of trial participants were recruited from Asia (Japan excluded) 38% (N=705), Europe 33% (N=608) and North America 16% (N=298)¹¹.

Table 23: Baseline Characteristics, Type 2 DM, Degludec/aspart Program

Characteristic	Randomization	
	Degludec/aspart (N=1000) n (%) or mean (SD)	Comparator (N=860) n (%) or mean (SD)
Age (years)	58.3 (9.7)	58.3 (9.8)
Males	540 (54.0)	461 (53.6)
Body Weight (kg)	78.8 (18.7)	80.0 (18.7)
BMI (kg/m²)	28.9 (5.1)	29.2 (5.2)
Ethnicity		
Hispanic or Latino	63 (6.3)	74 (8.6)
Not Hispanic or Latino	906 (90.6)	764 (88.8)
Not Applicable	31 (3.2)	22 (2.6)
Race		
White	437 (43.7)	441 (51.3)
Black or African American	43 (4.3)	29 (3.4)

¹⁰ Source Data NDA 203313: 5.3.5.3: ISE: Appendix 6.2: Tables 29, 31, 33, 35.

¹¹ Source Data NDA 203313: 5.3.5.3: ISE: Appendix 6.2: Table 25

Characteristic	Randomization	
	Degludec/aspart (N=1000) n (%) or mean (SD)	Comparator (N=860) n (%) or mean (SD)
Asian Indian	170 (17.0)	161 (18.7)
Asian non-Indian	345 (34.5)	224 (26.0)
Native Hawaiian or Pacific Islander	--	1 (0.1)
Other	5 (0.5)	4 (0.5)
Duration of Diabetes (years)	12.4 (7.5)	12.1 (7.4)
HbA1c (%)	8.5 (0.9)	8.6 (1.0)
FPG (mg/dL)	157.5 (51.3)	158.5 (52.6)
Diabetes Complications		
All	337 (33.7)	235 (27.3)
Cardiovascular	7 (0.7)	10 (1.2)
Dermal	10 (1.0)	7 (0.8)
Neurological	149 (14.9)	120 (14.0)
Ophthalmic	212 (21.2)	142 (16.5)
Renal	95 (9.5)	56 (6.5)
Other Commonly Reported Concomitant Illnesses (i.e., >10%)		
Hypertension	679 (68.0)	570 (66.5)
Hypercholesterolemia	88 (8.8)	87 (10.2)
Hyperlipidemia	268 (26.9)	237 (27.7)
Dyslipidemia	237 (23.7)	205 (23.9)
Cataract	136 (13.6)	88 (10.3)
Pre-trial Anti-Diabetic Regimen NN5401-3592		
Premix insulin OD +/- OADs	16 (7.1)	12 (5.4)
Premix insulin BID +/- OADs	203 (90.6)	206 (92.8)
Premix insulin TID +/- OADs	--	1 (0.5)
Basal Bolus insulin +/- OADs	4 (1.8)	3 (1.4)
Only OADs	1 (0.4)	--
Total Daily Insulin Dose (U/kg)	0.7 (0.4)	0.6 (0.3)
NN5401-3597		
Basal insulin +/- OADs	82 (29.3)	42 (29.6)
Premix insulin +/- OADs	195 (69.6)	98 (69.0)
Basal Bolus insulin +/- OADs	3 (1.1)	2 (1.4)
Total Daily Insulin Dose (U/kg)	0.6 (0.3)	0.5 (0.3)
NN5401-3593		
Basal OD + at least one OAD	226 (98.3)	229 (98.3)
Other	4 (1.7)	3 (1.7)
Total Daily Insulin Dose (U/kg)	0.3 (0.2)	0.4 (0.2)
NN5401-3590		
1 OAD	2 (0.8)	1 (0.4)
2 OADs	224 (84.2)	221 (84.0)
> 2 OADs	40 (15.0)	41 (15.6)
Oral Antidiabetic Drug Class		
Alpha-Glucosidase Inhibitor n (%)	29 (2.9)	31 (3.6)
Acarbose n (%)	24 (2.4)	23 (2.7)
mean (SD) daily dose in mg	156.3 (103.3)	142.4 (90.9)
Miglitol n (%)	2 (0.2)	2 (0.2)
mean (SD) daily dose in mg	37.5 (17.7)	75.0 (35.4)
Voglibose n (%)	3 (0.3)	6 (0.7)
mean (SD) daily dose in mg	0.5 (0.3)	0.3 (0.1)
Biguanide n (%)		
Metformin n (%)	826 (82.6)	747 (86.9)
mean (SD) daily dose in mg	1772.6 (621.7)	1797.1 (601.4)
DDP-4 inhibitor n (%)	50 (5.0)	66 (7.7)
Saxagliptin n (%)	2 (0.2)	--
mean (SD) daily dose in mg	--	--
Sitagliptin n (%)	38 (3.8)	53 (6.2)
mean (SD) daily dose in mg	103.9 (33.7)	97.2 (20.6)
Vildagliptin n (%)	10 (1.0)	13 (1.5)
mean (SD) daily dose in mg	75.0 (26.4)	84.6 (24.0)
Glinide n (%)	29 (2.9)	33 (3.8)
Mitiglinide n (%)	--	1 (0.1)
mean (SD) daily dose in mg	--	30.0
Nateglinide n (%)	8 (0.8)	27 (3.1)
mean (SD) daily dose in mg	330.0 (55.5)	252.0 (65.7)

Table 24: Subject Disposition, Pooled Type 1 DM trials, Degludec Program

	Degludec N (%)	Comparator N (%)	Total N (%)
Screened			1783 (100.0)
Screening Failures			205 (11.5)
Randomized	1104 (100.0)	474 (100.0)	1578 (100.0)
Exposed	1102 (99.8)	467 (98.5)	1569 (99.4)
Withdrawn*	140 (12.7)	47 (9.9)	187 (11.9)
Reason for Withdrawal			
Adverse Event*	24 (2.2)	4 (0.8)	28 (1.8)
Ineffective Therapy	5 (0.5)	3 (0.6)	8 (0.5)
Non-Compliance With Protocol	22 (2.0)	10 (2.1)	32 (2.0)
Withdrawal Criteria*	33 (3.0)	8 (1.7)	41 (2.6)
Other	56 (5.1)	22 (4.6)	78 (4.9)
Completed Trial	964 (87.3)	427 (90.1)	1391 (88.1)
Full Analysis Set	1103 (99.9)	474 (100.0)	1577 (99.9)
Per Protocol Analysis Set	1032 (93.5)	447 (94.3)	1479 (93.7)

Source Data: NDA 203314; Module 2.7.3; SCE; Table 3-1.

N: Number of subjects; %: Proportion of randomized subjects; Ineffective Therapy: Either documented by HbA1c or undocumented and at investigator discretion.

* Proportion nominally higher in degludec arm

Withdrawals for 'Other'

Cases of withdrawal listed under the category "Others" were reviewed and manually categorized by the sponsor. Reasons for withdrawal in this subset of patients were matched except for 'hypoglycemia' and 'lack of effect'. This is summarized in Table 25. After review of line listings it appears that subjects mentioned hypoglycemia as the reason for no longer wanting to participate in the study. No details surrounding the exact nature of hypoglycemic events are provided.

Table 25: Categorization of Withdrawal Events Classified as "Others", Pooled Type 1 DM trials, Degludec Program

	Degludec N (%)	Comparator N (%)
	1102 (100)	467 (100)
Randomized in Error	8 (0.7)	2 (0.4)
Withdrew consent	11 (1.0)	7 (1.5)
Lost to follow-up	4 (0.4)	1 (0.2)
Site Closure or Move	6 (0.5)	4 (0.9)
Lack of effect	1 (0.1)	0
Hypoglycemia	7 (0.6)	
Safety other than hypoglycemia	0 (0.0)	0
Miscellaneous	19 (1.7%)	8 (1.7%)

Source: NDA203314; Module 2.7.4. SCS, Table 1-11

Withdrawals due to 'Adverse Events'

The proportion of subjects with T1DM discontinuing the trial due to adverse events was 2.2% for degludec and 0.8% for comparators. Subjects randomized to degludec had a higher number (AEs: 38 versus 4 events and SAEs: 14 versus 3) and rate of both total adverse events (5.2 vs. 1.4 'adverse event' leading to discontinuations per 100 patient-years) and serious adverse events leading to discontinuations (2.2 versus 1.0 'serious adverse event' leading to discontinuation per 100 patient-years)¹⁵.

Nearly half of the adverse events leading to withdrawal in subjects with T1DM in the degludec arm and the majority of the adverse event in the comparators group were serious adverse events. Most events were derived from the metabolism and nutrition disorders system organ class and the two most common preferred terms were hypoglycemia and hypoglycemia unconsciousness¹⁶. I review hypoglycemia related withdrawals in greater details below.

Withdrawals due to Hypoglycemia

Reviewer Comment: More subjects with type 1 DM diabetes in the degludec arm withdrew due to hypoglycemia and more of these withdrawals were due to serious adverse events or were judged by the investigators to be causing a safety problem.

Hypoglycemia leading to withdrawal was reported across multiple withdrawal categories. Table 26 compares the proportion of individuals who withdrew due to hypoglycemia between degludec and comparator. The data show a numerical imbalance not favoring degludec across all categories. Overall, 2.5% of participants in the degludec arm versus 0.85% in the glargine arm withdrew due to hypoglycemia.

Table 26: Withdrawals Due to Hypoglycemia Across All Categories of Withdrawal, Pooled Type 1 DM Trials, Degludec Program

	Degludec N=1102 N (%)	Comparator N=467 N (%)
Hypoglycemia SAE	6 (0.5)	1 (0.2)
Hypoglycemia non SAE	3 (0.3)	0 (0.0)
Hypoglycemia causing a safety problem withdrawal criteria	12 (1.1)	3 (0.6)
Hypoglycemia caterorized as 'Other'	7 (0.6)	0 (0.0)

¹⁵ Source 203314: 5.3.5.3: ISS: Appendix 1.12 Tables 6 and 7.

¹⁶ Source 203314: 5.3.5.3: ISS: Appendix 1.12 Tables 6 and 7.

reason for withdrawal		
Source: 203314: 2.7.4 SCS: Table 2-48 p.160		

More subjects randomized to degludec [N=6 (0.5%)] withdrew due to a serious adverse event of hypoglycemia [N=1 (0.2%)].

Note: The proportion of individuals with serious adverse events of hypoglycemia (i.e., whether or not they led to withdrawal) were similar between groups and will be shown later.

Reviewer comment: Narratives for each of these cases were reviewed (Source ISS Table 2-83). The sponsor states that at least 2 events were intentional overdoses. For one case this appears to be justified. For the other (Subject 743001), not enough information is provided to determine the cause. The narratives are summarized below.

- **Trial 1250-3583 Subject 402006:** The case describes a 39 year old male. The patient experienced a severe hypoglycemic event while canoeing. The episode occurred after lunch, 192 days after the patient had been randomized to **degludec**. The patient fell in the water, had to be rescued and was treated with glucose on shore. No risk factors except for physical activity or warning signs were identified.
- **Trial 1250-3583 Subject 631002:** The case describes a 55 year old female with longstanding type 1 DM (1955). Seven days after the patient had been randomized to **degludec**, the patient experienced a severe hypoglycemic a night (2 AM). The patient had injected aspart at 9:00PM and degludec at 10:00 PM. The patient was unresponsive and paramedics administered intravenous glucose. Patient withdrew consent and stated that she could not 'feel' hypoglycemic episodes on her new regimen.
- **Trial 1250-3583 Subject 643005:** The case describes a 46 year old male with longstanding type 1 DM (1990). 138 days after the patient had been randomized to **degludec**, the patient presented with an intentional insulin aspart overdose. The patient had self-injected two insulin aspart pens. The narrative states that the patient was depressed because of marital problems. The patient remained responsive and had a reported blood glucose of 20 mg/dL. He was treated in the emergency room and transferred to a psychiatric inpatient unit for treatment of depression.
- **Trial 1250-3583 Subject 657006:** The case describes a 21 year old male with longstanding type 1 DM (1992). 193 days after the patient had been randomized to **degludec**, the patient had an episode of hypoglycemia with seizure and unconsciousness while visiting a friend at 9:00 AM. Paramedics were called; blood glucose was reported to be 52 mg/dL.

Inpatient workup revealed a frontal lobe lesion per CT scan (not further described; patient advised to follow-up with MRI and neurology). Patient had drunk three alcoholic drinks prior to event.

- **Trial 1250-3585 Subject 402004:** The case describes a 64 year old male with longstanding type 1 DM (1971). 35 days after the patient had been randomized to **detemir**, the patient lost consciousness while sitting down for lunch. Patient's spouse administered glucagon and patient recovered. Two days later the patient had another severe hypoglycemic episode and the patient was withdrawn.
- **Trial 1250-3770 Subject 726002:** The case describes a 62 year old male with longstanding type 1 DM (1993), peripheral vascular disease, CAD and GERD. 49 days after the patient had been randomized to **degludec**, had a severe hypoglycemic episode while driving. The patient pulled over, lost consciousness and was surrounded by paramedics when he regained consciousness. Patient was told by paramedics that his blood glucose was 30 mg/dL.
- **Trial 1250-3770 Subject 743001:** The case describes a 46 year old female with longstanding type 1 DM (1990). 158 days after the patient had been randomized to **degludec**, the patient "possibly attempted suicide" and drank alcohol. The patient was found in a diabetic coma nine hours after "drinking had stopped." The patient died. No information concerning insulin dose is available. History of relationship issues and suicide notes is noted in narrative.

Reviewer Comment: I also reviewed narratives for serious adverse events that led to withdrawal with preferred terms that could represent misclassified severe hypoglycemic events. In all but two cases, information provided in the narrative was not sufficient to rule in or out the diagnosis. One of the two cases likely representing misclassified hypoglycemia (Subject 722001) occurred in a degludec treated individual. The other (Subject 631005) in the glargine arm.

- **Trial 1250-3770, Subject 743001, TIA:** The case describes a 58 year old male with longstanding type 1 DM (1989) and ASCVD. The patient developed slurred speech and left sided weakness, three days after he had been randomized to **degludec**. A brain MRI was negative. Thoracic MRI revealed cervical myelopathy. The patient was diagnosed with an acute TIA. The narrative does not contain details to confirm diagnosis. *Reviewer Comment: Hypoglycemia is not invoked as a putative cause. Neuroglycopenia can cause TIA like symptoms. Details to rule this in or out are not available.*
- **Trial 1250-3585, Subject 108006, Fracture:** The case describes a 46 year old female with type 1 DM. 81 days after starting **degludec** the

patient was involved in a traffic accident which resulted in fractures to the pelvis and ribs. *Reviewer Comment: Hypoglycemia is not invoked as a putative cause. Other details to rule this in or out are not available.*

- **Trial 1250-3770, Subject 722001, Adrenal Insufficiency:** The case describes a 65 year old female with type 1 DM. 10 days after she had been randomized to **degludec** the patient developed 'severe adrenal insufficiency'. No other information is provided. The patient recovered the same day after being administered 50% IV dextrose. *Reviewer Comment: This likely represents a misclassified case of severe hypoglycemia. Severe adrenal insufficiency would not be expected to respond to IV dextrose. Severe adrenal insufficiency is treated with corticosteroids.*
- **Trial 1250-3583, Subject 631005, Convulsion:** The case describes a 69 year old female with type 1 DM (1986). Three months after starting **degludec** the patient had two seizures. Blood glucose measured before and after the event was reported to be 200 and 229 mg/dL respectively. The patient was found to be hypertensive during the event. CT-scan of the brain was not consistent with hemorrhagic or ischemic stroke.
- **Trial 1250-3583, Subject 631005, Dead in Bed:** The case describes a 26 year old female with type 1 DM (1988) who was found 'dead in bed' by a relative 32 days after randomization to **glargine**. *Reviewer Comment: This event could represent an episode of unrecognized hypoglycemia.*

Withdrawals due to 'Withdrawal Criteria'

Between 1% and 3% of randomized individuals in each trial were withdrawn due to meeting one or more predefined withdrawal criteria (see **5.5.12** for criteria). Table 27 summarizes these data. The most frequent withdrawal criterion met was 'Hypoglycemia Causing a Safety Problem': 1.1% and 0.6% of subjects randomized to degludec and comparator were withdrawn on this basis. This was driven by Trials 3583 (0.8% versus 0.0% for degludec versus glargine) and the fixed flexible degludec arm in trial 3770 (2.4% versus 0.6% for degludec versus glargine). Protocol deviations and lack of effect after 12-weeks were the next two most frequent withdrawal criteria which occurred most frequently in the degludec group. Protocol deviations occurred most frequently in Trials 3583 (Basal-bolus 52-weeks) and 3585 (Basal-bolus Asia).

Table 27: Withdrawals due to Withdrawal Criteria, Degludec, Type 1 DM

	Degludec N (%)	Comparator N (%)
	1103 (100)	474 (100)
Pregnancy	4 (0.4)	3 (0.6)
Hypoglycemia causing a safety problem	12 (1.1)	3 (0.6)

Protocol deviation	11 (1.0)	0 (0.0)
Significant change in treatment	3 (0.3)	1 (0.2)
Lack of effect after 12-weeks	4 (0.4)	1 (0.2)
Failure to comply with SMBG	1 (0.1)	0 (0.0)
Source: 203314: ISS: 5.3.5.3: Appendix 6.2: Table 6.		

Withdrawals due to Ineffective Therapy

Withdrawals due to ineffective therapy were reported across the following categories of withdrawal: 'Reason for Withdrawal', 'Withdrawal Criteria' and the category 'Other'. Table 28 shows withdrawal due to ineffective therapy across all categories. In the pool of patients with type 1 DM a similar small proportion of patients withdrew due to ineffective therapy in the degludec and comparator arm (0.4% versus 0.3%).

Table 28: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 1 DM

	Degludec N (%)	Comparator N (%)
	1103	474
Ineffective therapy	5 (0.5)	3 (0.6)
Withdrawal Criterion 'lack of effect after 12 weeks'	4 (0.4)	1 (0.2)
Other	1 (0.1)	0
Adapted from Source: 203314; 2.7.4; SCS: Table 1-12		

7.2. Disposition Type-2 DM Trials Degludec Program

5983 subjects with type 2 DM were screened for eligibility. 32% of the population was ineligible. The most frequent reason for ineligibility was failure to meet one or more of the specified inclusion/exclusion criteria.

2713 and 1339 subjects with type 2 diabetes were exposed to degludec and comparator respectively in the six degludec once daily trials. These six trials contributed a cumulative exposure to degludec and comparator of 1889 and 827 patient-years, respectively, at the time of NDA filing¹⁷. In addition, 460 and 463 subjects were exposed to degludec and comparator in two degludec three times per week trials. These two trials contributed an additional 221 and 217 patient-years of exposure to degludec and comparator, respectively.

The completion rate for the pooled population of subjects with type 2 DM was 83% and was balanced between degludec and comparator (shown in **Table 29**). The proportion of randomized subjects who completed the six confirmatory type 2 DM trials ranged from 76% in trial **3580** (degludec versus sitagliptin) to 91% in trial **3586** (degludec + OAD Asia).

¹⁷ Source Data: 203314: 5.3.5.3: ISE: Appendix 6.2: Tables 494-496.

The most frequent reason for withdrawal (9%) in both arms was the category “Other”. A slightly greater proportion of participants withdrew from the degludec arm due to adverse events. The proportion of subjects with T2DM discontinuing the trial due to adverse events in the six confirmatory efficacy studies was 2.6% for degludec and 1.9% for comparators. For the other categories, frequency of withdrawal was balanced between arms. No relationship between proportion of withdrawals and trial duration was seen in the six confirmatory type 2 DM trials (data not shown)¹⁸.

Reviewer Comment: Review of disposition by individual trials¹⁹ and in particular for study 3668 (Fixed Flexible Schedule) or 3672 (Degludec U200 OD) was consistent with the pooled estimates. Addition of the two three times per week trials (3718 and 3724) results in qualitatively similar findings to those shown in the table below (data not shown)²⁰.

Table 29: Subject Disposition, Pooled Type 2 DM, Degludec Once Daily trials*

	Degludec N (%)	Comparator N (%)	Total N (%)
Screened			5983 (100)
Screening Failures			1907 (31.8)
Randomized	2733 (100.0)	1343 (100.0)	4076 (100.0)
Exposed [%]	2713 (99.3)	1339 (99.7)	4052 (99.4)
Withdrawn	469 (17.2)	221 (16.5)	690 (16.9)
Reason for Withdrawal			
Adverse Event	70 (2.6)	25 (1.9)	95 (2.3)
Ineffective Therapy	15 (0.5)	6 (0.4)	21 (0.5)
Non-Compliance With Protocol	90 (3.3)	49 (3.6)	139 (3.4)
Withdrawal Criteria	45 (1.6)	27 (2.0)	72 (1.8)
Other	249 (9.1)	114 (8.5)	363 (8.9)
Completed Trial	2264 (82.8)	1122 (83.5)	3386 (83.1)
Full Analysis Set	2716 (99.4)	1332 (99.2)	4048 (99.3)
Per Protocol Analysis Set	2423 (88.7)	1200 (89.4)	3623 (88.9)
Source Data: NDA 203314; 2.7.3; SCE; Table 3-2			
N: Number of subjects; %: Proportion of randomized subjects; Ineffective Therapy: Either documented by HbA1c or undocumented and at investigator discretion.			
% Safety Analysis Set			
*Comparator: IGlax (3582, 3579, 3672, 3586, 3668) and Sitagliptin (3580)			

Withdrawals for ‘Other’

¹⁸ Source Data: NDA 203314: 5.3.5.3 ISS; Appendix 1.3 Figure 24

¹⁹ Source Data: NDA 203314: 5.3.5.3 ISE; Appendix 6.2 Table 2 and 3

²⁰ Source Data: NDA 203314: 5.3.5.3 SCE Table 1-13

Cases of withdrawal listed as “Others” for the pool of eight trials performed in type 2 DM subjects [i.e., exposure includes the two three times per week trials (3718 and 3724)], were reviewed and manually categorized by the sponsor. Reasons for withdrawal in this subset of patients were matched except for withdrawal of consent and hypoglycemia. The proportion in each category was small. This is summarized in Table 25.

Table 30: Categorization of Withdrawal Events Classified as “Others”, Pooled Type 2 DM trials, Degludec Program

	Degludec N (%)	Comparator N (%)
	3173	1807
Randomized in Error	86 (2.7%)	54 (3.0%)
Withdrew consent	72 (2.3%)	30 (1.7%)
Lost to follow-up	27 (0.9%)	17 (0.9%)
Site Closure or Move	33 (1.0%)	16 (0.9%)
Lack of effect	8 (0.3%)	1 (0.1%)
Hypoglycemia	4 (0.1%)	0
Safety other than hypoglycemia	9 (0.3%)	4 (0.2%)
Miscellaneous	40 (1.3%)	19 (1
Source: 203314: Module 2.7.4. SCS: Table 1-14		
Note: Greater total exposure reflects addition of three times per week trials 3718 and 3724		

Reviewer Comment: To verify the sponsor’s categorization, I audited the listing²¹ of withdrawals for reason “Other” in subjects randomized to degludec in the six type 2 DM trials (N=2733) and used similar categories as those proposed by the sponsor. Overall, I confirmed the sponsor’s finding. In my review I found 78 (2.9%) events of withdrawals due to randomization errors or protocol violations. The most common error was violation of ≥ 1 inclusion/exclusion criterion; the most common violation was patients randomized on less than a $\frac{1}{2}$ maximal dose of OAD. The other common protocol violation was subject on prohibited OAD. The next most common categories were miscellaneous [$\sim 2.4\%$ (i.e., patients no longer wanted to participate, professional reasons)], withdrawal of consent (1.5%) and lost to follow-up (0.7%). I counted 5 withdrawal events where the word hypoglycemia was listed in the reason for withdrawal in the degludec arm and 0 in the comparator arm. Events with the words adverse events and weight gain listed in the reason were low ($<0.2\%$) and balanced between arms.

Withdrawals due to ‘Adverse Events’

To analyze withdrawals due to adverse events (AEs) in participants with T2DM, the sponsor pooled participants from eight clinical trials conducted in this population (see

²¹ Source 203314: 5.3.5.3: ISE: Appendix 2.2 Listing 12.

Table 4). Subjects randomized to degludec were slightly more likely to discontinue due to an adverse event (2.3% versus 1.4%). The rate of adverse events resulting in discontinuation was also greater in the degludec arm (4.5 events per 100 patient-years versus 2.7 events per 100 patient-years). Half of the events leading to withdrawal in the degludec group and a majority of the adverse events in the comparator groups were serious adverse events. The rates of the serious adverse events leading to withdrawal were similar for degludec and comparator (2.4 versus 1.9 events per 100 patient years). There was no imbalance between intervention arms with regards to types of events. Two participants discontinued due to hypoglycemia (0.2%) in each arm in this pool of patients.

Withdrawals due to Hypoglycemia

Hypoglycemia leading to withdrawal was reported across multiple withdrawal categories. Table 26 compares the number of individuals who withdrew due to hypoglycemia across all categories of withdrawal in the pool of studies examining once daily degludec in type 2 diabetes (i.e., the two degludec three times per week studies are excluded).

Reviewer Comment: The data shows that the proportion of withdrawal due to hypoglycemia across all categories was low and balanced between degludec and comparators (0.6% versus 0.5%).

Table 31: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 2 DM Trials, Degludec Program

	Degludec N=2487 N (%)	Comparator N=1111 N (%)
Hypoglycemia SAE	0 (0.0)	2 (0.2)
Hypoglycemia non SAE	2 (0.1)	0 (0.0)
Hypoglycemia causing a safety problem withdrawal criteria	9 (0.4)	4 (0.4)
Hypoglycemia caterorized as "Other" reason for withdrawal	4 (0.2)	0 (0.0)

Source: 203314: Module 2.7.4 SCS: Table 2-50 p.165

Withdrawals due to 'Withdrawal Criteria'

Between 1.1 and 4.2% of randomized individuals, in each of the six degludec once daily trials, were withdrawn due to meeting one or more of the predefined withdrawal criteria. The pooled data for these participants summarizing the frequency of withdrawals according to each predefined withdrawal criteria is shown below (see Table 27). The withdrawal criteria most frequently resulting in

withdrawals were 'Protocol deviation' and 'Hypoglycemia causing a safety problem.'

1.1% of subjects randomized to degludec and comparator were withdrawn due to protocol deviations. In the degludec arm the trials with the highest withdrawals due to protocol deviations were Trials **3586** (Asia) (3.5% versus 0.7% for degludec versus glargine) and **3668** (1.7% versus 0.9% for degludec flexible versus glargine).

In the comparator arm, protocol deviation was most frequently reported as a withdrawal criterion in Trial 3579 (1.3 versus 3.2% for degludec versus glargine). The frequency of withdrawal for the hypoglycemia criteria was balanced overall. Trial **3582** (Basal-bolus) showed the largest imbalance in withdrawals due to meeting the hypoglycemia withdrawal criterion [0.5% (n=4) versus 0.0% for degludec and glargine].

Table 32: Withdrawals Due To Withdrawal Criteria, Degludec, Type 2 DM

	Degludec N (%)	Comparator N (%)
	2716	1332
Pregnancy	2 (0.1)	0 (0.0)
Hypoglycemia causing a safety problem	9 (0.3)	4 (0.3)
Protocol deviation	29 (1.1)	14 (1.1)
Significant change in treatment	5 (0.2)	7 (0.5)
Lack of effect after 12-weeks	1 (0.0)	0 (0.0)
Donation of blood	1 (0.0)	0 (0.0)
Source: 203314: module 5.3.5.3: ISS: Appendix 6.2: Tables 7 and 8.		

Withdrawals due to Ineffective Therapy

Withdrawals due to ineffective therapy were reported across the following categories of withdrawal: reason for withdrawal, withdrawal criteria and the category other. **Table 33** shows withdrawal due to ineffective therapy across all categories. In the pool of patients with type 2 DM a similar small proportion of patients withdrew due to ineffective therapy in the degludec and comparator arm (0.8% versus 0.5%).

Table 33: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 2 DM

	Degludec N (%)	Comparator N (%)
	3173	1802
Ineffective therapy	18 (0.6)	9 (0.5)
Withdrawal Criterion 'lack of effect after 12 weeks'	1 (0.0)	0 (0.0)

Other	8 (0.3)	1 (0.1)
Adapted from Source: 203314; 2.7.4; SCS: Table 1-15		
Note: Greater total exposure reflects addition of three times per week trials 3718 and 3724		

7.3. Disposition Type 1 DM Trials Degludec/aspart Program

22% of individuals were found ineligible to participate at the screening visit because they did not meet one or more of the inclusion/exclusion criteria.

362 and 180 subjects with type 1 diabetes were exposed to Degludec/aspart and Comparator, respectively, in one Degludec/aspart trial. This trial contributed a cumulative exposure to Degludec/aspart and Comparator of 297 and 146 patient years respectively at the time of NDA filing²².

A high proportion of randomized subjects completed the first 26 weeks of the confirmatory type 1 DM trials (i.e., 87% and 86% in the Degludec/aspart and detemir arm respectively). The most frequent reason for withdrawal in both arms was the category "Other". No relationship between proportion of withdrawals and trial duration was seen²³.

Table 34: Subject Disposition, Type 1 DM trial NN5401-3594, Degludec/aspart Program

	Degludec/aspart N (%)	Detemir N (%)	Total N (%)
Screened			706
Screening Failure			158 (22.4)
Randomized	366 (100.0)	182 (100.0)	548 (100.0)
Exposed	362 (98.9)	180 (98.9)	542 (98.9)
Withdrawn	46 (12.6)	26 (14.3)	72 (13.1)
Reason for Withdrawal			
Adverse Event	4 (1.1)	3 (1.6)	7 (1.3)
Ineffective Therapy	2 (0.5)	0 (0)	2 (0.4)
Non-Compliance With Protocol	8 (2.2)	6 (3.3)	14 (2.6)
Withdrawal Criteria	7 (1.9)	5 (2.7)	12 (2.2)
Other	25 (6.8)	12 (6.6)	37 (6.8)
Completed Trial	320 (87.4)	156 (85.7)	476 (86.9)
Full Analysis Set	366 (100.0)	182 (100.0)	548 (100.0)
Per Protocol Analysis Set	336 (91.8)	168 (92.3)	504 (92.0)
Source Data: NDA 203313; module 2.7.3; SCE; Table 3-1			
N: Number of subjects; %: Proportion of randomized subjects; Ineffective Therapy: Either documented by HbA1c or undocumented and at investigator discretion.			

²² Source Data: 203313; 5.3.5.3: ISE: Appendix 6.2: Table 313.

²³ Source: NDA 203313; 5.3.5.1 report-body nn5401-3594 Figure 14.1.3

Reviewer Comment: In the Summary of Clinical Safety the sponsor analyzes disposition and reasons for withdrawal by pooling both the parent (3594) and extension trial (3645). Results are qualitatively similar to the parent trial (refer to Table 35). The analyses that follow include both parent and extension trial.

Table 35: Disposition, Type 1 DM trial, Parent (3594) and Extension trial (3645)

	Degludec/aspart N (%)	Detemir N (%)	Total N (%)
Screened			706
Screening Failure			158 (22.4)
Randomized	366 (100.0)	182 (100.0)	548 (100.0)
Exposed	362 (98.9)	180 (98.9)	542 (98.9)
Withdrawn	67 (18.3)	35 (19.2)	102 (18.6)
Reason for Withdrawal			
Adverse Event	7 (1.9)	3 (1.6)	10 (1.8)
Ineffective Therapy	2 (0.5)	0 (0)	2 (0.4)
Non-Compliance With Protocol	12 (3.3)	7 (3.8)	19 (3.5)
Withdrawal Criteria	9 (2.5)	6 (3.3)	15 (2.7)
Other	37 (10.1)	19 (10.4)	56 (10.2)
Completed Parent and Extension Trial	233 (63.7)	113 (62.1)	346 (63.1)
Completed Parent Trial (26-weeks) but Did Not Enter Extension	66 (18.0)	34 (18.7)	100 (18.2)
Entered Into Extension Trial	254 (69.4)	122 (67.0)	376 (68.6)

Source Data: NDA 203313; 2.7.4; SCS; Table 1-9
N: Number of subjects; %: Proportion of randomized subjects; Ineffective Therapy: Either documented by HbA1c or undocumented and at investigator discretion.

Withdrawals for reason 'Other'

The sponsor reviewed the cause of withdrawal for this category and categorized them in Table 36. The majority of subjects withdrew citing miscellaneous reasons which included: belief that the treatment was ineffective, unwillingness or inability to comply with protocol demands due to issues related to lifestyle. Another frequently cited reason in the category "other" was withdrawal of consent without providing explanation. Hypoglycemia was a reason more frequently given by participants treated with Degludec/aspart than those treated with detemir 4 (1.1%) versus 1 (0.6%).

Table 36: Withdrawals Events Classified as "Others", Type 1 DM, Degludec/aspart Parent and Extension Trial (N5401-3594/3645)

	Degludec N (%)	Comparator N (%)
	362	180

Randomized in Error	3 (0.8)	1 (0.6)
Withdrew consent	7 (1.9)	7 (3.9)
Lost to follow-up	3 (0.8)	4 (2.2)
Site Closure or Move	2 (0.8)	1 (0.6)
Lack of effect	3 (0.8)	1 (0.6)
Hypoglycemia	4 (1.1)	1 (0.6)
Safety other than hypoglycemia	1 (0.3)	2 (1.1)
Miscellaneous	14 (3.9)	2 (1.1)
Source: 203313: module 2.7.4; SCS; Table 1-10.		

Withdrawals for reason 'Adverse Events'

Seven (1.9%) and three (1.3%) subjects randomized to Degludec/aspart and Detemir, respectively, withdrew due to an adverse event. More withdrawals were due to serious adverse events in the Degludec/aspart (N=6) arm compared to the detemir arm (N=1). Four out of six events were related to hypoglycemia (discussed below).

Withdrawals due to Hypoglycemia

Hypoglycemia leading to withdrawal was reported across multiple withdrawal categories. Table 37 compares the proportion of individuals who withdrew for hypoglycemia across all categories of withdrawal in the single study examining Degludec/aspart in type 1 diabetes.

Withdrawals for hypoglycemia across all categories accounted for 3% and 2% of all withdrawals in the Degludec/aspart and detemir arm, respectively. In contrast to detemir, more withdrawals due to hypoglycemia in the Degludec/aspart arm were due to serious adverse events and safety reasons (i.e., 7 versus 3).

Table 37: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 1 DM Trials, Degludec/aspart Program

	Degludec/aspart N=362 N (%)	Detemir N=180 N (%)
Hypoglycemia SAE	5 (1.4)	0 (0.0)
Hypoglycemia non SAE	0 (0.0)	0 (0.0)
Hypoglycemia causing a safety problem withdrawal criteria	2 (0.6)	3 (1.7)
Hypoglycemia caterorized as "Other" reason for withdrawal	4 (1.1)	1 (0.6)
Source: 203313: module 2.7.4; SCS: Table 2-51 p.159		

In the Degludec/aspart group, most withdrawals due to serious adverse events (N=4) were related to hypoglycemia related preferred terms [(i.e., hypoglycemic unconsciousness (2 events), hypoglycemia (1 event), hypoglycemia seizure (1 event)]²⁴. No hypoglycemia related events led to withdrawal in the detemir group. One serious event of diabetic ketoacidosis led to withdrawal in the detemir group. Narratives for withdrawals due serious adverse events of hypoglycemia are provided below.

- **Trial NN5401-3594, Subject 103022, Hypoglycemia Unconsciousness:** The case describes a 62 year old female from Poland with a past medical history significant for type 1 DM since 2007 and hypothyroidism, hypercholesterolemia and hypertension. 39 days after the patient was randomized to Degludec/aspart she was hospitalized for a severe hypoglycemic episode (27 mg/dL) with loss of consciousness. The patient's Degludec/aspart dose was decreased. Four days after the initial event and while still in the hospital, she had another severe hypoglycemic episode (29 mg/dL). Degludec/aspart was discontinued. The patient was switched to Humalog and Humulin N. She experienced a third episode of severe hypoglycemia seven days after the initial event.
- **Trial NN5401-3594, Subject 107004, Hypoglycemia Unconsciousness:** The case describes a 40 year old female from Poland with type 1 DM arterial hypertension and depression who experienced four episodes of severe hypoglycemia 13, 15, 17 and 21 days after being randomized to Degludec/aspart. The fourth episode was associated with loss of consciousness and led to permanent discontinuation of the trial product.
- **Trial NN5401-3594, Subject 402001, Hypoglycemia Unconsciousness:** The case describes a 53 year old male from Denmark with type 1 DM (1968). The patient experienced two severe hypoglycemic episodes with altered consciousness 37 and 95 days after being randomized to Degludec/aspart and discontinued the trial.
- **Trial NN5401-3594, Subject 503007, Hypoglycemic Seizure:** The case describes a 30 year old female from the United Kingdom with type 1 DM (1998). The patient experienced two early morning (i.e., 6:30-7:00 am) hypoglycemic seizures 114 and 131 days after being randomized to Degludec/aspart and discontinued the trial.

Withdrawals for reason 'Withdrawal Criteria'

15 subjects (9 vs. 6 in Degludec/aspart vs. Detemir) were withdrawn because they met one of the protocol-defined withdrawal criteria. Hypoglycemia causing a

²⁴ Source: 233013: 5.3.5.3: ISS: Appendix 1.12. Table 7.

safety problem was more frequently reported in subjects randomized to detemir. Otherwise withdrawals in this category were balanced. These data are summarized in the table below by category.

Table 38: Withdrawals Due to Withdrawal Criteria, Type 1 DM, Degludec/aspart Parent and Extension Trial (N5401-3594/3645)

	Degludec N (%)	Detemir N (%)
	366	182
Pregnancy	2 (0.5)	1 (0.5)
Hypoglycemia causing a safety problem	2 (0.5)	3 (1.6)
Protocol deviation	0 (0.0)	2 (1.1)
Significant change in treatment	3 (0.8)	0 (0.0)
Lack of effect after 12-weeks	1 (0.3)	0 (0.0)
Donation of blood	1 (0.3)	0 (0.0)

Adapted from Source: 203313: module 5.3.5.3; ISS; Appendix 1.3: Table 14.

Withdrawals due to Ineffective Therapy

Withdrawals due to ineffective therapy could be reported across the following categories of withdrawal: reason for withdrawal, withdrawal criteria and the category other. Table 33 shows withdrawal due to ineffective therapy across all categories. In the pool of patients with type 1 DM a higher proportion of patients withdrew due to ineffective therapy in the Degludec/aspart arm [2.0% (n=7) versus 0.6% (n=1)].

Table 39: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 1 DM, Degludec/aspart Program

	Degludec/aspart N (%)	Detemir N (%)
	362	180
Category 'Ineffective therapy'	2 (0.6)	(0.0)
Withdrawal Criterion 'lack of effect'	1 (0.3)	0
Withdrawal Criterion 'lack of effect after 12 weeks'	1 (0.3)	0 (0.0)
Category 'Other'	3 (0.8)	1 (0.6)

Adapted from Source: 203313; 2.7.4; SCS: Table 1-11

7.4. Disposition Type-2 DM Trials Degludec/aspart Program

33% of the 2785 individuals screened to participate in the degludec/aspart program were ineligible. The most important reason for failing the screening visit was failure to meet one or more of the inclusion/exclusion criteria.

998 and 857 subjects with type 2 diabetes were exposed to Degludec/aspart and Comparator, respectively, in the four Degludec/aspart trials. These four trials contributed a cumulative exposure to Degludec/aspart and Comparator of 453 and 393 patient-years, respectively, at the time of NDA filing.²⁵

The proportion of randomized subjects who completed the four confirmatory type 2 DM trials was high and ranged from 85% to 88%. The completion rate for the pooled population of subjects with type 2 DM was 86% and was balanced between Degludec/aspart and comparator arms (shown in Table 40). The most frequent reason for withdrawal was the category "Other" (5.7%) followed by the category "Withdrawal Criteria" (4.1%). A slightly greater proportion of participants withdrew from the Degludec/aspart arm due to "Withdrawal Criteria" (discussed below). The proportion of subjects with T2DM discontinuing the trial due to other categories withdrawal was balanced between arms. No relationship between proportion of withdrawals and trial duration was seen in the six confirmatory type 2 DM trials (data not shown)²⁶.

Table 40: Subject Disposition, Pooled Type 2 DM Trials, Degludec/aspart Program

	Degludec/aspart N (%)	Comparator N (%)	Total N (%)
Screened			2785
Screening Failure			919 (33.0)
Randomized	1004 (100.0)	862 (100.0)	1866 (100.0)
Exposed	998 (99.4)	857 (99.4)	1855 (99.4)
Withdrawn	147 (14.6)	111 (12.9)	258 (13.8)
Adverse Event	18 (1.8)	13 (1.5)	31 (1.7)
Ineffective Therapy	9 (0.9)	6 (0.7)	15 (0.8)
Non-Compliance With Protocol	17 (1.7)	12 (1.4)	15 (0.8)
Withdrawal Criteria	45 (4.5)	31 (3.6)	76 (4.1)
Other	58 (5.8)	49 (5.7)	107 (5.7)
Completed	857 (85.4)	751 (87.1)	1608 (86.2)
Full Analysis Set	1000(99.6)	860 (99.8)	1860 (99.7)
Per Protocol Analysis Set	895 (89.1)	776 (90.0)	1671 (89.5)
Source Data: NDA 203313; 2.7.3; SCE; Table 3-2			

²⁵ Source Data: 203313; 5.3.5.3: ISE; Appendix 6.2: Table 314.

²⁶ Source Data: NDA 203313; 5.3.5.3 ISS; Appendix 1.3 Figure 19

Withdrawals for ‘Other’

Cases of withdrawal listed as “Others” for the pool of four trials performed in type 2 DM subjects were reviewed and manually categorized by the sponsor. Reasons for withdrawal in this subset of patients were matched. The proportion in each category was small. This is summarized below.

Table 41: Categorization of Withdrawal Events Classified as “Others”, Pooled Type 2 DM trials, Degludec/aspart Program

	Degludec/aspart N (%)	Comparator N (%)
	998	857
Randomized in Error	28 (2.8)	20 (2.3)
Withdrew consent	19 (1.9)	10 (1.2)
Lost to follow-up	1 (0.1)	5 (0.5)
Site Closure or Move	2 (0.2)	2 (0.2)
Lack of effect	1 (0.1)	0 (0.0)
Hypoglycemia	1 (0.1)	3 (0.4)
Safety other than hypoglycemia	1 (0.1)	1 (0.1)
Miscellaneous	5 (0.5)	9 (1.1)
Source: 203313: 2.7.4. SCS: Table 1-13		

Withdrawals due to ‘Adverse Events’

In the pool of four Degludec/aspart trials in patient with type 2 diabetes, no difference in the proportion of subjects who discontinued due to an adverse event was noted (1.8% versus 1.5%)²⁷. The rate of adverse events resulting in discontinuation was also similar (4.2 versus 4.3 events per 100 patient years). Most of the events leading to withdrawal in both arms were serious adverse events. The rates of serious adverse events leading to withdrawal were similar for Degludec/aspart and comparator (2.9 versus 3.1 events per 100 patient years). There was no clear imbalance between intervention arms with regards to type of events (See section for further discussion). Two participants discontinued due to a hypoglycemia related PT in the Degludec/aspart versus 1 in the comparator arm.

Withdrawals due to Hypoglycemia

Hypoglycemia leading to withdrawal was reported across multiple withdrawal categories. Table 42 compares hypoglycemia as a reason for withdrawal across all categories of withdrawal in the pool of studies examining Degludec/aspart in type 2 diabetes. The data shows that the proportions of participants with type 2 DM who withdrew due to hypoglycemia across all categories of withdrawal were

²⁷ Source 203313: 5.3.5.3: ISS: Appendix 1.12 Tables 9 and 10.

low and balanced between Degludec/aspart and comparators (0.8% versus 0.7%).

However, most events in the Degludec/aspart arm were either identified as serious or as causing a safety problem.

Table 42: Withdrawals Due To Hypoglycemia, Across All Categories Of Withdrawal, Pooled Type 2 DM Trials, Degludec/aspart Program

	Degludec/aspart N=998 N (%)	Comparator N=857 N (%)
Hypoglycemia SAE	2 (0.2)	1 (0.1)
Hypoglycemia non SAE	0 (0.0)	0 (0.0)
Hypoglycemia causing a safety problem withdrawal criteria	5 (0.5)	1 (0.1)
Hypoglycemia caterorized as "Other" reason for withdrawal	1 (0.1)	3 (0.4)
Source: 203313: 2.7.4 SCS: Table 2-53 p.164		

Withdrawals due to 'Withdrawal Criteria'

Forty four and 31 subjects with type 2 diabetes randomized to Degludec/aspart and Comparator, respectively, were withdrawn due to meeting one or more of the predefined withdrawal criteria (see **5.5.12** for criteria). The proportion of subjects withdrawn for each predefined withdrawal criteria is shown below (see Table 43). The withdrawal criterion most frequently resulting in withdrawals for both arms was 'Protocol deviation'. 'Hypoglycemia causing a safety problem' was a more frequent cause of withdrawal in the Degludec/aspart arm.

Table 43: Withdrawals Due To Withdrawal Criteria, Degludec/aspart, Type 2 DM

	Degludec/aspart N (%)	Comparator N (%)
	1000	860
Hypoglycemia causing a safety problem	5 (0.5)	1 (0.1)
Protocol deviation	35 (3.5)	25 (2.9)
Significant change in treatment	3 (0.3)	5 (0.6)
Lack of effect after 12-weeks	2 (0.2)	0 (0.0)
Adapted from 203313: Module 5.3.5.3: ISS: Appendix 1.3: Table 20.		

Withdrawals due to Ineffective Therapy

Withdrawals due to ineffective therapy were reported across the following categories of withdrawal: reason for withdrawal, withdrawal criteria and the category other. Table 44 shows withdrawal due to ineffective therapy across all categories. In the pool of patients with type 2 DM a higher proportion of patients withdrew due to ineffective therapy in the Degludec/aspart arm (1.2% versus 0.7%).

Table 44: Withdrawals Due To Ineffective Therapy, Across All Categories of Withdrawals, Type 2 DM

	Degludec/aspart N (%)	Comparator N (%)
	998	857
Ineffective therapy	9 (0.9)	6 (0.7)
Withdrawal Criterion 'lack of effect after 12 weeks'	2 (0.2)	0 (0.0)
Other	1 (0.3)	0 (0.0)

Adapted from: 203313; Module 2.7.4; SCS: Table 1-14

8. EFFICACY FINDINGS:

Refer to the statistical review package by Drs. Cynthia Liu and Dongmei Liu for FDA analyses and discussions of key efficacy findings. The sponsor's reported findings were generally consistent with FDA analyses and are shown below.

8.1. Primary Analyses

Table 45: Primary Efficacy Findings, Type 1 DM, Insulin Degludec Program

Study# (weeks)	Treatment Arms	n	Mean Baseline HbA1c (SD)	LSMean Change in HbA1c (SE)	Treatment Difference (95% Confidence Interval)	Mean Total Daily Basal Insulin* in U/kg (SD)	Mean Total Daily Prandial* Insulin in U/kg (SD)
Basal Insulin Once Daily and Prandial Insulin with Meals							
3583 (52)	Degludec	472	7.69 (0.9)	-0.36 (0.05)	-0.01 (-0.14; 0.11)	0.35 (0.18)	0.40 (0.24)
	Glargine	157	7.72 (1.0)	-0.34 (0.07)		0.39 (0.19)	0.44 (0.27)
3585 (26)	Degludec	302	7.98 (1.0)	-0.71 (0.06)	-0.09 (-0.23; 0.05)	0.36 (0.19)	0.54 (0.40)
	Detemir	153	7.99 (0.9)	-0.61 (0.07)		0.41 (0.25)	0.63 (0.38)
3770 (26)	Degludec FF	164	7.69 (1.0)	-0.40 (0.05)	0.17 (0.04; 0.30) [‡] 0.01 (-0.13; 0.14) [#]	0.42 (0.25)	0.35 (0.15)
	Degludec OD	165	7.70 (0.9)	-0.41 (0.05)		0.38 (0.23)	0.33 (0.23)
	Glargine	164	7.73 (0.9)	-0.57 (0.05)		0.42 (0.23)	0.42 (0.46)

Adapted from NDA 203314; Clinical Summary of efficacy; module 2.7.3; Tables 3-12 and 3-13 and Tables 14.2.10 (or 9) and 14.2.22 of individual study reports (section 5.3.5.1)

Analysis performed on full analysis set using LOCF to impute missing data. Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline HbA1c and age as covariates in the model. LSMean; model-based adjusted mean change in HbA1c from baseline (i.e., $\Delta\text{HbA1c} = \text{end of trial} - \text{baseline}$).

*Insulin doses were derived from the safety data set at end of treatment with LOCF to impute missing data.

[‡] Degludec flexible dosing interval (FF) versus Glargine once daily (primary objective).

Degludec flexible dosing interval (FF) versus Degludec once daily

Table 46: Primary Efficacy Findings, Type 2 DM, Insulin Degludec Program

Study# (weeks)	Treatment Arms	n	Mean Baseline HbA1c (SD)	LSMean Change in HbA1c (SE)	Treatment Difference (95% Confidence Interval)	Mean Total Daily Basal Insulin* in U/kg (SD)	Mean Total Daily Prandial* Insulin in U/kg (SD)
Basal Insulin Once Daily and Prandial Insulin with Meals, added to OADs							
3582 (52)	Degludec	744	8.27 (0.8)	-1.10 (0.06)	0.08 (-0.05; 0.21)	0.75 (0.43)	0.72 (0.58)
	Glargine	248	8.36 (0.9)	-1.18 (0.08)		0.69 (0.40)	0.74 (0.58)
Basal Insulin, Once Daily, Added to Combination of OADs							
3579 (52)	Degludec	773	8.16 (0.8)	-1.06 (0.04)	0.09 (-0.04; 0.22)	0.59 (0.35)	--
	Glargine	257	8.21 (0.8)	-1.15 (0.06)		0.60 (0.32)	--
3672 (26)	Degludec _{U200}	228	8.29 (1.0)	-1.18 (0.09)	0.04 (-0.11; 0.19)	0.62 (0.32)	--
	Glargine	229	8.24 (0.9)	-1.22 (0.08)		0.66 (0.30)	--
3586 (26)	Degludec	289	8.45 (0.8)	-1.42 (0.06)	0.11 (-0.03; 0.24)	0.28 (0.17)	--
	Glargine	146	8.46 (0.8)	-1.52 (0.07)		0.35 (0.23)	--
3580 (26)	Degludec	225	8.77 (1.0)	-1.52 (0.07)	-0.43 (-0.61; -0.24)	0.50 (0.30)	--
	Sitagliptin	222	8.97 (1.0)	-1.09 (0.10)		--	--
3668 (26)	Degludec FF	229	8.50 (1.0)	-1.17 (0.08)	0.04 (-0.12; 0.20) [‡]	0.55 (0.34)	--
	Degludec OD	228	8.38 (1.0)	-1.03 (0.08)	-0.13 (-0.29; 0.03) [#]	0.52 (0.31)	--
	Glargine	230	8.41 (0.9)	-1.21 (0.08)		0.52 (0.25)	--
Adapted from NDA 203314; Clinical Summary of efficacy; module 2.7.3; Tables 3-14 and 3-15 and Tables 14.2.10 of individual study reports (section 5.3.5.1) Analysis performed on full analysis set using LOCF to impute missing data. Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline HbA1c and age as covariates in the model. LSMean; model-based adjusted mean change in HbA1c from baseline (i.e., ΔHbA1c = end of trial – baseline). *Insulin doses were derived from the safety data set at end of treatment with LOCF to impute missing data. Mean and median insulin dose values were similar (difference between mean and median was in most instances < 0.10) in all trials with mean values being slightly larger. ‡ Degludec flexible dosing interval (FF) versus Glargine once daily (primary objective). # Degludec flexible dosing interval (FF) versus Degludec once daily							

Table 47: Primary Efficacy Findings, Type 1 and 2 DM, Degludec/aspart Program

Study# (weeks)	Treatment Arms	n	Mean Baseline HbA1c (SD)	LSMean Change in HbA1c (SE)	Treatment Difference (95% Confidence Interval)	Mean Total Daily Basal ^Δ Insulin* in U/kg (SD)	Mean Total Daily Prandial* Insulin in U/kg (SD)
Premix or Basal Insulin Once Daily, Prandial [‡] Insulin with Meals, Type 1 DM							
3594 (26)	IDegAsp OD	366	8.30 (0.8)	-0.75 (0.06)	-0.05 (0.18; 0.08)	0.37 (0.16)	0.49 (0.29)
	Detemir OD	182	8.28 (0.7)	-0.70 (0.08)		0.46 (0.23)	0.54 (0.42)
Premix or Basal Insulin Once Daily, Added to Combination of OADs, Type 2 DM							
3590 (26)	IDegAsp OD	266	8.86 (1.0)	-1.72 (0.08)	0.03 [-0.14; 0.20]	0.75 (0.39)	--
	Glargine OD	263	8.91 (0.9)	-1.75 (0.03)		0.67 (0.33)	--

3593 (26)	IDegAsp OD	230	8.29 (0.8)	-1.00 (0.08)	-0.03 [-0.20; 0.14]	0.69 (0.34)	--
	Glargine OD	233	8.36 (1.0)	-0.97 (0.08)		0.69 (0.36)	--
Premix or Basal Twice Daily, Added to Combination of OADs, Type 2 DM							
3592 (26)	IDegAsp BID	224	8.33 (0.8)	-1.31 (0.09)	-0.03 [-0.18; 0.13]	1.08 (0.53)	--
	BIAsp 30 BID	222	8.40 (0.9)	-1.29 (0.10)		1.20 (0.57)	--
3597 (26)	IDegAsp BID	280	8.45 (0.8)	-1.39 (0.05)	0.05 [-0.10; 0.20]	0.79 (0.48)	--
	BIAsp 30 BID	142	8.44 (0.9)	-1.44 (0.10)		0.99 (0.61)	--
Adapted from NDA 203313; Clinical Summary of efficacy; module 2.7.3; Tables 3-13 to and 3-16 and Tables 14.2.10 of individual study reports (section 5.3.5.1) Analysis performed on full analysis set using LOCF to impute missing data. Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline HbA1c and age as covariates in the model. LSMean; model-based adjusted mean change in HbA1c from baseline (i.e., $\Delta\text{HbA1c} = \text{end of trial} - \text{baseline}$). *Insulin doses were derived from the safety data set at end of treatment with LOCF to impute missing data. Mean and median values insulin dose were similar (difference between mean and median was in most instances < 0.10 for type 2 DM and 0.05 U/kg for type 1 DM) in all trials with mean values being slightly larger. Δ Basal refers to DegAsp in all trials except 3594 where DegAsp units shown are actually basal degludec component units only. Aspart component are shown in total daily prandial units column. ‡ Degludec flexible dosing interval (FF) versus Glargine once daily (primary objective). # Degludec flexible dosing interval (FF) versus Degludec once daily							

8.2. Secondary Analyses: Weight Change

Table 48: Change in Body Weight (Kg), Type 1 DM, Degludec Program

Study# (weeks)	Treatment Arms	n	Mean Baseline Weight (SD)	LS Mean Change in Weight (SE)	Treatment Difference (95% Confidence Interval)
Basal Insulin Once Daily and Prandial Insulin with Meals					
3583 (52)	Degludec	472	79.0 (14.3)	2.14 (0.30)	0.18 [-0.54; 0.91]
	Glargine	157	78.3 (16.2)	1.95 (0.40)	
3585 (26)	Degludec	302	66.5 (14.9)	1.50 (0.20)	1.08 [0.58; 1.57]
	Detemir	153	66.7 (13.4)	0.42 (0.24)	
3770 (26)	Degludec FF	164	81.7 (15.5)	1.26 (0.26)	0.33 [-0.38; 1.03] # -0.44 [-1.14; 0.27] ‡
	Degludec OD	165	79.6 (15.5)	0.93 (0.26)	
	Glargine	164	80.4 (15.6)	1.70 (0.26)	

Adapted from NDA 203314; module 5.3.5.3 Tables; 336 and 337
LSMean; model-based adjusted mean change in weight from baseline to end of treatment in full analysis set using LOCF for missing values (i.e., change in weight = end of trial – baseline).
Treatment difference=IDeg-Comparator
Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline weight and age as covariates in the model.
‡ Degludec flexible dosing interval (FF) versus Glargine once daily (primary objective).
Deagludec flexible dosing interval (FF) versus Deagludec once daily

Table 49: Change in Body Weight (Kg), Type 2 DM, Degludec Program

Study# (weeks)	Treatment Arms	n	Mean Baseline Weight (SD)	LS Mean Change in Weight (SE)	Treatment Difference (95% Confidence Interval)
Basal Insulin Once Daily and Prandial Insulin with Meals, added to OADs					
3582 (52)	Degludec	744	92.6 (17.9)	3.23 (0.33)	-0.31 [-0.98; 0.37]
	Glargine	248	92.2 (17.2)	3.54 (0.41)	
Basal Insulin, Once Daily, Added to Combination of OADs					
3579 (52)	Degludec	773	89.4 (17.7)	2.57 (0.17)	0.28 [-0.32; 0.88]
	Glargine	257	91.8 (15.8)	2.29 (0.27)	
3672 (26)	Degludec _{U200}	228	92.2 (18.5)	2.30 (0.36)	0.44 [-0.20; 1.08]
	Glargine	229	92.7 (18.4)	1.86 (0.35)	
3586 (26)	Degludec	289	64.9 (11.5)	1.54 (0.17)	-0.17 [-0.59; 0.26]
	Glargine	146	67.4 (11.6)	1.71 (0.21)	
3580 (26)	Degludec	225	83.9 (19.3)	2.71 (0.44)	2.75 [1.97; 3.54]
	Sitagliptin	222	86.1 (19.8)	-0.05 (0.43)	
3668 (26)	Degludec FF	229	81.4 (16.2)	1.86 (0.27)	-0.00 [-0.53; 0.52]
	Degludec OD	228	81.7 (17.1)	1.59 (0.26)	
	Glargine	230	82.0 (16.5)	1.86 (0.25)	

Adapted from NDA 203314; module 5.3.5.3 Tables; 339-343
LSMean; model-based adjusted mean change in weight from baseline to end of treatment in full analysis set using LOCF for missing values (i.e., change in weight = end of trial – baseline).
Treatment difference=IDeg-Comparator
Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline weight and age as covariates in the model.
‡ Degludec flexible dosing interval (FF) versus Glargine once daily (primary objective).
Degludec flexible dosing interval (FF) versus Degludec once daily

Table 50: Body Weight Changes, Type 1 and 2 DM, Degludec/Aspart

Study# (weeks)	Treatment Arms	n	Mean Baseline Weight (SD)	LS Mean Change in Weight (SE)	Treatment Difference (95% Confidence Interval)
Premix or Basal Insulin Once Daily, Prandial Insulin with Meals, Type 1 DM					
3594 (26)	IDegAsp OD	366	76.7 (14.6)	2.7 (0.32)	1.04 (0.38; 1.69)
	Detemir OD	182	76.0 (14.0)	1.7 (0.42)	
Premix or Basal Insulin Once Daily, Added to Combination of OADs, Type 2 DM					
3590 (26)	IDegAsp OD	266	85.0 (17.9)	2.9 (0.28)	1.31 [0.72; 1.89]
	Glargine OD	263	85.1 (18.6)	1.6 (0.26)	
3593 (26)	IDegAsp OD	230	84.7 (19.9)	1.7 (0.24)	0.33 [-0.17; 0.83]
	Glargine OD	233	83.9 (19.2)	1.4 (0.23)	
Premix or Basal Twice Daily, Added to Combination of OADs, Type 2 DM					
3592 (26)	IDegAsp BID	224	81.5 (18.1)	2.2 (0.31)	-0.62 [-1.15; -0.10]
	BIAsp 30 BID	222	78.9 (17.6)	2.8 (0.33)	
3597 (26)	IDegAsp BID	280	66.1 (11.2)	1.3 (0.19)	-0.38 [-0.96; 0.21]
	BIAsp 30 BID	142	66.0 (11.2)	1.7 (0.25)	

Adapted from NDA 203313; module 5.3.5.3; Appendix 6.2 Tables 220-221 and 223-224.
LSMean; model-based adjusted mean change in weight from baseline to end of treatment in full analysis set using LOCF for missing values (i.e., change in weight = end of trial – baseline).

Treatment difference=IDeg-Comparator
Treatment difference analyzed by ANCOVA with treatment assignment, anti-diabetic therapy at screening regions and sex, used as fixed factors and baseline weight and age as covariates in the model.

9. RELIABILITY AND GENERALIZABILITY OF THE HYPOGLYCEMIA DERIVED DATA

Reviewer Comment: The sponsor performed several pre-specified secondary analyses of hypoglycemia data in individual trials in the degludec and degludec/aspart program and a pre-planned meta-analysis to compare the risk of “confirmed hypoglycemic events” between insulin degludec and insulin glargine. The results of these analyses are reviewed in the background documents by Drs. Andraca-Carrera and Cynthia Iiu. In the next section of this background package I summarize factors that could impact the reliability and generalizability of the trial-derived hypoglycemia data to the actual clinical use of degludec. These factors should be considered in assessing whether the data support a comparative claim of benefit of degludec over comparators with respect to a reduced hypoglycemic risk.

Clinically meaningful hypoglycemia has been identified as a barrier to achievement of good glycemic control. A novel insulin preparation that offers a comparative advantage in terms of hypoglycemic risk over existing insulins should theoretically allow individuals to achieve a superior level of glycemic control compared to one that does not. In trials comparing two products, subjects randomized to such therapy could in theory be more likely to achieve glycemic goals.

Clinically meaningful hypoglycemic episodes, can be defined as those episodes that lead to either immediate (i.e., life-threatening) or future (i.e., predisposes to future and/or recurrent hypoglycemia) adverse clinical outcomes.

It is difficult to capture all clinically meaningful hypoglycemic episodes in large clinical trials because neither biochemical evidence of a low blood glucose alone nor symptoms alone are specific. The lack of specificity results from the fact that blood glucose measurements can be falsely low for any number of reasons (see below) and that many clinical conditions, other than hypoglycemia, mimic the clinical presentation of this disorder.

To address this lack of specificity, the ADA workgroup²⁸ has proposed several definitions of hypoglycemia for use in clinical trials. The most specific but least sensitive of these definitions is the definition for “severe hypoglycemia”. “Severe hypoglycemia” captures episodes characterized by the presence of life-threatening neuroglycopenic symptoms and by the inability of the affected individual to self-treat. For all episodes that do not fall in this category, the ADA

²⁸ Diabetes Care, Volume 28, Number 5, May 2005

workgroup recommends defining events based on both biochemistry (i.e., < 70 mg/dL) and symptoms (i.e., 'documented symptomatic hypoglycemia'). The magnitude of the reduction that would be considered clinically meaningful differs according to the definition used. The ADA workgroup proposes that an agent that reduces 'severe' and 'symptomatic hypoglycemia' by 10 and 30% respectively would be clinically meaningful.

9.1. Issues related to the design of phase 3 trials:

Specific exclusion of patients at most risk: Patients with hypoglycemia unawareness and patient with frequent hypoglycemic episodes were excluded from the confirmatory trials. Lack of information on the most susceptible individuals limits generalizability of the findings.

Open-label nature of trials: This may have influenced capture/reporting of events, patient/investigator behavior and have introduced bias.

Completeness of data capture: Hypoglycemia was captured by patients at the point of care. Completeness of data capture is uncertain (e.g., in type 2 trials up to 40% of patients reported no events at all). Reliability of the estimate assumes that all patients with clinically meaningful hypoglycemia at some point in the trial: recognized the event, self-measured blood glucose, accurately recorded blood glucose in their diaries, reported this information to the investigator, who in turn transmitted this information to the sponsor. In the clinical setting, blood glucose in the hypoglycemic range that is not associated with symptoms would go unnoticed (this is more likely to occur at night). Alternatively, a patient may self-treat at the appearance of symptoms, which may or may not be related to hypoglycemia, before checking blood glucose. **(See issues related to endpoints)**

Familiarity with comparator product: A large proportion of participants in the comparator arm were familiar with the comparator product(s). This may have influenced use behavior and/or capture/reporting behavior and have introduced bias.

