CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

203313Orig1s000
203314Orig1s000

STATISTICAL REVIEW(S)

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 MEMO

CLINICAL STUDIES

NDA/BLA #:	NDA 203314, NDA 203313
Drug Name:	Tresiba (insulin degludec)
	Ryzodeg (insulin degludec/insulin aspart)
Indication(s):	Improve glycemic control in adult patients with diabetes mellitus
Applicant:	Novo Nordisk
Date(s):	Submitted: 03/26/2015
	Goal date: 09/26/2015
Review Priority:	Standard
Biometrics Division:	Division of Biostatistics II
Statistical Reviewer:	Jiwei He, Ph.D.
Concurring Reviewers:	Mark Rothmann, Ph.D., Team Leader
Medical Division:	Division of Metabolism and Endocrinology Products
Clinical Team:	Tania Condarco, M.D., Medical Officer
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Project Manager:	Callie CappelLynch, M.S.

Keywords: NDA review, clinical studies

This memo is on the second cycle resubmission of the New Drug Applications for Tresiba (insulin degludec injection) and Ryzodeg (insulin degludec/insulin aspart injection).

No new efficacy data or results were submitted. NDA 203314 for Tresiba was previously reviewed by Cynthia Liu (in DARRTs on 11/14/2012). NDA 203313 for Ryzodeg was previously reviewed by Dongmei Liu (in DARRTs on 11/16/2012). I concur with the conclusions in the previous statistical reviews.

Reference ID: 3814371

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/s/

JIWEI HE
09/01/2015

MARK D ROTHMANN
09/02/2015
I concur

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 AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-314, NDA 203-313
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250)
	Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted: March 26, 2015
	Goal Date: September 26, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D.
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Keywords: diabetes mellitus, cardiovascular safety, cardiovascular outcomes trial, major adverse cardiovascular event (MACE)

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1 EXECUTIVE SUMMARY

During the review cycle of the original submissions of NDA 203-314 (insulin degludec, IDeg) and NDA 203-313 (insulin degludec/insulin aspart, IDegAsp) submitted to the Agency on September 29, 2011, a potential adverse cardiovascular (CV) signal was observed in the IDeg/IDegAsp phase 3 development program, based upon a pre-specified meta-analysis to assess the CV risk associated with IDeg/IDegAsp. This was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. Of the 17 trials, 7 included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the statistical analysis plan (SAP). The meta-analysis results suggested an increase in CV risk of IDeg/IDegAsp relative to the pooled comparator arm, using both the pre-specified primary major adverse cardiovascular event (MACE+: composite of CV death, myocardial infarction, stroke and unstable angina pectoris) and a strict MACE endpoint which excluded the unstable angina component from MACE+.

These 17 phase 3 efficacy trials were designed to primarily assess glycemic control, rather than characterizing CV risk. Due to the inherent deficiencies associated with a meta-analysis of open-label efficacy trials, the CV signal was considered uncertain which warranted a further trial designed specifically for the evaluation of cardiovascular risk. On February 8, 2013, the FDA issued a Complete Response Letter (CRL) to the applicant (Novo Nordisk), which outlined the cardiovascular safety deficiency of insulin degludec and requested additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial (CVOT) to be submitted to address the deficiency. As such, DEVOTE was designed and initiated as a dedicated cardiovascular outcomes trial to provide further definitive evidence of the CV safety profile of insulin degludec. The design and analysis of the DEVOTE trial was agreed upon with the Agency with incorporation of specific design elements to overcome deficiencies of the meta-analysis of open-label efficacy trials.

DEVOTE is a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled, event-driven trial which was designed and powered with a primary objective to confirm cardiovascular safety of insulin degludec compared to that of insulin glargine (IGlar) when added to standard of care in male and female subjects with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular events. The study objective is to be supported by a non-excessive risk analysis to demonstrate that the hazard ratio (HR) of a primary MACE composite endpoint (3-component: CV death including deaths of unknown cause, non-fatal myocardial infarction, or non-fatal stroke) for IDeg versus IGlar is no greater than 1.8 before resubmission of IDeg/IDegAsp NDAs, assessed by a pre-planned single interim analysis when 150 adjudicated primary MACEs have been accrued. The study will continue until the planned

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trial conclusion when 633 MACE events have been collected and confirmed. A final analysis will then be performed to further demonstrate non-excessive risk of MACE against a risk margin of 1.3. All potential MACE events are to be adjudicated by an independent and blinded event adjudication committee (EAC).

The applicant resubmitted the NDAs of IDeg and IDegAsp on March 26, 2015. They seek to address the question of cardiovascular safety primarily based on the interim information derived from the DEVOTE study. This review focused on the pre-approval evaluation of cardiovascular safety of IDeg relative to IGlar based upon the interim CV data obtained from the ongoing DEVOTE trial. The statistical goal of this evaluation is to assess whether the hazard ratio of MACE associated with IDeg relative to IGlar met the risk margin of 1.8 set forth in the Complete Response Letter.

1.1 Conclusions and Recommendations

On November 28, 2014, DEVOTE reached its full enrollment of 7638 subjects, with 3818 subjects randomized to receive IDeg and 3820 subjects randomized to receive IGlar. As of the date of interim data cut-off on January 19, 2015, a total of 150 adjudicated first MACEs had been collected. By the time of interim data cut-off, the study withdrawal and treatment discontinuation rates were low and similar between IDeg and IGlar. Approximately 46% of the subjects had at least 6 months of follow-up, 21% had follow-up longer than 9 months, and only 5% of the randomized population had follow-up longer than one year. Treatment exposure was similar in both study arms; median exposure in both arms was 174 days.

The interim database of DEVOTE contained a total of 150 EAC-confirmed first MACEs observed during the study based on the intention-to-treat (ITT) population of all randomized subjects, corresponding to an incidence rate (IR) of (b) (4) per 100 patient years: (b) (4) MACEs were observed among 3818 subjects randomized to IDeg (b) (4) MACEs per 100 patient years) and (b) (4) events were observed among 3820 subjects randomized to IGlar (b) (4) MACEs per 100 patient years). The pre-specified Cox proportional hazards model based on the interim data estimated a hazard ratio (HR) of MACE associated with IDeg compared to IGlar of (b) (4) with a 95% confidence interval (CI) of (b) (4)**)**. The upper bound of the 95% confidence interval ruled out the risk margin of 1.8 set forth in the Complete Response Letter. No component of the primary MACE endpoint raised any statistical concerns, nor did any additional sensitivity analyses performed by the applicant or the FDA.

Table 1: Pre-specified Analysis of Primary MACE Endpoint (ITT, on-study)

	IDeg **N = 3818** **PY* = 1856.6**	**IGlar** **N = 3820** **PY* = 1852.6**
MACE (IR/100 PY)	(b) (4)	(b) (4)
HR $_{IDeg/IGlar}$ (95% CI)	(b) (4)	

*: PY = patient years of follow-up.
Source: Created by reviewer.

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1.2 Statistical Issues and Findings

The DEVOTE trial was a standalone, randomized, double-blinded, active-controlled cardiovascular outcomes trial, designed specifically to assess cardiovascular safety of insulin degludec. A total of 7638 randomized subjects were included in the ITT population. By the date of interim data cut-off, the trial was generally well-conducted and there were no significant statistical issues about trial design, conduct or analysis. The pre-specified primary safety endpoint in DEVOTE was time from randomization to first EAC-confirmed MACE. The upper bound of the 95% confidence interval for the hazard ratio estimate of MACE associated with IDeg relative to IGlar was (b) (4), thus it successfully ruled out a risk margin larger than 1.8. The CV safety of IGlar was evaluated in the ORIGIN study, where subjects with pre-diabetes and new onset T2DM were treated with IGlar versus standard of care. ORIGIN showed no difference in MACE observed between the treatment groups[1].

Analysis results of pre-specified sensitivity analyses using various on-treatment censoring schemes were consistent with that of the primary MACE analysis. The pre-specified sensitivity analysis including additional pending-adjudication CV events was supportive of the primary result. In addition, analyses of components of primary MACE, all-cause mortality and MACE+ (MACE plus unstable angina pectoris requiring hospitalization) showed no evidence of increased harm associated with IDeg. With no reason for statistical concern indicated in these analyses, it can be concluded that the analysis of MACE in DEVOTE met the 1.8 risk margin and the deficiency of the cardiovascular safety listed in the FDA Complete Response Letter was successfully addressed from a statistical perspective.

In conclusion, DEVOTE demonstrated that the cardiovascular safety of IDeg lies within acceptable bounds for marketing approval.

2 INTRODUCTION

2.1 Overview

Insulin degludec is an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. The proposed indication of IDeg is to improve glycemic control in adults with diabetes mellitus as a once daily, ultra-long-acting human insulin analog.

Insulin degludec/insulin aspart is composed of IDeg and insulin aspart, a rapid-acting human insulin analog. Insulin aspart (trade name: NovoLog) was approved by the Agency on June 7, 2000 under NDA 20-986. The proposed indication of this co-formulated product is to improve glycemic control in adults with diabetes mellitus with once or twice-daily dosing at any main meal.

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The original NDAs 203-314 (IDeg) and 203-313 (IDegAsp) were submitted to the Agency for review on September 29, 2011. During the review cycle of the original NDA applications, a potential adverse cardiovascular signal was observed in the IDeg/IDegAsp phase 3 development program, based upon a pre-specified statistical analysis plan for a meta-analysis to assess the CV risk associated with IDeg/IDegAsp. This was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. Of the 17 trials, 7 included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the SAP and agreed upon with the Agency prior to the NDA submission.

The primary meta-analysis was based upon MACE+, a composite endpoint, which consisted of four components: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina pectoris. Additionally, the Agency requested the applicant assess a strict MACE endpoint which excluded the unstable angina pectoris component from MACE+. A Cox proportional hazards model, stratified by trial, was the pre-specified primary analysis method to estimate the hazard ratio of IDeg/IDegAsp relative to the pooled comparators along with the corresponding 95% confidence interval. Table 2 depicts the primary analysis results as reported in the statistical review of the original NDA submission of IDeg/IDegAsp by Dr. Bo Li (dated 12/13/2012). Based upon the Cox model, the estimated HR for MACE+ was 1.30 with a corresponding 95% CI of (0.88, 1.93). The estimated HR for the strict MACE endpoint was 1.67 with a corresponding 95% CI of (1.01, 2.75). Both endpoints suggested an increase in CV risk of IDeg/IDegAsp relative to the pooled comparator arm while a consistent trend of the increase was observed in additional analyses.

Table 2: Primary Meta-analysis Results for Original NDA Submission (ITT, on-treatment + 7 days)

		IDeg/IDegAsp (*N* = 5794) [PYE* = 5153.6]	**Comparator** (*N* = 3461) [PYE* = 2562.7]
MACE+ Endpoint			
	Events [IR/1000PYE]	95 [18.4]	37 [14.4]
	HR (95% CI)†	1.30 (0.88, 1.93)	
MACE Endpoint			
	Events [IR/1000PYE]	70 [13.6]	21 [8.2]
	HR (95% CI)†	1.67 (1.01, 2.75)	

*: PYE = patient years of exposure.
†: Cox proportional hazards model stratified by trial.
Source: Page 32, statistical review of the original NDA 203-313/203-314, authored by Dr. Bo Li dated on 12/13/2012.

The 17 IDeg/IDeagAsp clinical trials included in the CV meta-analysis were designed to assess glycemic control of the agents in both Type 1 and Type 2 diabetes mellitus population. Multiple active comparators including insulin glargine, insulin detemir, biphasic insulin aspart, and sitagliptin, were used across the trials. Most trials were of relatively short duration with skewed

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randomization of 1:2 or 1:3, and the treated populations were T1DM and T2DM patients with a low to moderate risk for CV events, and the focus was on achieving equivalent glycemic control between arms in open-label setting. The overall discontinuation rate of study treatment was approximately 22%, varying across trials, and subjects were not followed up after treatment discontinuation. In summary, these phase 3 efficacy trials were designed to primarily assess glycemic control, rather than characterizing CV risk. The meta-analyses were conducted using heterogeneous efficacy trials which lacked the design attributes of a robust dedicated cardiovascular outcomes trial. To determine if the increase in CV risk as seen from the meta-analysis is real, further evidence from a dedicated CVOT would be needed.

Upon completion of the review, on February 8, 2013, the Agency issued a Complete Response Letter which outlined the cardiovascular safety deficiency and requested that the following be submitted to address the deficiency:

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

An End-of-Review Meeting was held between the Agency and the applicant on April 4, 2013 to determine a path forward for definitively assessing the cardiovascular risk of insulin degludec. In that meeting, and subsequent communications between the Agency and the applicant, the design elements for the degludec cardiovascular outcomes trial DEVOTE (EX1250-4080) were agreed upon, including the study population, primary endpoint, glycemic targets, and the conduct of an interim analysis after accrual of 150 first MACE events.

DEVOTE is a long-term, multi-center, multi-national, randomized, double-blind, parallel group, active-controlled, dedicated CVOT designed specifically to assess the cardiovascular safety of IDeg and to rule out or detect the CV signal identified from the meta-analyses of Phase 3 trials. The purpose of this CVOT is to evaluate the cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in subjects with type 2 diabetes mellitus at high CV risk.

DEVOTE, initiated on October 29, 2013 (first patient first visit), fully enrolled 7638 subjects on November 28, 2014 (last patient first visit), and is currently ongoing. A pre-planned interim analysis occurred when 150 adjudicated first MACEs had been accrued by January 19, 2015. The

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interim analysis was performed solely for regulatory purposes with no impact on the continuation of the trial (no early stopping). No changes to the trial design and trial conduct will be made based on the results of the interim analysis. The applicant established operational processes and procedures to preserve confidentiality and blinding of the trial and thereby ensure that the integrity of the ongoing trial is maintained after the interim analysis is conducted, submitted, and acted upon by the Agency. These processes were described in detail in a Data Access Management Plan (DAMP) developed by the applicant, which was shared with the Agency before the data base lock (DBL) of the interim analysis (refer to Section 3.2.1.2 for review/summary of this plan).

This review primarily focuses on the assessment of cardiovascular risk in the degludec cardiovascular outcomes trial DEVOTE based on its interim data to determine if the resubmissions, dated on March 26, 2015, have addressed the cardiovascular safety deficiency outlined in the Complete Response Letter.

2.2 Data Sources

The applicant submitted clinical study report and analysis datasets of DEVOTE (SN0049) separately from the submission of an integrated summary of safety (SN0047) to the same NDA (NDA 203-314). The Electronic Document Room (EDR) link to the study report of the DEVOTE trial is provided below:

\\cdsesub1\evsprod\nda203314\0049\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5351-stud-rep-contr\study-report-ex1250-4080\report-body.pdf

The analysis datasets of the DEVOTE trial utilized in this review for the assessment of CV safety are available at:

\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adsl.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adadj.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adae.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adex.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adtte.xpt

No statistical programs were provided with the initial NDA resubmission but were subsequently submitted in the 04/29/2015 response to an FDA information request (SN0051).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports in this submission were submitted electronically in support of NDAs 203-314/203-313. The format, content and documentation of the submitted data were adequate to conduct a statistical evaluation of the CV risk associated with insulin degludec. This review does

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not evaluate the efficacy of insulin degludec. For a statistical evaluation of efficacy results, please refer to the statistical review authored by Dr. Jiwei He.

3.2 Evaluation of Safety

This review is focused on the statistical analysis of cardiovascular risk based upon the interim data obtained from the DEVOTE study.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

DEVOTE is a Phase 3b study titled: "A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events." This study is a long-term, multi-center, multi-national, randomized, double-blinded, parallel group, active-controlled trial. The primary objective of DEVOTE is to demonstrate cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events.

The current resubmission is based on a pre-specified interim analysis of DEVOTE designed to show that the hazard ratio of MACE associated with IDeg relative to IGlar is no larger than 1.8. DEVOTE will continue until the full pre-specified number of 633 first MACEs are observed in the trial; at which time the hazard ratio of MACE will be tested against a risk margin of 1.3.

DEVOTE planned to randomize a total of 7,500 male and female subjects with T2DM at elevated risk for cardiovascular events based on the following two categories:

- Subjects aged ≥ 50 years with established CV diseases; and,
- Subjects aged ≥ 60 years with risk factors for CV diseases.

The number of randomized subjects aged 60 years or older with CV risk factors only was limited to 1,500 to secure a study population with sufficient overall cardiovascular risk. Subjects were randomized 1:1 in a double-blinded manner to receive one of the investigational products:

- insulin degludec, or
- insulin glargine.

A "treat-to-target" concept was applied targeting similar glycemic control for all subjects in both arms with titration aiming for an HbA1c < 7%.

This trial is event-driven and will continue until a planned number of 633 positively adjudicated first MACEs have been collected. The protocol pre-specified that an interim analysis would be conducted to assess the preliminary non-excessive risk of IDeg relative to IGlar for MACE with a risk margin of 1.8 after at least 150 first MACEs had been accrued. The trial design is shown schematically in Figure 1 below.

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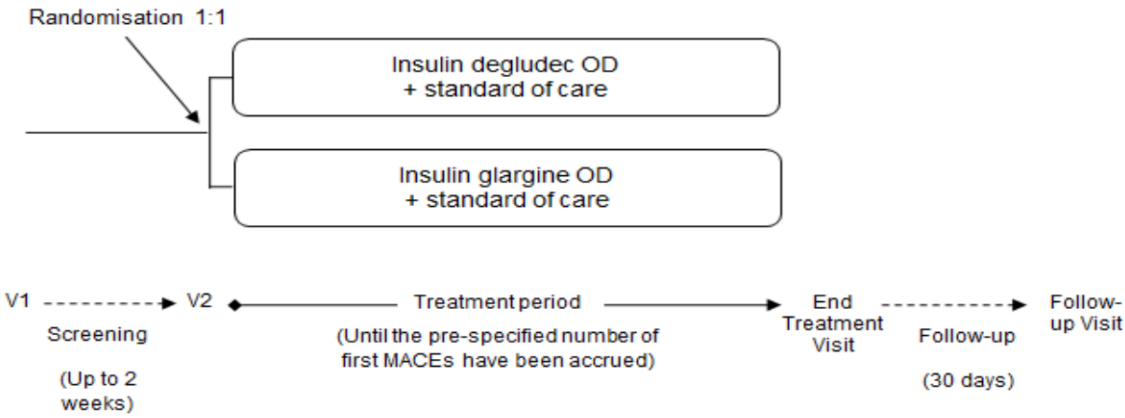
Figure 1: Flow Chart of DEVOTE Study Design



Source: Figure 9-1, page 30, CSR of DEVOTE. OD= once daily; V= visit.

The trial period consists of a screening period of up to 2 weeks, a randomization visit (V2) at which the subjects are randomized to IDeg or IGlar, an estimated treatment period of up to 59 months (depending on actual rate of MACE accrual) and a 30-day post-treatment follow-up period. For each subject, the maximum follow-up in the trial is estimated to be 60.5 months. Efforts will be made to follow all randomized subjects and collect outcome data for the complete duration of the trial. Subjects are scheduled to attend the study site once every month during the first 6 months and every third month during the rest of the trial, and to have monthly phone contacts with the investigator between the site visits. These visits and phone contacts will assess the occurrence of safety and efficacy outcomes, study medication compliance and accountability, and concomitant therapy or intervention.

Safety data collection in this large outcomes trial is limited to serious adverse events (SAEs), adverse events (AEs) associated with drug discontinuation, and episodes of severe hypoglycemia. Non-serious AEs and non-severe hypoglycemic episodes are systematically reported only in Japanese subjects as requested by the Japanese authorities. Adverse events of potential MACE, unstable angina pectoris (UAP) requiring hospitalization, deaths and episodes of severe hypoglycemia are adjudicated and evaluated by an external event adjudication committee based on predefined diagnostic criteria, in an independent and blinded manner. An EAC charter including event definitions, operational procedures and EAC membership was submitted to the Agency as part of the NDA resubmission package.

An external independent data monitoring committee (DMC) performs ongoing and independent evaluation of accumulated data from the trial. The DMC has access to semi-blinded (e.g., Group A, Group B; decode provided separately in a secured manner) and un-blinded data and makes recommendations to the applicant’s internal safety committee on whether to continue, modify or

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terminate the trial. The DMC charter and DMC meeting minutes from all closed and open DMC sessions were submitted to the Agency as part of the NDA application package.

3.2.1.2 Interim Analysis and Data Unblinding

DEVOTE is an event-driven CVOT. Its sample size is based on a log-rank test showing that a total of 633 EAC-confirmed first MACEs will provide 91% power to rule out hazard ratios exceeding 1.3, assuming a true hazard ratio of 1.0 and an overall 1-sided 2.5% confidence level.

Under the assumption of a true hazard ratio of 1.0, a total of 150 EAC-confirmed first MACEs will provide 95% power to rule out hazard ratios exceeding 1.8. The study protocol pre-specified a single interim analysis to be conducted when at least 150 adjudicated first MACEs have been collected, to assess the preliminary non-excessive risk margin of 1.8 for the regulatory approval of the investigational products IDeg and IDegAsp. The interim analysis is performed solely for regulatory purposes. No changes to the study design, study conduct or to the statistical analyses for the final data will be made based on the results of the interim analysis.

The pre-defined number of 150 adjudicated first MACEs was achieved on January 19, 2015, at which time an interim data cut-off was made. The trial subject recruitment was completed prior to the data cut-off for the interim analysis with a date of first patient first visit (FPFV) of October 29, 2013 and a date of last patient first visit (LPFV) of November 28, 2014. All EAC-confirmed first MACEs captured in the database as of January 19, 2015 and loaded into the database as of January 21, 2015 (date of database lock) were included in the primary analysis. This statistical review will focus on the interim data and interim analyses of DEVOTE included in the NDA resubmission package.

Operational processes executed in connection with the interim analysis of an ongoing CVOT should be prospectively established and agreed upon in order to preserve the confidentiality, integrity, and blinding of the trial after the interim analysis is conducted, submitted, and acted upon by regulatory authorities. A data access management plan which defines such operational processes/procedures is regarded as a critical component of the interim analysis planning. The applicant prepared and finalized their DAMP (dated 11/05/2014) prior to the interim database lock of the DEVOTE trial and submitted it to the Agency with a DAMP addendum (dated 03/16/2015) as part of the resubmission. This document described who, following DBL of the interim data, will gain access to unblinded data or unblinded output/results, at which level and for what purposes in order to support the resubmission of the NDAs. The DAMP covers employees internally at Novo Nordisk and individuals external to Novo Nordisk such as the independent external statisticians a [redacted] (b) (4)) as well as members of the DEVOTE Steering Committee (StC) and refers to the relations to the Data Monitoring Committee. Furthermore, the document defines the rules of conduct and the responsibilities of the internal unblinded team at Novo Nordisk denoted as the 'Interim DEVOTE Reporting Team'

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(IDRT) and describes the restriction established to prevent inadvertent communication of the interim results. The DAMP Addendum outlines the role of (b) (4) and any named external advisors/consultants. A brief summary of the DAMP is given below:

- The IDRT has been granted authority to make the decision whether to file or not to file the NDAs based on the interim analysis, and to agree with the Agency whether the interim results fulfill the deficiencies outlined in the Complete Response Letter. Further, the IDRT is responsible for preparing the unblinded sections of the clinical study report (CSR) of the DEVOTE trial and for answering questions posed by the Agency related to the interim analysis including requests for additional data or analysis.
- To avoid unblinding of the results and to protect the integrity of the ongoing trial, none of the results or conclusions made based on unblinded interim data will be communicated publically, unless a critical safety concern is identified.
- Once unblinded, members of the IDRT will no longer report into the part of the Novo Nordisk project organization working with trials in the Degludec portfolio, nor will they participate in operational or strategic activities or decision making related to the conduct of the DEVOTE trial until DBL for the completed trial.
- In addition to the IDRT, the statistical contractor, (b) (4) the regulatory consultancy company, (b) (4) and a limited number of named external advisors/consultants will be unblinded to the results of the DEVOTE interim analysis in order to assist in the interpretation of the data, provide input to the regulatory strategy, review submission documents, and participate in activities related to a potential Advisory Committee meeting.
- A Secure IT system in Novo Nordisk was to be created to provide a secure and confidential computing environment in order to handle and store the unblinded data/results from the DEVOTE interim analysis

Reviewer's Comments: *The DAMP was shared with the Agency and was considered acceptable. According to the DAMP, all data related to the interim cardiovascular evaluation including both the adjudicated CV data and adverse events data should remain blinded, except for those instances specified in the DAMP.*

3.2.1.3 Endpoints

Per the statistical analysis plan of the interim analysis, the pre-specified primary endpoint is the time from randomization to first EAC-confirmed occurrence of a 3-component MACE: CV death (including unknown cause of death), non-fatal MI, or non-fatal stroke.

The SAP lists the following as secondary safety endpoints:

- Time from randomization to all-cause deaths
- Number of serious adverse events (SAEs)

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- Number of positively adjudicated severe hypoglycemia
- Number of positively adjudicated unstable angina pectoris requiring hospitalization
- Number of adverse events (AEs) leading to discontinuation of investigational product
- Number of medication errors leading to SAEs
- Number of technical complaints related to AEs

Reviewer's Comments: *This review will focus on the assessment of MACE. The adjudicated events of UAP requiring hospitalization will be incorporated into the assessment of a post-hoc endpoint MACE+ by the reviewer. In addition, the evaluation of all-cause deaths is considered relevant to the characterization of safety for IDeg.*

3.2.2 Statistical Methodologies

The statistical analysis plan (dated 10/09/2014), included in the NDAs resubmission of IDeg/IDegAsp, documented the pre-specified statistical methods to be used for the interim analysis. Statistical methodologies used by the applicant and additional analyses performed by the statistical reviewer are discussed below.

Reviewer's Note: *An earlier version of the SAP dated 04/24/2014 was shared with the Agency. The proposed statistical methods were generally agreed upon by the Agency, except for alternative censoring schemes of "on-treatment analysis" for which the Agency provided a written response. The subsequent amendment of the SAP for the interim analysis (dated 10/09/2014) was included in the NDA resubmission. The pre-specified statistical methods discussed in the following sections are based on the interim SAP dated 10/09/2014.*

3.2.2.1 Hypothesis Testing

The following hypothesis was pre-specified to compare the hazard of MACE in IDeg relative to IGlar at the interim analysis when at least 150 EAC-confirmed first MACEs had been accrued:

H_0: HR $\geq$ 1.8; vs. H_a: HR < 1.8.

Since the interim analysis was designed to test a separate hypothesis than the final evaluation of the study (to rule out a hazard ratio of 1.3), and since the findings of the interim analysis have no impact on the study design, conduct or analyses of the final data, no adjustment of the alpha level for the statistical test at the interim analysis is considered necessary. If the upper bound of the 95% confidence interval of the hazard ratio estimate is below 1.8, preliminary non-excessive CV risk of IDeg compared to IGlar will be considered confirmed.

3.2.2.2 Analysis Methods

3.2.2.2.1 Analysis Populations and Event Ascertainment

As pre-specified in the SAP, the interim analysis will be based on the full analysis set (FAS) which consists of all randomized subjects. The statistical evaluation of the FAS will follow the

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intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomized" regardless of their adherence to randomized treatment. Observation time for the FAS was defined as the time period from the date of randomization to the date of the last direct contact. All analyses reported in this review were based on the FAS unless specified otherwise.

For the primary analysis of MACE, an "on-study" censoring scheme is utilized for event ascertainment:

- EAC-confirmed first MACE events observed during the course of the study before the date of interim data cut-off are captured and included in the analysis;
- Subjects without EAC-confirmed MACE are censored at their last direct contact before the interim DBL.

As pre-specified in the study protocol, subjects may discontinue their treatment with trial products at the discretion of the investigator. The discontinuation could be either temporary or permanent and will not lead to subject withdrawal from the study. Subjects with a temporary treatment pause may resume treatment at the discretion of the investigator. In order to evaluate the robustness of the primary analysis to alternative censoring schemes, four "on-treatment" sensitivity analyses were conducted by the applicant considering a temporary treatment pause between two treatment periods as "off-treatment" :

- "on-treatment": The first EAC-confirmed MACE occurring during a treatment period for each subject was captured as an event, irrespective of whether the subject in question had experienced an earlier MACE during any off-treatment period. For subjects who did not experience MACE during a treatment period, two censoring strategies were used:
  - Not counting any off-treatment MACE (Sensitivity analysis #1, **SA1**): subjects are censored at the date of latest treatment discontinuation, or last direct contact, or DBL, whichever occurs first.
  - Counting off-treatment MACE (Sensitivity analysis #2, **SA2**): subjects are censored at the date of first off-treatment MACE, latest treatment discontinuation, or last direct contact, or DBL, whichever occurs first.
- "on-treatment +30 days": The first EAC-confirmed MACE occurring during a treatment period + 30 days for each subject was captured as an event, irrespective of whether the subject in question had experienced an earlier MACE during any off-treatment period. For subjects who did not experience MACE during an on-treatment + 30 days period , two censoring strategies were used:
  - Not counting any MACE that occurred 30 days or more after the beginning of off-treatment periods (Sensitivity analysis #3, **SA3**): subjects are censored at the date of latest treatment discontinuation + 30 days, or last direct contact, or DBL, whichever occurs first.

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- Counting MACE that occurred 30 days or more after the beginning of off-treatment periods (Sensitivity analysis #4, **SA4**): subjects are censored at the date of first off-treatment MACE that occurred 30 days or more after the beginning of an off-treatment period, latest treatment discontinuation + 30 days, or last direct contact, or DBL, whichever occurs first.

Reviewer's Comments: *A typical "on-treatment" censoring scheme is slightly different from what the applicants utilized, regarding the intermittent off-treatment pause between two treatment periods. The typical "on-treatment" period refers to the time from the first dose of study drug to the last dose of study drug before the end of a trial (or before the DBL for an interim analysis); the intermittent off-treatment pauses are not considered. We conducted the following post-hoc sensitivity analyses based on this different definition of "on-treatment" period:*

- *Sensitivity analysis #5 (**SA5**): An on-treatment analysis that captures first MACE events that occurred while the subject was on the study treatment (first dose date to last dose date before DBL).*
- *Sensitivity analysis #6 (**SA6**):An on-treatment + 7 days analysis that captures first MACE events that occurred while the subject was on the study treatment or within 7 days after the latest treatment discontinuation (first dose date to last dose date + 7 days before DBL).*
- *Sensitivity analysis #7 (**SA7**):An on-treatment + 30 days analysis that captures first MACE events that occurred while the subject was on the study treatment or within 30 days after the latest treatment discontinuation (first dose date to last dose date + 30 days before DBL).*

These on-treatment sensitivity analyses conducted by the reviewer excluded 29 subjects who had never been exposed to study treatment before the interim DBL. The results from these analyses will be discussed in Section 3.2.4.1.

In addition, a pre-specified sensitivity analysis (Sensitivity analysis #8, **SA8**) was performed by counting all EAC-confirmed MACEs included in the primary analysis, plus all potential first events (either a fatal event, acute coronary syndrome or cerebrovascular event) qualified for adjudication at the date of interim DBL but lacking an adjudication outcome, i.e., events pending in the adjudication pipeline.

3.2.2.2.2 Analysis Methods for Primary MACE Endpoint

The primary analysis is based upon time-to-event methods for MACE. If a subject experienced multiple events of interest, only the first event will be included in the analysis. The agreed upon primary analysis method for MACE was a Cox proportional hazards regression model with a fixed effect for treatment to estimate the hazard ratio, and corresponding two-sided 95%

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confidence interval, of IDeg versus IGlar, based on first MACEs occurred during the study in the FAS population. This analysis was not adjusted for covariates.

Sensitivity analyses for MACE using various censoring schemes conducted by the applicant (SA1 – SA4) used the same Cox model as the one used in the primary analysis. The same model was also adopted for the analysis SA8 which includes all pending adjudication first events.

Reviewer's Comments: *The sensitivity analyses SA5, SA6 and SA7 were conducted by the reviewer using the same Cox regression model as the primary analysis for the time-to-event data.*

Reviewer's Comments: *To further investigate the sensitivity of the primary analysis on MACE, the reviewer conducted similar time-to-event analyses of the individual components of MACE: CV death, non-fatal MI and non-fatal stroke, based on an on-study censoring in FAS for each individual component.*

3.2.2.2.3 Analysis Methods for Secondary Endpoints

This review considered the secondary endpoint of all-cause death. In addition, the reviewer assessed a post-hoc, not pre-specified supportive endpoint MACE+, which is defined as a four-component composite of CV death, non-fatal MI, non-fatal stroke and hospitalization for UAP. The applicant submitted a Kaplan Meier plot of all-cause death by treatment group (IDeg and IGlar).

Reviewer's Comments: *The reviewer used the same Cox regression model with treatment as a single fixed effect factor to perform the time-to-event analysis for all-cause mortality based on the ITT population FAS with an on-study censoring scheme. The reviewer used a similar Cox model to conduct analyses of MACE+.*

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The date of first patient first visit was October 29, 2013 and the date of last patient first visit was November 28, 2014. At the time of data cut-off for the interim analysis (01/19/2015), the trial had completed its full enrollment. Overall, 8203 subjects were screened for DEVOTE. Among these, 7638 subjects were randomized 1:1 to receive IDeg (3818 subjects) or IGlar (3820 subjects); they comprise the FAS population which was used for all analyses of cardiovascular endpoints presented in this review. A total of 29 subjects had not been exposed to trial products at the time of cut-off for the interim analysis. In total, 3807 subjects were exposed to IDeg and 3802 subjects were exposed to IGlar.

Following finalization of the SAP for the interim analysis and prior to DBL for the interim data, the applicant identified a total of 6 subjects which had been randomized at 2 different trial sites and thus had 2 subject IDs. Then a decision was taken to withdraw the subjects at site 2 and continue at site 1. These subjects were only counted as one subject in the statistical analyses. To be consistent with the ITT principle, data recorded at the first site (i.e., first randomized subject

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ID) was used in data presentations and analyses. Four subjects were included in the IDeg group, of these, 3 subjects were also randomized to IDeg at the second site and one subject was randomized to IGlar at the second site. Two of the 6 subjects were included in the IGlar treatment group; both had been randomized to IDeg at the second site. As per cut-off for the interim analysis, none of the 6 subjects had EAC-confirmed MACE.

The trial population of DEVOTE, which enrolled T2DM patients enriched for higher CV risk, consists of subjects with existing, or high risk of CV disease. Approximately 14.6% of the population (1114 subjects) was enrolled based solely on risk factors for CV disease, fulfilling the pre-defined criteria of a maximum of 1,500 subjects in this group in order to secure a study population with sufficiently high overall CV risk to accrue 633 first MACEs in a timely manner.

Based on Table 3, the IDeg and IGlar treatment arms were well-balanced with regard to baseline demographics and disease characteristics, as would be expected for a trial of such a size. In the FAS population, there were more male subjects than female subjects (63% versus 37%). Approximately 76% of subjects were White, 11% were Black, 10% were Asian and 3% belong to other race categories. Nearly 70% of the total population were recruited from sites in the U.S. Approximately 15% of the subjects in the FAS population were Hispanic or of Latino ethnicity.

Approximately half of the subjects in the FAS were between 60 and 69 years of age, with a mean age of 65 years. The average body mass index (BMI) was 33.6 kg/m^2. The mean duration of T2DM at baseline was 16 years. For the interim analysis, baseline HbA1c was reported only for the combined population. A majority of subjects (83%) had inadequate glycemic control as reflected by a baseline HbA1c $\geq$ 7.0 despite the use of multiple anti-hyperglycemic agents. The mean baseline HbA1c for the FAS population was 8.4%. Approximately 16% of subjects were insulin-naïve at baseline, equally distributed between IDeg and IGlar.

Overall, about 85% of the FAS population had established cardiovascular disease prior to randomization. More than 90% of the FAS subjects received anti-hypertensive therapy at baseline. The majority of the subjects were non-smokers: 45% had never smoked and 44% were previous smokers, while only 11% were current smokers at baseline.

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Table 3: Demographics and Baseline Characteristics (FAS)

	IDeg (N = 3818)	**IGlar (N = 3820)**
Age ± SD **(years)**	65 ± 7.3	65 ± 7.5
< 60	22.4%	23.1%
60-69	50.9%	50.3%
>= 70	26.7%	26.6%
Female	37.2%	37.6%
Race		
White	76.1%	75.2%
Black	10.5%	11.3%
Asian	10.2%	10.1%
Other	3.1%	3.4%
Region		
North America	68.8%	69.3%
Europe	11.5%	11.4%
Asia	7.4%	7.8%
Rest of world	12.4%	11.5%
BMI ± SD (kg/m²)	33.6 ± 6.9	33.6 ± 6.9
Duration of T2DM ± SD (yrs)	16.2 ± 8.8	15.8 ± 8.9
Prior CV disease	85.5%	84.9%
CV risk factor only (Age >= 60)	14.3%	14.9%
Current smoker	11.3%	11.0%
Baseline Antihypertensive	93.6%	93.5%
Insulin naïve	15.9%	16.2%
HbA1c ± SD (%) *	8.4 ± 1.6	

*: Baseline HbA1c was blinded.
Source: Created by reviewer.

Table 4 shows subject disposition for the ITT population (FAS). Of the 7638 randomized subjects, 7609 (99.6%) have been exposed to the study medications. Overall, the study withdrawal and treatment discontinuation rates were low and similar in both IDeg and IGlar groups. At the time of cut-off for the interim analysis, 95.7% of subjects (3655) on IDeg and 94.7% of subjects (3618) on IGlar were on study treatment. At the time of DBL, a total of 252 subjects were on treatment pause either permanently or temporarily, with similar percentages of treatment discontinuation between the two arms (3.0% vs. 3.6%). Nine randomized subjects had withdrawn from the trial, of these, one agreed to be contacted when the trial completes. Note that this number does not include discontinuation of treatment due to fatal events. In total, (b) (4) randomized subjects had died by the time of DBL for the interim analysis, (b) (4) having occurred in the IGlar group: (b) (4) deaths for IDeg arm and (b) (4) deaths for IGlar arm.

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In FAS, the follow-up period for primary MACE was defined as the time period from the date of randomization to the date of first EAC-confirmed MACE or the date of last direct contact, whichever occurred first. At the cut-off date for the interim analysis, the total patient-years of follow-up were 3709 years, corresponding to a mean length of approximately 6 months of follow-up per subject. The total patient-years of exposure to treatment at the interim were 3654 years excluding all periods of treatment pauses. Both the follow-up and exposure time were distributed evenly between the two comparison groups.

Table 4: Subject Disposition (FAS)

Disposition	IDeg	IGlar
All randomized (FAS)	**3818 (100%)**	**3820 (100%)**
Exposed	3807 (99.7%)	3802 (99.5%)
At interim DBL		
On treatment	3655 (95.7%)	3618 (94.7%)
Treatment paused	116 (3.0%)	136 (3.6%)
Deaths		(b) (4)
Study withdrawn	6 (0.2%)	3 (0.1%)
Total years of follow-up at interim*	**1856.6**	**1852.6**
Total years of exposure	**1839.6**	**1832.9**
Total years of exposure (excluding treatment pauses) **	**1830.8**	**1823.2**

*: For each subject, follow-up time is calculated as the time from randomization to first MACE, or last direct contact before DBL of interim data, whichever came first. The numbers are smaller than those reported in Table 10-1 on Page 84 of the DEVOTE CSR because the applicant used the entire follow-up period until the date of last direct contact for subjects who experienced a MACE during the study before DBL.
**: The numbers are slightly different from those reported in Table 10-1 on Page 84 of the DEVOTE CSR. The reviewer identified 12 subjects with incorrect calculation by the applicant for their treatment exposure.
Source: Created by reviewer.

Information on length of subject follow-up in the study for the primary MACE endpoint before DBL is presented in Table 5 and Figure 2 below. Table 5 shows that the mean and median follow-up was similar in both treatment arms. Approximately 46% of the subjects had at least 6 months of follow-up, 21% had follow-up longer than 9 months, and only 5% of the FAS population had follow-up longer than one year. As such, the interim data of DEVOTE provides limited information on the cardiovascular risk beyond 9 months of follow-up and almost no information beyond one year of follow-up. Figure 2 shows the distribution of the time of follow-up until either first MACE or the date of last direct contact before interim data cut-off for both treatment arms of DEVOTE. Graphically, the distribution of follow-up time appears similar between the two arms.

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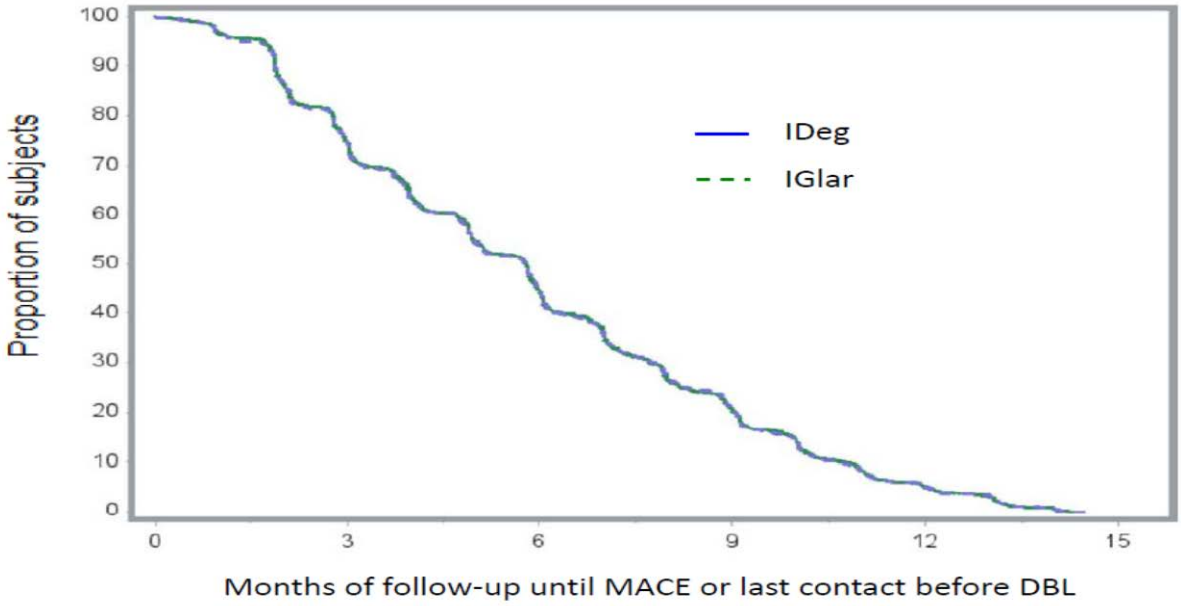
Table 5: Subject Follow-up until First MACE or Last Direct Contact (FAS)

	IDeg (N=3818)	IGlar (N=3820)
Days of follow-up		
Mean (SD)	177.6 (99.7)	177.1 (100.0)
Median	175	175
Min, Max	1, 430	1, 435
% Subjects with follow-up		
≥ 3 months	75.8%	75.6%
≥ 6 months	45.6%	45.7%
≥ 9 months	21.1%	21.4%
≥ 12 months	5.2%	5.1%

Source: Created by the reviewer.

Figure 2: Study Follow-up for Primary MACE (FAS)



Source: Created by reviewer.

Summary statistics in Table 6 below show treatment exposure for the subset of FAS who had been exposed to the study treatment before the data cut-off date for interim analysis (3807 subjects in IDeg arm and 3802 subjects in IGlar arm, see Table 4). The median treatment exposure time was 174 days for both treatment groups. Overall, the distribution of treatment exposure time was similar across both arms either including all intermittent treatment pauses or excluding the pauses.

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Table 6: Statistics on Days of Exposure in Subjects Exposed to Study Medication

	IDeg (N=3807)	IGlar (N=3802)
Days of exposure		
Mean (SD)	176.5 (99.7)	176.1 (99.8)
Median	174	174
Min, Max	1, 430	1, 434
Days of exposure (excluding treatment pauses)		
Mean (SD)	175.7 (99.4)	175.2 (99.5)
Median	173	172
Min, Max	1, 430	1, 434

Source: Created by reviewer.

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoint MACE

As described in Section 3.2.1.3, the agreed upon primary endpoint was MACE: a composite endpoint of CV death (including death of unknown cause), non-fatal MI and non-fatal stroke.

The statistical evaluation of the FAS follows the ITT principle, where subjects contribute to the analyses "as randomized". Subjects in the FAS were followed to capture MACE events that occurred from the date of randomization to the date of last direct contact (on-site visit or phone contact with subject) before the cut-off date of interim data. A total of (b) (4) EAC-confirmed MACEs (of which not all events were first events) had been observed at the data cut-off date for the interim analysis. Of these, a total of 150 adjudicated first MACEs have been identified for the interim analysis, corresponding to an aggregate event rate of (b) (4)/100 patient years. Table 7 shows the classification of the first MACE events by treatment: (b) (4) out of 3818 subjects randomized to IDeg ((b) (4)%) and (b) (4) out of 3820 randomized to IGlar ((b) (4)%) experienced MACE during the trial through the cut-off date of interim data. The incidence rate of first MACE was (b) (4) treatment arms: (b) (4) MACEs per 100 PY on IDeg vs. (b) (4) MACEs per 100 PY on IGlar. Among the 150 first MACE events, a total of (b) (4) first events were adjudicated as CV death (including death with unknown/undetermined cause), non-fatal MI, and non-fatal stroke, respectively. The number of subjects who experienced CV death and non-fatal stroke as their first MACE were (b) (4) treatment arms. (b) (4) subjects randomized to IGlar than IDeg (b) (4)) experienced non-fatal MI as their first MACE.

Table 7: Classification of First MACE by Treatment (FAS, on-study)

	IDeg (N=3818) PY = 1856.6	IGlar (N=3820) PY = 1852.6
MACE	(b) (4)	
CV Death (unknown cause)		
Non-fatal MI		
Non-fatal stroke		

Source: Created by reviewer.

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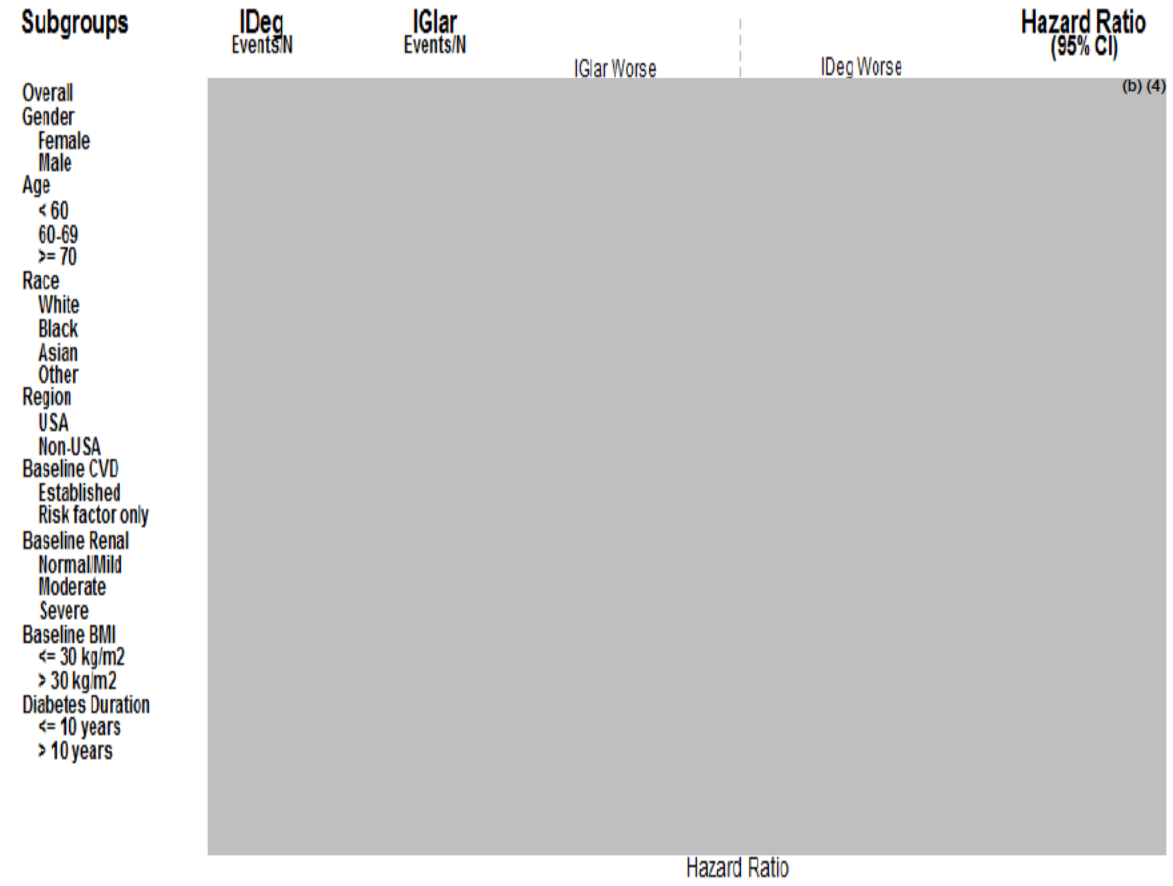
Summary of Subgroup Analyses

A forest plot of the hazard ratio and corresponding 95% confidence interval is provided in Figure 5 below as a summary of the findings in subgroup analyses discussed in Section 4.1 and Section 4.2.

Figure 5: Forest Plot of Hazard Ratios for MACE by Baseline Subgroups (FAS, on-study)



Source: Created by reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the review cycle of the original NDAs submission of IDeg and IDegAsp, a potential signal of excess cardiovascular risk associated with IDeg/IDegAsp relative to pooled comparators was observed in a pre-specified cardiovascular meta-analysis of Phase III efficacy clinical trials in the IDeg/IDegAsp clinical development program (refer to Section 2.1 for the

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regulatory history). As specified by the Agency in the Complete Response Letter, further evidence from a dedicated CV outcomes trial was required to better characterize the CV safety of IDeg/IDegAsp as a condition of approval. Therefore, DEVOTE, a dedicated CVOT was designed specifically to assess the CV safety of IDeg and to rule out or detect the CV signal generated from the phase 3 meta-analysis. The design, conduct and analyses of DEVOTE were agreed upon with the Agency.

DEVOTE is a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled trial with a primary objective to confirm cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events. The CV safety of IGlar was evaluated in the ORIGIN study, where subjects with pre-diabetes and new onset T2DM were treated with IGlar versus standard of care. ORIGIN showed no difference in MACE observed between the treatment groups. In DEVOTE, to overcome issues inherent in open-label trials, IDeg and IGlar was supplied and administered using indistinguishable vials and syringes to allow a double-blind design of the CVOT. DEVOTE is an event-driven trial designed and powered to evaluate the CV risk associated with the use of IDeg, relative to IGlar. A pre-specified interim analysis of DEVOTE was planned to show that the hazard ratio of MACE associated with IDeg relative to IGlar is no larger than 1.8. As planned, DEVOTE will continue until the full pre-specified number of 633 first MACEs are observed in the trial; at which time the hazard ratio of MACE will be tested against a risk margin of 1.3.

DEVOTE was initiated on October 29, 2013 (FPFV) and was fully enrolled with 7638 subjects on November 28, 2014 (LPFV), which occurred before the date of database lock for the pre-planned interim analysis when 150 first MACE events were achieved on January 19, 2015. By the time of the interim data cut-off, the disposition of subjects suggested that DEVOTE was well-conducted: a total of 9 subjects had withdrawn from the study, (b) (4) subjects had died, and 98.5% of randomized subjects remained in the trial for primary CV events follow-up. The maximum observed length of subject follow-up time was 14.5 months with a median of approximately 6 months. Approximately 46% of the subjects had at least 6 months of follow-up for the primary MACE endpoint and 21% had follow-up longer than 9 months.

The primary endpoint of DEVOTE was time from randomization to first adjudicated MACE (CV death/death with unknown cause, non-fatal MI and non-fatal stroke). The pre-specified primary analysis was based upon a Cox proportional hazards model including treatment (IDeg vs. IGlar) as a fixed effect factor for the ITT population that included all events observed during the study (on-study censoring) before the interim data cut-off date (i.e. this analysis was based on all randomized subjects including all events that occurred either on or off treatment). The primary objective of this analysis was to demonstrate that the upper bound of the 95% confidence interval for the hazard ratio of MACE associated with IDeg compared to IGlar was smaller than the risk margin of 1.8 with a reassuring point estimate of the hazard ratio, as specified in the CRL issued

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on February 8, 2013. There are no statistical concerns on the design, conduct, and pre-specified analysis of the primary endpoint. In order to assess the robustness of the primary analysis, additional sensitivity analyses of MACE were requested that account for event ascertainment relative to treatment exposure (on-treatment censoring). These analyses censored subjects at a fixed window of time after treatment discontinuation thereby including only events that occurred within this fixed observation window (on-treatment, on-treatment + 30 days). The reviewer conducted time-to-event analysis utilizing a different definition of "on-treatment" censoring scheme from that used by the applicant, with various ascertainment windows (on-treatment, on-treatment + 7 days, on-treatment + 30 days).

The reviewer also performed time-to-event analysis for each component of primary MACE, for all-cause mortality, as well as for a post-hoc MACE+ endpoint comprising 4-components: CV death/deaths with unknown cause, non-fatal MI, non-fatal stroke and unstable angina pectoris requiring hospitalization. In addition, to study the effect of the events pending adjudication at interim, the applicant conducted a pre-specified sensitivity analysis which counted all EAC-confirmed MACEs included in the primary analysis, plus all potential first CV events pending in the adjudication pipeline. These sensitivity analyses were conducted using the same Cox regression model as that for the primary analysis based on on-study censoring for all randomized subjects. More details of the statistical methodologies used in this review are provided in Section 3.2.2.

5.2 Collective Evidence

A total of 3818 subjects were randomized to IDeg and 3820 subjects were randomized to IGlar in DEVOTE. As of the interim data cut-off date on January 19, 2015, the study withdrawal and treatment discontinuation rates were low and similar between IDeg and IGlar. A total of 150 EAC-confirmed first MACEs had been collected by data cut-off for the interim analysis, corresponding to an aggregate MACE event rate of (b) (4)/100 patient years. (b) (4)MACEs were observed among 3818 subjects randomized to IDeg (b) (4) MACEs per 100 patient years) and (b) (4) events observed among 3820 subjects randomized to IGlar (b) (4) MACEs per 100 patient years).

As shown in Table 23 below, the estimated hazard ratio of IDeg compared to IGlar was (b) (4) with a 95% CI of ((b) (4)) for MACE based on the pre-specified Cox proportional hazards model. The upper bound of the 95% confidence interval met the risk margin of 1.8 specified in the Complete Response Letter. Sensitivity analyses using various on-treatment censoring schemes, sensitivity analysis including additional CV events pending adjudication, and post-hoc time-to-event analyses of components of primary MACE, all-cause mortality and MACE+ are all supportive of this conclusion. Detailed analysis results were provided in Section 3.2.4.1 and 3.2.4.2.

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Table 23: Pre-specified Primary Analysis Results of MACE (ITT, on-study)

	IDeg N = 3818 PY = 1856 6	IGlar N = 3820 PY = 1852 6
MACE (IR/100 PY)	(b) (4)	
$HR_{IDeg/IGlar}$ (95% CI)		

Source: Created by reviewer.

5.3 Conclusions and Recommendations

A signal of cardiovascular risk associated with IDeg/IDegAsp was observed during the FDA review of the initial NDA submissions of IDeg (203-314) and IDegAsp (203-313), based upon a pre-specified meta-analysis of MACE+ observed in 17 efficacy clinical trials from the phase 3 development program of IDeg/IDegAsp. Due to the inherent deficiencies associated with a meta-analysis of open-label efficacy trials, the CV signal was considered uncertain which warranted a further trial designed specifically for the evaluation of cardiovascular risk. On February 8, 2013, FDA issued a Complete Response Letter to the applicant which outlined the cardiovascular safety deficiency and requested additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial to be submitted to address the deficiency. As such, DEVOTE was designed and initiated as a dedicated CVOT to provide definitive evidence of the CV safety profile of IDeg. The design and analysis of the DEVOTE trial was agreed upon with the Agency with incorporation of specific design elements to overcome deficiencies of the meta-analysis.

Based on a planned interim analysis of 150 first adjudicated MACE (3-component: cardiovascular death/deaths with unknown cause, non-fatal myocardial infarction, or non-fatal stroke), the pre-specified Cox proportional hazards model obtained an estimated hazard ratio of (b) (4) with associated 95% confidence interval of (b) (4) The upper bound of this 95% confidence interval was below 1.8 and therefore met the pre-approval hazard ratio risk margin specified in the Complete Response Letter. Pre-specified sensitivity analyses considering alternative event censoring schemes and pending adjudication events at interim were supportive of the primary analysis result. Post-hoc analyses of components of primary MACE, all-cause mortality and MACE+ obtained consistent results with that of the primary analysis and showed no evidence of increased harm associated with IDeg compared to IGlar.

The interim data of DEVOTE provided only 24% of the total anticipated primary events in the trial with limited length of follow-up and drug exposure. The final confirmation of the CV safety of IDeg versus IGlar in terms of excluding the risk margin of 1.3 will be evaluated when at least 633 first MACE events have been accrued in DEVOTE. In order to preserve the confidentiality, integrity, and blinding of the ongoing DEVOTE trial after the interim analysis is conducted, submitted, and acted upon by regulatory authorities, operational processes/procedures executed in connection with the interim analysis were prospectively established and agreed upon. The data

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integrity and reliability of DEVOTE at the final analysis depends on how strict these processes and procedures described in the DAMP are executed and are subject to the Agency's continuing inspection.

In conclusion, the interim results from the DEVOTE trial addressed the deficiencies related to cardiovascular safety of insulin degludec for approval, outlined in the FDA Complete Response Letter dated on 02/08/2013.

6 REFERENCES

1. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, Maggioni AP, Pogue J, Probstfield J, Ramachandran A, Riddle MC, Rydén LE, Yusuf S. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012 Jul 26;367(4):319-28

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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 AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-314, NDA 203-313
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250)
	Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted: March 26, 2015
	Goal Date: September 26, 2015
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D.
Concurring Reviewers:	Eugenio Andraca-Carrera, Ph.D.
	Mat Soukup, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
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Project Manager:	Callie CappelLynch, M.S. (DMEP)

Keywords: diabetes mellitus, cardiovascular safety, cardiovascular outcomes trial, major adverse cardiovascular event (MACE)

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1 EXECUTIVE SUMMARY

During the review cycle of the original submissions of NDA 203-314 (insulin degludec, IDeg) and NDA 203-313 (insulin degludec/insulin aspart, IDegAsp) submitted to the Agency on September 29, 2011, a potential adverse cardiovascular (CV) signal was observed in the IDeg/IDegAsp phase 3 development program, based upon a pre-specified meta-analysis to assess the CV risk associated with IDeg/IDegAsp. This was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. Of the 17 trials, 7 included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the statistical analysis plan (SAP). The meta-analysis results suggested an increase in CV risk of IDeg/IDegAsp relative to the pooled comparator arm, using both the pre-specified primary major adverse cardiovascular event (MACE+: composite of CV death, myocardial infarction, stroke and unstable angina pectoris) and a strict MACE endpoint which excluded the unstable angina component from MACE+.

These 17 phase 3 efficacy trials were designed to primarily assess glycemic control, rather than characterizing CV risk. Due to the inherent deficiencies associated with a meta-analysis of open-label efficacy trials, the CV signal was considered uncertain which warranted a further trial designed specifically for the evaluation of cardiovascular risk. On February 8, 2013, the FDA issued a Complete Response Letter (CRL) to the applicant (Novo Nordisk), which outlined the cardiovascular safety deficiency of insulin degludec and requested additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial (CVOT) to be submitted to address the deficiency. As such, DEVOTE was designed and initiated as a dedicated cardiovascular outcomes trial to provide further definitive evidence of the CV safety profile of insulin degludec. The design and analysis of the DEVOTE trial was agreed upon with the Agency with incorporation of specific design elements to overcome deficiencies of the meta-analysis of open-label efficacy trials.

DEVOTE is a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled, event-driven trial which was designed and powered with a primary objective to confirm cardiovascular safety of insulin degludec compared to that of insulin glargine (IGlar) when added to standard of care in male and female subjects with type 2 diabetes mellitus (T2DM) at high risk of cardiovascular events. The study objective is to be supported by a non-excessive risk analysis to demonstrate that the hazard ratio (HR) of a primary MACE composite endpoint (3-component: CV death including deaths of unknown cause, non-fatal myocardial infarction, or non-fatal stroke) for IDeg versus IGlar is no greater than 1.8 before resubmission of IDeg/IDegAsp NDAs, assessed by a pre-planned single interim analysis when 150 adjudicated primary MACEs have been accrued. The study will continue until the planned

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trial conclusion when 633 MACE events have been collected and confirmed. A final analysis will then be performed to further demonstrate non-excessive risk of MACE against a risk margin of 1.3. All potential MACE events are to be adjudicated by an independent and blinded event adjudication committee (EAC).

The applicant resubmitted the NDAs of IDeg and IDegAsp on March 26, 2015. They seek to address the question of cardiovascular safety primarily based on the interim information derived from the DEVOTE study. This review focused on the pre-approval evaluation of cardiovascular safety of IDeg relative to IGlar based upon the interim CV data obtained from the ongoing DEVOTE trial. The statistical goal of this evaluation is to assess whether the hazard ratio of MACE associated with IDeg relative to IGlar met the risk margin of 1.8 set forth in the Complete Response Letter.

1.1 Conclusions and Recommendations

On November 28, 2014, DEVOTE reached its full enrollment of 7638 subjects, with 3818 subjects randomized to receive IDeg and 3820 subjects randomized to receive IGlar. As of the date of interim data cut-off on January 19, 2015, a total of (b) (4) adjudicated first MACEs had been collected. By the time of interim data cut-off, the study withdrawal and treatment discontinuation rates were low and similar between IDeg and IGlar. Approximately 46% of the subjects had at least 6 months of follow-up, 21% had follow-up longer than 9 months, and only 5% of the randomized population had follow-up longer than one year. Treatment exposure was similar in both study arms; median exposure in both arms was 174 days.

The interim database of DEVOTE contained a total of 150 EAC-confirmed first MACEs observed during the study based on the intention-to-treat (ITT) population of all randomized subjects, corresponding to an incidence rate (IR) of (b) (4) per 100 patient years: (b) (4) MACEs were observed among 3818 subjects randomized to IDeg (b) (4) MACEs per 100 patient years) and (b) (4) events were observed among 3820 subjects randomized to IGlar (b) (4) MACEs per 100 patient years). The pre-specified Cox proportional hazards model based on the interim data estimated a hazard ratio (HR) of MACE associated with IDeg compared to IGlar of (b) (4) with a 95% confidence interval (CI) of (b) (4)). The upper bound of the 95% confidence interval ruled out the risk margin of 1.8 set forth in the Complete Response Letter. No component of the primary MACE endpoint raised any statistical concerns, nor did any additional sensitivity analyses performed by the applicant or the FDA.

Table 1: Pre-specified Analysis of Primary MACE Endpoint (ITT, on-study)

	IDeg **N = 3818** **PY* = 1856.6**	**IGlar** **N = 3820** **PY* = 1852.6**
MACE (IR/100 PY)	(b) (4)	
HR $_{IDeg/IGlar}$ (95% CI)		

*: PY = patient years of follow-up.
Source: Created by reviewer.

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1.2 Statistical Issues and Findings

The DEVOTE trial was a standalone, randomized, double-blinded, active-controlled cardiovascular outcomes trial, designed specifically to assess cardiovascular safety of insulin degludec. A total of 7638 randomized subjects were included in the ITT population. By the date of interim data cut-off, the trial was generally well-conducted and there were no significant statistical issues about trial design, conduct or analysis. The pre-specified primary safety endpoint in DEVOTE was time from randomization to first EAC-confirmed MACE. The upper bound of the 95% confidence interval for the hazard ratio estimate of MACE associated with IDeg relative to IGlar was (b) (4), thus it successfully ruled out a risk margin larger than 1.8. The CV safety of IGlar was evaluated in the ORIGIN study, where subjects with pre-diabetes and new onset T2DM were treated with IGlar versus standard of care. ORIGIN showed no difference in MACE observed between the treatment groups[1].

Analysis results of pre-specified sensitivity analyses using various on-treatment censoring schemes were consistent with that of the primary MACE analysis. The pre-specified sensitivity analysis including additional pending-adjudication CV events was supportive of the primary result. In addition, analyses of components of primary MACE, all-cause mortality and MACE+ (MACE plus unstable angina pectoris requiring hospitalization) showed no evidence of increased harm associated with IDeg. With no reason for statistical concern indicated in these analyses, it can be concluded that the analysis of MACE in DEVOTE met the 1.8 risk margin and the deficiency of the cardiovascular safety listed in the FDA Complete Response Letter was successfully addressed from a statistical perspective.

In conclusion, DEVOTE demonstrated that the cardiovascular safety of IDeg lies within acceptable bounds for marketing approval.

2 INTRODUCTION

2.1 Overview

Insulin degludec is an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. The proposed indication of IDeg is to improve glycemic control in adults with diabetes mellitus as a once daily, (b) (4) human insulin analog.

Insulin degludec/insulin aspart is composed of IDeg and insulin aspart, a rapid-acting human insulin analog. Insulin aspart (trade name: NovoLog) was approved by the Agency on June 7, 2000 under NDA 20-986. The proposed indication of this co-formulated product is to improve glycemic control in adults with diabetes mellitus with once or twice-daily dosing at any main meal.

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The original NDAs 203-314 (IDeg) and 203-313 (IDegAsp) were submitted to the Agency for review on September 29, 2011. During the review cycle of the original NDA applications, a potential adverse cardiovascular signal was observed in the IDeg/IDegAsp phase 3 development program, based upon a pre-specified statistical analysis plan for a meta-analysis to assess the CV risk associated with IDeg/IDegAsp. This was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the evaluation of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent and blinded committee. Of the 17 trials, 7 included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the SAP and agreed upon with the Agency prior to the NDA submission.

The primary meta-analysis was based upon MACE+, a composite endpoint, which consisted of four components: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina pectoris. Additionally, the Agency requested the applicant assess a strict MACE endpoint which excluded the unstable angina pectoris component from MACE+. A Cox proportional hazards model, stratified by trial, was the pre-specified primary analysis method to estimate the hazard ratio of IDeg/IDegAsp relative to the pooled comparators along with the corresponding 95% confidence interval. Table 2 depicts the primary analysis results as reported in the statistical review of the original NDA submission of IDeg/IDegAsp by Dr. Bo Li (dated 12/13/2012). Based upon the Cox model, the estimated HR for MACE+ was 1.30 with a corresponding 95% CI of (0.88, 1.93). The estimated HR for the strict MACE endpoint was 1.67 with a corresponding 95% CI of (1.01, 2.75). Both endpoints suggested an increase in CV risk of IDeg/IDegAsp relative to the pooled comparator arm while a consistent trend of the increase was observed in additional analyses.

Table 2: Primary Meta-analysis Results for Original NDA Submission (ITT, on-treatment + 7 days)

		IDeg/IDegAsp (*N* = 5794) [PYE* = 5153.6]	**Comparator** (*N* = 3461) [PYE* = 2562.7]
MACE+ Endpoint			
	Events [IR/1000PYE]	95 [18.4]	37 [14.4]
	HR (95% CI)†	1.30 (0.88, 1.93)	
MACE Endpoint			
	Events [IR/1000PYE]	70 [13.6]	21 [8.2]
	HR (95% CI)†	1.67 (1.01, 2.75)	

*: PYE = patient years of exposure.
†: Cox proportional hazards model stratified by trial.
Source: Page 32, statistical review of the original NDA 203-313/203-314, authored by Dr. Bo Li dated on 12/13/2012.

The 17 IDeg/IDeagAsp clinical trials included in the CV meta-analysis were designed to assess glycemic control of the agents in both Type 1 and Type 2 diabetes mellitus population. Multiple active comparators including insulin glargine, insulin detemir, biphasic insulin aspart, and sitagliptin, were used across the trials. Most trials were of relatively short duration with skewed

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randomization of 1:2 or 1:3, and the treated populations were T1DM and T2DM patients with a low to moderate risk for CV events, and the focus was on achieving equivalent glycemic control between arms in open-label setting. The overall discontinuation rate of study treatment was approximately 22%, varying across trials, and subjects were not followed up after treatment discontinuation. In summary, these phase 3 efficacy trials were designed to primarily assess glycemic control, rather than characterizing CV risk. The meta-analyses were conducted using heterogeneous efficacy trials which lacked the design attributes of a robust dedicated cardiovascular outcomes trial. To determine if the increase in CV risk as seen from the meta-analysis is real, further evidence from a dedicated CVOT would be needed.

Upon completion of the review, on February 8, 2013, the Agency issued a Complete Response Letter which outlined the cardiovascular safety deficiency and requested that the following be submitted to address the deficiency:

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

An End-of-Review Meeting was held between the Agency and the applicant on April 4, 2013 to determine a path forward for definitively assessing the cardiovascular risk of insulin degludec. In that meeting, and subsequent communications between the Agency and the applicant, the design elements for the degludec cardiovascular outcomes trial DEVOTE (EX1250-4080) were agreed upon, including the study population, primary endpoint, glycemic targets, and the conduct of an interim analysis after accrual of 150 first MACE events.

DEVOTE is a long-term, multi-center, multi-national, randomized, double-blind, parallel group, active-controlled, dedicated CVOT designed specifically to assess the cardiovascular safety of IDeg and to rule out or detect the CV signal identified from the meta-analyses of Phase 3 trials. The purpose of this CVOT is to evaluate the cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in subjects with type 2 diabetes mellitus at high CV risk.