Influence of different timing of injections: Timing of injections between degludec and comparators differed. This may have biased the timing of hypoglycemic events to specific time periods during the day (i.e., nocturnal versus other) based on the different pharmacokinetic and pharmacodynamic profiles of the investigational and comparator insulins (see below).

Primary analysis: The pre-specified primary analysis for all trials except 3580 was to test non-inferiority between degludec and comparators based on HbA1c. Non-inferiority is not equivalence. A product can be declared non-inferior but still afford slightly worst glucose control than comparator. The point estimate in clinical trials involving type 2 DM was to the left of unity suggesting a slightly worst outcome for degludec-treated patients. The magnitude of the observed

difference was not unacceptably worst (i.e., the upper bound of the 95% CI was contained within the pre-specified non-inferiority margin).

9.2. Issues related to endpoints selected for analyses

Novo Nordisk ‘Confirmed Hypoglycemia’: The definition for the endpoint ‘Novo confirmed hypoglycemia’ used in hypoglycemia analyses did not require the presence of contemporaneous hypoglycemic symptoms. The endpoint ‘Novo confirmed hypoglycemia’ represents all hypoglycemic events that were considered serious + all recorded self monitored blood glucose of ≤ 56 mg/dL regardless of symptoms or other considerations (i.e., timing in relation to meals).

The analytical accuracy of point of care devices in the clinical setting can be affected by multiple factors (discussed below) and definitions that include symptoms are regarded as more specific. The sponsor was asked to perform sensitivity analyses using the ADA definition for ‘documented symptomatic hypoglycemia’ which relies on both biochemical evidence of a low blood glucose (e.g., < 70 mg/dL) and the presence of clinical symptoms.

Sensitivity analyses are important to gauge the clinical relevance of the observed findings. The clinical relevance of an observed effect suggesting a comparative advantage for one drug over another would be difficult to interpret in a scenario where:

- No advantage was seen for severe hypoglycemic events
- The advantage seen using a less specific definition was not consistent across other less specific definitions (i.e., Novo Confirmed definition versus ADA documented symptomatic definition).

‘Nocturnal’ Hypoglycemia: The sponsor had prospectively defined ‘nocturnal hypoglycemia’ as events of ‘Novo confirmed hypoglycemia’ occurring between 00:01 and 05:59 am across Phase 3 trials. In a Phase 2 trial (e.g., **NN5401-1792**) the sponsor had defined nocturnal hypoglycemia as events occurring between 23:00-05:59. This illustrates that from a clinical science perspective there is no accepted definition of “nocturnal” per se.

In head-to-head, open-label comparisons, an observation of a reduced number of hypoglycemic events for a specific bracket of time during a 24-hour period could be a true finding or could be an artifact reflecting differences related to: timing of injection (e.g., time to reach maximal effect of degludec at steady state is ~ 12 hours and 4 hours for glargine in T1DM see Figure 1), missing data, and or familiarity with comparator product rather than a true benefit. The applicant was asked to test the robustness of the observed significant difference for the ‘nocturnal period’ by testing the remainder of the day alone, or changing the bracket by ± 2 hours.

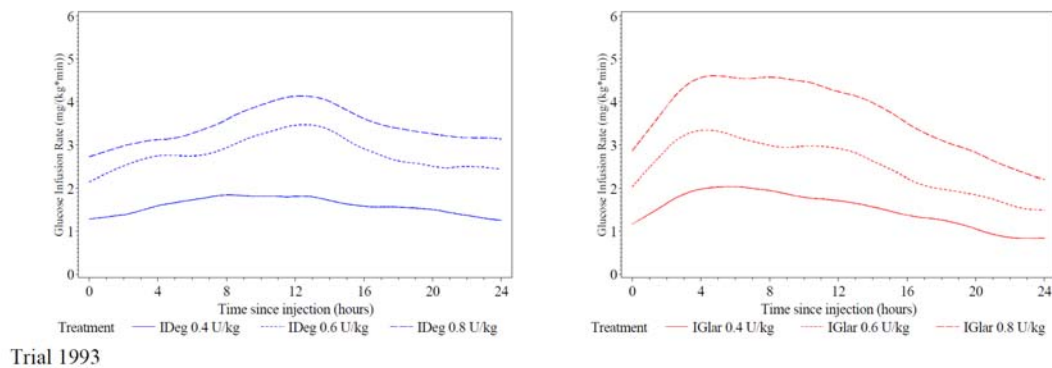


Figure 2: Mean Glucose Infusion Rate Over 24 Hours At Steady State in Type 1 DM Subjects Treated with Degludec Insulin and Glargine Insulin (Source: NDA 203314; Module 2.7.2; Figure 3-35).

A reduction in nocturnal episodes absent a demonstrated reduction in total episodes over the entire 24-hour period is problematic to interpret. Patients are less likely to check their blood glucose while sleeping and completeness of data capture in this setting is even more uncertain. For example, results for the nocturnal time period in the degludec arm of trial 3583 are based on about 1/10th the number of confirmed events those for the 24-hour time period (refer to **Table 51** and **Table 53**).

Incidence rate versus event rate: The sponsor presents analyses using event rates (total number of events per 100 patient-year of exposure). Since event rate differences could be driven by a few individuals contributing a lot of events, the applicant was recommended to confirm findings based on event rates by also examining incidence rates (i.e., number of patients with at least one event per 100 patient year of exposure).

9.3. Issues related to analytical accuracy of point of care glucose meter devices.

Point-of-care glucose meter devices can lack accuracy in the clinical setting increasing the likelihood that observed differences between groups based on a dichotomous endpoint (i.e., presence or absence of a hypoglycemic event based on crossing a glucose threshold) may be due to chance.

Analytical accuracy: Analytical accuracy of glucose meter device is usually defined in terms of closeness of agreement between a glucose meter derived value and a clinical laboratory reference method (i.e., YSI glucose analyzer method). In the US, a device could be approved if 95% of all device measured values fall within +/- 15 mg/dL of the reference method measured values when the true glucose concentration is ≤ 75 mg/dL. This means that a point of care glucose meter-derived value of 55 mg/dL, could reflect a laboratory measured glucose value of 40 mg/dL (i.e., severe hypoglycemia) or 70 mg/dL (i.e., low normal fasting glucose) and still be considered “analytically” accurate.

Analytical accuracy in the clinical setting: Accuracy is expected to be worst in the clinical outpatient setting.

There are many factors in the clinical setting which could worsen further analytical accuracy of point of care glucose meter devices. These can be categorized into environmental (e.g., air exposure of strips, altitude, humidity, temperature), physiologic (e.g., hematocrit, prandial state, hyperlipidemia, oxygenation and pH), operational (e.g., hemolysis, anticoagulants, improper calibration, defective or wrong strips, reuse of strips), and drug (e.g., maltose, acetaminophen, ascorbate, mannitol, dopamine) related factors. These factors are hard to capture and their influence hard to quantify in large clinical trials.

The precision Xtra® meter used in all trials, for example, requires that patient perform calibration with each new box of strips²⁹. If this was not consistently done accuracy could have been affected. Another example of an event potentially affecting the quality of data derived from patients concerns a recall in December 2010 by Abbott inc. for certain lots of precision Xtra® glucose test strips due to an error potentially causing falsely low readings. Potentially defective strips were used at some US sites in trials # 3583, 3672, 3770 and 3889 but according to the sponsor the likelihood that data quality was impacted is low.

9.4. Issues related to pooling multiple trials for the purpose of a meta-analysis of hypoglycemia data.

On October 8th 2010 the Agency communicated, via responses to a meeting request, concerns regarding the poolability of the data Novo Nordisk planned to use for their hypoglycemia meta-analysis. The Agency stated that it was unlikely that we would allow the sponsor to label results for such an analysis given the trial design issues highlighted above and reservations related to the poolability of the data. The applicant was told that a final decision regarding labeling would not be made until after review of the data.

Hypoglycemia data were pooled from trials with a heterogeneous patient population. Heterogeneity stemmed from differences in: the type of disease studied (i.e., Type 1 DM versus Type 2 DM), the stage of disease (advanced versus early) and geographical location of study participants (i.e., in some trials participants were recruited predominantly from North America and Europe, in other trials participants were recruited exclusively in Asia). In addition, differences in terms of concomitant therapies used for glucose control and concomitant diseases at baseline are expected to result in heterogeneity within pooled data. In the sponsor's meta-analysis of hypoglycemia, data from trials using insulin comparators other than glargine (i.e., detemir) are excluded.

²⁹ <https://www.abbottdiabetescare.com/products/patient/pxtra-overview/pxtra-owners-guide.html>

10. HYPOGLYCEMIA

Refer to background documents by Drs. Cynthia Liu, Dongmei Liu and Andraca-Carrera for statistical analyses of hypoglycemia data. This section summarizes the descriptive data for hypoglycemia for each trial. The descriptive data show a lack of consistency across trials, across hypoglycemia definitions, across time period considered and across comparators and do not suggest an advantage of degludec over comparator for the risk of hypoglycemia.

10.1. Capture of Hypoglycemia

Hypoglycemic episodes were considered treatment emergent from randomization to seven days after the last dose of the randomized trial product.

These data were obtained from patient diaries and transferred at site visits and telephone contacts into the electronic case report form by investigators. Data in diaries could be derived from glucose meter devices or continuous glucose monitoring systems provided these were entered in the patient diary.

Reviewer Note: CGMS devices are even less accurate than glucose meter devices.

10.2. Definitions of Hypoglycemia

Statistical analyses were based on “**confirmed**” **hypoglycemic episodes** and **nocturnal episodes**.

A “**confirmed**” **hypoglycemic episode** was defined as sum of episodes qualifying as either severe hypoglycemic episodes or as Novo Nordisk minor hypoglycemic episodes.

1. Severe hypoglycemic episode: An episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions
2. Novo Nordisk minor hypoglycemic episode: An episode not requiring third party assistance where a plasma glucose < 56 mg/dl or whole blood glucose < 50 mg/dl was recorded (i.e., with or without presence of hypoglycemic symptoms).

A nocturnal episode was defined as a “confirmed” episode occurring between 00:01 and 05:59am.

Documented symptomatic hypoglycemia was another definition used in descriptive analyses which describes an episode of hypoglycemia during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration of ≤ 70 mg/dl.

10.3. Hypoglycemia Descriptive Data: Degludec Program

Table 51: Hypoglycemia, Type 1 DM, Degludec Program, Across Definitions

Study# (weeks)	Treatment Arms	N	ADA Severe			ADA Documented Symptomatic			Novo Nordisk Confirmed		
			n (%)	Event	Event Rate	n (%)	Event	Event Rate	n (%)	Event	Event Rate
3583 (52)	Degludec	472	58 (12.3)	90	21	450 (95.3)	25517	5902	451 (95.6)	18389	4254
	Glargine	154	16 (10.4)	23	16	151 (98.1)	8155	5653	147 (95.5)	5796	4018
3585 (26)	Degludec	301	32 (10.6)	45	31	286 (95.0)	10116	6948	280 (93.0)	6673	4583
	Detemir	152	16 (10.5)	28	39	143 (94.1)	4503	6244	139 (91.4)	3295	4569
3770 (26)	Degludec FF	164	17 (10.4)	25	34	154 (93.9)	7471	10277	154 (93.9)	5988	8238
	Degludec OD	165	21 (12.7)	28	37	161 (97.6)	9467	12425	164 (99.4)	6724	8825
	Glargine	162	16 (9.9)	37	47	153 (95.0)	7964	10139	156 (96.9)	6263	7973
<p>Source 203314: module 5.3.5.3: ISE: Appendix 6.2 Table 260 Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure <u>Definitions:</u> ADA Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions ADA Documented Symptomatic: Episode associated with both symptoms of hypoglycemia and a documented blood glucose < 70 mg/dL Novo Nordisk Confirmed: The sum of ADA severe and episodes where blood glucose < 56 mg/dL was recorded (i.e., with or without symptoms)</p>											

Table **51** summarizes the results for hypoglycemia at any time of the day across the three pivotal type 1 DM trials for three definitions of hypoglycemia (**ADA Severe**, **ADA Documented Symptomatic**, **Novo Nordisk Confirmed**).

Overall the descriptive data do not suggest a clear benefit or harm of degludec over comparators for hypoglycemia in type 1 diabetes. Consistent findings related to hypoglycemia for degludec over comparator are lacking between trials, between endpoints (i.e., proportion versus event count) and across definitions used.

10.3.1. Severe Hypoglycemia Type 1 DM

The proportion (%) of study participants randomized to degludec who experienced at least one protocol defined **ADA severe** hypoglycemic event was slightly but consistently greater compared to control across all trials (degludec – comparator difference: 1.9%, 0.1%, 2.8% in trials **3583**, **3585** (no US sites) and **3770** respectively).

Proportions were consistent with event rates for **ADA severe** hypoglycemia except in the detemir arm in trial **3585** and glargine arm in trial **3770**. The observed difference is accounted for by the occurrence of a higher number of events in these two arms compared to the rest (1.8 and 2.3 events per individuals respectively versus < 1.6 for all other intervention arms).

Hypoglycemia reported as a serious adverse event³⁰ across the entire degludec type 1 DM program is shown in Table 52 by system organ class and preferred term. 58 patients experienced at least one serious adverse event related to hypoglycemia on degludec (7.99 incident cases per 100 patient years) and 22 on comparators (7.46 incident cases per 100 patient years). Event rates were similar between groups.

Note: In the fixed flexible arm of 3770 there were 11 serious adverse events related to hypoglycemia ‘preferred-terms’ versus 6 in the degludec once daily arm and 8 in the glargine once daily arm (Source: 203314: 5.3.5.1: Report Body nn1250-3770: Table 12-12).

10.3.2. Hypoglycemia Broad Definitions Type 1 DM

Greater than 90% of participants had at least one event which met the protocol definition of an **ADA Documented Symptomatic** or a **Novo Nordisk Confirmed Event**. In trial **3583** the direction of the findings (i.e., not favoring degludec) was consistent across all three definitions. This was not the case for trials **3585** (no US sites) and **3770**. In these trials the event rate for **ADA Severe** hypoglycemia was not consistent with event rates for the two, broader, less specific definitions. Event rates

³⁰ Serious adverse event is an event that results in death, is life-threatening, results in permanent damage or disability, results in congenital anomaly or requires medical/surgical intervention to prevent permanent impairment.

between **ADA Documented Symptomatic** and **Novo Nordisk Confirmed** definitions were consistent (i.e., same general direction). Rate ratios ($\text{Event Rate}_{\text{Degludec}} / \text{Event Rate}_{\text{Comparator}}$) using the **Novo Nordisk Confirmed** definition were more favorable than rate ratios using **ADA Documented Symptomatic** episodes (i.e., 1.06, 1.00, 1.10 versus 1.04, 1.11, 1.23 for **Novo Nordisk Confirmed** versus **ADA Documented Symptomatic** in trials 3583, 3585 and 3770 respectively).

Table 52: Hypoglycemia Reported as Serious Adverse Events, Type 1 DM, Degludec

	Degludec			Comparator		
Safety Analysis Set (N)	1102			467		
Total Exposure (yrs)	726.8			294.9		
	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Metabolism and Nutrition SOC						
Hypoglycemia	32 (2.9)	40	5.5	12 (2.6)	16	5.4
Hypoglycemia Unconsciousness	20 (1.8)	22	3.0	8 (1.7)	8	2.7
Hypoglycemia Seizure	1 (0.1)	1	0.1	2 (0.4)	2	0.7
Nervous System Disorders SOC						
Hypoglycemic Coma	5 (0.5)	5	(0.7)	0 (0.0)		
All Hypoglycemia Related Preferred Terms						
Serious Adverse Event Related To Hypoglycemia		63	8.7		26	8.8
Adapted From: 203314: module 5.3.5.3: SCE: Table 2-11. Discreet events across preferred terms and SOCs were added to derive "Serious adverse event related to hypoglycemia" Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure						

Table 53: Novo Nordisk Nocturnal Hypoglycemia, Type 1 DM, Degludec Program, Across Definitions

			Nocturnal ADA Severe			Nocturnal ADA Documented Symptomatic			Nocturnal Novo Nordisk Confirmed		
Study# (weeks)	Treatment Arms	N	n (%)	Event	Event Rate	n (%)	Event	Event Rate	n (%)	Event	Event Rate
3583 (52)	Degludec	472	18 (3.8)	23	5.2	341 (72.2)	2553	591	341 (72.2)	1905	441
	Glargine	154	3 (1.9)	3	2.1	114 (74)	1062	736	114 (74.4)	845	586
3585 (26)	Degludec	301	12 (4.0)	12	8.9	182 (60.5)	900	618	176 (58.5)	603	414
	Detemir	152	5 (3.3)	6	8.3	93 (61.2)	561	779	89 (58.6)	428	594
3770 (26)	Degludec FF	161	5 (3.0)	5	6.9	106 (64.9)	537	739	111 (67.7)	453	623
	Degludec OD	164	5 (3.0)	5	6.6	115 (69.7)	910	1194	121 (73.2)	732	961
	Glargine	162	5 (3.1)	13	16.6	114 (70.8)	843	1073	117 (72.7)	782	996
<p>Source 203314: module 5.3.5.3: ISE: Appendix 6.2 Table 264 Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure Nocturnal period: Defined as the time period between 00:01 and 5:59 AM inclusive. ADA Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions ADA Documented Symptomatic: Episode associated with both symptoms of hypoglycemia and a documented blood glucose < 70 mg/dL Novo Nordisk Confirmed: The sum of ADA severe and episodes where blood glucose < 56 mg/dL was recorded (i.e., with or without symptoms)</p>											

10.3.3. Nocturnal Hypoglycemia Type 1 DM Degludec Program

Table 53 summarizes the results for hypoglycemic events that occurred between 00:01 and 5:59 am (***Novo Nordisk Nocturnal Hypoglycemia***) across the three pivotal type 1 DM trials for three definitions of hypoglycemia (***ADA Severe***, ***ADA Documented Symptomatic***, ***Novo Nordisk Confirmed***).

10.3.3.1. Severe Nocturnal Hypoglycemia

The proportion (%) of study participants randomized to degludec who experienced at least one protocol defined ***ADA severe*** hypoglycemic event at night was greater in trial **3583** but similar to controls in trials **3585** (detemir) and **3770** (glargine). Proportions were consistent with event rates for ***ADA severe*** hypoglycemic episodes except in the glargine arm for trial **3770**. The difference between proportion and event rate is accounted for by more numerous events per individuals in the glargine arm (2.6 versus < 1.3 events per individuals for all other intervention arms).

10.3.3.2. Nocturnal Hypoglycemia Broad Definitions

Between 59 to 74% of participants experienced at least one event which met the protocol definition of an ***ADA Documented Symptomatic*** or a ***Novo Nordisk Confirmed*** nocturnal hypoglycemic event. In trial **3583** the direction of the findings and conclusions to be drawn from the findings were not consistent across definitions. Relative to glargine participants on degludec were 2.5-fold (Rate Ratio) more likely to experience an ***ADA severe*** event but 25% less likely to experience a ***Novo Nordisk Confirmed*** event. Event rates between ***ADA documented*** and ***Novo Nordisk Confirmed*** were consistent (i.e., same general direction) except for the degludec OD versus glargine comparison in trial **3770** where the direction changed to favor degludec if the ***Novo Nordisk Confirmed*** definition was used over the ***ADA Documented Symptomatic*** definition. Rate ratios ($\text{Event Rate}_{\text{Degludec}}/\text{Event Rate}_{\text{Comparator}}$) calculated using the ***Novo Nordisk Confirmed*** definition were slightly more favorable than rate ratios calculated using the ***ADA Documented Symptomatic*** definition except in trial **3585** (Asia) (i.e., 0.75, 0.70, 0.96 versus 0.80, 0.79, 1.11 ***Novo Nordisk Confirmed*** versus ***ADA Documented*** in trials **3583**, **3585** and **3770** respectively).

10.3.4. Inferential Testing: Hypoglycemia Type 1 DM

In trial **3583** and **3585** the Applicant had prospectively designated '***Nocturnal Novo Nordisk Confirmed***' hypoglycemia as the first key secondary endpoint to test in their hierarchical ordering of secondary endpoints. In trial **3583**, the observed rate of '***Nocturnal Novo Nordisk Confirmed***' hypoglycemic episodes per 100 patient-years was 441 episodes with degludec and 586 episodes with glargine. Statistical superiority of degludec over glargine was demonstrated in terms of a lower rate of nocturnal confirmed hypoglycemic episodes [estimated rate ratio (95% CI): 0.75 (0.59; 0.96)]. In trial **3585**, the observed rate of nocturnal confirmed hypoglycemic episodes per 100

patient-years was 414 episodes with degludec and 594 episodes with detemir. Statistical superiority of degludec over detemir was demonstrated in terms of a lower rate of nocturnal confirmed hypoglycemic episodes; [estimated rate ratio (95% CI) 0.66 (0.49; 0.88)]³¹.

Reviewer Comment: Trial **3583** shows a numerically worst outcome for degludec over glargine across all hypoglycemic definitions when hypoglycemic episodes across a 24 hour period are considered. When one considers only the nocturnal period an imbalance not favoring degludec is seen for ADA severe episode (i.e., the most objective definition). Given these findings it is difficult to interpret the clinical meaning of the statistically significant result for '**Nocturnal Novo Nordisk Confirmed**' hypoglycemia.

Recall that all subjects randomized to degludec, except those in the fixed flexible schedule, were told to inject degludec with the evening meal while subjects randomized to glargine could inject at anytime of the day. Since the maximum glucose lowering effect at steady state for type 1 DM is not achieved until 12 hours, timing of injection could have biased estimate of the rate of nocturnal hypoglycemia (i.e., one would expect more hypoglycemic episode in the early morning as degludec effect reaches a maximum). To explore the relationship between timing of injection and hypoglycemic episodes rate and assess the robustness of the findings the following, May 21, 2012, information request was issued.

“For each of the eight individual studies evaluating degludec once daily (including the flexible schedule arms), provide an updated set of analyses for 'confirmed nocturnal hypoglycemia' by defining the nocturnal time period as episodes occurring between 00:01-7:59 AM for one set of analyses and 9:59PM-05:59AM for another set of analyses. Present the data in table format and include N (%), Event, and Event Rate for degludec and control groups.”

The Applicant responded on May 25th 2012. When 2 hours are added to the nocturnal time period (i.e., 00:01-7:59 AM), the advantage of degludec over comparator disappears (source data: Addendum to NDA 203314, eCTD sequence #24, Date 5/25/2012, Section 1.2, Table 1). The rate ratios for nocturnal **Novo Nordisk Confirmed** episodes change from 0.75, 0.70, 0.96 to 0.90, 0.80, 1.14 for trial **3583**, **3585** and **3770** respectively. When 2 hours are taken away from the sponsor's defined nocturnal time period (i.e., 9:59-5:59 AM) the advantage of degludec over comparator also disappears (source same as above Table 4). In this scenario, the rate ratios for nocturnal **Novo Nordisk Confirmed** episodes change from 0.75, 0.70, 0.96 to 0.86, 0.90, 0.90 for trial **3583**, **3585** and **3770** respectively.

Reviewer Comment: These data support the notion that occurrence of hypoglycemia at night was influenced by timing of injection (i.e., more hypoglycemic episodes in the early

³¹ **Note:** to calculate this estimated ratio the Applicant uses a rate of 391 and 592 for degludec and detemir respectively refer to Source 203314: 5.3.5.3: ISE: Appendix 6.2 Table 331, the discrepancy between the reported rate and the rate used for inferential testing was not explored.

morning as degludec action peaks). If both degludec and glargine were to have been injected in the morning conclusions regarding the risk of hypoglycemia at night could have been different.

Table 54: Hypoglycemia, Type 2 DM, Degludec Program, Across Definitions

Study# (weeks)	Treatment Arms	N	ADA Severe			ADA Documented Symptomatic			Novo Nordisk Confirmed		
			n (%)	Event	Event Rate	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Basal Insulin Once Daily and Prandial Insulin with Meals added to OADs											
3582 (52)	Degludec	753	34 (4.5)	41	6.1	637 (84.6)	13820	2061	609 (80.9)	7437	1109
	Glargine	251	11 (4.4)	12	5.2	215 (85.7)	5360	2342	206 (82.1)	3120	1363
Basal Insulin Once Daily added to OADs											
3579 (52)	Degludec	766	2 (0.3)	2	0.3	428 (55.9)	2678	401	356 (46.5)	1014	152
	Glargine	257	5 (1.9)	5	2.3	132 (51.4)	806	370	119 (46.3)	403	185
3672 (26)	Degludec _{U200}	228	0 (0.0)	0	0.0	93 (40.8)	357	338	65 (28.5)	129	122
	Glargine	228	0 (0.0)	0	0.0	96 (42.1)	388	363	70 (30.7)	152	142
3586 (26)	Degludec	284	0 (0.0)	0	0.0	209 (73.6)	1286	964	142 (50.0)	397	298
	Glargine	146	0 (0.0)	0	0.0	99 (67.8)	627	892	78 (53.4)	260	370
3580 (26)	Degludec	226	1 (0.4)	1	1.0	96 (42.5)	452	446	96 (42.5)	311	307
	Sitagliptin	228	0 (0.0)	0	0.0	32 (14)	120	123	29 (12.7)	123	126
3668 (26)	Degludec FF	230	1 (0.4)	2	2.0	149 (64.8)	841	790	139 (60.7)	803	760
	Degludec OD	226	2 (0.9)	2	2.0	124 (54.9)	770	739	99 (43.8)	378	363
	Glargine	229	2 (0.9)	2	2.0	117 (50.9)	388	364	113 (49.3)	368	348
Source 203314: module 5.3.5.3: ISE: Appendix 6.2 Table 261-262 Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure <u>Definitions</u> ADA Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions ADA Documented Symptomatic: Episode associated with both symptoms of hypoglycemia and a documented blood glucose < 70 mg/dL Novo Nordisk Confirmed: The sum of ADA severe and episodes where a blood glucose < 56 mg/dL was recorded (i.e., with or without symptoms)											

Table 54 summarizes the results for hypoglycemia at any time of the day across the six pivotal type 2 DM trials for three definitions of hypoglycemia (**ADA Severe**, **ADA Documented Symptomatic**, **Novo Nordisk Confirmed**). The table shows proportions, event counts and event rates for each definition.

Overall the descriptive data do not suggest a clear benefit or harm of degludec over comparators for hypoglycemia in type 2 diabetes. Consistency in the effect of degludec versus comparator for hypoglycemia is lacking between trials, between statistics considered (i.e., proportion versus event count) and across definitions used.

10.3.5. Severe Hypoglycemia Type 2 DM

The proportion (%) of study participants who experienced at least one protocol defined **ADA Severe** hypoglycemic event was low (i.e., <5%) and in some trials no trial participants in either arm experienced a severe event. This is consistent with that fact that enrollees were not at risk for hypoglycemia. The trial with the largest proportion of individuals with severe hypoglycemic events was trial **3582**. In this trial participants were at higher risk of hypoglycemia as they were receiving both basal and prandial insulin for glycemic control. There was no consistent trend favoring degludec across type 2 DM trials. Proportions were generally consistent with severe event rates.

Hypoglycemia reported as a serious adverse event (see footnote 29) is shown in **Table 55** by system organ class and preferred term. 23 patients experienced at least one serious adverse event related to hypoglycemia on degludec (1.0 incident cases per 100 patient years) and 6 on comparators (0.6 incident cases per 100 patient years). Event rates were also higher in the degludec compared to active control groups (1.3 versus 0.6 events per 100 patient years for degludec versus comparator).

*Reviewer Comment: In trial 3580 the comparator was sitagliptin (i.e., DPP4-inhibitor) which is known to have a lower hypoglycemic risk than insulin. In this trial, a greater risk of hypoglycemic is seen for degludec vs. sitagliptin across all three definitions (**ADA Severe**, **ADA Documented Symptomatic** and **Novo Nordisk Confirmed**). This level of consistency is lacking across trials for the different comparator.*

10.3.6. Hypoglycemia Broad Definitions Type 2 DM

The proportion of participants with at least one event which met the protocol definition of an **ADA Documented Symptomatic** or a **Novo Nordisk Confirmed** event ranged from 29 to 86%. The proportion of individuals with events was highest in subjects treated with basal and prandial insulin (i.e., ~80% with at least one event over 12 months). In trials studying addition of degludec or glargine, delivered at fixed timed intervals, to a regimen of OAD, similar proportions of subjects experience at least one event were seen. A higher proportion of individuals with at least one event and a higher event rate was seen in trial 3668 in patients injecting degludec on a flexible schedule.

In trial **3582** the direction of the results and the conclusion one would draw from the results changes based on the definition considered. In this trial the rate of **ADA Severe**

hypoglycemic episode is observed to be 17% higher for degludec (i.e., 6.1/5.2 events per 100 patient treated for one year suggesting harm) but the rate of **Novo Nordisk Confirmed** events is 19% lower (suggesting benefit). Event rates between **ADA Documented Symptomatic** and **Novo Nordisk Confirmed** definitions were not consistent in trials **3579**, **3586** and **3668** (i.e., not going in the same general direction). Rate ratios (Event Rate_{Degludec}/Event Rate_{glargine}) using the **Novo Nordisk Confirmed** definition were more favorable than rate ratios using the definition for **ADA Documented Symptomatic** episodes (i.e., 0.81, 0.82, 0.86, 0.81, 1.0 versus 0.88, 1.1, 0.93, 1.1, 2.0 for **Novo Nordisk Confirmed versus ADA Documented Symptomatic** in trials **3582**, **3579**, **3672**, **3586** and **3668** respectively).

Reviewer Comment: The low observed severe event rates highlights the fact that subjects enrolled in the type 2 DM program were not particularly susceptible to hypoglycemia.

A drug that reduces hypoglycemic episodes in a clinically meaningful way should reduce the proportion and number of life-threatening episodes in an at risk population. No consistent reduction in life threatening episodes or in the number of life threatening episode was seen when a definition for severe episode was used or when one considers episodes coded as serious adverse events. Because severe/serious hypoglycemic events tend to be clinically dramatic events, they are less susceptible to being false positive events and are more reliable measures of hypoglycemic risk.

Other definitions may be more sensitive but are less specific. It is difficult to argue that the definition proposed by Novo Nordisk is more clinically meaningful than the one proposed by the ADA (i.e., documented symptomatic). Both seek to capture events that lead to recurrent hypoglycemic episodes and its associated deleterious clinical consequences (i.e., severe episodes and inability to achieve control). Even if one considers the Novo Nordisk definition to be able to reliably quantify risk, the impact on clinical outcome of the observed 14-19% risk reduction for this particular endpoint remains uncertain.

The results for Nocturnal Hypoglycemia in the Type 2 DM degludec program are shown in **Table 56**. Inconsistencies across definitions are highlighted in yellow.

Table 55: Hypoglycemia Reported as Serious Adverse Events, Type 2 DM, Degludec

	Degludec			Comparator		
Safety Analysis Set (N)	3173			1802		
Total Exposure (yrs)	2101.4			1044.2		
	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Metabolism and Nutrition SOC						
Hypoglycemia	17 (0.5)	17	0.8	5 (0.3)	5	0.5
Hypoglycemia Unconsciousness	6 (0.2)	8	0.4	1 (0.1)	1	0.1
Hypoglycemia Unawareness	1 (0.0)	1	0.0			
Hypoglycemia Seizure	1 (0.0)	1	0.0			
All Hypoglycemia Related Preferred Terms						
Serious Adverse Event Related To Hypoglycemia		27	1.3		6	0.6
Adapted From: 203314: Summary of Clinical Safety: Table 2-13. Discreet events across preferred terms and SOC's were added to derive "Serious adverse event related to hypoglycemia" Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure						

Table 56: Nocturnal Hypoglycemia, Type 2 DM, Degludec Program, Across Definitions

			Nocturnal ADA Severe			Nocturnal ADA Documented Symptomatic			Nocturnal Novo Nordisk Confirmed		
Study# (weeks)	Treatment Arms	N	n (%)	Event	Event Rate	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Basal Insulin Once Daily and Prandial Insulin with Meals added to OADs											
3582 (52)	Degludec	753	10 (1.3)	14	2.1	339 (45.0)	1380	206	298 (39.6)	930	139
	Glargine	251	3 (1.2)	3	1.3	134 (53.4)	643	281	119 (47.4)	422	184
3579 (52)	Degludec	766	1 (0.1)	1	0.1	156 (20.4)	429	64	106 (13.8)	169	25
	Glargine	257	0 (0.0)	0	0	58 (22.6)	198	91	39 (15.2)	84	36
3672 (26)	Degludec _{U200}	228	0 (0.0)	0	0	29 (12.7)	52	49	14 (6.1)	19	18
	Glargine	228	0 (0.0)	0	0	34 (14.9)	67	63	20 (8.8)	30	28
3586 (26)	Degludec	284	0 (0.0)	0	0	93 (32.7)	325	244	58 (20.4)	104	78
	Glargine	146	0 (0.0)	0	0	48 (32.8)	194	276	35 (24.0)	87	124
3580 (26)	Degludec	226	0 (0.0)	0	0	28 (12.4)	66	65	29 (12.8)	53	52
	Sitagliptin	228	0 (0.0)	0	0	8 (3.5)	18	19	13 (5.7)	29	30
3668 (26)	Degludec FF	230	1 (0.4)	2	1.9	62 (27.0)	138	130	31 (13.5)	67	63
	Degludec OD	226	0 (0.0)	0	0	47 (19.0)	119	114	24 (10.6)	58	56
	Glargine	229	0 (0.0)	0	0	61 (26.6)	158	150	49 (21.4)	79	75

NDA 203314; 5.3.5.3; Appendix 6.2; Tables 265-266

Population: Safety analysis set

n: number of subjects with at least one episode

Event: Total event count (i.e., more than one event could have occurred in a single patient)

Event Rate: Total event count normalized to exposure and presented per 100 years of exposure

Nocturnal period: Defined as the time period between 00:01 and 5:59 AM inclusive.

Definitions:

ADA Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions

ADA Documented Symptomatic: Episode associated with both symptoms of hypoglycemia and a documented blood glucose < 70 mg/dL

Novo Nordisk Confirmed: The sum of ADA severe and episodes where a blood glucose < 56 mg/dL was recorded (i.e., with or without symptoms)

10.4. Hypoglycemia Descriptive Data Degludec/Aspart Program

10.4.1. Hypoglycemia Type 1 DM

Table 57 summarizes hypoglycemia data across three definitions and five degludec/aspart trials. 13% of patients with type 1 DM (3594) randomized to degludec/aspart versus 18% of individuals randomized to detemir (once or twice daily) experienced at least one event of severe hypoglycemia. Hypoglycemic risk with degludec/aspart was numerically lower than risk with detemir for all definitions considered. The number and rate of hypoglycemic events categorized as 'serious events' were higher in degludec/aspart compared to detemir (see **Table 58**).

10.4.2. Hypoglycemia Type 2 DM

The number of individuals with severe events was low. A comparative advantage for severe events was suggested by one trial examining once daily degludec/aspart compared to glargine but not confirmed in the other. Compared to subjects injecting glargine once daily, subjects injecting degludec/aspart once daily were more likely to experience hypoglycemia defined using broad definitions of hypoglycemia. One trial comparing twice daily degludec/aspart to twice daily 70/30 aspart insulin suggested an advantage of degludec/aspart over 70/30 aspart insulin across all definitions. This was not confirmed in the other trials.

Table 57: Hypoglycemia, IDegAsp Program, Across Three Definitions

			ADA Severe			ADA Documented Symptomatic			Novo Nordisk Confirmed		
Study# (weeks)	Treatment Arms	N	n (%)	Event	Event Rate	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Type 1 DM Once Daily											
3594 (52)	IDegAsp OD	362	48 (13.3)	79	26.6	330 (91.2)	14038	4729	344 (95.0)	9450	3183
	Detemir OD	180	33 (18.3)	65	44.7	162 (90.0)	7611	5233	169 (93.9)	5342	3673
Type 2 DM Once Daily											
3590 (26)	IDegAsp OD	265	1 (0.4)	1	0.8	160 (60.4)	987	835	132 (49.8)	500	423
	Glargine OD	261	1 (0.4)	1	0.8	146 (55.9)	679	557	96 (36.8)	226	185
3593 (26)	IDegAsp OD	230	0 (0.0)	0	0.0	138 (60.0)	858	821	121 (52.6)	451	431
	Glargine OD	233	3 (1.3)	4	3.7	149 (63.9)	904	841	112 (48.1)	344	320
Type 2 DM Twice Daily											
3592 (26)	IDegAsp BID	224	7 (3.1)	9	8.8	168 (75.0)	2330	2280	148 (66.1)	993	972
	BIAsp 30 BID	222	16 (7.2)	25	25.3	176 (79.3)	2533	2565	153 (68.9)	1379	1396
3597 (26)	IDegAsp BID	279	4 (1.4)	6	4.7	219 (78.5)	2741	2136	205 (73.5)	1227	956
	BIAsp 30 BID	141	2 (1.4)	2	3.1	120 (85.1)	1228	1883	107 (75.9)	621	952
NDA 203313; 5.3.5.3; Appendix 6.2; Tables 151-156 Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure Definitions: ADA Severe: an episode requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions ADA Documented Symptomatic: Episode associated with both symptoms of hypoglycemia and a documented blood glucose < 70 mg/dL Novo Nordisk Confirmed: The sum of ADA severe and episodes where a blood glucose < 56 mg/dL was recorded (i.e., with or without symptoms)											

Table 58: Hypoglycemia Reported as a Serious Adverse Event, Type 1 DM, Trial NN5401-3594/3465

	IDegAsp			Comparator		
Safety Analysis Set (N)	362			180		
Total Exposure (yrs)	296 (yrs)			146		
	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Metabolism and Nutrition SOC						
Hypoglycemia	15 (4.1)	25	8.4	9 (5.0)	9	6.2
Hypoglycemia Unconsciousness	7 (1.9)	7	2.4	4 (2.2)	4	2.7
Hypoglycemia Seizure	2 (0.6)		1.0	1 (0.6)	1	0.7
Nervous System Disorders SOC						
Hypoglycemic Coma	1 (0.3)	2	0.7	0	0	0
All Hypoglycemia Related Preferred Terms						
Serious Adverse Event Related To Hypoglycemia		39	13.2		14	9.6
Adapted From: 203313: module 5.3.5.3: ISS: Table 2-17. Discreet events across preferred terms and SOCs were added to derive "Serious adverse event related to hypoglycemia" Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure						

Table 59: Hypoglycemia Reported as Serious Adverse Events, Type 2 DM, Degludec/Aspart

	Degludec			Comparator		
Safety Analysis Set (N)	998			857		
Total Exposure (yrs)	453.4			393.4		
	n (%)	Event	Event Rate	n (%)	Event	Event Rate
Metabolism and Nutrition SOC						
Hypoglycemia	3 (0.3)	5	1.1	7 (0.3)	7	1.8
Hypoglycemia Unconsciousness	3 (0.3)	3	0.7	7 (0.1)	7	1.8
All Hypoglycemia Related Preferred Terms						
Serious Adverse Event Related To Hypoglycemia		8	1.8		14	3.6
Adapted From: 203313: module 5.3.5.3: ISS: Table 2-19. Discreet events across preferred terms and SOC's were added to derive "Serious adverse event related to hypoglycemia" Population: Safety analysis set n: number of subjects with at least one episode Event: Total event count (i.e., more than one event could have occurred in a single patient) Event Rate: Total event count normalized to exposure and presented per 100 years of exposure						

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Clinical Safety Review

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

November 8, 2012

**NDA 203314: Insulin Degludec (Tresiba)
NDA 203313: Insulin Degludec/Insulin Aspart (Ryzodeg)**

Applicant: Novo Nordisk

Prepared by:

Karim Anton Calis, PharmD, MPH

Division of Metabolism and Endocrinology Products

Office of Drug Evaluation II, Office of New Drugs

Center for Drug Evaluation and Research

Food and Drug Administration

1. Introduction

Insulin is a life-saving therapy for type 1 diabetes mellitus (T1DM), and it is also important in the management of type 2 diabetes (T2DM). Safety concerns with insulin products must be balanced against their known beneficial effects in managing hyperglycemia and ameliorating its attendant clinical consequences. Important safety concerns with insulin products include hypoglycemia and weight gain. Other safety issues include potential hypersensitivity and injection-site reactions. A recent safety concern for insulin products is based on observational studies linking insulin glargine to an increased risk of certain cancers. However, the evidence presented in these studies is inconclusive due to methodological limitations, and, at present, there are no definitive data to suggest that such a risk actually exists for insulin glargine or other insulin products.

Tresiba and Ryzodeg are both insulin products that contain insulin degludec, a human insulin analog, which is produced by recombinant DNA technology (rDNA origin) utilizing *Saccharomyces cerevisiae*. The proposed to-be-marketed formulations are clear, sterile solutions for subcutaneous injection. Tresiba (insulin degludec) is a long-acting insulin analog intended for once-daily use as a basal insulin for the treatment of patients with type 1 and type 2 diabetes; Ryzodeg is a fixed-ratio combination of long- and short-acting insulin analogs (insulin degludec 70% and insulin aspart 30%) to be given once or twice daily. The dosage of both drugs is to be individualized based on glycemic response. Following subcutaneous administration, insulin degludec is slowly absorbed and demonstrates a flat pharmacokinetic profile (i.e., no identifiable peak plasma concentration). Two other long-acting insulin analog products—insulin glargine (Lantus) and insulin detemir (Levemir)—are currently approved for use in the United States. Insulin degludec was recently approved for marketing in Japan, but it has not to date been approved in other countries. As such, post-marketing experience with Tresiba and Ryzodeg are not available at this time.

This section of the briefing document contains highlights from the clinical safety review for Tresiba (NDA 203314) and Ryzodeg (NDA 203313). Insulin degludec (Tresiba) is abbreviated as IDeg throughout the review. The combination product containing insulin degludec and insulin aspart (Ryzodeg) is referred to as IDegAsp. A general overview of these two applications, along with relevant background information and highlights from the review of efficacy (including demographics, baseline characteristics, and subject disposition) can be found in the preceding sections above. Given the similarities in the IDeg and IDegAsp development programs, this review discusses both applications together but highlights key differences where they exist. Except where specifically noted, the safety analyses presented in this review generally address the pooled IDeg and IDegAsp data from the safety analysis dataset.

2. Summary of Clinical Safety

The efficacy and purported benefits of insulin degludec and insulin degludec/insulin aspart are addressed in Dr. Jean-Marc Guettier's clinical efficacy review above (Section 9). The review suggests that both of these insulin products are generally effective for their intended use.

Overall, the study populations of both the IDeg and comparator groups and the IDegAsp and comparator groups were generally well matched with respect to subject demographics and baseline characteristics. Exposure to the investigational products in terms of both the number and type of subjects exposed and also in terms of the duration and extent of exposure is reasonably adequate to assess the safety of IDeg and IDegAsp relative to the comparators. The overall safety assessment plan used in both development programs was adequate in terms of the nature and frequency of assessments.

Treatment-emergent adverse events (TEAE) were generally comparable between the IDeg regimens and comparators, and most adverse events in all treatment groups were generally tolerable, reversible, and self-limiting. The most frequently reported AEs for both IDeg and comparators and for IDegAsp and comparators included nasopharyngitis, upper respiratory tract infection, headache, and diarrhea. Other common AEs in both programs included sinusitis, oropharyngeal pain, nausea, gastroenteritis, influenza, cough, back pain, peripheral edema, weight gain, lipodystrophy, and injection-site reactions. The most frequently reported severe adverse events were for hypoglycemia.

In both development programs, serious adverse events (SAEs) were few and reasonably balanced among the study treatment arms, and the adverse events experienced by subjects in the trial were generally consistent with the established safety profiles of approved insulin products, including the two long-acting insulin analogs, insulin glargine and insulin detemir. In subjects with T1DM, the most frequently reported SAEs ($\geq 1\%$ of the subjects) were events of hypoglycemia in the Metabolism and nutrition disorders System Organ Class (SOC), and rates were similar for both IDeg and comparators. In subjects with T2DM, $\geq 1\%$ of those in the IDeg group reported SAEs in the Cardiac disorders and Infections and infestations SOCs. For IDegAsp and comparators, the most frequently reported SAEs were events of hypoglycemia. Overall, the types and rates of SAEs across trials, as well as withdrawal due to SAEs, were generally similar between IDeg and comparators and also IDegAsp and comparators.

A CV meta-analysis conducted by the applicant raised concerns regarding the possibility of excess risk of major adverse cardiovascular events (MACE) in the pooled IDeg and IDegAsp data compared to the pool of active controls. Given that additional data were available from trials that were ongoing at the time of the original NDA filing, an information request was sent to the Sponsor to provide an updated CV safety analysis (the information request is presented in Appendix A). The updated analyses (described in the FDA biostatistical review below) consistently pointed to potential harm associated with use of the insulin degludec products. Subject demographics and selected baseline characteristics for the updated CV analysis data set are presented in Appendix B.

3. Methods of Clinical Safety Evaluation

a. Safety Database

In these two new drug applications, the applicant submitted data from 62 clinical studies combined to support the safety and efficacy of insulin degludec and insulin degludec/insulin aspart for improving glycemic control in adults with type 1 and type 2 diabetes mellitus. The applicant is relying on the therapeutic confirmatory trials as the primary source of data to serve as the foundation for scientific evidence in support of safety and efficacy. Overall, these trials were similar in design. In general, they were non-inferiority trials with a randomized, controlled, open-label, parallel-group, treat-to-target design whereby IDeg was compared to an active insulin comparator (mostly insulin glargine but also insulin detemir), except for one superiority trial which used oral sitagliptin as the comparator. The inclusion and exclusion criteria employed in these trials, as well as subject characteristics at baseline are described in Sections 6 and 7 of the clinical review above. The duration of the therapeutic confirmatory trials was either 26 weeks or 52 weeks. Five of the IDeg therapeutic confirmatory trials (3 in subjects with T1DM and 2 in subjects with T2DM) were extended by an additional trial period of 26 or 52 weeks with the goal of investigating long-term safety. Similarly, two of the IDegAsp confirmatory trials (Trials 3594 and 3590 in T1DM and T2DM, respectively) were extended for an additional 26-week period. Updated information about serious adverse events from the completed therapeutic confirmatory trials was included after the database lock and until March 31, 2011.

Reviewer's Comment: An open-label design in clinical trials has inherent limitations, with the potential to introduce bias particularly when assessing differences in subjective study outcome measures. Nonetheless, it is widely acknowledged that use of masking in insulin studies may not be practical or safe considering the need for individualized dosage and careful titration during the course of a clinical trial.

Note: Sources of clinical data, along with tabular summaries and detailed descriptions of the clinical trials, are addressed above in the clinical review of efficacy. Key issues of relevance to the understanding and interpretation of the safety findings such as study objectives, design, study inclusion and exclusion criteria, formulations, dosing and administration, comparators, and concomitant medications are addressed in the efficacy review above.

The following is a brief summary of the clinical data sources for the two applications insofar as they apply to the evaluation of clinical safety:

Insulin Degludec: The clinical safety review for IDeg included the 41 clinical studies completed as of the January 31, 2011 cut-off date for the application. These studies included 25 clinical pharmacology trials, 3 therapeutic exploratory trials, 11 therapeutic confirmatory trials, and 2 trials that did not fit any of these categories. Six insulin degludec studies were still ongoing at the time of NDA filing. Five of these studies are extensions of completed therapeutic confirmatory trials, and one study is a 26-week trial

comparing the efficacy and safety of two titration algorithms of IDeg. As of the date of the 120-day safety update, three of the five extension studies were completed (Trials 3585, 3770, and 3582) with a cutoff date of October 6, 2012, while four studies were newly initiated and three studies were still ongoing. The focus of the safety evaluation was based on the 11 therapeutic confirmatory trials because these were randomized and controlled, were of sufficiently long duration, and evaluated the to-be-commercialized formulation.

Insulin Degludec/Insulin Aspart: The clinical safety review for IDegAsp included the 21 clinical studies completed as of the January 31, 2011 cut-off date for this application. These studies included 13 clinical pharmacology trials, 3 therapeutic exploratory trials, and 5 therapeutic confirmatory trials. Two IDegAsp trials were still ongoing at the time of NDA filing. Trial 3726 is an extension of Trial 3590, a completed therapeutic confirmatory study. Trial 3896 was another therapeutic confirmatory trial being conducted in Japan. At the time of 120-day safety update, both of these were completed with a cutoff date of October 6, 2011. One additional study, a bioequivalence study comparing IDegAsp 100 units/mL to IDegAsp 200 units/mL is included in the updated safety database with a cutoff date of November 11, 2011. The focus of the safety evaluation was based on the 5 therapeutic confirmatory trials because these were randomized and controlled, were of sufficiently long duration, and evaluated the to-be-commercialized formulation.

Reviewer's Comment: Overall, the data submitted in this NDA were of sufficient quality and completeness to permit a comprehensive review of safety. The long-term therapeutic confirmatory studies and study extensions were particularly informative in regards to rare or unusual adverse experiences or adverse experiences that may occur with prolonged exposure to the drug.

Reviewer's Comment: Trial 3718 and Trial 3724 compared thrice weekly administration of insulin degludec to once daily basal insulin. The Sponsor included these two trials in the overall safety assessment. It should be noted that differences in exposure to insulin degludec compared to the daily dosing used in the other trials could bias the interpretation of safety. However, the contribution from these two trials was relatively small and is unlikely to have substantially confounded important safety endpoints.

b. Analysis Datasets

The safety datasets provided by the Sponsor were Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) compliant.

-Safety analysis set: included all subjects receiving at least one dose of the investigational product or its comparator. Subjects in the safety set contribute to the evaluation 'as treated.'

-Full analysis set: included all randomized subjects. The statistical evaluation of the full analysis set follows the intention-to-treat principle, and subjects contribute to the evaluation ‘as randomized.’

Descriptive safety data provided by the applicant were based on the safety analysis set. The statistical analyses of body weight, lipids, and QTc were based on pre-specified analyses for each individual trial and based on the full analysis set.

Two separate, prospectively planned meta-analyses—one for hypoglycemia and one for cardiovascular safety—were provided by the applicant. These are addressed in separate FDA biostatistical reviews. Hypoglycemia was considered by the applicant to be an efficacy parameter and is addressed as a safety and efficacy outcome in the clinical efficacy section above.

c. Pooling of Data and Review Strategy

The evaluation of safety considered all IDeg and IDegAsp clinical studies. The safety pool was comprised of the completed therapeutic confirmatory trials, which accounted overwhelmingly for the overall exposures reported in both development programs. Given that IDeg is the basal component of IDegAsp, and given that there was considerable exposure to IDeg in the IDegAsp therapeutic confirmatory trials, most of the major safety data were pooled for IDeg and IDegAsp as this provides a broad perspective on the overall safety experience. Pooled data were also presented separately for subjects with T1DM, and also for subjects with T2DM. Data for most key safety endpoints were provided for selected subpopulations, including those with T1DM and insulin-naïve subjects with T2DM. All references in this review to the *combined* pooled safety data for IDeg and IDegAsp follow the abbreviation IDeg+IDegAsp. Because of the potential for variation in safety profiles that may be attributable to inherent pharmacokinetic, pharmacodynamic, or formulation differences with the two insulin products (insulin degludec vs. insulin aspart) or to the two concentrations of insulin degludec investigated (U100 vs. U200), safety data were appropriately not pooled but rather presented separately for the purpose of investigating selected endpoints, including hypoglycemia, injection-site reactions, and antibody formation.

d. Categorization of Adverse Events

All serious and non-serious adverse events reported in the therapeutic confirmatory trials were recorded on a standardized AE-collection form and was included as part of the case report forms. If more than one sign or symptom was reported, a separate AE form was to be used for each. AE records included a description of the event, level of seriousness, onset and resolution date, severity, relationship to trial medication as judged by the investigator, any action taken, and outcome. For SAEs, a separate form was used in addition to the standard AE form.

AEs were defined as any undesirable medical event occurring in a subject in the clinical trial, whether or not related to the trial products. AEs were assessed at every study visit

and were categorized by the investigator as mild, moderate, or severe; and causality was assessed as probable, possible, or unlikely according to commonly accepted criteria. SAEs were in accordance with FDA's definition, and included hospitalization, life threatening illness, and death. TEAEs in the therapeutic confirmatory trials were defined as an event that has onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment.

The applicant identified certain medical events to be of special interest and developed specific reporting procedures for these events. In the therapeutic confirmatory trials (including the extension trials), the applicant planned to capture additional information for AEs of special interest (severe hypoglycemia, cardiovascular events, neoplasms, and allergic reactions) even if these events were not assessed as serious.

Note: For hypoglycemia and cardiovascular adverse events, the applicant conducted separate meta-analyses which are the subject of two separate FDA biostatistical reviews.

AEs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) Version 13.0 or Version 13.1 for classification of adverse event data into the SOC. Differences in preferred terms between these two versions were reviewed and do not appear to be significant enough to alter this safety review in a meaningful way.

Reviewer's Comment: This reviewer compared a random sample of the terms used by the investigators in describing an AE to the preferred term. AEs appear to have been appropriately classified.

e. Safety Endpoints

The safety endpoints routinely collected in therapeutic confirmatory trials of IDeg and IDegAsp were as follows:

- Extent of Exposure to Investigational Product
- Adverse Events
 - Treatment-Emergent Adverse Events
 - Deaths and Other Serious Adverse Events
 - Other Severe or Significant AEs
 - Withdrawals due to AEs
- Hypoglycemic Episodes
- Physical exam
- Fundoscopic exams/fundus photography
- Vital signs
- Electrocardiography (ECG)
- Body weight changes
- Pregnancy
- Clinical laboratory parameters
 - Insulin antibodies
 - Hematology parameters

- Biochemistry parameters
- Lipid parameters
- Cardiovascular risk markers
- Urinalysis

Note: Hematology parameters, biochemistry values, vital signs, ECG, fundoscopy, and physical examination were evaluated by the applicant for all of the therapeutic confirmatory trials. For the clinical pharmacology trials and the therapeutic exploratory trials, these safety parameters were not included in the applicant's assessment of the safety data but were included in the individual trial reports and were considered in this clinical review of safety.

f. Summary of Exposures

A total of 7510 subjects were exposed to IDeg and/or IDegAsp. A small number of subjects in crossover clinical pharmacology studies were exposed to both IDeg and IDegAsp and, therefore, may be counted in more than one study treatment arm. Because of the skewed randomization to ensure adequate exposure to IDeg and IDegAsp, the pooled comparator group consisted of only 4404 subjects. As expected, the therapeutic confirmatory trials accounted for the majority of the exposures to IDeg and IDegAsp, both in terms of number of subjects exposed and exposure duration.

In the IDeg clinical development program, 5624 subjects were exposed to IDeg, with 4275 subjects coming from the therapeutic confirmatory trials. A total of 3758 subjects (88%) were exposed for at least 6 months, and a total of 1635 subjects (38%) were exposed for at least 12 months in the therapeutic confirmatory trials. The duration of exposure for IDeg is presented in Table 1.

Table 1. IDeg Exposure Duration (Safety Analysis Set)

	Any exposure		>= 6 months		>= 9 months		>= 12 months		Total Exposure
	N	%	N	%	N	%	N	%	in Subject Years
Therapeutic Confirmatory Trials									
All Subjects									
IDeg	4275	(100.0)	3758	(87.9)	1686	(39.4)	1635	(38.2)	2828.2
Comparator	2269	(100.0)	2010	(88.6)	565	(24.9)	548	(24.2)	1339.1
Subjects with T1DM									
IDeg	1102	(100.0)	991	(89.9)	418	(37.9)	404	(36.7)	726.8
Comparator	467	(100.0)	436	(93.4)	140	(30.0)	137	(29.3)	294.9
Subjects with T2DM									
IDeg	3173	(100.0)	2767	(87.2)	1268	(40.0)	1231	(38.8)	2101.4
Comparator	1802	(100.0)	1574	(87.3)	425	(23.6)	411	(22.8)	1044.2
Insulin-naïve Subjects with T2DM									
IDeg	1964	(100.0)	1702	(86.7)	633	(32.2)	611	(31.1)	1219.9
Comparator	1322	(100.0)	1144	(86.5)	205	(15.5)	199	(15.1)	709.7
Insulin-treated Subjects with T2DM									
IDeg	1209	(100.0)	1065	(88.1)	635	(52.5)	620	(51.3)	881.4
Comparator	480	(100.0)	430	(89.6)	220	(45.8)	212	(44.2)	334.5

N = Number of subjects, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus, A month is defined as 30 days

Completers in 26 weeks and 52 weeks trials counts as having 6 months and 12 months

Source: N203314, SCC, Table I-3.

In the IDegAsp clinical development program, 2031 subjects were exposed to IDegAsp, with 1360 subjects coming from the therapeutic confirmatory trials. A total of 1181 subjects (87%) were exposed to IDegAsp for at least 6 months, and a total 235 subjects (17%) were exposed to IDegAsp for at least 12 months. Exposure duration for IDegAsp is presented in Table 2.

Table 2. IDegAsp Exposure Duration (Safety Analysis Set)

	Any exposure		>= 6 months		>= 9 months		>= 12 months		Total Exposure
	N	%	N	%	N	%	N	%	in Subject Years
Therapeutic Confirmatory Trials									
All Subjects									
IDegAsp	1360	(100.0)	1181	(86.8)	245	(18.0)	235	(17.3)	750.2
Comparator	1037	(100.0)	910	(87.8)	119	(11.5)	114	(11.0)	538.8
Subjects with T1DM									
IDegAsp	362	(100.0)	322	(89.0)	245	(67.7)	235	(64.9)	296.9
Comparator	180	(100.0)	157	(87.2)	119	(66.1)	114	(63.3)	145.5
Subjects with T2DM									
IDegAsp	998	(100.0)	859	(86.1)	0		0		453.4
Comparator	857	(100.0)	753	(87.9)	0		0		393.4
Insulin-naïve Subjects with T2DM									
IDegAsp	265	(100.0)	220	(83.0)	0		0		118.3
Comparator	261	(100.0)	232	(88.9)	0		0		122.0
Insulin-treated Subjects with T2DM									
IDegAsp	733	(100.0)	639	(87.2)	0		0		335.1
Comparator	596	(100.0)	521	(87.4)	0		0		271.4

N = Number of subjects, T1DM = Type 1 diabetes mellitus, T2DM = Type 2 diabetes mellitus, A month is defined as 30 days

Completers in 26 weeks and 52 weeks trials counts as having 6 months and 12 months exposure respectively

Source: N203313, SCC, Table I-3.

In the pooled IDeg+IDegAsp population, the number of subjects exposed to IDeg or IDegAsp for at least 6 months in the therapeutic confirmatory trials increased to 4939 subjects, and for at least 12 months increased to 1870 subjects.

Subjects included in the two development programs were reasonably representative of the broader diabetic population in the U.S. with respect to type of diabetes, disease severity, sex, age, and race/ethnicity. The trial population in the IDeg program was 57% male, and 20% of the subjects were greater than 65 years of age. North America (U.S. and Canada combined) accounted for 41% of the trial population, with 39%, 10%, and 5% from Europe, Asia, and Japan, respectively. Whites accounted for 75% of the trial population, while Asians, Hispanics/Latinos, and Blacks/African-Americans accounted for 18%, 10%, and 6%, respectively. The majority of exposed subjects in the therapeutic confirmatory trials (74%) had T2DM, including those with early-stage disease who were insulin-naïve at baseline as well as subjects who were receiving multiple oral antidiabetic medications (with or without insulin) or insulin alone. Within the exposed T2DM population approximately 61% were noted to be insulin-naïve. Mean BMI and body weight were generally higher in trials with subjects with T2DM than T1DM. Mean duration of diabetes was generally longer in trials with subjects with T1DM than T2DM. Lastly, mean HbA_{1c} was generally lower in trials with subjects with T1DM than T2DM.

Exposure by type of insulin degludec regimen and dose is addressed in the efficacy section above. In total, 3587 subjects (84%; 2510 patient-year exposure) were exposed to IDeg 100 U/mL (all subjects with T1DM and subjects with T2DM in Trials 3668, 3579, 3586, 3580 and 3582). A total of 688 subjects (16%; 318 patient-year exposure) were exposed to IDeg 200 U/mL (all insulin-naïve subjects with T2DM in Trials 3672, 3718 and 3724).

The trial population in the IDegAsp program was 54% male, and 19% of the subjects were greater than 65 years of age. Unlike the IDeg program, Europe and Asia recruited the majority of subjects, each accounting for 38% of the total. The U.S. and Canada combined accounted for 18% of the trial population. Overall, Whites accounted for 56% of the trial population, while Asians, Hispanics/Latinos, and Blacks/African-Americans accounted for 38%, 5%, and 4%, respectively. The majority of exposed subjects in the therapeutic confirmatory trials (73%) had T2DM, including those with early-stage disease who were insulin-naïve at baseline as well as subjects who were receiving multiple oral antidiabetic medications (with or without insulin) or insulin alone. Within the exposed T2DM population approximately 27% were noted to be insulin-naïve.

Study subject demographics and baseline characteristics (including diabetes-related characteristics) for IDeg vs. comparators are presented in Table 3 and Table 4. Likewise, demographics and baseline characteristics for IDegAsp vs. comparators are presented in Table 5 and Table 6.

Table 3. IDeg Demographics and Baseline Characteristics (Safety Analysis Set)

	IDeg N (%)	Comparator N (%)	Total N (%)
Safety Analysis Set	4275	2269	6544
Sex			
Female	1849 (43.3)	1002 (44.2)	2851 (43.6)
Male	2426 (56.7)	1267 (55.8)	3693 (56.4)
Age (years)			
18 - 65 years	3420 (80.0)	1834 (80.8)	5254 (80.3)
> 65 - 75 years	752 (17.6)	370 (16.3)	1122 (17.1)
> 65 years	855 (20.0)	435 (19.2)	1290 (19.7)
> 75 years	103 (2.4)	65 (2.9)	168 (2.6)
Ethnicity			
Hispanic or Latino	427 (10.0)	250 (11.0)	677 (10.3)
Not Hispanic or Latino	3806 (89.0)	1988 (87.6)	5794 (88.5)
Not Applicable	42 (1.0)	31 (1.4)	73 (1.1)
Race			
White	3203 (74.9)	1697 (74.8)	4900 (74.9)
Black or African American	239 (5.6)	131 (5.8)	370 (5.7)
Asian Indian	240 (5.6)	152 (6.7)	392 (6.0)
Asian non-Indian	507 (11.9)	249 (11.0)	756 (11.6)
American Indian or Alaska Native	7 (0.2)	3 (0.1)	10 (0.2)
Native Hawaiian or Oth. Pacific Islander	3 (0.1)	6 (0.3)	9 (0.1)
Other	75 (1.8)	26 (1.1)	101 (1.5)
Not Applicable	1 (0.0)	5 (0.2)	6 (0.1)
BMI (kg/m ²)			
[0;25[945 (22.1)	440 (19.4)	1385 (21.2)
[25;30[1479 (34.6)	737 (32.5)	2216 (33.9)
[30;35[1131 (26.5)	656 (28.9)	1787 (27.3)
[35;[720 (16.8)	436 (19.2)	1156 (17.7)

N= Number of subjects, %= Percentage of subjects.

Some subjects from France did not provide information about race or ethnicity and are categorised under Not Applicable.

Source: N203314, SCC, Table 1-16.