DEVOTE, initiated on October 29, 2013 (first patient first visit), fully enrolled 7638 subjects on November 28, 2014 (last patient first visit), and is currently ongoing. A pre-planned interim analysis occurred when 150 adjudicated first MACEs had been accrued by January 19, 2015. The

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interim analysis was performed solely for regulatory purposes with no impact on the continuation of the trial (no early stopping). No changes to the trial design and trial conduct will be made based on the results of the interim analysis. The applicant established operational processes and procedures to preserve confidentiality and blinding of the trial and thereby ensure that the integrity of the ongoing trial is maintained after the interim analysis is conducted, submitted, and acted upon by the Agency. These processes were described in detail in a Data Access Management Plan (DAMP) developed by the applicant, which was shared with the Agency before the data base lock (DBL) of the interim analysis (refer to Section 3.2.1.2 for review/summary of this plan).

This review primarily focuses on the assessment of cardiovascular risk in the degludec cardiovascular outcomes trial DEVOTE based on its interim data to determine if the resubmissions, dated on March 26, 2015, have addressed the cardiovascular safety deficiency outlined in the Complete Response Letter.

2.2 Data Sources

The applicant submitted clinical study report and analysis datasets of DEVOTE (SN0049) separately from the submission of an integrated summary of safety (SN0047) to the same NDA (NDA 203-314). The Electronic Document Room (EDR) link to the study report of the DEVOTE trial is provided below:

\\cdsesub1\evsprod\nda203314\0049\m5\53-clin-stud-rep\535-rep-effic-safety-stud\diabetes-mellitus\5351-stud-rep-contr\study-report-ex1250-4080\report-body.pdf

The analysis datasets of the DEVOTE trial utilized in this review for the assessment of CV safety are available at:

\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adsl.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adadj.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adae.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adex.xpt
\\cdsesub1\evsprod\nda203314\0049\m5\datasets\ex1250-4080\analysis\adam\datasets\adtte.xpt

No statistical programs were provided with the initial NDA resubmission but were subsequently submitted in the 04/29/2015 response to an FDA information request (SN0051).

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

Data and reports in this submission were submitted electronically in support of NDAs 203-314/203-313. The format, content and documentation of the submitted data were adequate to conduct a statistical evaluation of the CV risk associated with insulin degludec. This review does

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not evaluate the efficacy of insulin degludec. For a statistical evaluation of efficacy results, please refer to the statistical review authored by Dr. Jiwei He.

3.2 Evaluation of Safety

This review is focused on the statistical analysis of cardiovascular risk based upon the interim data obtained from the DEVOTE study.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

DEVOTE is a Phase 3b study titled: "A trial comparing cardiovascular safety of insulin degludec versus insulin glargine in subjects with type 2 diabetes at high risk of cardiovascular events." This study is a long-term, multi-center, multi-national, randomized, double-blinded, parallel group, active-controlled trial. The primary objective of DEVOTE is to demonstrate cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events.

The current resubmission is based on a pre-specified interim analysis of DEVOTE designed to show that the hazard ratio of MACE associated with IDeg relative to IGlar is no larger than 1.8. DEVOTE will continue until the full pre-specified number of 633 first MACEs are observed in the trial; at which time the hazard ratio of MACE will be tested against a risk margin of 1.3.

DEVOTE planned to randomize a total of 7,500 male and female subjects with T2DM at elevated risk for cardiovascular events based on the following two categories:

- Subjects aged ≥ 50 years with established CV diseases; and,
- Subjects aged ≥ 60 years with risk factors for CV diseases.

The number of randomized subjects aged 60 years or older with CV risk factors only was limited to 1,500 to secure a study population with sufficient overall cardiovascular risk. Subjects were randomized 1:1 in a double-blinded manner to receive one of the investigational products:

- insulin degludec, or
- insulin glargine.

A "treat-to-target" concept was applied targeting similar glycemic control for all subjects in both arms with titration aiming for an HbA1c < 7%.

This trial is event-driven and will continue until a planned number of 633 positively adjudicated first MACEs have been collected. The protocol pre-specified that an interim analysis would be conducted to assess the preliminary non-excessive risk of IDeg relative to IGlar for MACE with a risk margin of 1.8 after at least 150 first MACEs had been accrued. The trial design is shown schematically in Figure 1 below.

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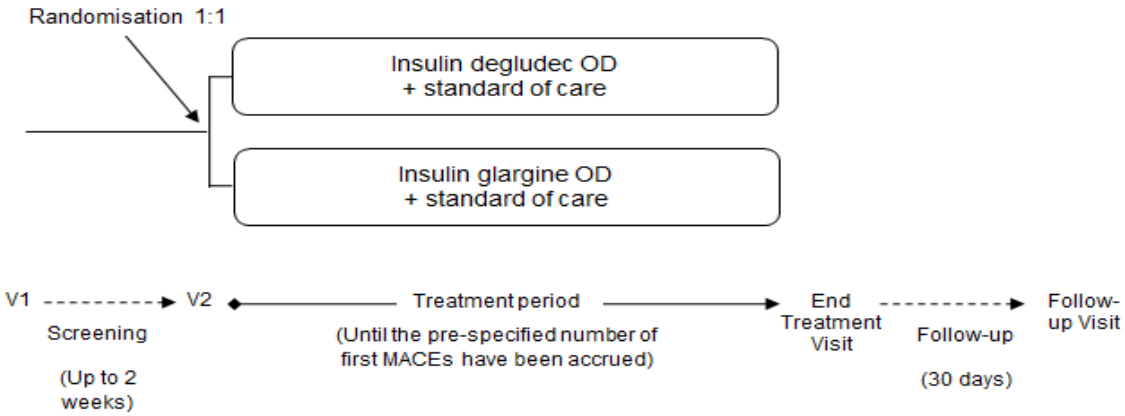
Figure 1: Flow Chart of DEVOTE Study Design



Source: Figure 9-1, page 30, CSR of DEVOTE. OD= once daily; V= visit.

The trial period consists of a screening period of up to 2 weeks, a randomization visit (V2) at which the subjects are randomized to IDeg or IGlar, an estimated treatment period of up to 59 months (depending on actual rate of MACE accrual) and a 30-day post-treatment follow-up period. For each subject, the maximum follow-up in the trial is estimated to be 60.5 months. Efforts will be made to follow all randomized subjects and collect outcome data for the complete duration of the trial. Subjects are scheduled to attend the study site once every month during the first 6 months and every third month during the rest of the trial, and to have monthly phone contacts with the investigator between the site visits. These visits and phone contacts will assess the occurrence of safety and efficacy outcomes, study medication compliance and accountability, and concomitant therapy or intervention.

Safety data collection in this large outcomes trial is limited to serious adverse events (SAEs), adverse events (AEs) associated with drug discontinuation, and episodes of severe hypoglycemia. Non-serious AEs and non-severe hypoglycemic episodes are systematically reported only in Japanese subjects as requested by the Japanese authorities. Adverse events of potential MACE, unstable angina pectoris (UAP) requiring hospitalization, deaths and episodes of severe hypoglycemia are adjudicated and evaluated by an external event adjudication committee based on predefined diagnostic criteria, in an independent and blinded manner. An EAC charter including event definitions, operational procedures and EAC membership was submitted to the Agency as part of the NDA resubmission package.

An external independent data monitoring committee (DMC) performs ongoing and independent evaluation of accumulated data from the trial. The DMC has access to semi-blinded (e.g., Group A, Group B; decode provided separately in a secured manner) and un-blinded data and makes recommendations to the applicant's internal safety committee on whether to continue, modify or

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terminate the trial. The DMC charter and DMC meeting minutes from all closed and open DMC sessions were submitted to the Agency as part of the NDA application package.

3.2.1.2 Interim Analysis and Data Unblinding

DEVOTE is an event-driven CVOT. Its sample size is based on a log-rank test showing that a total of 633 EAC-confirmed first MACEs will provide 91% power to rule out hazard ratios exceeding 1.3, assuming a true hazard ratio of 1.0 and an overall 1-sided 2.5% confidence level.

Under the assumption of a true hazard ratio of 1.0, a total of 150 EAC-confirmed first MACEs will provide 95% power to rule out hazard ratios exceeding 1.8. The study protocol pre-specified a single interim analysis to be conducted when at least 150 adjudicated first MACEs have been collected, to assess the preliminary non-excessive risk margin of 1.8 for the regulatory approval of the investigational products IDeg and IDegAsp. The interim analysis is performed solely for regulatory purposes. No changes to the study design, study conduct or to the statistical analyses for the final data will be made based on the results of the interim analysis.

The pre-defined number of 150 adjudicated first MACEs was achieved on January 19, 2015, at which time an interim data cut-off was made. The trial subject recruitment was completed prior to the data cut-off for the interim analysis with a date of first patient first visit (FPFV) of October 29, 2013 and a date of last patient first visit (LPFV) of November 28, 2014. All EAC-confirmed first MACEs captured in the database as of January 19, 2015 and loaded into the database as of January 21, 2015 (date of database lock) were included in the primary analysis. This statistical review will focus on the interim data and interim analyses of DEVOTE included in the NDA resubmission package.

Operational processes executed in connection with the interim analysis of an ongoing CVOT should be prospectively established and agreed upon in order to preserve the confidentiality, integrity, and blinding of the trial after the interim analysis is conducted, submitted, and acted upon by regulatory authorities. A data access management plan which defines such operational processes/procedures is regarded as a critical component of the interim analysis planning. The applicant prepared and finalized their DAMP (dated 11/05/2014) prior to the interim database lock of the DEVOTE trial and submitted it to the Agency with a DAMP addendum (dated 03/16/2015) as part of the resubmission. This document described who, following DBL of the interim data, will gain access to unblinded data or unblinded output/results, at which level and for what purposes in order to support the resubmission of the NDAs. The DAMP covers employees internally at Novo Nordisk and individuals external to Novo Nordisk such as the independent external statisticians at [redacted] (b) (4)) as well as members of the DEVOTE Steering Committee (StC) and refers to the relations to the Data Monitoring Committee. Furthermore, the document defines the rules of conduct and the responsibilities of the internal unblinded team at Novo Nordisk denoted as the 'Interim DEVOTE Reporting Team'

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(IDRT) and describes the restriction established to prevent inadvertent communication of the interim results. The DAMP Addendum outlines the role of [redacted] (b) (4) and any named external advisors/consultants. A brief summary of the DAMP is given below:

- The IDRT has been granted authority to make the decision whether to file or not to file the NDAs based on the interim analysis, and to agree with the Agency whether the interim results fulfill the deficiencies outlined in the Complete Response Letter. Further, the IDRT is responsible for preparing the unblinded sections of the clinical study report (CSR) of the DEVOTE trial and for answering questions posed by the Agency related to the interim analysis including requests for additional data or analysis.
- To avoid unblinding of the results and to protect the integrity of the ongoing trial, none of the results or conclusions made based on unblinded interim data will be communicated publically, unless a critical safety concern is identified.
- Once unblinded, members of the IDRT will no longer report into the part of the Novo Nordisk project organization working with trials in the Degludec portfolio, nor will they participate in operational or strategic activities or decision making related to the conduct of the DEVOTE trial until DBL for the completed trial.
- In addition to the IDRT, the statistical contractor, [redacted] (b) (4)), the regulatory consultancy company, [redacted] (b) (4) and a limited number of named external advisors/consultants will be unblinded to the results of the DEVOTE interim analysis in order to assist in the interpretation of the data, provide input to the regulatory strategy, review submission documents, and participate in activities related to a potential Advisory Committee meeting.
- A Secure IT system in Novo Nordisk was to be created to provide a secure and confidential computing environment in order to handle and store the unblinded data/results from the DEVOTE interim analysis

Reviewer's Comments: *The DAMP was shared with the Agency and was considered acceptable. According to the DAMP, all data related to the interim cardiovascular evaluation including both the adjudicated CV data and adverse events data should remain blinded, except for those instances specified in the DAMP.*

3.2.1.3 Endpoints

Per the statistical analysis plan of the interim analysis, the pre-specified primary endpoint is the time from randomization to first EAC-confirmed occurrence of a 3-component MACE: CV death (including unknown cause of death), non-fatal MI, or non-fatal stroke.

The SAP lists the following as secondary safety endpoints:

- Time from randomization to all-cause deaths
- Number of serious adverse events (SAEs)

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- Number of positively adjudicated severe hypoglycemia
- Number of positively adjudicated unstable angina pectoris requiring hospitalization
- Number of adverse events (AEs) leading to discontinuation of investigational product
- Number of medication errors leading to SAEs
- Number of technical complaints related to AEs

Reviewer's Comments: *This review will focus on the assessment of MACE. The adjudicated events of UAP requiring hospitalization will be incorporated into the assessment of a post-hoc endpoint MACE+ by the reviewer. In addition, the evaluation of all-cause deaths is considered relevant to the characterization of safety for IDeg.*

3.2.2 Statistical Methodologies

The statistical analysis plan (dated 10/09/2014), included in the NDAs resubmission of IDeg/IDegAsp, documented the pre-specified statistical methods to be used for the interim analysis. Statistical methodologies used by the applicant and additional analyses performed by the statistical reviewer are discussed below.

Reviewer's Note: *An earlier version of the SAP dated 04/24/2014 was shared with the Agency. The proposed statistical methods were generally agreed upon by the Agency, except for alternative censoring schemes of "on-treatment analysis" for which the Agency provided a written response. The subsequent amendment of the SAP for the interim analysis (dated 10/09/2014) was included in the NDA resubmission. The pre-specified statistical methods discussed in the following sections are based on the interim SAP dated 10/09/2014.*

3.2.2.1 Hypothesis Testing

The following hypothesis was pre-specified to compare the hazard of MACE in IDeg relative to IGlar at the interim analysis when at least 150 EAC-confirmed first MACEs had been accrued:

H_0: HR $\geq$ 1.8; vs. H_a: HR < 1.8.

Since the interim analysis was designed to test a separate hypothesis than the final evaluation of the study (to rule out a hazard ratio of 1.3), and since the findings of the interim analysis have no impact on the study design, conduct or analyses of the final data, no adjustment of the alpha level for the statistical test at the interim analysis is considered necessary. If the upper bound of the 95% confidence interval of the hazard ratio estimate is below 1.8, preliminary non-excessive CV risk of IDeg compared to IGlar will be considered confirmed.

3.2.2.2 Analysis Methods

3.2.2.2.1 Analysis Populations and Event Ascertainment

As pre-specified in the SAP, the interim analysis will be based on the full analysis set (FAS) which consists of all randomized subjects. The statistical evaluation of the FAS will follow the

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intention-to-treat (ITT) principle and subjects will contribute to the evaluation "as randomized" regardless of their adherence to randomized treatment. Observation time for the FAS was defined as the time period from the date of randomization to the date of the last direct contact. All analyses reported in this review were based on the FAS unless specified otherwise.

For the primary analysis of MACE, an "on-study" censoring scheme is utilized for event ascertainment:

- EAC-confirmed first MACE events observed during the course of the study before the date of interim data cut-off are captured and included in the analysis;
- Subjects without EAC-confirmed MACE are censored at their last direct contact before the interim DBL.

As pre-specified in the study protocol, subjects may discontinue their treatment with trial products at the discretion of the investigator. The discontinuation could be either temporary or permanent and will not lead to subject withdrawal from the study. Subjects with a temporary treatment pause may resume treatment at the discretion of the investigator. In order to evaluate the robustness of the primary analysis to alternative censoring schemes, four "on-treatment" sensitivity analyses were conducted by the applicant considering a temporary treatment pause between two treatment periods as "off-treatment" :

- "on-treatment": The first EAC-confirmed MACE occurring during a treatment period for each subject was captured as an event, irrespective of whether the subject in question had experienced an earlier MACE during any off-treatment period. For subjects who did not experience MACE during a treatment period, two censoring strategies were used:
    - Not counting any off-treatment MACE (Sensitivity analysis #1, **SA1**): subjects are censored at the date of latest treatment discontinuation, or last direct contact, or DBL, whichever occurs first.
    - Counting off-treatment MACE (Sensitivity analysis #2, **SA2**): subjects are censored at the date of first off-treatment MACE, latest treatment discontinuation, or last direct contact, or DBL, whichever occurs first.
- "on-treatment +30 days": The first EAC-confirmed MACE occurring during a treatment period + 30 days for each subject was captured as an event, irrespective of whether the subject in question had experienced an earlier MACE during any off-treatment period. For subjects who did not experience MACE during an on-treatment + 30 days period , two censoring strategies were used:
    - Not counting any MACE that occurred 30 days or more after the beginning of off-treatment periods (Sensitivity analysis #3, **SA3**): subjects are censored at the date of latest treatment discontinuation + 30 days, or last direct contact, or DBL, whichever occurs first.

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. Counting MACE that occurred 30 days or more after the beginning of off-treatment periods (Sensitivity analysis #4, **SA4**): subjects are censored at the date of first off-treatment MACE that occurred 30 days or more after the beginning of an off-treatment period, latest treatment discontinuation + 30 days, or last direct contact, or DBL, whichever occurs first.

Reviewer's Comments: *A typical "on-treatment" censoring scheme is slightly different from what the applicants utilized, regarding the intermittent off-treatment pause between two treatment periods. The typical "on-treatment" period refers to the time from the first dose of study drug to the last dose of study drug before the end of a trial (or before the DBL for an interim analysis); the intermittent off-treatment pauses are not considered. We conducted the following post-hoc sensitivity analyses based on this different definition of "on-treatment" period:*

- *Sensitivity analysis #5 (**SA5**): An on-treatment analysis that captures first MACE events that occurred while the subject was on the study treatment (first dose date to last dose date before DBL).*
- *Sensitivity analysis #6 (**SA6**):An on-treatment + 7 days analysis that captures first MACE events that occurred while the subject was on the study treatment or within 7 days after the latest treatment discontinuation (first dose date to last dose date + 7 days before DBL).*
- *Sensitivity analysis #7 (**SA7**):An on-treatment + 30 days analysis that captures first MACE events that occurred while the subject was on the study treatment or within 30 days after the latest treatment discontinuation (first dose date to last dose date + 30 days before DBL).*

These on-treatment sensitivity analyses conducted by the reviewer excluded 29 subjects who had never been exposed to study treatment before the interim DBL. The results from these analyses will be discussed in Section 3.2.4.1.

In addition, a pre-specified sensitivity analysis (Sensitivity analysis #8, **SA8**) was performed by counting all EAC-confirmed MACEs included in the primary analysis, plus all potential first events (either a fatal event, acute coronary syndrome or cerebrovascular event) qualified for adjudication at the date of interim DBL but lacking an adjudication outcome, i.e., events pending in the adjudication pipeline.

3.2.2.2.2 Analysis Methods for Primary MACE Endpoint

The primary analysis is based upon time-to-event methods for MACE. If a subject experienced multiple events of interest, only the first event will be included in the analysis. The agreed upon primary analysis method for MACE was a Cox proportional hazards regression model with a fixed effect for treatment to estimate the hazard ratio, and corresponding two-sided 95%

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confidence interval, of IDeg versus IGlar, based on first MACEs occurred during the study in the FAS population. This analysis was not adjusted for covariates.

Sensitivity analyses for MACE using various censoring schemes conducted by the applicant (SA1 – SA4) used the same Cox model as the one used in the primary analysis. The same model was also adopted for the analysis SA8 which includes all pending adjudication first events.

Reviewer's Comments: *The sensitivity analyses SA5, SA6 and SA7 were conducted by the reviewer using the same Cox regression model as the primary analysis for the time-to-event data.*

Reviewer's Comments: *To further investigate the sensitivity of the primary analysis on MACE, the reviewer conducted similar time-to-event analyses of the individual components of MACE: CV death, non-fatal MI and non-fatal stroke, based on an on-study censoring in FAS for each individual component.*

3.2.2.2.3 Analysis Methods for Secondary Endpoints

This review considered the secondary endpoint of all-cause death. In addition, the reviewer assessed a post-hoc, not pre-specified supportive endpoint MACE+, which is defined as a four-component composite of CV death, non-fatal MI, non-fatal stroke and hospitalization for UAP. The applicant submitted a Kaplan Meier plot of all-cause death by treatment group (IDeg and IGlar).

Reviewer's Comments: *The reviewer used the same Cox regression model with treatment as a single fixed effect factor to perform the time-to-event analysis for all-cause mortality based on the ITT population FAS with an on-study censoring scheme. The reviewer used a similar Cox model to conduct analyses of MACE+.*

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

The date of first patient first visit was October 29, 2013 and the date of last patient first visit was November 28, 2014. At the time of data cut-off for the interim analysis (01/19/2015), the trial had completed its full enrollment. Overall, 8203 subjects were screened for DEVOTE. Among these, 7638 subjects were randomized 1:1 to receive IDeg (3818 subjects) or IGlar (3820 subjects); they comprise the FAS population which was used for all analyses of cardiovascular endpoints presented in this review. A total of 29 subjects had not been exposed to trial products at the time of cut-off for the interim analysis. In total, 3807 subjects were exposed to IDeg and 3802 subjects were exposed to IGlar.

Following finalization of the SAP for the interim analysis and prior to DBL for the interim data, the applicant identified a total of 6 subjects which had been randomized at 2 different trial sites and thus had 2 subject IDs. Then a decision was taken to withdraw the subjects at site 2 and continue at site 1. These subjects were only counted as one subject in the statistical analyses. To be consistent with the ITT principle, data recorded at the first site (i.e., first randomized subject

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ID) was used in data presentations and analyses. Four subjects were included in the IDeg group, of these, 3 subjects were also randomized to IDeg at the second site and one subject was randomized to IGlar at the second site. Two of the 6 subjects were included in the IGlar treatment group; both had been randomized to IDeg at the second site. As per cut-off for the interim analysis, none of the 6 subjects had EAC-confirmed MACE.

The trial population of DEVOTE, which enrolled T2DM patients enriched for higher CV risk, consists of subjects with existing, or high risk of CV disease. Approximately 14.6% of the population (1114 subjects) was enrolled based solely on risk factors for CV disease, fulfilling the pre-defined criteria of a maximum of 1,500 subjects in this group in order to secure a study population with sufficiently high overall CV risk to accrue 633 first MACEs in a timely manner.

Based on Table 3, the IDeg and IGlar treatment arms were well-balanced with regard to baseline demographics and disease characteristics, as would be expected for a trial of such a size. In the FAS population, there were more male subjects than female subjects (63% versus 37%). Approximately 76% of subjects were White, 11% were Black, 10% were Asian and 3% belong to other race categories. Nearly 70% of the total population were recruited from sites in the U.S. Approximately 15% of the subjects in the FAS population were Hispanic or of Latino ethnicity.

Approximately half of the subjects in the FAS were between 60 and 69 years of age, with a mean age of 65 years. The average body mass index (BMI) was 33.6 kg/m^2. The mean duration of T2DM at baseline was 16 years. For the interim analysis, baseline HbA1c was reported only for the combined population. A majority of subjects (83%) had inadequate glycemic control as reflected by a baseline HbA1c $\geq$ 7.0 despite the use of multiple anti-hyperglycemic agents. The mean baseline HbA1c for the FAS population was 8.4%. Approximately 16% of subjects were insulin-naïve at baseline, equally distributed between IDeg and IGlar.

Overall, about 85% of the FAS population had established cardiovascular disease prior to randomization. More than 90% of the FAS subjects received anti-hypertensive therapy at baseline. The majority of the subjects were non-smokers: 45% had never smoked and 44% were previous smokers, while only 11% were current smokers at baseline.

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Table 3: Demographics and Baseline Characteristics (FAS)

	IDeg (N = 3818)	**IGlar (N = 3820)**
Age ± SD **(years)**	65 ± 7.3	65 ± 7.5
< 60	22.4%	23.1%
60-69	50.9%	50.3%
>= 70	26.7%	26.6%
Female	37.2%	37.6%
Race		
White	76.1%	75.2%
Black	10.5%	11.3%
Asian	10.2%	10.1%
Other	3.1%	3.4%
Region		
North America	68.8%	69.3%
Europe	11.5%	11.4%
Asia	7.4%	7.8%
Rest of world	12.4%	11.5%
BMI ± SD (kg/m²)	33.6 ± 6.9	33.6 ± 6.9
Duration of T2DM ± SD (yrs)	16.2 ± 8.8	15.8 ± 8.9
Prior CV disease	85.5%	84.9%
CV risk factor only (Age >= 60)	14.3%	14.9%
Current smoker	11.3%	11.0%
Baseline Antihypertensive	93.6%	93.5%
Insulin naïve	15.9%	16.2%
HbA1c ± SD (%) *	8.4 ± 1.6	

*: Baseline HbA1c was blinded.
Source: Created by reviewer.

Table 4 shows subject disposition for the ITT population (FAS). Of the 7638 randomized subjects, 7609 (99.6%) have been exposed to the study medications. Overall, the study withdrawal and treatment discontinuation rates were low and similar in both IDeg and IGlar groups. At the time of cut-off for the interim analysis, 95.7% of subjects (3655) on IDeg and 94.7% of subjects (3618) on IGlar were on study treatment. At the time of DBL, a total of 252 subjects were on treatment pause either permanently or temporarily, with similar percentages of treatment discontinuation between the two arms (3.0% vs. 3.6%). Nine randomized subjects had withdrawn from the trial, of these, one agreed to be contacted when the trial completes. Note that this number does not include discontinuation of treatment due to fatal events. In total, (b) (4) randomized subjects had died by the time of DBL for the interim analysis, with (b) (4) having occurred in the IGlar group: (b) (4) deaths for IDeg arm and (b) (4) deaths for IGlar arm.

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In FAS, the follow-up period for primary MACE was defined as the time period from the date of randomization to the date of first EAC-confirmed MACE or the date of last direct contact, whichever occurred first. At the cut-off date for the interim analysis, the total patient-years of follow-up were 3709 years, corresponding to a mean length of approximately 6 months of follow-up per subject. The total patient-years of exposure to treatment at the interim were 3654 years excluding all periods of treatment pauses. Both the follow-up and exposure time were distributed evenly between the two comparison groups.

Table 4: Subject Disposition (FAS)

Disposition	IDeg	IGlar
All randomized (FAS)	**3818 (100%)**	**3820 (100%)**
Exposed	3807 (99.7%)	3802 (99.5%)
At interim DBL		
On treatment	3655 (95.7%)	3618 (94.7%)
Treatment paused	116 (3.0%)	136 (3.6%)
Deaths		(b) (4)
Study withdrawn	6 (0.2%)	3 (0.1%)
Total years of follow-up at interim*	**1856.6**	**1852.6**
Total years of exposure	**1839.6**	**1832.9**
Total years of exposure (excluding treatment pauses) **	**1830.8**	**1823.2**

*: For each subject, follow-up time is calculated as the time from randomization to first MACE, or last direct contact before DBL of interim data, whichever came first. The numbers are smaller than those reported in Table 10-1 on Page 84 of the DEVOTE CSR because the applicant used the entire follow-up period until the date of last direct contact for subjects who experienced a MACE during the study before DBL.
**: The numbers are slightly different from those reported in Table 10-1 on Page 84 of the DEVOTE CSR. The reviewer identified 12 subjects with incorrect calculation by the applicant for their treatment exposure.
Source: Created by reviewer.

Information on length of subject follow-up in the study for the primary MACE endpoint before DBL is presented in Table 5 and Figure 2 below. Table 5 shows that the mean and median follow-up was similar in both treatment arms. Approximately 46% of the subjects had at least 6 months of follow-up, 21% had follow-up longer than 9 months, and only 5% of the FAS population had follow-up longer than one year. As such, the interim data of DEVOTE provides limited information on the cardiovascular risk beyond 9 months of follow-up and almost no information beyond one year of follow-up. Figure 2 shows the distribution of the time of follow-up until either first MACE or the date of last direct contact before interim data cut-off for both treatment arms of DEVOTE. Graphically, the distribution of follow-up time appears similar between the two arms.

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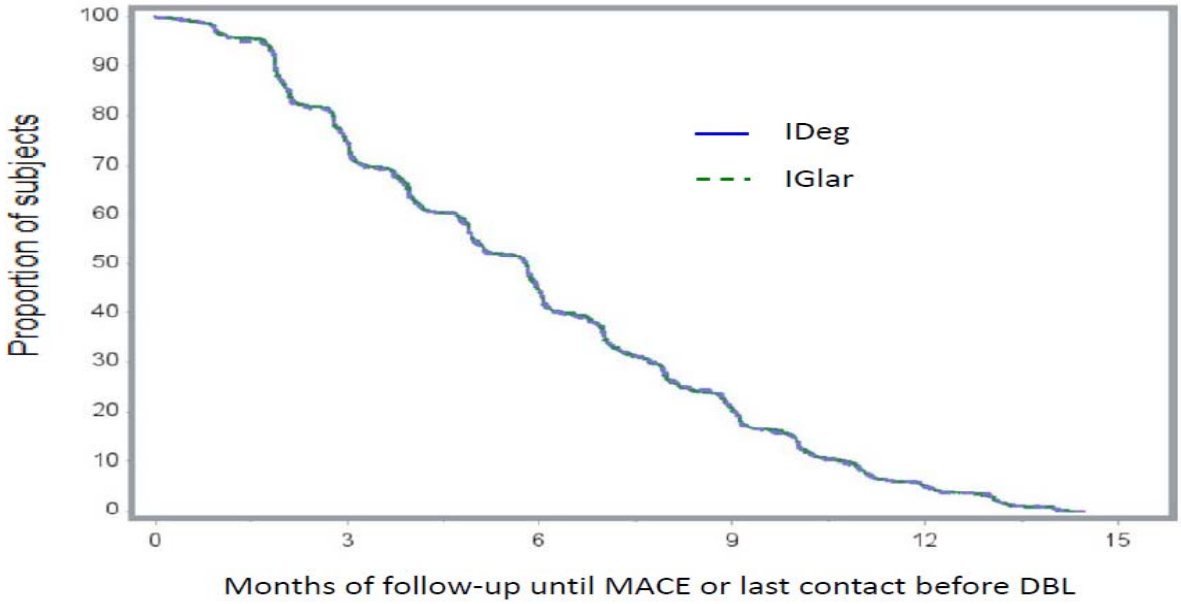
Table 5: Subject Follow-up until First MACE or Last Direct Contact (FAS)

	IDeg (N=3818)	IGlar (N=3820)
Days of follow-up		
Mean (SD)	177.6 (99.7)	177.1 (100.0)
Median	175	175
Min, Max	1, 430	1, 435
% Subjects with follow-up		
≥ 3 months	75.8%	75.6%
≥ 6 months	45.6%	45.7%
≥ 9 months	21.1%	21.4%
≥ 12 months	5.2%	5.1%

Source: Created by the reviewer.

Figure 2: Study Follow-up for Primary MACE (FAS)



Source: Created by reviewer.

Summary statistics in Table 6 below show treatment exposure for the subset of FAS who had been exposed to the study treatment before the data cut-off date for interim analysis (3807 subjects in IDeg arm and 3802 subjects in IGlar arm, see Table 4). The median treatment exposure time was 174 days for both treatment groups. Overall, the distribution of treatment exposure time was similar across both arms either including all intermittent treatment pauses or excluding the pauses.

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Table 6: Statistics on Days of Exposure in Subjects Exposed to Study Medication

	IDeg (N=3807)	IGlar (N=3802)
Days of exposure		
Mean (SD)	176.5 (99.7)	176.1 (99.8)
Median	174	174
Min, Max	1, 430	1, 434
Days of exposure (excluding treatment pauses)		
Mean (SD)	175.7 (99.4)	175.2 (99.5)
Median	173	172
Min, Max	1, 430	1, 434

Source: Created by reviewer.

3.2.4 Results and Conclusions

3.2.4.1 Primary endpoint MACE

As described in Section 3.2.1.3, the agreed upon primary endpoint was MACE: a composite endpoint of CV death (including death of unknown cause), non-fatal MI and non-fatal stroke.

The statistical evaluation of the FAS follows the ITT principle, where subjects contribute to the analyses "as randomized". Subjects in the FAS were followed to capture MACE events that occurred from the date of randomization to the date of last direct contact (on-site visit or phone contact with subject) before the cut-off date of interim data. A total of (b) (4) EAC-confirmed MACEs (of which not all events were first events) had been observed at the data cut-off date for the interim analysis. Of these, a total of 150 adjudicated first MACEs have been identified for the interim analysis, corresponding to an aggregate event rate of (b) (4)/100 patient years. Table 7 shows the classification of the first MACE events by treatment: (b) (4) out of 3818 subjects randomized to IDeg ((b) (4)%) and (b) (4) out of 3820 randomized to IGlar (b) (4)%) experienced MACE during the trial through the cut-off date of interim data. The incidence rate of first MACE was (b) (4) treatment arms: (b) (4) MACEs per 100 PY on IDeg vs. (b) (4) MACEs per 100 PY on IGlar. Among the 150 first MACE events, a total of (b) (4) first events were adjudicated as CV death (including death with unknown/undetermined cause), non-fatal MI, and non-fatal stroke, respectively. The number of subjects who experienced CV death and non-fatal stroke as their first MACE were similar between the two treatment arms. (b) (4) randomized to IGlar than IDeg (b) (4)) experienced non-fatal MI as their first MACE.

Table 7: Classification of First MACE by Treatment (FAS, on-study)

	IDeg (N=3818) PY = 1856.6	IGlar (N=3820) PY = 1852.6
MACE	(b) (4)	
CV Death (unknown cause)		
Non-fatal MI		
Non-fatal stroke		

Source: Created by reviewer.

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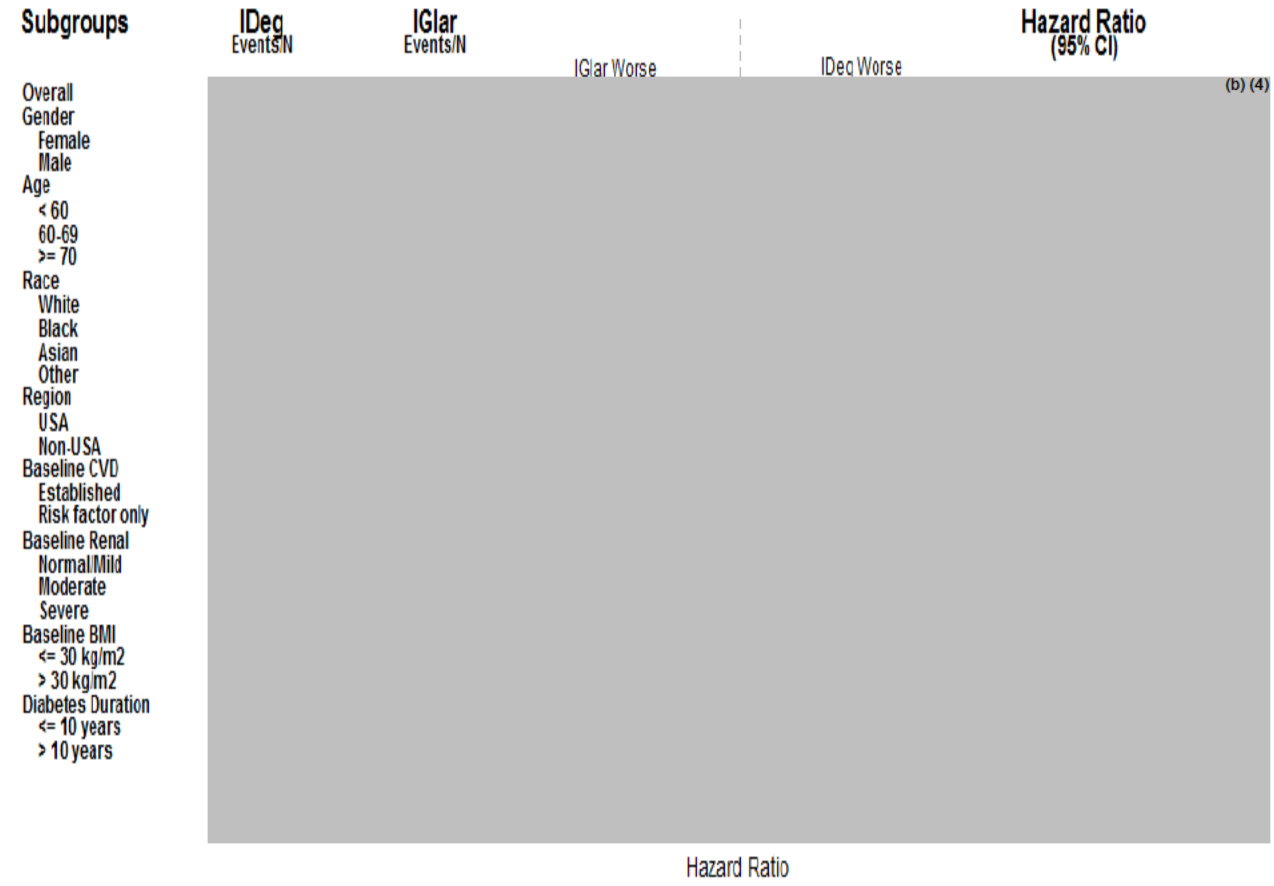
Summary of Subgroup Analyses

A forest plot of the hazard ratio and corresponding 95% confidence interval is provided in Figure 5 below as a summary of the findings in subgroup analyses discussed in Section 4.1 and Section 4.2.

Figure 5: Forest Plot of Hazard Ratios for MACE by Baseline Subgroups (FAS, on-study)



Source: Created by reviewer.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

During the review cycle of the original NDAs submission of IDeg and IDegAsp, a potential signal of excess cardiovascular risk associated with IDeg/IDegAsp relative to pooled comparators was observed in a pre-specified cardiovascular meta-analysis of Phase III efficacy clinical trials in the IDeg/IDegAsp clinical development program (refer to Section 2.1 for the

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regulatory history). As specified by the Agency in the Complete Response Letter, further evidence from a dedicated CV outcomes trial was required to better characterize the CV safety of IDeg/IDegAsp as a condition of approval. Therefore, DEVOTE, a dedicated CVOT was designed specifically to assess the CV safety of IDeg and to rule out or detect the CV signal generated from the phase 3 meta-analysis. The design, conduct and analyses of DEVOTE were agreed upon with the Agency.

DEVOTE is a long-term, multi-center, multi-national, 1:1 randomized, double-blinded, parallel group, active-controlled trial with a primary objective to confirm cardiovascular safety of insulin degludec compared to that of insulin glargine when added to standard of care in male and female subjects with type 2 diabetes mellitus at high risk of cardiovascular events. The CV safety of IGlar was evaluated in the ORIGIN study, where subjects with pre-diabetes and new onset T2DM were treated with IGlar versus standard of care. ORIGIN showed no difference in MACE observed between the treatment groups. In DEVOTE, to overcome issues inherent in open-label trials, IDeg and IGlar was supplied and administered using indistinguishable vials and syringes to allow a double-blind design of the CVOT. DEVOTE is an event-driven trial designed and powered to evaluate the CV risk associated with the use of IDeg, relative to IGlar. A pre-specified interim analysis of DEVOTE was planned to show that the hazard ratio of MACE associated with IDeg relative to IGlar is no larger than 1.8. As planned, DEVOTE will continue until the full pre-specified number of 633 first MACEs are observed in the trial; at which time the hazard ratio of MACE will be tested against a risk margin of 1.3.

DEVOTE was initiated on October 29, 2013 (FPFV) and was fully enrolled with 7638 subjects on November 28, 2014 (LPFV), which occurred before the date of database lock for the pre-planned interim analysis when 150 first MACE events were achieved on January 19, 2015. By the time of the interim data cut-off, the disposition of subjects suggested that DEVOTE was well-conducted: a total of 9 subjects had withdrawn from the study, (b) (4) subjects had died, and 98.5% of randomized subjects remained in the trial for primary CV events follow-up. The maximum observed length of subject follow-up time was 14.5 months with a median of approximately 6 months. Approximately 46% of the subjects had at least 6 months of follow-up for the primary MACE endpoint and 21% had follow-up longer than 9 months.

The primary endpoint of DEVOTE was time from randomization to first adjudicated MACE (CV death/death with unknown cause, non-fatal MI and non-fatal stroke). The pre-specified primary analysis was based upon a Cox proportional hazards model including treatment (IDeg vs. IGlar) as a fixed effect factor for the ITT population that included all events observed during the study (on-study censoring) before the interim data cut-off date (i.e. this analysis was based on all randomized subjects including all events that occurred either on or off treatment). The primary objective of this analysis was to demonstrate that the upper bound of the 95% confidence interval for the hazard ratio of MACE associated with IDeg compared to IGlar was smaller than the risk margin of 1.8 with a reassuring point estimate of the hazard ratio, as specified in the CRL issued

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on February 8, 2013. There are no statistical concerns on the design, conduct, and pre-specified analysis of the primary endpoint. In order to assess the robustness of the primary analysis, additional sensitivity analyses of MACE were requested that account for event ascertainment relative to treatment exposure (on-treatment censoring). These analyses censored subjects at a fixed window of time after treatment discontinuation thereby including only events that occurred within this fixed observation window (on-treatment, on-treatment + 30 days). The reviewer conducted time-to-event analysis utilizing a different definition of "on-treatment" censoring scheme from that used by the applicant, with various ascertainment windows (on-treatment, on-treatment + 7 days, on-treatment + 30 days).

The reviewer also performed time-to-event analysis for each component of primary MACE, for all-cause mortality, as well as for a post-hoc MACE+ endpoint comprising 4-components: CV death/deaths with unknown cause, non-fatal MI, non-fatal stroke and unstable angina pectoris requiring hospitalization. In addition, to study the effect of the events pending adjudication at interim, the applicant conducted a pre-specified sensitivity analysis which counted all EAC-confirmed MACEs included in the primary analysis, plus all potential first CV events pending in the adjudication pipeline. These sensitivity analyses were conducted using the same Cox regression model as that for the primary analysis based on on-study censoring for all randomized subjects. More details of the statistical methodologies used in this review are provided in Section 3.2.2.

5.2 Collective Evidence

A total of 3818 subjects were randomized to IDeg and 3820 subjects were randomized to IGlar in DEVOTE. As of the interim data cut-off date on January 19, 2015, the study withdrawal and treatment discontinuation rates were low and similar between IDeg and IGlar. A total of 150 EAC-confirmed first MACEs had been collected by data cut-off for the interim analysis, corresponding to an aggregate MACE event rate of (b) (4)/100 patient years. (b) (4) MACEs were observed among 3818 subjects randomized to IDeg (b) (4) MACEs per 100 patient years) and (b) (4) events observed among 3820 subjects randomized to IGlar ((b) (4) MACEs per 100 patient years).

As shown in Table 23 below, the estimated hazard ratio of IDeg compared to IGlar was (b) (4) with a 95% CI of (b) (4)) for MACE based on the pre-specified Cox proportional hazards model. The upper bound of the 95% confidence interval met the risk margin of 1.8 specified in the Complete Response Letter. Sensitivity analyses using various on-treatment censoring schemes, sensitivity analysis including additional CV events pending adjudication, and post-hoc time-to-event analyses of components of primary MACE, all-cause mortality and MACE+ are all supportive of this conclusion. Detailed analysis results were provided in Section 3.2.4.1 and 3.2.4.2.

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Table 23: Pre-specified Primary Analysis Results of MACE (ITT, on-study)

	IDeg N = 3818 PY = 1856.6	IGlar N = 3820 PY = 1852.6
MACE (IR/100 PY)	(b) (4)	
$HR_{IDeg/IGlar}$ (95% CI)		

Source: Created by reviewer.

5.3 Conclusions and Recommendations

A signal of cardiovascular risk associated with IDeg/IDegAsp was observed during the FDA review of the initial NDA submissions of IDeg (203-314) and IDegAsp (203-313), based upon a pre-specified meta-analysis of MACE+ observed in 17 efficacy clinical trials from the phase 3 development program of IDeg/IDegAsp. Due to the inherent deficiencies associated with a meta-analysis of open-label efficacy trials, the CV signal was considered uncertain which warranted a further trial designed specifically for the evaluation of cardiovascular risk. On February 8, 2013, FDA issued a Complete Response Letter to the applicant which outlined the cardiovascular safety deficiency and requested additional clinical trial data from a dedicated, double-blind, cardiovascular outcomes trial to be submitted to address the deficiency. As such, DEVOTE was designed and initiated as a dedicated CVOT to provide definitive evidence of the CV safety profile of IDeg. The design and analysis of the DEVOTE trial was agreed upon with the Agency with incorporation of specific design elements to overcome deficiencies of the meta-analysis.

Based on a planned interim analysis of 150 first adjudicated MACE (3-component: cardiovascular death/deaths with unknown cause, non-fatal myocardial infarction, or non-fatal stroke), the pre-specified Cox proportional hazards model obtained an estimated hazard ratio of (b) (4) with associated 95% confidence interval of (b) (4) The upper bound of this 95% confidence interval was below 1.8 and therefore met the pre-approval hazard ratio risk margin specified in the Complete Response Letter. Pre-specified sensitivity analyses considering alternative event censoring schemes and pending adjudication events at interim were supportive of the primary analysis result. Post-hoc analyses of components of primary MACE, all-cause mortality and MACE+ obtained consistent results with that of the primary analysis and showed no evidence of increased harm associated with IDeg compared to IGlar.

The interim data of DEVOTE provided only 24% of the total anticipated primary events in the trial with limited length of follow-up and drug exposure. The final confirmation of the CV safety of IDeg versus IGlar in terms of excluding the risk margin of 1.3 will be evaluated when at least 633 first MACE events have been accrued in DEVOTE. In order to preserve the confidentiality, integrity, and blinding of the ongoing DEVOTE trial after the interim analysis is conducted, submitted, and acted upon by regulatory authorities, operational processes/procedures executed in connection with the interim analysis were prospectively established and agreed upon. The data

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integrity and reliability of DEVOTE at the final analysis depends on how strict these processes and procedures described in the DAMP are executed and are subject to the Agency's continuing inspection.

In conclusion, the interim results from the DEVOTE trial addressed the deficiencies related to cardiovascular safety of insulin degludec for approval, outlined in the FDA Complete Response Letter dated on 02/08/2013.

6 REFERENCES

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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 AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-314, NDA 203-313
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250)
	Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted: September 29, 2011
	Major Amendment: May 16, 2012
	Goal Date: December 14, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D.
	Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer (efficacy): Jean-Marc Guettier, M.D.
	Medical Officer (safety): Karim Calis, M. D.
Project Manager:	Rachel Hartford, M.S. (DMEP)

Keywords: clinical studies, meta-analysis, diabetes mellitus, cardiovascular safety, major adverse cardiovascular event (MACE)

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1 EXECUTIVE SUMMARY

Dr. Xiao Ding performed the statistical review (signed on April 16, 2012) of NDAs 203-313 and 203-314 to evaluate the cardiovascular (CV) safety of IDeg and IDegAsp based upon data available at the time of NDA submission. Findings from this cardiovascular meta-analysis raised concerns about a potential increase of CV risk associated with IDeg/IDegAsp use. These findings triggered an information request to the applicant to provide additional data from trials that were still ongoing at the time of NDA submission as well as an updated study report for CV meta-analysis. This additional data included information from 1 new Phase 3 trial and data from 6 planned extension trials that were integrated into the updated meta-analysis. An area of consideration is whether data from the extension trials should be incorporated into the meta-analysis as enrollment into the extension trials was based upon a voluntary election of trial participants. Our assessment of the updated database found it to be robust and appropriate for the evaluation of the CV risk of IDeg/IDegAsp as presented in Section 3.3.3.1.

This statistical review assesses cardiovascular related safety endpoints by utilizing the updated database that includes 17 randomized Phase 3 clinical trials, including data from planned extension trials, for which IDeg (Studies 3579+3643, 3580, 3582+3667, 3583+3644, 3585+3725, 3586, 3668, 3672, 3718, 3724 and 3770+ext) as well as IDegAsp (Studies 3590+3726, 3592, 3593, 3594+3645, 3597 and 3896) were investigated for safety and efficacy. This database includes information on 9,255 randomized subjects (5,794 randomized to IDeg/IDegAsp and 3,461 randomized to comparator) with a total exposure of roughly 7,700 person years (5,154 PY for subjects randomized to IDeg/IDegAsp, and 2,563 PY for subjects randomized to comparator). Refer to Section 2 for a description of the 17 trials. This review focuses solely on the evaluation of CV safety as measured by two composite major adverse cardiovascular event endpoints.

Based upon both the pre-specified primary analysis and additional analyses, the meta-analysis of these 17 randomized phase 3 trials showed an increased risk of developing major adverse cardiovascular event (MACE+: composite of CV death, acute coronary syndrome including unstable angina pectoris and myocardial infarction, and stroke) in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) compared to the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Utilizing the pre-specified Cox proportional hazards model stratified by trial, the estimate of the MACE+ hazard ratio was 1.30 with a 95% CI of (0.88, 1.93). Secondary analyses, based upon the risk difference and incidence rate difference, showed similar trends. The risk difference of MACE+ between IDeg/IDegAsp and all comparator was 0.33%, with a 95% CI of (-0.15%, 0.81%). The difference of MACE+ incidence rates between IDeg/IDegAsp and all comparator was 4.27 per 1,000 person-years of exposure with a 95% CI of (-1.84, 10.4) per 1,000 person-years of exposure. See Section 3.3.4.1.1 for full analysis results of the MACE+ endpoint.

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In addition to the additional data that were submitted in response to the Agency's information request, the Agency also requested the applicant to assess CV effects on a strict MACE endpoint that excluded hospitalization for unstable angina from the MACE+ composite endpoint – this is referred to as the MACE composite endpoint. A total of 91 MACE were reported across the 17 trials, of which 70 were reported (incidence rate of 13.6 events per 1,000 person years) on the IDeg/IDegAsp treatment arm and 21 were reported (incidence rate of 8.2 events per 1,000 person years) on the comparator arm. This resulted in a hazard ratio estimate of 1.67 with a 95% CI of (1.01, 2.75) calculated by Cox proportional hazards model stratified by trial. This result suggests an increase in risk of developing a strict MACE event associated with IDeg/IDegAsp use with a greater magnitude of CV risk compared to MACE+.

In addition to assessing CV risk with alternate composite endpoints, statistical analyses were conducted to assess CV risk using alternate statistical effect measures, databases (i.e. inclusion/exclusion of extension trial data), analysis methods, and subgroup analyses. In general, a consistent trend showing an increase in CV risk associated with IDeg/IDegAsp was seen. To determine if the increase in CV risk as seen from the meta-analysis of these 17 trials is a chance finding, further evidence from a dedicated CV outcome trial would be needed.

2 INTRODUCTION

2.1 Overview

Insulin degludec (IDeg) is an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. The proposed indication of IDeg is to improve glycemic control in adults with diabetes mellitus as a once daily, (b) (4) human insulin analog.

Insulin degludec/insulin aspart (IDegAsp) is composed of IDeg and insulin aspart, a rapid-acting human insulin analog. Insulin aspart (trade name: NovoLog) was approved by the Agency on June 7, 2000 under NDA 20-986. The proposed indication of this co-formulated product is to improve glycemic control in adults with diabetes mellitus with once or twice-daily dosing at any main meal.

The initial cardiovascular related safety meta-analyses utilized an integrated dataset of IDeg and 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). For the details of each of the 16 trials and the original meta-analysis of the CV risk of these 16 trials, please refer to the review signed by Dr. Xiao Ding on April 16, 2012.

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Results from the initial analysis and Dr. Ding's review 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 applicant 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 database.

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[1] (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). The extension trials maintained the randomized treatment assignment of the main trials and enrollment into these trials was voluntary. Further details on utilizing the extension trial information is provided in Section 3.3.3.1. Trial 3846 investigated two titration algorithms with IDeg in 222 subjects with type 2 diabetes and Trial 3923 evaluated treatment with IDeg 200 U/mL versus IDeg 100 U/mL in 373 subjects with type 2 diabetes. Both were open-label, randomized trials of 26 and 22 weeks duration, respectively, that randomized subjects to either of the two IDeg treatment arms. Therefore, while these two trials 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 included 17 trials. Note that this update does include the trial information provided in the original submission. This review primarily focuses on the updated safety analyses and database submitted by the applicant in May 2012, as a response to the Agency's information request. A summary of design characteristics of these 17 trials is presented in Table 1.

2.2 Data Sources

As a response to the Agency's information request, the applicant submitted an NDA major amendment which included the results of the updated meta-analysis as well as the updated database, as described above. This update was received on May 11, 2012. The EDR link to the study report is provided below.

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On May 16, 2012, the applicant submitted pooled analysis datasets for the meta-analysis of cardiovascular safety. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review:

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\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\mabrt.xpt
\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\mana.xpt

[1] The main trial and the corresponding extension trial are notated as main trial ID + extension trial ID.

Reference ID: 3250682

\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\manat.xpt

As requested by the Agency for additional information, the applicant also submitted electronic datasets for the following as such information was not provided for the updated trial database:

- subject disposition,
- adverse events, and
- baseline characteristics including cardiovascular risk factors.

This data can be accessed from the eCTD locations

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\\Cdsesub1\evsprod\NDA203314\0026\m5\datasets\cv-metaanalysis\analysis\adv-1.xpt
\\Cdsesub1\evsprod\NDA203314\0031\m5\datasets\cv-metaanalysis\analysis\base1.xpt
.

Table 1: 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 3.3.3.
* The duration of Study 3594 was 26 weeks. Study 3645 was a 26-week treatment extension to 3594. They are included in the original NDA submission.
Source: Created by reviewer.

3 STATISTICAL EVALUATION

Reference ID: 3250682

This review is focused on the meta-analysis of CV risk, based upon the updated database which included the trial information from the original submission and the additional data described in Section 2.1. A separate safety evaluation focused on hypoglycemia was reviewed by Dr. Eugenio Andraca-Carrera. For a statistical evaluation of efficacy results, please refer to the review authored by Dr. Cynthia Liu for IDeg and the review authored by Dr. Dongmei Liu for IDegAsp.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The reviewer was able to perform all analyses using the submitted data and the additional data submissions provided in response to the information requests.

3.2 Evaluation of Efficacy

This review does not evaluate efficacy submitted to the NDA. The reader is referred to the statistical reviews by Drs. Cynthia Liu and Dongmei Liu.

3.3 Evaluation of Safety

Seventeen trials were utilized to evaluate the association between IDeg/IDegAsp and CV safety, compared with other comparators. This included data from 11 randomized trials (5 with planned voluntary extensions) for IDeg (Studies 3579+3643, 3580, 3582+3667, 3583+3644, 3585+3725, 3586, 3668, 3672, 3718, 3724 and 3770+ext) and 6 randomized trials (2 with planned voluntary extensions) for IDegAsp (Studies 3590+3726, 3592, 3593, 3594+3645, 3597 and 3896).

3.3.1 Study Design and Endpoints

3.3.1.1 Study Design

All the seventeen trials were Phase 3, open-label, randomized, multi-center and active-controlled. In general, these trials were designed to establish the non-inferiority of IDeg/IDegAsp relative to an active control with a treat-to-target design. For the details of study design of each individual trial included in the original NDA submission, please refer to the review authored by Dr. Xiao Ding on April 16, 2012. As of the cut-off date of the NDA submission, only one extension trial (Trial 3645) was completed and included in the NDA submission.

The updated database included additional data from 6 extension trials (Trial 3643, 3667, 3644, 3725, 3770 ext. and 3726) and one new confirmatory trial 3896, which were all completed by the database lock at May 1, 2012. Generally said, an extension trial design is based upon the trial design of its respective main trial, i.e. a controlled, open label, multi-center, and treat-to-target trial design. All subjects who completed the main trial were eligible to volunteer to participate in the extension trial and continued to receive treatment as randomly allocated in the main trial.

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The new trial included in the updated database, NN5401-3896 (Study 3896), was a phase 3 multi-center, randomized, open-labeled, treat to target, two-arm parallel study. Study 3896 was conducted in Japan, in male and female subjects ≥ 20 years of age with type 2 diabetes with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 296 insulin-naïve subjects were randomized in a 1:1 fashion to IDegAsp or insulin glargine (IGlar), with or without oral anti-diabetic drugs. Study 3896 was powered to provide 80% or greater power to demonstrate the non-inferiority of IDegAsp compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

3.3.1.2 Endpoints

In the original submission, the agreed upon primary endpoint for CV safety analysis is major adverse cardiovascular event (MACE+), which is pre-specified as a composite endpoint consisting of acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and myocardial infarction (MI), stroke, and CV death. As a response to the Agency's comments, the applicant conducted additional analyses based on a more strict MACE definition which excludes UAP from the original specification. Throughout the rest of this review, "MACE+" refers to the applicant's initial definition and "MACE" refers to the strict definition.

The Agency's statistical review of the original NDA noted that the applicant only conducted analysis of treatment-emergent events (events occurring within 7 days of treatment discontinuation) even though the statistical analysis plan (SAP) did not pre-specify that the analysis should only focus on the treatment-emergent events. As a response to the Agency's information request, the applicant submitted the updated data in which the MACE+/MACE events were ascertained either within 7 days or within 30 days after treatment discontinuation.

All events were adjudicated using a thorough, prospective adjudication plan.

3.3.2 Statistical Methodologies

All the 17 completed Phase 3 trials (including extensions) in the clinical development programs of IDeg and IDegAsp in subjects with type 1 and type 2 diabetes mellitus as of the cut-off date (May 1, 2012) are included in the meta-analysis of CV safety.

An extension trial was included in the across trial analysis by joining the extension data with its respective main trial data and thereafter the joined data is considered as one trial using the combined trial ID as the identifier. The combined dataset was the basis for summaries, analyses and presentation of CV safety evaluation. Baseline was defined as the randomization visit in the main trial.

3.3.2.1 Methods of Imputing Missing

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As specified in the SAP, if a subject has no adjudicated MACE+ (or MACE) event at the time of database lock then the primary endpoint will be censored at the subject's last visit date recorded in the Case Report Form (CRF).

3.3.2.2 Analysis Methods for MACE+ and MACE

All comparative analyses are between the randomized treatment groups. All IDeg regimens as well as IDegAsp regimens are combined into the pooled IDeg/IDegAsp group, and all the comparator groups are combined into the pooled all comparator group.

The primary analysis is based upon time-to-event methods for MACE+/MACE. If a subject experienced multiple events of interest, only the event that occurred first will be included in the analysis. The agreed upon primary analysis method was a Cox proportional hazards regression model stratified by trial with a fixed effect for treatment to estimate the hazard ratio (HR), and corresponding 95% confidence interval, of IDeg/IDegAsp group versus the pooled all comparator group. Trials with no events on both arms are excluded from the Cox regression analysis.

In this review, as a secondary analysis, stratified Mantel-Haenszel (M-H) 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 including trials with no events of interest. 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 Agency conducted sensitivity and subgroup analyses under various scenarios. These various analyses included the following assessments,

1. Assessment of the individual component of MACE+/MACE.
2. Trial-level subgroup analysis utilizing only the set of IGlar-controlled trials.
3. Trial-level subgroup analysis on the set of IDeg trials.
4. Trial-level subgroup analysis of type 1 and type 2 diabetics

The subgroup analyses were performed using a stratified Cox proportional hazard model and using the stratified Mantel-Haenszel method described above. Note that most of these analyses were not pre-specified in the protocol or SAP, but were requested by the clinical review team. As such, these exploratory analyses should be considered in context of the primary agreed upon analysis.

3.3.2.3 Handling of trials with zero events

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For the primary analysis method (stratified Cox regression) used in this review, trials with zero events were excluded from the analysis. The secondary analysis methods (M-H RD and IRD) do not require special handling of trials with zero events.

3.3.3 Patient Disposition, Demographic and Baseline Characteristics

The protocol defined full analysis set (FAS) was a modified intent-to-treat (ITT) population, which included all randomized subjects with the exclusion of a small number of subjects (N = 36) based upon the applicant's criteria. It was pre-specified that the primary analyses will be based on the FAS population. All analyses reported in this review are based on the FAS population.

The SAP of CV meta-analysis specified that all Phase 3 therapeutic confirmatory trials and any planned controlled extension of these trials would be included in the CV meta-analysis. Due to date of database lock, data from all trials except 6 of the 7 planned extension trials were included in the CV meta-analysis at the time of original NDA submission – this will be referred to as the "original database". In April 2012, the Agency inquired of the applicant on their ongoing program and learned that all planned extensions intended for consideration in the CV meta-analysis were completed. An information request was sent for an updated CV meta-analysis of all the trials specified in the SAP and the single one new trial 3896. In response, the applicant submitted an updated database which was locked on May 1, 2012 – this will be referred to as the "updated database". Table 2 provides a high level summary of the total number of subjects and total person-years of exposure (PYE) for the combined IDeg/IDegAsp arm and all comparator arm respectively, in the original and updated databases. While the updated database includes only one additional main trial from the original database, the inclusion of the extension trial information results in approximately 40% more person-years of exposure.

Table 2: Comparison of the Original and Updated CV Meta-analysis Database (FAS)

	Original Database (16 trials)		**Updated Database (17 trials)**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
Sample Size (N)	5647	3312	5794	3461
Person Years of Exposure (PYE)	3569.9	1873.9	5153.6	2562.7

Source: Created by reviewer.

3.3.3.1 Trials with extension

The majority of additional data in the updated database are from the extension trials. Despite the fact that it was pre-specified in the SAP to include these extension trials in the primary analysis, the Agency assessed the 7 trials with extension separately to evaluate the robustness and appropriateness of including the data from the extension trials in the CV meta-analysis. The focus of the Agency's evaluation are on retention rates of extension trials and the similarity

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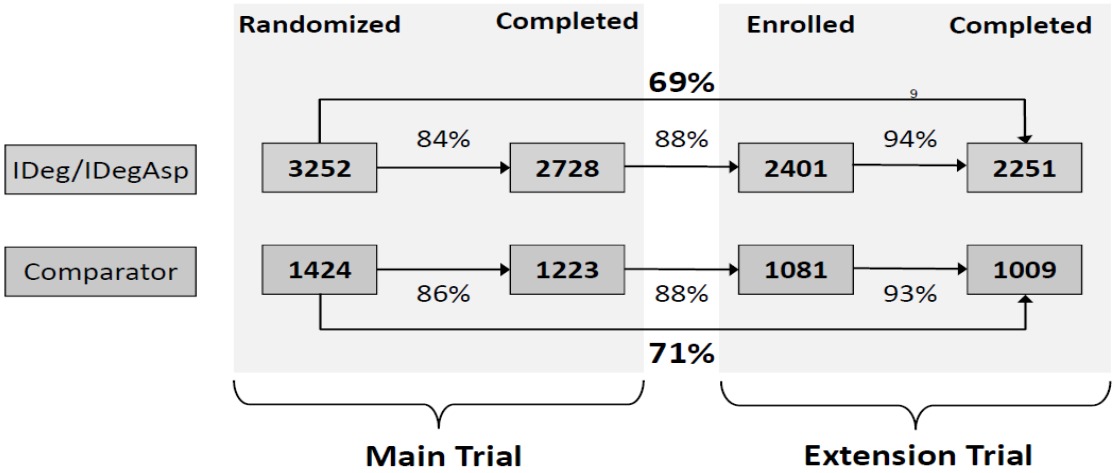
between the subjects initially randomized in the main trials and the subjects enrolled in the extension trials.

In total, the 7 trials with extensions randomized 3,252 subjects to the IDeg/IDegAsp group and 1,424 to the comparator group. The number of subjects remaining for each of the four stages of the trials (randomization, completion of main trial, extension trial enrollment and completion of extension trial) is shown in Figure 1. The retention rates above the arrows are calculated by stage. For example, 84% of subjects randomized to IDeg/IDegAsp completed the main trials and of those 2,728 completers, 88% enrolled in the extension trials. Of the 2,401 subjects who enrolled in the extension trials 94% stayed through the entire extension period. The retention rates are very similar between the treatment arm and the comparator arm. The overall completion rates, from time of randomization to end of the extension trials, are around 70% and balanced between the two comparison arms.

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



Source: Created by reviewer.

Based upon Table 3 shown on the following page, demographics and baseline characteristics that include baseline CV risk factors for the subjects who enrolled in the extension trials are similar to those of the randomized subjects in the 7 trials with extension. Overall, there are negligible difference between the two groups in terms of body mass index, HbA1c, type and duration of diabetes, hypertension, prior CV disease, renal impairment and concomitant drug use. Thus, subjects who enrolled in the extension trials retain similar baseline characteristics as the randomized group.

Based on these findings, it was determined that the updated database including all main and extension trials was robust and appropriate for the evaluation of CV safety which coincides with the pre-specified statistical analysis plan.

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Table 3: Demographics and Baseline Characteristics (FAS, Trials with Extension)

	Randomized		Enrolled in extension	
	IDeg/IDegAsp (N = 3252)	Comparator (N = 1424)	IDeg/IDegAsp (N = 2401)	Comparator (N = 1081)
Age, yrs	51±14	51±14	51±14	51±13
Female	44.2%	45.1%	42.8%	44.2%
Race				
White	83.5%	81.8%	83.2%	81.6%
Black	5.4%	4.6%	5.0%	3.7%
Asian	9.0%	11.4%	10.1%	12.8%
Other	2.1%	2.2%	1.7%	1.9%
US	42%	38%	40%	36%
BMI, kg/m²	29.0±5.2	28.8±5.2	28.9±5.2	28.9±5.1
Duration of diabetes, yrs	13.9±10.0	13.6±9.7	13.8±9.8	13.3±9.3
HbA1c, %	8.1±0.9	8.2±0.9	8.1±0.9	8.2±1.0
Type I Diabetes	45.2%	46.1%	45.5%	45.8%
Hypertension	54.0%	52.5%	54.6%	53.0%
Prior CV disease	14.3%	12.5%	14.6%	12.9%
Renal Impairment	11.3%	11.2%	10.9%	11.2%
Concomitant medications				
Lipid-lowering drug	47.5%	46.6%	47.6%	46.4%
Aspirin	29.2%	28.4%	29.2%	30.0%
Beta-blocker	16.7%	13.8%	16.8%	14.2%
R/A system inhibitors	50.0%	48.2%	50.6%	49.4%

Source: Created by reviewer.

3.3.3.2 Updated database

In the original NDA submission, among the 8,995 randomized subjects in the ITT population, a total of 8,959 subjects were included in the FAS population. The updated database included only one new trial 3896, which provided 296 additional subjects (147 subjects were treated with IDegAsp and 149 subjects were treated with insulin glargine). Therefore, among the 9,255 randomized subjects in the FAS population from the 17 phase 3 trials included in the updated database, 4,281 (46.3%) subjects were randomized to receive IDeg, while 1,513 (16.3%) subjects were randomized to receive IDegAsp, and 3,461 (37.4%) subjects were randomized to receive active comparator drugs.

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Based upon Table 4, demographic characteristics and baseline CV risk factors for the 9,255 subjects in the 17 trials included in the primary analysis were similar among the treatment groups. In the FAS population, there were slightly more male subjects than female subjects (56% versus 44%). Approximately 68% of subjects were White and about 25% were Asian, while 5% of subjects were Black or African American. Furthermore, about 9% subjects in the FAS population were with Hispanic or Latino ethnicity. About 21% of subjects in the FAS were above 65 years of age, while the mean age was about 54 years. More than 41% of subjects had a body mass index (BMI) greater than 30 kg/m2, while the mean BMI was about 29 kg/m2. Approximately 77% of subjects had type 2 diabetes mellitus (T2DM) with a mean duration of 10.8 years. About 23% of subjects had type 1 diabetes mellitus (T1DM) with a mean duration of 17.3 years.

Table 4: Demographics and Baseline Characteristics by Treatment Group (FAS, Updated Database)

	IDeg/IDegAsp (N = 5794)	**Comparator (N = 3461)**
Age, yrs	54±13	55±12
18-65	79.7%	78.8%
65-75	17.7%	18.2%
>75	2.6%	3.0%
Female	43.9%	44.8%
Race		
White	68.5%	66.5%
Black	5.1%	4.8%
Asian	24.5%	27.1%
Other	1.9%	1.6%
US	31%	30%
BMI, kg/m²	29.0±5.3	29.5±5.4
<25	24.7%	22.5%
25-30	35.1%	34.0%
30-35	25.5%	27.0%
>35	14.7%	16.5%
Duration of diabetes, yrs	12.6±9.0	11.8±8.4
HbA1c, %	8.2±0.9	8.3±0.9
Hypertension	59.9%	62.0%
Prior CV disease	16.2%	15.3%
Renal Impairment	16.5%	16.6%

Source: Created by reviewer.