Table 4. IDeg Baseline Diabetes-Related Characteristics (Safety Analysis Set)

	IDeg	Comparator	Total
Safety Analysis Set	4275	2269	6544
Age (years)			
N	4275	2269	6544
Mean (SD)	54.2 (12.9)	54.4 (12.3)	54.3 (12.7)
Median	56.0	55.9	56.0
Min ; Max	18.1 ; 87.0	18.1 ; 86.3	18.1 ; 87.0
Weight (kg)			
N	4275	2269	6544
Mean (SD)	84.2 (19.0)	85.8 (19.2)	84.7 (19.0)
Median	83.0	85.0	83.5
Min ; Max	36.3 ; 150.1	39.0 ; 157.9	36.3 ; 157.9
BMI (kg/m ²)			
N	4275	2269	6544
Mean (SD)	29.4 (5.4)	30.1 (5.5)	29.6 (5.4)
Median	29.1	29.7	29.3
Min ; Max	14.7 ; 45.2	16.2 ; 45.5	14.7 ; 45.5
Duration of Diabetes (years)			
N	4275	2269	6544
Mean (SD)	12.3 (9.1)	11.1 (8.2)	11.9 (8.8)
Median	10.2	9.5	9.8
Min ; Max	0.5 ; 63.2	0.5 ; 54.3	0.5 ; 63.2
HbA _{1c} (%)			
N	4275	2269	6544
Mean (SD)	8.2 (0.9)	8.3 (0.9)	8.2 (0.9)
Median	8.1	8.2	8.1
Min ; Max	4.9 ; 11.4	5.4 ; 12.2	4.9 ; 12.2
FPG (mmol/L)			
N	4243	2244	6487
Mean (SD)	9.3 (3.1)	9.5 (3.1)	9.4 (3.1)
Median	9.0	9.3	9.1
Min ; Max	0.9 ; 25.4	1.5 ; 28.1	0.9 ; 28.1

N= Number of subjects, SD= Standard Deviation, BMI= Body Mass Index
HbA_{1c}= Haemoglobin A_{1c}, FPG= Fasting Plasma Glucose

Source: N203314, SCC, Table 1-17.

Table 5. IDegAsp Demographics and Baseline Characteristics (Safety Analysis Set)

	IDegAsp N (%)	Comparator N (%)	Total N (%)
Safety Analysis Set	1360	1037	2397
Sex			
Female	632 (46.5)	495 (47.7)	1127 (47.0)
Male	728 (53.5)	542 (52.3)	1270 (53.0)
Age (years)			
18 - 65 years	1095 (80.5)	795 (76.7)	1890 (78.8)
> 65 - 75 years	229 (16.8)	213 (20.5)	442 (18.4)
> 65 years	265 (19.5)	242 (23.3)	507 (21.2)
> 75 years	36 (2.6)	29 (2.8)	65 (2.7)
Ethnicity			
Hispanic or Latino	72 (5.3)	78 (7.5)	150 (6.3)
Not Hispanic or Latino	1242 (91.3)	929 (89.6)	2171 (90.6)
Not Applicable	46 (3.4)	30 (2.9)	76 (3.2)
Race			
White	767 (56.4)	599 (57.8)	1366 (57.0)
Black or African American	53 (3.9)	35 (3.4)	88 (3.7)
Asian Indian	171 (12.6)	161 (15.5)	332 (13.9)
Asian non-Indian	347 (25.5)	226 (21.8)	573 (23.9)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	1 (0.1)	2 (0.2)	3 (0.1)
Other	6 (0.4)	6 (0.6)	12 (0.5)
Not Applicable	15 (1.1)	8 (0.8)	23 (1.0)
BMI (kg/m ²)			
[0;25]	407 (29.9)	255 (24.6)	662 (27.6)
[25;30]	496 (36.5)	385 (37.1)	881 (36.8)
[30;35]	321 (23.6)	262 (25.3)	583 (24.3)
[35;]	136 (10.0)	135 (13.0)	271 (11.3)

N= Number of Subjects, %= Percentage of Subjects.

Some subjects from France did not provide information about race or ethnicity and are categorised under Not Applicable.

Source: N203313, SCC, Table I-15.

Table 6. IDegAsp Baseline Diabetes-Related Characteristics (Safety Analysis Set)

	IDegAsp	Comparator	Total
Safety Analysis Set	1360	1037	2397
Age (years)			
N	1360	1037	2397
Mean (SD)	53.5 (13.1)	55.6 (12.1)	54.4 (12.8)
Median	54.9	57.0	55.9
Min ; Max	18.3 ; 88.8	18.1 ; 88.5	18.1 ; 88.8
Weight (kg)			
N	1360	1037	2397
Mean (SD)	78.2 (17.7)	79.4 (18.0)	78.7 (17.9)
Median	76.0	77.3	76.5
Min ; Max	38.2 ; 144.2	38.7 ; 149.5	38.2 ; 149.5
BMI (kg/m ²)			
N	1360	1037	2397
Mean (SD)	28.2 (5.0)	28.7 (5.1)	28.4 (5.0)
Median	27.5	28.3	27.8
Min ; Max	16.2 ; 43.8	17.1 ; 47.7	16.2 ; 47.7
Duration of Diabetes (years)			
N	1360	1037	2397
Mean (SD)	13.7 (8.9)	13.1 (8.8)	13.4 (8.9)
Median	11.9	11.6	11.7
Min ; Max	0.6 ; 59.7	0.6 ; 56.6	0.6 ; 59.7
HbA1c (%)			
N	1360	1037	2397
Mean (SD)	8.4 (0.9)	8.5 (0.9)	8.5 (0.9)
Median	8.3	8.4	8.4
Min ; Max	6.5 ; 11.6	5.3 ; 11.7	5.3 ; 11.7
FPG (mmol/L)			
N	1353	1030	2383
Mean (SD)	9.2 (3.5)	9.2 (3.4)	9.2 (3.5)
Median	8.7	8.5	8.7
Min ; Max	1.8 ; 30.2	2.5 ; 28.4	1.8 ; 30.2

N= Number of Subjects, SD= Standard Deviation, BMI= Body Mass Index
HbA1c= Hemoglobin A1c, FPG= Fasting Plasma Glucose

Source: N203313, SCC, Table 1-16.

Reviewer's Comment: Overall, the study populations of both the IDeg and comparator groups and the IDegAsp and comparator groups were generally well matched with respect to subject demographics and baseline characteristics.

Reviewer's Comment: Exposure to the investigational products in terms of both the number and type of subjects exposed and also in terms of the duration and extent of exposure is reasonably adequate to assess the safety of IDeg and IDegAsp relative to the comparators. Also, the overall safety assessment plan used in both development programs was adequate in terms of the nature and frequency of assessments.

Note: Subject disposition is addressed in the efficacy section above. Withdrawals or discontinuations due to adverse events are addressed in Section 4 of this review.

g. Concomitant Diseases

Concomitant illnesses were recorded for all study subjects as part of the medical history, a subset of which included known diabetes-related complications. Except where specifically noted, these were generally similar for IDeg and comparators and also for IDegAsp and comparators. Of note, in the IDeg program, diabetes complications at

screening were reported by approximately 24% of all subjects with T1DM and 22% in those with T2DM. Approximately 86% of all subjects with T1DM in the therapeutic confirmatory trials were reported to have a medical history/concomitant illness at the time of screening, and the most frequent were hypertension (27.5%), hyperlipidemia (18.1%), diabetic retinopathy (17.0%), and mild or moderate renal impairment (12%) based on estimated creatinine clearance. Approximately 97% of all subjects with T2DM in the therapeutic confirmatory trials were reported to have a medical history/concomitant illness at the time of screening, and the most frequent were hypertension (69.0%), hyperlipidemia (49.3%), and mild or moderate renal impairment (16% in IDeg vs. 13% in comparator) based on estimated creatinine clearance.

In the IDegAsp program, diabetes complications at screening were reported by approximately 35% of all subjects with T1DM (32.9% vs. 38.9% for comparators) and 31% (33.8% vs. 27.4% in comparators) in those with T2DM. A total of 91.5% of all subjects with T1DM in the therapeutic confirmatory trials were reported to have a medical history/concomitant illness at the time of screening, and the most frequent were hypertension (32% vs. 40% for comparators), diabetic retinopathy (24.6% vs. 31.7% for comparators), diabetic neuropathy (19.3% vs. 15% for comparator), and mild or moderate renal impairment (6% vs. 11% for comparators) based on estimated creatinine clearance. Approximately 97% of all subjects with T2DM in the therapeutic confirmatory trials were reported to have a medical history/concomitant illness at the time of screening, and the most frequent were hypertension (67.3%), hyperlipidemia (51%), and mild or moderate renal impairment (23%) based on estimated creatinine clearance.

h. Concomitant Medications

Concomitant medications taken at screening or during the trial were recorded for all subjects in the therapeutic confirmatory trials, and experience with IDeg and IDegAsp was similar. In all, for subjects with T1DM, the most common concomitant medications included antidiabetics, antihypertensives, antihypercholesterolemics, and medications for general pain and for thyroid hormone replacement. Apart from insulin products, the most common concomitant medications taken by $\geq 10\%$ of all subjects with T1DM were acetylsalicylic acid and simvastatin at screening, and acetylsalicylic acid, ibuprofen, acetaminophen, simvastatin, and levothyroxine during the trial treatment period. With the exception of an overall increase in the use of acetaminophen during the trial period compared to baseline and also a slightly lower proportion (14% vs. 20% in the comparators) of simvastatin use among subjects with T1DM specifically in the IDegAsp program, the use of concomitant medications, both at screening and after randomization, did not differ appreciably between treatment groups. For subjects with T2DM, the most common concomitant medications used at screening and during the trial treatment period included antidiabetics, antihypertensives, antihypercholesterolemics, and medications for general pain. As expected, metformin was the most widely used concomitant antidiabetic medication in these subjects. Acetylsalicylic acid also was used by at least one third of the subjects and, according to the applicant, its use did not differ between the treatment groups.

4. Clinical Safety Findings

a. Treatment-Emergent Adverse Events

For both IDeg and IDegAsp and their comparators, the majority of AEs were reported in the following SOC: Infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue, nervous system disorders, metabolism and nutrition disorders, and general disorders and administration-site conditions. The most frequently reported AEs for both IDeg and comparators and for IDegAsp and comparators included nasopharyngitis, upper respiratory tract infection, headache, and diarrhea. Other common AEs in both programs included sinusitis, oropharyngeal pain, nausea, gastroenteritis, influenza, cough, back pain, peripheral edema, weight gain, lipodystrophy, and injection-site reactions. The most frequently reported severe adverse events were for hypoglycemia, which is addressed in greater detail in the efficacy review (Section 11). In general, no major differences were observed between the IDeg and IDegAsp regimens and their comparators for any of the AE preferred terms across the major SOC. With a few minor exceptions favoring either the comparators or IDeg/IDegAsp, major cross-study differences in AEs—particularly in the therapeutic confirmatory trials—were not readily apparent. Exceptions favoring the comparator in the IDeg program included AE rates that were higher for IDeg compared to insulin detemir in Trial 3585 (subjects with T1DM) and also compared to insulin glargine in Trial 3718 (insulin-naïve subjects with T2DM). In the IDegAsp program, exceptions favoring comparator included AE rates that were higher for IDegAsp compared to insulin glargine in Trial 3590 (insulin-naïve subjects with T2DM). Treatment-emergent adverse events in all subjects from the pooled therapeutic confirmatory trials for IDeg vs. comparators and IDegAsp vs. comparators are presented in Table 7 and Table 8, respectively. Adverse events occurring in $\geq 5\%$ of subjects from the pooled therapeutic confirmatory trials are presented by SOC and preferred term in Table 9 and Table 10, respectively, for IDeg vs. comparators and IDegAsp vs. comparators.

According to the applicant, the rates of AEs for all subjects in the confirmatory trials were similar for IDeg (428.1 events per 100 patient-years of exposure [PYE]) and comparators (418.4 events per 100 PYE). The majority of the AEs were rated as mild in both groups. The rates of severe AEs were similar for IDeg (20.3 events per 100 PYE) and comparators (21.1 events per 100 PYE). Common adverse events were similar overall with IDeg and comparators in subjects with T1DM and also in those with T2DM. In subjects with T1DM, the rate of headache was higher and the rate of cough was lower for IDeg relative to comparators. Of note, there was no apparent difference in the rate of injection-site reactions between the IDeg 100 U/mL and IDeg 200 U/mL products. AEs reported with the 200 U/mL product were generally similar to those reported with the insulin glargine comparator (Trial 3672 in insulin-naïve subjects with T2DM). Differences in adverse events in the other two IDeg 200 U/mL studies (Trial 3718 and 3724) are not addressed in this review as the applicant is not pursuing the three-time weekly dosing regimen studied in these trials and also because of the limited exposure and small contribution to the overall safety findings.

For IDegAsp, the rates of AEs including all subjects in the therapeutic confirmatory trials were similar (387.3 events per 100 PYE vs. 392.7 events per 100 PYE for comparators). The majority of the AEs were rated as mild in severity in both groups. However, the rates of severe AEs were lower for IDegAsp (19.6 events per 100 PYE) than comparators (25.4 events per 100 PYE). The difference was driven largely by higher reported rates of hypoglycemia in the insulin detemir comparator group. Common adverse events were similar overall with IDeg and comparators in subjects with T1DM and also in those with T2DM. In subjects with T1DM, the rate of headache was higher and the rate of hypoglycemia was lower for IDegAsp relative to insulin detemir.

Table 7. IDeg Treatment-Emergent Adverse Events (Safety Analysis Set)

	IDeg N	(%)	E	R	Comparator N	(%)	E	R
Safety Analysis Set	4275				2269			
All Adverse Events	3018	(70.6)	12106	428.1	1530	(67.4)	5603	418.4
Serious Adverse Events	337	(7.9)	427	15.1	147	(6.5)	181	13.5
Adverse Events leading to Death	14	(0.3)	17	0.6	7	(0.3)	8	0.6
Adverse Events Possibly or Probably Related to IMP	646	(15.1)	1093	38.6	305	(13.4)	472	35.2
Severity								
Mild	2649	(62.0)	8654	306.0	1327	(58.5)	3958	295.6
Moderate	1282	(30.0)	2877	101.7	658	(29.0)	1361	101.6
Severe	405	(9.5)	574	20.3	178	(7.8)	282	21.1
Unknown	1	(0.0)	1	0.0	2	(0.1)	2	0.1
Adverse Events withdrawals	98	(2.3)	132	4.7	30	(1.3)	32	2.4

N = Number of subjects with adverse events

% = Proportion of subjects in analysis set having adverse events

E = Number of adverse events

R = Number of events divided by subject years of exposure multiplied by 100

IMP = Investigational Medicinal Product

Source: N203314, SCC, Table 2-1.

Table 8. IDegAsp Treatment-Emergent Adverse Events (Safety Analysis Set)

	IDegAsp N (%)	E	R	Comparator N (%)	E	R
Safety Analysis Set	1360			1037		
All Adverse Events	886 (65.1)	2906	387.3	642 (61.9)	2116	392.7
Serious Adverse Events	115 (8.5)	149	19.9	80 (7.7)	101	18.7
Adverse Events leading to Death	4 (0.3)	4	0.5	1 (0.1)	1	0.2
Adverse Events Possibly or Probably Related to IMP	171 (12.6)	247	32.9	133 (12.8)	235	43.6
Severity						
Mild	761 (56.0)	2140	285.2	555 (53.5)	1532	284.3
Moderate	347 (25.5)	619	82.5	249 (24.0)	447	83.0
Severe	108 (7.9)	147	19.6	81 (7.8)	137	25.4
Adverse Events withdrawals	25 (1.8)	28	3.7	16 (1.5)	24	4.5

N = Number of Subjects with adverse events

% = Proportion of subjects in analysis set having adverse events

E = Number of adverse events

R = Number of events divided by Subject years of exposure multiplied by 100

IMP = Investigational Medicinal Product

Source: N203313, SCC, Table 2-1.

Table 9. IDeg Treatment-Emergent Adverse Events (> 2%) by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg N (%)	E	R	Comparator N (%)	E	R
Safety Analysis Set	4275			2269		
Total Exposure (yrs)	2828.2			1339.1		
All Adverse Events	3018 (70.6)	12106	428.1	1530 (67.4)	5603	418.4
Infections and infestations						
Nasopharyngitis	642 (15.0)	855	30.2	278 (12.3)	371	27.7
Upper respiratory tract infection	373 (8.7)	499	17.6	174 (7.7)	226	16.9
Influenza	151 (3.5)	166	5.9	64 (2.8)	76	5.7
Bronchitis	146 (3.4)	166	5.9	64 (2.8)	74	5.5
Sinusitis	132 (3.1)	167	5.9	63 (2.8)	71	5.3
Gastroenteritis	126 (2.9)	137	4.8	55 (2.4)	56	4.2
Urinary tract infection	120 (2.8)	140	5.0	48 (2.1)	54	4.0
Gastrointestinal disorders						
Diarrhoea	244 (5.7)	310	11.0	152 (6.7)	184	13.7
Nausea	157 (3.7)	188	6.6	95 (4.2)	107	8.0
Vomiting	122 (2.9)	135	4.8	65 (2.9)	77	5.1
Musculoskeletal and connective tissue disorders						
Back pain	198 (4.6)	239	8.5	98 (4.3)	130	9.7
Pain in extremity	137 (3.2)	155	5.5	66 (2.9)	74	5.5
Arthralgia	135 (3.2)	151	5.3	63 (2.8)	80	6.0
Nervous system disorders						
Headache	408 (9.5)	699	24.7	171 (7.5)	259	19.3
Dizziness	85 (2.0)	101	3.6	65 (2.9)	76	5.7
General disorders and administration site conditions						
Fatigue	92 (2.2)	114	4.0	52 (2.3)	55	4.1
Oedema peripheral	104 (2.4)	123	4.3	39 (1.7)	43	3.2
Injury, poisoning and procedural complications						
Wrong drug administered	112 (2.6)	119	4.2	22 (1.0)	23	1.7
Respiratory, thoracic and mediastinal disorders						
Cough	183 (4.3)	197	7.0	85 (3.7)	103	7.7
Oropharyngeal pain	131 (3.1)	149	5.3	63 (2.8)	71	5.3
Metabolism and nutrition disorders						
Hypoglycaemia	132 (3.1)	185	6.5	57 (2.5)	84	6.3
Eye disorders						
Diabetic retinopathy	91 (2.1)	94	3.3	44 (1.9)	45	3.4
Vascular disorders						
Hypertension	118 (2.8)	125	4.4	50 (2.2)	52	3.9

N= Number of subjects with adverse events, %= Proportion of subjects in analysis set having adverse events, E= Number of adverse events, R= Number of events divided by subject years of exposure multiplied by 100.

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

Source: N203314, SCC, Table 2-2.

Table 10. IDegAsp Treatment-Emergent Adverse Events (> 2%) by System Organ Class and Preferred Term (Safety Analysis Set)

	IDegAsp N (%)	E	R	Comparator N (%)	E	R
Safety Analysis Set	1360			1037		
Total Exposure (yrs)	750.2			538.8		
All Adverse Events	886 (65.1)	2906	387.3	642 (61.9)	2116	392.7
Infections and infestations						
Nasopharyngitis	200 (14.7)	266	35.5	119 (11.5)	164	30.4
Upper respiratory tract infection	90 (6.6)	112	14.9	69 (6.7)	89	16.5
Gastroenteritis	31 (2.3)	32	4.3	24 (2.3)	25	4.6
Influenza	32 (2.4)	32	4.3	21 (2.0)	25	4.6
Gastrointestinal disorders						
Diarrhoea	53 (3.9)	65	8.7	46 (4.4)	52	9.7
Nausea	24 (1.8)	35	4.7	29 (2.8)	33	6.1
Vomiting	27 (2.0)	28	3.7	22 (2.1)	23	4.3
Dyspepsia	13 (1.0)	14	1.9	22 (2.1)	29	5.4
Musculoskeletal and connective tissue disorders						
Back pain	47 (3.5)	52	6.9	35 (3.4)	41	7.6
Arthralgia	37 (2.7)	41	5.5	31 (3.0)	32	5.9
Pain in extremity	37 (2.7)	42	5.6	21 (2.0)	23	4.3
Nervous system disorders						
Headache	91 (6.7)	169	22.5	66 (6.4)	91	16.9
Dizziness	30 (2.2)	33	4.4	12 (1.2)	12	2.2
General disorders and administration site conditions						
Pyrexia	37 (2.7)	42	5.6	23 (2.2)	24	4.5
Oedema peripheral	26 (1.9)	35	4.7	23 (2.2)	23	4.3
Metabolism and nutrition disorders						
Hypoglycaemia	50 (3.7)	77	10.3	47 (4.5)	81	15.0
Eye disorders						
Diabetic retinopathy	48 (3.5)	49	6.5	32 (3.1)	32	5.9
Respiratory, thoracic and mediastinal disorders						
Cough	32 (2.4)	35	4.7	19 (1.8)	20	3.7
Oropharyngeal pain	30 (2.2)	33	4.4	19 (1.8)	21	3.9
Vascular disorders						
Hypertension	44 (3.2)	48	6.4	21 (2.0)	22	4.1

N= Number of Subjects with adverse events, %= Proportion of subjects in analysis set having adverse events, E= Number of adverse events, R= Number of events divided by Subject years of exposure multiplied by 100.

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

Source: N203313, SCC, Table 2-2.

b. Deaths

In total, 21 deaths (14 subjects treated with IDeg and 7 treated with comparators) were reported in the completed IDeg clinical trials. All of the deaths occurred in the therapeutic confirmatory trials where 4275 subjects were exposed to IDeg and 2269 subjects were exposed to comparators. Adjusted for the skewed randomization, the rate of fatal adverse events leading to death was similar for both IDeg and the comparators (0.6 events per 100 PYE). Of all the 21 subjects who died, four subjects had T1DM and 17 subjects had T2DM (five of whom were insulin-naïve). A summary of the subjects who died in the IDeg program is presented in Table 11. Although many of the deaths

were considered by the study investigators as “unlikely” to be related to the study medication, a review of the narratives of all fatal events, albeit incomplete and inconclusive in some cases, suggests that at least five of the cardiovascular-related deaths in IDeg-treated subjects could possibly have been related to the study product. MACE endpoints are discussed in Section 5 of this review and in the FDA biostatistical review.

In total, 6 deaths (4 subjects treated with IDegAsp and 2 treated with biphasic insulin aspart [BIAsp30]) were reported in the completed IDegAsp clinical trials. Five of the deaths occurred in the therapeutic confirmatory trials. Two of the deaths in IDegAsp-exposed subjects were noted to be due to interstitial lung disease that was apparently absent at baseline. Another case of apical lung fibrosis described as “mild” was noted in the IDegAsp program in a 49-year-old woman with T1DM who had been on IDegAsp for 183 days when the AE was detected. She had normal renal function and was noted to have hyperlipidemia, additional details were not available and the case continued to be listed as unresolved. A summary of the subjects who died in the IDegAsp program is presented in Table 12. Review of the narratives for these deaths supported the causality assessment provided by the investigators in all six cases.

Table 11. Deaths in Completed IDeg Trials

Trial ID	IMP	Case Number/ Subject ID	Age (years) /Sex	Type of Diabetes	Preferred Term	Investigator's causality to IMP
3583*	IGlar	307002/ 300375	26/Female	T1DM	Sudden death	Probable
3582	IGlar	600002/ 303905	61/Male	Insulin-treated T2DM	Metastatic neoplasm	Unlikely
3582*	IGlar	802016/ 313420	49/Male	Insulin-treated T2DM	Myocardial infarction	Possible
3668*	IGlar	805002/ 309299	63/Male	Insulin-treated T2DM	Death	Unlikely
3579	IGlar	927007/ 303733	73/Male	Insulin-naïve T2DM	Urosepsis	Unlikely
3672*	IGlar	213003/ 311549	64/Male	Insulin-naïve T2DM	Myocardial ischaemia	Unlikely
3672*	IGlar	527006/ 313608	55/Male	Insulin-naïve T2DM	Pneumonia Acute myocardial infarction	Unlikely
3770	IDeg	314540/ 743001	46/Female	T1DM	Completed suicide Hypoglycaemic coma	Probable
3583*	IDeg	302907/ 306006	67/Male	T1DM	Myocardial infarction	Unlikely
3583*	IDeg	303708/ 633005	60/Male	T1DM	Myocardial infarction	Unlikely
3668	IDeg	306248/ 809008	72/Female	Insulin-treated T2DM	Anaemia Myelodysplastic syndrome	Unlikely
3582*	IDeg	301937/ 127017	65/Male	Insulin-treated T2DM	Arteriosclerosis Hypertensive heart disease	Unlikely
3582*	IDeg	302881/ 140007	58/Male	Insulin-treated T2DM	Myocardial infarction	Unlikely
3582*	IDeg	302224/ 154007	69/Male	Insulin-treated T2DM	Haemorrhage intracranial	Unlikely
3582*	IDeg	292730/ 168001	63/Male	Insulin-treated T2DM	Cardio-respiratory arrest	Unlikely
3582	IDeg	310274/ 310006	69/Male	Insulin-treated T2DM	Haematemesis	Unlikely
3582*	IDeg	300310/ 406011	67/Female	Insulin-treated T2DM	Cardiac arrest	Unlikely
3582	IDeg	300432/ 507005	53/Male	Insulin-treated T2DM	Myocardial infarction	Unlikely
3582	IDeg	292922/ 800010	57/Male	Insulin-treated T2DM	Road traffic accident	Unlikely
3580*	IDeg	314363/ 707013	49/Male	Insulin-naïve T2DM	Myocardial infarction	Unlikely
3586	IDeg	310793/ 202018	69/Male	Insulin-naïve T2DM	Drowning	Possible

* Fatal events in these subjects were also categorised as Major Adverse Cardiovascular Events (MACEs)

One fatal event was considered non-treatment-emergent and not included in the above table:

Trial ID = NN1250-3579, Subject ID = 664003, SRC Reported Term = Sudden cardiac death;

Source: N203314, SCC, Table 2-5.

Table 12. Deaths in Completed IDegAsp Trials

Trial Number	IMP	Case number/ Subject Id	Age of subject (years old)/ Sex	Type of Diabetes	Preferred Term	Investigator's causality to IMP
1792	BIAsp 30	276820/ 501015	59 / Male	T2DM/ insulin naïve	Cardiac failure	Unlikely
3592	BIAsp 30	304848/ 404011	71/ Male	T2DM/ insulin treated	Head injury	Unlikely
3590	IDegAsp	307439/ 606002	62/ Male	T2DM/ insulin-naïve	Metastasis to liver	Unlikely
3590*	IDegAsp	306620/ 702002	60/ Male	T2DM/ Insulin naïve	Death	Probably
3592	IDegAsp	304661/ 704013	41/ Male	T2DM/ Insulin treated	Interstitial lung disease	Unlikely
3597	IDegAsp	313622/ 311002	85/ Female	T2DM/ Insulin treated	Interstitial lung disease	Unlikely

* Fatal events in these subjects were also categorised as Major Adverse Cardiovascular Events (MACEs)

Source: N203313, SCC, Table 2-5.

c. Nonfatal Serious Adverse Events

The rates of SAEs were relatively low and generally similar with IDeg and comparators. SAEs reported in the therapeutic confirmatory trials were slightly higher for IDeg (15.1 events per 100 PYE) than comparators (13.5 events per 100 PYE), and study withdrawal due to an SAE was 1.3% for IDeg and 0.9% for comparators. In subjects with T1DM, the most frequently reported SAEs ($\geq 1\%$ of the subjects) were events of hypoglycemia in the Metabolism and nutrition disorders SOC, and rates were similar for both IDeg and comparators. Hypoglycemia is addressed in the efficacy review. In subjects with T2DM, $\geq 1\%$ of the subjects in the IDeg group reported SAEs in the Cardiac disorders and Infections and infestations SOCs. In the comparators group, $\geq 1\%$ of the subjects reported SAEs in the Cardiac disorders SOC. SAEs reported in $\geq 1\%$ of subjects are presented by SOC and preferred term in Table 13. Overall, the types and rates of SAEs across trials, as well as withdrawal due to SAEs, were generally similar between IDeg and comparators with few exceptions. The SAE rate was higher for IDeg compared to sitagliptin in Trial 3580 and also for IDeg compared to insulin glargine in Trial 3672 (both trials involved insulin-naïve subjects with T2DM).

In the IDegAsp program, the rates of SAEs were similar for IDegAsp (19.9 events per 100 PYE) and comparators (18.7 events per 100 PYE). The percentages of subjects who withdrew from the trial due to an SAE was 1.4% for IDegAsp and 1.1% for comparators, and the rates were 2.8 events per 100 PYE and 2.4 events per 100 PYE for IDegAsp and comparators, respectively. As with the IDeg program, the most frequently reported SAEs were events of hypoglycemia for both IDegAsp and comparators. Overall, the types and rates of SAEs across trials, as well as withdrawal due to SAEs, were generally similar between IDegAsp and comparators. The SAE rate was higher for IDegAsp compared to insulin glargine in Trial 3590 (insulin-naïve subjects with T2DM). In subjects with T1DM, the most frequently reported SAEs ($\geq 1\%$ of the subjects) were events of hypoglycemia in the Metabolism and nutrition disorders SOC, and rates were higher with

IDegAsp than comparators. The difference was driven by a single subject who experienced eight separate hypoglycemic episodes that were classified as SAEs. In the subjects with T2DM, most SAEs for both IDegAsp and comparators were reported in the Cardiac disorders, Infections and infestations, and Metabolism and nutrition disorders SOCs. SAEs reported in $\geq 1\%$ of subjects are presented by SOC and preferred term in Table 14. Within the Cardiac disorders SOC, splitting of preferred terms may be obscuring potential differences in CV events.

Table 13. IDeg Serious Adverse Events (> 1%) by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg N	(%)	E	R	Comparator N	(%)	E	R
Safety Analysis Set	4275				2269			
Total Exposure (yrs)	2828.2				1339.1			
All Adverse Events	337	(7.9)	427	15.1	147	(6.5)	181	13.5
Metabolism and nutrition disorders	81	(1.9)	97	3.4	28	(1.2)	36	2.7
Hypoglycaemia	49	(1.1)	57	2.0	17	(0.7)	21	1.6
Hypoglycaemic unconsciousness	26	(0.6)	30	1.1	9	(0.4)	9	0.7
Diabetic ketoacidosis	4	(0.1)	4	0.1				
Hypoglycaemic seizure	2	(0.0)	2	0.1	2	(0.1)	2	0.1
Dehydration					1	(0.0)	1	0.1
Diabetes mellitus inadequate control	1	(0.0)	1	0.0				
Hypercalcaemia					1	(0.0)	1	0.1
Hyperglycaemia					1	(0.0)	1	0.1
Hyperkalaemia					1	(0.0)	1	0.1
Hypoglycaemia unawareness	1	(0.0)	1	0.0				
Hyponatraemic syndrome	1	(0.0)	1	0.0				
Ketosis	1	(0.0)	1	0.0				
Cardiac disorders	65	(1.5)	74	2.6	25	(1.1)	30	2.2
Coronary artery disease	13	(0.3)	14	0.5	3	(0.1)	3	0.2
Myocardial infarction	9	(0.2)	9	0.3	2	(0.1)	2	0.1
Angina unstable	9	(0.2)	9	0.3				
Acute myocardial infarction	6	(0.1)	6	0.2	1	(0.0)	1	0.1
Cardiac failure congestive	3	(0.1)	3	0.1	4	(0.2)	4	0.3
Acute coronary syndrome	3	(0.1)	3	0.1	3	(0.1)	4	0.3
Atrial fibrillation	3	(0.1)	3	0.1	3	(0.1)	3	0.2
Angina pectoris	3	(0.1)	3	0.1	2	(0.1)	2	0.1
Coronary artery occlusion	3	(0.1)	3	0.1	1	(0.0)	1	0.1
Coronary artery stenosis	1	(0.0)	1	0.0	3	(0.1)	3	0.2
Myocardial ischaemia	2	(0.0)	2	0.1	2	(0.1)	2	0.1
Atrial flutter	1	(0.0)	1	0.0	1	(0.0)	1	0.1
Cardiac failure	2	(0.0)	2	0.1				
Tachyarrhythmia	2	(0.0)	2	0.1				
Tachycardia	2	(0.0)	2	0.1				
Aortic valve incompetence	1	(0.0)	1	0.0				
Bradycardia	1	(0.0)	1	0.0				
Cardiac arrest	1	(0.0)	1	0.0				
Cardiac asthma					1	(0.0)	1	0.1
Cardio-respiratory arrest	1	(0.0)	1	0.0				
Cardiomyopathy	1	(0.0)	1	0.0				
Cardiopulmonary failure					1	(0.0)	1	0.1
Congestive cardiomyopathy	1	(0.0)	1	0.0				
Coronary artery thrombosis	1	(0.0)	1	0.0				
Hypertensive heart disease	1	(0.0)	1	0.0				
Mitral valve incompetence	1	(0.0)	1	0.0				
Sinus bradycardia					1	(0.0)	1	0.1
Supraventricular tachycardia					1	(0.0)	1	0.1
Ventricular hypokinesia	1	(0.0)	1	0.0				
Ventricular tachycardia	1	(0.0)	1	0.0				

Table 13 (Continued). IDeg Serious Adverse Events (> 1%) by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg N	(%)	E	R	Comparator N	(%)	E	R
Infections and infestations	47	(1.1)	52	1.8	21	(0.9)	22	1.6
Cellulitis	8	(0.2)	8	0.3	1	(0.0)	1	0.1
Pneumonia	2	(0.0)	2	0.1	5	(0.2)	5	0.4
Diverticulitis	2	(0.0)	2	0.1	2	(0.1)	2	0.1
Gastroenteritis	1	(0.0)	1	0.0	3	(0.1)	3	0.2
Appendicitis	3	(0.1)	3	0.1				
Pyelonephritis	3	(0.1)	3	0.1				
Urinary tract infection	2	(0.0)	2	0.1	1	(0.0)	1	0.1
Bronchitis	2	(0.0)	2	0.1				
Erysipelas					2	(0.1)	2	0.1
Gastroenteritis viral	1	(0.0)	1	0.0	1	(0.0)	1	0.1
Lobar pneumonia	2	(0.0)	2	0.1				
Localised infection	2	(0.0)	2	0.1				
Pyelonephritis acute	1	(0.0)	1	0.0	1	(0.0)	1	0.1
Wound infection	2	(0.0)	2	0.1				
Abscess jaw	1	(0.0)	1	0.0				
Abscess limb	1	(0.0)	1	0.0				
Abscess oral	1	(0.0)	1	0.0				
Arthritis bacterial	1	(0.0)	1	0.0				
Bronchopneumonia					1	(0.0)	1	0.1
Bronchopulmonary aspergillosis	1	(0.0)	1	0.0				
Campylobacter infection					1	(0.0)	1	0.1
Cholecystitis infective					1	(0.0)	1	0.1
Diabetic foot infection	1	(0.0)	1	0.0				
Endocarditis	1	(0.0)	1	0.0				
Herpes zoster	1	(0.0)	1	0.0				
Incision site abscess	1	(0.0)	1	0.0				
Infected sebaceous cyst	1	(0.0)	1	0.0				
Influenza	1	(0.0)	1	0.0				
Pneumonia bacterial	1	(0.0)	1	0.0				
Pneumonia primary atypical	1	(0.0)	1	0.0				
Pneumonia staphylococcal	1	(0.0)	1	0.0				
Pulmonary tuberculoma					1	(0.0)	1	0.1
Pulmonary tuberculosis					1	(0.0)	1	0.1
Pyelonephritis chronic	1	(0.0)	1	0.0				
Respiratory tract infection	1	(0.0)	1	0.0				
Salmonella sepsis	1	(0.0)	1	0.0				
Streptococcal bacteraemia	1	(0.0)	1	0.0				
Subcutaneous abscess	1	(0.0)	1	0.0				
Tracheobronchitis	1	(0.0)	1	0.0				
Urosepsis					1	(0.0)	1	0.1
Vaginal infection	1	(0.0)	1	0.0				

N= Number of subjects with adverse events

%= Proportion of subjects in analysis set Having adverse events

E= Number of adverse events

R= Number of events divided by subject years of exposure multiplied by 100

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

Source: N203314, SCC, Table 2-9.

Table 14. IDegAsp Serious Adverse Events (> 1%) by System Organ Class and Preferred Term (Safety Analysis Set)

	IDegAsp N (%)	E	R	Comparator N (%)	E	R
Safety Analysis Set	1360			1037		
Total Exposure (yrs)	750.2			538.8		
All Adverse Events	115 (8.5)	149	19.9	80 (7.7)	101	18.7
Metabolism and nutrition disorders	31 (2.3)	47	6.3	28 (2.7)	31	5.8
Hypoglycaemia	18 (1.3)	30	4.0	16 (1.5)	16	3.0
Hypoglycaemic unconsciousness	10 (0.7)	10	1.3	11 (1.1)	11	2.0
Diabetic ketoacidosis	2 (0.1)	3	0.4	3 (0.3)	3	0.6
Hypoglycaemic seizure	2 (0.1)	3	0.4	1 (0.1)	1	0.2
Diabetic foot	1 (0.1)	1	0.1			
Infections and infestations	17 (1.3)	17	2.3	9 (0.9)	9	1.7
Gastroenteritis	4 (0.3)	4	0.5	3 (0.3)	3	0.6
Cellulitis	2 (0.1)	2	0.3	1 (0.1)	1	0.2
Pneumonia	1 (0.1)	1	0.1	1 (0.1)	1	0.2
Pulmonary tuberculosis	1 (0.1)	1	0.1	1 (0.1)	1	0.2
Vestibular neuronitis	1 (0.1)	1	0.1	1 (0.1)	1	0.2
Abscess limb	1 (0.1)	1	0.1			
Bronchitis	1 (0.1)	1	0.1			
Laryngitis	1 (0.1)	1	0.1			
Malaria				1 (0.1)	1	0.2
Meningitis	1 (0.1)	1	0.1			
Osteomyelitis	1 (0.1)	1	0.1			
Subcutaneous abscess	1 (0.1)	1	0.1			
Tooth abscess	1 (0.1)	1	0.1			
Urinary tract infection				1 (0.1)	1	0.2
Wound infection	1 (0.1)	1	0.1			
Cardiac disorders	13 (1.0)	13	1.7	12 (1.2)	12	2.2
Angina pectoris	2 (0.1)	2	0.3	3 (0.3)	3	0.6
Acute myocardial infarction	2 (0.1)	2	0.3	2 (0.2)	2	0.4
Coronary artery stenosis	3 (0.2)	3	0.4			
Myocardial infarction	2 (0.1)	2	0.3			
Acute coronary syndrome				1 (0.1)	1	0.2
Angina unstable				1 (0.1)	1	0.2
Arrhythmia supraventricular				1 (0.1)	1	0.2
Atrial fibrillation	1 (0.1)	1	0.1			
Cardiac asthma				1 (0.1)	1	0.2
Cardiac failure	1 (0.1)	1	0.1			
Cardiac failure congestive				1 (0.1)	1	0.2
Coronary artery disease	1 (0.1)	1	0.1			
Myocardial ischaemia				1 (0.1)	1	0.2
Pericardial effusion	1 (0.1)	1	0.1			
Tachyarrhythmia				1 (0.1)	1	0.2

N= Number of Subjects with adverse events

%= Proportion of subjects in analysis set having adverse events

E= Number of adverse events

R= Number of events divided by Subject years of exposure multiplied by 100

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

Source: N203313, SCC, Table 2-8.**d. Adverse Events Leading to Dose Reduction**

The percentages of subjects reporting AEs leading to dose reduction were 4.4% for IDeg and 3.3% for comparators. The rates of AEs leading to dose reduction were 8.8 events per 100 PYE for IDeg and 6.6 events per 100 PYE for comparators. The most frequent AEs leading to dose reduction were events of hypoglycemia. In subjects with T1DM, AEs leading to dose reduction were reported in 8.7% of those receiving IDeg and 7.5% of comparators. The percentages of subjects with T1DM reporting AEs leading to dose reduction and the rates of these AEs were higher than those reported for all subjects. In subjects with T2DM, AEs leading to dose reduction were reported in 2.9% of those receiving IDeg and 2.2% of comparators.

The percentages of subjects reporting AEs leading to dose reduction were 3.5% for IDegAsp and 5.2% for comparators. The rate of AEs leading to dose reduction was lower for IDegAsp (8.5 events per 100 PYE) than comparators (13.5 per 100 PYE). The most frequent AEs leading to dose reduction were events of hypoglycemia. This was consistent for subjects with T1DM and also for T2DM.

e. Dropouts and/or Discontinuations Due to Adverse Events

In the IDeg program, the percentage of subjects who withdrew from study due to an AE was 2.3% for IDeg and 1.3% for comparators. In the therapeutic confirmatory trials, the rates of AEs leading to withdrawal were higher for IDeg (4.7 events per 100 PYE) than comparators (2.4 events per 100 PYE). Nearly half of the AEs leading to withdrawal in IDeg group and majority of the AEs in the comparators group were SAEs. The rates of SAEs leading to withdrawal were similar for the IDeg (2.3 events per 100 PYE) and the comparators (1.7 events per 100 PYE) groups. No specific patterns in AEs or SAEs leading to withdrawal were observed, and differences between IDeg and comparators were relatively small. In the IDeg group, the most frequent AEs that led to withdrawal of subjects were events of hypoglycemia (8 events), weight increased (7 events), and myocardial infarction (6 events). Of the AEs leading to withdrawal, 17 events in the IDeg group and 6 events in the comparators group were reported as MACE. In subjects with T1DM, 2.2% in the IDeg group discontinued study due to AEs as did 0.9% in the comparator. The rates of AEs leading to withdrawal were higher for IDeg (5.2 events per 100 PYE) than the comparators (1.4 events per 100 PYE). In subjects with T2DM, 2.3% in the IDeg group discontinued study due to AEs as did 1.4% in the comparator. The rates of AEs leading to withdrawal were higher for IDeg (4.5 events per 100 PYE) than the comparators (2.7 events per 100 PYE). Of the AEs leading to withdrawal of subjects with T2DM, 15 events in the IDeg group and five events in the comparator group were reported as MACE. Of these MACE, nine events resulted in death.

In the IDegAsp program, the percentages of subjects discontinuing study due to AEs were 1.8% for IDegAsp and 1.5% for comparators. The majority of the AEs leading to withdrawal were SAEs in both IDegAsp and comparators group. The percentages of subjects who withdrew from study due to an SAE was 1.4% for IDegAsp and 1.1% for comparators, and the rates were 2.8 events per 100 PYE and 2.4 events per 100 PYE for IDegAsp and comparators, respectively. As with the IDeg program, the most frequently reported SAEs were events of hypoglycemia for both IDegAsp and comparators. Substantial differences in rates of withdrawal across IDegAsp trials and among treatment groups were not observed. No specific patterns in AEs or SAEs leading to withdrawal were observed, and differences between IDeg and comparators were relatively small. Of the AEs leading to withdrawal, 2 events in the IDegAsp group and 3 events in the comparators group were reported as MACE. The majority of AEs leading to withdrawals were reported under the SOC, Metabolism and nutrition disorders in the IDegAsp group.

f. Other Supportive Safety Results

i. Immunogenicity/Allergic Reactions

Immunogenicity-related adverse events (allergic or hypersensitivity reactions) are local and/or systemic reactions ranging from urticaria to potentially fatal anaphylactic reactions. Allergic reactions were considered AEs of special interest in the IDeg and the IDegAsp development programs, and potential reactions were assessed based on an evaluation of the events reported in all the completed trials. In total, 65 immunogenicity-related AEs were identified in all trials with IDeg and IDegAsp. Allergic reactions by SOC and preferred term for IDeg+IDegAsp are presented in Table 15. Urticaria was the most common allergic reaction both in IDeg+IDegAsp and comparators. Three allergic reactions with IDeg were categorized as serious, while none were considered serious in any of the comparators. One case of anaphylaxis was listed in the section on rare adverse events. Overall, the number of allergic reactions was relatively low, and differences between IDeg+IDegAsp and comparators were not readily apparent.

Reviewer's Comment: Subject 0023 in clinical pharmacology Trial 3538 was a 29-year-old woman who experienced an "anaphylactic reaction" with generalized pruritus, redness, and swelling of lips and upper eye lids one hour after the first dose of IDeg. She apparently did not receive any treatment for the event, and the symptoms resolved spontaneously. A blood sample collected 10 days after the event revealed the presence of insulin IgE antibodies (possibly cross-reacting), but the concentrations at that time were slightly below the cut-off value. This case perhaps might be better described as an anaphylactoid reaction.

Reviewer's Comment: Immunogenicity-related adverse events were relatively uncommon and appeared to be mostly balanced between treatment groups. In some cases the narratives lacked sufficient detail about the allergic reaction to allow for adequate assessment of causality.

Table 15. Allergic Reactions for IDeg+IDegAsp by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg	+ IDegAsp		Comparator			
	N	(%)	E R	N	(%)	E R	
Safety Analysis Set	5635			3306			
Total Exposure (yrs)	3578.4			1878.0			
All Adverse Events	44 (0.8)	45 1.3	16 (0.5)	17 0.9	
Skin and subcutaneous tissue disorders (Selected PTs#)	31 (0.6)	31 0.9	13 (0.4)	13 0.7	
Urticaria	23 (0.4)	23 0.6	8 (0.2)	8 0.4	
Swelling face	3 (0.1)	3 0.1	4 (0.1)	4 0.2	
Angioedema	2 (0.0)	2 0.1	1 (0.0)	1 0.1	
Circumoral oedema	1 (0.0)	1 0.0				
Exfoliative rash	1 (0.0)	1 0.0				
Urticaria chronic	1 (0.0)	1 0.0				
Eye disorders (Selected PTs#)	5 (0.1)	5 0.1	1 (0.0)	1 0.1	
Eye swelling	3 (0.1)	3 0.1	1 (0.0)	1 0.1	
Eyelid oedema	1 (0.0)	1 0.0				
Periorbital oedema	1 (0.0)	1 0.0				
Gastrointestinal disorders (Selected PTs#)	4 (0.1)	4 0.1	1 (0.0)	2 0.1	
Lip swelling	2 (0.0)	2 0.1	1 (0.0)	2 0.1	
Swollen tongue	2 (0.0)	2 0.1				
General disorders and administration site conditions (Selected PTs#)	4 (0.1)	4 0.1	1 (0.0)	1 0.1	
Face oedema	4 (0.1)	4 0.1	1 (0.0)	1 0.1	
Vascular disorders (Selected PTs#)	1 (0.0)	1 0.0				
Circulatory collapse	1 (0.0)	1 0.0				

N= Number of subjects with adverse events,

%= Proportion of subjects in analysis set having adverse events,

E= Number of adverse events,

R= Number of events divided by subject years of exposure multiplied by 100

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

#Only PTs under the selection as per listing 15 (Appendix 2.2) appear under this SOC

Source: N203314, SCC, Table 2-15.**ii. Injection-Site Reactions & Lipodystrophy**

Injection-site reactions of redness, swelling, itching, pain, and hematoma at the injection site were assessed as potential risks associated with subcutaneous administration of IDeg and IDegAsp. Occasionally, injection-site reactions may be associated with a systemic allergic reaction. In the IDeg therapeutic confirmatory trials, the rates of injection-site reactions were 7.6 events per 100 PYE in the IDeg group and 8.4 events per 100 PYE in the comparator group. For IDegAsp the rate was 5.1 events per 100 PYE vs. 8.4 events per 100 PYE in the comparator group.

The majority of the reactions with both IDeg and IDegAsp were categorized as mild or moderate, and none (except for 3 comparator cases) were assessed as severe. None of the reactions in either development program and in any study arm were considered serious. For IDeg, the rates were higher in subjects with T2DM for both treatment groups. For IDegAsp, the rates in subjects with T2DM were higher for IDegAsp than comparators (6.2 vs. 3.3 events, respectively, per 100 PYE).

The rates of lipodystrophy in the therapeutic confirmatory trials were low for both IDeg (0.5 events per 100 PYE) and comparators (0.4 events per 100 PYE), and none were assessed as severe or serious. The rates of lipodystrophy in the IDegAsp therapeutic confirmatory trials were lower for IDegAsp than comparators (0.3 vs. 2.2 events, respectively, per 100 PYE). None of them were assessed as severe or serious. Also, no differences were observed between IDeg and comparators in the time of onset or duration (typically resolved several days after onset) of the injection-site reactions.

iii. Peripheral Edema

The rates of peripheral edema for IDeg and comparators were 4.3 and 3.2 events, respectively, per 100 PYE. The majority of events occurred in subjects with T2DM and were mild or moderate in severity. No serious events were reported. The rates of peripheral edema for IDegAsp and comparators were 4.7 and 4.3 events, respectively, per 100 PYE. The rates were similar for IDegAsp in the subjects with T1DM and the subjects with T2DM.

iv. Neoplasia

A potential relationship between insulin analogues and an increased risk of cancer—possibly mediated by increased IGF-1 receptor activation or by sustained signaling by the insulin receptor—has been proposed but remains a hypothesis. The applicant considered neoplasms to be events of special interest in the IDeg and IDegAsp development programs. The following is a summary as reported by the applicant: A total of 211 events of neoplasms reported with IDeg, IDegAsp, or comparators in the therapeutic confirmatory trials were sent for classification by an external consultant. Of these, 140 events were classified as benign neoplasms, 46 events were classified as malignant, and 25 events were assessed as unclassifiable. No differences were observed between IDeg+IDegAsp and comparators in any of the three categories. The rates of malignant neoplasms were similar between IDeg+IDegAsp (0.9 events per 100 PYE) and comparator (0.8 events per 100 PYE). The five most frequently reported types of malignancies involved the skin, gastrointestinal tract, breast, thyroid, and bladder. Skin and gastrointestinal malignant neoplasms were reported slightly more in IDeg+IDegAsp, whereas breast, thyroid, and bladder malignant neoplasms were reported slightly more in the comparator group. The majority of the malignant neoplasms in the IDeg+IDegAsp group (52%) were reported within 3 months after start of study treatment. The rates of benign neoplasms were similar between IDeg+IDegAsp (2.7 events per 100 PYE) and comparators (2.2 events per 100 PYE). Clustering of events was observed within the gastrointestinal system (polyps and adenomas) and the urogenital system (renal cysts). The rates of unclassifiable neoplasms were very low for IDeg+IDegAsp and comparators (0.6 events per 100 PYE vs. 0.3 events per 100 PYE in comparator). The majority of events assessed as ‘unclassifiable’ were reported within the gastrointestinal disorders SOC.

v. Medication Errors

According to the applicant, most medication errors were reported in clinical trials using a basal bolus regimen and resulted from confusion between bolus and basal insulin and in a few cases led to serious adverse events. Higher rates of errors were observed in the IDeg group than in the comparators (7.3 and 4.2 events, respectively, per 100 PYE), which the applicant speculates is likely due to a greater focus on medication errors with a new insulin product and also because of possible familiarity with the commercial products among the subjects randomized to the comparator.

vi. Diabetic Retinopathy

Given that abrupt improvement in glycemic control can be associated with temporary worsening of diabetic retinopathy and severe hypoglycemic episodes can worsen proliferative retinopathy, diabetic retinopathy was assessed as an AE of special interest. Overall rates of diabetic retinopathy were similar between those treated with IDeg or IDegAsp and their comparators. There were no differences in the time to onset or in the duration of the events between the treatment groups, and the majority of events occurred after 6 months of treatment. In subjects with T1DM, the rate of retinopathy events was lower for IDegAsp (5.4 events per 100 PYE) than insulin detemir (8.9 events per 100 PYE), whereas in subjects with T2DM the rates of retinopathy events were higher for IDegAsp (10.1 events per 100 PYE) than comparators (7.9 events per 100 PYE).

vii. Rare Events

Rare adverse events were assessed in all studies across both development programs. In all, 26 and 15 rare events were reported in the IDeg+IDegAsp and the comparator groups, respectively. The rates of these events were similar for IDeg+IDegAsp (0.7 events per 100 PYE) and the comparator group (0.8 events per 100 PYE). Approximately half of these events in both groups were classified as serious. The specific rare events for IDeg+IDegAsp are presented by SOC and preferred term in Table 16.

Table 16. Rare Adverse Events for IDeg+IDegAsp by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg + IDegAsp*		Comparator	
	N (%)	E R	N (%)	E R
Safety Analysis Set	6382		3754	
Total Exposure (yrs)	3771.2		1966.7	
All Adverse Events	24 (0.4)	26 0.7	13 (0.3)	15 0.8
Cardiac disorders (Selected PTs#)				
(Selected PTs #)	8 (0.1)	8 0.2	3 (0.1)	3 0.2
Acute myocardial infarction	8 (0.1)	8 0.2	3 (0.1)	3 0.2
Nervous system disorders				
(Selected PTs#)	6 (0.1)	6 0.2	1 (0.0)	1 0.1
Cerebrovascular accident	5 (0.1)	5 0.1	1 (0.0)	1 0.1
Convulsion	1 (0.0)	1 0.0		
Renal and urinary disorders				
(Selected PTs#)	3 (0.0)	3 0.1	2 (0.1)	2 0.1
Renal failure acute	3 (0.0)	3 0.1	2 (0.1)	2 0.1
Vascular disorders (Selected PTs#)				
Peripheral arterial occlusive disease	2 (0.0)	3 0.1	3 (0.1)	5 0.3
	2 (0.0)	3 0.1	3 (0.1)	5 0.3
Respiratory, thoracic and mediastinal disorders				
(Selected PTs#)	3 (0.0)	3 0.1	1 (0.0)	1 0.1
Acute respiratory failure			1 (0.0)	1 0.1
Pulmonary embolism	1 (0.0)	1 0.0		
Pulmonary fibrosis	1 (0.0)	1 0.0		
Pulmonary hypertension	1 (0.0)	1 0.0		
Gastrointestinal disorders				
(Selected PTs#)	2 (0.0)	2 0.1	1 (0.0)	1 0.1
Gastrointestinal haemorrhage	2 (0.0)	2 0.1	1 (0.0)	1 0.1
Blood and lymphatic system disorders (Selected PTs#)				
Thrombocytopenia	1 (0.0)	1 0.0	1 (0.0)	1 0.1
	1 (0.0)	1 0.0	1 (0.0)	1 0.1
General disorders and administration site conditions (Selected PTs#)				
Sudden death			1 (0.0)	1 0.1
			1 (0.0)	1 0.1

N= Number of subjects with adverse events

%= Proportion of subjects in analysis set having adverse events

E= Number of adverse events

R= Number of events divided by subject years of exposure multiplied by 100

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

* Includes all formulations

#Only PTs under the selection as per listing 15 (Appendix 2.2) appear under this SOC

*Source: N203314, SCC, Table 2-46.***g. Hypoglycemia**

Hypoglycemia is addressed in detail in Section 11 of the clinical efficacy review above.

h. Clinical Laboratory Parameters

Blood and other fluids were sampled at specified time points depending on the parameter (most at baseline, 26 weeks, and 52 weeks for some studies). Samples were sent to a central laboratory for analysis.

i. Insulin Antibodies

The applicant tested for development of IDeg-specific antibodies and insulin antibodies cross-reacting with human insulin and concluded that there were no interactions between development of insulin antibodies and injection-site reactions or hypoglycemic episodes. In the therapeutic confirmatory trials, the mean change from baseline to 27 and 53 weeks of treatment in antibodies cross-reacting with human insulin and in specific insulin analogue antibodies was low in both the IDeg and the comparator group, and there was no difference between the treatment groups. A relationship between the development of cross-reacting antibodies and change in glycemic control also was not observed. The proportion of subjects experiencing an increase in cross-reacting antibody levels and possible lack of effect (as assessed by HbA_{1c}) in the IDeg group was similar to the comparator group. The magnitude of dose changes was similar with IDeg and the comparators both for subjects with T1DM and subjects with T2DM. The applicant inferred the absence of neutralizing antibodies based on the low magnitude of the dose changes (i.e., IDeg doses were not increased substantially).

A total of 18 subjects with T1DM in the IDeg group experienced an increase in the level of cross-reacting antibodies of more than 10% (absolute) and an increase in HbA_{1c} of more than 0.2% (absolute). For 6 of these subjects, the total insulin dose increased during the trials, and the IDeg dose increased for 2 subjects. The IDeg dose was increased by 2 U and 16 U over a 12-month period. In the comparator group, a total of 8 subjects experienced an increase in the level of cross-reacting antibodies of more than 10% (absolute) and an increase in HbA_{1c} of more than 0.2% (absolute). For 7 of these subjects, the total insulin dose as well as the basal insulin dose increased during the trials. The increase in comparator dose ranged from 1 U to 39 U from baseline to the end of the trial.

A total of 4 subjects with T2DM in the IDeg group experienced an increase in the level of cross-reacting antibodies of more than 10% (absolute) and did not have a decrease in HbA_{1c} of more than 0.2% (absolute). For 3 of these subjects, the total insulin dose increased during the trials. The IDeg dose increases from baseline to the end of the trial ranged from 20 U to 68 U. In the comparator group, a total of 5 subjects with T2DM experienced an increase in the level of cross-reacting antibodies of more than 10% (absolute) and did not have a decrease in HbA_{1c} of more than 0.2% (absolute). For 3 of these subjects, the total insulin dose increased during the trials. The comparator dose change ranged from -2 U to 58 U from baseline to the end of the trials.

ii. Hematology

In the therapeutic confirmatory trials, blood samples were drawn at the screening visit, after 26 weeks (all trials), and after 52 weeks (Trials 3579, 3582, and 3583) to determine the following hematology parameters: hemoglobin, erythrocytes, leucocytes, thrombocytes, hematocrit, and differential count). Only a few clinically significant changes were noted, and, in general, there were no major differences observed among the treatment groups.

iii. Biochemistry

In the therapeutic confirmatory trials, blood samples were drawn at the screening visit and at the end of the trial to determine concentrations of the following: creatinine, total protein, alanine aminotransferase (ALAT), aspartate aminotransferase (ASAT), alkaline phosphatase, sodium, potassium, albumin and total bilirubin. Few subjects had changes from normal to high or low in biochemistry values from baseline to 26 weeks or 52 weeks, and there was no difference between the two treatment groups for any of the measured parameters. There were no cases meeting the biochemical definition of Hy's Law in either the IDeg or IDegAsp programs. Changes from baseline to week 26 or 52 in renal function (based on estimated creatinine clearance, CL_{CR}) from normal ($CL_{CR} > 80$ mL/min) to mild ($CL_{CR} > 50 - \leq 80$ mL/min) or moderate ($CL_{CR} > 30 - \leq 50$ mL/min) renal impairment was investigated for all subjects. Few subjects (both T1DM and T2DM) had changes in renal function from baseline to 26 or 52 weeks, and there was no difference between the treatment groups.

iv. Lipids

In the therapeutic confirmatory trials, blood samples were drawn at the randomization visit and at the end of the trial (26 or 52 weeks) to determine concentrations of the following: HDL cholesterol, LDL cholesterol, total cholesterol and triglycerides. The subjects were to be fasting for these samples. For all subjects, the mean lipid values remained stable during the trials, and there was no difference between the IDeg or IDegAsp groups and comparators. Only a few subjects had changes from normal to high or low in lipid values from baseline to 26 weeks or 52 weeks, and there was no difference observed between the two treatment groups for any of the parameters tested. Few clinical laboratory abnormalities were regarded as clinically significant and reported as AEs. Overall, there were no statistically significant differences in the lipid endpoints between IDeg or IDegAsp and their pooled comparators, although some minor differences of minimal significance were observed in a few studies.

v. Cardiovascular Risk Indicators

In two of the IDeg therapeutic confirmatory trials (Trials 3579 and 3582, both in subjects with T2DM), blood samples were drawn at the randomization visit and after 26 and 52 weeks to determine levels of high sensitivity C-reactive protein (hsCRP), for which the subject had to be fasting, and brain natriuretic peptide (NT proBNP). In Trial 3579, the mean cardiovascular risk markers remained stable during the trial, and there was no apparent difference between the two treatment groups in mean values or mean change in values during the trial.

In Trial 3582, the mean cardiovascular risk markers remained stable during the trial, and no clinically relevant differences between the two treatment groups in mean values or mean change in values during the trial were observed. In addition, no difference was found in the change from baseline of the measured cardiovascular risk markers analyzed separately using an ANOVA method.

vi. Urinalysis

In the therapeutic confirmatory trials, urine samples were collected at screening and at the end of the trial (26 or 52 weeks) and analyzed by dip stick for blood, protein, and ketones. Microalbuminuria and a spot urine albumin/creatinine ratio were collected at randomization and at the end of the trial (26 or 52 weeks). Only a few subjects had changes from normal to high or low in urine stick values from baseline to 26 weeks or 52 weeks, and there was no overall difference between the treatment groups for any of the parameters tested. For all subjects, subjects with T1DM and subjects with T2DM, the urine albumin/creatinine ratio values remained stable during the trial, and there was no difference between the IDegAsp and comparator groups.

i. Vital Signs

In the therapeutic confirmatory trials, systolic blood pressure, diastolic blood pressure, and pulse were assessed at the screening visit and at the end of the trial (26 or 52 weeks). Measurements were performed with the subject sitting after having rested in a chair for 5 minutes. For blood pressure at the screening visit, three measurements were performed and all three values were entered into the case report form. Any clinically significant worsening of the result from baseline was to be reported as an AE. Overall, there were no clinically relevant differences between IDeg or IDegAsp and the comparators in vital signs after 26 or 52 weeks of treatment. Mean systolic and diastolic blood pressure in the confirmatory therapeutic trials was essentially unchanged from baseline in the IDeg and IDegAsp groups (approximately 130/77 mmHg and 131/78 mmHg) relative to the comparators.

j. Physical Exam

The physical examination was performed locally by the investigator and reported as “normal,” “abnormal, not clinically significant,” and “abnormal, clinically significant.” Any clinically significant worsening from baseline was reported as an AE. Overall, there were no clinically relevant differences between IDeg or IDegAsp and the comparators in physical examination after 26 or 52 weeks of treatment.

k. Electrocardiograms (ECG)

In the therapeutic confirmatory trials, a 12-lead ECG was performed at screening and at the end of the trial (26 or 52 weeks). If a 12-lead ECG had already been performed and was available within eight weeks before the randomization visit (Visit 2) and if the results were available, the procedure was not to be repeated. The ECG was performed and interpreted locally by the investigator. The interpretation followed the categories: “normal,” “abnormal, not clinically significant,” and “abnormal, clinically significant.” Any clinically significant worsening from baseline of the ECG was reported as an AE. Overall, there were no clinically relevant differences between IDeg or IDegAsp and the comparators in ECG after 26 or 52 weeks of treatment.

In Trial 3579, the QT interval was measured and analyzed. No statistically significant difference between IDeg and the comparator in change from baseline in QTc intervals were observed.

l. Fundoscopic exams/fundus photography

The funduscopy/fundusphotography was performed and interpreted locally by the investigator. The interpretation followed these categories: “normal,” “abnormal, not clinically significant,” and “abnormal, clinically significant.” Overall, there were no clinically relevant differences between IDeg or IDegAsp and the comparators in funduscopy/fundusphotography after 26 or 52 weeks of treatment.

m. Body weight changes

Changes in body weight are addressed in the clinical efficacy review (Tables 48-50).

n. Additional Safety Information

i. Dose or Time Dependency of Adverse Events

In the therapeutic confirmatory studies, the dose of IDeg and IDegAsp was titrated to response in a treat-to-target manner. Excessive doses of insulin are expected to produce profound hypoglycemia as might occur in accidental or intentional overdose. There was no notable time dependency for most AEs.

ii. Drug-Drug, Drug-disease, & Drug-Demographic interactions

Formal drug interaction studies were not presented. The applicant investigated the potential for drug interactions by assessing whether concomitant administration of a given group of drugs (glucose increasing, glucose lowering, or protein binding drugs) was associated with a difference in rates of events of hyperglycemia or confirmed hypoglycemic episodes. These data were largely unremarkable and generally consistent with the experience from approved short- and long-acting insulin products.

Adverse event data were investigated with regards to possible differences due to various intrinsic factors. Except for some minor differences in reporting rates (e.g., higher in women than in men for both IDeg/IDegAsp and comparator groups), most factors such as age, race/ethnicity, body mass index, end-organ function, and certain baseline co-morbidities did not influence AE reporting rates. Although true differences in AE rates might be expected based on factors such as renal dysfunction, statistically significant and clinically meaningful differences were not apparent most likely because of the relatively small overall number of events.

o. Human reproduction and pregnancy data

Human reproduction data are not available, and studies in pregnant or lactating women were not included in these applications. The applicant reports a total of 13 pregnancies in the IDeg clinical development program (7 in the IDeg group, 3 in the comparator group, and 3 from ongoing trials). Of the 7 pregnancies in the IDeg group, two women had spontaneous abortions, one had an elective abortion, one was a normal delivery of a healthy baby, one was a premature delivery of a baby who recovered from medical complications, one was a case of intrauterine death, and one was a case where the pregnancy was still ongoing. In the comparator (insulin glargine), one woman had a Cesarean delivery of a healthy baby, and two were cases where the pregnancy was still ongoing. In the IDegAsp program, 5 pregnancies were reported (3 in the IDegAsp group and 2 in the comparator group). In the IDegAsp group, one woman chose to have an induced abortion, one woman with a history of a previous spontaneous abortion experienced a spontaneous abortion in gestational week 6, and one woman gave birth to a healthy female infant in gestational week 34 by Caesarean section. In the comparator group, one woman chose to have an induced abortion and one woman was lost to follow-up.

p. Pediatrics and assessment of effects on growth

Pediatric patients were excluded from studies of IDeg and IDegAsp, and there were no data provided for subjects under the age of 18 years.

q. 120-Day Safety Update

The 120-day safety update provided by the applicant was unremarkable and did not add substantially in either quantity or quality to the adverse events originally included at filing. These data are not further addressed in this review as they do not alter the interpretation of the original safety results or otherwise further inform the risk profiles of IDeg or IDegAsp.

r. Published Literature

This clinical reviewer conducted an independent review of the published medical literature which included a search of PubMed and Embase performed in May of 2012. The literature search focused on safety-related findings with insulin degludec. The search strategy included selected indexing terms and the text words “degludec” and “insulin degludec.” The search yielded 20 publications in PubMed and 77 publications in Embase specifically pertaining to the investigational drug insulin degludec. These citations consisted mostly of review articles and some published study reports. The applicant conducted a similar search of the published literature and reported a similar finding. In all, safety concerns identified in the published literature were already identified by the applicant and were adequately addressed in the clinical safety review.

5. Cardiovascular (CV) Safety Assessment and CV Meta-analysis

Given the prevalence of heart disease in diabetic patients, the applicant sought to better characterize cardiovascular adverse events by designating them as medical events of special interest (MESI). Accordingly, the applicant also designed and prospectively conducted a CV meta-analysis of adjudicated major adverse cardiovascular events (MACE) in the pool of IDeg+IDegAsp therapeutic confirmatory trials in order to demonstrate that these two new insulin products are not associated with an increased risk of cardiovascular disease compared to active controls.

a. Meta-analysis

i. Objectives

The primary objective of the meta-analysis was to characterize the cardiovascular safety profile of IDeg. This was done by comparing the pooled insulin degludec products (IDeg and IDegAsp) to the pooled comparator products used in the therapeutic confirmatory phase 3a trials in terms of the hazard ratio for adjudicated MACE. The comparators consisted of other insulin products (most commonly insulin glargine and also insulin detemir and biphasic insulin aspart). Oral sitagliptin was used as a comparator in one trial in subjects with T2DM.

The secondary objective was to explore similarities and/or differences in subgroups of age, sex, race, ethnicity, type of diabetes, and cardiovascular history as they relate to MACE across the IDeg and IDegAsp therapeutic confirmatory trials.

ii. Definition of MACE

For purposes of the meta-analysis, the applicant defined MACE as the composite endpoint including the following: acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and myocardial infarction (non-ST-elevation myocardial infarction [NSTEMI] and ST-elevation myocardial infarction [STEMI]), stroke or cardiovascular death. In all trial protocols, MACE were required to be reported as medical events of special interest (MESI). The trial protocols included a list of diagnoses (international classification of diseases [ICD]-10 codes) that were to be linked to ACS, stroke, or cardiovascular death.

Note: The applicant uses the term MACE to include UAP. FDA defines strict MACE as excluding UAP. The term MACE is used in a general sense throughout this review. However, for the purpose of presenting statistical analyses of CV events, FDA staff will refer to “MACE” for the strict MACE definition which excludes UAP and to “MACE+” for the applicant’s original definition which includes UAP.

iii. Event Capture

In order to increase the likelihood of capturing all MACE occurring in the IDeg+IDegAsp confirmatory therapeutic trials, a thorough collection procedure was established. MESI were collected using the electronic case record form. In addition to events reported by the investigator as MESI, events reported as adverse events but not initially classified as cardiovascular MESI, were evaluated through a pre-defined standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) search performed by an internal Novo Nordisk Cardiovascular Events Evaluation Group (CEEG) independent of the degludec development program. Events assessed to be possibly related to ACS, stroke, or cardiovascular death were sent for clarification with the investigator. Once confirmed as MESI by the investigator, these events were sent for adjudication. The applicant noted that if the investigator could sufficiently substantiate the event classification as non-MESI, the event would not be sent for adjudication, but the frequency of such cases and other details were not provided. Of note, 39 of the 185 total events sent for adjudication were not initially reported as MESI but rather identified by CEEG using other screening mechanisms. Those events not sent for clarification with the investigator and those appearing to not meet the SMQ criteria were subsequently evaluated (to ensure no events were overlooked) by a medical doctor from Novo Nordisk Global Safety who is independent of the degludec development program.

iv. Adjudication Process

All collected cardiovascular MESI and suspected cardiovascular MESI were adjudicated in accordance with a pre-defined set of diagnostic criteria. This was done in order to ensure an impartial identification of events from the therapeutic confirmatory phase 3a clinical program for IDeg and IDegAsp. This was accomplished by an external, blinded independent adjudication group referred to as the Cardiovascular Event Committee (CEC). The CEC was appointed by a contract research organization (CRO) which coordinated and oversaw the work of the adjudication process. The selected committee members and chair were approved by Novo Nordisk. The objective of the CEC was to independently perform a blinded adjudication of the specific cardiovascular events based on pre-defined definitions and classifications. A charter describing the adjudication process was developed by the CRO and submitted to the FDA. The overall adjudication process was based on data sets collected by Novo Nordisk based on advice from the CRO. The CEC included a cardiologist as the chair, two additional cardiologist members, and one neurologist. Two primary adjudicators reviewed all cases according to their area of expertise. Each primary adjudicator of the CEC reviewed the data package individually and independently on an ongoing basis during the conduct of the therapeutic confirmatory program. Each adjudicator performed the assessments using an electronic review and analysis system. The outcome of the adjudication process was a list of MACE. Events rejected during the adjudication process were not included in the meta-analysis.

v. Data Process and Quality Control

Source documents required for the adjudication were provided by the investigators at the study sites. Once the CEEG received copies of all the required source documents from the sites, the document package was checked for completeness. The CEEG then transferred the package to the CRO for redaction and processing. All reviews and assessments performed by the CEC adjudicators were captured and audited in compliance with the ICH guidelines for Good Clinical Practice (GCP) and 21 CFR Part 11. The audit trail collected date and time stamps and user identity.

vi. Trials Included

The cross-trial analysis of MACE included data from 16 therapeutic confirmatory trials with IDeg or IDegAsp, which were completed as of the cut-off date of 31 January 2011. Clinical trials conducted with IDeg are identified by the project number NN1250 followed by a unique 4-digit number, and clinical trials with IDegAsp are identified by the project number NN5401 followed by a unique 4-digit number. A list of the trials included in the meta-analysis is included in the FDA biostatistical review.

vii. Trial Design

A total of 16 controlled therapeutic confirmatory trials were conducted to evaluate the efficacy and safety of IDeg (100 U/mL and 200 U/mL) and IDegAsp (100 U/mL). These trials covered early-onset T2DM to more advanced stages of T2DM and also individuals with T1DM of at least 1-year duration. All trials were randomized, controlled, open-label, multicentre, multinational trials of 26- or 52-weeks duration. All trials were carried out using a treat-to-target approach with the intent of achieving a predefined target fasting plasma glucose below 90 mg/dL and glycosylated hemoglobin (HbA1c) below 7.0%, as recommended as an appropriate target level of glycemia for patients with diabetes without serious complications. Trial design is addressed in greater detail in the clinical efficacy review.

viii. Trial Extensions

The intent of the applicant was to include completed extension studies in the CV meta-analysis. As of the cut-off date, only one extension trial (Trial 3645) was completed. This trial was included in the analysis by joining the data from the controlled extensions with the main trial data. The joined data were considered as one trial, and “baseline” was defined as the randomization visit in the main trial.

ix. Statistical Methods & Analysis Sets

The statistical methods of the original meta-analysis and the updated analyses are addressed in the FDA biostatistical review. For the primary statistical analysis and the sensitivity analyses of time to event, the results were presented as the estimated hazard ratio (IDeg+IDegAsp versus comparators) with the corresponding 95% CI. The primary

statistical analysis of MACE and all descriptive summaries were based on the full analysis set, which included all randomized subjects. As part of the sensitivity analyses the primary statistical analysis was repeated on the safety analysis set.

x. Calculation of Exposure

Extent of exposure was derived as time from the first dose administration until last dose administration of the trial product. The total exposure was used to calculate the number of MACE per 100 PYE. Withdrawn subjects contributed to the calculation of exposure until the point of withdrawal.

xi. Primary Endpoint

The endpoint used in the primary analysis was defined as the time in days from first trial drug administration to first adjudicated MACE. The analysis of MACE was described in all study protocols to be based on TEAEs, defined as an event that has onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment.

b. Cardiovascular Adverse Events

CV adverse events were considered medical events of special interest in the IDeg and IDegAsp development programs. According to the applicant, overall rates of CV events in the therapeutic confirmatory trials (reported in the SOC Cardiac Disorders and Vascular Disorders) were similar between IDeg+IDegAsp and comparators for both T1DM and T2DM. The rates of the events in the SOC Cardiac Disorders were similar between IDeg+IDegAsp (6.4 events per 100 PYE) vs. comparators (6.9 events per 100 PYE). As described above, a subset of CV events were classified as MACE by an independent, blinded external adjudication panel. MACE for IDeg+IDegAsp are presented by SOC and preferred term in Table 17.

A meta-analysis of MACE was performed by the applicant. The original analysis included a total of 80 subjects experiencing at least one MACE, and the primary endpoint was time from randomization until first MACE. The incidence rate of MACE was 1.48 events per 100 PYE in the IDeg+IDegAsp group and 1.44 events per 100 PYE in the comparator group. The incidence rates were based on 53 subjects with MACE in the IDeg+IDegAsp group and 27 subjects with MACE in the comparator group. The estimated hazard ratio for IDeg+IDegAsp versus comparators was 1.10 (95% confidence interval [CI]: [0.68; 1.77]). Of note, three MACE were considered non-treatment-emergent cardiovascular events and were not included in the original primary analysis: one event of 'Sudden cardiac death' which occurred 11 days after stopping treatment, one event of 'non S-T elevation myocardial infarction', which occurred nine days after stopping of treatment, and one event of 'Acute Pontine Stroke' which occurred 18 days after stopping treatment.

Based on the totality of the data, the applicant concluded that there is no evidence that IDeg+IDegAsp is associated with a differential cardiovascular risk relative to comparators. However, as noted elsewhere in this review, updated data were received from the applicant, and this has since been the subject of extensive investigation and FDA biostatistical analysis and review.

Table 17. MACE for IDeg+IDegAsp vs. Comparator by System Organ Class and Preferred Term (Safety Analysis Set)

	IDeg N	+ IDegAsp (%)	E	R	Comparator N	(%)	E	R
Safety Analysis Set	5635				3306			
Total Exposure (yrs)	3578.4				1878.0			
All Adverse Events	54 (1.0)		56	1.6	27 (0.8)		28	1.5
Cardiac disorders	41 (0.7)		43	1.2	18 (0.5)		19	1.0
Myocardial infarction	10 (0.2)		10	0.3	1 (0.0)		1	0.1
Acute myocardial infarction	7 (0.1)		7	0.2	3 (0.1)		3	0.2
Angina unstable	7 (0.1)		7	0.2	3 (0.1)		3	0.2
Coronary artery disease	6 (0.1)		7	0.2	1 (0.0)		1	0.1
Acute coronary syndrome	2 (0.0)		2	0.1	4 (0.1)		4	0.2
Angina pectoris	2 (0.0)		2	0.1	4 (0.1)		4	0.2
Cardiac failure congestive	1 (0.0)		1	0.0	1 (0.0)		1	0.1
Coronary artery occlusion	2 (0.0)		2	0.1				
Myocardial ischaemia					2 (0.1)		2	0.1
Cardiac arrest	1 (0.0)		1	0.0				
Cardio-respiratory arrest	1 (0.0)		1	0.0				
Coronary artery thrombosis	1 (0.0)		1	0.0				
Hypertensive heart disease	1 (0.0)		1	0.0				
Ischaemic cardiomyopathy	1 (0.0)		1	0.0				
Nervous system disorders	11 (0.2)		11	0.3	4 (0.1)		4	0.2
Cerebrovascular accident	4 (0.1)		4	0.1	1 (0.0)		1	0.1
Ischaemic stroke	2 (0.0)		2	0.1	2 (0.1)		2	0.1
Cerebral infarction	2 (0.0)		2	0.1				
Carotid artery occlusion	1 (0.0)		1	0.0				
Haemorrhage intracranial	1 (0.0)		1	0.0				
Haemorrhagic stroke	1 (0.0)		1	0.0				
Thalamic infarction					1 (0.0)		1	0.1
General disorders and administration site conditions	2 (0.0)		2	0.1	3 (0.1)		3	0.2
Chest pain	1 (0.0)		1	0.0	1 (0.0)		1	0.1
Death	1 (0.0)		1	0.0	1 (0.0)		1	0.1
Sudden death					1 (0.0)		1	0.1
Injury, poisoning and procedural complications					1 (0.0)		1	0.1
In-stent coronary artery restenosis					1 (0.0)		1	0.1
Vascular disorders					1 (0.0)		1	0.1
Arteriosclerosis					1 (0.0)		1	0.1

N= Number of subjects with adverse events,

%= Proportion of subjects in analysis set having adverse events,

E= Number of adverse events, R= Number of events divided by subject years of exposure multiplied by 100

Total Exposure (yrs)= Total Exposure in years for Safety Analysis Set

3 MACE were considered non-treatment-emergent and not included in the above table:

Trial ID = NN1250-3579, Subject ID = 664003, SRC Reported Term = Sudden cardiac death;

Trial ID = NN1250-3579, Subject ID = 960001, SRC Reported Term = non S-T elevation

myocardial infarction

Trial ID = NN1250-3724, Subject ID = 426001, SRC Reported Term = Acute Pontine Stroke

Source: N203314, SCC, Table 2-25.

c. Assessment of CV Safety Parameters

Cardiovascular safety was evaluated based on vital signs (including heart rate and blood pressure), body weight, electrocardiograms, clinical laboratory data, and incidence of CV-related TEAEs and study withdrawals due to CV adverse events. These and other available safety parameters were adequately analyzed across all study subjects and study treatment arms to explore similarities and/or differences in MACE among subgroups of age, sex, race, ethnicity, type of diabetes, and cardiovascular history.

6. Overview of Cardiovascular Safety Signal

Diabetes mellitus is associated with an increased risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this population. Risk factors for heart disease and stroke worldwide include smoking, obesity, diabetes, hypercholesterolemia, and hypertension. An FDA guidance document dated December 2008 is available to advise the pharmaceutical industry on evaluation of the CV risk of new medications used to treat type 2 diabetes. The guidance makes recommendations about how to demonstrate that new therapies for diabetes are not intrinsically associated with an unacceptable degree of excess CV risk beyond that inherent to the underlying glycemic disorder. Although some have proposed that exogenous insulin administration itself can increase CV risk through direct atherogenic effects, this remains largely theoretical and unproven. The guidance does not specifically address the use of insulin for type 2 diabetes but recognizes that “the absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term CV risk may not be practical.” It is worth noting that exposure to insulin degludec in the clinical development programs represented in these two new drug applications involved mainly subjects with type 2, not type 1 diabetes mellitus. After progressive beta-cell destruction or in cases when other therapies have failed, insulin may be the only viable treatment option for some patients with type 2 diabetes. Insulin therapy may prove useful even earlier in the disease process for optimal glycemic control in some patients with this condition.

Review of these two applications has identified a CV safety signal that requires further investigation. Based on the applicant’s own meta-analysis of cardiovascular events from the 16 therapeutic confirmatory trials across the IDeg and IDegAsp development programs (as confirmed by FDA biostatistical review), the risk of major adverse cardiovascular events (MACE) in the pooled IDeg and IDegAsp group was consistently higher than the pooled all-comparator group, albeit the confidence interval crossed unity in all of the applicant’s major analyses. The applicant pre-defined MACE as a composite endpoint of the following: acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and myocardial infarction (non-ST-elevation myocardial infarction [NSTEMI] and ST-elevation myocardial infarction [STEMI]), stroke or cardiovascular death. There were relatively few CV deaths reported, and the differences in the overall composite endpoint appear to have been largely driven by the higher rate of ST-segment elevation myocardial infarction (12 vs. 2 cases for IDeg+IDegAsp and comparator, respectively).

The original analyses conducted by the applicant, along with subsequent re-analyses of the original data and updated analyses using data from trials or trial extensions that were completed after the original cutoff date of January 31, 2011, are presented in the statistical section below (the new cutoff date for the updated analyses was May 1, 2012). While there is uncertainty in these findings, the point estimates and confidence intervals in the updated analyses do not provide reassurance about the absence of excess CV risk but rather raise added concern because the data consistently trend toward harm. The re-analysis of the original data using a stricter definition of MACE (i.e., excluding unstable angina), and the updated analysis using data mostly from trial extensions completed after the original cutoff date, only amplify the CV signal and suggest even greater potential for risk with IDeg+IDegAsp relative to the pooled comparators. Refer to the biostatistical review for a summary of the CV safety findings.

It should be noted that cardiovascular toxicity was not noted in extensive nonclinical studies. The validity of the cardiovascular safety data, however, are supported by the applicant's own detailed report describing the methodology for capturing and assessing MACE events for inclusion in their CV meta-analysis. Although admittedly these data were not derived from dedicated CV safety studies (i.e., trials in which cardiovascular outcomes were the primary endpoints), the process described by the applicant—which was developed *a priori* and conducted prospectively—appears to be sound and robust. In all confirmatory therapeutic trials, MACE endpoints were required to be reported as medical events of special interest. Other reported AEs that were not initially classified as CV events of special interest were also carefully evaluated using a predefined, standardized Medical Dictionary for Regulatory Activities (MedDRA) query (SMQ) searches.

All CV events and suspected events of special interest were adjudicated by a masked, independent panel of experts using pre-specified, objective measures. The fact that these studies were open-label in design may raise legitimate concerns about the quality of the data, but this limitation does not diminish the overall validity of the CV safety signal, particularly because of the relatively objective endpoints and the systematic and pre-specified manner by which CV events were ascertained and evaluated. A limitation of the CV meta-analysis is the limited statistical power owing to the relatively small number of MACE in the original data set, which would be expected to contribute to the wide observed confidence intervals. The unbalanced randomization in favor of insulin degludec would not be expected to bias the overall finding but it also likely contributed to the widening of the confidence intervals.

Review of data regarding subject withdrawal from the therapeutic confirmatory trials did not identify a high number of withdrawals due to non-MACE cardiovascular-related adverse events (e.g., chest pain) that might have progressed to or otherwise contributed to hard MACE endpoints. With the exception of hypoglycemia and increased weight, there were no substantial differences among the treatment groups in other AEs leading to early withdrawal that might by their nature be expected to introduce bias in the hard MACE endpoint.

Overall, there were no obvious imbalances in key baseline parameters (e.g., demographics, concomitant medications, glycemic control, co-morbidities) sufficient to introduce bias in favor of the comparator arms and falsely amplify the CV safety signal. Specifically, study subject characteristics of potential relevance to the cardiovascular system, including sex, age, weight, BMI, blood pressure, heart rate, ECG findings, lipid parameters, HbA1c, renal function, duration of diabetes, and concomitant antidiabetic medications were not substantially different at baseline among the study arms, both for patients with type 1 and type 2 diabetes. Also, use of medications that affect the cardiovascular system, such as aspirin or antihyperlipidemics, did not differ among groups at baseline.

Treatment-related differences between the study arms in terms of important clinical endpoints of relevance to CV health were also not present. Substantial end-of-study differences in endpoints such as heart rate, blood pressure, ECG findings, lipid parameters, and pro-coagulant markers or markers of inflammation (where available) were not detected. Furthermore, there were no convincing data to suggest a relationship between MACE and differences in glycemic control or in the incidence of severe hypoglycemic episodes. The use of concomitant medications with potential to affect MACE endpoints (e.g., aspirin, antihyperlipidemics, antihypertensives) did not differ appreciably between the treatment groups during the course of the trials. Differences among the study arms in terms of baseline characteristics or treatment response, if present, could possibly have informed the apparent imbalance in MACE. Nonetheless, the absence of a confirmed biological mechanism does not negate or diminish the validity of the CV signal.

The applicant asserts that the open-label design may be associated with reporting bias illustrated by either lack of reporting or a considerably longer reporting time of potential MACE in the comparator arm than in the IDeg+IDegAsp arm, particularly during the trial extensions. While it is true that an open-label design has limitations compared to a double-masked scheme, the applicant has not provided convincing evidence to support their assertion about the lack of reporting or longer reporting time, and why such reporting bias, if it truly exists, would disproportionately favor the comparator. Furthermore, the applicant has not addressed why reporting biases would be more pronounced in the trial extensions, given that a majority of study participants entered the controlled trial extensions and also given that the same intensive CV safety monitoring plan that was in place for the main trials was also utilized for the study extensions. The applicant claims that familiarity of the investigators with the comparator insulins (mostly insulin glargine and insulin detemir) may have biased the reporting of rare events, including MACE. However, there is no compelling reason to assume that investigators in these trials would have preferentially reported serious MACE endpoints for insulin degludec over comparators.

The applicant also asserts that the majority of events “occurred outside the clinical trial setting” thereby possibly contributing to underreporting of events. While this is possible with all clinical trials, it should be noted that the investigators were well aware that MACE endpoints were medical events of special interest and presumably would have

been equally vigilant in identifying and reporting AEs for all the study treatments. Again, it cannot be assumed that potential underreporting in this circumstance would necessarily be biased in favor of the comparators. In response to our May 17, 2012 information request, the applicant correctly asserts that underreporting of events in the comparator arms during the extension studies, if truly present, would have a disproportionate effect on the hazard ratio given the skewed randomization scheme (exposure is 3 times lower in the comparator arms) used in the therapeutic confirmatory trial extensions. As such, one unreported MACE in the comparator arm would have a larger impact than one unreported MACE in the IDeg+IDegAsp arm. The applicant also notes that the reporting time for CV events sent for adjudication was longer for the comparators vs. IDeg+IDegAsp (median of 15 vs. 8 days, respectively) during the extension phase of the trials compared to the main trial periods (median of 8 vs. 6 days, respectively) thereby lending credibility to the possibility of reporting bias.

In conclusion, a potentially important and credible CV safety signal has been identified in the IDeg and IDegAsp development programs. Although causation has not been proven and a plausible mechanism remains to be elucidated, careful investigation of this CV safety signal is nonetheless imperative.

Appendix A. Information Request to Applicant Dated April 27, 2012

Additional submissions related to CV safety were provided by the applicant on May 11, 2012 in response to the following information request:

1. Repeat all of the original analyses (including sensitivity analyses) using the original dataset with a cut-off date of January 31, 2011. In these repeat analyses, define MACE as a composite of cardiovascular death, nonfatal MI, and nonfatal stroke only. Include all events reported up to 30 days after drug discontinuation.
2. Update the original cardiovascular safety analyses using data from trials or trial extensions that have been completed since the previous cut-off of January 31, 2011. Clearly delineate how this new dataset differs from the original dataset. Provide the new cut-off date and briefly describe (preferably in tabular format) all the additional trials, including the number of additional patients and patient-year exposure for each trial and overall for all included trials. Confirm that all additional events included in the dataset were prospectively and blindly adjudicated. Repeat the original analyses (including sensitivity analyses) using the new cut-off date and present these analyses using *both* your original broader definition of MACE and the Agency's definition (i.e., cardiovascular death, nonfatal MI, and nonfatal stroke). Include events reported up to 30 days after drug discontinuation.
3. Repeat all of the analyses with the expanded dataset as outlined in item 2 above (present analyses using both definitions of MACE and including events reported up to 30 days after drug discontinuation) *but* include only studies using other insulin products as a comparator (exclude the study employing sitagliptin as the comparator) and present the findings in two ways: 1) including the studies of patients with T1DM only and 2) including the studies of subjects with both T1DM and T2DM.

Appendix B. Demographics and Selected Baseline Characteristics for Updated CV Analysis Dataset (FAS Population)

	IDeg+IDegAsp	Comparators	MACE	MACE+
Total Number of Subjects	5794	3461	91	132
Gender				
Male	56.10%	55.20%	71.43%	68.18%
Female	43.90%	44.80%	28.57%	31.82%
Age (years)	54.2±12.9	55.1±12.2	61.9±9.1	61.8±8.9
18-65	79.70%	78.80%	61.54%	62.12%
65-75	17.70%	18.20%	34.07%	33.33%
>75	2.60%	3.00%	4.40%	4.55%
Race				
White	68.50%	66.50%	74.73%	77.27%
Black	5.10%	4.80%	5.49%	6.06%
Asian	24.50%	27.10%	18.68%	15.91%
Other	1.90%	1.60%	1.10%	0.76%
Ethnicity				
Hispanic or Latino	8.50%	9.30%	10.99%	9.85%
Not Hispanic or Latino	90.00%	88.90%	89.01%	90.15%
Not Applicable	1.50%	1.80%		
Diabetes				
Type 1	25.30%	19.00%	9.89%	10.61%
Type 2	74.70%	81.00%	90.11%	89.39%
Diabetes Duration (years)	12.6±9.0	11.8±8.4	14.4±9.4	15.0±9.9
BMI (kg/m²)	29.0±5.3	29.5±5.4	30.6±5.3	30.8±5.1
<25	24.70%	22.50%	13.19%	12.88%
25-30	35.10%	34.00%	36.26%	33.33%
30-35	25.50%	27.00%	25.27%	31.06%
>35	14.70%	16.50%	25.27%	22.73%
Region				
U.S.	31.46%	29.67%	37.36%	43.18%
Non-U.S.	68.54%	70.33%	62.64%	56.82%

Source: Dr. Bo Li, FDA, October 2012.



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF BIostatISTICS

STATISTICAL BRIEFING CLINICAL STUDIES

NDA/Serial Number: 203314/N-000

Drug Name: Tresiba™ (insulin degludec [rDNA origin] injection)

Indication(s): Treatment of Diabetes Mellitus

Applicant: Novo Nordisk Inc.

Date(s): Received 09/29/2011; user fee (extended) 10/29/2012

Review Priority: Standard

Biometrics Division: Division of Biometrics II (HFD-715)

Statistical Reviewer: Cynthia Liu, MA

Concurring Reviewer(s): Todd Sahlroot, Ph.D., Statistical Team Leader and Deputy Director of Biometrics II

Medical Division: Division of Metabolic and Endocrine Products (HFD-510)

Clinical Team: Karim Calis, M.D., Medical Reviewer
Jean-Marc Guettier, M.D., Medical Team Leader

Project Manager: Rachel Hartford

TABLE OF CONTENTS

1. INTRODUCTION	3
2. STUDY DESIGN AND ENDPOINTS	3
3. STATISTICAL EVALUATION	5
3.1 Statistical Methods	5
3.2 Subject Disposition	6
3.3 Demographic and Baseline Characteristics	7
3.4 Efficacy Results and Discussion	12
4. CONCLUSIONS	20
5. APPENDIX I	23

1. INTRODUCTION

Novo Nordisk is developing a novel, ultra-long-acting human insulin analog, called Tresiba™ (insulin degludec, NN1250), for the treatment of hyperglycemia associated with type 1 and type 2 diabetes mellitus in adults. It is expected that the timing of the injection can vary from day to day (about 8-40 hours between injections), independent of meals, depending on the needs of the individual patient. The sponsor submitted the original NDA on 09/29/2011, comprising a total of 41 completed clinical trials. The efficacy of insulin degludec (IDeg) in patients with diabetes will be determined primarily based on the results from 3 Phase 3a confirmatory trials for type 1 diabetes mellitus (T1DM) and 6 for type 2 diabetes mellitus (T2DM). This briefing document focuses on the efficacy evaluation (HbA1c and FPG) of these trials with some discussion related to hypoglycemic episodes, body weight, and insulin dose.

Throughout this report, the prefix (NN1250) before each study number is omitted for the ease of discussion. For example, Study NN1250-3579 is referred as Study 3579. Unless otherwise stated, all the tables and graphs in this report were generated by this reviewer.

2. STUDY DESIGN AND ENDPOINTS

All the 9 efficacy studies reviewed here were randomized, open-label, parallel-group, active-controlled, multicenter, multinational, treat-to-target trials (Table 1). Except for Study 3672 (T2DM) where IDeg 200 U/mL was evaluated, all others investigated the efficacy and safety of IDeg 100 U/mL. The active comparator was insulin glargine (IGlar, Lantus®) 100 U/mL for all trials, except for Study 3585 (T1DM) and Study 3580 (T2DM) where insulin detemir (IDet, Levemir®) 100 U/mL and sitagliptin (Januvia®, a DPP-4 inhibitor) 100 mg were used, respectively. Insulin aspart (IAsp, NovoRapid®/NovoLog®) 100 U/mL was the bolus therapy for the basal-bolus trials. The 6 T2DM trials each had different OAD(s) as the background medication (see footnotes in Table 1).

Unless otherwise noted, IDeg was injected at the main evening meal or in the evening from the start of main evening meal to bedtime. Study 3770 (T1DM) and Study 3668 (T2DM) each had 3 treatment arms: IDeg Flex, IDeg, and IGlar. The IDeg Flex arm used the fixed-flexible (FF) dosing schedule which was defined as Mondays, Wednesdays, and Fridays (injection in the morning) and Tuesdays, Thursdays, Saturdays, and Sundays (injection in the evening), resulting in intervals of a minimum of 8 hours and a maximum of 40 hours between doses. The primary objective for these 2 studies was to confirm the efficacy of IDeg administered in a FF dosing schedule in controlling glycemia when compared with IGlar. Study 3580 (T2DM) also utilized a flexible dosing regimen for IDeg, which was injected at *any time* of the day (not FF) and at varying times from day to day, but also with a minimum of 8 hours and a maximum of 40 hours interval between injections.

Table 1 – Study Designs

Study	WK	Treatment groups	Back-ground med.	Random-ized pts	Stratifying factor	HbA1c at entry	HbA1c collection
Table 1 Diabetes Mellitus (T1DM)							
3583 (09/09 – 11/10)	52	IDeg 100 vs. IGLar 100	IAsp	629 (472:157)	None	≤ 10.0%	Weeks -1, 0, 12, 16, 26, 40, 52
3585 (02/10 – 12/10)	26	IDeg 100 vs. IDet 100	IAsp	456 (303:153)	Region (Europe, South America, Japan, India)	≤ 10.0%	Weeks -1, 0, 12, 16, 26
3770 (11/09 – 09/10)	26	IDeg 100 Flex vs. IDeg 100 vs. IGLar 100	IAsp	493 (164:165:164)	None	≤ 10.0%	Weeks -1, 0, 12, 16, 26
Table 2 Diabetes Mellitus (T2DM)							
3582 (09/09 – 10/10)	52	IDeg 100 vs. IGLar 100	IAsp ± OAD(s)	1006 (755:251)	Previous insulin (basal-bolus, basal only, other)	7.0% – 10.0%	Weeks -1, 0, 12, 16, 26, 40, 52
3579 (09/09 – 01/11)	52	IDeg 100 vs. IGLar 100	OAD(s)	1030 (773:257)	None	7.0% – 10.0%	Weeks -1, 0, 12, 16, 26, 40, 52
3672 (03/10 – 11/10)	26	IDeg 200 vs. IGLar 100	OAD(s)	460 (230:230)	None	7.0% – 10.0%	Weeks -1, 0, 12, 16, 26
3586 (02/10 – 12/10)	26	IDeg 100 vs. IGLar 100	OAD(s)	435 (289:146)	Region (Japan, Asia w/o Japan)	7.0% – 10.0%	Weeks -1, 0, 12, 16, 26
3668 (11/09 – 09/10)	26	IDeg 100 Flex vs. IDeg 100 vs. IGLar 100	OAD(s)	687 (229:228:230)	Previous therapy (basal, OAD(s), basal + OAD(s))	7.0% – 11.0% ^a	Weeks -1, 0, 12, 16, 26
3580 (01/10 – 11/10)	26	IDeg 100 Flex vs. Sitagliptin	OAD(s)	458 (229:229)	Use of pioglitazone at screening	7.5% – 11.0% ^b	Weeks -1, 0, 12, 16, 26
<p>The OAD(s) for Study 3582 were ± metformin ± pioglitazone.</p> <p>The OAD(s) for Studies 3579 and 3672 were + metformin ± DPP-4 inhibitor.</p> <p>The OAD(s) for Study 3586 were ± metformin ± SU/glinide ± α-GI.</p> <p>The OAD(s) for Studies 3668 and 3580 were ± metformin ± SU/glinide ± pioglitazone.</p> <p>^a Specifically, HbA1c at entry was 7.0% - 11.0% if treated with OAD(s) alone or 7.0% - 10.0% if treated with basal insulin ± OAD(s).</p> <p>^b For patients from Argentina, HbA1c at entry was 7.5% - 10.0%.</p>							

Except for Study 3580 (a superiority trial), all others were designed to show non-inferiority (NI) of IDeg to their comparator, with the NI margin of 0.4%. The primary endpoint was change in HbA1c from baseline to end of treatment for all trials. The confirmatory secondary endpoints were prioritized for the purpose of statistical testing by the sponsor and were different from trial to trial (Table 2). Since not all the statistically significant endpoints will be of interest or informative for the labeling, HbA1c, FPG, body weight, hypoglycemia, and insulin doses were chosen to be the focus of this report by this reviewer irrespective of the planned testing orders of the confirmed secondary endpoints.

Table 2 – Prioritized Confirmed (Key) Secondary Endpoints

Study	Nocturnal confirmed hypoglycemia	Confirmed Hypoglycemia	FPG	Within-subject variability in SMPG	HbA1c < 7% without conf. hypoglycemia	HbA1c < 7%
Table 1 Diabetes Mellitus						
3583	1 st	2 nd	3 rd	4 th	--	--
3585	1 st	2 nd	3 rd	4 th	--	--
3770	--	--	--	--	--	--
Table 2 Diabetes Mellitus						
3582	--	1 st	2 nd	3 rd	4 th	--
3579	--	1 st	2 nd	3 rd	4 th	--
3672	--	1 st	2 nd	3 rd	4 th	--
3586	2 nd	1 st	3 rd	4 th	5 th	--
3668	--	--	--	--	--	--
3580	--	--	1 st	--	3 rd	2 nd

3. STATISTICAL EVALUATION

3.1 Statistical Methods

The primary efficacy endpoint, change from baseline in HbA1c at the end of treatment, was analyzed using an ANCOVA model with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline HbA1c as covariates for all trials (sponsor's model). Non-inferiority (NI) of IDeg to comparator in terms of glycemic control was considered confirmed if the upper bound of the two-sided 95% confidence interval of the treatment difference (IDeg minus comparator) was < 0.4%. Superiority of IDeg to comparator was considered confirmed if the upper bound of the confidence interval was < 0%. Note that the NI margin 0.4% is used routinely by the Division in active controlled trials that use insulin as the control group.

FPG and body weight data were analyzed using the methods similar to the primary efficacy endpoint. Hypoglycemic episodes were analyzed by this reviewer using Fisher's Exact test

for incidence rate (= no. of patients with events / total no. of patients) and Wilcoxon test for event rate (= total no. of events / total exposure in year).

Full Analysis Set (FAS) consisting of all randomized subjects was the primary analysis population for the sponsor. As a result, subjects who were randomized but not exposed to treatment were also included in the sponsor's primary analyses (< 2% in each study). This reviewer excluded them in her own analyses and found similar results to the sponsor's. Unless otherwise stated, results in this review report were based on the randomized subjects who had a baseline and at least 1 post-baseline efficacy measurements.

To examine the robustness of the primary analysis method based on the FAS population with the LOCF technique for missing data, several sensitivity analyses were performed by the sponsor and/or this reviewer as listed below. The results from the sensitivity analyses were all similar to the results from the primary analyses.

- The primary analysis was repeated based on the PP analysis set.
- The primary analysis was repeated based on the completer cohort.
- The primary endpoint was analyzed using the mixed model repeated measures (MMRM) analysis method which took the within-subject variation over time into consideration and did not require imputation for missing values.
- The primary endpoint was analyzed using a simpler model consisting of terms for treatment, stratifying factor (if any), and baseline HbA1c only.
- Recoded the levels of the stratifying factor for Studies 3668 and 3580 using the levels defined in the protocols.
- Replaced region with country in the primary analysis model for Studies 3585 and 3586.
- Repeated the primary analysis by including the disqualified Site 109 for Study 3582 and Site 704 for Study 3580.
- Repeated the primary analysis by excluding the subjects with Visit 2 (Week 0, baseline) HbA1c value beyond the Visit 1 inclusion criterion range.

3.2 Subject Disposition

In general, the overall reasons for withdrawal and time of discontinuation were comparable between the study groups for most of the trials. Except for Studies 3579 and 3580 (both T2DM), at least 80% of the randomized subjects in each study completed their treatment periods (Table 3). The proportions of completers between treatment groups were similar in most trials, except for Study 3770 (T1DM) and Study 3586 (T2DM) where the number of discontinuations in the IGlax group was much smaller than that in the IDeg group. According to the sponsor, Site 109 (11 IDeg, 3 IGlax) in Study 3582 and Site 704 (4 IDeg, 7 sitagliptin)

in Study 3580 were closed during the trial periods due to major issues related to data quality. After consulting with the Agency, the sponsor decided to exclude those subjects from the FAS populations for the primary efficacy analyses.

The lower percentage of completers in Studies 3579 and 3580 were due to higher dropout rates in the US sites when compared to the other countries. The majority of the US withdrawn subjects had violations of inclusion criteria.

3.3 Demographic and Baseline Characteristics

In general, the treatment groups were similar with respect to age, gender, race, country, BMI, duration of diabetes, HbA1c, and FPG at baseline in most trials based on the sponsor's FAS population (Table 4).

Studies 3585, 3586, and 3668 did not enroll any subjects from the USA. In fact, Study 3586 only recruited patients from the Asian countries to support requirements for obtaining approval in Japan. There were a total of 2698 patients exposed to IDeg and 1329 patients exposed to IGLar or sitagliptin across the 6 T2DM trials. Among them, 1500 IDeg-treated and 852 comparator-treated patients were insulin-naïve.

The mean age at entry was between 40 and 45 years across the 3 T1DM trials and between 55 and 60 years across the 6 T2DM trials. Less than 10% of the population was geriatric (> 65 years) across the T1DM trials, while between 15% and 30% of the population was geriatric across the T2DM trials. The mean BMI at entry was less than 33 kg/m² for all trials.

The mean HbA1c at baseline was less than or equal to 8.0% for the T1DM trials, but was above 8.0% for all the T2DM trials. The mean FPG at baseline was between 8.0 and 10.0 mmol/L for all trials. As expected, the mean duration of diabetes in years was longer in the T1DM trials than in the T2DM trials.

Table 3 – Subject Disposition of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) Trials

	T1DM							T2DM	
Study	3583 (52-week)		3585 (26-week)		3770 (26-week)			3582 (52-week)	
Group	IDeg	IGlar	IDeg	IDet	IDeg Flex	IDeg	IGlar	IDeg	IGlar
Randomized	472	157	303	153	164	165	164	755	251
Exposed	472 (100)	154 (98.1)	301 (99.3)	152 (99.3)	164 (100)	165 (100)	161 (98.2)	753 (99.7)	251 (100)
Safety	472 (100)	154 (98.1)	301 (99.3)	152 (99.3)	164 (100)	165 (100)	161 (98.2)	753 (99.7)	251 (100)
Sponsor FAS ¹	472 (100)	157 (100)	302 (99.7)	153 (100)	164 (100)	165 (100)	164 (100)	744 (98.5) ³	248 (98.8) ³
Reviewer FAS ²	472 (100)	154 (98.1)	301 (99.3)	152 (99.3)	164 (100)	165 (100)	161 (98.2)	742 (98.3) ³	248 (98.8) ³
Completed	404 (85.6)	137 (87.3)	283 (93.4)	138 (90.2)	138 (84.1)	139 (84.2)	152 (92.7)	618 (81.9)	211 (84.1)
Withdrawn at/after Randomization	68 (14.4)	20 (12.7)	20 (6.6)	15 (9.8)	26 (15.9)	26 (15.8)	12 (7.3)	137 (18.1)	40 (15.9)
Adverse Event	12 (2.5)	2 (1.3)	3 (1.0)	1 (0.7)	5 (3.0)	4 (2.4)	1 (0.6)	31 (4.1)	9 (3.6)
Ineffective Therapy	2 (0.4)	0 (0)	0 (0)	2 (1.3)	2 (1.2)	1 (0.6)	1 (0.6)	3 (0.4)	0 (0)
Non-compliance with Protocol	11 (2.3)	2 (1.3)	3 (1.0)	4 (2.6)	6 (3.7)	2 (1.2)	4 (2.4)	23 (3.0)	12 (4.8)
Withdrawal Criteria	15 (3.2)	3 (1.9)	6 (2.0)	3 (2.0)	6 (3.7)	6 (3.6)	2 (1.2)	8 (1.1)	2 (0.8)
Other	28 (5.9)	13 (8.3)	8 (2.6)	5 (3.3)	7 (4.3)	13 (7.9)	4 (2.4)	72 (9.5)	17 (6.8)

¹ Sponsor's FAS population consisted of all randomized subjects including the ones not exposed to treatment.

² Reviewer's FAS population consisted of subjects who were randomized and exposed to treatment.

³ Study 3582: All 14 randomized subjects (11 IDeg and 3 IGlar) from Site 109 in the US were excluded from the sponsor and reviewer's FAS populations after the site was closed as a result of major data quality issues reported by the monitor.

Table 3 – Subject Disposition of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) Trials (Continued)

	T2DM										
Study	3579 (52-week)		3672 (26-week)		3586 (26-week)		3668 (26-week)			3580 (26-week)	
Group	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg	IGlar	IDeg Flex	DPP-4
Randomized	773	257	230	230	289	146	229	228	230	229	229
Exposed	766 (99.1)	257 (100)	228 (99.1)	228 (99.1)	284 (98.3)	146 (100)	228 (99.6)	228 (100)	229 (99.6)	226 (98.7)	228 (99.6)
Safety	766 (99.1)	257 (100)	228 (99.1)	228 (99.1)	284 (98.3)	146 (100)	230 ³	226 (99.1) ³	229 (99.6)	226 (98.7)	228 (99.6)
Sponsor FAS ¹	773 (100)	257 (100)	228 (99.1)	229 (99.6)	289 (100)	146 (100)	229 (100)	228 (100)	230 (100)	225 (98.3) ⁴	222 (96.9) ⁴
Reviewer FAS ²	766 (99.1)	257 (100)	228 (99.1)	228 (99.1)	284 (98.3)	146 (100)	228 (99.6)	228 (100)	229 (99.6)	222 (96.9) ⁴	221 (96.5) ⁴
Completed	607 (78.5)	197 (76.7)	200 (87.0)	201 (87.4)	258 (89.3)	136 (93.2)	203 (88.6)	204 (89.5)	203 (88.3)	174 (76.0)	174 (76.0)
Withdrawn at/after Randomization	166 (21.5)	60 (23.3)	30 (13.0)	29 (12.6)	31 (10.7)	10 (6.8)	26 (11.4)	24 (10.5)	27 (11.7)	55 (24.0)	55 (24.0)
Adverse Event	20 (2.6)	5 (1.9)	5 (2.2)	4 (1.7)	2 (0.7)	3 (2.1)	2 (0.9)	1 (0.4)	2 (0.9)	9 (3.9)	2 (0.9)
Ineffective Therapy	7 (0.9)	2 (0.8)	0 (0)	2 (0.9)	1 (0.3)	0 (0)	2 (0.9)	2 (0.9)	1 (0.4)	0 (0)	1 (0.4)
Non-compliance with Protocol	46 (6.0)	18 (7.0)	5 (2.2)	2 (0.9)	3 (1.0)	2 (1.4)	3 (1.3)	3 (1.3)	3 (1.3)	7 (3.1)	12 (5.2)
Withdrawal Criteria	9 (1.2)	5 (1.9)	3 (1.3)	9 (3.9)	13 (4.5)	2 (1.4)	5 (2.2)	4 (1.8)	4 (1.7)	3 (1.3)	5 (2.2)
Other	84 (10.9)	30 (11.7)	17 (7.4)	12 (5.2)	12 (4.2)	3 (2.1)	14 (6.1)	14 (6.1)	17 (7.4)	36 (15.7)	35 (15.3)

¹ Sponsor's FAS population consisted of all randomized subjects including the ones not exposed to treatment.

² Reviewer's FAS population consisted of subjects who were randomized and exposed to treatment.

³ Study 3668: Two subjects were randomized to IDeg, but were treated according to the IDeg Flex regimen by mistake. These subjects were included in the safety analysis set "as treated".

⁴ Study 3580: All 11 randomized subjects (4 IDeg and 7 DPP-4 inhibitor) from Site 704 in the US were excluded from the sponsor and reviewer's FAS populations after the site was closed as a result of major data quality issues reported by the monitor.

Table 4 – Demographic and Baseline Characteristics of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) Trials

	T1DM							T2DM	
Study	3583 (52-week)		3585 (26-week)		3770 (26-week)			3582 (52-week)	
Group	IDeg (n = 472)	IGlar (n = 157)	IDeg (n = 302)	IDet (n = 153)	IDeg Flex (n = 164)	IDeg (n = 165)	IGlar (n = 164)	IDeg (n = 744)	IGlar (n = 248)
Sponsor FAS									
Gender:									
Male	278 (58.9)	90 (57.3)	150 (49.7)	86 (56.2)	102 (62.2)	94 (57.0)	88 (53.7)	405 (54.4)	133 (53.6)
Female	194 (41.1)	67 (42.7)	152 (50.3)	67 (43.8)	62 (37.8)	71 (43.0)	76 (46.3)	339 (45.6)	115 (46.4)
Race:									
White	437 (92.6)	148 (94.3)	133 (44.0)	70 (45.8)	158 (96.3)	161 (97.6)	162 (98.8)	619 (83.2)	203 (81.9)
Black	9 (1.9)	3 (1.9)	2 (0.7)	0 (0)	5 (3.0)	3 (1.8)	1 (0.6)	67 (9.0)	27 (10.9)
Asian	6 (1.3)	3 (1.9)	165 (54.6)	82 (53.6)	1 (0.6)	0 (0)	1 (0.6)	50 (6.7)	13 (5.2)
Other	20 (4.2)	3 (1.9)	2 (0.7)	1 (0.7)	0 (0)	1 (0.6)	0 (0)	8 (1.1)	5 (2.0)
Country:									
USA	328 (69.5)	111 (70.7)	0 (0)	0 (0)	90 (54.9)	88 (53.3)	84 (51.2)	377 (50.7)	123 (49.6)
Non-USA	144 (30.5)	46 (29.3)	302 (100)	153 (100)	74 (45.1)	77 (46.7)	80 (48.8)	367 (49.3)	125 (50.4)
Age (yrs)	42.8 ± 13.7	43.7 ± 13.3	41.1 ± 14.9	41.7 ± 14.4	42.6 ± 13.4	44.5 ± 13.1	44.1 ± 12.6	59.2 ± 9.1	58.1 ± 10.0
≤ 65 years	443 (93.9)	147 (93.6)	277 (91.7)	141 (92.2)	155 (94.5)	151 (91.5)	156 (95.1)	540 (72.6)	183 (73.8)
> 65 years	29 (6.1)	10 (6.4)	25 (8.3)	12 (7.8)	9 (5.5)	14 (8.5)	8 (4.9)	204 (27.4)	65 (26.2)
BMI (kg/m ²)	26.3 ± 3.7	26.4 ± 4.2	24.0 ± 3.5	23.7 ± 3.4	27.0 ± 3.8	26.4 ± 4.0	26.8 ± 4.0	32.3 ± 4.7	31.9 ± 4.5
HbA1c (%)	7.7 ± 0.9	7.7 ± 1.0	8.0 ± 1.0	8.0 ± 0.9	7.7 ± 1.0	7.7 ± 0.9	7.7 ± 0.9	8.3 ± 0.8	8.4 ± 0.9
FPG (mmol/L)	9.1 ± 4.0 (n = 465)	9.7 ± 4.4 (n = 155)	9.9 ± 4.0 (n = 301)	9.5 ± 4.0 (n = 148)	9.6 ± 4.1 (n = 161)	10.0 ± 4.0 (n = 164)	9.7 ± 4.2 (n = 162)	9.2 ± 3.0 (n = 740)	9.2 ± 3.2 (n = 248)
Duration of Diabetes (yrs)	19.1 ± 12.2	18.2 ± 11.4	13.7 ± 10.6	14.4 ± 9.7	17.3 ± 12.2	20.0 ± 12.5	18.2 ± 11.9	13.6 ± 7.4	13.4 ± 6.9

Table 4 – Demographic and Baseline Characteristics of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) Trials (Continued)

	T2DM										
Study	3579 (52-week)		3672 (26-week)		3586 (26-week)		3668 (26-week)			3580 (26-week)	
Group	IDeg	IGlar	IDeg	IGlar	IDeg	IGlar	IDeg Flex	IDeg	IGlar	IDeg Flex	DPP-4
Sponsor FAS	(n = 773)	(n = 257)	(n = 228)	(n = 229)	(n = 289)	(n = 146)	(n = 229)	(n = 228)	(n = 230)	(n = 225)	(n = 222)
Gender:											
Male	471 (60.9)	167 (65.0)	119 (52.2)	124 (54.1)	158 (54.7)	75 (51.4)	135 (59.0)	124 (54.4)	111 (48.3)	141 (62.7)	121 (54.5)
Female	302 (39.1)	90 (35.0)	109 (47.8)	105 (45.9)	131 (45.3)	71 (48.6)	94 (41.0)	104 (45.6)	119 (51.7)	84 (37.3)	101 (45.5)
White	680 (88.0)	231 (89.9)	180 (78.9)	178 (77.7)	0 (0)	0 (0)	151 (65.9)	153 (67.1)	154 (67.0)	135 (60.0)	139 (62.6)
Black	57 (7.4)	16 (6.2)	31 (13.6)	32 (14.0)	0 (0)	0 (0)	3 (1.3)	8 (3.5)	6 (2.6)	17 (7.6)	17 (7.7)
Asian	18 (2.3)	3 (1.2)	8 (3.5)	9 (3.9)	289 (100)	146 (100)	70 (30.6)	66 (28.9)	70 (30.4)	57 (25.3)	55 (24.8)
Other	18 (2.3)	7 (2.7)	9 (3.9)	10 (4.4)	0 (0)	0 (0)	5 (2.2)	1 (0.4)	0 (0)	16 (7.1)	11 (5.0)
Country:											
USA	295 (38.2)	89 (34.6)	115 (50.4)	104 (45.4)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	91 (40.4)	99 (44.6)
Non-USA	478 (61.8)	168 (65.4)	113 (49.6)	125 (54.6)	289 (100)	146 (100)	229 (100)	228 (100)	230 (100)	134 (59.6)	123 (55.4)
Age (yrs)	59.3 ± 9.7	58.7 ± 9.9	57.8 ± 9.0	57.3 ± 9.4	58.8 ± 9.8	58.1 ± 10.1	56.2 ± 10.3	56.5 ± 9.6	56.7 ± 8.8	56.4 ± 10.2	54.9 ± 11.4
≤ 65 years	551 (71.3)	187 (72.8)	184 (80.7)	180 (78.6)	206 (71.3)	107 (73.3)	186 (81.2)	192 (84.2)	188 (81.7)	183 (81.3)	181 (81.5)
> 65 years	222 (28.7)	70 (27.2)	44 (19.3)	49 (21.4)	83 (28.7)	39 (26.7)	43 (18.8)	36 (15.8)	42 (18.3)	42 (18.7)	41 (18.5)
BMI (kg/m ²)	30.9 ± 4.8	31.6 ± 4.4	32.2 ± 5.4	32.7 ± 5.3	24.6 ± 3.4	25.8 ± 3.7	29.3 ± 4.6	29.4 ± 4.9	30.0 ± 4.7	30.0 ± 5.1	30.8 ± 5.2
HbA1c (%)	8.2 ± 0.8	8.2 ± 0.8	8.3 ± 1.0	8.2 ± 0.9	8.4 ± 0.8	8.5 ± 0.8	8.5 ± 1.0	8.4 ± 0.9	8.4 ± 0.9	8.8 ± 1.0	9.0 ± 1.0
FPG (mmol/L)	9.6 ± 2.6 (n = 762)	9.7 ± 2.6 (n = 256)	9.6 ± 2.9 (n = 228)	9.7 ± 2.6 (n = 226)	8.4 ± 2.1 (n = 288)	8.6 ± 1.9 (n = 145)	9.0 ± 2.6 (n = 226)	8.8 ± 2.8 (n = 228)	9.0 ± 2.8 (n = 225)	9.4 ± 2.6 (n = 221)	9.9 ± 3.1 (n = 218)
Duration of Diabetes(yrs)	9.4 ± 6.3	8.6 ± 5.7	8.4 ± 6.7	8.0 ± 5.6	11.8 ± 6.5	11.1 ± 6.5	10.8 ± 6.9	10.3 ± 6.7	10.8 ± 6.4	7.8 ± 6.2	7.7 ± 5.9

3.4 Efficacy Results and Discussion

The collective evidence here is summarized across the 9 Phase 3a efficacy trials.

HbA1c. Table 5 below shows the mean HbA1c at baseline and endpoint as well as the mean changes from baseline for all trials. Table 6 shows the statistical hypothesis testing results for HbA1c for all trials using the FAS population (randomized and exposed) with LOCF.

As shown in Table 5, regardless of IDeg arm or comparator arm, HbA1c reductions from baseline were generally smaller in type 1 diabetic patients (mean reduction < 1%) than in type 2 diabetic patients (mean reduction > 1%). This was probably due to lower HbA1c at baseline in patients with T1DM (< 8%) when compared with that in patients with T2DM (> 8%).

Across the 9 studies, mean HbA1c decreased during the first 12-16 weeks and then was sustained or continued to decrease or increase slightly for the duration of the trial. The mean reductions in HbA1c from baseline in the IDeg group were consistently less than, or similar to, that in the comparator group at all the collection time points in all trials except for Study 3585 (T1DM) and Study 3580 (T2DM). Study 3580 was a superiority trial comparing IDeg with sitagliptin, a DPP-4 inhibitor. Superiority of IDeg in lowering HbA1c was established in this trial as the upper bound of the 95% CI of the treatment difference (IDeg – sitagliptin) in mean change from baseline in HbA1c at Week 26 was < 0% (treatment difference = -0.44%, $p < 0.0001$).

For the four 2-parallel-group, non-inferiority T2DM trials (Studies 3582, 3579, 3672, 3586), the mean reductions in HbA1c from baseline to end of the 52- or 26-week trials were numerically **less**, but not statistically significant, in the IDeg group than in the IGlax group. Non-inferiority of IDeg (either 100 or 200 U/mL) in lowering HbA1c was established in these trials; the upper bounds of the 95% CI of the treatment difference in mean change from baseline in HbA1c were all 0.2%, less than the pre-defined NI margin 0.4%. However, superiority of IDeg in these trials was not confirmed since the 95% CI of the treatment difference contained 0 ($p > 0.2$ for these trials).

For the two 2-parallel-group, non-inferiority T1DM trials (Studies 3583 and 3585), the mean reductions in HbA1c from baseline to end of the 52- or 26-week trials were numerically **greater**, but not statistically significant, in the IDeg group than in the IGlax or IDet groups. Non-inferiority of IDeg in lowering HbA1c was established in these trials since the upper bounds of the 95% CI of the treatment difference in mean change from baseline in HbA1c were both about 0.1%, less than the pre-defined NI margin 0.4%. However, superiority of

IDeg in these trials was not confirmed since the 95% CI of the treatment difference contained 0 ($p > 0.2$ for these trials).

For the two 3-parallel-group, non-inferiority trials (Study 3770 for T1DM and Study 3668 for T2DM), the mean reductions in HbA1c from baseline to end of the 26-week trials were numerically less in the IDeg Flex group than in the IGlax group. Non-inferiority of IDeg Flex in lowering HbA1c (primary objective) was established in these trials since the upper bounds of the 95% CI of the treatment difference in mean change from baseline in HbA1c were 0.3% for Study 3770 and 0.2% for Study 3668, less than the pre-defined NI margin 0.4%. However, the IDeg Flex group was statistically worse in lowering HbA1c than the IGlax group in Study 3770, but not in Study 3668, since the lower bound of the 95% CI of the treatment difference was above 0 ($p = 0.01$). The sponsor's secondary objective in these trials was to compare IDeg Flex with IDeg in glycemic control. It was found that there was no statistically significant difference between the 2 treatment groups in either trial, but the mean reduction in HbA1c was numerically less in the IDeg group than in the IDeg Flex group in Study 3668, while almost the same mean reductions were observed in Study 3770. Although it was neither a primary nor a secondary objective, this reviewer also compared IDeg with IGlax for these 2 trials. A statistically significantly less mean reduction in HbA1c from baseline to endpoint was observed in the IDeg group than in the IGlax group in both studies. However, if the same NI criterion was applied, IDeg could be shown to be clinically non-inferior to IGlax in lowering HbA1c in these trials as their upper bounds of the 95% CI of the treatment difference were 0.3%, less than the NI margin 0.4%.

As shown in Table 7, the proportion of subjects achieving HbA1c level $< 7.0\%$ at endpoint was numerically smaller, but not statistically significant, in the IDeg group than in the comparator group for all trials, except for Study 3585 (T1DM) and Study 3580 (T2DM). In Study 3585, the IDeg group showed a higher % of patients achieving the target level when compared with the IDet group; but the difference was not statistically significant. However, in Study 3580, a statistically significantly higher % of patients achieving the target level was observed in the IDeg group when compared with the sitagliptin group. The findings from responders across trials were somewhat in line with the findings from the continuous HbA1c variable discussed above.

In general, this reviewer was able to verify the sponsor's results and her own analyses results were similar to the sponsor's findings. All the supportive analyses such as using the MMRM method, different populations, and other statistical models also yielded similar results. In particular, results from the completer analyses were similar to the ones based on the FAS/LOCF population, indicating that the dropouts in each study did not have any major impact on the reduction of HbA1c.

Table 5 – Summary Statistics for HbA1c (%) across Trials

Study (Duration)	Treatment Group (FAS with LOCF)	N	Baseline Mean (SD)	Endpoint Mean (SD)	Change From Baseline	
					Raw Mean (SD)	LS Mean (SE)
Type 1 Diabetes Mellitus (T1DM)						
3583 (52-week)	IDeg + IAsp	472	7.69 (0.94)	7.29 (0.98)	-0.40 (0.73)	-0.36 (0.05)
	IGlar + IAsp	154	7.73 (0.99)	7.33 (1.09)	-0.40 (0.84)	-0.35 (0.07)
3585 (26-week)	IDeg + IAsp	301	7.98 (0.98)	7.25 (0.99)	-0.73 (0.88)	-0.70 (0.06)
	IDet + IAsp	152	7.99 (0.87)	7.33 (0.90)	-0.65 (0.86)	-0.62 (0.07)
3770 (26-week)	IDeg Flex + IAsp	164	7.69 (1.00)	7.29 (0.92)	-0.40 (0.59)	-0.40 (0.05)
	IDeg + IAsp	165	7.70 (0.94)	7.29 (0.90)	-0.41 (0.71)	-0.41 (0.05)
	IGlar + IAsp	161	7.74 (0.90)	7.15 (0.82)	-0.59 (0.72)	-0.58 (0.05)
Type 2 Diabetes Mellitus (T2DM)						
3582 (52-week)	IDeg + IAsp ± OAD(s)	742	8.26 (0.80)	7.09 (0.97)	-1.17 (1.03)	-1.11 (0.06)
	IGlar + IAsp ± OAD(s)	248	8.36 (0.89)	7.07 (1.02)	-1.29 (0.98)	-1.18 (0.08)
3579 (52-week)	IDeg + OAD(s)	766	8.16 (0.83)	7.08 (0.99)	-1.07 (1.01)	-1.07 (0.04)
	IGlar + OAD(s)	257	8.21 (0.78)	7.03 (0.95)	-1.19 (0.97)	-1.15 (0.06)
3672 (26-week)	IDeg 200 + OAD(s)	228	8.29 (0.98)	6.99 (0.95)	-1.30 (1.04)	-1.18 (0.09)
	IGlar + OAD(s)	228	8.24 (0.86)	6.92 (0.98)	-1.32 (0.98)	-1.22 (0.08)
3586 (26-week)	IDeg + OAD(s)	284	8.45 (0.79)	7.18 (0.68)	-1.26 (0.86)	-1.44 (0.05)
	IGlar + OAD(s)	146	8.46 (0.76)	7.10 (0.80)	-1.35 (0.87)	-1.53 (0.07)
3668 (26-week)	IDeg Flex + OAD(s)	228	8.49 (0.95)	7.20 (0.86)	-1.29 (1.00)	-1.17 (0.08)
	IDeg + OAD(s)	228	8.38 (0.94)	7.31 (1.03)	-1.07 (0.99)	-1.03 (0.08)
	IGlar + OAD(s)	229	8.41 (0.93)	7.14 (0.92)	-1.27 (1.07)	-1.21 (0.08)
3580 (26-week)	IDeg Flex + OAD(s)	222	8.78 (1.01)	7.20 (1.01)	-1.58 (1.08)	-1.53 (0.10)
	Sitagliptin + OAD(s)	221	8.97 (1.01)	7.74 (1.19)	-1.23 (1.16)	-1.09 (0.10)

LS mean (SE) was obtained using the sponsor's model, but was based on the FAS subjects who were randomized and exposed to treatment.

Table 6 – Efficacy Results for HbA1c (%) across Trials

Study	Duration	Treatment Group (FAS with LOCF ^a)	Primary Hypothesis	Treatment Difference (IDeg – Control)			Reviewer’s Conclusion
				LS Mean (SE)	95% CI	p-value ^b	
Type 1 Diabetes Mellitus (T1DM)							
3583	52-week	<ul style="list-style-type: none">IDeg + IAsp (472)IGlar + IAsp (154)	Non-inferiority	-0.01 (0.07)	(-0.14, 0.12)	0.8800	➤ NI
3585	26-week	<ul style="list-style-type: none">IDeg + IAsp (301)IDet + IAsp (152)	Non-inferiority	-0.08 (0.07)	(-0.23, 0.06)	0.2546	➤ NI
3770	26-week	<ul style="list-style-type: none">IDeg Flex + IAsp (164)IDeg + IAsp (165)IGlar + IAsp (161)	Non-inferiority	IDeg Flex vs. IGlar (<i>primary</i>): +0.17 (0.07)	(0.04, 0.31)	0.0102	➤ NI for both endpoints ➤ Statistically worse for both IDeg Flex and IDeg
				IDeg vs. IGlar (additional): +0.17 (0.07)	(0.04, 0.30)	0.0119	
Type 2 Diabetes Mellitus (T2DM)							
3582	52-week	<ul style="list-style-type: none">IDeg + IAsp ± OAD(s) (742)IGlar + IAsp ± OAD(s) (248)	Non-inferiority	+0.07 (0.07)	(-0.06, 0.20)	0.2677	➤ NI
3579	52-week	<ul style="list-style-type: none">IDeg + OAD(s) (766)IGlar + OAD(s) (257)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.21)	0.2293	➤ NI
3672	26-week	<ul style="list-style-type: none">IDeg 200 + OAD(s) (228)IGlar + OAD(s) (228)	Non-inferiority	+0.05 (0.08)	(-0.11, 0.20)	0.5478	➤ NI
3586	26-week	<ul style="list-style-type: none">IDeg + OAD(s) (284)IGlar + OAD(s) (146)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.22)	0.2177	➤ NI
3668	26-week	<ul style="list-style-type: none">IDeg Flex + OAD(s) (228)IDeg + OAD(s) (228)IGlar + OAD(s) (229)	Non-inferiority	IDeg Flex vs. IGlar (<i>primary</i>): +0.04 (0.08)	(-0.12, 0.19)	0.6421	➤ NI for both endpoints ➤ Statistically worse for IDeg, but not for IDeg Flex
				IDeg vs. IGlar (additional): +0.18 (0.08)	(0.02, 0.33)	0.0244	
3580	26-week	<ul style="list-style-type: none">IDeg Flex + OADs (222)Sitagliptin + OAD(s) (221)	Superiority	-0.44 (0.09)	(-0.62, -0.25)	< 0.0001	➤ Superiority
^a The FAS population in this review used subjects who were randomized and exposed to treatment. ^b Statistical significance was based on 2-sided superiority test.							