As summarized in Table 5, among the 9,255 subjects in the FAS population, approximately 21.6% of subjects (2,001/9,255) did not complete the trial (including those who completed the main trial but did not enroll in the extension trials). As presented in Figure 2, the percentage of subjects with premature discontinuation tended to be slightly lower in the comparator groups

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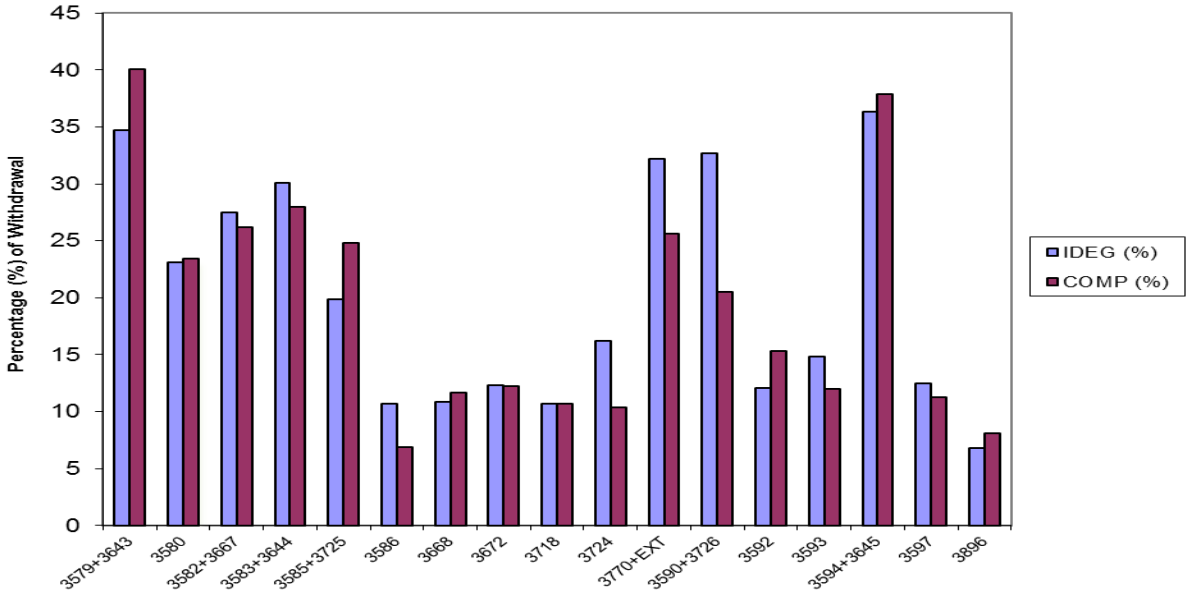
than in the IDeg/IDegAsp groups. On average, 23.0% of the subjects in the combined IDeg/IDegAsp group discontinued study medication, which was not statistically significantly higher than the combined comparator group (19.4%) with p-value = 0.28 (CMH test stratified by trial). In general, the trials with an extension period have higher drop-out rates compared to the trials without extension, due to the longer duration of these trials and because subjects that elected NOT to enroll in the extension trials are counted as dropouts. As presented in Figures 3 and 4, there was no clear difference overall in time-to-dropout between the combined IDeg/IDegAsp group and the comparator group, either for all 17 trials (Figure 3) or for the 7 trials with an extension (Figure 4).

Table 5: Patient Disposition (FAS, Updated Database)

Disposition	IDeg/IDegAsp *N* = 5794	Comparator *N* = 3461
Completed the study	4464 (77.0%)	2790 (80.6%)
Discontinued	1330 (23.0%)	671 (19.4%)
Adverse event	147 (2.5%)	59 (1.7%)
Ineffective Therapy	41 (0.7%)	23 (0.7%)
Non-compliance	163 (2.8%)	98 (2.8%)
Withdraw criteria	170 (2.9%)	93 (2.7%)
Not enrolled in extension trial	327 (5.6%)	142 (4.1%)
Other	482 (8.3%)	256 (7.4%)

Source: Created by reviewer.

Figure 2: Percentage of Subjects with Discontinuation by Study and Treatment Group (FAS, Updated Database)



Source: Created by reviewer.

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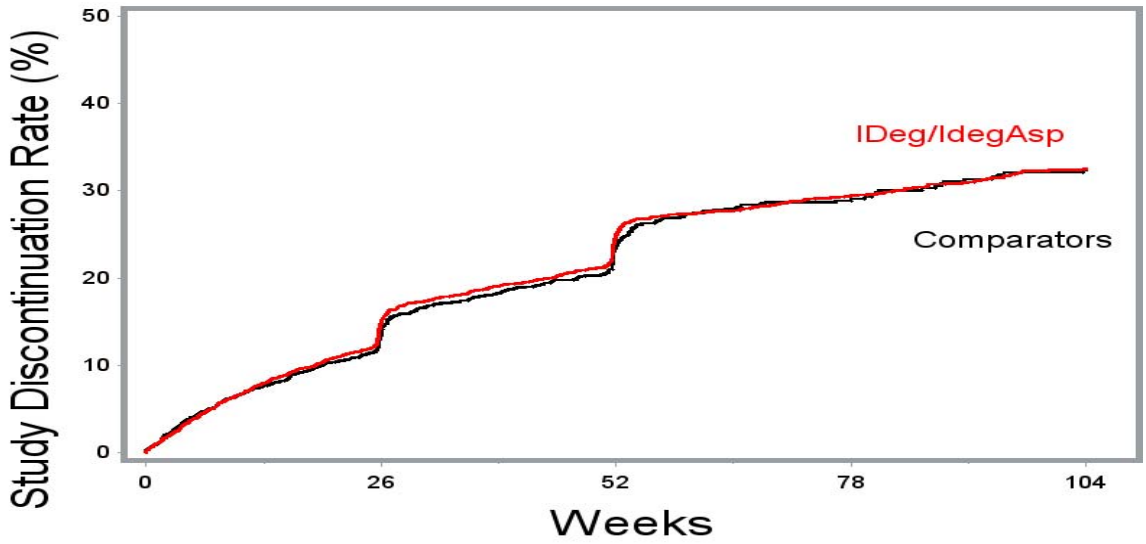
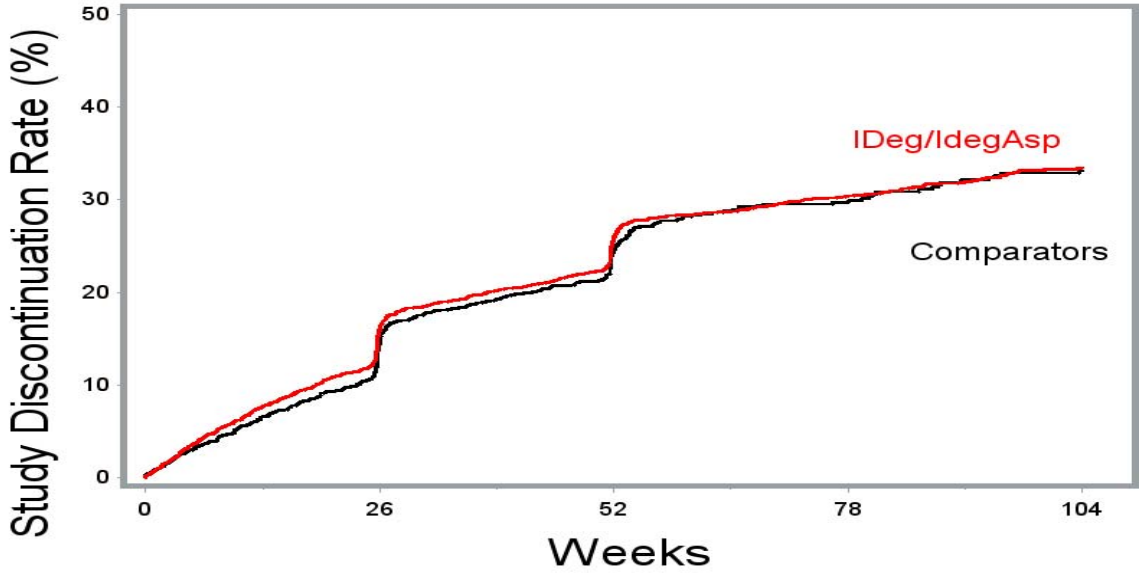
Figure 3: Study Discontinuation Rate in All Trials (FAS, Updated Database)



Source: Created by reviewer.

Figure 4: Study Discontinuation Rate in Trials with Extension (FAS, Updated Database)



Source: Created by reviewer.

3.3.4 Results and Conclusions

As described in Section 3.3.1.2, the agreed upon primary endpoint was MACE+; however additional analyses were requested to assess a strict MACE endpoint. In addition, alternate censoring times (7 days and 30 days) were requested for each endpoint definition. Below, results

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are presented for each endpoint broken down by censoring window. These analyses incorporate all extension trial information (updated database) unless mentioned.

A summary of the observed MACE+ events, along with its individual components, is presented in Table 6 for the 17 trials included in the updated database. 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. Among the 132 subjects who experienced a MACE+ event within a 7 days censoring window, a total of 84, 30, and 18 subjects reported to have ACS (including 41 UAP and 43 MI), stroke, and CV death, respectively. When excluding UAP events, among the 9,255 subjects in the FAS population, 91 subjects have at least one event that was adjudicated as treatment-emergent MACE. A total of 70 subjects in the pooled IDeg/IDegAsp group experienced MACE events (incidence rate of 13.6 per 1,000 person-years), and a total of 21 subjects (incidence rate of 8.2 per 1,000 person-years) in the pooled all comparator group experienced MACE events censored at 7 days.

Table 6: 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.
Source: Created by reviewer.

Table 7 shown on the following page provides the trial level details of individual components of MACE+ events using the 7 days censoring window, broken down by treatment groups.

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Table 7: Summary of MACE+ Events by Study and Treatment Group (FAS, 7 Day Censoring)

Study	Arms	N	MACE+ n (%)	MI n (%)	Stroke n (%)	CV Death n (%)	UAP n (%)
3579+3643	**IDeg**	773	29(3.8)	13(1.7)	8(1.0)	-	8(1.0)
	IGlar	257	4(1.6)	2(0.8)	2(0.8)	-	-
3580	**IDeg**	225	3(1.3)	1(0.4)	1(0.4)	1(0.4)	-
	Sitagliptin	222	3(1.4)	-	1(0.5)	-	2(0.9)
3582+3667	**IDeg**	744	28(3.8)	7(0.9)	7(0.9)	5(0.7)	9(1.2)
	IGlar	248	7(2.8)	3(1.2)	-	1(0.4)	3(1.2)
3583+3644*	**IDeg**	472	8(1.7)	1(0.2)	-	4(0.8)	3(0.6)
	IGlar	157	2(1.3)	-	-	2(1.3)	-
3585+3725*	**IDeg**	302	1(0.3)	-	1(0.3)	-	-
	IDet	153	0(0.0)	-	-	-	-
3586	**IDeg**	289	2(0.7)	1(0.3)	1(0.3)	-	-
	IGlar	146	0(0.0)	-	-	-	-
3668	**IDeg/IDeg Flex**	457	2(0.4)	1(0.2)	1(0.2)	-	-
	IGlar	230	2(0.9)	-	-	1(0.4)	1(0.4)
3672	**IDeg**	228	3(1.3)	2(0.9)	-	-	1(0.4)
	IGlar	229	3(1.3)	1(0.4)	1(0.4)	1(0.4)	-
3718	**IDeg**	233	1(0.4)	-	-	-	1(0.4)
	IGlar	234	2(0.9)	-	-	-	2(0.9)
3724	**IDeg**	229	2(0.9)	1(0.4)	-	-	1(0.4)
	IGlar	230	2(0.9)	-	-	-	2(0.9)
3770+ext*	**IDeg/IDeg Flex**	329	1(0.3)	1(0.3)	-	-	-
	IGlar	164	2(1.2)	-	-	-	2(1.2)
3590+3726	**IDegAsp**	266	7(2.6)	3(1.1)	1(0.4)	2(0.8)	1(0.4)
	IGlar	263	1(0.4)	-	-	1(0.4)	-
3592	**IDegAsp**	224	3(1.3)	2(0.9)	1(0.4)	-	-
	BIAsp	222	2(0.9)	-	-	-	2(0.9)
3593	**IDegAsp**	230	2(0.9)	1(0.4)	-	-	1(0.4)
	IGlar	233	1(0.4)	-	-	-	1(0.4)
3594+3645*	**IDegAsp**	366	0(0.0)	-	-	-	-
	IDet	182	0(0.0)	-	-	-	-
3597	**IDegAsp**	280	1(0.4)	-	1(0.4)	-	-
	BIAsp	142	5(3.5)	3(2.1)	1(0.7)	-	1(0.7)
3896	**IDegAsp**	147	2(1.4)	-	2(1.4)	-	-
	IGlar	149	1(0.7)	-	1(0.7)	-	-
Overall		9255	132(1.4)	43(0.5)	30(0.3)	18(0.2)	41(0.4)

*

Trials in T1DM patients.
Source: Created by reviewer.

3.3.4.1 Time to Event Analysis

The pre-specified primary analysis was the Cox proportional hazards (CPH) model stratified by trial with treatment as a fixed effect. In the following subsections, results for MACE+ (Section 3.3.4.1.1) and MACE (Section 3.3.4.1.2) are presented for the time to event analyses.

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3.3.4.1.1 MACE+ Results

In Table 8, results are presented for the MACE+ endpoint broken down by censoring window (7 and 30 days) utilizing data provided in the original submission (original database) and data provided in the major amendment to the NDA (updated database). With more data incorporated in the updated analyses, the results show an increase in all the HR point estimates for the MACE+ endpoint, compared to the original analyses. Based upon the 7 day censoring window, the HR of IDeg/IDegAsp compared to comparator was 1.30 with a 95% CI of (0.88, 1.93) for MACE+.

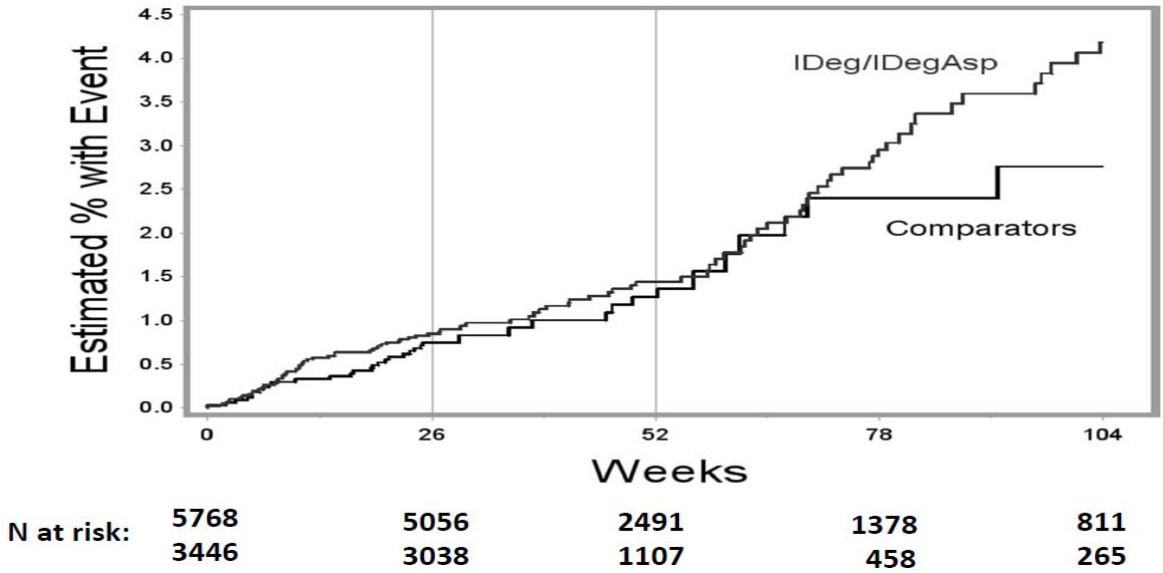
Table 8: CPH Analysis Results for MACE+ based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Database		Updated Database	
	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)

Source: Created by reviewer.

Based on the Kaplan Meier (K-M) method, the cumulative probability of developing a CV-related event as measured by MACE+ (7 day censoring) is shown in Figure 5 for the updated database. For MACE+ the K-M plot shows that the two curves are close to each other up through 73 weeks and then separate around 73 weeks due to only few events collected on the comparator group.

Figure 5: Time to Event Analysis of MACE+ (FAS, 7 Day Censoring)



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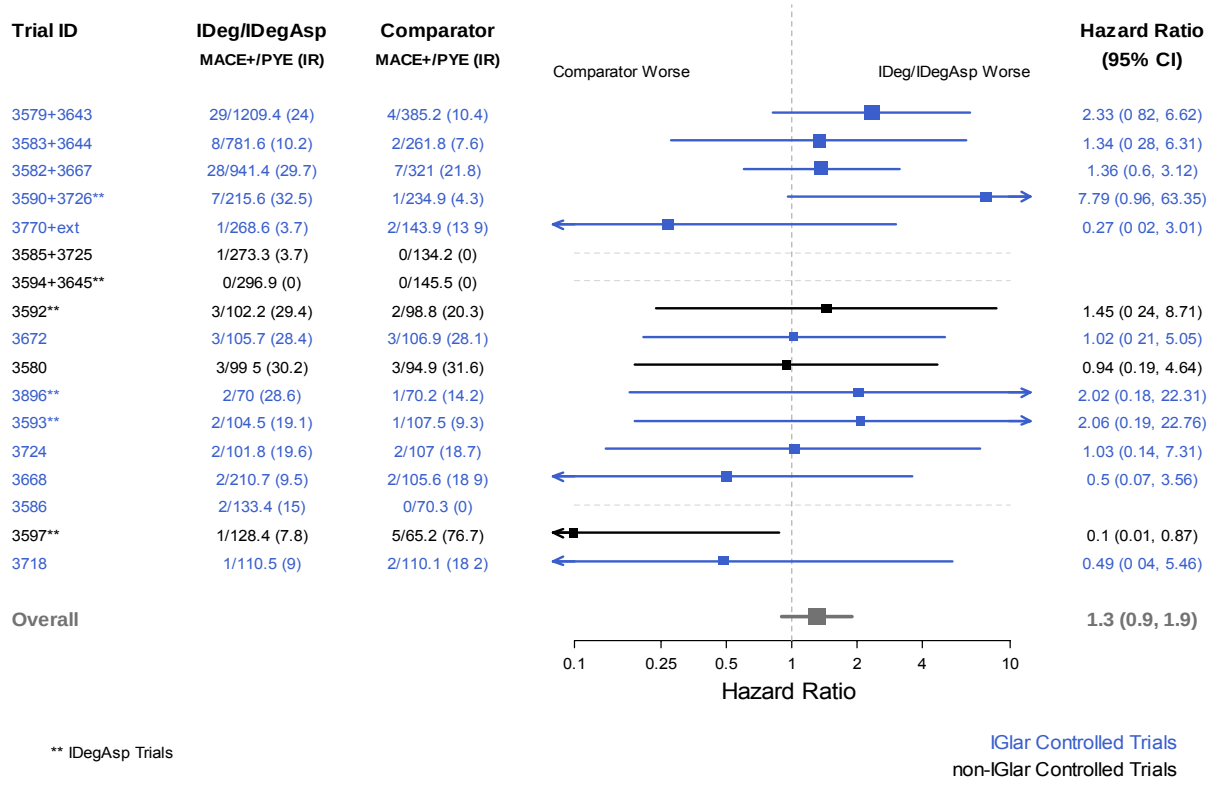
Reference ID: 3250682

The forest plot of the hazard ratios of the MACE+ composite endpoint (censoring at 7 days) is presented in Figure 6 for the updated database. Trials are ordered by the planned duration of treatment (trials with the longest planned treatment duration are presented on the top of the figure and trials with the shortest planned treatment duration are presented at the bottom 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% CI of each trial calculated 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 plot only trials where MACE+ events were observed on both treatment arms include a point estimate for the hazard ratio and the corresponding 95% CI.

Figure 6: Forest Plot of Time-to-Event Analysis of MACE+ (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.1.2 MACE Results

Analogous to the assessment of MACE+, Table 9 depicts analysis results for the MACE endpoint broken down by censoring window (7 and 30 days) and database (original and updated). Similar to results observed with MACE+, estimates of the HR increased with the inclusion of additional data. The estimated HR for MACE was 1.67 with a 95% confidence

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interval of (1.01, 2.75) demonstrating a statistically significant increase in the risk of MACE associated with IDeg/IDegAsp use when using the updated database and a censoring window of 7 days.

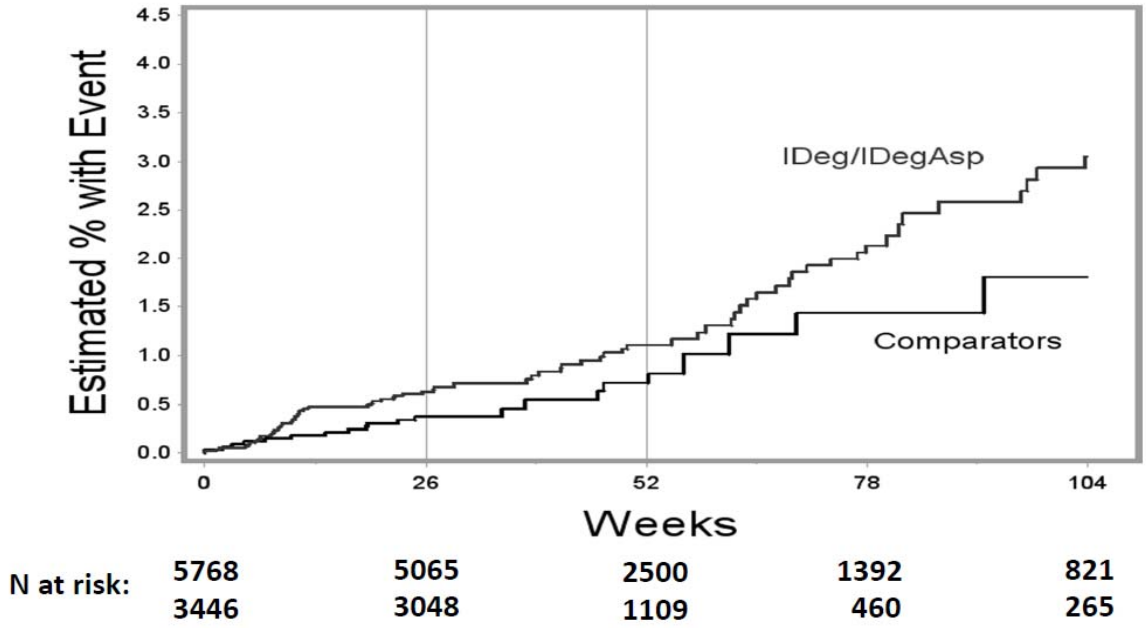
Table 9: CPH Analysis Results for MACE based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (*N* = 5647)	**Comparator** (*N* = 3312)	**IDeg/IDegAsp** (*N* = 5794)	**Comparator** (*N* = 3461)
Censoring: 7 Days				
MACE	39	15	70	21
HR (95% CI)	-	1.39 (0.76, 2.57)	-	1.67 (1.01, 2.75)
Censoring: 30 Days				
MACE	42	15	74	23
HR (95% CI)	-	1.50 (0.82, 2.75)	-	1.61 (1.00, 2.61)

Source: Created by reviewer.

Figure 7 depicts the K-M plot for MACE. In the pooled IDeg/IDegAsp group, MACE events occurred earlier and more often than those in the pooled all comparator group. Overall, the IDeg/IDegAsp treatment arm consistently has a higher percentage of MACE events over time.

Figure 7: Time to Event Analysis of MACE (FAS, 7 Day Censoring)

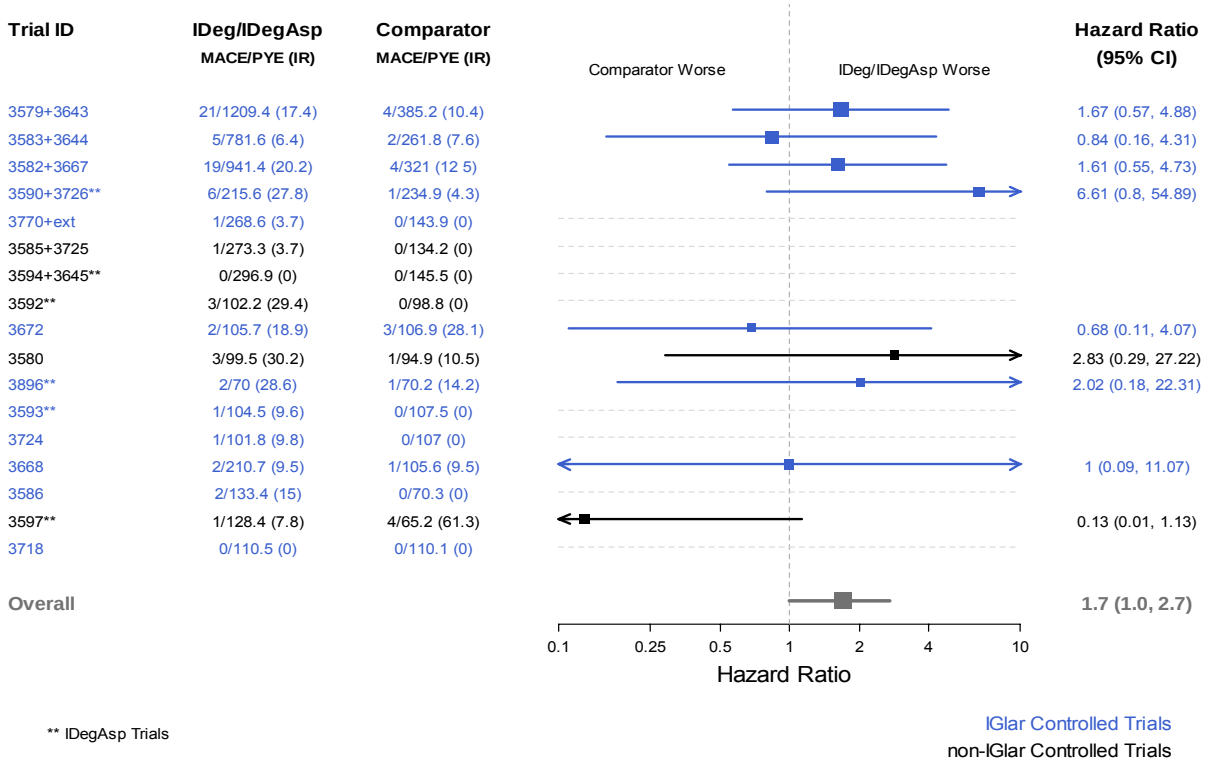


Source: Created by reviewer.

The forest plot for MACE is presented in Figure 8. Construction of this figure follows that previously described for MACE+. Due to the fewer number of MACE events as compared to MACE+, within-trial HR estimates cannot be calculated for more trials with zero MACE on one or both arms.

Reference ID: 3250682

Figure 8: Forest Plot of Time-to-Event Analysis of MACE (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.2 Secondary Analysis

Trials with no events were excluded from the time-to-event analysis method when using the Cox proportional hazards model stratified by trial. In order to incorporate trials with zero events, risk difference and the difference of incidence rates were calculated using Mantel-Haenszel methods.

3.3.4.2.1 MACE+ Results

The results for the updated database when censoring at 7 days or 30 days are shown below in Table 10 for MACE+. Consistent with the primary analysis, the results from the secondary analysis also suggest an increased CV risk for subjects randomized to IDeg/IDegAsp over comparator.

Table 10: Updated Database Secondary Analysis Results for MACE+ (FAS, 7 and 30 Day Censoring)

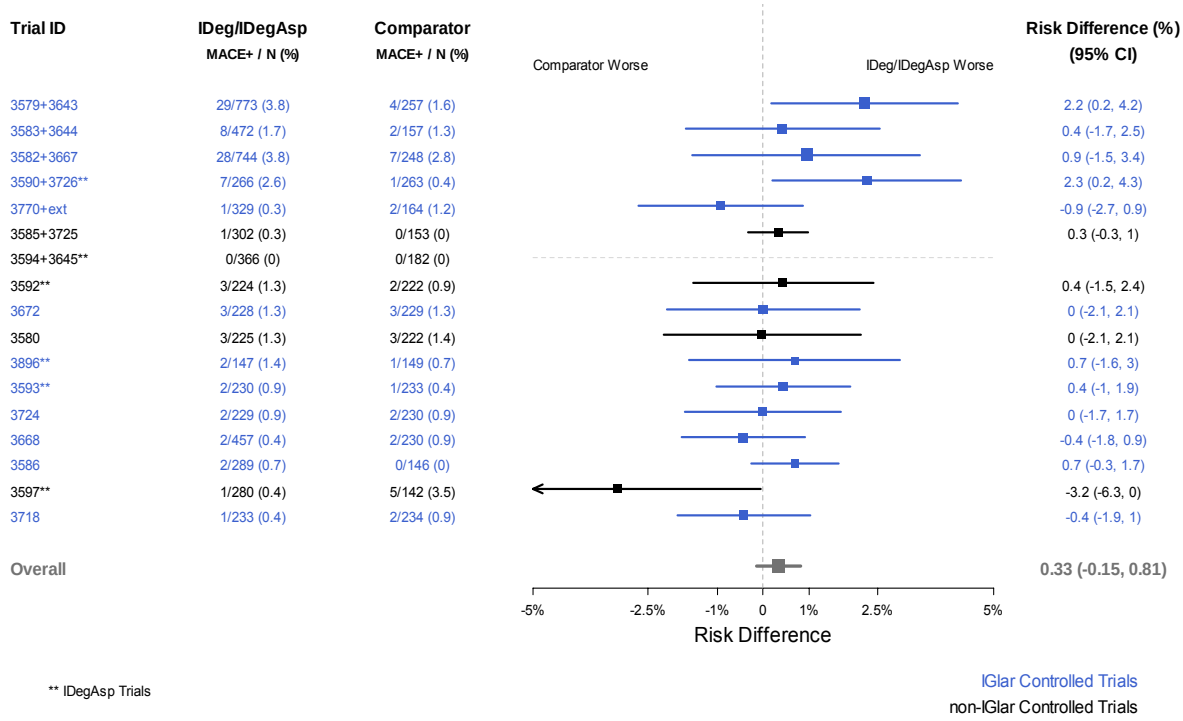
	Censoring: 7 Days		*Censoring: 30 Days*	
	Estimate	95% CI	Estimate	95% CI
M-H Risk Difference (%)	0.33	(-0.15, 0.81)	0.33	(-0.16, 0.82)
M-H Incidence Rate Difference†	4.27	(-1.84, 10.4)	4.27	(-1.97, 10.5)

† Incidence per 1,000 PYE
Source: Created by reviewer.

Reference ID: 3250682

Following a similar construct as Figures 6 and 8, a forest plot based upon the risk difference is presented in Figure 9 for the MACE+ endpoint when censoring at 7 days. Within a trial, asymptotic methods are used to provide an estimate of the risk difference and the corresponding 95% confidence interval 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 9: Forest Plot of Risk Difference of MACE+ (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.2.2 MACE Results

Similar to the MACE+ composite endpoint, Table 11 provides the secondary analysis results for MACE in the updated database when censoring at 7 days and 30 days respectively. Consistent with the primary analysis, the results suggest a statistically significant increase of risk to develop a MACE event for subjects randomized to IDeg/IDegAsp compared to control.

Table 11: Updated Database Secondary Analysis Results for MACE (FAS, 7 and 30 Day Censoring)

	Censoring: 7 Days		*Censoring: 30 Days*	
	Estimate	95% CI	Estimate	95% CI
M-H Risk Difference (%)	0.42	(0.03, 0.82)	0.42	(0.02, 0.83)
M-H Incidence Rate Difference†	5.41	(0.37, 10.5)	5.42	(0.20, 10.6)

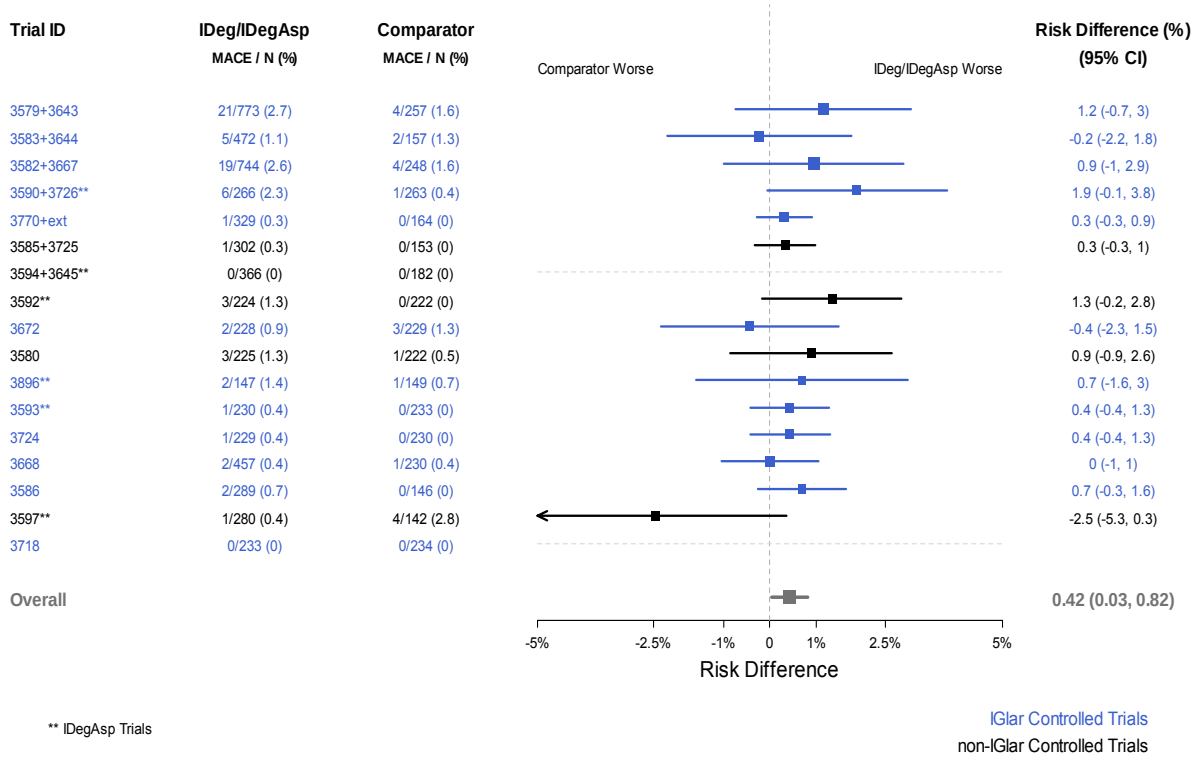
† Incidence per 1,000 PYE

Source: Created by reviewer.

Reference ID: 3250682

Figure 10 is the forest plot based upon the risk difference for the MACE endpoint when censoring at 7 days. None of the 17 randomized phase 3 trials show a statistically significant difference between IDeg/IDegAsp and comparator; however, 11 of 17 trials had estimates of the risk difference in favor of the comparator and the lower bound of 95% CI of overall risk difference is above the null value.

Figure 10: Forest Plot of Risk Difference of MACE (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.3 Sensitivity Analysis

3.3.4.3.1 Assessment of the individual components of MACE+

To explore which cardiovascular event components of MACE+ contributed to the composite primary endpoint, the hazard ratio for each component was calculated using a stratified Cox regression model similar to that used in the primary analysis. Figure 11 presents a forest plot of these hazard ratios in reference to the hazard ratio for the composite primary endpoint. It can be observed in this figure that of the individual components comprising MACE+, myocardial infarction and stroke have HR point estimates around 2, whereas CV death has a HR point estimate near 1. The HR point estimate for unstable angina was below 1 suggesting an increase in risk for the pooled comparator arm. The exclusion of UAP demonstrates why the point estimate of CV risk is higher for strict MACE versus MACE+. Note that none of the individual components of MACE+ demonstrated a statistically significant increase.