Table 7 – Summary of Responder Rate for HbA1c < 7.0% at End Time Point (FAS with LOCF)

DM ^b	Study	End of Treatment	IDeg	Comparator	Difference in Proportion	Asymptotic 95% CI
T1	3583	Week 52	188/472 (39.8%)	66/154 (42.9%)	-3.0%	(-12.0%, 5.9%)
T1	3585	Week 26	124/301 (41.2%)	57/152 (37.5%)	+3.7%	(-5.8%, 13.2%)
T1	3770	Week 26	61/164 (37.2%) ^a	65/161 (40.4%)	-3.2%	(-13.8%, 7.4%)
			61/165 (37.0%)		-3.4%	(-14.0%, 7.2%)
T2	3582	Week 52	368/742 (49.6%)	124/248 (50.0%)	-0.4%	(-7.6%, 6.8%)
T2	3579	Week 52	400/766 (52.2%)	139/257 (54.1%)	-1.9%	(-8.9%, 5.2%)
T2	3672	Week 26	119/228 (52.2%)	128/228 (56.1%)	-3.9%	(-13.1%, 5.2%)
T2	3586	Week 26	118/284 (41.5%)	71/146 (48.6%)	-7.1%	(-17.0%, 2.8%)
T2	3668	Week 26	89/228 (39.0%) ^a	101/229 (44.1%)	-5.1%	(-14.1%, 4.0%)
			93/228 (40.8%)		-3.3%	(-12.4%, 5.7%)
T2	3580	Week 26	92/222 (41.4%)	62/221 (28.1%)	+13.4%	(4.6%, 22.2%)

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

FPG. The mean FPG at baseline was between 8.0 and 10.0 mmol/L for all trials. Across the 9 studies, mean FPG decreased during the first 12-16 weeks and then continued to decrease or increase for the duration of the trial. The mean reductions in FPG from baseline in the IDeg group were consistently greater than, or similar to, that in the comparator group at all the collection time points in most trials. Table 8 below summarizes the statistical results of mean change from baseline in FPG at endpoint, favoring the treatment with IDeg.

Table 8 – Efficacy Results for FPG (mmol/L) across Trials

DM ^b	Study	LS Mean Chang from Baseline ± SE (n)		Treatment Diff LS Mean ± SE	95% CI	p-value
		IDeg	Comparator			
T1	3583	-1.56 ± 0.29 (465)	-1.16 ± 0.39 (152)	-0.40 ± 0.36	(-1.10, 0.31)	0.27
T1	3585	-2.42 ± 0.28 (300)	-0.74 ± 0.35 (148)	-1.68 ± 0.36	(-2.38, -0.97)	< 0.0001
T1	3770	-1.40 ± 0.30 (161) ^a	-1.41 ± 0.30 (160)	+0.01 ± 0.41	(-0.80, 0.82)	0.98
		-2.34 ± 0.30 (164)		-0.93 ± 0.41	(-1.73, -0.13)	0.02
T2	3582	-2.26 ± 0.17 (739)	-1.96 ± 0.22 (248)	-0.30 ± 0.18	(-0.65, 0.05)	0.10
T2	3579	-3.80 ± 0.08 (758)	-3.33 ± 0.14 (256)	-0.46 ± 0.15	(-0.77, -0.16)	0.003
T2	3672	-3.95 ± 0.20 (228)	-3.53 ± 0.20 (225)	-0.41 ± 0.18	(-0.77, -0.05)	0.03
T2	3586	-3.08 ± 0.13 (283)	-2.95 ± 0.16 (145)	-0.14 ± 0.16	(-0.45, 0.18)	0.40
T2	3668	-3.05 ± 0.20 (226) ^a	-2.64 ± 0.20 (225)	-0.42 ± 0.20	(-0.82, -0.02)	0.04
		-3.01 ± 0.19 (228)		-0.37 ± 0.20	(-0.77, 0.03)	0.07
T2	3580	-3.42 ± 0.24 (220)	-1.25 ± 0.23 (218)	-2.17 ± 0.22	(-2.60, -1.74)	< 0.0001

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

Body Weight. Mean body weight increased steadily over the treatment period in all trials, except for the sitagliptin group in Study 3580 where mean body weight decreased slightly during the course of the study. As Table 9 shows, type 1 diabetic patients seemed to have smaller mean weight gains than the type 2 diabetic patients at the end of treatment with either IDeg or comparator. For the 8 non-inferiority studies, the mean weight gain was about 1-2 kg for the 26-week trials and 2-3 kg for the 52-week trials in general. Although the IDeg group tended to show more weight gain than the comparator group in most trials, the differences were not statistically significant (except for Study 3585).

Table 9 – Results for Body Weight (kg) across Trials

DM ^b	Study	LS Mean Chang from Baseline \pm SE (n)		Treatment Diff LS Mean \pm SE	95% CI	p-value
		IDeg	Comparator			
T1	3583	2.13 \pm 0.30 (472)	1.98 \pm 0.40 (154)	+0.15 \pm 0.37	(-0.58, 0.88)	0.69
T1	3585	1.51 \pm 0.20 (301)	0.43 \pm 0.24 (152)	+1.08 \pm 0.25	(0.58, 1.58)	< 0.0001
T1	3770	1.27 \pm 0.26 (164) ^a	1.72 \pm 0.27 (161)	-0.46 \pm 0.36	(-1.17, 0.25)	0.21
		0.94 \pm 0.26 (165)		-0.79 \pm 0.36	(-1.49, -0.08)	0.03
T2	3582	3.24 \pm 0.33 (742)	3.54 \pm 0.41 (248)	-0.30 \pm 0.34	(-0.97, 0.38)	0.39
T2	3579	2.59 \pm 0.17 (766)	2.29 \pm 0.27 (257)	+0.30 \pm 0.31	(-0.30, 0.90)	0.33
T2	3672	2.30 \pm 0.36 (228)	1.86 \pm 0.35 (228)	+0.44 \pm 0.33	(-0.21, 1.08)	0.18
T2	3586	1.57 \pm 0.18 (284)	1.71 \pm 0.21 (146)	-0.14 \pm 0.22	(-0.57, 0.29)	0.51
T2	3668	1.87 \pm 0.27 (228) ^a	1.59 \pm 0.26 (229)	+0.27 \pm 0.27	(-0.25, 0.80)	0.31
		1.87 \pm 0.26 (228)		+0.27 \pm 0.27	(-0.25, 0.80)	0.31
T2	3580	2.72 \pm 0.44 (222)	-0.06 \pm 0.43 (221)	+2.78 \pm 0.40	(1.99, 3.57)	< 0.0001

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

Confirmed Hypoglycemic Episodes. There was no statistical difference in % of patients with at least 1 confirmed hypoglycemic episode between the IDeg group and the comparator (IGlar or IDet) group across the non-inferiority trials ($p > 0.05$ according to the Fisher's Exact test). The number of confirmed events per subject and the event rate per year per subject were also not statistically different between the IDeg and comparator groups in these trials ($p > 0.05$ according to the Wilcoxon test). However, there was a significantly greater incidence/event rate observed in the IDeg group when compared with the sitagliptin group in Study 3580 (Table 10).

Table 10 – Results for Confirmed Hypoglycemic Episodes across Trials

DM ^b	Study	IDeg		Comparator	
		Incidence Rate ^c	Event Rate ^d	Incidence Rate ^c	Event Rate ^d

T1	3583	451/472 (95.6%)	18389/432.3 (42.5)	147/154 (95.5%)	5796/144.3 (40.2)
T1	3585	280/301 (93.0%)	6673/145.6 (45.8)	139/152 (91.4%)	3295/72.1 (45.7)
T1	3770	154/164 (93.9%) ^a 164/165 (99.4%)	5988/72.7 (82.4) ^a 6724/76.2 (88.2)	156/161 (96.9%)	6263/78.5 (79.8)
T2	3582	608/742 (81.9%)	7436/664.0 (11.2)	206/248 (83.1%)	3120/227.3 (13.7)
T2	3579	356/766 (46.5%)	1014/667.2 (1.52)	119/257 (46.3%)	403/217.9 (1.85)
T2	3672	65/228 (28.5%)	129/105.7 (1.22)	70/228 (30.7%)	152/106.9 (1.42)
T2	3586	142/284 (50.0%)	397/133.4 (2.98)	78/146 (53.4%)	260/70.3 (3.70)
T2	3668	117/228 (51.3%) ^a 99/228 (43.4%)	388/105.8 (3.67) ^a 378/104.9 (3.60)	113/229 (49.3%)	368/105.6 (3.48)
T2	3580	96/222 (43.2%)	311/99.5 (3.13)	29/221 (13.1%)	123/94.9 (1.30)

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

^c Incidence rate = # of pts with events / total # of pts

^d Event rate = total # of events / total exposure in year

Severe Hypoglycemic Episodes. As shown in Table 11, there were no marked differences in the rate of severe hypoglycemic episodes between the IDeg and comparator arms across the 3 T1DM trials. The numbers of severe hypoglycemic episodes in the T2DM trials were too few to have any valid comparison between groups.

Table 11 – Results for Severe Hypoglycemic Episodes across Trials

DM ^b	Study	IDeg		Comparator	
		Incidence Rate ^c	Event Rate ^d	Incidence Rate ^c	Event Rate ^d
T1	3583	58/472 (12.3%)	90/432.3 (0.21)	16/154 (10.4%)	23/144.3 (0.16)
T1	3585	32/301 (10.6%)	45/145.6 (0.31)	16/152 (10.5%)	28/72.1 (0.39)
T1	3770	17/164 (10.4%) ^a 21/165 (12.7%)	25/72.7 (0.34) ^a 28/76.2 (0.37)	16/161 (9.9%)	37/78.5 (0.47)
T2	3582	34/742 (4.6%)	41/664.0 (0.06)	11/248 (4.4%)	12/227.3 (0.05)
T2	3579	2/766 (0.3%)	2/667.2 (0.003)	5/257 (1.9%)	5/217.9 (0.023)
T2	3672	0/228 (0%)	0/105.7 (0)	0/228 (0%)	0/106.9 (0)
T2	3586	0/284 (0%)	0/133.4 (0)	1/146 (0.7%)	1/70.3 (0.01)
T2	3668	1/228 (0.44%) ^a 2/228 (0.88%)	2/105.8 (0.02) ^a 2/104.9 (0.02)	2/229 (0.87%)	2/105.6 (0.02)
T2	3580	1/222 (0.5%)	1/99.5 (0.01)	0/221 (0%)	0/94.9 (0)

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

^c Incidence rate = # of pts with events / total # of pts

^d Event rate = total # of events / total exposure in year

Nocturnal Confirmed Hypoglycemic Episodes. Although some studies showed statistical significance and some did not, the rate of nocturnal confirmed hypoglycemic episodes was numerically smaller in the IDeg group than in the comparator group in all the 8 non-inferiority trials. However, a significantly greater incidence/event rate was observed in the IDeg group when compared with the sitagliptin group in Study 3580 (Table 12).

Table 12 – Results for Nocturnal Confirmed Hypoglycemic Episodes across Trials

DM ^b	Study	IDeg		Comparator	
		Incidence Rate ^c	Event Rate ^d	Incidence Rate ^c	Event Rate ^d
T1	3583	341/472 (72.2%)	1905/432.3 (4.41)	114/154 (74.0%)	845/144.3 (5.86)
T1	3585	176/301 (58.5%)	603/145.6 (4.14)	89/152 (58.6%)	428/72.1 (5.94)
T1	3770	111/164 (67.7%) ^a	453/72.7 (6.23) ^a	117/161 (72.7%)	782/78.5 (9.96)
		121/165 (73.3%)	732/76.2 (9.61)		
T2	3582	298/742 (40.2%)	930/664.0 (1.40)	119/248 (48.0%)	422/227.3 (1.86)
T2	3579	106/766 (13.8%)	169/667.2 (0.25)	39/257 (15.2%)	84/217.9 (0.39)
T2	3672	14/228 (6.1%)	19/105.7 (0.18)	20/228 (8.8%)	30/106.9 (0.28)
T2	3586	58/284 (20.4%)	104/133.4 (0.78)	35/146 (24.0%)	87/70.3 (1.24)
T2	3668	31/228 (13.6%) ^a	67/105.8 (0.63) ^a	49/229 (21.4%)	79/105.6 (0.75)
		24/228 (10.5%)	58/104.9 (0.55)		
T2	3580	29/222 (13.1%)	53/99.5 (0.53)	13/221 (5.9%)	29/94.9 (0.31)

^a for IDeg Flex arm; ^b DM (diabetes mellitus): T1 = Type 1, T2 = Type 2

^c Incidence rate = # of pts with events / total # of pts

^d Event rate = total # of events / total exposure in year

Insulin Dose. As depicted in Appendix I, mean daily basal insulin doses were consistently lower in the IDeg group than in the IGlax group throughout the course of Studies 3579, 3672, and 3586. The mean total daily insulin doses (basal and bolus combined) were also consistently lower in the IDeg group (including IDeg Flex) than in the comparator (IGlax or IDet) group in Studies 3583, 3585, and 3770, even though the basal insulin doses in the IDeg Flex group were similar to those in the IGlax group in Study 3770. The mean daily basal insulin doses were also comparable among the 3 treatment groups in Study 3668. Study 3582 was the only study that had higher daily basal insulin doses of IDeg than IGlax, and consequently the total daily insulin doses, throughout the trial.

Subgroup Analyses. Treatment effects on mean change from baseline in HbA1c at endpoint were consistent across the subgroups defined by age (< 65 years or ≥ 65 years), gender, and race for all the 9 trials reviewed here, as no significant treatment-by-subgroup interactions were observed (all p > 0.10). Treatment effects on mean change from baseline in HbA1c at endpoint were also consistent across the subgroups defined by region, antidiabetic therapy at

screening, and country for all the 9 trials ($p > 0.10$), except for antidiabetic therapy at screening for Studies 3582 and 3580 where the interaction terms $p = 0.09$ and 0.08 , respectively.

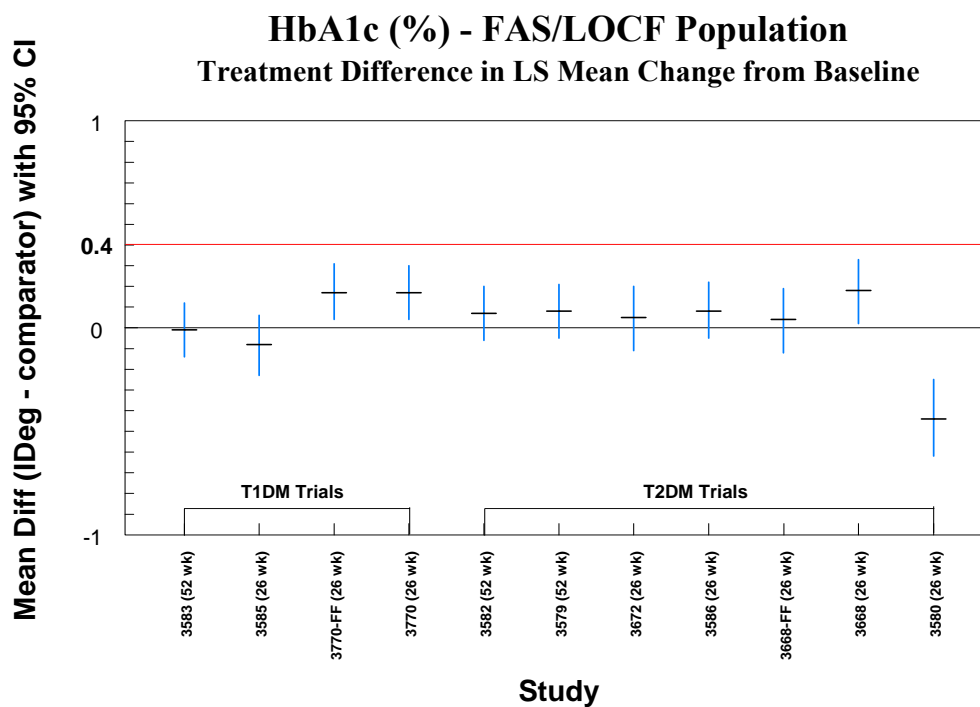
4. CONCLUSIONS

Data from the 9 submitted Phase 3a confirmatory trials have demonstrated that once-daily injection of insulin degludec (IDeg, Tresiba™), regardless of 100 or 200 U/mL, fixed or flexible (anytime of the day but with an 8-40 hours interval between injections) dosing, was effective in lowering HbA1c at the end of 26-week or 52-week treatment trials when combined with insulin aspart (IAsp, NovoRapid®/NovoLog®) 100 U/mL and/or OAD(s). The mean reduction in HbA1c at endpoint was generally smaller in type 1 diabetic patients ($< 1\%$) than in type 2 diabetic patients ($> 1\%$), which was probably in part due to the difference in baseline value ($< 8\%$ for T1DM and $> 8\%$ for T2DM).

Superiority of IDeg to sitagliptin (Januvia®), a DPP-4 inhibitor) 100 mg in improving HbA1c was confirmed based on the data from Study 3580 (T2DM). Non-inferiority of IDeg to insulin glargine (IGlar, Lantus®) 100 U/mL or insulin detemir (IDet, Levemir®) 100 U/mL in controlling glycemia was also confirmed (but not superiority) based on the data from 8 trials where the upper bounds of the two-sided 95% confidence intervals of the treatment differences were $< 0.4\%$ (a protocol-defined non-inferiority margin). As depicted in the 1st graph below, the mean reductions in HbA1c from baseline in these non-inferiority trials (except for 2 T1DM trials) were all numerically smaller in the IDeg group (fixed and flex dosing) than in the IGlar group.

The proportion of subjects achieving HbA1c level $< 7.0\%$ at endpoint was numerically smaller, but not statistically significant, in the IDeg group than in the comparator group for all trials, except for Study 3585 (T1DM) and Study 3580 (T2DM) where the IDeg group showed a higher % of patients achieving the target level when compared with the comparator group.

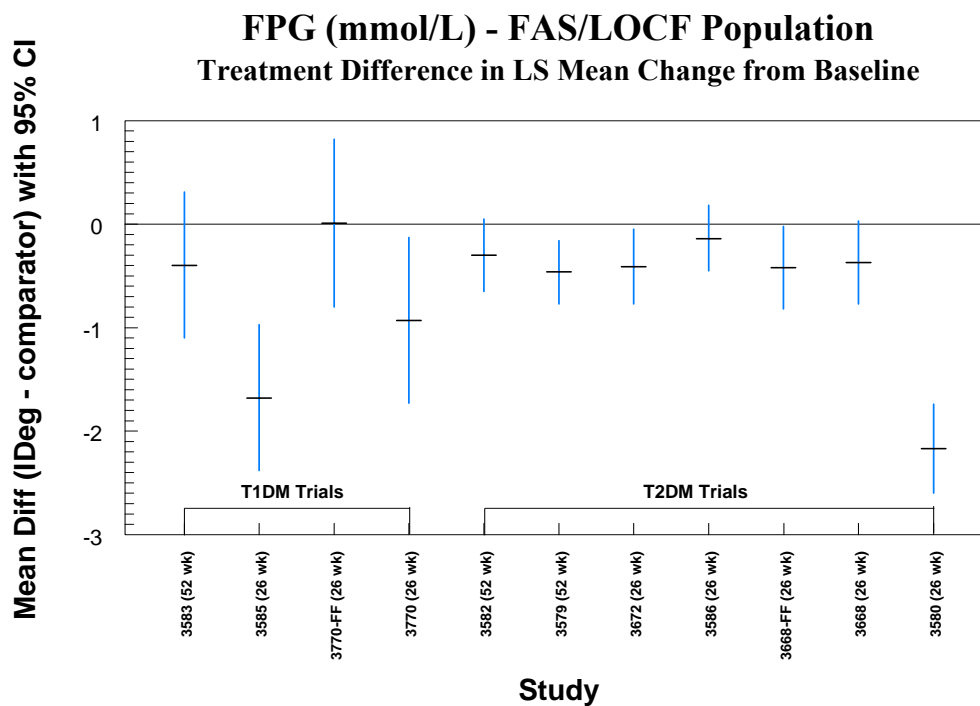
In contrast to HbA1c, treatment with IDeg consistently lowered FPG more than treatment with IGlar, IDet, or sitagliptin at the end of trials regardless of the strength of statistical significance, as shown in the 2nd graph below.



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.



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.

In all trials, mean body weight was increased steadily over the treatment periods of IDeg, IGLar, or IDet. However, the IDeg group tended to show a slightly more weight gain at the end of treatment than the IGLar or IDet group in most trials.

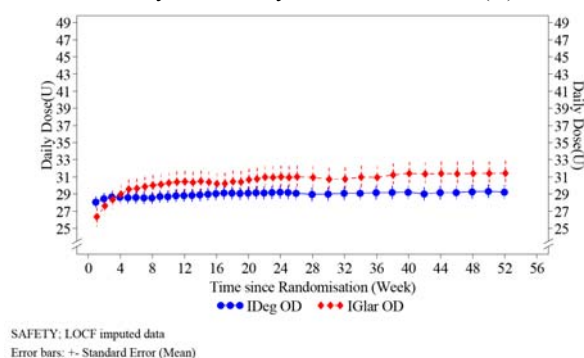
The rates of confirmed or severe hypoglycemic episodes between the treatment groups showed no statistically significant differences in each of the 8 non-inferiority trials. Although some studies showed statistical significance and some did not, a numerically smaller rate of nocturnal confirmed hypoglycemic episodes was consistently observed in the IDeg group than in the comparator group across the 8 non-inferiority trials. However, a significantly greater rate of confirmed and nocturnal confirmed hypoglycemic episodes were observed in the IDeg group when compared with the sitagliptin group in Study 3580. Nevertheless, the rates in the IDeg group in Study 3580 were in the range of the rates in the IDeg group of other T2DM studies.

Note that the mean total daily insulin doses were consistently lower in the IDeg group than in the comparator group in all the non-inferiority trials except for Studies 3668 and 3582 (both T2DM). In general, smaller insulin doses are associated with smaller reductions in HbA1c and fewer hypoglycemic episodes. However, these associations did not occur in a consistent manner across the eight non-inferiority trials.

5. APPENDIX I

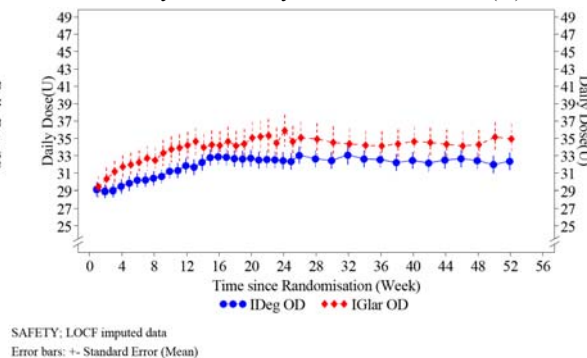
Insulin Dose Over Time (Sponsor's Graphs)

Study 3583: Daily Basal Insulin Dose (U)



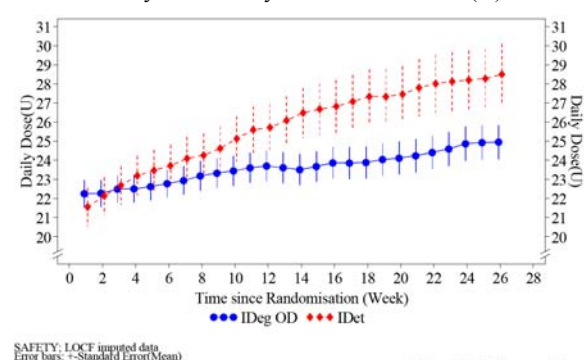
The graph is from the Sponsor's CSR, page 143.

Study 3583: Daily Bolus Insulin Dose (U)



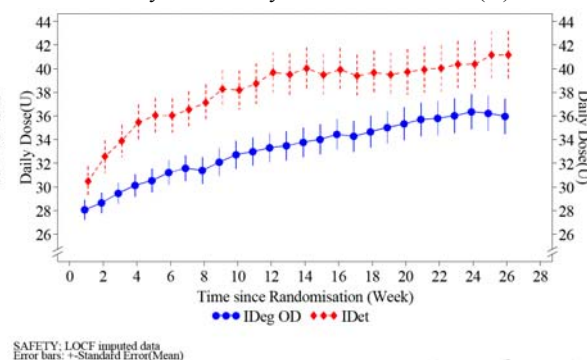
The graph is from the Sponsor's CSR, page 144.

Study 3585: Daily Basal Insulin Dose (U)



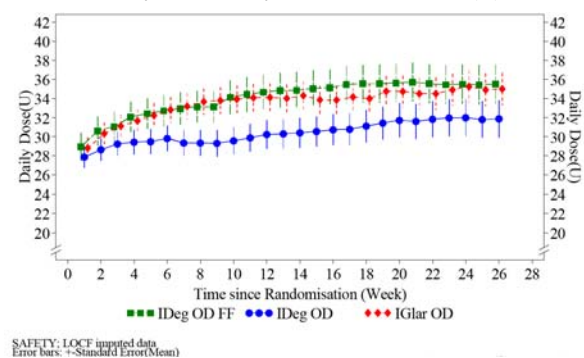
The graph is from the Sponsor's CSR, page 127.

Study 3585: Daily Bolus Insulin Dose (U)



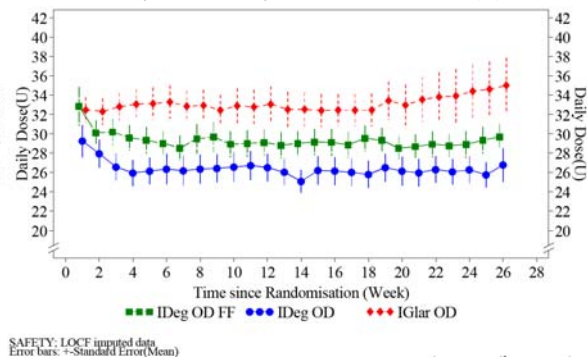
The graph is from the Sponsor's CSR, page 128.

Study 3770: Daily Basal Insulin Dose (U)

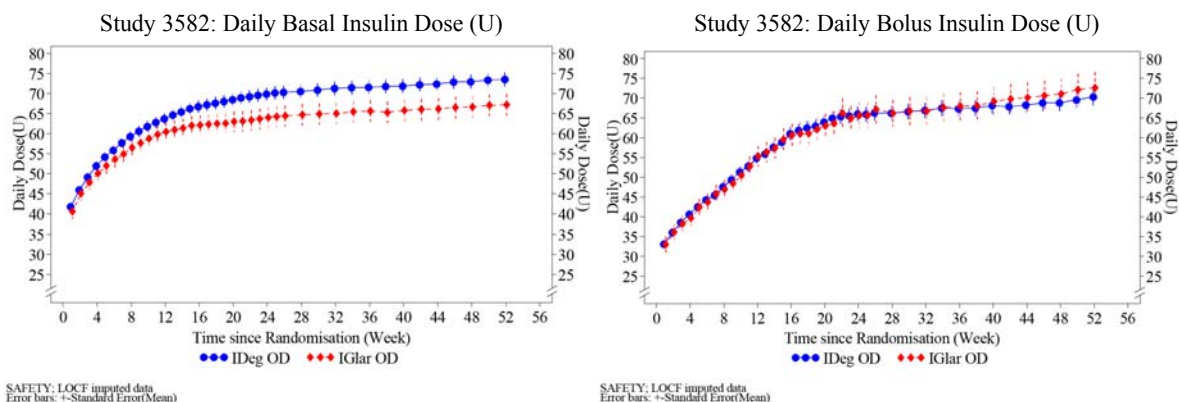


The graph is from the Sponsor's CSR, page 128.

Study 3770: Daily Bolus Insulin Dose (U)

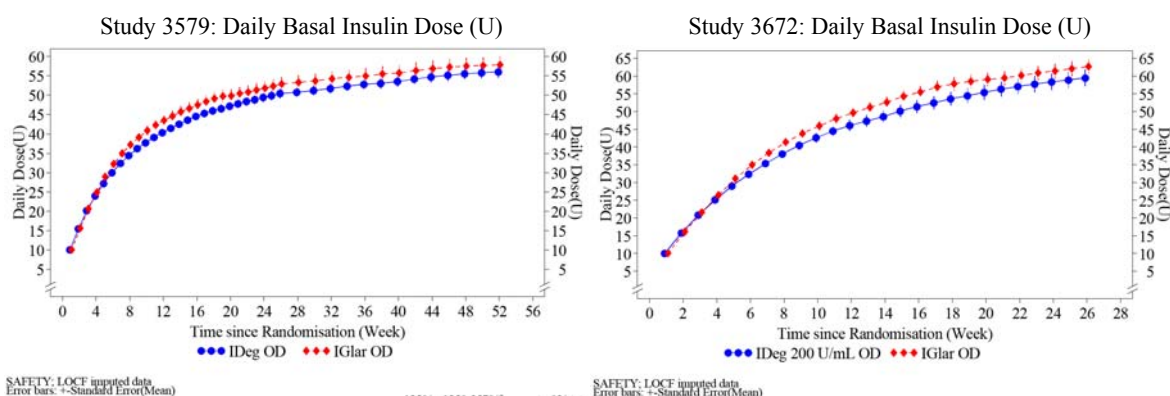


The graph is from the Sponsor's CSR, page 129.



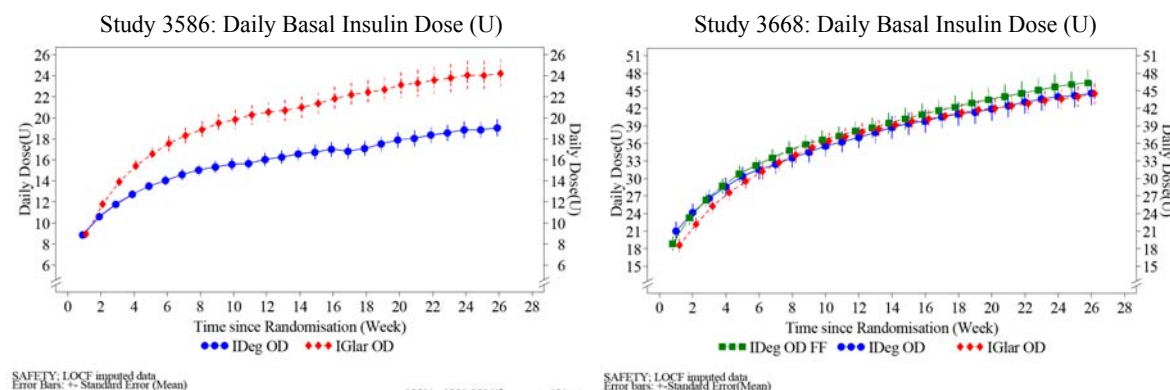
The graph is from the Sponsor's CSR, page 126.

The graph is from the Sponsor's CSR, page 128.



The graph is from the Sponsor's CSR, page 142.

The graph is from the Sponsor's CSR, page 120.



The graph is from the Sponsor's CSR, page 122.

The graph is from the Sponsor's CSR, page 136.



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Biostatistics

DRAFT STATISTICAL REVIEW AND EVALUATION CLINICAL STUDIES

NDA/Serial Number: 203313/0000

Drug Name: Ryzodeg (70% insulin degludec and 30% insulin aspart [rDNA origin] injection)

Indication(s): Improve glycaemic control in adult patients with diabetes mellitus

Applicant: Novo Nordisk

Date(s): Receipt date: September 29, 2011

Review Priority: Standard

Biometrics Division: Division of Biometrics II

Statistical Reviewer: Dongmei Liu, Ph.D.

Concurring Reviewers: Jon Todd Sahlroot, Ph.D., Team Leader, Deputy Division Director

Medical Division: Division of Metabolism and Endocrinology Products

Clinical Team: Karim Calis, M.D., Medical officer
Jean-Marc Guettier, M.D., Medical Team Leader
Mary Parks, M.D., Medical Division Director

Project Manager: Rachel Hartford

Keywords: NDA review, clinical studies

Table of Contents

LIST OF TABLES	3
LIST OF FIGURES	4
1. STUDY DESIGN	5
2. EFFICACY ENDPOINTS	7
3. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS	8
4. STATISTICAL METHODOLOGIES	21
5. RESULTS	22
6. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	29
7. SUMMARY AND CONCLUSIONS	33
APPENDIX	33

LIST OF TABLES

Table 1 Summary of trial design.....	5
Table 2 Summary of key secondary efficacy endpoints.	7
Table 3 Summary of patient dispositions.....	9
Table 4 Change of HbA1c (%) from baseline to end-of-trial.	22
Table 5 Summary of confirmatory secondary efficacy endpoints.	25
Table 6 Meta-analysis for Hypoglycemia with IDegAsp OD in T2DM subjects.....	27
Table 7 Meta-analysis for Hypoglycemia with IDegAsp BID in T2DM subjects.	27
Table 8 Change of body weight from baseline to Week 26.....	29
Table 9 HbA1c at baseline and week 26 by serum ALT group - T2DM - pooling trials (quoted from CSR).....	30
Table 10 Change of HbA1c from baseline to end-of-trial (per-protocol analysis).....	33

LIST OF FIGURES

Figure 1 Summary of patient disposition.....	10
Figure 2 Demographic characteristics summary for Trial 3594.....	11
Figure 3 Demographic characteristics summary for Trial 3590.....	12
Figure 4 Demographic characteristics summary for Trial 3593.....	13
Figure 5 Demographic characteristics summary for Trial 3592.....	14
Figure 6 Demographic characteristics summary for Trial 3597.....	15
Figure 7 Baseline and diabetes characteristics for patients in Trial 3594.....	16
Figure 8 Baseline and diabetes characteristics for patients in Trial 3590.....	17
Figure 9 Baseline and diabetes characteristics for patients in Trial 3593.....	18
Figure 10 Baseline and diabetes characteristics for patients in Trial 3592.....	19
Figure 11 Baseline and diabetes characteristics for patients in Trial 3597.....	20
Figure 12 Summary of HbA1c at baseline and week 26.....	24
Figure 13 Summary of change in HbA1c after 26 weeks of treatment (IDegAsp-Comparator)..	24
Figure 14 Ratio of hypoglycemic episodes in IDegAsp vs. Comparator.....	27
Figure 15 Summary of total daily insulin dose (Mean \pm SD).....	28
Figure 16 Change in HbA1c after 26 weeks of treatment by subgroups in T1DM subjects	31
Figure 17 Change in HbA1c after 26 weeks of treatment by subgroups in T2DM subjects.....	32

1. STUDY DESIGN

Novo Nordisk proposes Ryzodeg, the co-formulated 70% insulin degludec and 30% insulin aspart, for improving glycemic control in adult patients with diabetes mellitus. The review of efficacy is based on data from five phase 3 trials, which were all 26-week treatment + 1-week follow-up, multi-center, multi-national, open-label, randomized, 2-arm parallel group, active-controlled, non-inferiority, treat-to-target trials. Summary of trial design is given in Table 1.

Table 1 Summary of trial design.

Trial ID (in label)	Treatment arms	Number of subjects	Study population
NN5401-3594 (Study A)	IDegAsp: OD s.c. at any meal	366	T1DM
	+ IAsp s.c. for the remaining meals		
	IDet: OD or BID s.c.	182	
	+ IAsp s.c. at main meals		
NN5401-3590 (Study B)	IDegAsp: OD s.c. at breakfast	266	T2DM
	+ met p.o. + NPH s.c. in follow-up		
	IGlar: OD s.c.	263	
	+ met p.o. + NPH s.c. in follow-up		
NN5401-3593 (Study C)	IDegAsp: OD s.c. at main meal	230	T2DM
	+ met p.o. ± pio p.o. ± DPP-4l p.o.		
	IGlar: OD s.c.	233	
	+ met p.o. ± pio p.o. ± DPP-4l p.o.		
NN5401-3592 (Study D)	IDegAsp: BID s.c.	224	T2DM
	+ met p.o. ± pio p.o. ± DPP-4l p.o.		
	BIAsp 30: BID s.c.	222	
	+ met p.o. ± pio p.o. ± DPP-4l p.o.		
NN5401-3597 (Study E)	IDegAsp: BID s.c.	280	T2DM
	± met p.o. + BHI 30 s.c. in follow-up		
	BIAsp 30: BID s.c.	142	
	± met p.o. + BHI 30 s.c. in follow-up		
<div><div><ul style="list-style-type: none">• OD: once daily• IDet: insulin detemir• met: metformin• NPH: Neutral Protamine Hagedorn• BIAsp: biphasic insulin aspart• s.c.: subcutaneous</div><div><ul style="list-style-type: none">BID: twice dailyIGlar: insulin glarginepio: pioglitazoneDPP-4: di-peptidyl peptidase-4BHI: biphasic human insulinp.o.: per oral</div></div>			

Trial 3594 investigated the efficacy and safety of IDegAsp in patients with type 1 diabetes mellitus (T1DM). All patients in this trial were previously treated by insulin. IDegAsp was administered once daily (OD) at one meal and insulin aspart (IAsp) was administered at other meals. The active control was insulin detemir (IDet) + mealtime IAsp. In total, 548 subjects were randomized in 2:1 ratio to IDegAsp OD and IDet + mealtime IAsp. The trial had a 26-week extension period with exactly the same treatment regimen as main trial. The objective of the

second part of the trial was to investigate long-term safety and to compare efficacy after 52 weeks of treatment.

The other four trials, 3590, 3592, 3593, and 3597, investigated the efficacy and safety of IDegAsp in patients with type 2 diabetes mellitus (T2DM). IDegAsp was administered once daily in Trials 350 and 3593 and twice daily (BID) in Trials 3592 and 3597.

Trial 3590 recruited only insulin-naïve patients who were inadequately controlled by oral anti-diabetic drugs (OAD). IDegAsp was administered once daily with breakfast, insulin glargine (IGlar) was administered once daily according to the approved label as the active control. Both arms had metformin as combination treatment. In total, 530 subjects were randomized in 1:1 ratio to the two arms. At Week 26, the subjects discontinued all trial products and were switched to the intermediate acting neutral Protamine Hagedorn (NPH) insulin in order to provide basal insulin coverage while reducing the level of exogenous insulin present at antibody sampling and consequently to reduce the possibility for interference with antibody measurements.

Trial 3593 recruited both insulin-naïve and previously insulin-treated subjects. IDegAsp was administered once daily with dinner or the largest meal. IGlar was administered once daily according to the approved label as the active control. Both arms were investigated in combination with metformin \pm pioglitazone \pm DPP-4 inhibitor. In total, 465 subjects were randomized in 1:1 ratio to the two arms. At week 26, the subjects discontinued all trial products and were switched to marketed treatment at the discretion of the investigator.

Trial 3592 recruited both insulin-naïve and previously insulin-treated subjects. IDegAsp was administered twice daily. Insulin aspart (BIAsp 30 BID) was administered twice daily as the active control. Both arms were investigated in combination with metformin \pm pioglitazone \pm DPP-4 inhibitor. In total, 477 subjects were randomized in 1:1 ratio to the two arms. There were at least 7 days for wash-out of IDegAsp at the end of the trial.

Trial 3597 recruited both insulin-naïve and previously insulin-treated subjects. IDegAsp was administered twice daily. Biphasic insulin aspart (BIAsp 30 BID) was administered twice daily as the active control. Both arms were investigated in combination with metformin. In total, 424 subjects were randomized in 2:1 ratio to IDegAsp BID and BIAsp 30 BID. At week 26, the subjects discontinued all trial products and were switched to biphasic human insulin (BHI 30).

In T1DM (Trial 3594), subjects were transferred unit-to-unit from their pretrial insulin treatment to IDegAsp OD at one meal + IAsp at remaining meals or IDet OD + IAsp at all meals. Insulin-naïve subjects with T2DM in Trial 3590 were initiated on once-daily insulin treatment with 10 U IDegAsp or IGlar. In the other T2DM trials (Trials 3593, 3592 and 3597), subjects switching from basal, premix or self-mixed insulin therapy were transferred to IDegAsp or comparator at the identical total insulin doses (unit-to-unit) as the subject's previous total daily insulin dose. All trials were conducted with a treat-to-target principle; the dose was adjusted for each individual subject with the aim of achieving identical glycaemic targets for IDegAsp and comparator products.

The overall treatment goal in all trials was to achieve HbA1c < 7% and a pre-breakfast (fasting) self-measured plasma glucose (SMPG) < 5.0 mmol/L (90 mg/dL). In trials with BID dosing, an additional titration target of SMPG < 5.0 mmol/L before the main evening meal was applied for adjust of the morning dose. In all trials, insulin doses were adjusted based on mean SMPG taken three days prior to each site visit/phone contact. The titration of insulin doses was monitored and reviewed by a titration committee in a blinded fashion.

2. EFFICACY ENDPOINTS

The primary efficacy endpoint in all five trials was change from baseline in HbA1c after 26 weeks of treatment. The key secondary efficacy endpoints varied among trials and were ranked in different orders. The summary of key secondary efficacy endpoints is given in Table 2.

Table 2 Summary of key secondary efficacy endpoints.

Order	3594	3590	3593	3592	3597
1	Change in FPG	Prandial PG at breakfast	Prandial PG at main evening meal	Change in FPG	Change in FPG
2	HbA1c <7% without Hypoglycemia	Fluctuation in Nocturnal Interstitial Glucose	HbA1c <7% without Hypoglycemia	Number of Confirmed Hypoglycemia	Number of Confirmed Hypoglycemia
3	Number of Nocturnal Hypoglycemia	HbA1c <7% without Hypoglycemia	Fluctuation in Nocturnal Interstitial Glucose	HbA1c <7% without Hypoglycemia	HbA1c <7% without Hypoglycemia
4		Number of Nocturnal Hypoglycemia	Number of Nocturnal Hypoglycemia	Change in Body Weight	Change in Body Weight
5		Change in Body Weight	Change in Body Weight	Number of Nocturnal Hypoglycemia	Number of Nocturnal Hypoglycemia

- FPG: fasting plasma glucose
- All measurements were after 26 weeks of treatment.

For hypoglycemia, in addition to the standard ADA classification, the sponsor defined one more type — confirmed hypoglycemia. Confirmed hypoglycemia was defined as severe hypoglycemia (i.e. episode of hypoglycemia requiring assistance from another person to actively administer carbohydrate, glucagon, or other resuscitative actions) or episodes of hypoglycemia confirmed with a PG < 3.1 mmol/L (56 mg/dL), irrespective of symptoms. Events of nocturnal hypoglycemia in this submission were defined as episodes of hypoglycemia occurring between 12:01 am and 05:59am.

3. PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

The disposition of subjects in each trial is given in Table 3 and Figure 1. In each trial, similar proportion of exposed subjects withdrew after randomization in the two treatment groups. In all trials, majority of patients (85%~87%) completed the trial. The overall withdrawal pattern (reasons for withdrawal and time of withdrawal) was comparable between the two treatment groups. In general, the subject withdrawals occurred throughout the trial period, with no apparent clustering of withdrawals at any specific time point during the trial.

The demographic characteristics in each trial are summarized in Figure 2 to Figure 6. In each trial, the demographics and baseline characteristics in two treatment groups were similar. In all five trials, about equal number of females and males were randomized into each treatment arms, the majority of subjects were adults with 18 to 65 years of age and not Hispanic or Latino.

Trial 3594 recruited patients from Australia, Europe and North America. The majority of subjects were white. Trial 3590 recruited patients from Asia, Europe and North America. The majority of patients were white. Trial 3593 recruited patients from Asia, Europe, North and South America. The majority of subjects were white or Asian Indian. Trial 3592 recruited patients from Asia, Australia and Europe. The majority of patients were white or Asian. Trial 3597 recruited patients only from Asia, mainly from Japan. The majority of subjects were Asian non-Indian.

Trial 3590 recruited only insulin naïve subjects and subjects with previous short-term insulin treatment for up to 14 days. Treatment during hospitalization or during gestational diabetes was allowed for periods longer than 14 days. The exclusion criteria for all other four trials didn't include previous insulin treatment.

The baseline and diabetes characteristics in each trial are summarized by boxplot in Figure 7 to Figure 11. In each boxplot, the thick dark horizontal line in center of the box is the median; the lower line and the upper line of the box are the first and third quartiles; the lower whisker is the first quartile - $1.58 * \text{inter-quartile range} / \text{square root of } n$, where inter-quartile range is the third quartile - the first quartile and n is the number of data points ; the upper whisker is the third quartile + $1.58 * \text{inter-quartile range} / \text{square root of } n$; the idea of upper and lower whiskers is to give roughly the 95% of distribution centered at the median; the points beyond whiskers are considered outliers. As shown in the boxplots, in each trial the distribution of baseline and diabetes characteristics in two treatment groups were comparable.

Table 3 Summary of patient dispositions.

	3594		3590		3593		3592		3597	
	IDegAsp	IDet	IDegAsp	IGlar	IDegAsp	IGlar	IDegAsp	BIAsp	IDegAsp	BIAsp
Randomized	366	182	266	264	232	233	224	223	282	142
Exposed	363	180	265	261	230	233	224	222	279	141
Withdrawn at/after Randomization	42	24	46	29	34	28	27	34	34	15
Adverse Event	4	3	5	3	0	1	4	4	9	5
Ineffective Therapy	2	0	4	2	3	1	0	1	2	2
Non-compliance with Protocol	8	5	6	5	6	3	2	3	3	1
Withdrawal Criteria	7	5	21	11	10	10	4	6	9	4
Other	21	11	10	8	15	13	17	20	11	3
Completed	320	156	219	232	196	205	197	188	245	126

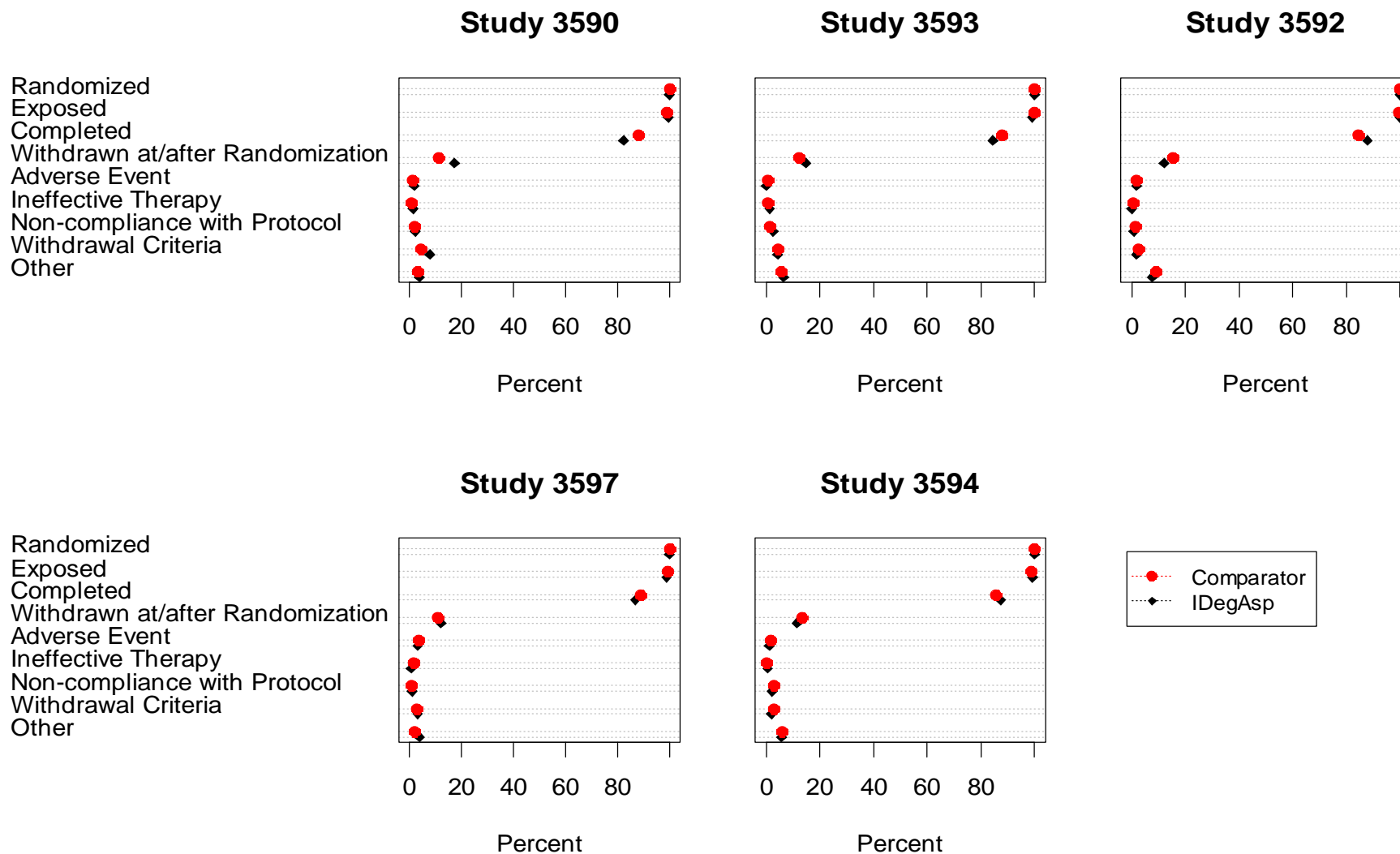


Figure 1 Summary of patient disposition.

Demographic and Baseline characteristics summary for Study3594

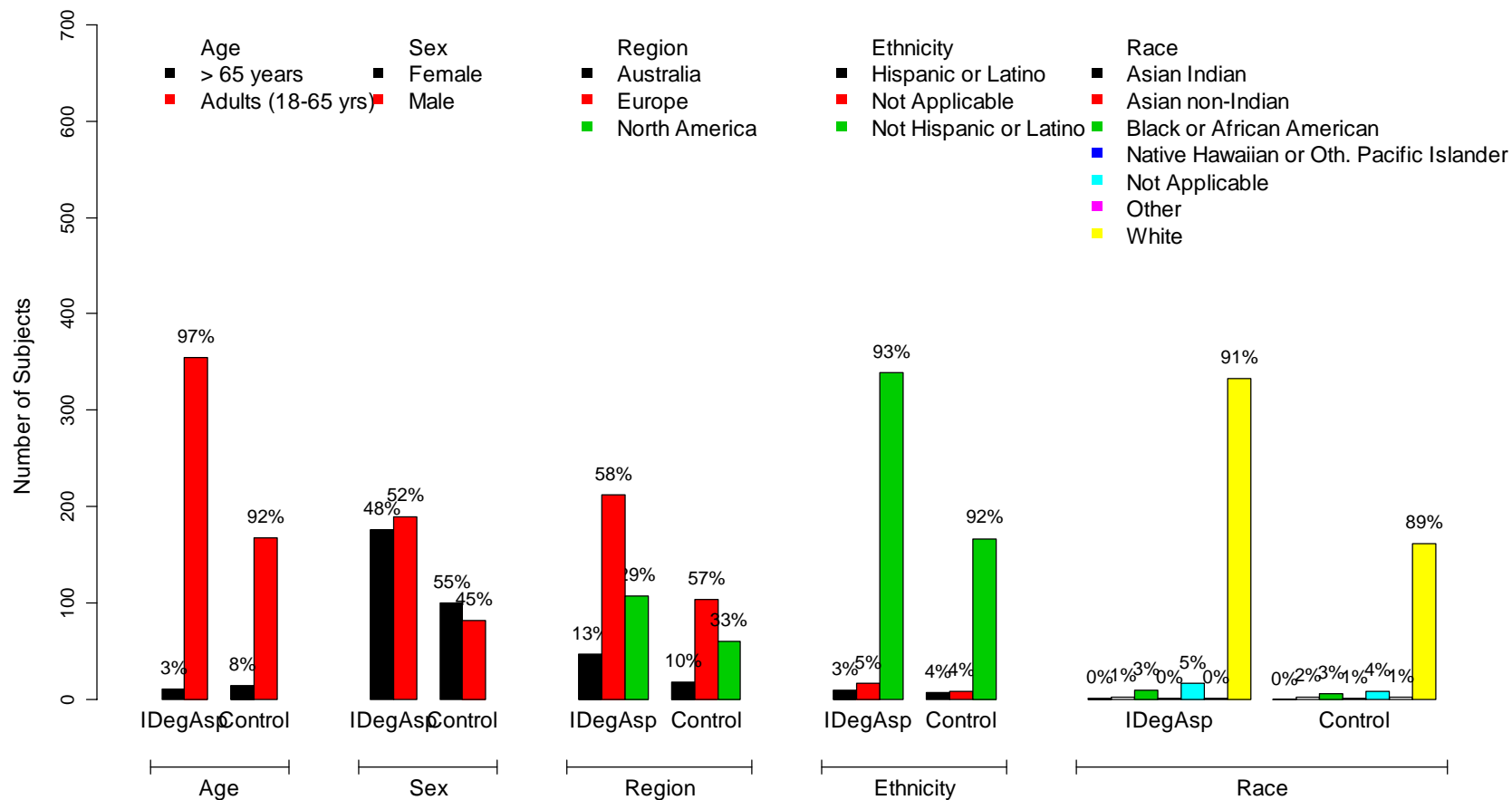


Figure 2 Demographic characteristics summary for Trial 3594.

Demographic and Baseline characteristics summary for Study3590

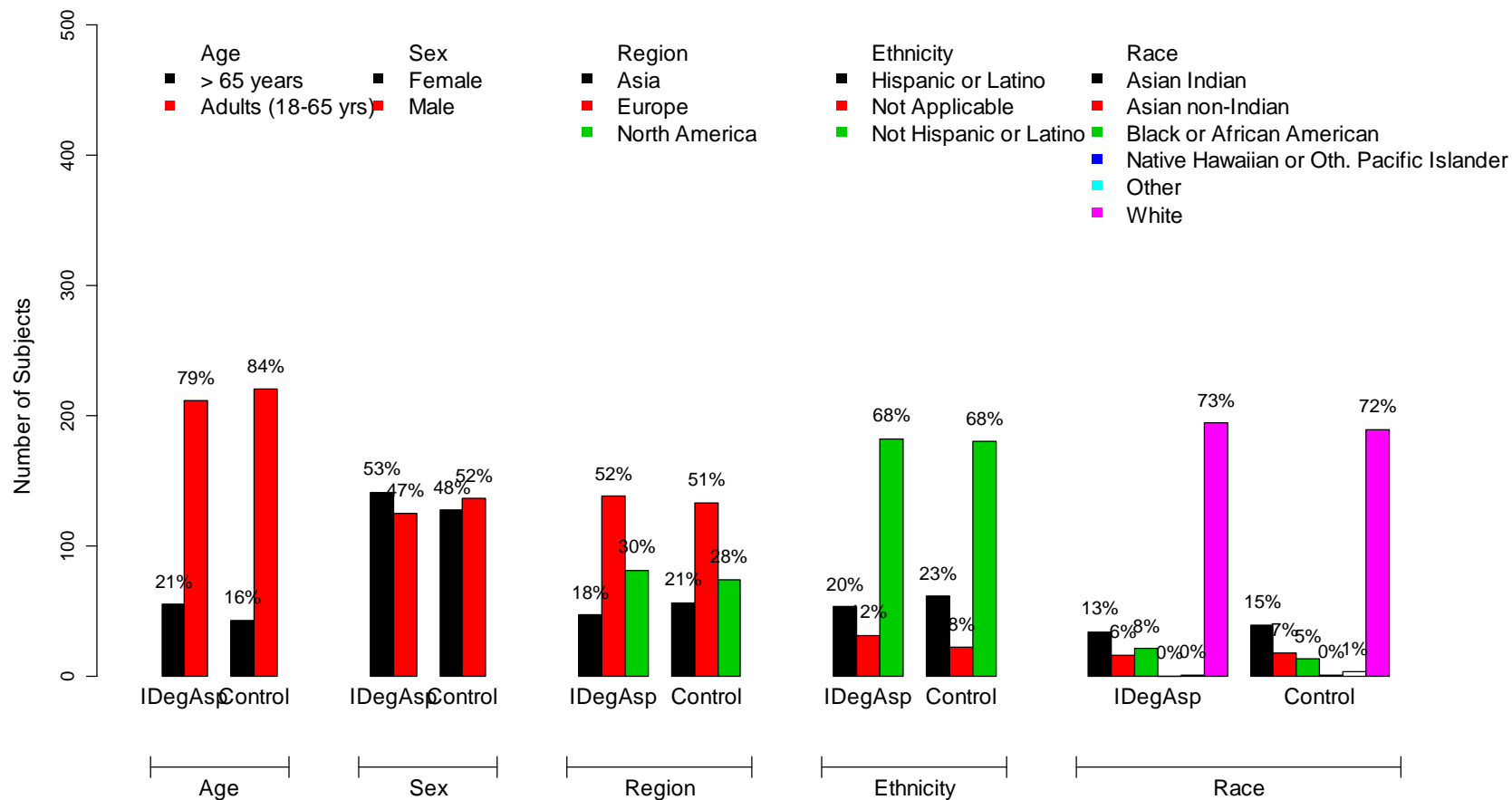


Figure 3 Demographic characteristics summary for Trial 3590.

Demographic and Baseline characteristics summary for Study3593

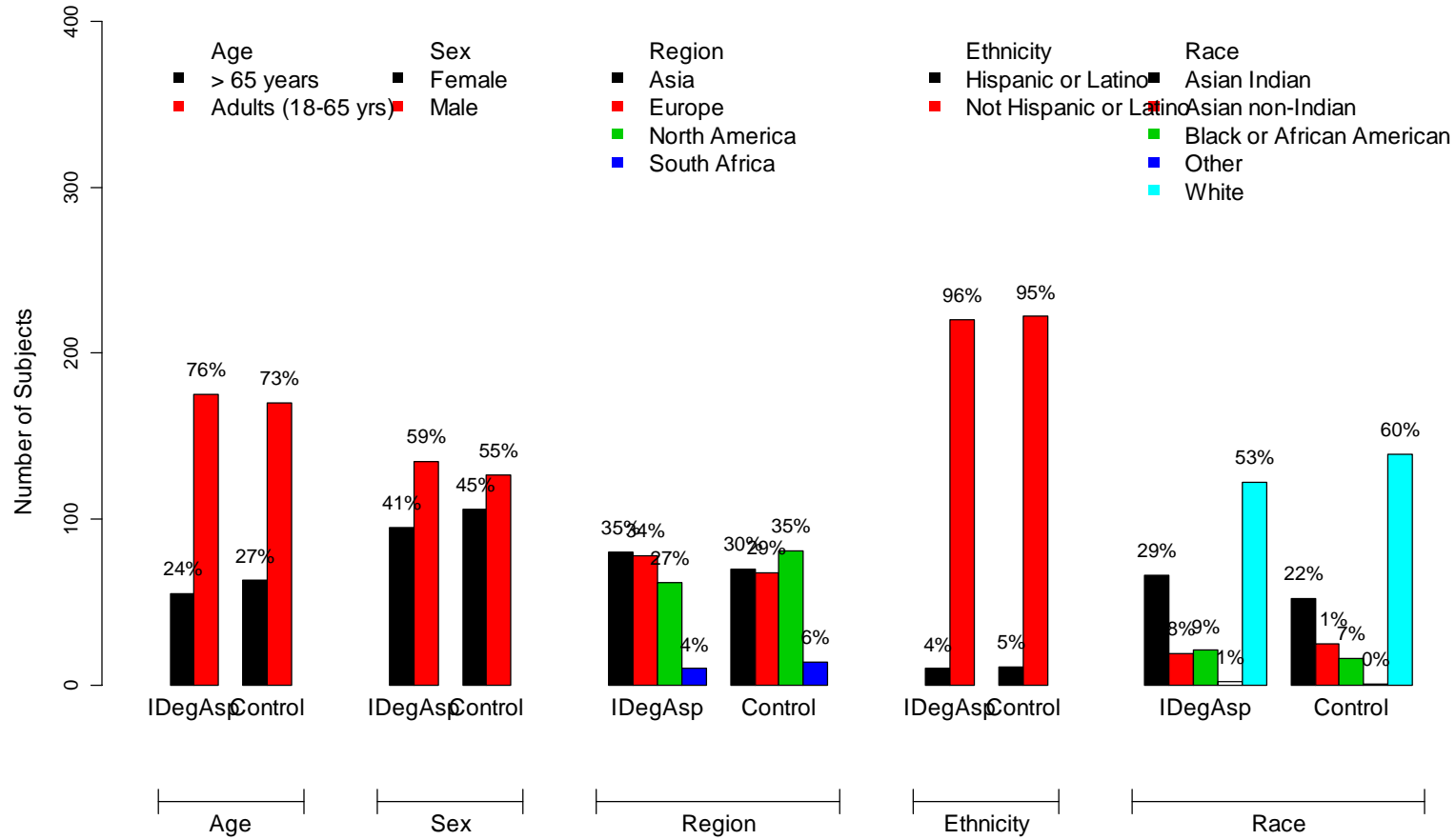


Figure 4 Demographic characteristics summary for Trial 3593.

Demographic and Baseline characteristics summary for Study3592

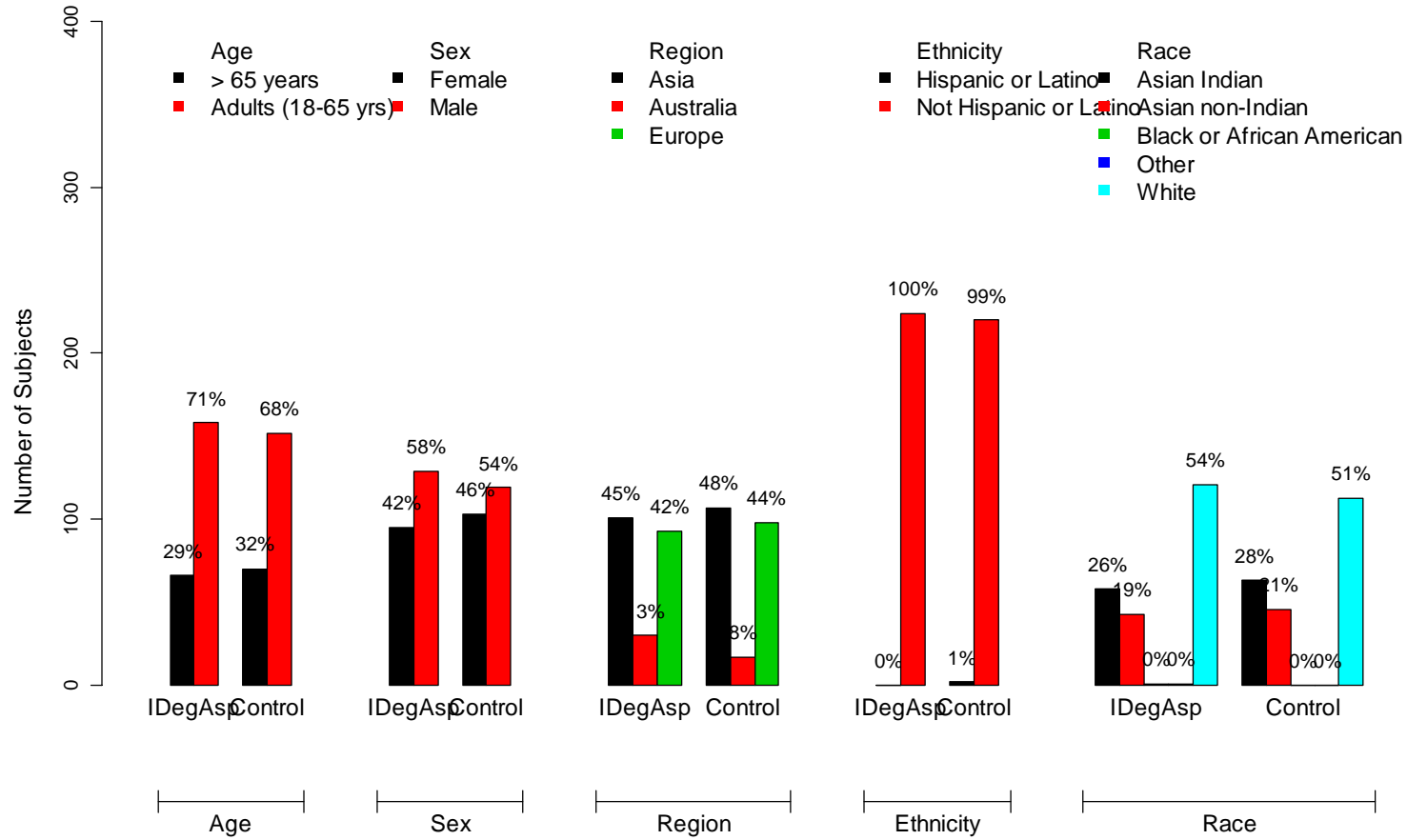


Figure 5 Demographic characteristics summary for Trial 3592.

Demographic and Baseline characteristics summary for Study3597

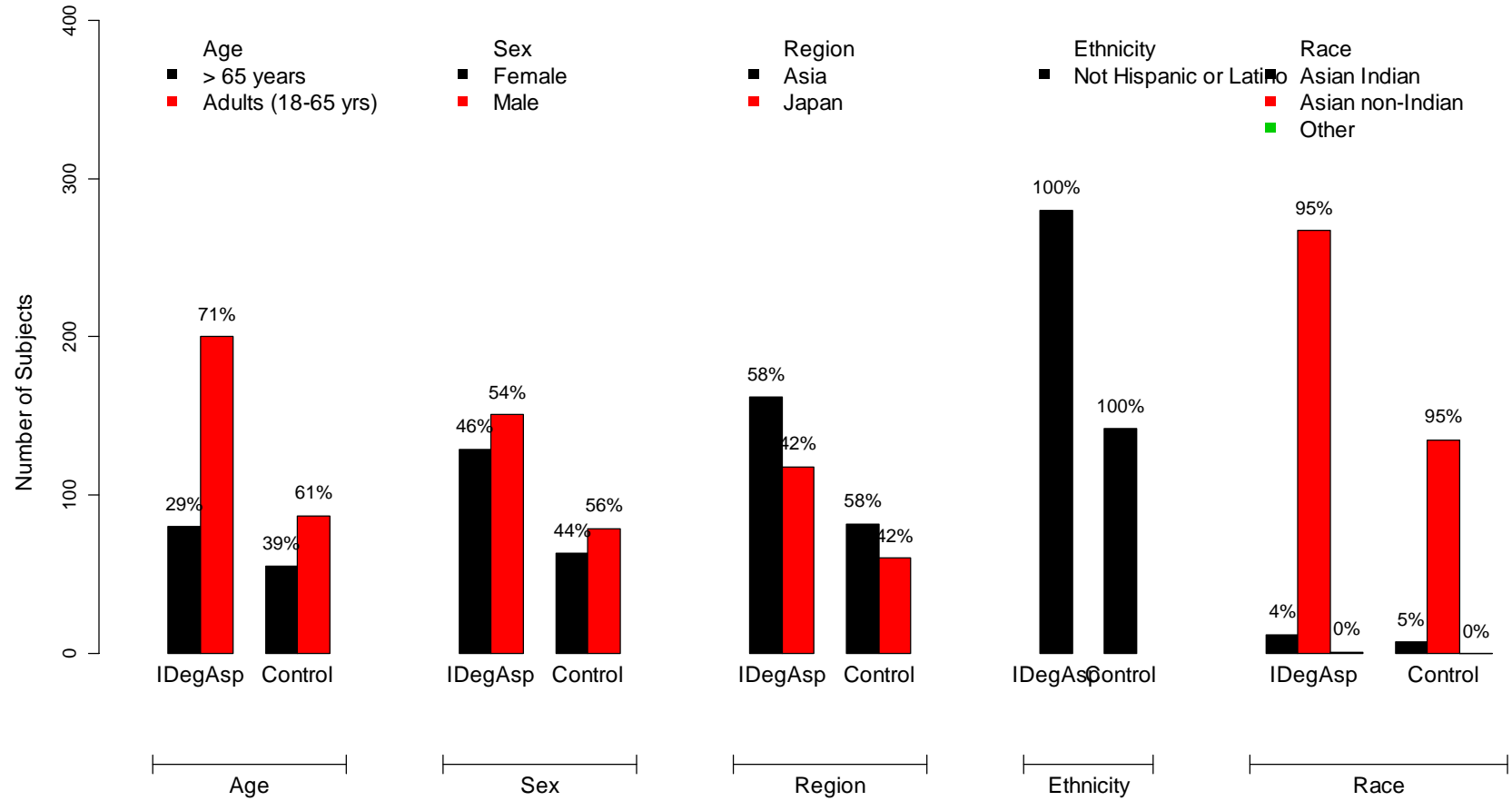


Figure 6 Demographic characteristics summary for Trial 3597.

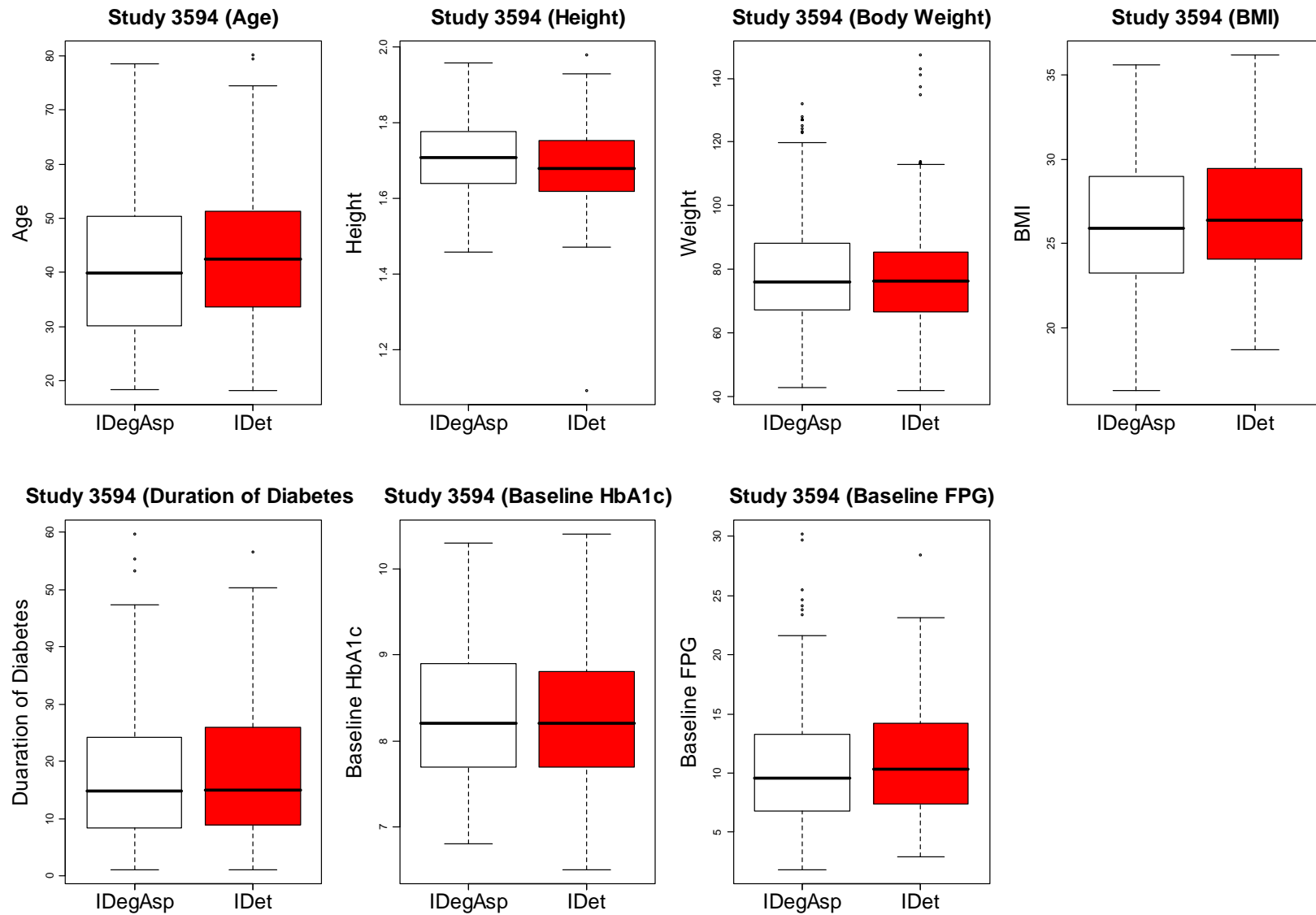


Figure 7 Baseline and diabetes characteristics for patients in Trial 3594.

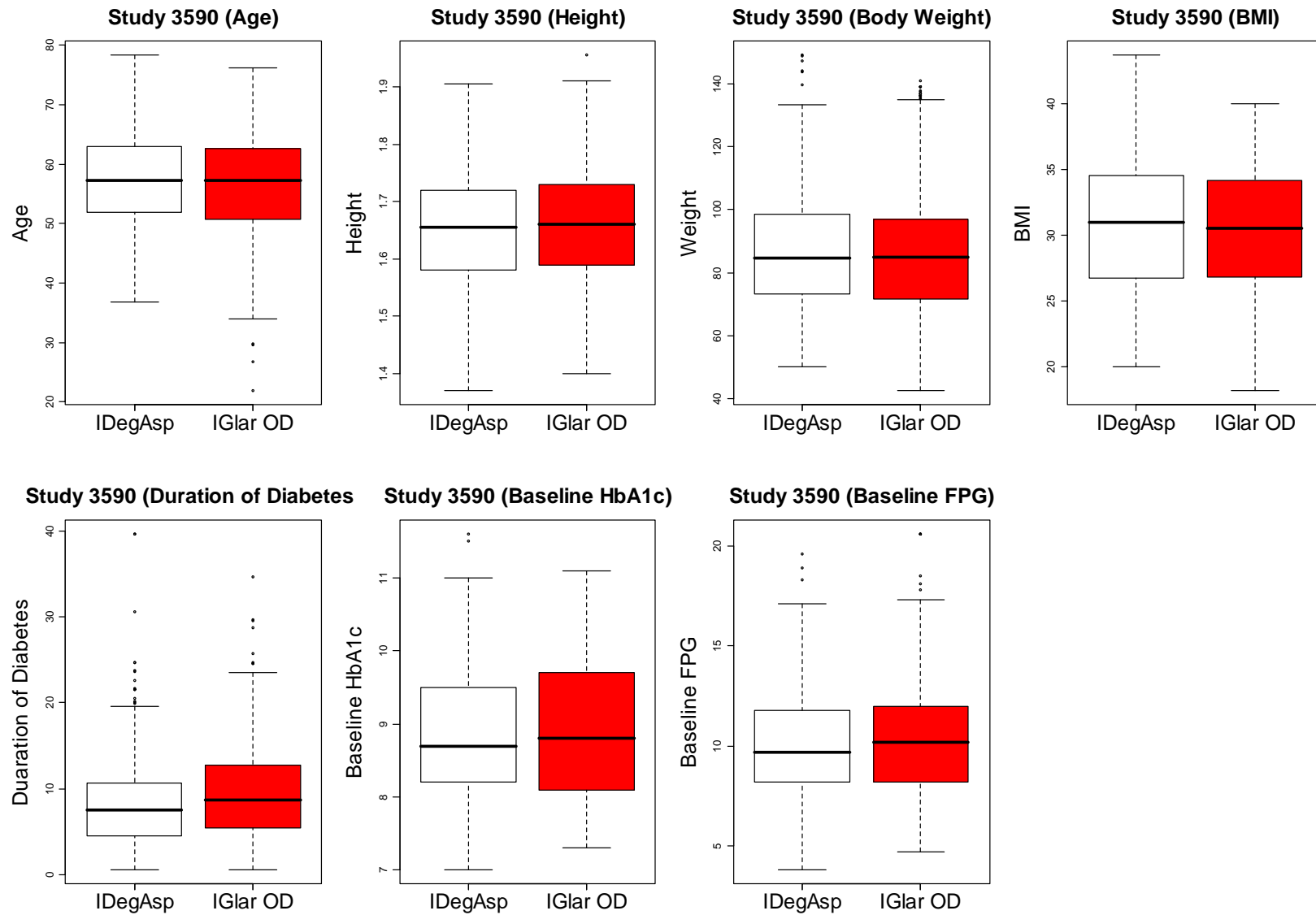


Figure 8 Baseline and diabetes characteristics for patients in Trial 3590.

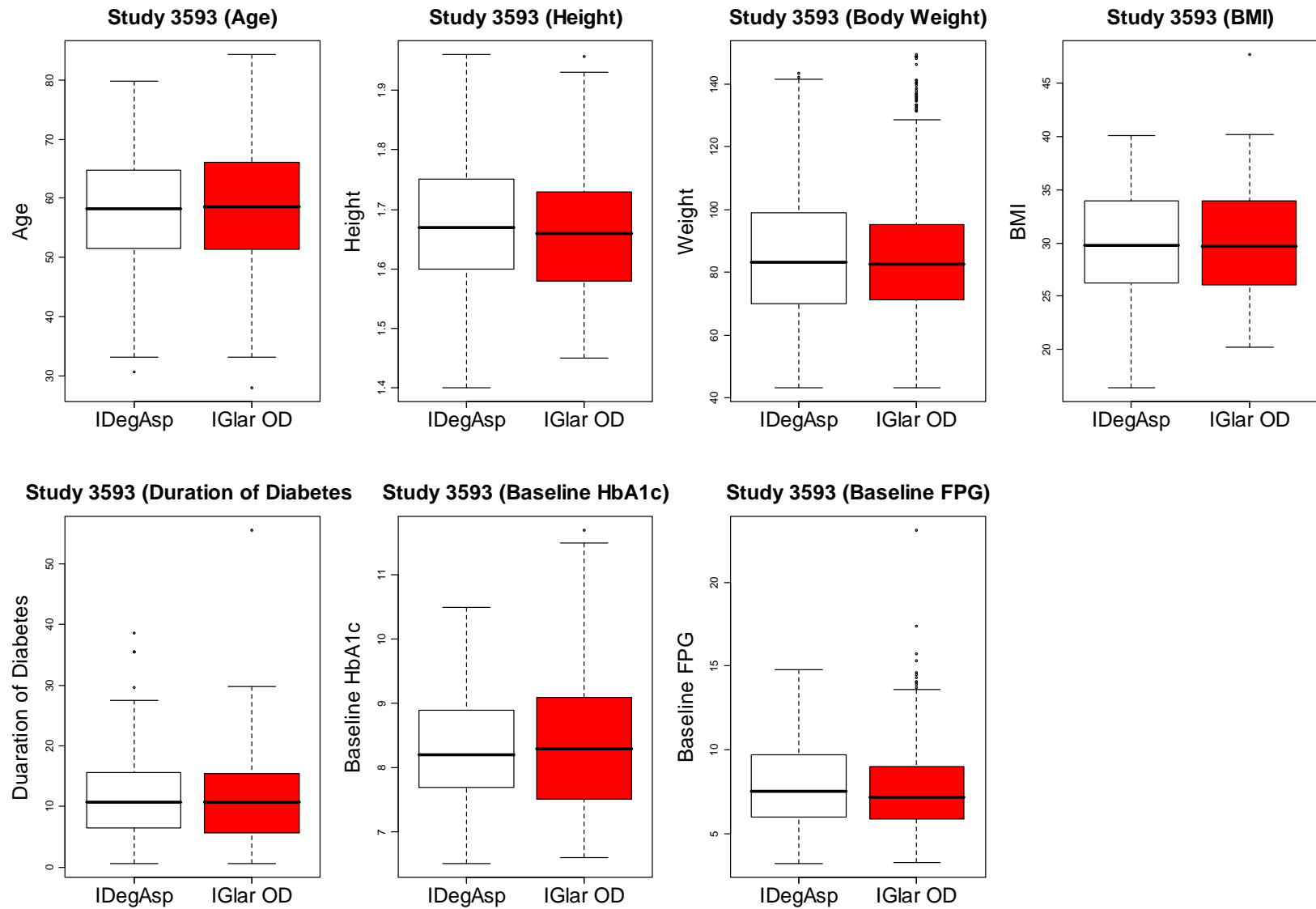


Figure 9 Baseline and diabetes characteristics for patients in Trial 3593.

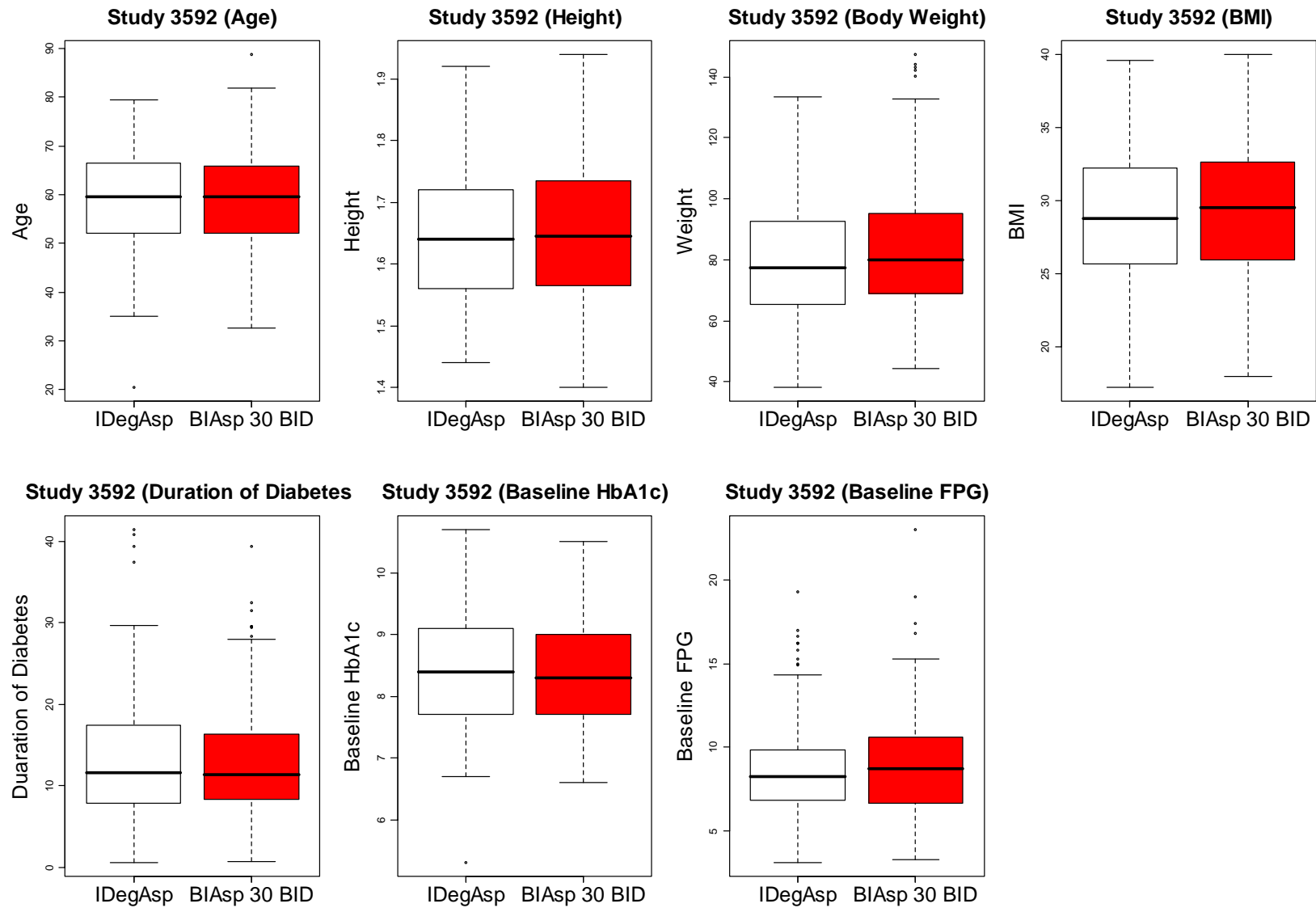


Figure 10 Baseline and diabetes characteristics for patients in Trial 3592.

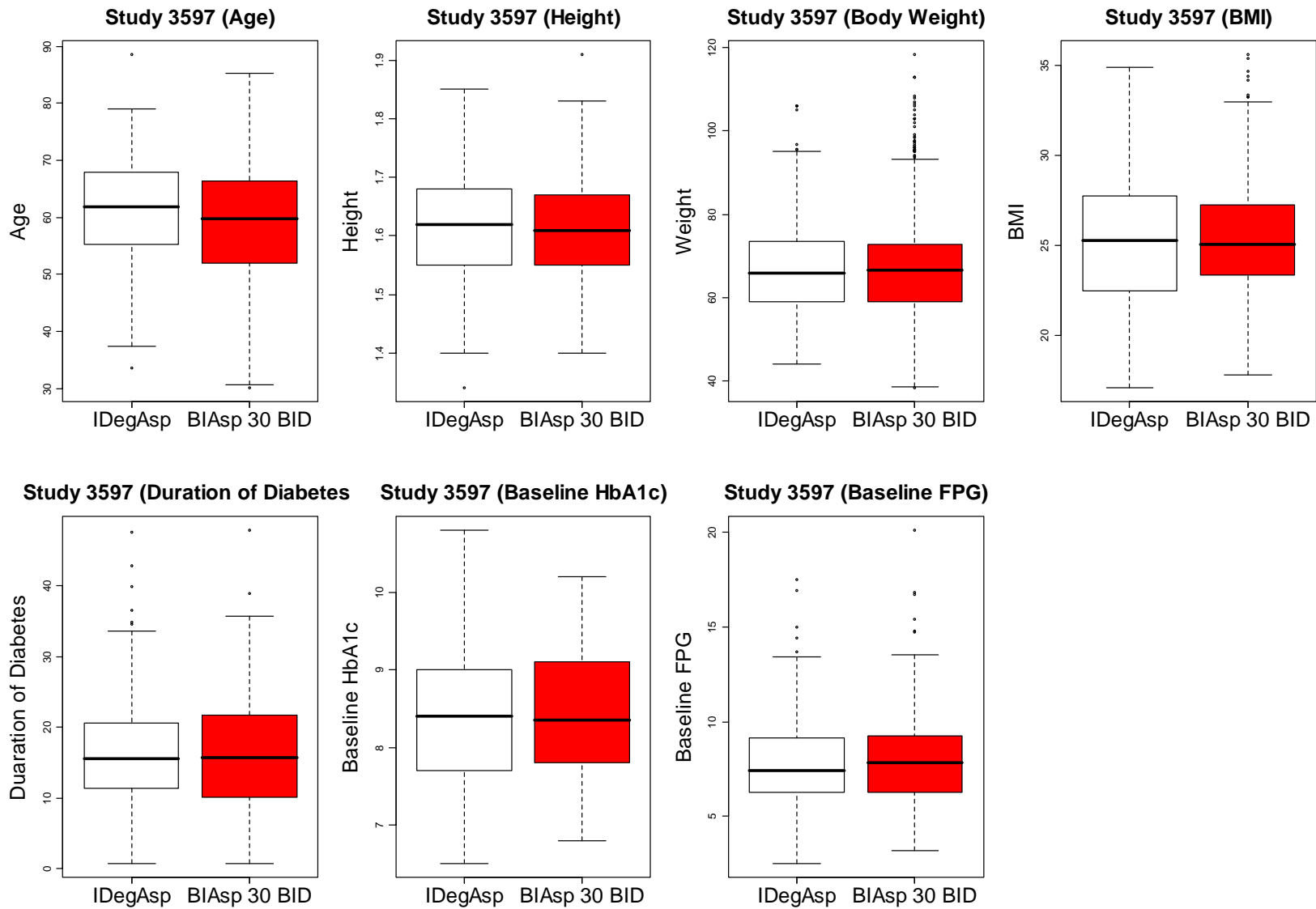


Figure 11 Baseline and diabetes characteristics for patients in Trial 3597.

4. STATISTICAL METHODOLOGIES

Change from baseline in HbA_{1c}, FPG and body weight after 26 weeks of treatment was analyzed using an Analysis of Variance (ANOVA) method with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline variable of interest as covariates.

For the analysis on HbA_{1c}, non-inferiority was to be considered confirmed if the upper bound of the two-sided 95% CI was below or equal to 0.4% or equivalently if the p-value for the one-sided test of $H_0: D > 0.4\%$ against $H_A: D \leq 0.4\%$ was less than or equal to 2.5%, where D is the treatment difference (IDegAsp - comparator). The non-inferiority margin 0.4% is used routinely by the Division in active controlled trials that use insulin as the control group. If non-inferiority was confirmed, the superiority of IDegAsp over comparator was to be investigated. Superiority was to be considered confirmed if the upper bound of the two-sided 95% CI from the analysis was below 0%.

Missing data on HbA_{1c} was imputed by last observation carried forward (LOCF) method. Two sensitivity analyses were performed for the primary efficacy endpoint.

All observed HbA_{1c} measurements available post randomization at scheduled measurement times were analyzed in a linear mixed model using an unstructured residual covariance matrix. This approach relies on the assumption that data are missing at random (MAR). The results were compared to the results of the LOCF method for dealing with missing data.

Change in HbA_{1c} from baseline was also analyzed using a model with only treatment as fixed factor and baseline HbA_{1c} as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates.

Responder (subjects with HbA_{1c} < 7% at the end of trial) without hypoglycemic episodes was analyzed by logistic regression model using the same factors and covariates for the analysis of HbA_{1c}.

Number of hypoglycemic episodes was analyzed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset. The model included the same factors and covariates as for the analysis of HbA_{1c}.

If non-inferiority was confirmed for the primary efficacy endpoint, superiority test on secondary efficacy endpoints would be done. To control the family-wise type I error rate, the superiority tests on secondary efficacy endpoints were carried out in a pre-specified hierarchical procedure (order shown in Table 2). The superiority of a secondary efficacy endpoint was only confirmed when all previous null-hypotheses had been rejected.

Analyses of efficacy endpoints were based on the full analysis set (FAS), which included all randomized subjects. Subjects in FAS set contribute to the evaluation as-randomized. The primary efficacy analysis was repeated on the per-protocol analysis set (PP), which included

subjects without any major protocol violations that may have affected the primary endpoint and the subjects must have been exposed to the investigational product or its comparator for more than 12 weeks and must have a valid assessment necessary for deriving the primary endpoint. Subjects in PP set contribute to the evaluation as-treated.

5. RESULTS

Summary of the primary efficacy endpoint is given in Table 4, Figure 12 and Figure 13. In all trials, IDegAsp effectively improved glycemic control. Non-inferiority of IDegAsp versus comparator was confirmed for the primary endpoint in all five trials, i.e. the upper limit of the 95% CIs were all below the predefined non-inferiority limit of 0.4%. Similar results were obtained for the extended period of Trial 3594 in subjects with T1DM, demonstrating the initial improvement in HbA1c was maintained for at least one year.

The observed reductions in HbA1c with IDegAsp were approximately 0.7% in T1DM subjects and between 1.0%~1.7% in T2DM subjects. The improvement in HbA1c during IDegAsp OD treatment of subjects with T2DM was more substantial for insulin-naïve subjects (Trial 3590) than for the subjects who were already on basal insulin at trial entry (Trial 3593). In previously insulin-treated subjects, the HbA1c reductions were greater with IDegAsp BID (Trials 3592 and 3597) than with IDegAsp OD (Trial 3593).

Table 4 Change of HbA1c (%) from baseline to end-of-trial.

Trial	IDegAsp			Comparator			IDegAsp - Comparator	
	N	LS Mean	SE	N	LS Mean	SE	Contrast	95% CI
T1DM								
3594 (main)	366	-0.75	0.06	182	-0.70	0.08	-0.05	(-0.18, 0.08)
3594 (extension)	366	-0.67	0.07	182	-0.57	0.08	-0.10	(-0.24, 0.03)
T2DM								
3590	266	-1.72	0.08	263	-1.75	0.08	0.03	(-0.14, 0.20)
3593	230	-1.00	0.08	233	-0.97	0.08	-0.03	(-0.20, 0.14)
3592	224	-1.31	0.09	222	-1.29	0.10	-0.03	(-0.18, 0.13)
3597	280	-1.39	0.05	142	-1.44	0.07	0.05	(-0.10, 0.20)

Summary of the confirmatory secondary efficacy endpoint is given in Table 5. The secondary endpoints differ across trials and were prioritized in different orders across trials (as shown in Table 2). At the End-of-Phase 2 meeting, the sponsor was asked to provide an explanation in the NDA submission of how the secondary endpoints were prioritized. However, this information was not provided. Since the secondary efficacy endpoints were tested in a hierarchical procedure to control the family-wise type I error, the order of secondary endpoints matters for testing purpose. However, because there is no obvious reason why the secondary endpoints should differ across trials and be prioritized in different orders and the design and study population were fairly similar in the T2DM trials, it is more reasonable to evaluate the results of secondary efficacy endpoints collectively across trials than to evaluate them separately in different order in each single trial.

To make the cross-trial evaluation, Table 5 includes not only results on pre-specified secondary endpoints in each trial but also endpoints that were specified in any other phase 3 trials. In summary, no consistent pattern was shown in all secondary endpoints across trials, except confirmed nocturnal hypoglycemia.

The rate of confirmed nocturnal hypoglycemia was lower with IDegAsp than that with comparators in T1DM subjects and two of the T2DM trials (Trials 3590 and 3592). In the rest of the two T2DM trials, there was no difference between IDegAsp and comparator.

At the End-of-Phase 2 meeting, the Division mentioned because reporting of hypoglycemia is somewhat observer-dependent, and because the trials are un-blinded, there may be bias in reporting of hypoglycemia events. The lower rate of confirmed nocturnal hypoglycemia in IDegAsp than that in comparators was not a very strong signal (i.e. two trials showed no difference). If only severe hypoglycemia was considered, the signal was completely lost and none of the trials showed a rate ratio excluding 1. Moreover, while considering nocturnal hypoglycemia and daytime hypoglycemia together, no consistent pattern was detected in total hypoglycemia across trials. From clinical perspective, hypoglycemia episodes happened during daytime are as important as nocturnal hypoglycemia. In this study, nocturnal hypoglycemia was defined as episodes occurring between 12:01 am and 05:59am. The time window for definition of nocturnal hypoglycemia was arbitrary and when it changes the results on nocturnal hypoglycemia changes as well. Thus total hypoglycemia is a more appropriate measure than nocturnal hypoglycemia for this endpoint. The results discussed in this paragraph are summarized in Figure 14.

Due to experience from previous development programs, at the End-of-Phase 2 meeting, the sponsor proposed meta-analysis of hypoglycemic events, which showed that even substantial differences in rates of hypoglycemia between treatments can fail to reach statistical significance due to the limited power in the statistical model for analyzing hypoglycemic events. However, the sponsor only submitted meta-analysis for the single component product IDeg, but not for the combination product IDegAsp. I conducted the meta-analysis for this review and the results are shown in Table 6 and Table 7. The meta-analysis was carried out on the pooled data across T2DM trials with a model similar to the one used for hypoglycemia analysis in a single trial, with an additional fixed effect on trials.

Without adjustment on multiplicity, among all comparisons, meta-analysis showed a statistically significant lower rate of confirmed nocturnal hypoglycemia in IDegAsp than in comparators in both OD and BID trials. IDegAsp also showed a lower rate of total confirmed hypoglycemia in BID trials compared to comparators. However, the rate of total confirmed hypoglycemia in IDegAsp was greater than in comparator for OD trials. In summary, the signal from meta-analysis is mixed. Furthermore, this meta-analysis is post-hoc exploratory analysis, the result should not be considered as confirmatory. It should only serve as an exploratory analysis for hypothesis generating. There was previous experience in other drug development that the conclusions of a meta-analysis can be shown to differ from a subsequent, large, more definitive, randomized trial. To confirm the potential lower rate of nocturnal hypoglycemia in IDegAsp than in comparators, results from a large confirmatory trial will be more assuring than results from post-hoc meta-analysis.

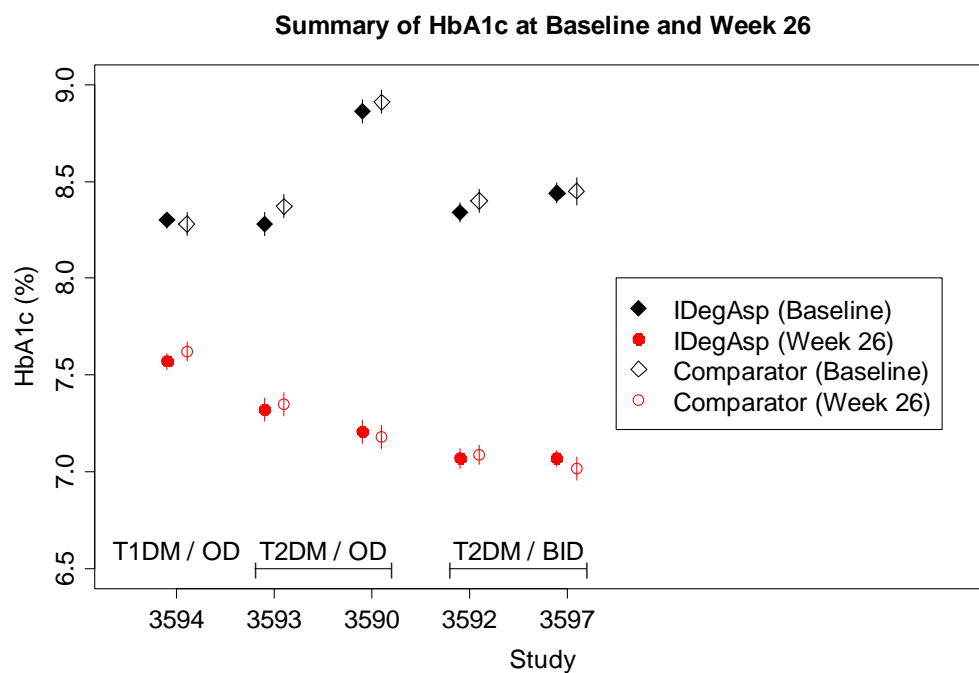


Figure 12 Summary of HbA1c at baseline and week 26.

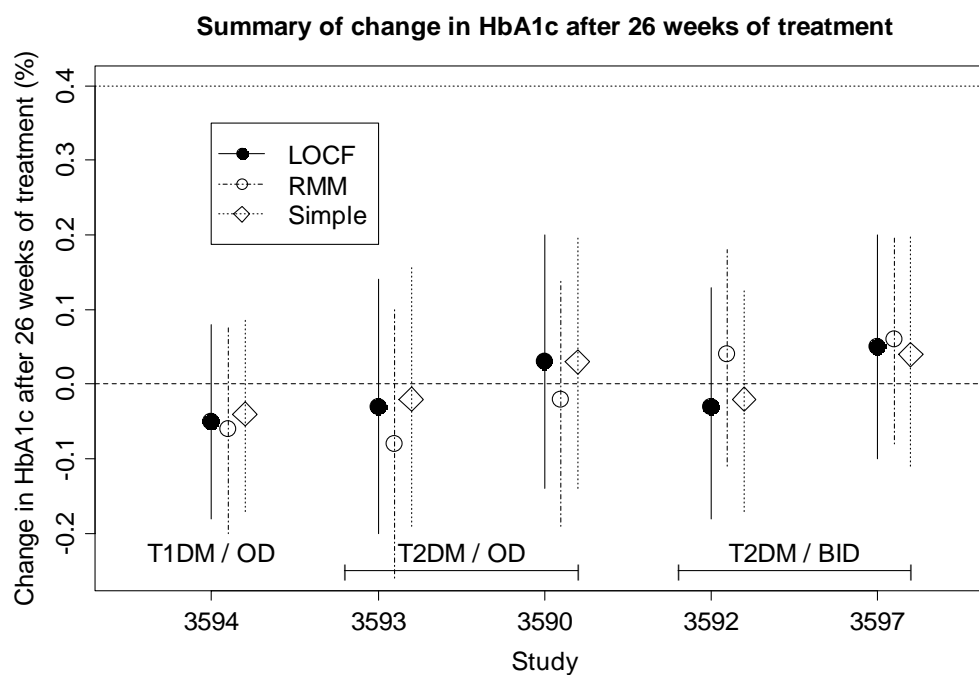


Figure 13 Summary of change in HbA1c after 26 weeks of treatment (IDegAsp-Comparator).

Table 5 Summary of confirmatory secondary efficacy endpoints.

	3594 (T1DM OD)		3590 (T2DM OD)		3593 (T2DM OD)		3592 (T2DM BID)		3597 (T2DM BID)	
	Mean ³	95% CI	Mean ³	95% CI	Mean ³	95% CI	Mean ³	95% CI	Mean ³	95% CI
HbA1c <7% without Hypoglycemia ¹	1.24	(0.77, 2.02)	0.61	(0.40, 0.94)	0.80	(0.50, 1.30)	1.60	(0.94, 2.72)	1.77	(0.97, 3.25)
Confirmed Nocturnal Hypoglycemia ¹	0.63	(0.49, 0.81)	0.29	(0.13, 0.65)	0.80	(0.49, 1.3)	0.27	(0.18, 0.41)	0.67	(0.43, 1.06)
Confirmed Hypoglycemia ¹	0.91	(0.76, 1.09)	2.17	(1.59, 2.94)	1.43	(1.07, 1.92)	0.68	(0.52, 0.89)	1.00	(0.76, 1.32)
Body weight ²	1.04	(0.38, 1.69)	1.31	(0.72, 1.89)	0.33	(-0.17, 0.83)	-0.62	(-1.15, -0.10)	-0.38	(-0.96, 0.21)
FPG ²	0.23	(-0.46, 0.91)	0.51	(0.09, 0.93)	0.33	(-0.11, 0.77)	-1.14	(-1.53, -0.76)	-1.06	(-1.43, -0.70)
Prandial PG at breakfast ²	-0.57	(-1.36, 0.21)	-1.40	(-1.92, -0.88)	-0.32	(-0.86, 0.21)	-0.54	(-1.09, 0.00)	0.06	(-0.54, 0.66)
Prandial PG at main evening meal ²	0.12	(-0.67, 0.92)	-0.19	(-0.70, 0.31)	-1.32	(-1.93, -0.72)	0.33	(-0.26, 0.92)	0.77	(-0.02, 1.55)
Fluctuation of Nocturnal IG ²	NA	NA	0.69	(0.25, 1.92)	0.97	(0.49, 1.3)	NA	NA	NA	NA

- 1 Treatments are compared using a ratio.
- 2 Treatments are compared using a difference.
- 3 “Mean” refers to treatment ratio or treatment difference.

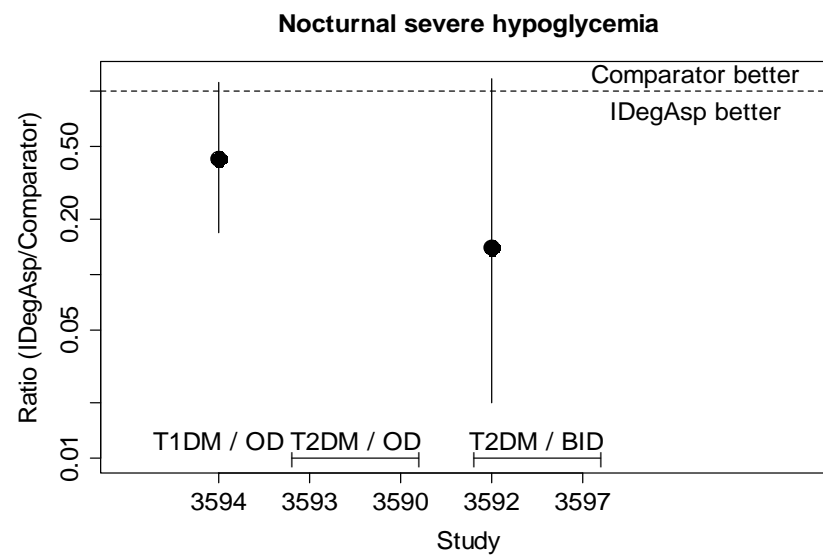
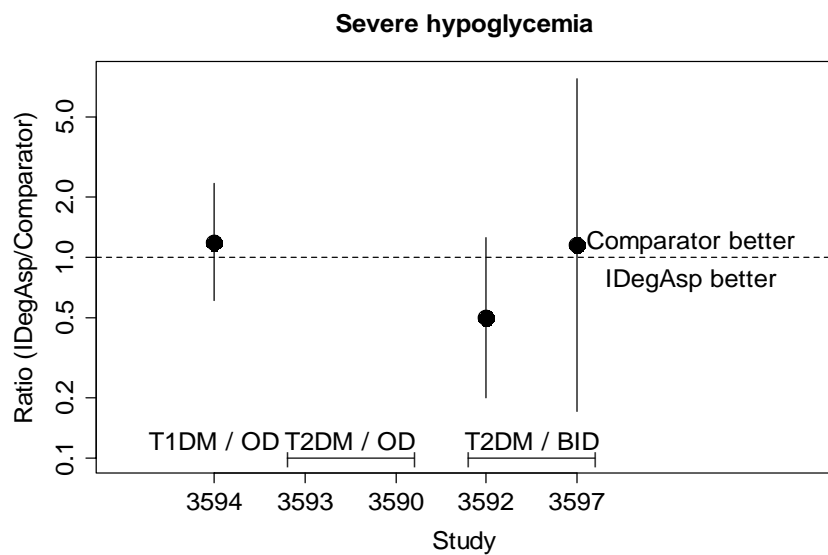
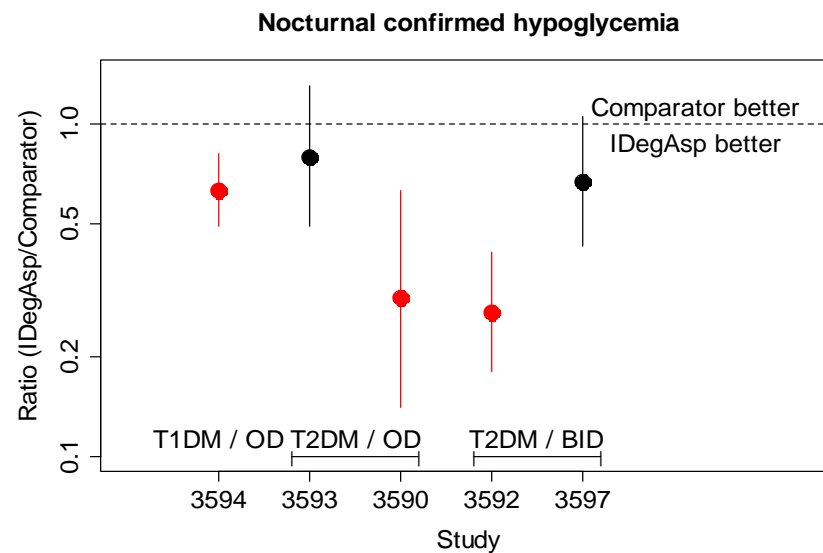
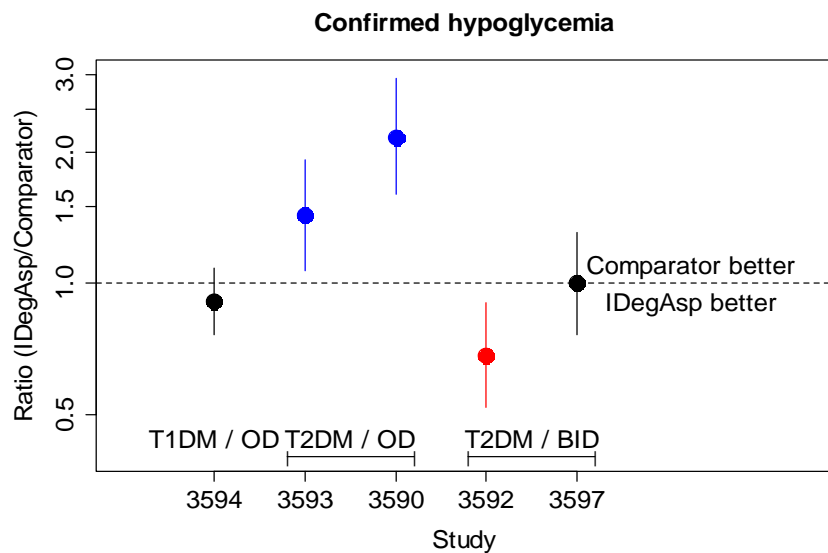


Figure 14 Ratio of hypoglycemic episodes in IDegAsp vs. Comparator.

Table 6 Meta-analysis for Hypoglycemia with IDegAsp OD in T2DM subjects.

Type	IDegAsp (NN=496; Exposure=222.8)			Comparator (NN=496; Exposure=229.4)			IDegAsp / Comparator	
	N	E	Rate	N	E	Rate	Ratio	95% CI
Confirmed Hypoglycemia	253	951	426.9	208	570	248.5	1.75	(1.42, 2.16)
Confirmed Nocturnal Hypoglycemia	57	108	48.5	79	164	71.5	0.58	(0.39, 0.87)
Severe Hypoglycemia	1	1	0.4	4	5	2.2	0.15	(0.01, 1.60)
Nocturnal Severe Hypoglycemia	0	0	0	0	0	0	NA	NA

- Exposure is in unit of person years; rate is in unit of episode per 100 person years.
- NN=total number of subject; N=number of subjects with episodes; E=number of events.

Table 7 Meta-analysis for Hypoglycemia with IDegAsp BID in T2DM subjects.

Type	IDegAsp (NN=504; Exposure=230.5)			Comparator (NN=364; Exposure=163.9)			IDegAsp / Comparator	
	N	E	Rate	N	E	Rate	Ratio	95% CI
Confirmed Hypoglycemia	353	2220	963.0	260	2000	1219.9	0.80	(0.60, 0.97)
Confirmed Nocturnal Hypoglycemia	122	219	95.0	124	351	214.1	0.41	(0.30, 0.56)
Severe Hypoglycemia	11	15	6.5	18	27	16.5	0.59	(0.26, 1.36)
Nocturnal Severe Hypoglycemia	2	2	0.9	8	9	0.5	0.25	(0.05, 1.23)

- Exposure is in unit of person years; rate is in unit of episode per 100 person years.
- NN=total number of subject; N=number of subjects with episodes; E=number of events.

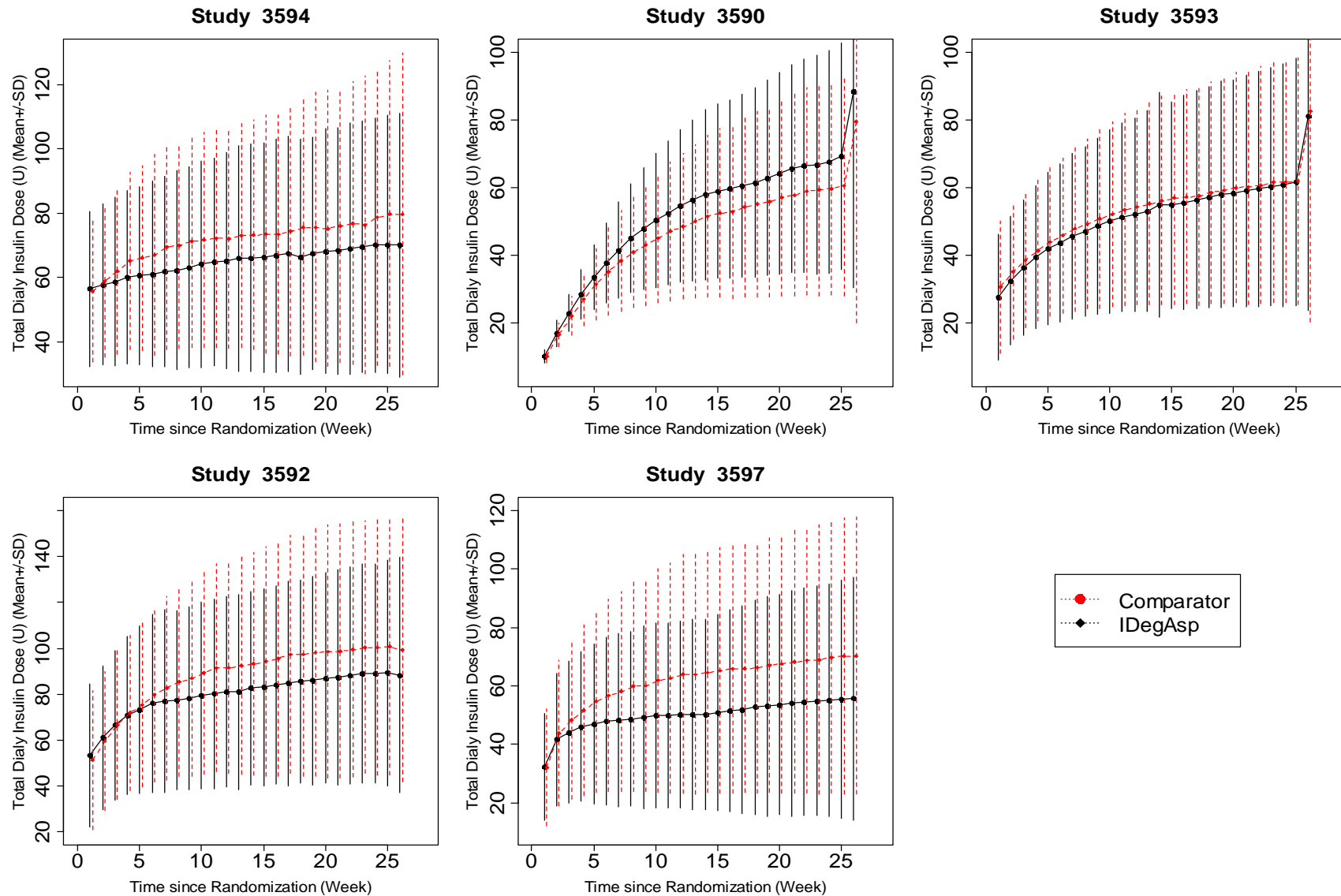


Figure 15 Summary of total daily insulin dose (Mean \pm SD).

Table 8 Change of body weight from baseline to Week 26.

Trial	IDegAsp			Comparator			IDegAsp - Comparator	
	N	LS Mean	SE	N	LS Mean	SE	Contrast	95% CI
T1DM								
3594 (main)	366	2.73	0.32	182	1.70	0.37	1.04	(0.38, 1.69)
T2DM								
3590	266	2.89	0.28	263	1.58	0.26	1.31	(0.72, 1.89)
3593	230	1.74	0.24	233	1.41	0.23	0.33	(-0.17, 0.83)
3592	224	2.21	0.31	222	2.83	0.33	-0.62	(-1.15, -0.10)
3597	280	1.30	0.19	142	1.67	0.25	-0.38	(-0.96, 0.21)

Total daily insulin doses over the 26-week treatment period were summarized by trials in Figure 15. In most of the cases, patients randomized to IDegAsp arm received on average lower dose of total daily insulin comparing to patients randomized to the control arm. The only exception was Trial 3590, where the direction was reversed.

Change of body weight from baseline at week 26 was summarized in Table 8. Comparing patients randomized to IDegAsp arm to patients randomized to the control arm, there was no consistent weight gain or weight loss across trials.

6. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Analysis of primary efficacy endpoint by subpopulations was summarized in Figure 16 for patients with T1DM and Figure 17 for patients with T2DM. Subgroup analyses on HbA1c were conducted by the mixed model, similar to the one used for the primary efficacy analysis, with the additional covariate on the subgroups being analyzed and interaction between treatment effect and subgroups. In T2DM, comparison of HbA1c in subgroups were assessed by pooling data in 4 trials (3593, 3590, 3592, 3597); in T1DM, comparison of HbA1c in subgroups were assessed by data from Trial 3594.

The factors considered for subgroup analyses include:

1. Intrinsic factors:
 - Age
 - Sex
 - BMI
 - Race
 - Ethnicity
2. Disease-related factors:
 - Diabetes duration
 - Baseline HbA1c
 - Renal function

- Hepatic function (serum ALT group)
- Serum creatinine

3. Extrinsic factors:

- Pretrial anti-diabetic treatment
- Concomitant medication

In general, the subgroup analysis results are consistent with the results of overall population. Among all comparisons, HbA1c in subjects with T2DM showed a statistically significant ($p=0.009$) treatment-by-hepatic function (serum ALT group) interaction, highlighted in red in Figure 17. However, the difference between the two serum ALT groups was very small (estimation of interaction term: mean=0.2%, se=0.09), it was not considered clinically relevant. Details of HbA1c at baseline and Week 26 by serum ALT groups in T2DM subjects are given in Table 9.

In T1DM subjects, no statistically significant treatment-by-subgroup interaction was found.

Table 9 HbA1c at baseline and week 26 by serum ALT group - T2DM - pooling trials (quoted from CSR).

Serum ATL group	IDe Asp							Com						
	Baseline			Week 26		Change		Baseline			Week 26		Change	
	N	Mean	SD	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD	Mean	SD
<75 th percentile	740	8.46	0.9	7.11	0.9	-1.35	1.0	643	8.53	1.0	7.21	1.0	-1.33	1.1
≥75 th percentile	258	8.59	0.9	7.30	0.9	-1.25	1.2	214	8.61	0.9	7.12	1.0	-1.49	1.1

- Test of interaction treatment-by-serum ALT group gives $p=0.009$.

Change in HbA1c after 26 weeks of treatment by subgroups (T1DM)

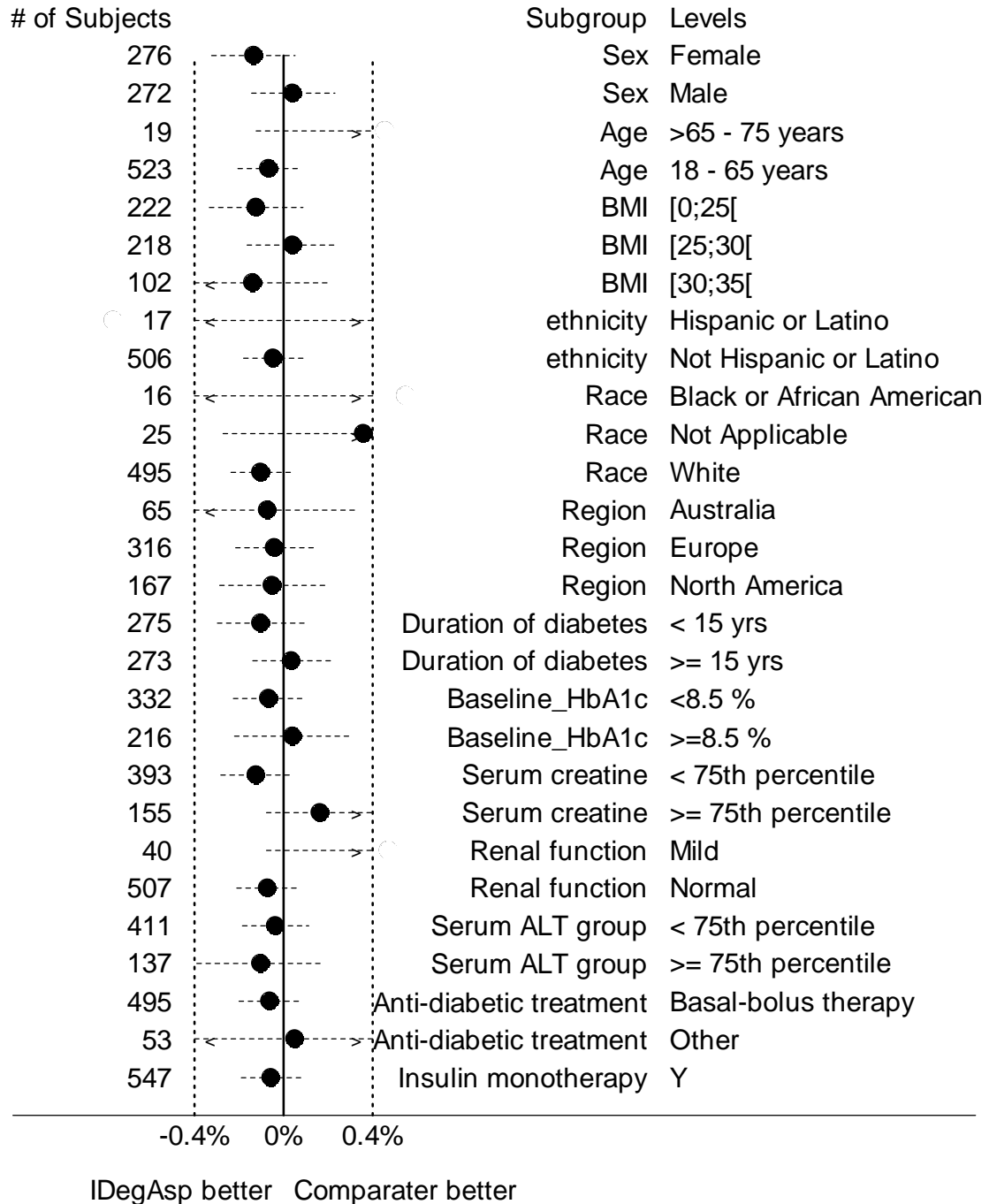


Figure 16 Change in HbA1c after 26 weeks of treatment by subgroups in T1DM subjects

Change in HbA1c after 26 weeks of treatment by subgroups (T2DM)

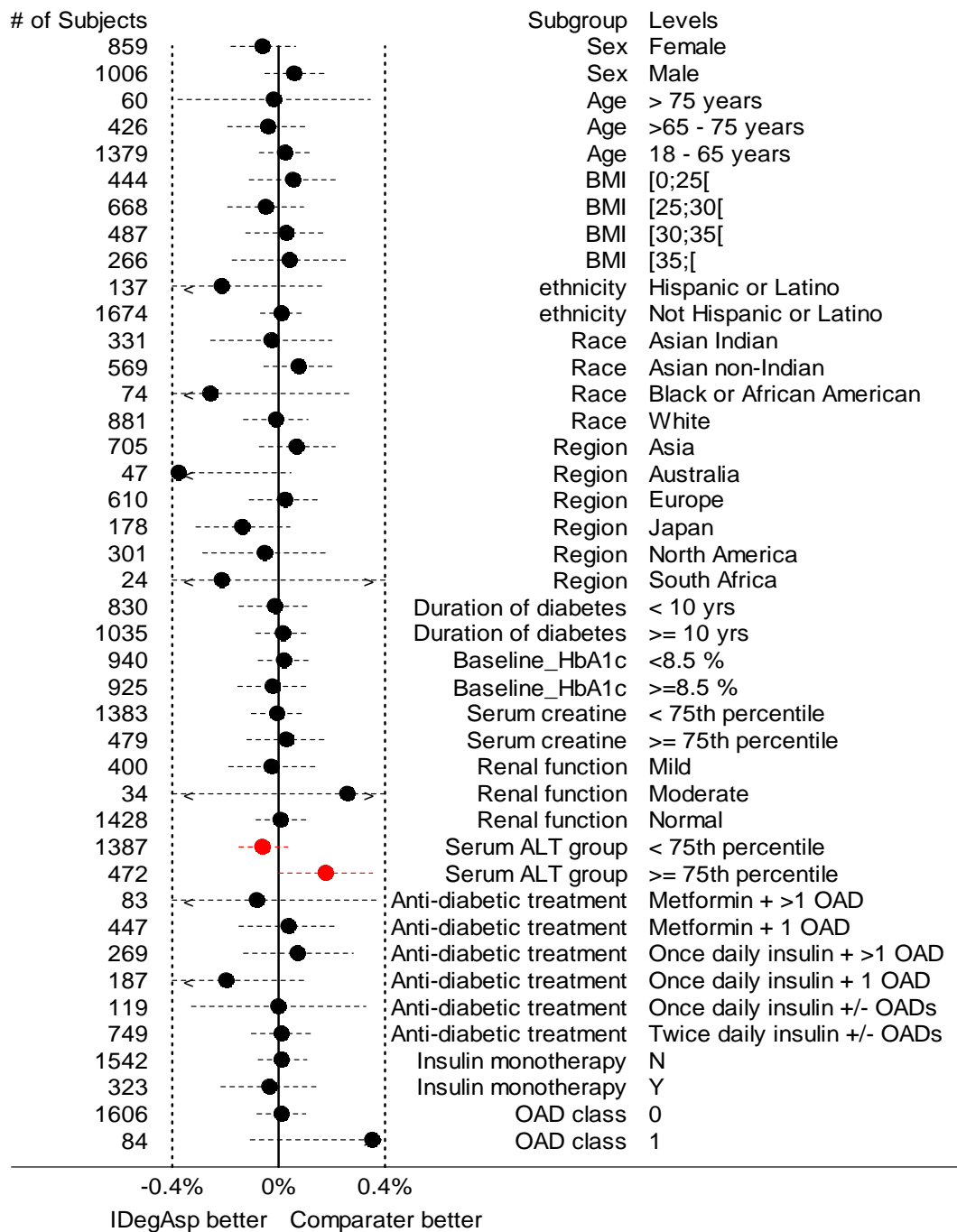


Figure 17 Change in HbA1c after 26 weeks of treatment by subgroups in T2DM subjects.

7. SUMMARY AND CONCLUSIONS

The primary efficacy endpoint was change from baseline in HbA1c after 26 weeks of treatment. In all trials, IDegAsp effectively improved glycemic control. Non-inferiority of IDegAsp versus comparator was confirmed for the primary endpoint in all five trials, i.e. the upper limit of the 95% confidence intervals were all below the predefined non-inferiority limit of 0.4%. Similar results were obtained for the extended period of Trial 3594 in subjects with T1DM, demonstrating the initial improvement in HbA1c was maintained for at least one year.

The main statistical issue in this submission is analysis on confirmatory secondary efficacy endpoints. The secondary endpoints differ across trials and were prioritized in different orders. This submission did not provide explanation on how the secondary endpoints were selected and prioritized. Because there is no obvious reason why the secondary endpoints should differ across trials and be prioritized in different orders and the design and study population were fairly similar in the T2DM trials, it is more reasonable to evaluate the results of secondary efficacy endpoints collectively across trials than to evaluate them separately in different order in each single trial. The collective evidence across trials showed no consistent pattern, i.e. advantage or disadvantage of IDegAsp over comparators, in all confirmatory secondary efficacy endpoints.

Specifically, rate of treatment emergent hypoglycemia episode was analyzed in further detail, including a post-hoc meta-analysis, for this review. No consistent strong signal of a lower rate of hypoglycemia in IDegAsp compared to comparators was detected. In addition, all the trials were open-label, despite the efforts to impose careful definitions, the measure on hypoglycemia could be still subjective, because in this design subjects knew the treatment they were getting. The results on hypoglycemia episode should be interpreted carefully. There was no consistent weight gain or weight loss across trials when comparing patients randomized to IDegAsp arm to patients randomized to the control arm. In general, patients randomized to IDegAsp arm received on average lower dose of total daily insulin comparing to patients randomized to the control arm. The only exception was Trial 3590, where the direction was reversed.