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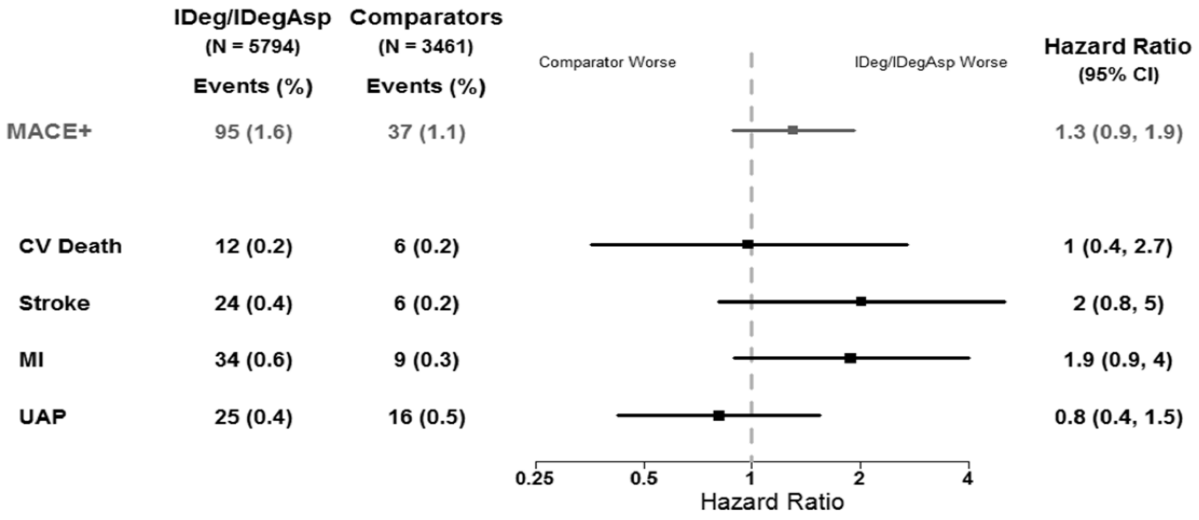
Figure 11: Forest Plot of Time-to-Event Analysis of MACE+ components (FAS, 7 Day censoring)



Source: Created by reviewer.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In the following sections, analysis results for CV related safety endpoints (censoring at 7 days for the updated database) are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted 95% confidence intervals for each of the subgroup analyses.

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender

Among the 9,255 subjects in the FAS population, 5,162 (55.8%) were male and 4,093 (44.2%) were female. Among the 132 subjects with MACE+ events, 90 were reported in male subjects and 42 were reported in female subjects. Among the 91 subjects with strict MACE events, 65 were reported in male subjects and 26 were reported in female subjects. The results of subgroup analysis by gender are presented in Table 12 for both MACE+ and MACE.

Among male subjects, the risk of developing a CV related event as measured by either MACE+ or MACE was higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. The signal is stronger in magnitude for strict MACE, compared to the broader definition MACE+. In contrast, among female subjects, there is no obvious difference in CV risk for the two comparison groups.

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Table 12: Subgroup Analysis Results by Gender (FAS, 7 Day Censoring)

	Female (*N* = 4093)	Male (*N* = 5162)
MACE+		
HR (95% CI)	1.03 (0.53, 1.99)	1.49 (0.91, 2.42)
MACE		
HR (95% CI)	1.09 (0.46, 2.56)	2.08 (1.11, 3.88)

Source: Created by reviewer.

4.1.2 Race

Among the 9,255 subjects in the FAS population, 6,271 (67.8%) were White, 460 (5.0%) were Black, 2,358 (25.5%) were Asian (including both Asian Indian and Asian non-Indian), and 166 (1.8%) were subjects with other races. Among the 132 subjects with MACE+ events, 102 were reported in White subjects, 8 were reported in Black subjects, 21 were reported in Asian subjects, and 1 was reported in a subject classified as other race. Among the 91 subjects with strict MACE events, 68 were reported in White subjects, 5 were reported in Black subjects, 17 were reported in Asian subjects, and 1 was reported in a subject classified as other race. The results of the subgroup analysis by race are presented in Table 13 for both endpoints.

Among White subjects, the risk of developing a CV related event as measured by MACE+ or MACE was higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. Similarly, among Black subjects, the risk was higher in the IDeg/IDegAsp group than in the comparator group, with a larger magnitude and wider 95% confidence interval due to the smaller sample of Black subjects. In contrast, among Asian subjects, the risk appeared to be lower in the IDeg/IDegAsp group while the difference was not statistically significant.

Table 13: Subgroup Analysis Results by Race (FAS, 7 Day Censoring)

	White (*N* = 6271)	Black (*N* = 460)	Asian (*N* = 2358)
MACE+			
HR (95% CI)	1.48 (0.93, 2.36)	3.65 (0.43, 31.0)	0.58 (0.24, 1.39)
MACE			
HR (95% CI)	2.13 (1.12, 4.02)	2.51 (0.26, 23.9)	0.69 (0.26, 1.83)

Source: Created by reviewer.

4.1.3 Age

Among the 9,255 subjects in the FAS population, 7,345 (79.4%) were 65 years or younger, and 1,910 (20.6%) were older than 65. Among the 132 subjects with MACE+ events, 82 events were reported in subjects aged 65 years or younger, while 50 events were reported in subjects older than 65 years. Among the 91 subjects with strict MACE, 56 events were reported in subjects aged 65 years or younger, while 35 events were reported in subjects older than 65. The results of subgroup analysis by age are presented in Table 14 for both endpoints.

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Among subjects aged 65 years or younger, the risk of developing a CV related event as measured by the composite endpoints MACE+ or MACE was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. Among subjects older than 65, the risk appeared to be higher in the IDeg/IDegAsp group, with a larger magnitude compared to the younger age group.

Table 14: Subgroup Analysis Results by Age (FAS, 7 Day Censoring)

	<= 65 yrs	**> 65 yrs**
	(*N* = 7345)	(*N* = 1910)
MACE+		
HR (95% CI)	1.10 (0.68, 1.77)	1.78 (0.89, 3.53)
MACE		
HR (95% CI)	1.30 (0.72, 2.37)	2.70 (1.03, 7.09)

Source: Created by reviewer.

4.1.3 Region

Among the 9,255 subjects in the FAS population, 2,850 (30.8%) were randomized in the USA, and 6,405 (69.2%) were randomized in other countries. Among the 132 subjects with MACE+ events, 57 events were reported in US participants, while 75 events were reported in other countries. Among the 91 subjects with strict MACE events, 34 events were reported in US participants, while 57 events were reported in other countries. The results of subgroup analysis by region are presented in Table 15 for both endpoints. In general, the HR estimates are consistent between US and non-US regions for the two endpoints and both show a risk increase in the combined IDeg/IDegAsp group, compared to control.

Table 15: Subgroup Analysis Results by Region (FAS, 7 Day Censoring)

	US	**Non-US**
	(*N* = 2850)	(*N* = 6405)
MACE+		
HR (95% CI)	1.31 (0.71, 2.41)	1.30 (0.78, 2.17)
MACE		
HR (95% CI)	1.77 (0.75, 4.16)	1.62 (0.87, 3.01)

Source: Created by reviewer.

4.2 Other Special/Subgroup Populations

Several special subgroup analyses were conducted at the trial level. These included assessments in IGlar controlled trials only, in trials using IDeg as treatment and in trials conducted in type 1 and type 2 diabetes subjects separately. In these trial-level subgroup analyses, a Cox proportional hazard model stratified by trial was used to calculate the HR and its 95% CI for the two endpoints MACE+ and MACE censored at 7 days. Estimates of risk difference and its 95% CI were also calculated using the stratified Mantel-Haenszel method.

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4.2.1 IGlar-controlled Trials

Among the various control arm treatments used in the IDeg/IDesAsp development programs, insulin glargine (IGlar) was the most commonly used comparator. A total of 12 studies utilized IGlar as the control (Studies 3579+3643, 3582+3667, 3583+3644, 3586, 3668, 3672, 3718, 3724, 3770+ext, 3590+3726, 3593, and 3896). In total, 6,937 subjects were randomized in the IGlar-controlled trials. The analysis results are presented in Table 16 for the trials using IGlar as the control arm. For MACE+, there is an estimated 54% elevated risk for IDeg/IDegAsp arm compared to IGlar. The estimated risk elevation increases to 82% for strict MACE.

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

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

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

4.2.2 IDeg Trials

Data from the 7 IDeg trials without using Insulin Aspart (IAsp) as background therapy were combined for a trial-level subgroup analysis (Studies 3579+3643, 3580, 3586, 3668, 3672, 3718 and 3724). A total of 3,982 subjects were randomized in these IDeg trials. The analysis results are presented in Table 17. In this trial-level subgroup, the estimated hazard ratios were 1.35 for MACE+ and 1.64 for MACE, both showing CV risk increase in IDeg arm compared with other comparators.

Table 17: Analysis Results for MACE+/MACE in IDeg Trials with no IAsp Use (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg	Comparator	IDeg	Comparator
N	2434	1548	2434	1548
Events (IR*)	42 (21.3)	16 (16.3)	31 (15.7)	9 (9.2)
HR (95% CI)	1.35 (0.75, 2.44)		1.64 (0.77, 3.51)	
RD (%) (95% CI)	0.41 (-0.27, 1.10)		0.43 (-0.13, 1.00)	

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

4.2.3 Type of Diabetes

Trials 3583+3644, 3585+3725, 3770+ext and 3594+3645 were conducted in type 1 diabetes subjects, while all other trials enrolled type 2 diabetes subjects. Among the 9,255 subjects in the FAS population, 2,125 (23.0%) were subjects with TIDM, and 7,130 (77.0%) were subjects with T2DM. Among the 132 subjects with MACE+ events, 14 events were reported in T1DM

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subjects while 118 events were reported in T2DM subjects. Among the 91 subjects with strict MACE events, 9 events were reported in T1DM subjects while 82 events were reported in T2DM subjects.

4.2.3.1 Type 1 Diabetes

As presented in Table 18, among T1DM subjects, the HR estimate of MACE+ is close to null and the risk of developing a strict MACE event was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. In these trials only a small number of events were observed with low incident rates.

Table 18: Analysis Results for MACE+/MACE in T1DM patients (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
N	1469	656	1469	656
Events (IR*)	10 (6.2)	4 (5.8)	7 (4.3)	2 (2.9)
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)	

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

4.2.3.2 Type 2 Diabetes

In contrast, among subjects with T2DM, the risk of either MACE+ or MACE tends to be higher in the IDeg/IDegAsp group than in the comparator group, as presented in Table 19.

Table 19: Analysis Results for MACE+/MACE in T2DM patients (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
N	4325	2805	4325	2805
Events (IR*)	85 (24.0)	33 (17.6)	63 (17.8)	19 (10.1)
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)	

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

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary agreed upon composite endpoint for CV safety evaluation was MACE+, comprised of unstable angina pectoris, myocardial infarction, stroke, and CV death. The agreed upon primary analysis was based on 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)

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versus the all comparator group which consisted of insulin glargine, insulin detemir, biphasic insulin aspart, and sitagliptin. An analysis of the data that was submitted to the NDA (original database) 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 NDA submission.

The additional data provided in the response to the information request formed the updated database which included data from 6 extension trials and one new trial. The inclusion of extension trials in the CV meta-analysis was pre-specified in the applicant's statistical analysis plan which was agreed upon with the Agency prior to the NDA submission. An area of consideration is whether such extension trial should be incorporated into the meta-analysis as enrollment into the extension trials was based upon a voluntary election of trial participants. Our assessment of the updated database found it to be robust and appropriate for the evaluation of the CV risk of IDeg/IDegAsp as shown in Section 3.3.3.1.

In the updated database, data from the 17 randomized therapeutic confirmatory Phase 3 trials and their extension trials were synthesized to evaluate the risk of developing a CV related event as measured by the primary composite endpoint. Additional analyses were conducted based on a more strict MACE definition which excludes UAP from the MACE+ endpoint. In the updated database, MACE+/MACE events were ascertained either within 7 days or within 30 days after treatment discontinuation. As a secondary analysis, the Mantel-Haenszel risk difference and incidence rate difference approach were also employed to evaluate the CV risk. In summary, the CV risk of IDeg/IDegAsp was assessed by applying stratified Cox regression model and Mantel-Haenszel methods to the MACE+ and MACE composite endpoints censoring data at 7 days and 30 days. The statistical methods applied to this application are similar to those used in other meta-analyses of CV risk which are felt to be sufficient in characterizing the CV risk. More details for the statistical methodologies used in this review are provided in Section 3.3.2.

5.2 Collective Evidence

Based on the updated pooled data of all 17 randomized phase 3 trials including extensions, a total of 132 subjects experienced at least one adjudicated MACE+ event censored at 7 days, with 95 subjects in the pooled IDeg/IDegAsp group and 37 subjects in the pooled all comparator group. The incidence rate of MACE+ was 18.4 per 1,000 person-years in the pooled IDeg/IDegAsp group, as compared to 14.4 per 1,000 person-years in the pooled all comparator group. The estimated hazard ratio of IDeg/IDegAsp compared to all comparator was 1.30 with a 95% CI of (0.88, 1.93) for MACE+. Detailed analysis results are provided in Section 3.3.4.1.1.

Using the strict definition of MACE, a total of 91 subjects experienced at least one adjudicated MACE event censored at 7 days, with 70 subjects reporting an event in the pooled IDeg/IDegAsp group and 21 subjects reporting an event in the pooled all comparator group. The

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incidence rate of MACE was 13.6 per 1,000 person-years in the pooled IDeg/IDegAsp group, as compared to 8.2 per 1,000 person-years in the pooled all comparator group. The estimated hazard ratio of IDeg/IDegAsp compared to all comparator was 1.67 with a 95% CI of (1.01, 2.75) for strict MACE. Detailed analysis results are provided in Section 3.3.4.1.2.

As shown in Section 3.3.4.2, the Mantel-Haenszel risk difference and incidence rate difference results are consistent with the primary analysis results based on the hazard ratio.

The difference between IDeg/IDegAsp and all comparator in developing a CV related event as measured by MACE+/MACE was also evaluated in subgroups by age, gender, race and region. Some trial-level subgroup analyses were also conducted in IGlar-controlled trials, IDeg trials, trials in T1DM and T2DM subjects separately. Most of the subgroup analysis results were in the same direction as the overall result. Detailed results for subgroup analyses are provided in Section 4.

5.3 Conclusions and Recommendations

The Agency considered the updated database robust and appropriate for the evaluation of cardiovascular safety. Based on the meta-analysis of the 17 randomized phase 3 trials and their extensions included in the updated database, the risk of developing a major adverse cardiovascular event, as measured by MACE+ censored at 7 days, was higher in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) relative to the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Compared to the pooled all comparator group, the estimated hazard ratio of IDeg/IDegAsp is 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) using a 7 day censoring window, as shown in Table 20 below.

Table 20: Primary Analysis Results for MACE+/MACE (Updated Database, FAS, 7 Day Censoring)

		IDeg/IDegAsp (*N* = 5794) [PYE = 5153.6]	**Comparator** (*N* = 3461) [PYE = 2562.7]
MACE+ Endpoint			
	Events [IRD*]	95 [18.4]	37 [14.4]
	HR (95% CI)†	1.30 (0.88, 1.93)	
MACE Endpoint			
	Events (IRD*)	70 [13.6]	21 [8.2]
	HR (95% CI)†	1.67 (1.01, 2.75)	

*: Per 1,000 PYE. †: Cox proportional hazards model stratified by trial
Source: Created by reviewer.

In addition to the above approaches, several additional analyses were conducted that explored various censoring windows, incorporated different effect measures (risk difference and incidence rate difference), and examined various subsets of trials and subgroup analyses. While various

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scenarios resulted in different values of the hazard ratio and risk difference point estimates, a consistent trend was observed – IDeg/IDegAsp was shown to be associated with an increase in CV risk.

To determine if the increase in CV risk as seen from the meta-analysis of these 17 trials is a chance finding, further evidence from a dedicated CV outcome trial would be needed.

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/s/

BO LI
12/13/2012
CV meta-analysis of IDeg/IDegAsp

MATTHEW J SOUKUP
12/13/2012
Concur with review

ALOKA G CHAKRAVARTY
12/13/2012

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/s/

BO LI
01/29/2013

MATTHEW J SOUKUP
01/29/2013
Concur with review

ALOKA G CHAKRAVARTY
01/29/2013

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

TEAM LEADER MEMORANDUM

NDA/BLA #:	NDA 203-314, NDA 203-313
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250) Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted: September 29, 2011 Major Amendment: May 16, 2012 (or May 11 for the report) Goal Date: December 14, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Team Lead:	Mat Soukup, Ph.D.
Concurring Reviewers:	Mark Levenson, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer (efficacy): Jean-Marc Guettier, M.D. Medical Officer (safety): Karim Calis, M. D.
Project Manager:	Rachel Hartford, M.S. (DMEP)

Introduction

This memorandum is meant to provide a statistical perspective on a future dedicated cardiovascular outcome trial (CVOT) to further assess the adverse cardiovascular signal observed in the Phase 3 development program of insulin degludec (IDeg) and insulin degludec/insulin aspart (IDegAsp). I concur with the statistical assessment of Dr. Bo Li as summarized in her statistical review. I briefly summarize the main statistical findings from her review followed by a discussion of design characteristics and sample size calculations that should be considered in the future dedicated CVOT.

Summary of Statistical Findings for CV Safety

Based upon a pre-specified statistical analysis plan for a meta-analysis to assess the cardiovascular risk of a pooled IDeg and IDegAsp arm relative to comparator, a potential adverse cardiovascular signal was observed. This was based upon the assessment of 17 randomized, open-label, treat-to-target, non-inferiority clinical trials which were designed primarily for the assessment of efficacy with prospective capture of key cardiovascular events that underwent adjudication by an independent, blinded committee. Of the 17 trials, 7 trials included voluntary enrollment into extension trials which were pre-specified to be included in the meta-analysis per the statistical analysis plan and agreed upon with the Agency prior to NDA submission.

The primary analysis was based upon major adverse cardiovascular events (MACE+), a composite endpoint, which consisted of four components: cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, and unstable angina pectoris. Additionally, the Agency requested the sponsor also assess a strict MACE endpoint which excluded the unstable angina component. A total of 132 **MACE+** events were observed in 9255 randomized subjects of which 95 events were reported in subjects randomized to IDeg/IDegAsp (rate of 1.6%, incidence rate of 18.4 per 1000 person years exposure) and 37 events were reported in subjects randomized to comparators (rate of 1.1%, incidence rate of 14.4 events per 1000 person years of exposure). A total of 91 **MACE** events were observed in 9255 randomized subjects of which 70 events were reported in subjects randomized to IDeg/IDegAsp (rate of 1.2%, incidence rate of 13.6 per 1000 person years exposure) and 21 events were reported in subjects randomized to comparators (rate of 0.6%, incidence rate of 8.2 events per 1000 person years of exposure).

A Cox proportional hazards model, stratified by trial, was the pre-specified primary analysis for the full analysis set to estimate the hazard ratio of IDeg/IDegAsp relative to the pooled comparators along with the corresponding 95% confidence interval. Table 1 depicts the analysis results as reported in Dr. Li's statistical review. Based upon the Cox proportional hazards model, the estimated HR for MACE was 1.30 with a corresponding 95% CI of (0.88, 1.93). The estimated HR for the strict MACE endpoint was 1.67 with a corresponding 95% CI of (1.01, 2.75). Both endpoints suggest an increase in CV risk of IDeg/IDegAsp relative to the pooled comparator arm.

Table 1. Summary of Primary Analysis (FAS, censoring time 7 days)

		IDeg/IDegAsp (*N* = 5794) [PYE = 5153.6]	Comparator (*N* = 3461) [PYE = 2562.7]
MACE+ Endpoint			
	Events [IRD]	95 [18.4]	37 [14.4]
	HR (95% CI)†		1.30 (0.88, 1.93)
MACE Endpoint			
	Events (IRD)	70 [13.6]	21 [8.4]
	HR (95% CI)†		1.67 (1.01, 2.75)

†Cox proportional hazards model stratified by trial.
Source: Dr. Bo Li's statistical review.

Dr. Li's statistical review includes additional analyses of which a consistent trend of an increase in CV risk was observed. These trends were observed across various endpoints, statistical effect measures, analysis methods, and subgroup analyses.

Design Elements for a Future Dedicated Cardiovascular Outcome Trial

To evaluate the cardiovascular potential of IDeg and IDegAsp, a randomized, event-driven trial should be conducted utilizing an appropriate control arm. If such a trial cannot be designed in a double-blind fashion, the trial should ensure, at a minimum, that adjudication of events and event ascertainment be conducted in such a manner to reduce any potential for bias in event capture. The trial should be designed to rule out an amount of excess of risk that is in agreement with the clinical review team (note that sample size calculations are provided below in Table 2 for various choices of the risk margin – i.e. the amount of relative excess risk to be ruled out). As the trial will be event-driven, the sponsor would be encouraged to recruit subjects at higher CV risk to minimize the number of person years needed to observe the targeted number of events (Table 2 depicts expected person years needed for several background event rates).

The primary statistical analysis should be based upon the Cox proportional hazards model using a two-sided alpha=0.05 statistical significance level. To meet the primary objective, the upper bound of the two-sided 95% confidence interval must be less than the risk margin with a reassuring HR point estimate.

Table 2 provides sample size calculations under the following assumptions – note that modifications to either the assumed true HR or the power would impact the size of the study and these should be determined by the sponsor.

- Power = 90%
- Type 1 error = 0.05 (two-sided)
- True HR = 1.0

The table is meant to serve as a guideline for the size of the trial for a given risk margin, where the size of the trial is depicted by the number of events (column 2) and the number of person years expected to observe the number of events based on the background event rate (columns 4 through 6).

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

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/s/

MATTHEW J SOUKUP
12/13/2012

MARK S LEVENSON
12/13/2012

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 AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 203-314, NDA 203-313
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250)
	Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted: September 29, 2011
	Major Amendment: May 16, 2012
	Goal Date: December 14, 2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Bo Li, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D.
	Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer (efficacy): Jean-Marc Guettier, M.D.
	Medical Officer (safety): Karim Calis, M. D.
Project Manager:	Rachel Hartford, M.S. (DMEP)

Keywords: clinical studies, meta-analysis, diabetes mellitus, cardiovascular safety, major adverse cardiovascular event (MACE)

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1 EXECUTIVE SUMMARY

Dr. Xiao Ding performed the statistical review (signed on April 16, 2012) of NDAs 203-313 and 203-314 to evaluate the cardiovascular (CV) safety of IDeg and IDegAsp based upon data available at the time of NDA submission. Findings from this cardiovascular meta-analysis raised concerns about a potential increase of CV risk associated with IDeg/IDegAsp use. These findings triggered an information request to the applicant to provide additional data from trials that were still ongoing at the time of NDA submission as well as an updated study report for CV meta-analysis. This additional data included information from 1 new Phase 3 trial and data from 6 planned extension trials that were integrated into the updated meta-analysis. An area of consideration is whether data from the extension trials should be incorporated into the meta-analysis as enrollment into the extension trials was based upon a voluntary election of trial participants. Our assessment of the updated database found it to be robust and appropriate for the evaluation of the CV risk of IDeg/IDegAsp as presented in Section 3.3.3.1.

This statistical review assesses cardiovascular related safety endpoints by utilizing the updated database that includes 17 randomized Phase 3 clinical trials, including data from planned extension trials, for which IDeg (Studies 3579+3643, 3580, 3582+3667, 3583+3644, 3585+3725, 3586, 3668, 3672, 3718, 3724 and 3770+ext) as well as IDegAsp (Studies 3590+3726, 3592, 3593, 3594+3645, 3597 and 3896) were investigated for safety and efficacy. This database includes information on 9,255 randomized subjects (5,794 randomized to IDeg/IDegAsp and 3,461 randomized to comparator) with a total exposure of roughly 7,700 person years (5,154 PY for subjects randomized to IDeg/IDegAsp, and 2,563 PY for subjects randomized to comparator). Refer to Section 2 for a description of the 17 trials. This review focuses solely on the evaluation of CV safety as measured by two composite major adverse cardiovascular event endpoints.

Based upon both the pre-specified primary analysis and additional analyses, the meta-analysis of these 17 randomized phase 3 trials showed an increased risk of developing major adverse cardiovascular event (MACE+: composite of CV death, acute coronary syndrome including unstable angina pectoris and myocardial infarction, and stroke) in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) compared to the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Utilizing the pre-specified Cox proportional hazards model stratified by trial, the estimate of the MACE+ hazard ratio was 1.30 with a 95% CI of (0.88, 1.93). Secondary analyses, based upon the risk difference and incidence rate difference, showed similar trends. The risk difference of MACE+ between IDeg/IDegAsp and all comparator was 0.33%, with a 95% CI of (-0.15%, 0.81%). The difference of MACE+ incidence rates between IDeg/IDegAsp and all comparator was 4.27 per 1,000 person-years of exposure with a 95% CI of (-1.84, 10.4) per 1,000 person-years of exposure. See Section 3.3.4.1.1 for full analysis results of the MACE+ endpoint.

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In addition to the additional data that were submitted in response to the Agency's information request, the Agency also requested the applicant to assess CV effects on a strict MACE endpoint that excluded hospitalization for unstable angina from the MACE+ composite endpoint – this is referred to as the MACE composite endpoint. A total of 91 MACE were reported across the 17 trials, of which 70 were reported (incidence rate of 13.6 events per 1,000 person years) on the IDeg/IDegAsp treatment arm and 21 were reported (incidence rate of 8.2 events per 1,000 person years) on the comparator arm. This resulted in a hazard ratio estimate of 1.67 with a 95% CI of (1.01, 2.75) calculated by Cox proportional hazards model stratified by trial. This result suggests an increase in risk of developing a strict MACE event associated with IDeg/IDegAsp use with a greater magnitude of CV risk compared to MACE+.

In addition to assessing CV risk with alternate composite endpoints, statistical analyses were conducted to assess CV risk using alternate statistical effect measures, databases (i.e. inclusion/exclusion of extension trial data), analysis methods, and subgroup analyses. In general, a consistent trend showing an increase in CV risk associated with IDeg/IDegAsp was seen. To determine if the increase in CV risk as seen from the meta-analysis of these 17 trials is a chance finding, further evidence from a dedicated CV outcome trial would be needed.

2 INTRODUCTION

2.1 Overview

Insulin degludec (IDeg) is an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. The proposed indication of IDeg is to improve glycemic control in adults with diabetes mellitus as a once daily, (b) (4) human insulin analog.

Insulin degludec/insulin aspart (IDegAsp) is composed of IDeg and insulin aspart, a rapid-acting human insulin analog. Insulin aspart (trade name: NovoLog) was approved by the Agency on June 7, 2000 under NDA 20-986. The proposed indication of this co-formulated product is to improve glycemic control in adults with diabetes mellitus with once or twice-daily dosing at any main meal.

The initial cardiovascular related safety meta-analyses utilized an integrated dataset of IDeg and 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). For the details of each of the 16 trials and the original meta-analysis of the CV risk of these 16 trials, please refer to the review signed by Dr. Xiao Ding on April 16, 2012.

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Results from the initial analysis and Dr. Ding's review 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 applicant 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 database.

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[1] (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). The extension trials maintained the randomized treatment assignment of the main trials and enrollment into these trials was voluntary. Further details on utilizing the extension trial information is provided in Section 3.3.3.1. Trial 3846 investigated two titration algorithms with IDeg in 222 subjects with type 2 diabetes and Trial 3923 evaluated treatment with IDeg 200 U/mL versus IDeg 100 U/mL in 373 subjects with type 2 diabetes. Both were open-label, randomized trials of 26 and 22 weeks duration, respectively, that randomized subjects to either of the two IDeg treatment arms. Therefore, while these two trials 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 included 17 trials. Note that this update does include the trial information provided in the original submission. This review primarily focuses on the updated safety analyses and database submitted by the applicant in May 2012, as a response to the Agency's information request. A summary of design characteristics of these 17 trials is presented in Table 1.

2.2 Data Sources

As a response to the Agency's information request, the applicant submitted an NDA major amendment which included the results of the updated meta-analysis as well as the updated database, as described above. This update was received on May 11, 2012. The EDR link to the study report is provided below.

\\Cdsesub1\evsprod \NDA203314\0018\m1\us\102-cover-letters\cover.pdf

On May 16, 2012, the applicant submitted pooled analysis datasets for the meta-analysis of cardiovascular safety. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review:

\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\mabr.xpt
\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\mabrt.xpt
\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\mana.xpt

[1] The main trial and the corresponding extension trial are notated as main trial ID + extension trial ID.

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\\Cdsesub1\evsprod\NDA203314\0020\m5\datasets\cv-metaanalysis\analysis\manat.xpt

As requested by the Agency for additional information, the applicant also submitted electronic datasets for the following as such information was not provided for the updated trial database:

- subject disposition,
- adverse events, and
- baseline characteristics including cardiovascular risk factors.

This data can be accessed from the eCTD locations

\\Cdsesub1\evsprod\NDA203314\0025\m5\datasets\cv-metaanalysis\analysis\disp1.xpt
\\Cdsesub1\evsprod\NDA203314\0026\m5\datasets\cv-metaanalysis\analysis\adv-1.xpt
\\Cdsesub1\evsprod\NDA203314\0031\m5\datasets\cv-metaanalysis\analysis\base1.xpt
.

Table 1: 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 3.3.3.
* The duration of Study 3594 was 26 weeks. Study 3645 was a 26-week treatment extension to 3594. They are included in the original NDA submission.
Source: Created by reviewer.

3 STATISTICAL EVALUATION

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This review is focused on the meta-analysis of CV risk, based upon the updated database which included the trial information from the original submission and the additional data described in Section 2.1. A separate safety evaluation focused on hypoglycemia was reviewed by Dr. Eugenio Andraca-Carrera. For a statistical evaluation of efficacy results, please refer to the review authored by Dr. Cynthia Liu for IDeg and the review authored by Dr. Dongmei Liu for IDegAsp.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The reviewer was able to perform all analyses using the submitted data and the additional data submissions provided in response to the information requests.

3.2 Evaluation of Efficacy

This review does not evaluate efficacy submitted to the NDA. The reader is referred to the statistical reviews by Drs. Cynthia Liu and Dongmei Liu.

3.3 Evaluation of Safety

Seventeen trials were utilized to evaluate the association between IDeg/IDegAsp and CV safety, compared with other comparators. This included data from 11 randomized trials (5 with planned voluntary extensions) for IDeg (Studies 3579+3643, 3580, 3582+3667, 3583+3644, 3585+3725, 3586, 3668, 3672, 3718, 3724 and 3770+ext) and 6 randomized trials (2 with planned voluntary extensions) for IDegAsp (Studies 3590+3726, 3592, 3593, 3594+3645, 3597 and 3896).

3.3.1 Study Design and Endpoints

3.3.1.1 Study Design

All the seventeen trials were Phase 3, open-label, randomized, multi-center and active-controlled. In general, these trials were designed to establish the non-inferiority of IDeg/IDegAsp relative to an active control with a treat-to-target design. For the details of study design of each individual trial included in the original NDA submission, please refer to the review authored by Dr. Xiao Ding on April 16, 2012. As of the cut-off date of the NDA submission, only one extension trial (Trial 3645) was completed and included in the NDA submission.

The updated database included additional data from 6 extension trials (Trial 3643, 3667, 3644, 3725, 3770 ext. and 3726) and one new confirmatory trial 3896, which were all completed by the database lock at May 1, 2012. Generally said, an extension trial design is based upon the trial design of its respective main trial, i.e. a controlled, open label, multi-center, and treat-to-target trial design. All subjects who completed the main trial were eligible to volunteer to participate in the extension trial and continued to receive treatment as randomly allocated in the main trial.

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The new trial included in the updated database, NN5401-3896 (Study 3896), was a phase 3 multi-center, randomized, open-labeled, treat to target, two-arm parallel study. Study 3896 was conducted in Japan, in male and female subjects ≥ 20 years of age with type 2 diabetes with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 296 insulin-naïve subjects were randomized in a 1:1 fashion to IDegAsp or insulin glargine (IGlar), with or without oral anti-diabetic drugs. Study 3896 was powered to provide 80% or greater power to demonstrate the non-inferiority of IDegAsp compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

3.3.1.2 Endpoints

In the original submission, the agreed upon primary endpoint for CV safety analysis is major adverse cardiovascular event (MACE+), which is pre-specified as a composite endpoint consisting of acute coronary syndrome (ACS) including unstable angina pectoris (UAP) and myocardial infarction (MI), stroke, and CV death. As a response to the Agency's comments, the applicant conducted additional analyses based on a more strict MACE definition which excludes UAP from the original specification. Throughout the rest of this review, "MACE+" refers to the applicant's initial definition and "MACE" refers to the strict definition.

The Agency's statistical review of the original NDA noted that the applicant only conducted analysis of treatment-emergent events (events occurring within 7 days of treatment discontinuation) even though the statistical analysis plan (SAP) did not pre-specify that the analysis should only focus on the treatment-emergent events. As a response to the Agency's information request, the applicant submitted the updated data in which the MACE+/MACE events were ascertained either within 7 days or within 30 days after treatment discontinuation.

All events were adjudicated using a thorough, prospective adjudication plan.

3.3.2 Statistical Methodologies

All the 17 completed Phase 3 trials (including extensions) in the clinical development programs of IDeg and IDegAsp in subjects with type 1 and type 2 diabetes mellitus as of the cut-off date (May 1, 2012) are included in the meta-analysis of CV safety.

An extension trial was included in the across trial analysis by joining the extension data with its respective main trial data and thereafter the joined data is considered as one trial using the combined trial ID as the identifier. The combined dataset was the basis for summaries, analyses and presentation of CV safety evaluation. Baseline was defined as the randomization visit in the main trial.

3.3.2.1 Methods of Imputing Missing

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As specified in the SAP, if a subject has no adjudicated MACE+ (or MACE) event at the time of database lock then the primary endpoint will be censored at the subject's last visit date recorded in the Case Report Form (CRF).

3.3.2.2 Analysis Methods for MACE+ and MACE

All comparative analyses are between the randomized treatment groups. All IDeg regimens as well as IDegAsp regimens are combined into the pooled IDeg/IDegAsp group, and all the comparator groups are combined into the pooled all comparator group.

The primary analysis is based upon time-to-event methods for MACE+/MACE. If a subject experienced multiple events of interest, only the event that occurred first will be included in the analysis. The agreed upon primary analysis method was a Cox proportional hazards regression model stratified by trial with a fixed effect for treatment to estimate the hazard ratio (HR), and corresponding 95% confidence interval, of IDeg/IDegAsp group versus the pooled all comparator group. Trials with no events on both arms are excluded from the Cox regression analysis.

In this review, as a secondary analysis, stratified Mantel-Haenszel (M-H) 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 including trials with no events of interest. 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 Agency conducted sensitivity and subgroup analyses under various scenarios. These various analyses included the following assessments,

1. Assessment of the individual component of MACE+/MACE.
2. Trial-level subgroup analysis utilizing only the set of IGlar-controlled trials.
3. Trial-level subgroup analysis on the set of IDeg trials.
4. Trial-level subgroup analysis of type 1 and type 2 diabetics

The subgroup analyses were performed using a stratified Cox proportional hazard model and using the stratified Mantel-Haenszel method described above. Note that most of these analyses were not pre-specified in the protocol or SAP, but were requested by the clinical review team. As such, these exploratory analyses should be considered in context of the primary agreed upon analysis.