The review on efficacy supports the claim of using IDegAsp for improving glycemic control in adult patients with diabetes mellitus.

APPENDIX

Table 10 Change of HbA1c from baseline to end-of-trial (per-protocol analysis).

Trial	IDegAsp			Comparator			IDegAsp - Comparator	
	N	LS Mean	SE	N	LS Mean	SE	Contrast	95% CI
T1DM								
3594 (main)	336	-0.83	0.07	168	-0.77	0.08	-0.06	(-0.20, 0.08)
T2DM								
3590	229	-1.86	0.08	244	-1.85	0.08	-0.02	(-0.19, 0.15)
3593	211	-1.07	0.09	211	-1.01	0.08	-0.06	(-0.23, 0.12)
3592	200	-1.46	0.09	193	-1.49	0.10	0.04	(-0.11, 0.18)
3597	255	-1.50	0.05	128	-1.56	0.06	0.06	(-0.08, 0.20)



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON Tresiba/Ryzodeg

Statistical briefing material for the Endocrinologic and Metabolic Drugs Advisory Committee,
November 8, 2012

Bo Li, PhD
Mat Soukup, PhD
Aloka Chakravarty, PhD

Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Document Date: October 10, 2012

1. Trial Database

The initial cardiovascular (CV) related safety meta-analyses utilized an integrated dataset of insulin degludec (IDeg) and insulin degludec/insulin aspart (IDegAsp) trials included in the original NDA submission. This original submission was based upon a cut-off date of January 31, 2011. A total of 16 randomized, active-controlled phase 3 trials were submitted by the applicant for CV safety evaluation at this time. This submission included 11 trials for IDeg (Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770) and 5 trials for IDegAsp (Studies 3590, 3592, 3593, 3594/3645, and 3597).

Results from the initial analysis of the CV safety suggested the potential for an increase in CV risk, though a statistically significant finding could not be determined. As several trials were ongoing at the time of the original NDA filing, an information request was sent to the sponsor to provide an updated CV safety analysis and information for all trials that were not included in the original submission. A new cut-off date of May 1, 2012 was designated for the requested analyses and data base.

During the period from January 31, 2011 to May 1, 2012, 9 additional trials with IDeg or IDegAsp had been completed, including 6 extension trials (Studies 3579+3643, 3582+3667, 3583+3644, 3585+3725, 3770+ext and 3590+3726), two phase 3b trials with IDeg (Studies 3846 and 3923) and one confirmatory trial with IDegAsp (Study 3896). While the two trials 3846 and 3923 contribute IDeg exposure data, they are not incorporated into the primary meta-analysis of CV safety as neither trial contains a non-IDeg comparator arm. As a result, the updated analyses of all completed studies as of May 1, 2012 include 17 trials. Note that this update does *include* the trial information provided in the original submission.

Table 1 provides a high level summary of the total number of subjects and total person-years of exposure for the combined IDeg/IDegAsp arm and all comparator arm respectively, in the original and updated analyses. While the updated database includes only one additional trial from the original database, the inclusion of the extension trial information into the updated database results in approximately 40% more person-years of exposure (PYE). A summary of design characteristics of the 17 trials included in the updated analysis is presented in Table 2.

Table 1: Comparison of the Original and Updated CV Meta-analysis Database

	Original Database (16 trials)		Updated Database (17 trials)	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
Sample Size (N)	5647	3312	5794	3461
Person Years Exposure (PYE)	3569.9	1873.9	5153.6	2562.7

Table 2: Summary of Design Characteristics of the 17 Randomized Phase 3 Trials Included in the Updated CV Meta-Analysis

Trial Name	Treatment Arms	Ratio	Study Size†	Duration	Population
3579+3643	IDeg, IGlar	3:1	1,030	52+52 weeks	Type 2 DM
3580	IDeg, sitagliptin	1:1	447	26 weeks	Type 2 DM
3582+3667	IDeg, IGlar	3:1	992	52+26 weeks	Type 2 DM
3583+3644	IDeg, IGlar	3:1	629	52+52 weeks	Type 1 DM
3585+3725	IDeg, IDet	2:1	455	26+26 weeks	Type 1 DM
3586	IDeg, IGlar	2:1	435	26 weeks	Type 2 DM
3668	IDeg, IDeg flex, IGlar	1:1:1	687	26 weeks	Type 2 DM
3672	IDeg, IGlar	1:1	457	26 weeks	Type 2 DM
3718	IDeg, IGlar	1:1	467	26 weeks	Type 2 DM
3724	IDeg, IGlar	1:1	459	26 weeks	Type 2 DM
3770 + ext	IDeg, IDeg flex, IGlar	1:1:1	493	26+26 weeks	Type 1 DM
3590+3726	IDegAsp, IGlar	1:1	529	26+26 weeks	Type 2 DM
3592	IDegAsp, BIAsp	1:1	446	26 weeks	Type 2 DM
3593	IDegAsp, IGlar	1:1	463	26 weeks	Type 2 DM
3594+3645	IDegAsp, IDet	2:1	548	26+26 weeks	Type 1 DM
3597	IDegAsp, BIAsp	2:1	422	26 weeks	Type 2 DM
3896	IDegAsp, IGlar	1:1	296	26 weeks	Type 2 DM

Rows highlighted correspond to trials that include additional information provided in the updated analysis.

IGlar = insulin glargine, IDet = insulin detemir, BIAsp = biphasic insulin aspart

† Study sizes correspond to the full analysis set (FAS) described in Section 2.2.

2. Statistical Methods

2.1 Primary Endpoint

In the original submission, the agreed upon primary endpoint for CV safety analysis was major adverse cardiovascular event (MACE), which was pre-specified as a composite endpoint consisting of the following adjudicated events: acute coronary syndrome (ACS) including unstable angina pectoris (UAS) and myocardial infarction, stroke, and CV death. As a response to the FDA information request, the applicant conducted additional analyses based on a more strict MACE definition which excludes UAS from the sponsor’s original MACE specification. Throughout the rest of this statistical assessment of CV safety, we will refer to “MACE” for the strict MACE definition and “MACE+” for the sponsor’s initial definition.

2.2 Analysis Methods and Censoring Window

The primary analysis of MACE+/MACE is based upon time-to-event methodology utilizing two different censoring times: subjects’ data could be censored 7 days after treatment discontinuation

or 30 days after treatment discontinuation. The protocol defined full analysis set (FAS) includes all randomized subjects with the exclusion of a small number of subjects ($N = 36$) based upon sponsor criteria. All analyses reported here are based on the FAS population.

The pre-specified primary analysis is the stratified Cox proportional hazards model that includes trial as the stratification factor to test the hazard ratio (HR) of IDeg/IDegAsp group versus the pooled all comparator group. Note that for trials that include an extension trial to the main trial (e.g. 3579+3643), the model includes only a single stratification factor. Trials with no events on both arms are excluded from the Cox regression analysis.

As a secondary analysis, stratified Mantel-Haenszel estimates of the overall risk difference (RD) and incidence rate difference (IRD) are calculated along with the associated 95% confidence interval using trial as a stratification factor. This method makes use of all trials. In incidence rate difference calculations, the unit of analysis is the subject-year or person-year of follow-up, whereas in risk difference calculations, the unit of analysis is the subject.

To further investigate the sensitivity of the primary analysis on the primary composite endpoint, the FDA conducted several sensitivity analyses that include the following:

- Analysis of the 12 IGlar-controlled trials,
- Analysis of the 11 IDeg trials,
- Analysis of the 6 IDegAsp trials, and
- Analysis by type of diabetes (Type 1 and Type 2).

These sensitivity analyses were conducted using a stratified Cox proportional hazard model and using the stratified Mantel-Haenszel method described above.

3. Results

A summary of the observed MACE+ events, along with its individual components, is presented in Table 3 for the 17 trials included in the updated analysis. When censoring MACE+ at 7 days, a total of 95 events (incidence rate of 18.4 per 1,000 person-years) were observed in the pooled IDeg/IDegAsp group, and 37 events (incidence rate of 14.4 per 1,000 person-years) were observed in the pooled all comparator group.

Table 3: Summary results of MACE+ in Updated Database (FAS, 7 and 30 Day Censoring)

	Censoring: 7 Days		Censoring: 30 Days	
	IDeg/IDegAsp (N = 5794) [PYE = 5153.6]	Comparator (N = 3461) [PYE = 2562.7]	IDeg/IDegAsp (N = 5794) [PYE = 5153.6]	Comparator (N = 3461) [PYE = 2562.7]
MACE+	95 (1.6) [18.4]	37 (1.1) [14.4]	99 (1.7) [19.2]	39 (1.1) [15.2]
Acute Coronary Syndrome	59 (1.0) [11.4]	25 (0.7) [9.8]	61 (1.1) [11.8]	25 (0.7) [9.8]
UAP *	25 (0.4) [4.9]	16 (0.5) [6.2]	25 (0.4) [4.9]	16 (0.5) [6.2]
MI	34 (0.6) [6.6]	9 (0.3) [3.5]	36 (0.6) [7.0]	9 (0.3) [3.5]
MI-STEMI	15 (0.3) [2.9]	3 (0.1) [1.2]	15 (0.3) [2.9]	3 (0.1) [1.2]
MI-NSTEMI	19 (0.3) [3.7]	6 (0.2) [2.3]	21 (0.4) [4.1]	6 (0.2) [2.3]
Stroke	24 (0.4) [4.7]	6 (0.2) [2.3]	25 (0.4) [4.9]	7 (0.2) [2.7]
CV Death	12 (0.2) [2.3]	6 (0.2) [2.3]	13 (0.2) [2.5]	7 (0.2) [2.7]

Results are reported as counts, (%), and [incident rate per 1,000 PYE]

* UAP is excluded from strict MACE.

The pre-specified primary analysis was the Cox proportional hazards (CPH) model stratified by trial. In Table 4 and Table 5, results are presented for each endpoint (MACE+/MACE) individually broken down by censoring window. With more data incorporated in the updated analyses, the results show an increase in all the HR point estimates for both MACE+ and MACE. While estimates and 95% CI's for the MACE+ endpoint suggest a smaller magnitude of CV risk than that of the MACE endpoint, both endpoints suggest an increase in CV risk for subjects randomized to IDeg/IDegAsp, of which lower bounds of the 95% CI for MACE are near or above 1.

Table 4: CPH Analysis Results for MACE+ based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (N = 5647)	Comparator (N = 3312)	IDeg/IDegAsp (N = 5794)	Comparator (N = 3461)
Censoring: 7 Days				
MACE+	53	27	95	37
HR (95% CI)	-	1.10 (0.68, 1.77)	-	1.30 (0.88, 1.93)
Censoring: 30 Days				
MACE+	56	27	99	39
HR (95% CI)	-	1.17 (0.73, 1.87)	-	1.29 (0.88, 1.89)

Table 5: CPH Analysis Results for MACE based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (N = 5647)	Comparator (N = 3312)	IDeg/IDegAsp (N = 5794)	Comparator (N = 3461)
<i>Censoring: 7 Days</i>				
MACE	39	15	70	21
HR (95% CI)	-	1.39 (0.76, 2.57)	-	1.67 (1.01, 2.75)
<i>Censoring: 30 Days</i>				
MACE	42	15	74	23
HR (95% CI)	-	1.50 (0.82, 2.75)	-	1.61 (1.00, 2.61)

Trials with no events were excluded from the time-to-event analysis methods when using the Cox Proportional Hazard Model stratified by trial. In order to incorporate trials with zero event rates, risk difference and the difference of incidence rates were calculated using Mantel-Haenszel methods. The results for the updated database when censoring at 7 days or 30 days are consistent, and as such, the results of these secondary analyses are shown below in Table 6 for the 7 day censoring window only. Consistent with the primary analysis, both the MACE+ and MACE endpoints suggest an increased CVrisk for subjects randomized to IDeg/IDegAsp over comparator.

Table 6: Updated Database Secondary Analysis Results for MACE+/MACE (FAS, 7 Day Censoring)

	MACE+		MACE	
	Estimate	95% CI	Estimate	95% CI
M-H Risk Difference (%)	0.33	(-0.15, 0.81)	0.42	(0.03, 0.82)
M-H Incidence Rate Difference[†]	4.27	(-1.84, 10.4)	5.41	(0.37, 10.5)

[†] Incidence per 1000 PYE

The forest plots of the hazard ratios of the MACE+ and MACE composite endpoints (censoring at 7 days) are presented in Figures 1 and 2 for the updated database. Trials are ordered by the planned duration of treatment (trials with the shortest planned treatment duration are presented in the bottom of the figure and trials with the longest planned treatment duration are presented at the top of the figure). Color of a trial corresponds to the control used in the trial (insulin glargine (IGlar) versus non-IGlar). The individual hazard ratio and the corresponding 95% CIs of each trial from a Cox regression model are shown where the size of the symbol for each hazard ratio corresponds to the size of the trial. In the forest plots only trials where MACE+/MACE events were observed on both treatment arms include point estimates for the hazard ratio and the corresponding 95% CIs which accounts for more estimates shown in the forest plot of MACE+ than the forest plot of MACE.

Figure 1: Forest Plot of Time-to-Event Analysis of MACE+ up to 7 Days after Treatment (FAS)

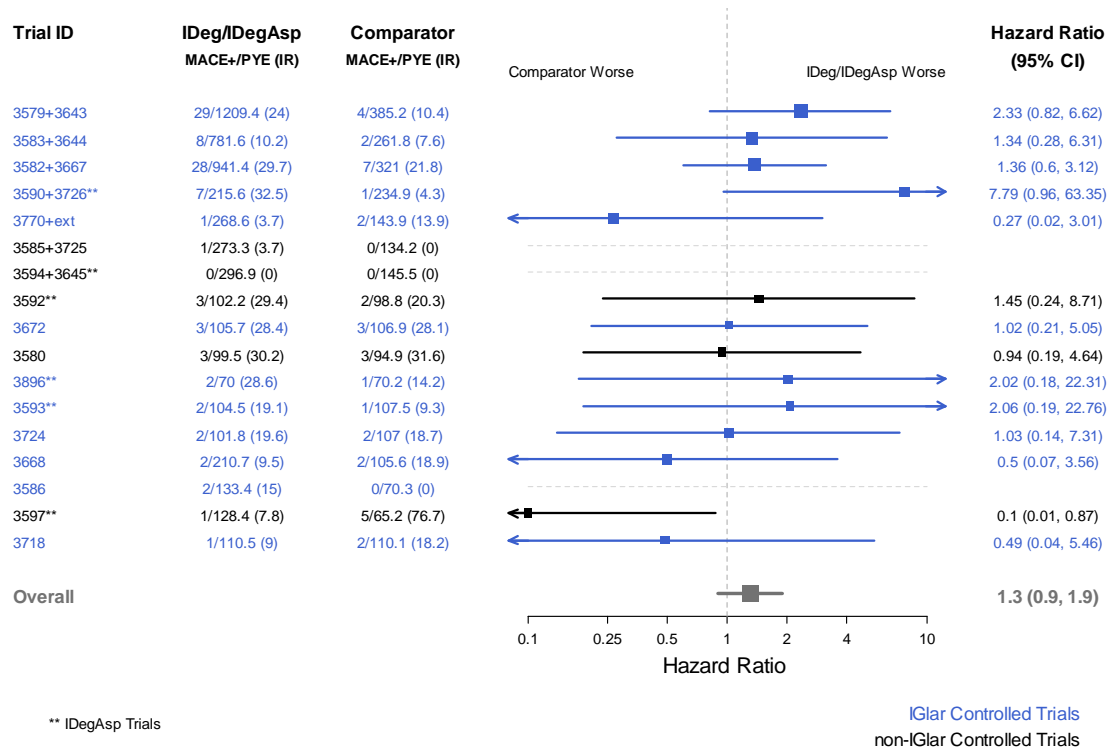
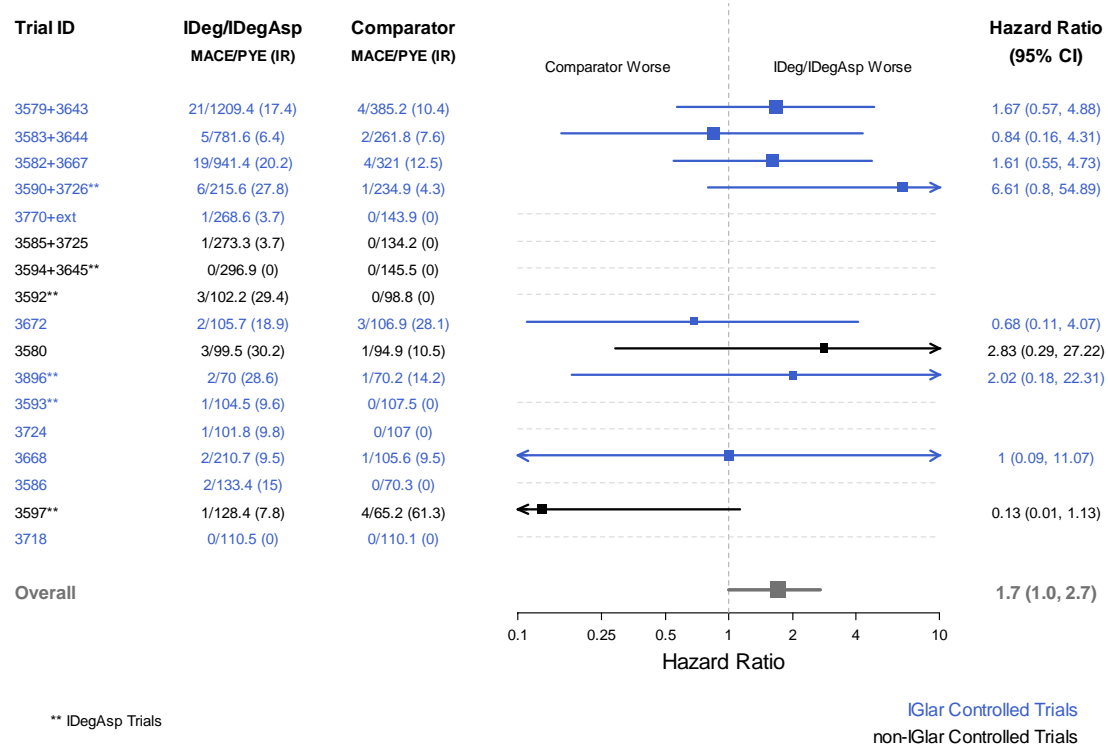


Figure 2: Forest Plot of Time-to-Event Analysis of MACE up to 7 Days after Treatment (FAS)



Following a similar construct as Figures 1 and 2, forest plots based upon the risk difference are presented in Figures 3 and 4 for the MACE+ and MACE composite endpoints with censoring at 7 days. Within a trial, asymptotic methods are used to provide estimates of the risk difference and the corresponding 95% CIs even when one of the treatment arms reports zero events. However, no estimates are provided for trials with zero events reported for both treatment arms. The result of risk difference analysis is consistent with that of hazard ratio calculation.

Figure 3: Forest Plot of Risk Difference of MACE+ up to 7 Days after Treatment (FAS)

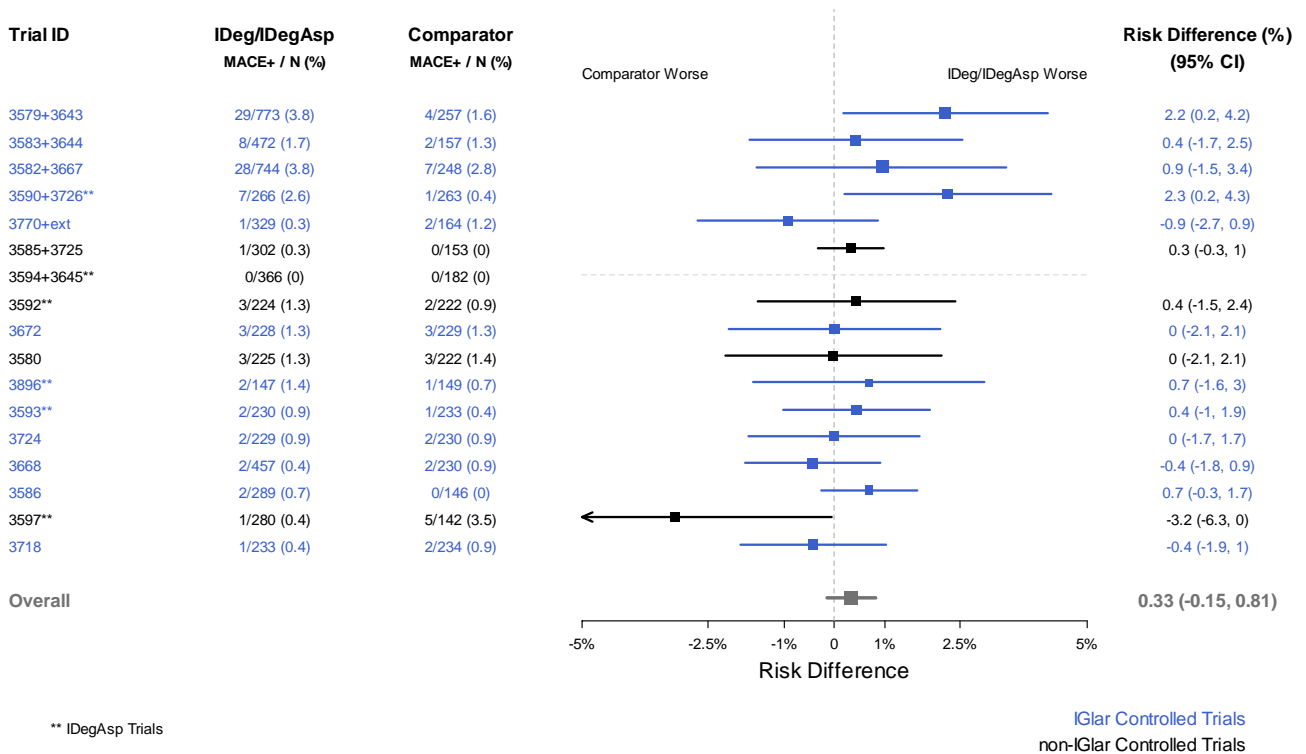
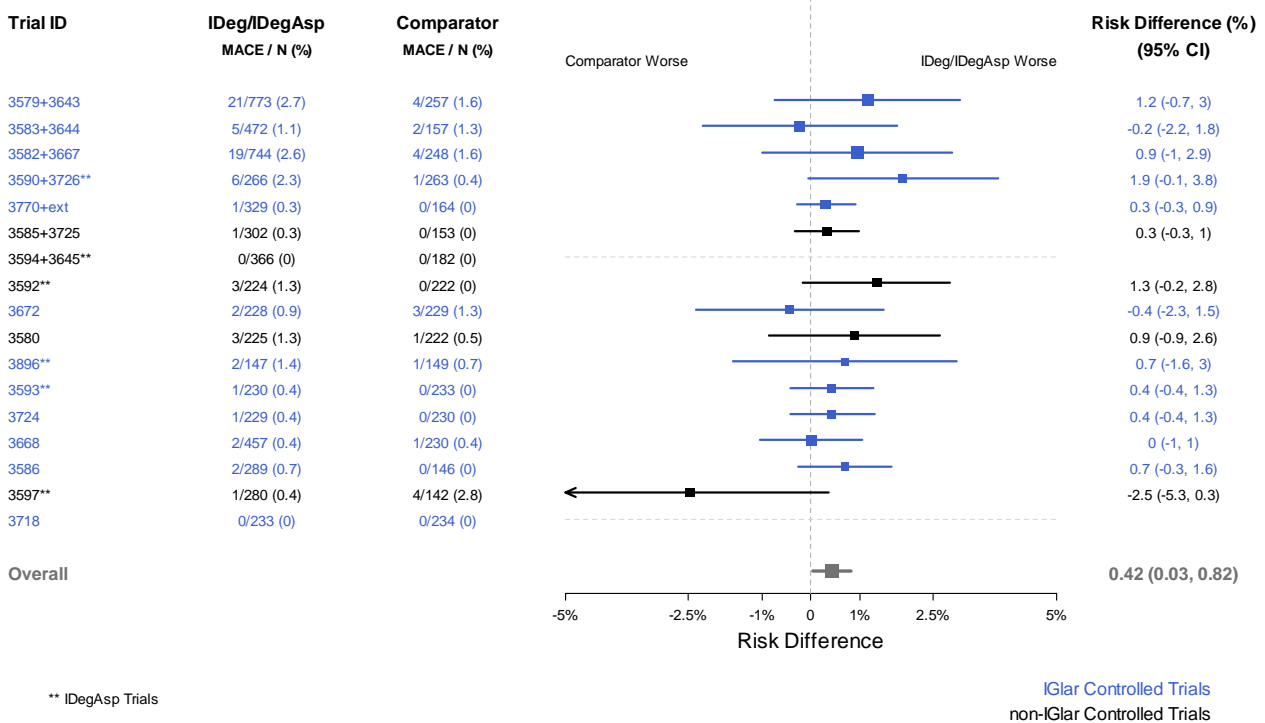


Figure 4: Forest Plot of Risk Difference of MACE up to 7 Days after Treatment (FAS)



Twelve of the 17 randomized trials included in the updated database utilized IGlar as the comparator. The forest plots in Figures 1 and 2 designate these trials utilizing a blue color. To assess the relative CV safety of IGlar to IDeg/IDegAsp, FDA conducted a sensitivity analysis that included only the 12 IGlar-controlled trials (see Table 2). Estimates and corresponding 95% CI's are presented in Table 7 for both the HR and RD based on the 7 day censoring window. Compared to IGlar alone, lower bounds of the 95% confidence intervals are near or above the null value (1 for HR and 0 for RD) for both the MACE+ and MACE endpoints.

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

	MACE+		MACE	
	IDeg/IDegAsp (N = 4397)	IGlar (N = 2540)	IDeg/IDegAsp (N = 4397)	IGlar (N = 2540)
Events (%)	87 (2.0%)	27 (1.1%)	62 (1.4%)	16 (0.6%)
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)

[†] Cox proportional hazard model stratified by trial

^{*} Stratified Mantel-Haenszel with trial as stratification factor

Of the 17 randomized, phase 3 trials, 11 trials included the investigational treatment IDeg. The remaining 6 trials included the investigational treatment IDegAsp (refer to Table 2 for a listing of these trials). A sensitivity analyses was conducted on each of these trial subsets to assess the relative safety of each investigational treatment separately. Estimates and corresponding 95% CI's are presented in Tables 8 and 9 for both the HR and RD based on the 7 day censoring window for IDeg and IDegAsp trials, respectively. In Table 8 and 9, the point estimates for both the HR and RD suggest an increase in CV risk for both the MACE+/MACE endpoints in both IDeg and IDegAsp, but none of the lower bounds of the 95% CI's are above the null value. The point estimates for strict MACE are higher than those for the broader definition, MACE+.

Table 8: Analysis Results for MACE+/MACE in IDeg Trials (FAS, 7 Day Censoring)

	MACE+		MACE	
	IDeg (N = 4281)	Comparator (N = 2270)	IDeg (N = 4281)	Comparator (N = 2270)
Events (%)	80 (1.9%)	27 (1.2%)	57 (1.3%)	15 (0.7%)
HR (95% CI)[†]	1.29	(0.83, 2.02)	1.59	(0.89, 2.83)
RD(%) (95% CI)[*]	0.38	(-0.21, 0.97)	0.43	(-0.05, 0.91)

[†] Cox proportional hazard model stratified by trial

^{*} Stratified Cochran-Mantel-Haenszel with trial as stratification factor

Table 9: Analysis Results for MACE+/MACE in IDegAsp Trials (FAS, 7 Day Censoring)

	MACE+		MACE	
	IDegAsp (N = 1513)	Comparator (N = 1191)	IDegAsp (N = 1513)	Comparator (N = 1191)
Events (%)	15 (1.0%)	10 (0.8%)	13 (0.9%)	6 (0.5%)
HR (95% CI)[†]	1.33	(0.59, 2.99)	1.91	(0.72, 5.08)
RD(%) (95% CI)[*]	0.23	(-0.56, 1.02)	0.41	(-0.28, 1.10)

[†] Cox proportional hazard model stratified by trial

^{*} Stratified Cochran-Mantel-Haenszel with trial as stratification factor

As shown in Table 2, both IDeg and IDegAsp were conducted in populations of either Type 1 or Type 2 diabetes. The majority of trials were conducted in a Type 2 diabetes population (13 trials). A sensitivity analyses was conducted for both the Type 1 and Type 2 diabetes populations. Estimates and corresponding 95% CI's are presented in Tables 10 and 11 for both the HR and RD based on the 7 day censoring window for Type 1 and Type 2, respectively. Overall, event rates were lower in the Type 1 diabetes subjects in comparison to the Type 2 subjects. Among subjects with Type 1 diabetes, the risk of developing MACE+ was similar between the IDeg/IDegAsp group and the all comparator group. Among subjects with Type 2

diabetes, the point estimates for both the HR and RD suggest an increase in CV risk for subjects randomized to IDeg/IDegAsp relative to the all comparator group.

Table 10: Analysis Results for MACE+/MACE in Type 1 Diabetes Trials (FAS, 7 Day Censoring)

	MACE+		MACE	
	IDeg/IDegAsp (N = 1469)	Comparator (N = 656)	IDeg/IDegAsp (N = 1469)	Comparator (N = 656)
Events (%)	10 (0.7%)	4 (0.6%)	7 (0.5%)	2 (0.3%)
HR (95% CI)[†]	0.96	(0.30, 3.09)	1.30	(0.27, 6.29)
RD(%) (95% CI)	-0.04	(-0.75, 0.68)	0.09	(-0.47, 0.65)

[†] Cox proportional hazard model stratified by trial

* Stratified Cochran-Mantel-Haenszel with trial as stratification factor

Table 11: Analysis Results for MACE+/MACE in Type 2 Diabetes Trials (FAS, 7 Day Censoring)

	MACE+		MACE	
	IDeg/IDegAsp (N = 4325)	Comparator (N = 2805)	IDeg/IDegAsp (N = 4325)	Comparator (N = 2805)
Events (%)	85 (2.0%)	33 (1.2%)	63 (1.5%)	19 (0.7%)
HR (95% CI)[†]	1.35	(0.89, 2.04)	1.71	(1.01, 2.90)
RD(%) (95% CI)[*]	0.43	(-0.14, 1.01)	0.52	(0.04, 0.99)

[†] Cox proportional hazard model stratified by trial

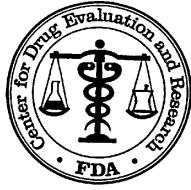
* Stratified Cochran-Mantel-Haenszel with trial as stratification factor

4. Summary of Findings

The agreed upon primary analysis was based upon a stratified Cox proportional hazards model with trial as the stratification factor for the MACE+ endpoint in this meta-analysis of CV risk. The primary comparison was between the combined IDeg and IDegAsp treatment arms (IDeg/IDegAsp) and the all comparator group which consisted of insulin glargine, insulin detemir, biphasic insulin aspart, and sitagliptin (denoted as Comparator in tables above). An initial analysis of the data originally submitted to NDA raised some concern about the potential for an increase in CV risk in subjects randomized to IDeg/IDegAsp relative to the comparator. This prompted the Agency to request additional CV data on several trials that were ongoing at the time of database lock for the original submission.

Utilizing the updated database, results from the agreed upon primary analysis (CPH model for MACE+) yielded an estimated HR of 1.30 with a 95% CI of (0.88, 1.93). Using a stricter definition of CV risk (MACE), the estimated HR was 1.67 with a 95% CI of (1.01, 2.75). In

addition to the above pre-specified approaches, several additional analyses were conducted that utilized a more strict MACE endpoint definition, explored various censoring windows, incorporated different effect measures (risk difference and incidence rate difference), and examined various subsets of trials. While various scenarios resulted in different values of the HR and RD point estimates, a consistent trend was observed – IDeg/IDegAsp was shown to be associated with an increase in CV risk.



Office of Biostatistics

U.S. Department of Health and Human Services
Food and Drug Administration
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STATISTICAL Review

BACKGROUND INFORMATION FOR ADVISORY COMMITTEE ON Tresiba/Ryzodeg

Statistical review for the Endocrinologic and Metabolic Drugs Advisory Committee,
November 8, 2012

Eugenio Andraca-Carrera, PhD
Mat Soukup, PhD
Aloka Chakravarty, PhD

Division of Biometrics 7
Office of Biostatistics
Office of Translational Sciences
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Document Date: October 15, 2012

1. Trials Included in the Meta-analysis of Hypoglycemia

On 26 August 2011, Novo Nordisk completed a meta-analysis of hypoglycemic episodes in seven Phase 3 randomized clinical trials comparing IDeg OD with Insulin glargine OD (IGlar OD). The primary endpoint of the meta-analysis was “**confirmed hypoglycemia**”, defined as hypoglycemia events with plasma glucose <3.1 mmol/L or requiring assistance from another person to actively administer carbohydrate, glucagons or resuscitative actions.

The goal of the meta-analysis was to show that IDeg OD is associated with a smaller rate of confirmed hypoglycemia than IGlar OD.

Out of the seven trials included in this meta-analysis, five trials were conducted among subjects with Type 2 diabetes mellitus (T2DM), (trials 3582, 3579, 3672, 3586 and 3668) and two trials were conducted among subjects with Type 1 diabetes mellitus (T1DM), (trials 3583 and 3770). Table 1, a subset from Table 4-1 in the Sponsor’s meta-analysis report, provides basic design information on the trials included in the meta-analysis of hypoglycemia.

Table 1. Trials Submitted for Meta-analysis of Hypoglycemic Episodes

Trial	Trial Description and Treatment ^a	Subjects Population	Antidiabetic Therapy at Screening	Duration (Weeks)	Randomised IDeg:Comp.	No. Subjects (FAS)
T1DM IDeg OD Basal-Bolus Therapy						
3583	IDeg OD vs. IGl ^a OD (+ IAsp TID)	T1DM Insulin-treated	Any basal-bolus regimen	52	3:1	IDeg: 472 IGlar: 157
3770	IDeg Flex vs. IGl ^a OD and IDeg Flex vs. IDeg OD (all arms + IAsp TID)	T1DM Insulin-treated	Any basal insulin (OD or BID) + any bolus insulin (≥3 daily injections)	26	1:1:1	IDeg FF: 164* IDeg: 165 IGlar: 164
T2DM IDeg OD Basal-Bolus Therapy						
3582	IDeg OD vs. IGl ^a OD (+ IAsp TID ± met ± PIO)	T2DM Insulin-treated	Any insulin regimen (with or without OADs)	52	3:1	IDeg: 744 IGlar: 248
T2DM IDeg OD OAD-Insulin Combination Therapy						
3579	IDeg OD vs. IGl ^a OD (+ met ± DPP-4I)	T2DM Insulin-naïve	met monotherapy met + [SU ± α-GI ± DPP-4I] in any combination	52	3:1	IDeg: 773 IGlar: 257
3672	IDeg 200 U/mL OD vs. IGl ^a OD (+ met ± DPP-4I)	T2DM Insulin-naïve	met monotherapy met + [SU/glin ± DPP-4I ± α-GI in any combination)	26	1:1	IDeg: 228 IGlar: 229
3586	IDeg OD vs. IGl ^a OD (+OAD except DPP-4I)	T2DM Insulin-naïve	monotherapy (met or SU); met + [SU ± α-GI ± DPP-4I]; SU + [α-GI ± DPP-4I]; met + SU + [α-GI or DPP-4I]	26	2:1	IDeg: 289 IGlar: 146
3668	IDeg Flex versus IGl ^a OD and IDeg Flex versus IDeg OD (all arms ± OADs acc. to label)	T2DM Insulin-naïve/ basal insulin-treated	OAD(s) only (any combination of met ± SU/glin ± PIO) basal insulin only basal insulin + OAD(s)	26	1:1:1	IDeg FF: 229* IDeg: 228 IGlar: 230

Source: “Meta-analysis of Hypoglycaemic Episodes.” Table 4-1. Completed by Novo Nordisk on 26 August 2011 and submitted to the FDA as part of the NDA application.

Abbreviations: α-GI: alpha-glucosidase inhibitor, BID: twice daily; DPP-4I: dipeptidyl peptidase-4 inhibitor, FAS: full analysis set, FF: fixed flexible, Glin: glinides, IAsp: insulin aspart, IGl^a: insulin glargine, met: metformin, OAD: oral antidiabetic drug, OD: once daily, PIO: pioglitazone, SU: sulphonylurea, TID: three times daily, U: unit(s).

2. Subject Disposition and Characteristics

The agreed upon population of interest in the meta-analysis consisted of all subjects randomized to IDeg OD 100U/mL, IDeg OD 200U/mL, or IGl^a OD in these seven trials; and excluded subjects randomized to an IDeg fixed-flexible (IDeg FF) dosing scheme alternating morning and night, because this dosing scheme does not correspond to clinical practice¹. In these seven trials, 4330 subjects contributed information to the meta-analysis: 2899 randomized to IDeg OD and 1431 randomized to IGl^a OD.

Table 2 depicts summary statistics for baseline characteristics of the 958 subjects enrolled in the two Type 1 diabetes trials. Table 3 shows baseline characteristics for the 3372 subjects enrolled in the five Type 2 diabetes trials. On average, subjects in the five T2DM trials tended to be older, have larger BMI and shorter diabetes duration at baseline than subjects in the two trials for T1DM.

¹The IDeg fixed-flexible dosing scheme was included in trials 3770 and 3668 only (see Table 1).

Table 2. Baseline Characteristics of Subjects with T1DM in the Primary Analysis

	IDeg OD (<i>N</i> =637) [PYE = 508.5]	IGlar OD (<i>N</i> =321) [PYE =222.8]
Percent Female	41.6%	44.5%
Age± SD (years)	43.3 ± 13.6	43.9 ± 13.0
≤ 40 years	41.9%	38.9%
41 – 50 years	27.0%	28.7%
51 - 65 years	24.3%	26.8%
> 65 years	6.8%	5.6%
BMI± SD (kg/m²)	26.3 ± 3.8	26.6 ± 4.1
≤ 25	38.5%	38.6%
26-30	44.3%	38.9%
> 30	17.2%	22.5%
Diabetes duration (years)	19.4 ± 12.2	18.2 ± 11.6
Race and Ethnicity		
White	93.9%	96.6%
Black	1.9%	1.3%
Other / Multiracial	4.2%	2.1%
Region		
Europe	30.8%	37.1%
North America	65.3%	60.7%
South Africa	3.9%	2.2%

Source: Created by reviewer. Trials: 3583, 3770.

Table 3. Baseline Characteristics of Subjects with T2DM in the Primary Analysis

	IDeg OD (<i>N</i> =2262) [PYE =1675.1]	IGlar OD (<i>N</i> =1110) [PYE = 728.1]
Percent Female	43.6%	45.1%
Age± SD (years)	58.7 ± 9.5	57.8 ± 9.6
≤ 50 years	18.3%	21.1%
51 – 65 years	55.9%	55.6%
66 - 75 years	22.9%	20.3%
> 75 years	2.9%	3.0%
BMI± SD (kg/m²)	30.6 ± 5.3	30.8 ± 5.1
≤ 25	15.2%	13.5%
26-30	31.8%	32.9%
> 30	53.0%	53.6%
Diabetes Duration (years)	11.1 ± 7.1	10.3 ± 6.5
Race and Ethnicity		
White	72.2%	69.0%
Black	7.2%	7.3%
Asian	19.1%	21.7%
Other / Multiracial	1.5%	2.0%
Region		
Asia	12.3%	15.4%
Europe	40.5%	41.3%
Japan	3.9%	4.0%
North America	39.4%	34.0%
South Africa	2.5%	3.2%
South America	1.3%	2.2%

Source: Created by reviewer. Trials: 3582, 3579, 3672, 3586 and 3668.

3. Distribution of Hypoglycemia Events by Type of Diabetes

Table 4 shows that the observed mean annualized rate of “confirmed hypoglycemia” in the seven trials included in the meta-analysis varied significantly by trial. Subjects enrolled in trials for T1DM (trials 3583 and 3770) had the highest observed mean annualized rate of confirmed hypoglycemia in both treatment arms among all trials. Subjects enrolled in trial 3582 had higher observed mean annualized rates than subjects in the other T2DM trials.

Table 4. Observed Rate of Confirmed Hypoglycemia Events by Trial

	Trial	Weeks	Annual Rate of Confirmed Hypoglycemia. Mean (SD)	
			IGlar OD	IDeg OD
T1DM IDeg OD Basal-Bolus Therapy	3583	52	39 (37)	41 (41)
	3770	26	75 (62)	87 (68)
T2DM IDeg OD Basal-Bolus Therapy	3582	52	13 (17)	11 (17)
T2DM IDeg OD OAD-Insulin Combination Therapy	3579	52	1.7 (4.1)	1.4 (2.5)
	3672	26	1.3 (3.1)	1.2 (2.7)
	3586	26	3.9 (6.1)	3.2 (5.8)
	3668	26	3.5 (6.9)	4.1 (15.8)

Source: Created by reviewer.

Table 5 depicts the observed distribution of the number of confirmed hypoglycemia events pooled across trials by type of diabetes. This table shows that a large proportion of subjects in the five trials for T2DM had no confirmed hypoglycemia events: 43.3% on IDeg OD and 47% on IGlar OD, pooled across the 5 trials. In contrast, among subjects with T1DM, only a small percentage had no confirmed hypoglycemia events: 3.5% on IDeg OD and 4.0% on IGlar OD.

These tables show clear differences in the distribution of confirmed hypoglycemia events between subjects with T1DM and subjects with T2DM. In the following sections, we discuss the meta-analysis of hypoglycemia events comparing IDeg OD to IGlar OD and show that there is evidence to suggest that the effect of IDeg OD relative to IGlar OD in terms of the risk of hypoglycemia is different among subjects with T1DM and T2DM.

Table 5. Distribution of Observed Rate of Confirmed Hypoglycemia by Type of Diabetes

T1DM			T2DM		
Events / year	IDeg OD	IGlar OD	Events / year	IDeg OD	IGlar OD
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%			

Source: Created by reviewer.

4. Statistical Methodology

4.1 Primary Analysis

The agreed upon primary analysis compared the rate ratio of confirmed hypoglycemia episodes between subjects randomized to IDeg OD and subjects randomized to IGlar OD. The number of treatment-emergent confirmed hypoglycemic episodes were counted for each subject and used as the primary endpoint.

Based on the pre-specified analysis, IDeg OD would be considered superior to IGlar OD in terms of the risk of confirmed hypoglycemia if the upper bound of the 95% confidence interval for the rate ratio was smaller than 1.

The pre-specified primary statistical model was a negative binomial model controlling for trial, treatment and the following baseline covariates: insulin use at baseline, gender, age and geographic region of randomization. The primary model assumed that the rate ratio of confirmed hypoglycemia associated with IDeg OD relative to IGlar OD was the same in all seven trials and did not include an interaction term for treatment by type of diabetes.

4.2 Secondary Analysis

A secondary analysis was fit with the same model as the primary analysis with the addition of an interaction term for treatment by type of diabetes. This model allowed for the rate ratio of confirmed hypoglycemia associated with IDeg OD relative to IGlar OD to be different in subjects with T1DM and subjects with T2DM.

5. Analysis Results

5.1 Primary Analysis Results

Table 6 shows the estimated rate ratio (RR) and corresponding 95% confidence interval for confirmed hypoglycemia events comparing IDeg OD vs. IGlar OD. This model adjusts for trial as a fixed effect, but assumes a constant RR across all trials. The estimated RR from this model is 0.91 with 95% CI (0.83, 0.99). Based on this model, there is evidence with borderline statistical significance that IDeg OD reduces the rate of confirmed hypoglycemia compared to IGlar OD considering all seven trials for T1DM and T2DM.

Table 6. Primary Analysis of Confirmed Hypoglycemia

	IDeg OD	IGlar OD
Total subjects randomized	2899	1431
Subjects used in analysis	2886	1421
Rate Ratio (95% CI)	0.91 (0.83, 0.99)	

Source: "Meta-analysis of Hypoglycaemic Episodes." Table 7-2. Completed by Novo Nordisk on 26 August 2011 and submitted to the FDA as part of the NDA application. Confirmed by reviewer.

5.2 Secondary Analysis Results

Figure 1 shows a forest plot of the estimated RR of confirmed hypoglycemia comparing IDeg OD to IGlax OD in each of the seven trials in the meta-analysis, controlling for all other covariates included in the primary model described in Section 4.1. The plot suggests that IDeg OD may be associated with an increased rate of confirmed hypoglycemia events in trials for T1DM, and with a decreased rate of confirmed hypoglycemia in trials for T2DM.

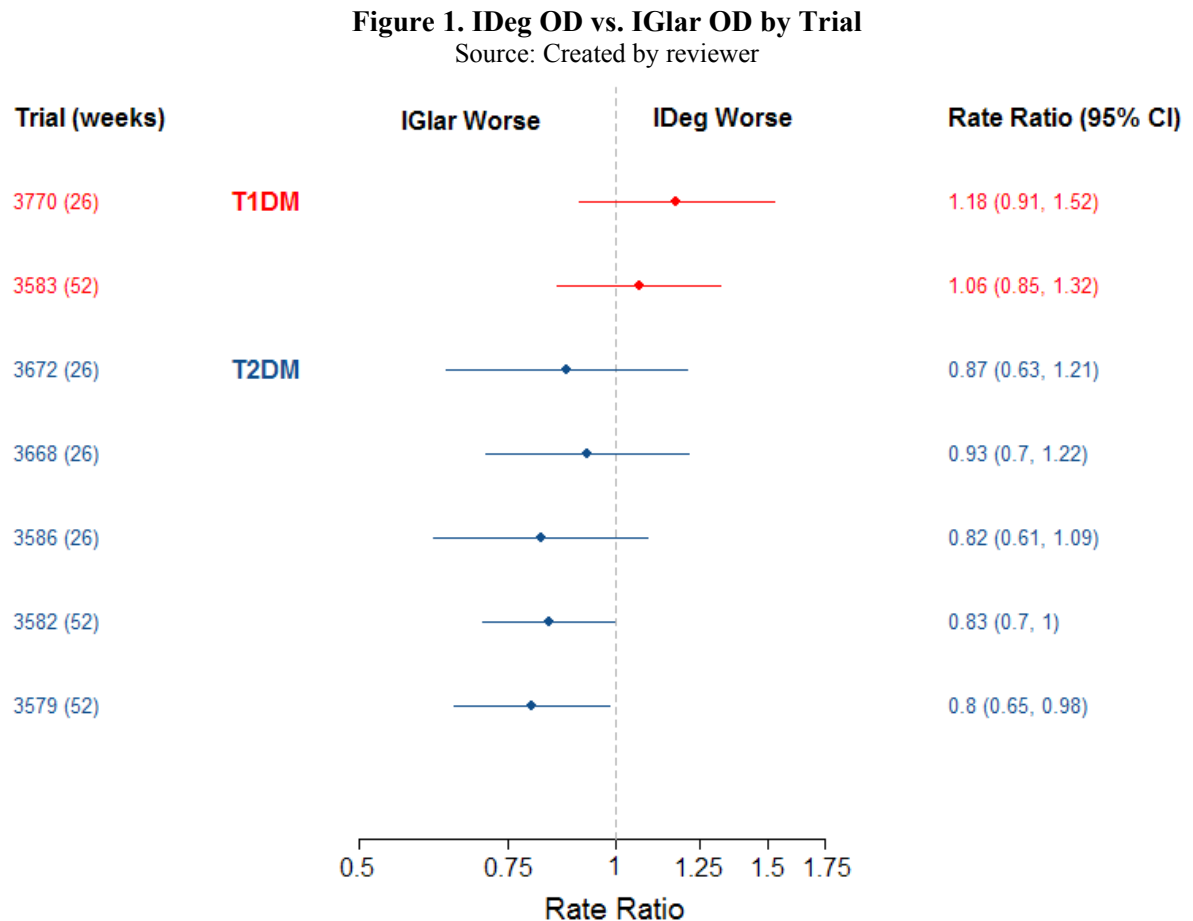


Table 7 shows parameter estimates and corresponding 95% confidence intervals for the RR of confirmed hypoglycemia in the secondary analysis including an interaction term of treatment by type of diabetes. The estimated interaction term was statistically significant with a p-value of 0.0057, and suggests that the RR of confirmed hypoglycemia associated with IDeg vs. IGlax is different among subjects with T1DM and subjects with T2DM. Among subjects with T1DM, the estimated RR and its 95% CI of 1.11 (0.94, 1.31) show no evidence of lower risk associated with IDeg OD. Among subjects with T2DM, IDeg OD was associated with a statistically significant reduction in the rate of confirmed hypoglycemia with an estimated RR and 95% CI of 0.84 (0.76, 0.93).

Table 7. Secondary Analysis: IDeg OD vs. IGlar OD by Type of Diabetes

	T1DM		T2DM	
	IDeg OD	IGlar OD	IDeg OD	IGlar OD
Total subjects randomized	637	321	2262	1110
Subjects used in analysis	637	316	2249	1105
Rate Ratio (95% CI)	1.11 (0.94, 1.31)		0.84 (0.76, 0.93)	

Source: "Meta-analysis of Hypoglycaemic Episodes." Table 7-3. Confirmed by reviewer.

5.3 Subgroup Analyses

Subgroups analyses were conducted by gender, age, race and country of randomization. Analysis results were consistent with results shown for the secondary analysis above. As such, these subgroup analyses (by gender, age and race) are not discussed further in this document. Subgroup analyses defined by country of randomization are presented in this section.

Among subjects with T1DM, 63.8% were randomized in the USA. Among subjects with T2DM, 32.7% were randomized in the USA.

Subjects randomized outside of the USA (Table 8) experienced a non-statistically significant increase in the rate of confirmed hypoglycemia associated with IDeg in T1DM, RR 1.28, 95% CI (0.96, 1.71), and a statistically significant decrease in confirmed hypoglycemia in T2DM, RR 0.79, 95% CI (0.69, 0.90). However, among subjects randomized in the USA (Table 9), there was no observed difference in the rate of confirmed hypoglycemia between IDeg and IGlar in either type of diabetes: T1DM RR 0.99, 95% CI (0.81, 1.20), and T2DM RR 0.97, 95% CI (0.81, 1.15).

Table 8. Confirmed Hypoglycemia Comparing IDeg OD vs. IGlar OD (Country ≠ USA)

	T1DM		T2DM	
	IDeg OD	IGlar OD	IDeg OD	IGlar OD
Total subjects randomized	221	126	1475	794
Rate Ratio (95% CI)	1.28 (0.96, 1.71)		0.79 (0.69, 0.90)	

Source: Created by reviewer.

Table 9. Confirmed Hypoglycemia Comparing IDeg OD vs. IGlar OD (Country = USA)

	T1DM		T2DM	
	IDeg OD	IGlar OD	IDeg OD	IGlar OD
Total subjects randomized	416	195	787	316
Subjects used in analysis	637	316	2249	1105
Rate Ratio (95% CI)	0.99 (0.81, 1.20)		0.97 (0.81, 1.15)	

Source: Created by reviewer.

5. Summary of Findings for Hypoglycemia

The meta-analysis showed statistically significant evidence to suggest that IDeg OD reduces the rate of confirmed hypoglycemia, compared to IGlar OD, in subjects with T2DM, but not in subjects with T1DM. The interaction between treatment and type of diabetes was statistically significant and was also observed in analyses of secondary endpoints and subgroup analyses. Among subjects with T1DM, the estimated rate ratio of confirmed hypoglycemia associated with IDeg OD was 1.11 with 95% CI (0.94, 1.31). Among subjects with T2DM, the estimated rate ratio of confirmed hypoglycemia was 0.84 with 95% CI (0.76, 0.93). The reduction in the risk of confirmed hypoglycemia among subjects with T2DM was not observed among subjects randomized in the USA.

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document contact Ilan Irony at 301-796-2290.

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2008
Clinical/Medical**

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

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5600 Fishers Lane
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**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**February 2008
Clinical/Medical**

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND AND TREATMENT GOALS.....	3
III.	DIAGNOSING DIABETES MELLITUS.....	4
IV.	PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES.....	5
A.	Type 1 Diabetes Mellitus	5
B.	Type 2 Diabetes Mellitus	5
C.	Insulins and Insulin Analogues.....	6
V.	CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES.....	6
A.	Trial Design and Conduct	6
1.	<i>Optimization of Glucose Control and Diabetes-Associated Comorbid Conditions.....</i>	<i>6</i>
2.	<i>Type 1 Diabetes Mellitus</i>	<i>7</i>
3.	<i>Type 2 Diabetes Mellitus</i>	<i>8</i>
a.	<i>Studies of a test agent as monotherapy</i>	<i>8</i>
b.	<i>Studies of new agents on a background of existing therapy</i>	<i>10</i>
B.	Study Assessments and Endpoints	10
1.	<i>General Considerations</i>	<i>10</i>
a.	<i>Pharmacokinetics</i>	<i>11</i>
b.	<i>Pharmacodynamic endpoints and biomarkers</i>	<i>11</i>
c.	<i>Efficacy endpoints</i>	<i>12</i>
d.	<i>Effects on markers of insulin resistance and diabetes comorbidities</i>	<i>12</i>
e.	<i>Effect of weight loss on diabetes</i>	<i>12</i>
2.	<i>Insulins.....</i>	<i>13</i>
a.	<i>Insulin mixes.....</i>	<i>13</i>
b.	<i>Insulin use in pumps (continuous subcutaneous insulin infusion)</i>	<i>13</i>
c.	<i>New insulin analogues or insulin receptor binding agonists.....</i>	<i>14</i>
d.	<i>Inhaled insulins.....</i>	<i>14</i>
3.	<i>Noninsulin Products</i>	<i>15</i>
4.	<i>Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus</i>	<i>16</i>
5.	<i>Prevention of Type 2 Diabetes Mellitus</i>	<i>17</i>
C.	Metabolic Syndrome.....	18
D.	Study Population Considerations	18
1.	<i>Pediatric Populations</i>	<i>18</i>
2.	<i>Other Study Populations</i>	<i>19</i>
E.	Sample Size and Study Duration	20
F.	Premarketing Safety Evaluation	22
G.	Important Statistical Considerations	23
1.	<i>Sample Size</i>	<i>23</i>
2.	<i>Preventing Missing Data from Subjects Who Prematurely Withdraw from Treatment.....</i>	<i>23</i>
3.	<i>Analysis Methods</i>	<i>24</i>
4.	<i>Graphical Methods</i>	<i>24</i>

APPENDIX A: PRECLINICAL CONSIDERATIONS FOR PEROXISOME	
PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS	26
APPENDIX B: HYPOGLYCEMIA.....	28
APPENDIX C: CURRENTLY AVAILABLE DRUG TREATMENTS.....	30
A. Insulin Products	30
B. Oral Agents for Type 2 Diabetes	30
C. Newer Classes of Therapeutic Products.....	30

Guidance for Industry

Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention

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I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment and prevention of diabetes mellitus. The intention of this guidance is to serve as a focus for continued discussions among the review divisions, pharmaceutical sponsors, academic community, and the public.² The organization of the guidance parallels the development plan for a particular drug or biologic. In the following discussion, we briefly describe type 1 and type 2 diabetes mellitus and treatment goals, discuss issues relevant to preclinical development, and then provide guidance on issues related to trial design, endpoints appropriate for different phases of development, and eligible populations. These issues are addressed for both type 1 and type 2 diabetes mellitus.

Although this guidance focuses more on the development of drug and therapeutic proteins to target the metabolic control of blood glucose in patients with diabetes, it also provides guidance on the development of products intended to prevent diabetes mellitus in high-risk individuals. Since the development of products for the prevention of diabetes is a relatively novel area, it is possible that specific guidances will be developed in the future for this topic as regulatory experience accrues. Therapeutic approaches to mitigate or reverse other clinical or pathophysiological hallmarks of what is often termed the metabolic syndrome are not addressed in this guidance.

¹ This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² In addition to consulting guidances, sponsors are encouraged to contact the division to discuss specific issues that arise during the development of diabetes drug or biological products. The FDA/NIH Joint Symposium on Diabetes, held on May 13 and 14, 2004, in Bethesda, Maryland, gathered relevant perspectives from academia and industry on issues covered in this guidance.

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In addition, we recognize other important topics surrounding the treatment and prevention of diabetes mellitus. However, the following discussions are beyond the scope of this guidance.

- A comprehensive treatment strategy involves dietary changes and interventions other than medications.
- Highly desirable treatments specifically targeted to have direct effects in preventing end organ damage and diabetes-associated acute and chronic complications.
- Significant advances in the development of treatments for diabetes have been made through experimental approaches other than drugs or therapeutic proteins, such as transplantation of pancreata, pancreatic islet cells, stem cells that may differentiate into insulin-producing cells, and closed-loop devices (or artificial pancreas) that constantly monitor blood or interstitial glucose and adjust automated insulin delivery via a pump accordingly.
- The expansion of available choices in diagnostic devices that allow accurate and instantaneous glucose measurements, continuous glucose monitoring, and the identification of parameters of glucose metabolism characterizing states of insulin resistance has been significant to patients and health care professionals.

Advice on the development of specific products for preventing or treating complications of diabetes (e.g., diabetic peripheral neuropathy) can be sought from the relevant review division and other existing guidances.

This guidance does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*.³ Instead, this guidance focuses on specific drug development and trial design issues that are unique to the study of diabetes mellitus, as measured by changes in hemoglobin A1c (HbA1c, glycosylated hemoglobin, or glycohemoglobin). Reductions in HbA1c directly reflect improvements in glycemic control. Therefore, HbA1c is considered a well-validated surrogate for the short-term clinical consequences of hyperglycemia and long-term microvascular complications of diabetes mellitus.

The FDA recognizes that diabetes mellitus is associated with an increased risk of macrovascular complications and that reducing long-term cardiovascular complications in patients with diabetes should be an important goal of disease management. However, a premarketing recommendation to demonstrate macrovascular risk reduction in the absence of a signal for an adverse cardiovascular effect may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy. A reasonable approach may be to conduct long-term cardiovascular studies post-approval in an established time frame. We recommend that the design of such trials be discussed with the FDA and perhaps with clinical

³ We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

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trialists and experts in endocrinology and cardiology. This approach is beyond the scope of this guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND AND TREATMENT GOALS

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although there are several drug treatments currently available (see Appendix C), the FDA recognizes the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs, therapeutic biologics, and devices).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure and has a heritable basis). Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial (DCCT)⁴ has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy. Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.⁵ There are also reasonably strong data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control, although macrovascular risk reduction in this patient population is less conclusive.⁶

⁴ N Engl J Med, 1993, 329:977-986

⁵ Diabetes, 2006, 55:3556-3565

⁶ Lancet, 1998, 352:837-853 and 854-865

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Glycemic control in these studies has been based on changes in HbA1c. This surrogate endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. In addition, there is a growing recognition that addressing cardiovascular disease risk factors, such as hypertension, smoking, and dyslipidemia, in patients with diabetes is particularly important, as diabetes is now considered an atherosclerotic heart disease equivalent.

III. DIAGNOSING DIABETES MELLITUS

Based on studies that have established a relationship between plasma glucose concentrations, measures of glycemic exposure, and risk of diabetic retinopathy, the following criteria have been adopted for the diagnosis of diabetes mellitus:

- Fasting plasma glucose greater than or equal to 126 mg/dL (7.0 mmol/L)
- Plasma glucose greater than or equal to 200 mg/dL (11.1 mmol/L) at 2 hours following ingestion of 75 g anhydrous glucose in an oral glucose tolerance test
- Random plasma glucose greater than 200 mg/dL (11.1 mmol/L) in a person with symptoms of diabetes

These criteria were recommended by the American Diabetes Association (ADA) and the World Health Organization (WHO) in 1997 and 1998, respectively.

Other important definitions include:

- Impaired glucose tolerance: a plasma glucose equal to or greater than 140 mg/dL (7.8 mmol/L) but less than 200 mg/dL (11.1 mmol/L) at 2 hours in the oral glucose tolerance test
- Impaired fasting glucose: fasting plasma glucose (FPG) equal to or greater than 100 mg/dL (5.6 mmol/L) but less than 126 mg/dL
- Gestational diabetes mellitus (GDM):
 - According to the ADA criteria, GDM is detected based on two or more values meeting or exceeding any of the following threshold values during a 75- or a 100-g oral glucose tolerance test:
 - FPG greater than or equal to 95 mg/dL (5.3 mmol/L)
 - Plasma glucose greater than or equal to 180 mg/dL (10 mmol/L) at 1 hour
 - Plasma glucose greater than or equal to 155 mg/dL (8.6 mmol/L) at 2 hours
 - Plasma glucose greater than or equal to 140 mg/dL (7.8 mmol/L) at 3 hours (the optional 3-hour time point only applies to the 100-g test)
 - GDM is diagnosed by the WHO criteria if FPG is greater than or equal to 126 mg/dL (7.0 mmol/L) or if the 2-hour glucose after a 75-mg oral glucose load is greater than or equal to 140 mg/dL (7.8 mmol/L)

Impaired fasting glucose and impaired glucose tolerance have recently gained importance because they identify groups of people at high risk for developing overt diabetes mellitus over

time, and because recent studies have demonstrated reductions in the progression to overt disease in these groups with specific therapeutic interventions. These individuals, along with women who have had a history of gestational diabetes, have been targeted for clinical evaluation of diabetes prevention.

IV. PRECLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES⁷

Preclinical development often includes pharmacology studies in which efficacy is assessed in animal models appropriate to the diabetes type being targeted for therapy. Toxicology studies for antidiabetic therapies generally should be conducted in the standard nondiabetic animal models.

A. Type 1 Diabetes Mellitus

In preclinical models that most closely mimic type 1 diabetes in humans, animals manifest spontaneous insulinitis and progressive beta-cell destruction. Non-obese diabetic (NOD) mice and diabetes-prone BioBreeding (BB) rats are the most commonly used rodent models for type 1 diabetes, in which proof-of-concept studies of prospective therapeutic agents can be conducted. Such studies examine parameters relevant to the treatment of human disease, such as preservation of beta cells and insulin secretory function and fasting and postprandial levels of C-peptide and glucose. Streptozotocin-induced diabetes in rats is a predictable metabolic model of human type 1 diabetes, but does not involve an autoimmune mechanism, and, therefore, should not be used in preclinical studies of immune-directed diabetes prevention strategies.

NOD mice develop type 1 diabetes by an autoimmune disease similar to humans. In these mice, approximately 90 percent of females and 60 percent of males become hyperglycemic and develop diabetes by 12 months of age.

Approximately 90 percent of mature diabetes-prone BB rats develop diabetes. Diabetes-resistant BB rats constitute a variant that develop type 1 diabetes after some environmental insult (e.g., Kilham rat viral infection).

B. Type 2 Diabetes Mellitus

Animal models of type 2 diabetes are characterized by insulin resistance, hyperglycemia, and hyperinsulinemia. Some of the most frequently used models of type 2 diabetes are the leptin-deficient mouse (*ob/ob*), the leptin-receptor-deficient mouse (*db/db*), the obese Zucker rat (*fa/fa*), the Wistar Kyoto rat (*fa/fa*), and knockout mice lacking relevant targets, such as insulin receptors or glucose transporter 4 genes.

For all peroxisome proliferator-activated receptor (PPAR) agonists, 2-year carcinogenicity evaluations in rats and mice should be conducted before the initiation of clinical studies longer than 6 months in duration, based on their known carcinogenic potential as a class. Additionally, for PPAR drugs with gamma agonist activity, the maximum tolerated dose for carcinogenicity

⁷ See 21 CFR part 58 for the FDA's good laboratory practices for conducting nonclinical laboratory studies.

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assessment should be defined as the dose that results in a 20 to 25 percent increase in heart weight in rodents in the 13-week dose finding studies. This recommended dose limitation is designed to prevent excess cardiac mortality in the 2-year bioassay secondary to fluid accumulation and cardiomegaly. Refer to Appendix A for further details on this issue.

C. Insulins and Insulin Analogues

In vitro studies of insulins and insulin analogues can be useful for describing insulin receptor binding affinities and dissociation rates, receptor autophosphorylation, phosphorylation of signaling elements, and promotion of mitogenesis. In addition, for insulin analogues, affinity to the insulin receptor relative to other targets of insulin action, such as the insulin-like growth factor 1 receptor, should be characterized and compared to that found with native-sequence human insulin.

V. CLINICAL DEVELOPMENT OF ANTIDIABETIC THERAPIES⁸

A. Trial Design and Conduct

1. Optimization of Glucose Control and Diabetes-Associated Comorbid Conditions

Individualization of therapy is essential to optimum control of glycemia in patients with diabetes. Consequently, some studies permit use of other antidiabetic therapies before randomization to ensure enrollment of patients whose diabetes control will be acceptable for clinical investigational purposes. Such studies often allow entry of patients using a specific class of antidiabetic drugs (e.g., baseline metformin therapy in patients with type 2 diabetes), to which either the investigational drug (or biologic) or a placebo will be added during randomization. Addition of new noninvestigational drugs or substantial changes in the dose of permissible baseline drug therapy after randomization may confound the results and interpretability of both efficacy and safety. For the results to be interpretable, any changes to these other therapies should be carefully documented.

When planning exploratory phase 2 studies, we recommend that sponsors include a run-in period before randomization to allow for diabetes education and for optimization of compliance with diet and exercise. This 6- to 8-week run-in period also is intended to allow for stabilization of parameters of metabolic control (e.g., HbA1c, fructosamine), so that the magnitude of the effect of different doses of the product can be most accurately estimated. Absence of this run-in period can result in overestimation of the *real world* treatment effects, given the intensive reinforcement of hygienic measures and compliance during clinical trials that is not reflected in typical treatment settings. In addition, placebo run-in periods in phase 3 studies can help screen out noncompliant subjects. We recommend providing efficacy data with a new product that result from rigorously designed studies.

⁸ See 21 CFR parts 312, 50, and 56 for regulations regarding investigational new drug applications and human subject protection, including informed consent.

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Adequate control of diabetic comorbidities in accordance with current standards of care should be incorporated in the criteria for eligibility in the study protocol. The addition of therapies to control diabetic comorbidities after randomization should be carefully documented (as should be the use of these therapies at baseline), because these therapies may confound the interpretation of both safety and efficacy of the investigational drug or biologic.

Improvement in HbA1c has become the standard surrogate outcome measure in many trial designs for a variety of therapies. In patients with diabetes, the following situations also can be considered a benefit of therapy: 1) a meaningful reduction of insulin requirements (in either type 1 or type 2 diabetes), or 2) a reduction in the number or doses of oral antidiabetic agents (in type 2 diabetes mellitus), both in the context of stable or improved HbA1c. Even though HbA1c is appropriate as a surrogate endpoint in many study designs, documented improvement in a serious morbidity or mortality related to diabetes (i.e., outcome studies) may be more persuasive evidence of benefit for drugs in which substantial safety issues or questions arise (see sections V.B., Study Assessments and Endpoints, and V.E., Sample Size and Study Duration, for additional considerations).

2. Type 1 Diabetes Mellitus

As stated earlier, insulin is the essential glucose-lowering therapy for the treatment of patients with type 1 diabetes. Therefore, all experimental treatments for type 1 diabetes (and their matching placebos, as applicable) that are not insulin analogues or other insulin receptor ligands should be studied as add-on therapies to insulin.

Preclinical data or knowledge of a particular mechanism of action may indicate that an investigational product has the potential to cause or worsen hypoglycemia, either by binding to insulin receptors or by affecting other aspects of glucose absorption and metabolism. If the investigational product is anticipated to have the potential to lead to hypoglycemia, either directly or through potentiation of insulin effect, the study design should include allowance for insulin dose adjustments to protect trial subjects from hypoglycemia. However, pharmacodynamic interactions with insulin, as well as the need to adjust insulin doses to prevent hypoglycemia, may pose significant challenges for study design, interpretation, and inference of the new drug's efficacy. For example, given the need to titrate insulin to control for glycemia and to guard against hypoglycemia, the blinding of subject and investigator to treatment allocation may not be practical or acceptably safe. Unblinded, controlled trials may be appropriate in some circumstances, particularly for trials incorporating clearly objective endpoints. On the other hand, unblinding can severely limit the interpretability of subjective endpoints (i.e., patient-reported outcomes) that might be incorporated as secondary assessments of efficacy.

In phase 1 and phase 2 trials of products intended to prevent or delay the progression of type 1 diabetes, sponsors are encouraged to conduct randomized, placebo-controlled studies, while investigating early pharmacodynamic markers of effect as well as the safety of the tested product.

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3. *Type 2 Diabetes Mellitus*

Efficacy and safety of new products for the treatment of type 2 diabetes can be evaluated in placebo-controlled monotherapy trials, placebo-controlled add-on therapy trials, and active-controlled trials. Given the progressive nature of type 2 diabetes and the requirement for multiple drug therapy, the clinical development program should involve evaluation of the investigational drug as monotherapy and in combination with many other approved antidiabetic drugs.

In the past, oral agents (i.e., sulfonylureas) to treat type 2 diabetes were approved largely on the basis of placebo-controlled trials with no underlying pharmacological therapy, in which all randomized subjects received only counseling for appropriate diet and an exercise program in addition to the product being tested. As medical care for diabetes has evolved, it may now be difficult to find patients who are appropriate candidates for purely placebo-controlled trials because a large proportion of those diagnosed with diabetes are receiving early pharmacological treatment. Considerations of withdrawal of existing therapy to enroll patients in a placebo-controlled trial of a new agent as initial monotherapy should include informed consent, severity and duration of disease, presence of diabetic comorbidities, and dose of the existing drug therapy. In addition, strict escape or withdrawal criteria for loss of glycemic control should be explicit in the study protocol.

The discontinuation of effective treatment for the purposes of making a patient eligible for inclusion in a placebo-controlled trial of significant duration (e.g., longer than 6 months) raises ethical issues, although placebo-controlled trials of 6 months or less in duration may be appropriate, provided that the protocol contains strict escape or rescue criteria related to hyperglycemia and poor glycemic control. In such trials, the number of patients meeting the escape criteria can be assessed as a measure of efficacy. In any case, we recognize that both placebo-controlled (with or without background therapy) and active-controlled studies can provide the essential safety and efficacy data to support approval.

a. *Studies of a test agent as monotherapy*

Many patients with type 2 diabetes who are potential candidates for studies of new therapeutic agents are likely being treated with one or more antidiabetic medications. Development of a new investigational product to support its indication as monotherapy in type 2 diabetes can be undertaken in subjects who are drug-naïve and whose diabetes is reasonably well controlled with diet and exercise. These subjects can participate in placebo- and dose-controlled studies for up to 24 weeks, provided that they continue to remain in reasonable metabolic control for the duration of the studies (see below for an example of escape or rescue criteria). Likewise, subjects on low doses of a single antidiabetic medication who are under reasonable glycemic control can discontinue their medications under strict glycemic supervision to participate in placebo-controlled studies of an agent to be used as monotherapy.

There also should be a reasonable expectation that placebo dropouts caused by further loss of glycemic control will be limited, thus enabling controlled assessments of both efficacy and safety.

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For either phase 2 or phase 3 studies, regardless of HbA1c at entry, subjects whose hyperglycemia persists or worsens beyond prespecified thresholds should be appropriately monitored and treated throughout the study. In developing these escape or rescue criteria, it is useful to consider that even for drugs that show therapeutic effects only after a matter of weeks (e.g., thiazolidinediones/PPAR agonists), most responders experience a reduction in fasting blood glucose of greater than 20 mg/dL (1.1 mmol/L) by 6 weeks. For agents that lower postprandial rather than fasting glucose levels, a clinically meaningful reduction in HbA1c (e.g., 0.3 percentage units) also usually is evident by 6 weeks. The following are examples of rescue criteria based on thresholds for FPG or HbA1c:

- FPG greater than 270 mg/dL (15 mmol/L) from baseline to Week 6
- FPG greater than 240 mg/dL (13.3 mmol/L) from Week 6 to Week 12
- FPG greater than 200 mg/dL (11.1 mmol/L) or HbA1c greater than 8.0 percent from Week 12 to Week 24

For agents that lower postprandial rather than fasting glucose levels, the sponsor is encouraged to enforce specific rescue criteria based on thresholds of unacceptable postprandial glucose encountered during the first 12 weeks of the study and unacceptable HbA1c encountered thereafter.

Even if the escape criteria related to poor glycemic control result in early discontinuation of a substantial proportion of participating subjects, the trial may still be interpretable, at least from the standpoint of efficacy. (For more details, see section V.G., Important Statistical Considerations.) The rate of meeting withdrawal criteria also can provide an assessment of efficacy using a time-to-event analysis if events are collected or responder analysis based on a binary outcome of treatment success or failure. Subjects meeting glycemic rescue criteria ideally should remain in the study even after receiving the additional or alternative therapy to allow for the assessment of safety of the investigational drug or biologic.

Phase 2 or phase 3 studies investigating the efficacy of a new product as monotherapy in subjects already on active therapy for their diabetes can be more problematic. The majority of these subjects will probably experience significant worsening of glycemic control when their medications for diabetes are discontinued. These subjects require a washout period with careful monitoring of glucose. An unknown, and likely high, proportion of subjects simply will either not qualify for studies because of loss of control before randomization or will discontinue because of worsening glycemia in the initial weeks of treatment with poorly effective doses of the investigational drug or with placebo. The washout period should take into account the pharmacokinetic properties of the existing treatment (e.g., 5 half-lives) and the fact that HbA1c reflects mean glycemic control over 2 to 3 months. The length of treatment with the test agent before endpoint ascertainment should account for the duration of the pharmacodynamic effects of previous treatments and the expected timing of a pharmacodynamic effect (e.g., plasma glucose, HbA1c) of the test agent.

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A difference between active drug and placebo (or between two active treatments such as a lower and higher dose of the test agent) in the proportion of subjects meeting criteria for glycemic rescue therapy can be used as a measure of efficacy.

b. Studies of new agents on a background of existing therapy

For subjects taking two or more antidiabetic agents to control glycemia, a potential approach in phase 2 or phase 3 can be a randomized study in which the investigational product or matching placebo is substituted for one of the drugs being taken. Sponsors can conduct extensive dose titration and dose exploration in phase 2 studies of this type, typically 12 to 16 weeks in duration.

For phase 3 studies of investigational agents as add-on therapy, the typical design is not that of substituting the investigational agent for an existing medication, but rather to add the investigational agent to the existing therapy. Typically, these studies are designed as placebo-controlled superiority or active-controlled noninferiority trials. In these studies, patients inadequately controlled on optimal or near-optimal doses of approved therapies should be randomized to one of several doses of the investigational agent or to placebo as add-on to the existing medications (or, in the case of active-controlled trials, to a therapy previously approved for such add-on use). Subjects should be on optimal or near-optimal doses of approved therapies for two reasons: 1) most practicing physicians titrate the dose of one therapeutic agent before considering addition of another antidiabetic agent to improve glycemic control; and 2) this approach allows for more rigorous assessment of the investigational product's efficacy by avoiding a confounding effect of any upward dose titration of the approved medication during the trial.

Another design less commonly used in studies directed at assessing efficacy is the randomized withdrawal. For example, all subjects can be treated with the test agent either as monotherapy or in addition to existing therapy. After a treatment period sufficient to reach pharmacodynamic steady state, subjects can be randomized, in double-blind fashion, either to continue test therapy or to switch to placebo for an additional period (e.g., 12 to 16 weeks). Subjects whose glycemic control deteriorates to the point of meeting escape criteria and requiring additional therapy may create a bias in the assessment of efficacy if the efficacy endpoint is defined as change of HbA1c from randomization to the study endpoint. The primary endpoint for the withdrawal design should be the time to therapeutic failure if event times are collected or, if not, the proportion of HbA1c treatment failures in each treatment group.

B. Study Assessments and Endpoints

1. General Considerations

Throughout development of new molecular entities, particularly within novel classes of therapeutic products, thorough safety evaluations are critical even in the early phase clinical studies. These early studies should be designed with conservative approaches to testing, initially in smaller numbers of subjects, with single doses, and with appropriate safety monitoring not only for glycemia-related parameters, but also for potential hazards identified based on

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preclinical or in vitro study results or on known effects seen with other members of the drug class (if available).

a. Pharmacokinetics

In general, pharmacokinetic parameters of noninsulin therapeutics should be evaluated in phase 1 studies. These studies can be performed in healthy volunteers to determine the basic pharmacokinetic parameters (e.g., absolute bioavailability, area under the curve (AUC), C_{\max} , T_{\max} , $T_{1/2}$). Additionally, pharmacokinetic studies also may be appropriate in the intended patient population. We recommend that exposure-response data be obtained during the phase 2 dose-finding studies. (See the guidance for industry *Exposure-Response Relationships: Study Design, Data Analysis, and Regulatory Applications*.)

In patients with diabetes, the high prevalence of altered glomerular filtration rates, delayed or deficient gastrointestinal transit and absorption, and the potential for interactions with commonly used medications usually dictate the need for the evaluation of the pharmacokinetics of new agents in the target population, beyond investigations in healthy volunteers. It is important to evaluate the in vivo and in vitro mechanisms of drug absorption and disposition. This information will provide the basis for the design of the drug interaction studies addressing the class effects of oral antidiabetic drugs (e.g., addressing the induction potential of CYP enzymes by thiazolidinediones, CYP2C-based interactions with sulfonylureas, and interactions with renal tubular secretion of metformin). We also recommend interaction studies with drugs that have a narrow therapeutic index and with drugs likely to be co-administered in the diabetic population. (See the draft guidance for industry *Drug Interaction Studies — Study Design, Data Analysis, and Implications for Dosing and Labeling* for details.)⁹

Effects of food on pharmacokinetics should be evaluated in the development of therapeutic products that are intended to be administered orally in temporal proximity to meals (e.g., agents designed to exert effects on glycemia peri- or postprandially, such as meglitinides). Because patients with diabetes may be a particularly sensitive population in terms of polypharmacy and underlying, often subclinical, cardiac disease, we also encourage sponsors to address the effect of the drug on the QT interval by conducting a thorough QT study.¹⁰

b. Pharmacodynamic endpoints and biomarkers

Products whose pharmacodynamics, by design, are restricted to effects on postprandial glucose (e.g., meglitinides) should be tested in dose-finding, proof-of-principle, short-term, oral glucose challenge studies. However, such demonstrations of pharmacodynamic activity are not sufficient evidence of efficacy for new drug application (NDA) approval,¹¹ because the link between a modifying effect on postprandial glucose excursions to clinical outcomes is not sufficiently

⁹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

¹⁰ See the ICH guidance for industry *E14 Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-Antiarrhythmic Drugs*.

¹¹ See 21 CFR part 314 for regulations regarding NDAs.

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Draft — Not for Implementation

strong to consider the use of this pharmacodynamic endpoint as a surrogate for efficacy. Such products should be shown to be safe and effective in improving overall glycemic control based on reduction in HbA1c. That said, description in labeling of the effects of the agent on excursions in postprandial serum glucose concentrations, thereby effecting reductions in overall glycemic exposure (as manifest by reductions in HbA1c), may be warranted in some cases to provide physicians with an understanding of the mechanism of action of the agent and its implication for method of use.

Glycated endogenous proteins with turnover rates faster than hemoglobin, such as fructosamine, can be used as preliminary indicators of a product's effects on integrated glycemic exposures in early phase studies of limited duration. Demonstration of reductions in HbA1c, with a concomitant meaningful decrease in mean daily insulin requirements in relevant patients, is desirable but not necessary for the preliminary inference of efficacy from these early studies. Changes in FPG, plasma glucose level after a standard meal, plasma glucose level after oral administration of 75 g of glucose, average blood glucose (mean of seven home measurements obtained before and after each meal and at bedtime), and fructosamine can be used as primary measures of efficacy in phase 2 studies. They also can be used as secondary, supportive measures of efficacy in phase 3 studies.

c. Efficacy endpoints

For purposes of drug approval and labeling, final demonstration of efficacy should be based on reduction in HbA1c (i.e., HbA1c is the primary endpoint of choice, albeit a surrogate), which will support an indication of glycemic control. Superiority or noninferiority hypotheses may be appropriate depending on the trial design. Refer to section V.G., Important Statistical Considerations, for a discussion of issues related to noninferiority trials and choice of noninferiority margins as they relate to studies in diabetes. Also see the ICH guidances for industry *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.

d. Effects on markers of insulin resistance and diabetes comorbidities

Treatment-associated reduction in endogenous hyperinsulinemia (in type 2 diabetes) or improvement in insulin sensitivity are arguably salutary health effects, but do not alone provide sufficient support of a new agent for approval purposes. Effects of antidiabetic agents on blood pressure and serum lipids are of obvious importance and can be described in labeling with disclaimers commensurate with the limitations of the trials regarding extrapolation of findings to conclusions about ultimate drug effects (i.e., on mortality or irreversible morbidity).

e. Effect of weight loss on diabetes

In recent years, the FDA has recommended to sponsors of weight loss products seeking an indication for the treatment of type 2 diabetes that they should demonstrate that the product's effect on glycemic control is independent of weight loss. The FDA has reconsidered the necessity of this recommendation. The FDA's current thinking is that a sponsor can gain approval for the treatment of type 2 diabetes for a drug or biologic whose principal mechanism

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of action appears to be weight loss by showing a clinically meaningful and statistically significant improvement in glycemia.

The development program to support a diabetes indication for these products should be comparable to the development programs used for antidiabetic products not intended for weight loss. For example, the product would need to be studied in subjects with a wide range of body mass indices (from lean to obese), different duration of diabetes (new onset to long-standing), and under different conditions of use (monotherapy and combination therapy). Sponsors interested in the development of weight loss products for the treatment of type 2 diabetes should discuss their plans with the Division of Metabolism and Endocrinology Products.

2. Insulins

In the case of a new insulin with perhaps unique pharmacokinetic characteristics dictating a specific method of use (i.e., dosing interval, timing relative to meals), efficacy can be assumed based on pharmacodynamic (e.g., clamp) studies. However, studies of clinical safety and efficacy usually will be necessary to demonstrate that the method of use leads to effective diabetes management and that the treatment is not associated with undue hypoglycemia (e.g., relative to an approved insulin and standard regimen). (See Appendix B for a discussion on hypoglycemia). These studies should be directed at achieving actual reductions in glycemia (as opposed to simple maintenance of pretrial levels of control) from baseline to end of study. Test and comparator groups should be treated to similar goals. Similar degrees of glycemic control (test noninferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.

a. Insulin mixes

When seeking approval of a new formulation of premixed short- and long-acting insulins, the sponsor should establish the distinctiveness and usefulness of the premixed products compared to each individual insulin component. We recommend that the premixed product's pharmacokinetic and pharmacodynamic profiles have a target difference of at least 20 percent from each of its single components (e.g., NPH and regular/rapid insulin) and also from each adjacent product within its product line. Such differences can be established by the maximum concentrations (C_{\max}) and the various partial AUCs (e.g., $AUC_{0-4 \text{ hr}}$ and $AUC_{4-12 \text{ hr}}$) from insulin plasma exposure versus time profiles. From a pharmacodynamic perspective, the maximum glucose infusion rate (GIR) and the various partial AUCs (e.g., $AUC_{\text{GIR}0-4 \text{ hr}}$ and $AUC_{\text{GIR}4-12 \text{ hr}}$) from glucose infusion rate versus time profiles can be used. In addition, the bioavailability of the new premixed product should remain comparable to the total bioavailability of the short-acting insulin product.

b. Insulin use in pumps (continuous subcutaneous insulin infusion)

Endpoints to be used in the development of insulins for use in pumps should include ascertainment of compatibility between the insulin or analogue and the pump and infusion sets. Likewise, the stability, sterility, and appearance of insulin under laboratory conditions simulating

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Draft — Not for Implementation

the conditions and stresses of actual use should be assessed. Assuming the use of approved pumps and approved insulins, clinical studies *per se* are not usually necessary for approval of the use of a particular insulin in a pump. However, glycemic control may need to be evaluated in a short-term clinical study for novel delivery systems. To clarify expectations for development and approval, additional discussion is encouraged between the FDA (including the Office of Combination Products) and sponsors of particular insulin pumps or insulins.¹²

c. New insulin analogues or insulin receptor binding agonists

In the development of new insulin analogues or insulin receptor binding agonists, sponsors should address the following three fundamental issues in randomized, controlled trials:

1. The risk of hypoglycemia under conditions of use ultimately recommended in labeling, relative to approved insulin products and regimens. In this regard, both test and control groups should achieve improved and similar glucose control as assessed by HbA1c.
2. Pharmacokinetic variability should be evaluated, according to injection site, thickness of fat layer, and other parameters known to affect absorption, distribution, metabolism, and excretion characteristics. Additionally, pharmacodynamic characteristics should be carefully studied to direct dosing interval (for long-acting products) and timing of dosing relative to meals (for short-acting products). Assessment of insulin receptor binding (affinity and dissociation rates), receptor autophosphorylation, phosphorylation of signaling elements and promotion of mitogenesis may add important data to the characterization of new insulin analogues.
3. As a complex biological protein, insulin has the potential to be immunogenic. Adequate assays should be developed that measure antibodies to the test product before the submission of an application. Antibody titers, the timing of their detection and disappearance (if applicable), and correlation with pharmacological effects should be ascertained. The potential for any of the antibodies to neutralize the effects of a new insulin should be assessed, particularly in the presence of high titers of antibodies, and in the presence of allergic reactions or suspicion of immune-complex deposition, or apparent loss of clinical effectiveness.

d. Inhaled insulins

Investigations of insulin delivered by inhalation should include preclinical safety, pulmonary safety, pharmacokinetics, pharmacodynamics, dose proportionality, and hypoglycemic risk. The extent of preclinical studies needed depend, in part, on the novelty of the formulation (e.g., what excipients are used) for the inhaled route. Typically, the minimum preclinical program should be comprised of two 14-day inhalation studies focusing on the histopathology of the respiratory tract, followed by a 6-month bridging study in the most appropriate species. The pharmacokinetics (including bioavailability), pharmacodynamics, and hypoglycemic risk of

¹² It should be noted that proposed labeling may affect the design of trials using a particular insulin with a particular pump.

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inhaled insulin in humans should be compared to that of subcutaneously administered insulin. Intrasubject pharmacokinetic variability should be evaluated.

We encourage sponsors of inhaled insulin products to enroll at least some patients with underlying pulmonary disease, such as chronic obstructive pulmonary disease and asthma, to assess not only effects of inhaled insulin on their pulmonary function, but also the effects of their disease on insulin kinetics. Cigarette smoking affects inhaled insulin bioavailability, and airway status may lead to alterations in drug delivery to the absorption site. Therefore, sponsors should investigate the potential effect of cigarette smoking and inhalational drugs for pulmonary disease on the efficacy and safety of the inhaled insulin product, including assessments of the effects on insulin pharmacokinetic and pharmacodynamic endpoints and the rates and timing of hypoglycemia.

Sponsors developing inhaled insulin products should evaluate the pulmonary safety of these inhaled insulin products (including excipients). Safety assessments should include pulmonary function as measured by the full battery of pulmonary function tests, including spirometry, lung volumes, and diffusion capacity. Serial pulmonary function tests should be performed and the long-term effects of the inhaled insulin product on pulmonary function should be established. Additional safety assessments include high resolution computed tomography of the chest at baseline and on treatment. Because of the potential effects of diabetes mellitus on the pulmonary system, a comparator group is recommended for these safety assessments. In addition, assessment of anti-insulin antibody responses is essential in the overall safety assessment of the inhaled insulins, because the inhaled route may lead to a different propensity toward immune responses. Pre-use storage and in-use handling conditions during these studies should be designed to mimic actual use of the products. Accuracy of use and dosing should be assessed and documented.

3. Noninsulin Products

A reduction in insulin dose is not sufficient stand-alone evidence of efficacy for approval or labeling of a noninsulin product. In addition to showing a meaningful reduction in the insulin dose, the drug should be shown to independently reduce HbA1c, or at least show that no increase in HbA1c accompanies the insulin reduction. In this context, the elimination of the need for insulin entirely in patients with type 1 diabetes or simplification of the insulin regimen while maintaining or improving glycemia (i.e., optimum control with a nonintensive insulin regimen resulting in reduced hypoglycemic risks) is considered clinically meaningful.

Novel approaches to the treatment of type 2 diabetes, such as the use of gastrointestinal neuropeptides or products that inhibit degradation of these peptides, have been shown to have effects beyond the control of insulin secretion and insulin action, such as rate of gastric emptying, food intake, and glucose counterregulation. Nonetheless, the recommended endpoints for approval of such products specifically for the treatment of diabetes will be the same as the traditional approaches used in the development of currently approved insulin secretagogues or insulin sensitizers (i.e., change from baseline in HbA1c).

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Products intended for the treatment of diabetes can be developed for use as monotherapy and for use in combination therapy regimens with other drug classes with different mechanisms of action.

A fixed-dose combination (FDC) of a new agent and an established agent should be studied in a manner that demonstrates that each of the individual components makes a contribution to the claimed effects of the FDC, and that the combination is acceptably safe. If the FDC consists of two currently approved and marketed drugs, and will be labeled for the same indications and patient populations as the separately approved therapies, and the safety and efficacy of these drugs have been established in co-administration, a full factorial efficacy trial may not be necessary to demonstrate the contribution of each FDC component to the claimed effects. In this setting, pharmacokinetic data defining any drug-drug interactions between the components generally should be sufficient. There are exceptions to this approach, such as situations where there are potential safety concerns with the co-administration of the two components. In addition, we recommend nonclinical toxicity studies for certain FDC products, even when the components are previously marketed drugs or biologics. For details, see the guidance for industry *Nonclinical Safety Evaluation of Drug or Biologic Combinations*.

4. Prevention of Type 1 Diabetes Mellitus or Preservation of Beta-Cell Function in Patients Newly Diagnosed with Type 1 Diabetes Mellitus

Studies of products aimed at the prevention of type 1 diabetes in high-risk subjects, or at preservation of beta-cell function in recent-onset type 1 diabetes with remaining endogenous insulin reserve, should evaluate metabolic outcomes, such as the following:

- Fasting and postprandial glucose and glycemic excursion
- Frequency and severity of hypoglycemic events
- Fasting and stimulated C-peptide levels
- Daily insulin requirements in the subjects with diabetes, expressed in international units (IU) per kilogram of body weight

These studies also should evaluate the variations in serum or plasma levels of immune markers, such as anti-insulin, antiglutamic acid decarboxylase 65 and 67, ICA512, and IA-2 beta antibodies. Other markers of cellular immune response (T-cell subpopulations, cytokines) also can be used. In phase 2 studies for the prevention of type 1 diabetes, genotyping and assessments of specific populations of pathogenetically relevant T-cells are encouraged. In particular, the correlation between genotypes and immunoreactive T-cell subpopulations, biomarkers related to glycemic control, and response to treatment may lead to more successful phase 3 studies.

Phase 2 and phase 3 studies of immunosuppressive products or immunomodulators for the prevention of type 1 diabetes also should evaluate their effects on general immune responses, including T-cell proliferation in response to conventional antigens, immunoglobulin subclasses, and titers of antibodies in response to primary antigens and recall responses. Depending on the known or suspected mechanism of action, as well as findings from previous clinical and nonclinical studies, other endpoints should be considered in the overall safety evaluation. These

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assessments should be conducted in patients with diabetes, and not borrow substantially from other patient populations, such as populations with neoplasia or post-transplant patients treated concomitantly with other immunosuppressants.

Phase 3 studies of investigational products intended for the prevention of type 1 diabetes mellitus in high-risk individuals typically will designate a delay in the diagnosis of type 1 diabetes as the criterion for defining efficacy. An appropriate endpoint to support efficacy can be the proportion of subjects in the treatment groups who develop frank diabetes after a prespecified period of time (the period being at least 1 year) compared across treatment groups.

Preservation of beta-cell function in patients recently diagnosed with type 1 diabetes is being actively pursued by the pharmaceutical industry and in government and academic collaborations. We acknowledge the evidence from the DCCT and other studies that have demonstrated clinical benefits in patients who achieve better glucose control, in terms of delaying the chronic complications of diabetes. Similarly, we acknowledge that patients who had greater preservation of endogenous insulin secretory function (as assessed by C-peptide in the serum) at baseline were more likely to have lower HbA1c with fewer hypoglycemic events over time.

Phase 3 development of investigational products intended to preserve endogenous beta-cell function in patients with newly diagnosed type 1 diabetes can designate a measure of C-peptide (e.g., AUC following a standardized mixed meal tolerance test) compared to control at 1 year as the primary efficacy endpoint. Sponsors should analyze the change from baseline to the study endpoint (typically 1 or 2 years) in both treatment groups, and demonstrate maintenance of C-peptide or an attenuation in the rate of decline compared to the control group. For this endpoint to provide convincing evidence of preserved endogenous beta-cell function, the trials should demonstrate a clinically meaningful reduction in mean daily insulin requirements accompanied by similar magnitude of glycemic control compared to the control arm. A favorable effect on these endpoints should be balanced against the risks of the particular intervention being tested. Subjects should continue to be monitored for an extended period (2 to 4 years or longer) to investigate both the durability of the effect and whether they experience a lower frequency of hypoglycemia, diabetic ketoacidosis, and long-term complications of diabetes.

As with most prevention claims, we generally will accept fewer risks for treatments intended to prevent type 1 diabetes compared with treatments that preserve endogenous beta-cell function in patients already diagnosed with type 1 diabetes.¹³ This distinction is made because some individuals exposed to prevention strategies have no chance for benefit, as they are not inexorably destined to develop diabetes. Therefore, some patients (who presumably cannot be pre-identified) would be subject to the risks of the treatment with no hope of benefit.

5. Prevention of Type 2 Diabetes Mellitus

In phase 3 studies for products intended to prevent the development of type 2 diabetes in high-risk individuals (such as individuals with impaired glucose tolerance, impaired fasting glucose, or with a history of gestational diabetes), potential endpoints supporting approval include delay in type 2 diabetes diagnosis or reduction in the proportion of patients diagnosed with type 2

¹³ See 21 CFR 56.111(a)(1)(i) regarding the unnecessary exposure of subjects to risk.

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diabetes by ADA criteria, relative to placebo. These study designs should include a follow-up (washout) period to assess whether the tested agent truly delays progression to diabetes or only masks diabetes during the treatment period. Such studies will likely be of substantial duration (years) and size. The FDA cannot *a priori* define the magnitude of a clinically meaningful effect size.

For prevention studies of drugs with a pharmacological action of improving glycemic parameters (e.g., approved treatments used in the prevention setting), improvement in clinical parameters beyond those that would be expected from glucose lowering alone should be demonstrated, since the forestalling of a biochemical diagnosis of frank diabetes from the prediabetic state may not itself be a sufficiently tangible benefit against which one can appropriately judge the risks. Such supportive evidence can include a demonstration of a durable delay in the onset of type 2 diabetes after the prevention therapy is stopped, or can show that the delay in progression to type 2 diabetes mellitus is accompanied by other indicators of clinical benefit (e.g., delay or lessening in microvascular or macrovascular complications). That said, the more modest the treatment effect, the higher the standard for safety and the more restricted (e.g., to subjects at highest risk for near-term conversion to frank type 2 diabetes) the indicated target population.

C. Metabolic Syndrome

The term *metabolic syndrome* represents a cluster of laboratory and clinical findings that serve as markers for increased risk for cardiovascular disease and type 2 diabetes, and, depending upon the definition used, is prevalent in as much as 25 percent of the adult American population. A host of therapies now exist to address individual or multiple components of the syndrome (e.g., lipid-altering agents, antihypertensives, insulin sensitizers). A therapeutic product intended to treat the metabolic syndrome ideally should normalize or improve all components of the syndrome and ultimately be shown to prevent the development of type 2 diabetes and reduce cardiovascular morbidity and mortality. As mentioned in the Introduction section, a full discussion of this syndrome is beyond the scope of this guidance.

D. Study Population Considerations

In general, premarket study populations should be representative of the population for which the product, once approved or licensed, is intended. Two specific considerations with regard to study populations are listed below.

1. Pediatric Populations

Under the Pediatric Research Equity Act (PREA), section 505B of the Federal Food, Drug, and Cosmetic Act (the Act) (21 U.S.C. § 355c), as amended by the Food and Drug Administration Amendments Act of 2007 (Public Law No. 110-85), sponsors must study a product in all relevant pediatric populations when submitting an application under section 505 of the Act (21 U.S.C. § 355) or section 351 of the Public Health Service Act (42 U.S.C. § 282) for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration. However, the PREA requirements may be waived or deferred in certain

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circumstances. Although a detailed discussion of how sponsors may comply with the PREA requirements is beyond the scope of this guidance, several relevant points are addressed below.

In the case of new molecular entities, particularly for new classes of therapeutic products with novel mechanisms of action, the early studies should enroll adult subjects only, reserving pediatric exposure until the metabolism, pharmacodynamics, and safety of the agent are reasonably well-defined. The same precaution can be applied to already approved agents with known toxicities in nondiabetic populations, such as immunosuppressive or immune modulatory products. Because many of the general aspects of the clinical pharmacology and safety profiles of an approved therapeutic are better understood, it may be appropriate to dose pediatric patients earlier in the development programs of approved versus unapproved investigational products.

In the initial development of insulins and other agents with potential to cause hypoglycemia, we recommend that subjects with particularly labile glucose control and a substantial history of recent hypoglycemia be excluded. Because of the high representation of children and adolescents in the population with type 1 diabetes, patients in these demographic subsets usually should be included early in the clinical development of treatments for type 1 diabetes. However, it is not appropriate to study all products for type 1 diabetes in children before approval. For example, inhaled insulins, which represent simply an alternate route of administration for a well-established active ingredient, should be developed for adult use initially because of uncertainties in the safety of new inhalation dosage forms. After additional safety data are developed, these products can be studied in children, including during the postmarketing period. In such cases, the initial approved labeling should specifically address dosing and administration in adults. Labeling for pediatric use can be developed and approved after additional studies are conducted in pediatric patients.

Given the increasing representation of children and adolescents with type 2 diabetes, studies of therapeutic products intended for the treatment of type 2 diabetes should at some point include patients younger than 18 years of age, assuming no obvious contraindications to such use (e.g., hypothetical effects on growth and development based on mechanism of action).

Sponsors may contact the review division for further information with regard to meeting the PREA requirements.

2. Other Study Populations

Type 2 diabetes occurs more frequently in Latino, African American, and Native American patients relative to patients of northern European descent. Therefore, attempts should be made to enroll representative numbers of individuals from these ethnic groups during the clinical development program, particularly during the phase 3 trials. Attention also should be paid to considerations in geriatric patients, including decreased renal function, autonomic dysfunction, poor glucose-counterregulatory response, hypoglycemia unawareness, and potentially dangerous interactions with other commonly used drugs. It is desirable to determine whether demographic, genetic, metabolic (e.g., C-peptide, body mass index, previous antidiabetic therapy), or other factors predict responses to a new antidiabetic agent, predispose patients to certain toxicities, or otherwise affect tolerability and compliance.

E. Sample Size and Study Duration

The ICH guidance for industry *E1A The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* recommends a total exposure of at least 1,500 subjects (300 to 600 for 6 months, 100 for 1 year) for the safety assessment of chronically administered drugs developed for the treatment of non-life-threatening conditions. However, exposures exceeding these recommendations should be used for products developed for the treatment of type 2 diabetes, given the large and growing size of the population with type 2 diabetes and the increasing complexity of treatment regimens. At the time of submission of the marketing application (either a biologics license application (BLA) or an NDA) for products intended for the treatment of type 2 diabetes mellitus, we recommend that phase 3 trial data be available for at least 2,500 subjects exposed to the investigational product with at least 1,300 to 1,500 of these subjects exposed to the investigational product for 1 year or more and at least 300 to 500 subjects exposed to the investigational product for 18 months or more.

These investigational products should be tested as monotherapy and in combination with antidiabetic medications with which they likely will be co-administered in clinical practice. As treatment of type 2 diabetes mellitus frequently requires combination therapy, overall exposures and length of duration should be weighted more in trials evaluating the investigational product with other antidiabetic medications. The guidance for industry *Premarketing Risk Assessment* also anticipates situations where larger numbers of exposures for longer periods might be needed, including for diseases where many sufficiently safe alternative treatments already exist or for a preventive treatment. Therefore, we encourage long-term extensions of 6- to 12-month controlled trials and anticipate that the safety information relevant for approval will be provided at the initial submission of an application.

Development of products intended to preserve beta-cell mass and function in type 1 or type 2 diabetes can be considered in enriched populations, where genetic or immunologic markers predicting the natural history of the disease exist. Testing the investigational product in high-risk populations enriched for such markers enhances power to detect an effect of the intervention (if one exists), as compared to testing the product in the general diabetic population. Even in enriched populations, pivotal studies may still need to be relatively long (e.g., 2 or more years) to show a meaningful effect, given the natural history of the decline in beta-cell function in the target populations and also recognizing the need for long-term safety information.

For all new development programs for drugs to treat diabetes, phase 3 studies should be sized to allow meaningful evaluation of the consistency of effects across subgroups based on sex, age, ethnic background, duration and severity of the disease (e.g., based on categories of HbA1c at baseline), interactions with other likely concomitant medications as combination therapies, and other relevant factors specific to the product and indication sought. Randomized treatment groups should be well balanced for these factors, and to fully ensure balanced assignment, randomization stratified for a limited number of factors may be desirable, with particular emphasis on those baseline variables hypothesized to affect either safety or efficacy.

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Most patients taking products intended to treat diabetes are titrated to achieve a particular effect on serum or plasma glucose or on HbA1c. The primary efficacy parameter should be assessed substantially after the end of the titration period (e.g., 3 months) to better reflect the steady-state effect of the dose regimens studied.

Regardless of the choice of control used in phase 3 studies, the duration of the controlled phase in an efficacy trial is an important issue. In studies of recently approved products that lasted more than 1 year, sponsors have typically conducted a randomized, controlled study lasting at least 6 months, followed by an extension phase lasting 6 months or longer. Sponsors should weigh the advantages and disadvantages when deciding between a controlled and uncontrolled extension phase, and should ensure that the chosen design will provide interpretable long-term data.

Although uncontrolled extensions still allow for an expanded safety database (both in numbers exposed and duration of treatment), interpretability of both efficacy and safety data in an uncontrolled study period is limited by lack of a control group.

Since diabetic populations are prone to certain morbidities (such as cardiovascular disease and renal dysfunction), only longer term comparative safety data would allow for an assessment of the relative rates of these common, but important morbidities in subjects assigned to the investigational agent versus the control. Studies lasting longer than 1 year that employ an appropriate active comparator with adjudication of safety endpoints of interest by an endpoint committee blinded to treatment are strongly encouraged and may be needed if preclinical or phase 2 or phase 3 studies reveal a safety signal. Longer term controlled data also allow for better assessments of the comparative durability of effects on glycemia. Such studies, however, may have high rates of dropouts; therefore, treatment algorithms for maintenance of adequate glycemic control should be considered in the study design.

Of note, all drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. The FDA currently bases approval of these drugs and biologics on HbA1c. We recognize that reducing long-term macrovascular complications in patients with diabetes should be an important goal of disease management. Although a recommendation to demonstrate macrovascular risk reduction premarketing may delay availability of many effective antidiabetic drugs for a progressive disease that often requires multiple drug therapy, sponsors should conduct large outcomes trials before submission of marketing applications for drugs in development that show nonclinical or clinical evidence of increasing macrovascular risk. Therapies that have not demonstrated a deleterious effect on cardiovascular outcome during extensive premarketing evaluation may need further post-approval assessment for their effects on long-term macrovascular disease. Interpretation of data resulting from such studies may be complicated by the need to identify conclusively the effect of a single drug within a multidrug regimen that usually is part of an adequate treatment for a complex, progressive condition such as type 2 diabetes and its associated comorbidities.

Phase 3 studies with a 6-month, placebo-controlled phase can be extended into a rigorously controlled, randomized, double-blind active-controlled phase that employs double-dummy agents.

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Before submitting a marketing application, assessment of the immunogenic potential of therapeutic proteins, including insulins and insulin analogues, and of monoclonal antibodies, should be performed over a period of at least 6 to 12 months in study subjects reasonably representative of the intended population. If adverse events characteristic of allergic or immunologic reactions are identified, we may ask for additional studies, with durations longer than 12 months. These additional studies may need to be conducted before submission of a marketing application or as a postmarketing commitment, based on the overall analysis of the risks and benefits of the product. The appropriate timing of additional studies in these circumstances can be discussed with the FDA at a pre-BLA meeting, pre-NDA meeting, or other similar advice meeting.

A licensed monoclonal antibody used only in allogeneic transplantation, where patients are immunosuppressed through multiple modalities, should be newly evaluated for immunogenic potential in the diabetic or high-risk prediabetic population.

F. Premarketing Safety Evaluation

The safety evaluation of a new drug is, in the end, directed by the findings of preclinical investigations, by concerns arising based on the mechanism of action of the drug, by known toxicities of agents with a similar chemical structure or mechanism of action, and by the findings of previous clinical trials. In other words, ultimately, the safety evaluation is an iterative process based on prior experience.

Additionally, new antidiabetic agents, used alone or in combination with approved agents, should be assessed for their tendency to cause or augment hypoglycemia, an event that is part of diabetes management. Acceptable hypoglycemic risk, although not defined in absolute terms, usually is risk that is comparable to existing therapies, to which the new drug is directly compared, when both drugs are used in trials in which subjects are treated to identical glycemic goals with comparable glycemic outcomes (e.g., ADA guidelines). Furthermore, patients with diabetes often use multiple medications, not only to control glycemia, but also to address cardiovascular disease risk factors, such as hypertension and hyperlipidemia, and microvascular and neuropathic complications of diabetes. Interactions between the new investigational product and these other medications can result in adverse events that should be considered, documented, and reported. Finally, worsening of comorbid conditions other than diabetes should be ascertained, reported, and analyzed in comparison to the rates of similar adverse events in the control group.

Findings of specific safety signals with a product or related product (whether cardiovascular or otherwise) during any development phase should be investigated further in controlled studies enriched with the population at risk for the signal. The timing of this investigation (pre-approval or post-approval) depends on the strength and nature of the signal and whether the treatment offers a major advance over existing therapies.

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For general issues related to risk assessment, pharmacovigilance, and risk minimization plans, refer to the following guidances:¹⁴

- Guidance for industry *Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment*
- Guidance for industry *Development and Use of Risk Minimization Action Plans*
- Guidance for industry *Premarketing Risk Assessment*
- ICH guidance for industry *E2C Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs* and addendum
- ICH guidance for industry *E2E Pharmacovigilance Planning*

G. Important Statistical Considerations

Standard statistical considerations apply to programs for drugs or biologics intended to treat diabetes. However, the following discussion highlights a few specific areas that are important to consider specifically for these therapeutic products.

1. Sample Size

Sample size calculations for superiority trials with HbA1c change from baseline as the primary endpoint should be based on two-sided tests of significance at the 5 percent level and at least 80 percent power. Effect sizes should represent clinically meaningful differences.

Sample sizes for noninferiority trials should be based on one-sided significance levels of 2.5 percent and at least 80 percent power. Because the calculations depend on the noninferiority margin, the sponsor should provide a rationale for the choice of margin and should be guided by the concept that this margin should not represent a clinically meaningful loss of efficacy relative to the active control. Typically, we accept a noninferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials. For additional guidance on noninferiority studies, refer to ICH E9 and ICH E10.

2. Preventing Missing Data from Subjects Who Prematurely Withdraw from Treatment

We encourage sponsors to obtain HbA1c measurements in all subjects, including those who withdraw prematurely or receive rescue medication because of poor glycemic control, near the calendar date at which they were scheduled to complete the trial. Complete data collection can facilitate the desired goal of a true intent-to-treat analysis (i.e., the analysis of all randomized subjects) and also serve as a measure of good clinical trial conduct.

¹⁴ See <http://www.fda.gov/cder/guidance/index.htm>.

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3. Analysis Methods

We recommend that the analysis of HbA1c change from baseline adjust for differences between groups in HbA1c at baseline (e.g., ANCOVA with baseline HbA1c as a covariate in the model). Factors in addition to treatment can be included in the model as appropriate, particularly variables with substantial correlation with the outcome and independence from the treatment, and variables used to stratify the randomization.

Although every reasonable attempt should be made to obtain complete HbA1c data on all subjects, dropouts are often unavoidable in diabetes clinical trials. The resulting missing data problems do not have a single general analytical solution. Statistical analysis using last observation carried forward (LOCF) is easy to apply and transparent in the context of diabetes trials. Assuming an effective investigational therapy, it is often the case that more placebo patients will drop out early because of a lack of efficacy, and as such, LOCF will tend to underestimate the true effect of the drug relative to placebo providing a conservative estimate of the drug's effect. The primary method the sponsor chooses for handling incomplete data should be robust to the expected missing data structure and the time-course of HbA1c changes, and whose results can be supported by alternative analyses. We also suggest that additional analyses be conducted in studies with missing data from patients who receive rescue medication for lack of adequate glycemic control. These sensitivity analyses should take account of the effects of rescue medication on the outcome.

The full analysis set as described in ICH E9 should be the primary analysis population for both superiority and noninferiority analyses. Supporting analyses in one or more subsets of the full analysis set also can be conducted and are encouraged in noninferiority analyses.

Analyses of data from studies using withdrawal designs depend on the type of primary endpoint. Survival analysis methods should be used if therapeutic failure times are collected. If the endpoint is therapeutic success or failure, categorical methods should be used.

If statistical significance is achieved on the primary endpoint, secondary assessments of efficacy can be considered. Type 1 error should be controlled across all clinically relevant secondary efficacy endpoints that may be intended for product labeling to provide statistical support for their inclusion in the label.

The sponsor should report least-square mean treatment differences and associated 95 percent confidence intervals from the primary statistical model for all continuous efficacy endpoints.

Rates of hypoglycemia should be compared statistically between groups. If count data are analyzed, the sponsor should use robust statistical methods that take account of the dependence of events within individual patients.

4. Graphical Methods

Graphical methods showing treatment effects over time for study completers should be presented. Additional graphical presentations of the data to illustrate the effect of the drug are

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1063 encouraged. For examples, see the guidance for industry *Clinical Studies Section of Labeling for*
1064 *Human Prescription Drug and Biological Products — Content and Format.*
1065

**APPENDIX A:
PRECLINICAL CONSIDERATIONS FOR PEROXISOME
PROLIFERATOR-ACTIVATED RECEPTOR AGONISTS**

Because of the effects of PPAR agonists on glucose and lipid metabolism, many compounds are being developed for the treatment of type 2 diabetes and/or dyslipidemia which activate PPAR α , PPAR γ , PPAR α and γ (dual agonist), or PPAR α , γ , and δ (pan agonist).

Recommendations for the Duration of Chronic Toxicology Studies

The ICH guidance regarding the duration of chronic toxicity studies in rodents and nonrodents has been adopted,¹⁵ and for the nonrodent chronic toxicity study, a 9-month duration generally is appropriate for supporting chronic human use. However, since the no observed adverse effect levels for some of the toxicities associated with PPAR agonists can be adequately defined only after chronic administration, a 1-year study in nonrodents is recommended for drugs in the PPAR class.

Because of the prevalence of positive carcinogenicity findings with PPAR agonists, 2-year carcinogenicity evaluations in mice and rats are recommended. Since heart weight increases of 25 percent or greater after 13-week treatment with PPAR agonists have been predictive of excess cardiac mortality with longer-term chronic dosing (greater than or equal to 12 months) in all animal models, a dose that results in 20 to 25 percent increases in heart weight is considered to define the maximum tolerated dose for use in the 2-year carcinogenicity study for agonists with gamma activity.

Recommendations for the preclinical evaluation of PPAR-related toxicities are as follows:

- **Cardiac Effects.** The effects on the heart should be characterized by reviewing electrocardiograms, clinical chemistry, and cardiac histopathology in rats and nonrodents. QT prolongation potential should be thoroughly evaluated in multiple dose nonrodent toxicity studies. For compounds with PPAR alpha or delta agonist activity, biomarkers of direct cardiac toxicity such as Troponin I and T should be monitored in animal studies.

Additional evaluations are recommended as follows:

- Correlation of heart weights with thickness of ventricular free wall and ventricular septum in chronic toxicology studies in rats and nonrodents.
- Morphometric measurements of ventricular myocardial hypertrophy in nonrodents.
- Presence of karyomegaly in myocardium of ventricles.
- Pattern and distribution of myocardial fibrosis.
- Characterization of myocardial inflammatory infiltrates.
- Determination of composition of serous effusions.
- Presence of fatty changes detected by stained heart tissue. The sections can be stained with Sudan IV or Oil Red-O.

¹⁵ See the ICH guidance for industry *S4 Duration of Chronic Toxicology Testing in Animals (Rodent and Nonrodent Toxicity Testing)*.

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- Characterization in animals and humans of the potential for plasma volume expansion.
- **Hepatic Effects.** The cause of any liver enlargement observed should be determined (peroxisome proliferation, mitochondrial proliferation/swelling). Liver tissues should be stained to detect the presence of fatty changes. The sections can be stained with Sudan IV or Oil Red-O. Liver enzyme levels and biochemical markers of peroxisome proliferation (Acyl CoA and CYP 4A) should be analyzed in rodents and nonrodents.
- **Bone Marrow Effects.** Bone marrow smears from femur and sternum should be quantified to assess for effects on cellularity.
- **Renal Effects.** Drug-related increases in urothelial tumors have been observed in rodent carcinogenicity studies with PPAR agonists. If such tumors are observed, mechanistic studies (e.g., urinalysis assessing crystalluria, urine pH, urinary electrolytes) are recommended.
- **Muscle Toxicity.** Skeletal and/or cardiac muscle degeneration have been commonly observed for agonists with PPAR alpha or PPAR delta activity. Creatine kinase and troponin evaluations should be performed in preclinical studies for these subtypes. Histopathological evaluations of skeletal muscle should include multiple sites to evaluate effects on both type I and type II muscle (e.g., diaphragm, gastrocnemius, soleus, intercostals muscles).
- **Other Known Toxicities.** Thymic and lymphoid atrophy, reproductive organ toxicity, adipose proliferation, and infiltration are toxicities commonly associated with the administration of PPAR agonists in preclinical studies. Preclinical study designs should include adequate assessments for these potential toxicities.
- **Electron Microscopy.** Electron microscopy evaluations should be conducted on established target organs for PPAR agonists (liver and heart mandatory) and on other compound specific target tissues, as identified (e.g., renal proximal tubules, skeletal muscle).

**APPENDIX B:
HYPOGLYCEMIA**

Severe episodes of hypoglycemia are often encountered when patients implement a program of intense glycemic control. These adverse occurrences are often the limiting factor in achieving improvements in metabolic control and reductions in HbA1c. There are often substantial differences in the interpretation and reporting of the severity of hypoglycemic episodes among investigators, studies, and clinical programs because of the diversity of the definitions used in clinical studies. To help in the interpretation of this important safety attribute of a new diabetes treatment that may cause hypoglycemia, we recommend standardization of definitions in individual protocols and across protocols within the development program. One recommended approach for such standardization is to use classifications of severity from well-accepted sources, such as the ADA.

The ADA Workgroup on Hypoglycemia classifies hypoglycemia as follows (Diabetes Care, 2005, 28: 1245):

- **Severe hypoglycemia.** An event requiring assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. These episodes may be associated with sufficient neuroglycopenia to induce seizure or coma. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration.
- **Documented symptomatic hypoglycemia.** An event during which typical symptoms of hypoglycemia are accompanied by a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L).
- **Asymptomatic hypoglycemia.** An event not accompanied by typical symptoms of hypoglycemia but with a measured plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since the glycemic threshold for activation of glucagon and epinephrine secretion as glucose levels decline is normally 65 to 70 mg/dL (3.6 to 3.9 mmol/L) and since antecedent plasma glucose concentrations of less than or equal to 70 mg/dL (3.9 mmol/L) reduce sympathoadrenal responses to subsequent hypoglycemia, this criterion sets the lower limit for the variation in plasma glucose in nondiabetic, nonpregnant individuals as the conservative lower limit for individuals with diabetes.
- **Probable symptomatic hypoglycemia.** An event during which symptoms of hypoglycemia are not accompanied by a plasma glucose determination, but was presumably caused by a plasma glucose concentration less than or equal to 70 mg/dL (3.9 mmol/L). Since many people with diabetes choose to treat symptoms with oral carbohydrate without a test of plasma glucose, it is important to recognize these events as probable hypoglycemia. Such self-reported episodes that are not confirmed by a contemporaneous low plasma glucose determination may not be suitable outcome measures for clinical studies that are aimed at evaluating therapy, but they should be reported.

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- **Relative hypoglycemia.** An event during which the person with diabetes reports any of the typical symptoms of hypoglycemia, and interprets the symptoms as indicative of hypoglycemia, but with a measured plasma glucose concentration greater than 70 mg/dL (3.9 mmol/L). This classification reflects the fact that patients with chronically poor glycemic control can experience symptoms of hypoglycemia at plasma glucose levels greater than 70 mg/dL (3.9 mmol/L) as plasma glucose concentrations decline toward that level. Though causing distress and interfering with the patient's sense of well-being, and potentially limiting the achievement of optimal glycemic control, such episodes probably pose no direct harm and, therefore, may not be a suitable outcome measure for clinical studies that are aimed at evaluating therapy, but they should be reported.

At a minimum, hypoglycemic events should be reported in each of the first three classifications: severe hypoglycemia, documented symptomatic hypoglycemia, and asymptomatic hypoglycemia.

Currently, there is no standardized convention for reporting the frequency of hypoglycemia in clinical studies. The ADA Workgroup recommends that both the proportion (percentage) of subjects affected and the event rates (e.g., episodes per subject-year or 100 subject-years) for each of the classifications of hypoglycemic events be reported. These data provide complementary information. In addition, we anticipate that the distribution of subjects having a specific number of hypoglycemic events will be reported (see also section V.G., Important Statistical Considerations). For the hypoglycemic episodes, sponsors should include information on potential precipitants (e.g., missed meal, exercise) and patterns (e.g., timing of the event during the course of the day or night).

**APPENDIX C:
CURRENTLY AVAILABLE DRUG TREATMENTS**

A. Insulin Products

A variety of recombinant human insulins and insulin analogues are available and these products serve as the primary basis for treating the glucose metabolic defects in type 1 diabetes. Insulin and its analogues also have an important role in the treatment of type 2 diabetes, particularly as the disease progresses. These products are used in different combinations according to the pharmacokinetic profile of each insulin type, and some are available in premixed combinations of different proportions of short- and long-acting agents. These insulins also can be used in conjunction with oral agents (described below) to achieve control of blood glucose. There has been tremendous interest and some success in developing noninjectable insulins (e.g., inhaled insulin). However, current development of these products has been aimed at supplementing or replacing short-acting insulin only and would not represent a full alternative to injectable insulin and its analogues.

B. Oral Agents for Type 2 Diabetes

The first oral products for the treatment of diabetes mellitus were the sulfonylureas, which are long-acting insulin secretagogues. The meglitinides constitute another class of insulin secretagogues that are taken with meals and have short-term effects, primarily on the postprandial elevations of plasma glucose. Metformin exerts its effect on endogenous hepatic glucose production. PPAR agonists enhance insulin sensitivity. Alpha glucosidase inhibitors prevent intestinal glucose absorption and have primary effects on the excursion of postprandial glucose.

C. Newer Classes of Therapeutic Products

More recently, an analogue of human amylin, pramlintide, was approved for the treatment of type 1 or type 2 diabetic patients as an adjunct to mealtime short-acting or rapid-acting insulin. Amylin, a neuroendocrine hormone that is co-secreted with insulin from pancreatic beta cells, slows intestinal carbohydrate absorption through decreased gastric emptying and suppresses hepatic gluconeogenesis by inhibiting glucagon secretion postprandially. Additionally, exenatide, a glucagon-like peptide 1 (GLP-1) analogue (belonging to the new class of incretin mimetics) has been approved for type 2 diabetes, in combination with other oral antidiabetic agents. In response to nutrients in the lumen of the gut, GLP-1 is secreted from the intestinal L cells. Similar to amylin, GLP-1 decreases gastric emptying and glucagon secretion. In addition, GLP-1 stimulates insulin secretion. Because the effects of GLP-1 are glucose-dependent, GLP-1 mediates glucose homeostasis without causing hypoglycemia. Both pramlintide and exenatide are injectables.

There is a newer class of oral drugs known as dipeptidyl peptidase 4 (DPP4) inhibitors that has been the focus of intense development. DPP4 is a serine protease responsible for the rapid metabolism of endogenous GLP-1. By inhibiting this enzyme, DPP4 inhibitors prevent the rapid catabolism of endogenous GLP-1, thereby potentiating the incretin effect of GLP-1.

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)**

**December 2008
Clinical/Medical**

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Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
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Silver Spring, MD 20993-0002
E-mail: druginfo@fda.hhs.gov
Fax: 301-847-8714
(Tel) 301-796-3400
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TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND	2
III.	RECOMMENDATIONS.....	3

Guidance for Industry¹

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.² Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

In March 2008, the FDA issued the draft guidance for industry *Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention*.³ Concerns related to cardiovascular risk will be addressed in the final version of that guidance. In the meantime, we are issuing this final guidance for immediate implementation to ensure that relevant issues related to minimizing cardiovascular risk are considered in ongoing drug development programs. We will address cardiovascular risk assessment for currently marketed antidiabetic therapies in a separate guidance.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

¹ This guidance has been prepared by the Division of Metabolism and Endocrinology Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

² For discussion of general issues of clinical trial design or statistical analysis, see the ICH guidances for industry *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials*. We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

³ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the CDER guidance Web page at <http://www.fda.gov/cder/guidance/index.htm>.

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cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

Diabetes mellitus has reached epidemic proportions in the United States and more recently worldwide. The morbidity and mortality associated with diabetes is anticipated to account for a substantial proportion of health care expenditures. Although several drug treatments currently are available, we recognize the need for new agents for the prevention and treatment of diabetes (e.g., development of drugs and therapeutic biologics).

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycemia caused by defective insulin secretion, resistance to insulin action, or a combination of both. Alterations of lipid and protein metabolism also are important manifestations of these defects in insulin secretion or action.

Most patients with diabetes mellitus have either type 1 diabetes (which is immune-mediated or idiopathic) or type 2 diabetes (with a complex pathophysiology that combines progressive insulin resistance and beta-cell failure). Both type 1 and type 2 diabetes have a heritable basis. Diabetes also can be related to the gestational hormonal environment, genetic defects, other endocrinopathies, infections, and certain drugs.

The treatment goals for patients with diabetes have evolved significantly over the last 80 years, from preventing imminent mortality, to alleviating symptoms, to the now recognized objective of normalization or near normalization of glucose levels with the intent of forestalling diabetic complications. The Diabetes Control and Complications Trial has conclusively demonstrated that tight glucose control in patients with type 1 diabetes significantly reduces the development and progression of chronic diabetic complications, such as retinopathy, nephropathy, and neuropathy.⁴ Long-term follow-up of these patients demonstrated beneficial effects on macrovascular outcomes in the Epidemiology of Diabetes Interventions and Complications study.⁵

There are also compelling data in patients with type 2 diabetes supporting a reduced risk of microvascular complications with improved long-term glycemic control. Glycemic control in these studies has been based on changes in HbA1c. This endpoint reflects a beneficial effect on the immediate clinical consequences of diabetes (hyperglycemia and its associated symptoms) and lowering of HbA1c is reasonably expected to reduce the long-term risk of microvascular complications. Therefore, reliance on HbA1c remains an acceptable primary efficacy endpoint for approval of drugs seeking an indication to treat hyperglycemia secondary to diabetes mellitus. However, diabetes mellitus is associated with an elevated risk of cardiovascular disease, which is the leading cause of morbidity and mortality in this patient population. Although this excess cardiovascular risk is present in both type 1 and type 2 diabetes, the

⁴ See N Engl J Med, 1993, 329:977-986.

⁵ See Diabetes, 2006, 55:3556-3565.

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absolute deficiency of insulin in patients with type 1 diabetes dictates the need for insulin therapy as an immediate lifesaving treatment for which evaluation of long-term cardiovascular risk may not be practical. For type 2 diabetes, the wider range of therapies available before insulin therapy is considered for controlling hyperglycemia allows for an opportunity to evaluate the effect of these therapies on cardiovascular risk, enabling a more informed decision on the management of type 2 diabetes.

On July 1 and 2, 2008, the Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the role of cardiovascular assessment in the premarketing and postmarketing settings. After considering the discussion at this meeting as well as other available data and information,⁶ we have determined that concerns about cardiovascular risk should be more thoroughly addressed during drug development.

III. RECOMMENDATIONS

To establish the safety of a new antidiabetic therapy to treat type 2 diabetes, sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk. To ensure that a new therapy does not increase cardiovascular risk to an unacceptable extent, the development program for a new type 2 antidiabetic therapy should include the following.

For new clinical studies in the planning stage:

- Sponsors should establish an independent cardiovascular endpoints committee to prospectively adjudicate, in a blinded fashion, cardiovascular events during all phase 2 and phase 3 trials. These events should include cardiovascular mortality, myocardial infarction, and stroke, and can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints.
- Sponsors should ensure that phase 2 and phase 3 clinical trials are appropriately designed and conducted so that a meta-analysis can be performed at the time of completion of these studies that appropriately accounts for important study design features and patient or study level covariates. To obtain sufficient endpoints to allow a meaningful estimate of risk, the phase 2 and phase 3 programs should include patients at higher risk of cardiovascular events, such as patients with relatively advanced disease, elderly patients, and patients with some degree of renal impairment. Because these types of patients are likely to be treated with the antidiabetic agent, if approved, this population is more appropriate than a younger and healthier population for assessment of other aspects of the test drug's safety.
- Sponsors also should provide a protocol describing the statistical methods for the proposed meta-analysis, including the endpoints that will be assessed. At this time, we believe it would be reasonable to include in a meta-analysis all placebo-controlled trials, add-on trials (i.e., drug versus placebo, each added to standard therapy), and active-

⁶ See Lancet, 1998, 352:837-853 and 854-865.

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controlled trials, and to preserve the study level randomized comparison but include, when possible in the meta-analysis, important identifiers of study differences or other factors (e.g., dose, duration of exposure, add-on drugs). It is likely that the controlled trials will need to last more than the typical 3 to 6 months duration to obtain enough events and to provide data on longer-term cardiovascular risk (e.g., minimum 2 years) for these chronically used therapies.

- Sponsors should perform a meta-analysis of the important cardiovascular events across phase 2 and phase 3 controlled clinical trials and explore similarities and/or differences in subgroups (e.g., age, sex, race), if possible.

For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA):

- Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. This can be accomplished in several ways. The integrated analysis (meta-analysis) of the phase 2 and phase 3 clinical trials described above can be used. Or, if the data from all the studies that are part of the meta-analysis will not by itself be able to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8, then an additional single, large safety trial should be conducted that alone, or added to other trials, would be able to satisfy this upper bound before NDA/BLA submission. Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8.
- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3. This can be achieved by conducting a single trial that is adequately powered or by combining the results from a premarketing safety trial with a similarly designed postmarketing safety trial. This clinical trial will be a required postmarketing safety trial.⁷
- If the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk (i.e., risk ratio) is less than 1.3 and the overall risk-benefit analysis supports approval, a postmarketing cardiovascular trial generally may not be necessary.

⁷ See the Food and Drug Administration Amendments Act of 2007, Title IX, subtitle A, section 901. This section will become section 505(o)(3)(A), 21 U.S.C. 355(o)(3)(A).

Contains Nonbinding Recommendations

- The report of this meta-analysis should contain sufficient detail for all the analyses; conventional graphical plots for meta-analysis finding by study, subgroup, and overall risk ratio; and all the analysis data sets that would allow a verification of the findings.

Sponsors are encouraged to contact the division to discuss specific issues that arise during the development of a new antidiabetic therapy to treat type 2 diabetes.