3.3.2.3 Handling of trials with zero events

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For the primary analysis method (stratified Cox regression) used in this review, trials with zero events were excluded from the analysis. The secondary analysis methods (M-H RD and IRD) do not require special handling of trials with zero events.

3.3.3 Patient Disposition, Demographic and Baseline Characteristics

The protocol defined full analysis set (FAS) was a modified intent-to-treat (ITT) population, which included all randomized subjects with the exclusion of a small number of subjects (N = 36) based upon the applicant's criteria. It was pre-specified that the primary analyses will be based on the FAS population. All analyses reported in this review are based on the FAS population.

The SAP of CV meta-analysis specified that all Phase 3 therapeutic confirmatory trials and any planned controlled extension of these trials would be included in the CV meta-analysis. Due to date of database lock, data from all trials except 6 of the 7 planned extension trials were included in the CV meta-analysis at the time of original NDA submission – this will be referred to as the "original database". In April 2012, the Agency inquired of the applicant on their ongoing program and learned that all planned extensions intended for consideration in the CV meta-analysis were completed. An information request was sent for an updated CV meta-analysis of all the trials specified in the SAP and the single one new trial 3896. In response, the applicant submitted an updated database which was locked on May 1, 2012 – this will be referred to as the "updated database". Table 2 provides a high level summary of the total number of subjects and total person-years of exposure (PYE) for the combined IDeg/IDegAsp arm and all comparator arm respectively, in the original and updated databases. While the updated database includes only one additional main trial from the original database, the inclusion of the extension trial information results in approximately 40% more person-years of exposure.

Table 2: Comparison of the Original and Updated CV Meta-analysis Database (FAS)

	Original Database (16 trials)		**Updated Database (17 trials)**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
Sample Size (N)	5647	3312	5794	3461
Person Years of Exposure (PYE)	3569.9	1873.9	5153.6	2562.7

Source: Created by reviewer.

3.3.3.1 Trials with extension

The majority of additional data in the updated database are from the extension trials. Despite the fact that it was pre-specified in the SAP to include these extension trials in the primary analysis, the Agency assessed the 7 trials with extension separately to evaluate the robustness and appropriateness of including the data from the extension trials in the CV meta-analysis. The focus of the Agency's evaluation are on retention rates of extension trials and the similarity

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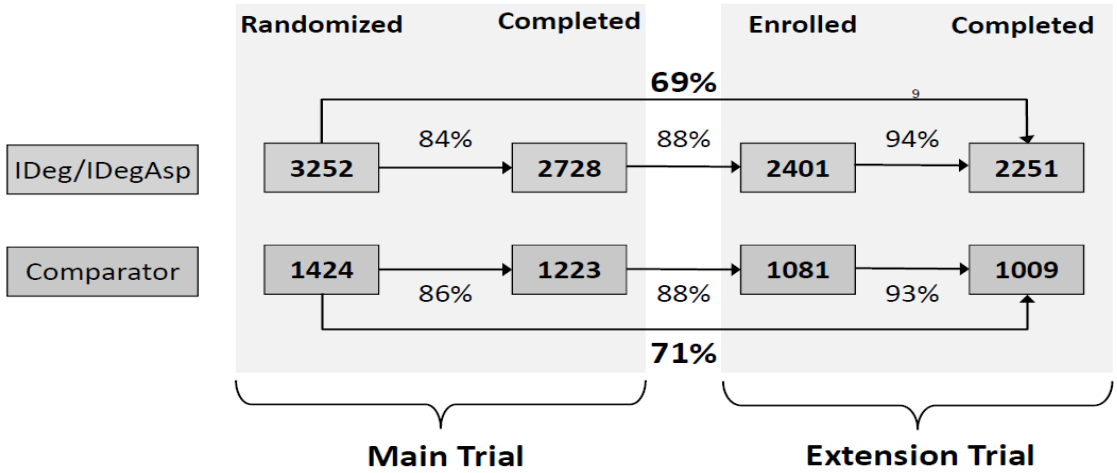
between the subjects initially randomized in the main trials and the subjects enrolled in the extension trials.

In total, the 7 trials with extensions randomized 3,252 subjects to the IDeg/IDegAsp group and 1,424 to the comparator group. The number of subjects remaining for each of the four stages of the trials (randomization, completion of main trial, extension trial enrollment and completion of extension trial) is shown in Figure 1. The retention rates above the arrows are calculated by stage. For example, 84% of subjects randomized to IDeg/IDegAsp completed the main trials and of those 2,728 completers, 88% enrolled in the extension trials. Of the 2,401 subjects who enrolled in the extension trials 94% stayed through the entire extension period. The retention rates are very similar between the treatment arm and the comparator arm. The overall completion rates, from time of randomization to end of the extension trials, are around 70% and balanced between the two comparison arms.

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



Source: Created by reviewer.

Based upon Table 3 shown on the following page, demographics and baseline characteristics that include baseline CV risk factors for the subjects who enrolled in the extension trials are similar to those of the randomized subjects in the 7 trials with extension. Overall, there are negligible difference between the two groups in terms of body mass index, HbA1c, type and duration of diabetes, hypertension, prior CV disease, renal impairment and concomitant drug use. Thus, subjects who enrolled in the extension trials retain similar baseline characteristics as the randomized group.

Based on these findings, it was determined that the updated database including all main and extension trials was robust and appropriate for the evaluation of CV safety which coincides with the pre-specified statistical analysis plan.

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Table 3: Demographics and Baseline Characteristics (FAS, Trials with Extension)

	Randomized		Enrolled in extension	
	IDeg/IDegAsp (N = 3252)	Comparator (N = 1424)	IDeg/IDegAsp (N = 2401)	Comparator (N = 1081)
Age, yrs	51±14	51±14	51±14	51±13
Female	44.2%	45.1%	42.8%	44.2%
Race				
White	83.5%	81.8%	83.2%	81.6%
Black	5.4%	4.6%	5.0%	3.7%
Asian	9.0%	11.4%	10.1%	12.8%
Other	2.1%	2.2%	1.7%	1.9%
US	42%	38%	40%	36%
BMI, kg/m²	29.0±5.2	28.8±5.2	28.9±5.2	28.9±5.1
Duration of diabetes, yrs	13.9±10.0	13.6±9.7	13.8±9.8	13.3±9.3
HbA1c, %	8.1±0.9	8.2±0.9	8.1±0.9	8.2±1.0
Type I Diabetes	45.2%	46.1%	45.5%	45.8%
Hypertension	54.0%	52.5%	54.6%	53.0%
Prior CV disease	14.3%	12.5%	14.6%	12.9%
Renal Impairment	11.3%	11.2%	10.9%	11.2%
Concomitant medications				
Lipid-lowering drug	47.5%	46.6%	47.6%	46.4%
Aspirin	29.2%	28.4%	29.2%	30.0%
Beta-blocker	16.7%	13.8%	16.8%	14.2%
R/A system inhibitors	50.0%	48.2%	50.6%	49.4%

Source: Created by reviewer.

3.3.3.2 Updated database

In the original NDA submission, among the 8,995 randomized subjects in the ITT population, a total of 8,959 subjects were included in the FAS population. The updated database included only one new trial 3896, which provided 296 additional subjects (147 subjects were treated with IDegAsp and 149 subjects were treated with insulin glargine). Therefore, among the 9,255 randomized subjects in the FAS population from the 17 phase 3 trials included in the updated database, 4,281 (46.3%) subjects were randomized to receive IDeg, while 1,513 (16.3%) subjects were randomized to receive IDegAsp, and 3,461 (37.4%) subjects were randomized to receive active comparator drugs.

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Based upon Table 4, demographic characteristics and baseline CV risk factors for the 9,255 subjects in the 17 trials included in the primary analysis were similar among the treatment groups. In the FAS population, there were slightly more male subjects than female subjects (56% versus 44%). Approximately 68% of subjects were White and about 25% were Asian, while 5% of subjects were Black or African American. Furthermore, about 9% subjects in the FAS population were with Hispanic or Latino ethnicity. About 21% of subjects in the FAS were above 65 years of age, while the mean age was about 54 years. More than 41% of subjects had a body mass index (BMI) greater than 30 kg/m2, while the mean BMI was about 29 kg/m2. Approximately 77% of subjects had type 2 diabetes mellitus (T2DM) with a mean duration of 10.8 years. About 23% of subjects had type 1 diabetes mellitus (T1DM) with a mean duration of 17.3 years.

Table 4: Demographics and Baseline Characteristics by Treatment Group (FAS, Updated Database)

	IDeg/IDegAsp (N = 5794)	**Comparator (N = 3461)**
Age, yrs	54±13	55±12
18-65	79.7%	78.8%
65-75	17.7%	18.2%
>75	2.6%	3.0%
Female	43.9%	44.8%
Race		
White	68.5%	66.5%
Black	5.1%	4.8%
Asian	24.5%	27.1%
Other	1.9%	1.6%
US	31%	30%
BMI, kg/m²	29.0±5.3	29.5±5.4
<25	24.7%	22.5%
25-30	35.1%	34.0%
30-35	25.5%	27.0%
>35	14.7%	16.5%
Duration of diabetes, yrs	12.6±9.0	11.8±8.4
HbA1c, %	8.2±0.9	8.3±0.9
Hypertension	59.9%	62.0%
Prior CV disease	16.2%	15.3%
Renal Impairment	16.5%	16.6%

Source: Created by reviewer.

As summarized in Table 5, among the 9,255 subjects in the FAS population, approximately 21.6% of subjects (2,001/9,255) did not complete the trial (including those who completed the main trial but did not enroll in the extension trials). As presented in Figure 2, the percentage of subjects with premature discontinuation tended to be slightly lower in the comparator groups

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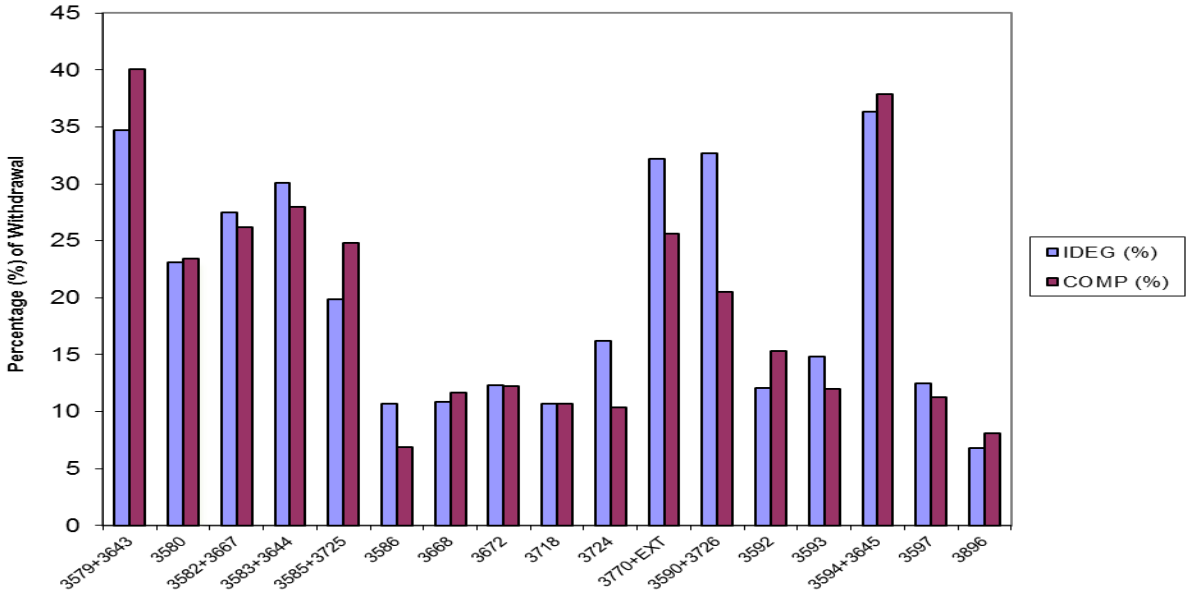
than in the IDeg/IDegAsp groups. On average, 23.0% of the subjects in the combined IDeg/IDegAsp group discontinued study medication, which was not statistically significantly higher than the combined comparator group (19.4%) with p-value = 0.28 (CMH test stratified by trial). In general, the trials with an extension period have higher drop-out rates compared to the trials without extension, due to the longer duration of these trials and because subjects that elected NOT to enroll in the extension trials are counted as dropouts. As presented in Figures 3 and 4, there was no clear difference overall in time-to-dropout between the combined IDeg/IDegAsp group and the comparator group, either for all 17 trials (Figure 3) or for the 7 trials with an extension (Figure 4).

Table 5: Patient Disposition (FAS, Updated Database)

Disposition	IDeg/IDegAsp *N* = 5794	Comparator *N* = 3461
Completed the study	4464 (77.0%)	2790 (80.6%)
Discontinued	1330 (23.0%)	671 (19.4%)
Adverse event	147 (2.5%)	59 (1.7%)
Ineffective Therapy	41 (0.7%)	23 (0.7%)
Non-compliance	163 (2.8%)	98 (2.8%)
Withdraw criteria	170 (2.9%)	93 (2.7%)
Not enrolled in extension trial	327 (5.6%)	142 (4.1%)
Other	482 (8.3%)	256 (7.4%)

Source: Created by reviewer.

Figure 2: Percentage of Subjects with Discontinuation by Study and Treatment Group (FAS, Updated Database)



Source: Created by reviewer.

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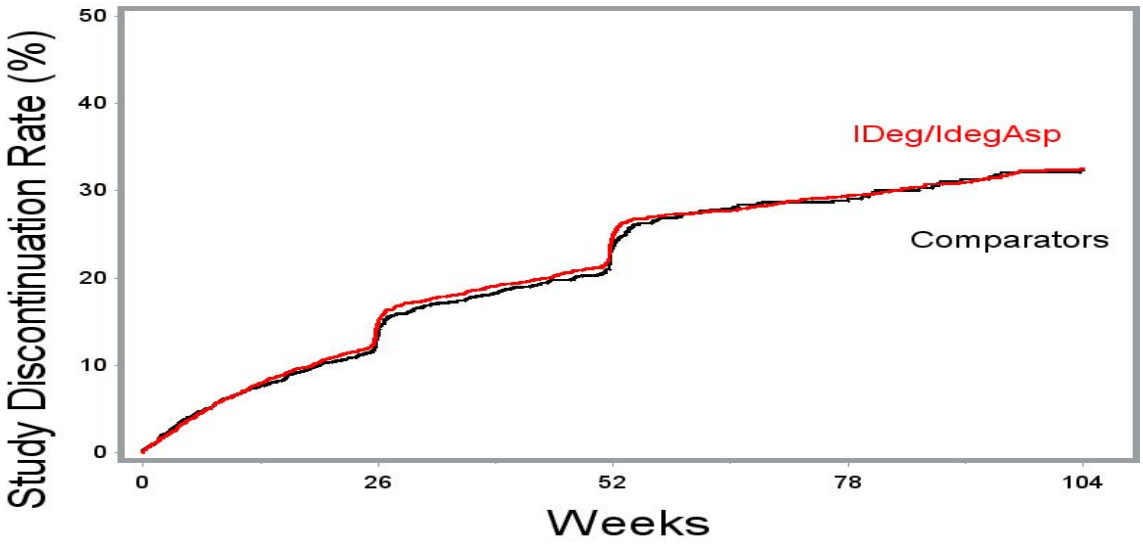
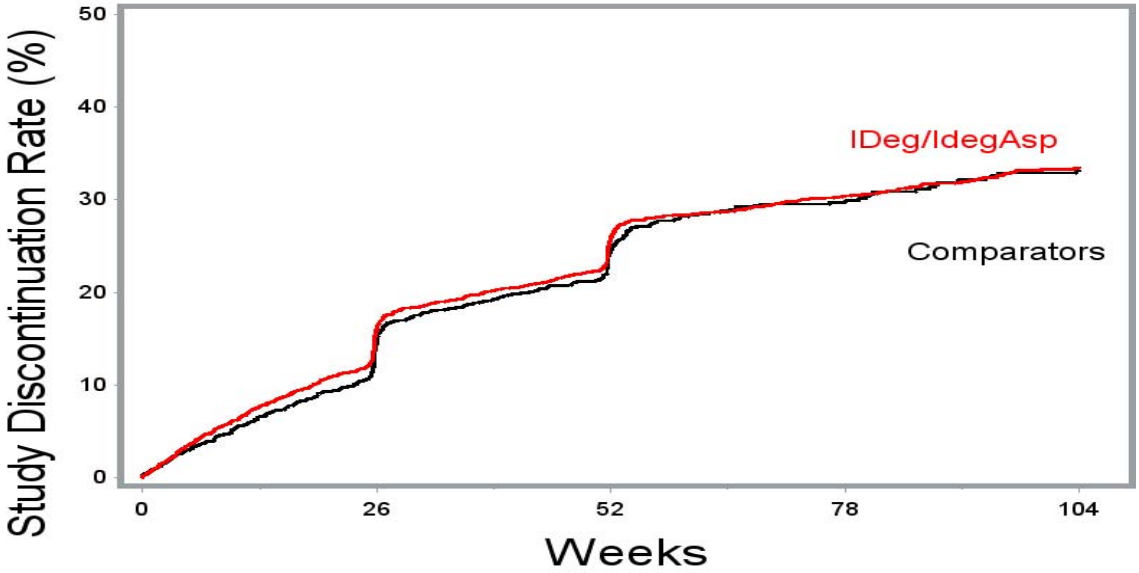
Figure 3: Study Discontinuation Rate in All Trials (FAS, Updated Database)



Source: Created by reviewer.

Figure 4: Study Discontinuation Rate in Trials with Extension (FAS, Updated Database)



Source: Created by reviewer.

3.3.4 Results and Conclusions

As described in Section 3.3.1.2, the agreed upon primary endpoint was MACE+; however additional analyses were requested to assess a strict MACE endpoint. In addition, alternate censoring times (7 days and 30 days) were requested for each endpoint definition. Below, results

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are presented for each endpoint broken down by censoring window. These analyses incorporate all extension trial information (updated database) unless mentioned.

A summary of the observed MACE+ events, along with its individual components, is presented in Table 6 for the 17 trials included in the updated database. 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. Among the 132 subjects who experienced a MACE+ event within a 7 days censoring window, a total of 84, 30, and 18 subjects reported to have ACS (including 41 UAP and 43 MI), stroke, and CV death, respectively. When excluding UAP events, among the 9,255 subjects in the FAS population, 91 subjects have at least one event that was adjudicated as treatment-emergent MACE. A total of 70 subjects in the pooled IDeg/IDegAsp group experienced MACE events (incidence rate of 13.6 per 1,000 person-years), and a total of 21 subjects (incidence rate of 8.2 per 1,000 person-years) in the pooled all comparator group experienced MACE events censored at 7 days.

Table 6: 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.
Source: Created by reviewer.

Table 7 shown on the following page provides the trial level details of individual components of MACE+ events using the 7 days censoring window, broken down by treatment groups.

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Table 7: Summary of MACE+ Events by Study and Treatment Group (FAS, 7 Day Censoring)

Study	Arms	N	MACE+ n (%)	MI n (%)	Stroke n (%)	CV Death n (%)	UAP n (%)
3579+3643	**IDeg**	773	29(3.8)	13(1.7)	8(1.0)	-	8(1.0)
	IGlar	257	4(1.6)	2(0.8)	2(0.8)	-	-
3580	**IDeg**	225	3(1.3)	1(0.4)	1(0.4)	1(0.4)	-
	Sitagliptin	222	3(1.4)	-	1(0.5)	-	2(0.9)
3582+3667	**IDeg**	744	28(3.8)	7(0.9)	7(0.9)	5(0.7)	9(1.2)
	IGlar	248	7(2.8)	3(1.2)	-	1(0.4)	3(1.2)
3583+3644*	**IDeg**	472	8(1.7)	1(0.2)	-	4(0.8)	3(0.6)
	IGlar	157	2(1.3)	-	-	2(1.3)	-
3585+3725*	**IDeg**	302	1(0.3)	-	1(0.3)	-	-
	IDet	153	0(0.0)	-	-	-	-
3586	**IDeg**	289	2(0.7)	1(0.3)	1(0.3)	-	-
	IGlar	146	0(0.0)	-	-	-	-
3668	**IDeg/IDeg Flex**	457	2(0.4)	1(0.2)	1(0.2)	-	-
	IGlar	230	2(0.9)	-	-	1(0.4)	1(0.4)
3672	**IDeg**	228	3(1.3)	2(0.9)	-	-	1(0.4)
	IGlar	229	3(1.3)	1(0.4)	1(0.4)	1(0.4)	-
3718	**IDeg**	233	1(0.4)	-	-	-	1(0.4)
	IGlar	234	2(0.9)	-	-	-	2(0.9)
3724	**IDeg**	229	2(0.9)	1(0.4)	-	-	1(0.4)
	IGlar	230	2(0.9)	-	-	-	2(0.9)
3770+ext*	**IDeg/IDeg Flex**	329	1(0.3)	1(0.3)	-	-	-
	IGlar	164	2(1.2)	-	-	-	2(1.2)
3590+3726	**IDegAsp**	266	7(2.6)	3(1.1)	1(0.4)	2(0.8)	1(0.4)
	IGlar	263	1(0.4)	-	-	1(0.4)	-
3592	**IDegAsp**	224	3(1.3)	2(0.9)	1(0.4)	-	-
	BIAsp	222	2(0.9)	-	-	-	2(0.9)
3593	**IDegAsp**	230	2(0.9)	1(0.4)	-	-	1(0.4)
	IGlar	233	1(0.4)	-	-	-	1(0.4)
3594+3645*	**IDegAsp**	366	0(0.0)	-	-	-	-
	IDet	182	0(0.0)	-	-	-	-
3597	**IDegAsp**	280	1(0.4)	-	1(0.4)	-	-
	BIAsp	142	5(3.5)	3(2.1)	1(0.7)	-	1(0.7)
3896	**IDegAsp**	147	2(1.4)	-	2(1.4)	-	-
	IGlar	149	1(0.7)	-	1(0.7)	-	-
Overall		9255	132(1.4)	43(0.5)	30(0.3)	18(0.2)	41(0.4)

*

Trials in T1DM patients.
Source: Created by reviewer.

3.3.4.1 Time to Event Analysis

The pre-specified primary analysis was the Cox proportional hazards (CPH) model stratified by trial with treatment as a fixed effect. In the following subsections, results for MACE+ (Section 3.3.4.1.1) and MACE (Section 3.3.4.1.2) are presented for the time to event analyses.

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3.3.4.1.1 MACE+ Results

In Table 8, results are presented for the MACE+ endpoint broken down by censoring window (7 and 30 days) utilizing data provided in the original submission (original database) and data provided in the major amendment to the NDA (updated database). With more data incorporated in the updated analyses, the results show an increase in all the HR point estimates for the MACE+ endpoint, compared to the original analyses. Based upon the 7 day censoring window, the HR of IDeg/IDegAsp compared to comparator was 1.30 with a 95% CI of (0.88, 1.93) for MACE+.

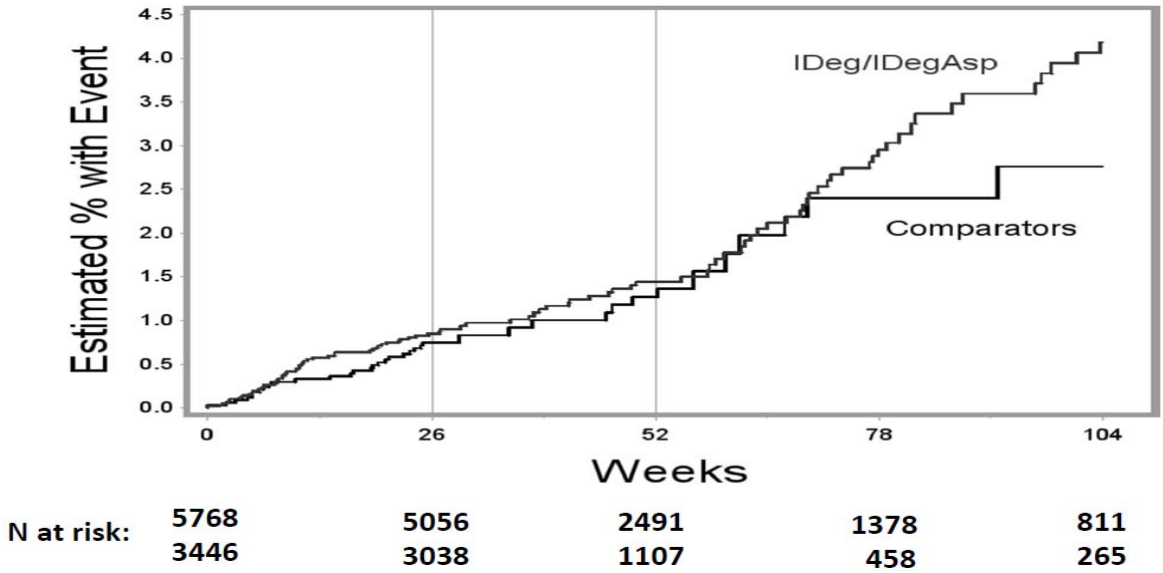
Table 8: CPH Analysis Results for MACE+ based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Database		Updated Database	
	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)

Source: Created by reviewer.

Based on the Kaplan Meier (K-M) method, the cumulative probability of developing a CV-related event as measured by MACE+ (7 day censoring) is shown in Figure 5 for the updated database. For MACE+ the K-M plot shows that the two curves are close to each other up through 73 weeks and then separate around 73 weeks due to only few events collected on the comparator group.

Figure 5: Time to Event Analysis of MACE+ (FAS, 7 Day Censoring)



Source: Created by reviewer.

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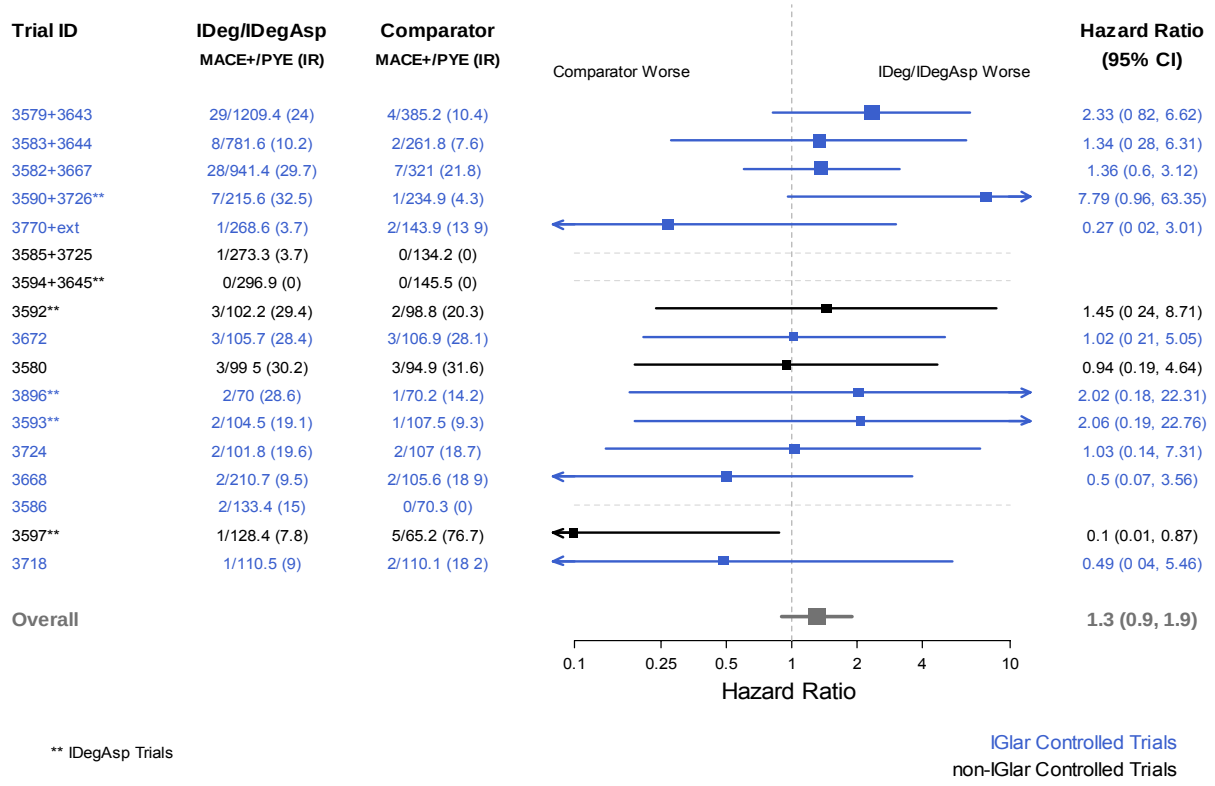
The forest plot of the hazard ratios of the MACE+ composite endpoint (censoring at 7 days) is presented in Figure 6 for the updated database. Trials are ordered by the planned duration of treatment (trials with the longest planned treatment duration are presented on the top of the figure and trials with the shortest planned treatment duration are presented at the bottom 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% CI of each trial calculated 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 plot only trials where MACE+ events were observed on both treatment arms include a point estimate for the hazard ratio and the corresponding 95% CI.

Figure 6: Forest Plot of Time-to-Event Analysis of MACE+ (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.1.2 MACE Results

Analogous to the assessment of MACE+, Table 9 depicts analysis results for the MACE endpoint broken down by censoring window (7 and 30 days) and database (original and updated). Similar to results observed with MACE+, estimates of the HR increased with the inclusion of additional data. The estimated HR for MACE was 1.67 with a 95% confidence

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interval of (1.01, 2.75) demonstrating a statistically significant increase in the risk of MACE associated with IDeg/IDegAsp use when using the updated database and a censoring window of 7 days.

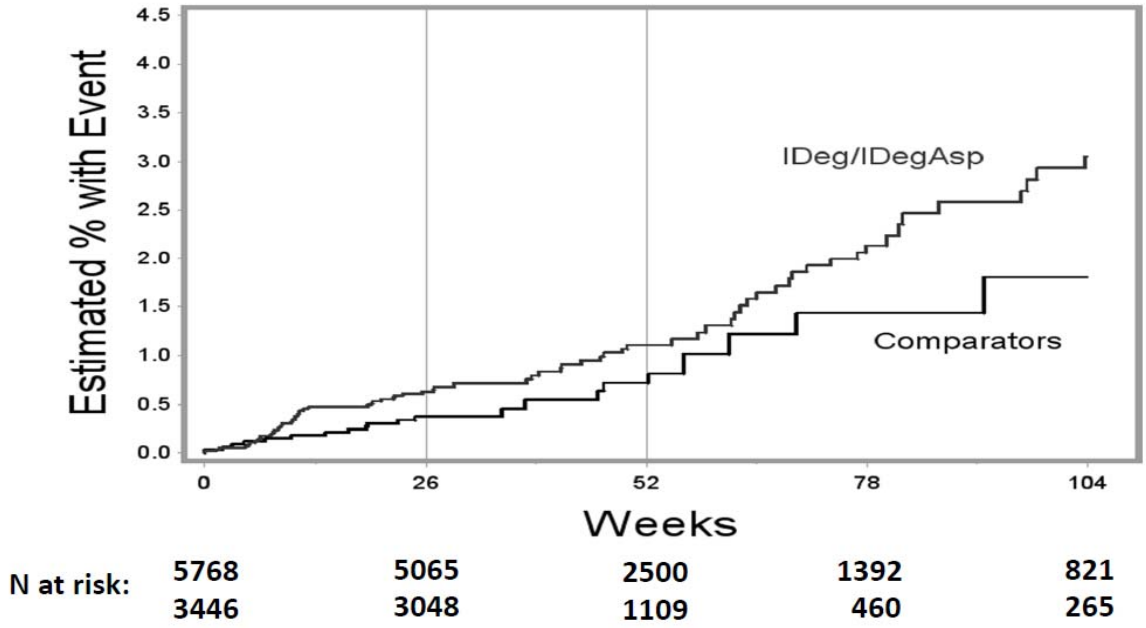
Table 9: CPH Analysis Results for MACE based on Original and Updated Databases (FAS, 7 and 30 Day Censoring)

	Original Analysis		Updated Analysis	
	IDeg/IDegAsp (*N* = 5647)	**Comparator** (*N* = 3312)	**IDeg/IDegAsp** (*N* = 5794)	**Comparator** (*N* = 3461)
Censoring: 7 Days				
MACE	39	15	70	21
HR (95% CI)	-	1.39 (0.76, 2.57)	-	1.67 (1.01, 2.75)
Censoring: 30 Days				
MACE	42	15	74	23
HR (95% CI)	-	1.50 (0.82, 2.75)	-	1.61 (1.00, 2.61)

Source: Created by reviewer.

Figure 7 depicts the K-M plot for MACE. In the pooled IDeg/IDegAsp group, MACE events occurred earlier and more often than those in the pooled all comparator group. Overall, the IDeg/IDegAsp treatment arm consistently has a higher percentage of MACE events over time.

Figure 7: Time to Event Analysis of MACE (FAS, 7 Day Censoring)



Source: Created by reviewer.

The forest plot for MACE is presented in Figure 8. Construction of this figure follows that previously described for MACE+. Due to the fewer number of MACE events as compared to MACE+, within-trial HR estimates cannot be calculated for more trials with zero MACE on one or both arms.

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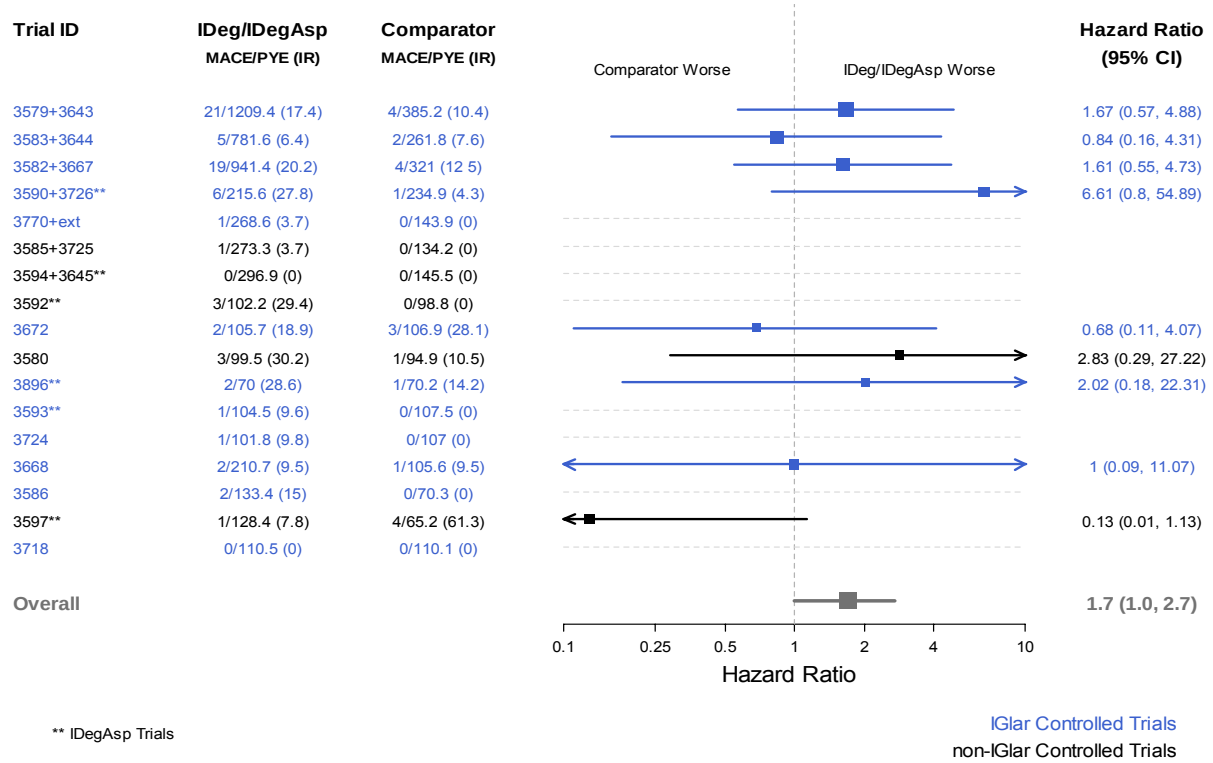
Figure 8: Forest Plot of Time-to-Event Analysis of MACE (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.2 Secondary Analysis

Trials with no events were excluded from the time-to-event analysis method when using the Cox proportional hazards model stratified by trial. In order to incorporate trials with zero events, risk difference and the difference of incidence rates were calculated using Mantel-Haenszel methods.

3.3.4.2.1 MACE+ Results

The results for the updated database when censoring at 7 days or 30 days are shown below in Table 10 for MACE+. Consistent with the primary analysis, the results from the secondary analysis also suggest an increased CV risk for subjects randomized to IDeg/IDegAsp over comparator.

Table 10: Updated Database Secondary Analysis Results for MACE+ (FAS, 7 and 30 Day Censoring)

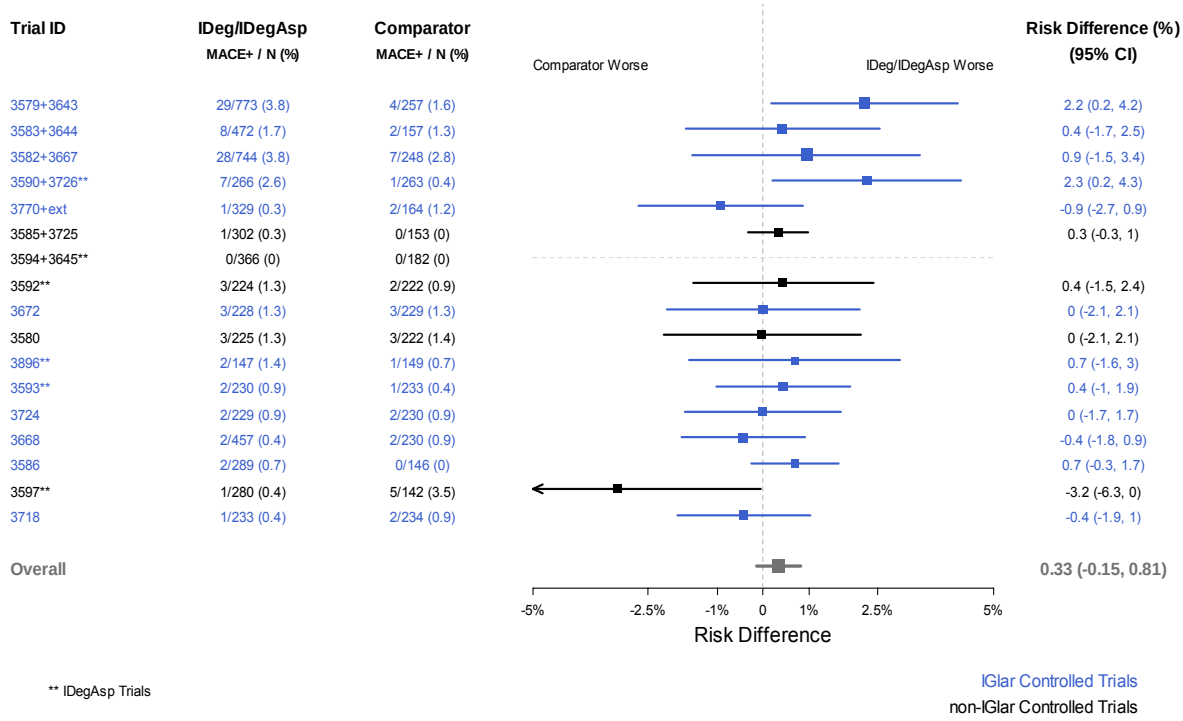
	Censoring: 7 Days		*Censoring: 30 Days*	
	Estimate	95% CI	Estimate	95% CI
M-H Risk Difference (%)	0.33	(-0.15, 0.81)	0.33	(-0.16, 0.82)
M-H Incidence Rate Difference†	4.27	(-1.84, 10.4)	4.27	(-1.97, 10.5)

† Incidence per 1,000 PYE
Source: Created by reviewer.

Reference ID: 3230612

Following a similar construct as Figures 6 and 8, a forest plot based upon the risk difference is presented in Figure 9 for the MACE+ endpoint when censoring at 7 days. Within a trial, asymptotic methods are used to provide an estimate of the risk difference and the corresponding 95% confidence interval 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 9: Forest Plot of Risk Difference of MACE+ (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.2.2 MACE Results

Similar to the MACE+ composite endpoint, Table 11 provides the secondary analysis results for MACE in the updated database when censoring at 7 days and 30 days respectively. Consistent with the primary analysis, the results suggest a statistically significant increase of risk to develop a MACE event for subjects randomized to IDeg/IDegAsp compared to control.

Table 11: Updated Database Secondary Analysis Results for MACE (FAS, 7 and 30 Day Censoring)

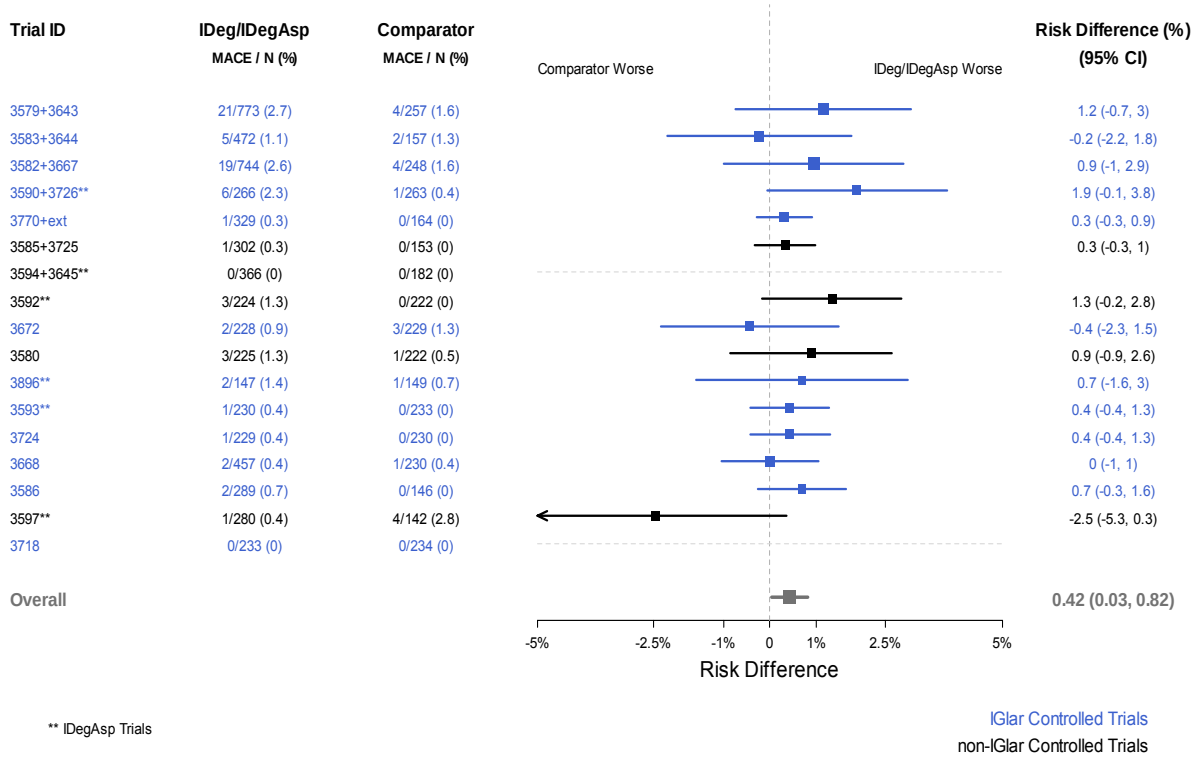
	Censoring: 7 Days		*Censoring: 30 Days*	
	Estimate	95% CI	Estimate	95% CI
M-H Risk Difference (%)	0.42	(0.03, 0.82)	0.42	(0.02, 0.83)
M-H Incidence Rate Difference†	5.41	(0.37, 10.5)	5.42	(0.20, 10.6)

† Incidence per 1,000 PYE
Source: Created by reviewer.

Reference ID: 3230612

Figure 10 is the forest plot based upon the risk difference for the MACE endpoint when censoring at 7 days. None of the 17 randomized phase 3 trials show a statistically significant difference between IDeg/IDegAsp and comparator; however, 11 of 17 trials had estimates of the risk difference in favor of the comparator and the lower bound of 95% CI of overall risk difference is above the null value.

Figure 10: Forest Plot of Risk Difference of MACE (FAS, 7 Day Censoring)



Source: Created by reviewer.

3.3.4.3 Sensitivity Analysis

3.3.4.3.1 Assessment of the individual components of MACE+

To explore which cardiovascular event components of MACE+ contributed to the composite primary endpoint, the hazard ratio for each component was calculated using a stratified Cox regression model similar to that used in the primary analysis. Figure 11 presents a forest plot of these hazard ratios in reference to the hazard ratio for the composite primary endpoint. It can be observed in this figure that of the individual components comprising MACE+, myocardial infarction and stroke have HR point estimates around 2, whereas CV death has a HR point estimate near 1. The HR point estimate for unstable angina was below 1 suggesting an increase in risk for the pooled comparator arm. The exclusion of UAP demonstrates why the point estimate of CV risk is higher for strict MACE versus MACE+. Note that none of the individual components of MACE+ demonstrated a statistically significant increase.

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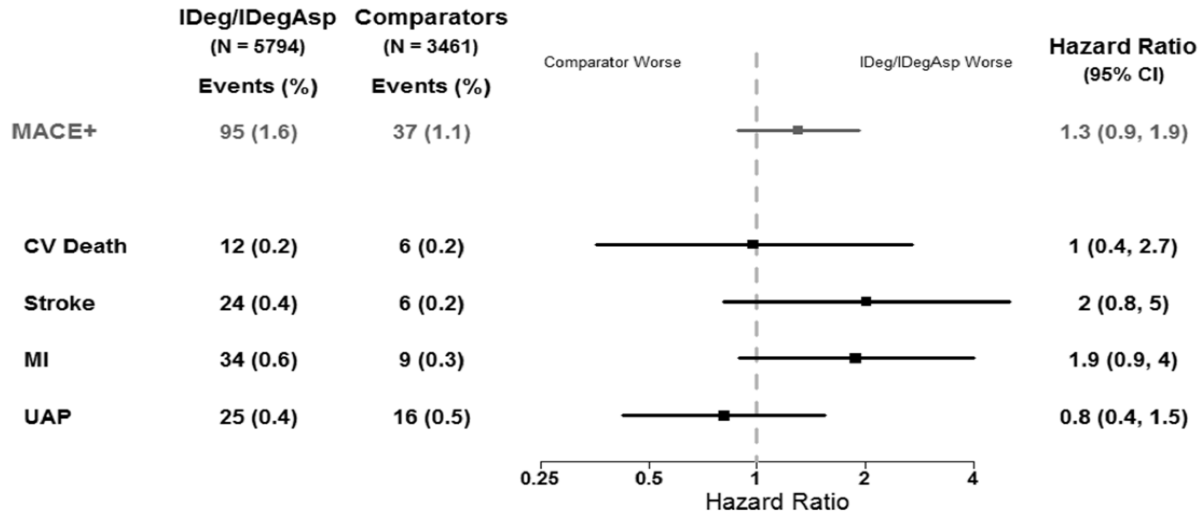
Figure 11: Forest Plot of Time-to-Event Analysis of MACE+ components (FAS, 7 Day censoring)



Source: Created by reviewer.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

In the following sections, analysis results for CV related safety endpoints (censoring at 7 days for the updated database) are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted 95% confidence intervals for each of the subgroup analyses.

4.1 Gender, Race, Age, and Geographic Region

4.1.1 Gender

Among the 9,255 subjects in the FAS population, 5,162 (55.8%) were male and 4,093 (44.2%) were female. Among the 132 subjects with MACE+ events, 90 were reported in male subjects and 42 were reported in female subjects. Among the 91 subjects with strict MACE events, 65 were reported in male subjects and 26 were reported in female subjects. The results of subgroup analysis by gender are presented in Table 12 for both MACE+ and MACE.

Among male subjects, the risk of developing a CV related event as measured by either MACE+ or MACE was higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. The signal is stronger in magnitude for strict MACE, compared to the broader definition MACE+. In contrast, among female subjects, there is no obvious difference in CV risk for the two comparison groups.

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Table 12: Subgroup Analysis Results by Gender (FAS, 7 Day Censoring)

	Female (*N* = 4093)	Male (*N* = 5162)
MACE+		
HR (95% CI)	1.03 (0.53, 1.99)	1.49 (0.91, 2.42)
MACE		
HR (95% CI)	1.09 (0.46, 2.56)	2.08 (1.11, 3.88)

Source: Created by reviewer.

4.1.2 Race

Among the 9,255 subjects in the FAS population, 6,271 (67.8%) were White, 460 (5.0%) were Black, 2,358 (25.5%) were Asian (including both Asian Indian and Asian non-Indian), and 166 (1.8%) were subjects with other races. Among the 132 subjects with MACE+ events, 102 were reported in White subjects, 8 were reported in Black subjects, 21 were reported in Asian subjects, and 1 was reported in a subject classified as other race. Among the 91 subjects with strict MACE events, 68 were reported in White subjects, 5 were reported in Black subjects, 17 were reported in Asian subjects, and 1 was reported in a subject classified as other race. The results of the subgroup analysis by race are presented in Table 13 for both endpoints.

Among White subjects, the risk of developing a CV related event as measured by MACE+ or MACE was higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. Similarly, among Black subjects, the risk was higher in the IDeg/IDegAsp group than in the comparator group, with a larger magnitude and wider 95% confidence interval due to the smaller sample of Black subjects. In contrast, among Asian subjects, the risk appeared to be lower in the IDeg/IDegAsp group while the difference was not statistically significant.

Table 13: Subgroup Analysis Results by Race (FAS, 7 Day Censoring)

	White (*N* = 6271)	Black (*N* = 460)	Asian (*N* = 2358)
MACE+			
HR (95% CI)	1.48 (0.93, 2.36)	3.65 (0.43, 31.0)	0.58 (0.24, 1.39)
MACE			
HR (95% CI)	2.13 (1.12, 4.02)	2.51 (0.26, 23.9)	0.69 (0.26, 1.83)

Source: Created by reviewer.

4.1.3 Age

Among the 9,255 subjects in the FAS population, 7,345 (79.4%) were 65 years or younger, and 1,910 (20.6%) were older than 65. Among the 132 subjects with MACE+ events, 82 events were reported in subjects aged 65 years or younger, while 50 events were reported in subjects older than 65 years. Among the 91 subjects with strict MACE, 56 events were reported in subjects aged 65 years or younger, while 35 events were reported in subjects older than 65. The results of subgroup analysis by age are presented in Table 14 for both endpoints.

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Among subjects aged 65 years or younger, the risk of developing a CV related event as measured by the composite endpoints MACE+ or MACE was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. Among subjects older than 65, the risk appeared to be higher in the IDeg/IDegAsp group, with a larger magnitude compared to the younger age group.

Table 14: Subgroup Analysis Results by Age (FAS, 7 Day Censoring)

	<= 65 yrs (*N* = 7345)	**> 65 yrs** (*N* = 1910)
MACE+		
HR (95% CI)	1.10 (0.68, 1.77)	1.78 (0.89, 3.53)
MACE		
HR (95% CI)	1.30 (0.72, 2.37)	2.70 (1.03, 7.09)

Source: Created by reviewer.

4.1.3 Region

Among the 9,255 subjects in the FAS population, 2,850 (30.8%) were randomized in the USA, and 6,405 (69.2%) were randomized in other countries. Among the 132 subjects with MACE+ events, 57 events were reported in US participants, while 75 events were reported in other countries. Among the 91 subjects with strict MACE events, 34 events were reported in US participants, while 57 events were reported in other countries. The results of subgroup analysis by region are presented in Table 15 for both endpoints. In general, the HR estimates are consistent between US and non-US regions for the two endpoints and both show a risk increase in the combined IDeg/IDegAsp group, compared to control.

Table 15: Subgroup Analysis Results by Region (FAS, 7 Day Censoring)

	US (*N* = 2850)	**Non-US** (*N* = 6405)
MACE+		
HR (95% CI)	1.31 (0.71, 2.41)	1.30 (0.78, 2.17)
MACE		
HR (95% CI)	1.77 (0.75, 4.16)	1.62 (0.87, 3.01)

Source: Created by reviewer.

4.2 Other Special/Subgroup Populations

Several special subgroup analyses were conducted at the trial level. These included assessments in IGlar controlled trials only, in trials using IDeg as treatment and in trials conducted in type 1 and type 2 diabetes subjects separately. In these trial-level subgroup analyses, a Cox proportional hazard model stratified by trial was used to calculate the HR and its 95% CI for the two endpoints MACE+ and MACE censored at 7 days. Estimates of risk difference and its 95% CI were also calculated using the stratified Mantel-Haenszel method.

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4.2.1 IGlar-controlled Trials

Among the various control arm treatments used in the IDeg/IDesAsp development programs, insulin glargine (IGlar) was the most commonly used comparator. A total of 12 studies utilized IGlar as the control (Studies 3579+3643, 3582+3667, 3583+3644, 3586, 3668, 3672, 3718, 3724, 3770+ext, 3590+3726, 3593, and 3896). In total, 6,937 subjects were randomized in the IGlar-controlled trials. The analysis results are presented in Table 16 for the trials using IGlar as the control arm. For MACE+, there is an estimated 54% elevated risk for IDeg/IDegAsp arm compared to IGlar. The estimated risk elevation increases to 82% for strict MACE.

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

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

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

4.2.2 IDeg Trials

Data from the 7 IDeg trials without using Insulin Aspart (IAsp) as background therapy were combined for a trial-level subgroup analysis (Studies 3579+3643, 3580, 3586, 3668, 3672, 3718 and 3724). A total of 3,982 subjects were randomized in these IDeg trials. The analysis results are presented in Table 17. In this trial-level subgroup, the estimated hazard ratios were 1.35 for MACE+ and 1.64 for MACE, both showing CV risk increase in IDeg arm compared with other comparators.

Table 17: Analysis Results for MACE+/MACE in IDeg Trials with no IAsp Use (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg	Comparator	IDeg	Comparator
N	2434	1548	2434	1548
Events (IR*)	42 (21.3)	16 (16.3)	31 (15.7)	9 (9.2)
HR (95% CI)	1.35 (0.75, 2.44)		1.64 (0.77, 3.51)	
RD (%) (95% CI)	0.41 (-0.27, 1.10)		0.43 (-0.13, 1.00)	

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

4.2.3 Type of Diabetes

Trials 3583+3644, 3585+3725, 3770+ext and 3594+3645 were conducted in type 1 diabetes subjects, while all other trials enrolled type 2 diabetes subjects. Among the 9,255 subjects in the FAS population, 2,125 (23.0%) were subjects with TIDM, and 7,130 (77.0%) were subjects with T2DM. Among the 132 subjects with MACE+ events, 14 events were reported in T1DM

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subjects while 118 events were reported in T2DM subjects. Among the 91 subjects with strict MACE events, 9 events were reported in T1DM subjects while 82 events were reported in T2DM subjects.

4.2.3.1 Type 1 Diabetes

As presented in Table 18, among T1DM subjects, the HR estimate of MACE+ is close to null and the risk of developing a strict MACE event was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group. In these trials only a small number of events were observed with low incident rates.

Table 18: Analysis Results for MACE+/MACE in T1DM patients (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
N	1469	656	1469	656
Events (IR*)	10 (6.2)	4 (5.8)	7 (4.3)	2 (2.9)
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)	

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

4.2.3.2 Type 2 Diabetes

In contrast, among subjects with T2DM, the risk of either MACE+ or MACE tends to be higher in the IDeg/IDegAsp group than in the comparator group, as presented in Table 19.

Table 19: Analysis Results for MACE+/MACE in T2DM patients (FAS, 7 Day Censoring)

	MACE+		**MACE**	
	IDeg/IDegAsp	Comparator	IDeg/IDegAsp	Comparator
N	4325	2805	4325	2805
Events (IR*)	85 (24.0)	33 (17.6)	63 (17.8)	19 (10.1)
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)	

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

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

The primary agreed upon composite endpoint for CV safety evaluation was MACE+, comprised of unstable angina pectoris, myocardial infarction, stroke, and CV death. The agreed upon primary analysis was based on 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)

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versus the all comparator group which consisted of insulin glargine, insulin detemir, biphasic insulin aspart, and sitagliptin. An analysis of the data that was submitted to the NDA (original database) 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 NDA submission.

The additional data provided in the response to the information request formed the updated database which included data from 6 extension trials and one new trial. The inclusion of extension trials in the CV meta-analysis was pre-specified in the applicant's statistical analysis plan which was agreed upon with the Agency prior to the NDA submission. An area of consideration is whether such extension trial should be incorporated into the meta-analysis as enrollment into the extension trials was based upon a voluntary election of trial participants. Our assessment of the updated database found it to be robust and appropriate for the evaluation of the CV risk of IDeg/IDegAsp as shown in Section 3.3.3.1.

In the updated database, data from the 17 randomized therapeutic confirmatory Phase 3 trials and their extension trials were synthesized to evaluate the risk of developing a CV related event as measured by the primary composite endpoint. Additional analyses were conducted based on a more strict MACE definition which excludes UAP from the MACE+ endpoint. In the updated database, MACE+/MACE events were ascertained either within 7 days or within 30 days after treatment discontinuation. As a secondary analysis, the Mantel-Haenszel risk difference and incidence rate difference approach were also employed to evaluate the CV risk. In summary, the CV risk of IDeg/IDegAsp was assessed by applying stratified Cox regression model and Mantel-Haenszel methods to the MACE+ and MACE composite endpoints censoring data at 7 days and 30 days. The statistical methods applied to this application are similar to those used in other meta-analyses of CV risk which are felt to be sufficient in characterizing the CV risk. More details for the statistical methodologies used in this review are provided in Section 3.3.2.

5.2 Collective Evidence

Based on the updated pooled data of all 17 randomized phase 3 trials including extensions, a total of 132 subjects experienced at least one adjudicated MACE+ event censored at 7 days, with 95 subjects in the pooled IDeg/IDegAsp group and 37 subjects in the pooled all comparator group. The incidence rate of MACE+ was 18.4 per 1,000 person-years in the pooled IDeg/IDegAsp group, as compared to 14.4 per 1,000 person-years in the pooled all comparator group. The estimated hazard ratio of IDeg/IDegAsp compared to all comparator was 1.30 with a 95% CI of (0.88, 1.93) for MACE+. Detailed analysis results are provided in Section 3.3.4.1.1.

Using the strict definition of MACE, a total of 91 subjects experienced at least one adjudicated MACE event censored at 7 days, with 70 subjects reporting an event in the pooled IDeg/IDegAsp group and 21 subjects reporting an event in the pooled all comparator group. The

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incidence rate of MACE was 13.6 per 1,000 person-years in the pooled IDeg/IDegAsp group, as compared to 8.2 per 1,000 person-years in the pooled all comparator group. The estimated hazard ratio of IDeg/IDegAsp compared to all comparator was 1.67 with a 95% CI of (1.01, 2.75) for strict MACE. Detailed analysis results are provided in Section 3.3.4.1.2.

As shown in Section 3.3.4.2, the Mantel-Haenszel risk difference and incidence rate difference results are consistent with the primary analysis results based on the hazard ratio.

The difference between IDeg/IDegAsp and all comparator in developing a CV related event as measured by MACE+/MACE was also evaluated in subgroups by age, gender, race and region. Some trial-level subgroup analyses were also conducted in IGlar-controlled trials, IDeg trials, trials in T1DM and T2DM subjects separately. Most of the subgroup analysis results were in the same direction as the overall result. Detailed results for subgroup analyses are provided in Section 4.

5.3 Conclusions and Recommendations

The Agency considered the updated database robust and appropriate for the evaluation of cardiovascular safety. Based on the meta-analysis of the 17 randomized phase 3 trials and their extensions included in the updated database, the risk of developing a major adverse cardiovascular event, as measured by MACE+ censored at 7 days, was higher in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) relative to the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Compared to the pooled all comparator group, the estimated hazard ratio of IDeg/IDegAsp is 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) using a 7 day censoring window, as shown in Table 20 below.

Table 20: Primary Analysis Results for MACE+/MACE (Updated Database, FAS, 7 Day Censoring)

		IDeg/IDegAsp (*N* = 5794) [PYE = 5153.6]	**Comparator** (*N* = 3461) [PYE = 2562.7]
MACE+ Endpoint			
	Events [IRD*]	95 [18.4]	37 [14.4]
	HR (95% CI)†	1.30 (0.88, 1.93)	
MACE Endpoint			
	Events (IRD*)	70 [13.6]	21 [8.2]
	HR (95% CI)†	1.67 (1.01, 2.75)	

*: Per 1,000 PYE. †: Cox proportional hazards model stratified by trial
Source: Created by reviewer.

In addition to the above approaches, several additional analyses were conducted that explored various censoring windows, incorporated different effect measures (risk difference and incidence rate difference), and examined various subsets of trials and subgroup analyses. While various

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scenarios resulted in different values of the hazard ratio and risk difference point estimates, a consistent trend was observed – IDeg/IDegAsp was shown to be associated with an increase in CV risk.

To determine if the increase in CV risk as seen from the meta-analysis of these 17 trials is a chance finding, further evidence from a dedicated CV outcome trial would be needed.

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/s/

BO LI
12/13/2012
CV meta-analysis of IDeg/IDegAsp

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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

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
	PDUFA date: January 18, 2013
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
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Project Manager:	Rachel Hartford

Keywords: NDA review, clinical studies

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Novo Nordisk proposes Ryzodeg, the co-formulated 70% insulin degludec and 30% insulin aspart, for improving glycemic control in adult patients with diabetes mellitus. Insulin degludec is a new molecular entity and an ultra-long-acting human insulin analog. Insulin aspart is a rapid-acting human insulin analog. Based on evaluation of change in glycosylated hemoglobin (HbA1c) from baseline to end of trial, the applicant claims insulin degludec/insulin aspart (IDegAsp) is effective in improving glycemic control in adult patients with diabetes mellitus. My review of the statistical evidence suggests support for the claim. This NDA is approvable from statistical point of view.

1.2 Brief Overview of Clinical Studies

Five phase 3 trials were reviewed for this NDA submission. They 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.

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 ± pioglitazone ± DPP-4 inhibitor. In total, 465 subjects were

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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 ± pioglitazone ± 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).

1.3 Statistical Issues and Findings

The primary efficacy endpoint in all five trials was change from baseline in HbA1c after 26 weeks of treatment. As mentioned in the Diabetes Guidance, when HbA1c is the primary efficacy endpoint, the division accepts a non-inferiority margin of 0.3% or 0.4% for active-controlled trials. When insulin is the active control, the non-inferiority margin is usually set at 0.4%. 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 (CI) 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).

The key secondary efficacy endpoints varied among trials and were ranked in different orders. In protocol, the applicant specified superiority test on secondary efficacy endpoints. 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. The superiority of a secondary efficacy endpoint was only confirmed when all previous null-hypotheses had been rejected.

Because study population were fairly similar in the T2DM trials and there is no obvious reason why the secondary endpoints should differ across trials and be prioritized in different orders and the design, it is more reasonable to evaluate the secondary efficacy endpoints collectively across trials than to evaluate them separately in different order in each single trial. The collective

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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 everyone knew the treatment they were getting. The results on hypoglycemia episode should be interpreted carefully. Comparing patients randomized to IDegAsp arm to patients randomized to the control arm, there was no consistent weight gain or weight loss across trials. In general, patients randomized to IDegAsp arm received on average lower dose of total daily insulin comparing to patients randomized to the active 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.

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2 INTRODUCTION

2.1 Overview

2.1.1 Class and Indication

Ryzodeg (IDegAsp: 70% insulin degludec and 30% insulin aspart) is composed of a new molecular entity, insulin degludec, an ultra-long-acting human insulin analog and insulin aspart, a rapid-acting human insulin analog. The co-formulated product is intended for once or twice-daily dosing at any main meal and indicated to improve glycaemic control in adults with diabetes mellitus. The formulation of this product is developed to obtain a clear distinction between the effects of the bolus (insulin aspart) and basal (insulin degludec) components of IDegAsp.

The product is available in strength of 100 units of insulin degludec/insulin aspart per mL and is administrated via subcutaneous injection. Insulin requirements vary on an individual basis and dosage is adjusted on the basis of glycaemic response.

2.1.2 History of drug development

NovoLog (insulin aspart) was approved on June 7, 2000 to improve glycemic control in patients with diabetes mellitus. Insulin degludec (IDeg) is a new molecular entity and is under investigation, submitted to IND 76,496 on September 5, 2007, for the treatment of patients with diabetes mellitus [redacted] (b) (4). The combination product (IDegAsp) was submitted for investigation to IND 73,198 on March 20, 2008. Along with this NDA submission, Novo Nordisk submitted a separate NDA (203,314) for the single component product, Tresiba (insulin degludec). The applicant is seeking approval for both products at the same time.

The End-Of-Phase 2 (EOP2) meeting for IDegAsp was held on February 24, 2009. Statistical testing procedure for the confirmatory secondary endpoints was discussed at the meeting. The Division suggested the sponsor to control the type 1 error rate for key secondary endpoints, which the sponsor would like to include in the label, and include justification in NDA submission for why the selected endpoints should be included in the package insert. There was concern on proposed key secondary endpoints differs across trials and the sponsor was asked to provide an explanation of how the secondary endpoints were prioritized. Specifically, the Division explained [redacted] (b) (4), 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 sponsor proposed meta-analysis of hypoglycemic events due to experience from previous development programs, 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.

2.1.3 Specific studies reviewed

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Five phase 3 trials were reviewed for this NDA submission. They were all 26-week treatment + 1-week follow up, multi-center, multi-national, open-label, randomized, 2-arm parallel group, active-controlled, treat-to-target trials. Trial 3594 had a 26-week extension period. The objective of extension period was to investigate long-term safety and to compare efficacy after 52 weeks of treatment. Details of trial design are available 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 + IAsp s.c. for the remaining meals	366	T1DM
	IDet: OD or BID s.c. + IAsp s.c. at main meals	182	
NN5401-3590 (Study B)	IDegAsp: OD s.c. at breakfast + met p.o. + NPH s.c. in follow-up	266	T2DM
	IGlar: OD s.c. + met p.o. + NPH s.c. in follow-up	263	
NN5401-3593 (Study C)	IDegAsp: OD s.c. at main meal + met p.o. ± pio p.o. ± DPP-41 p.o.	230	T2DM
	IGlar: OD s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	233	
NN5401-3592 (Study D)	IDegAsp: BID s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	224	T2DM
	BIAsp 30: BID s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	222	
NN5401-3597 (Study E)	IDegAsp: BID s.c. ± met p.o. + BHI 30 s.c. in follow-up	280	T2DM
	BIAsp 30: BID s.c. ± met p.o. + BHI 30 s.c. in follow-up	142	

- OD: once daily
- IDet: insulin detemir
- met: metformin
- NPH: Neutral Protamine Hagedorn
- BIAsp: biphasic insulin aspart
- s.c.: subcutaneous

BID: twice daily
IGlar: insulin glargine
pio: pioglitazone
DPP-4: di-peptidyl peptidase-4
BHI: biphasic human insulin
p.o.: per oral

2.2 Data Sources

The data and final study report were submitted electronically. The submission was archived under the network path location <\\CDSESUB1\EVSPROD\NDA203313\203313.enx>. The information needed for this review was contained in Module 1 FDA Regional Information (cover letter, meeting correspondence, and labeling), Module 2.5 Clinical Overview, Module 2.7 Clinical Summary, and Module 5 Clinical Study Report. This review focuses on documents submitted to serial number 0000.

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3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This submission is in electronic common technical document (eCTD) format with xml backbone. All required documents that are necessary for statistical review are submitted. No additional information request was made for statistical review.

Study datasets are provided as SAS XPORT transport files version 5. No software code was submitted. This review covered datasets from five individual trials (listed in Table 1) and one integrated summary of efficacy which pooled data across the five trials.

For the individual trials, both tabulation and analysis datasets are provided. Tabulation datasets include the source data without any derivations or enrichments, whereas analysis datasets also include derived and enriched data (such as formatted variables, populations, derived endpoints, LOCF information, etc.). The tabulation and analysis datasets are joinable by the unique record identifier (USUBJID). The integrated summary of efficacy datasets are primarily stacking of the individual trial analysis datasets for selected variables. They are mainly used for subgroup analysis on HbA1c and meta-analysis on hypoglycemia events in this review.

The datasets are in good organization. Variables in study datasets are consistently named and used across trials, with clear description in the Define.pdf file. The reported analysis results are in good quality. I was able to reproduce the results on the primary and secondary efficacy endpoints in the Clinical Study Report (CSR).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

Summary of trial design for the five trials reviewed for this submission is given in Table 1. They were all 26-week treatment + 1-week follow up, multi-center, multi-national, open-label, randomized, 2-arm parallel group, active-controlled, treat-to-target trials. In Trials 3594 and 3597, patients were randomized in 2:1 ratio to IDegAsp and comparators. In the other three trials, patients were randomized in 1:1 ratio to IDegAsp and comparators. Stratification for randomization was carried out according to previous anti-diabetic treatment.

Trial 3594 investigated the efficacy and safety of IDegAsp in patients with T1DM. It had a 26-week extension period with exactly the same treatment regimen as main trial to investigate long-term safety and to compare efficacy after 52 weeks of treatment. Majority of patients (69%) who randomized in the main trial participated the extension period. The other four trials, 3590, 3592, 3593, and 3597, investigated the efficacy and safety of IDegAsp in patients with T2DM. IDegAsp was administered once daily in T1DM. In T2DM, both once daily and twice daily dosing were investigated.

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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.

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.

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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.

3.2.2 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 * inter-quartile range / 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 * inter-quartile range / 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.

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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

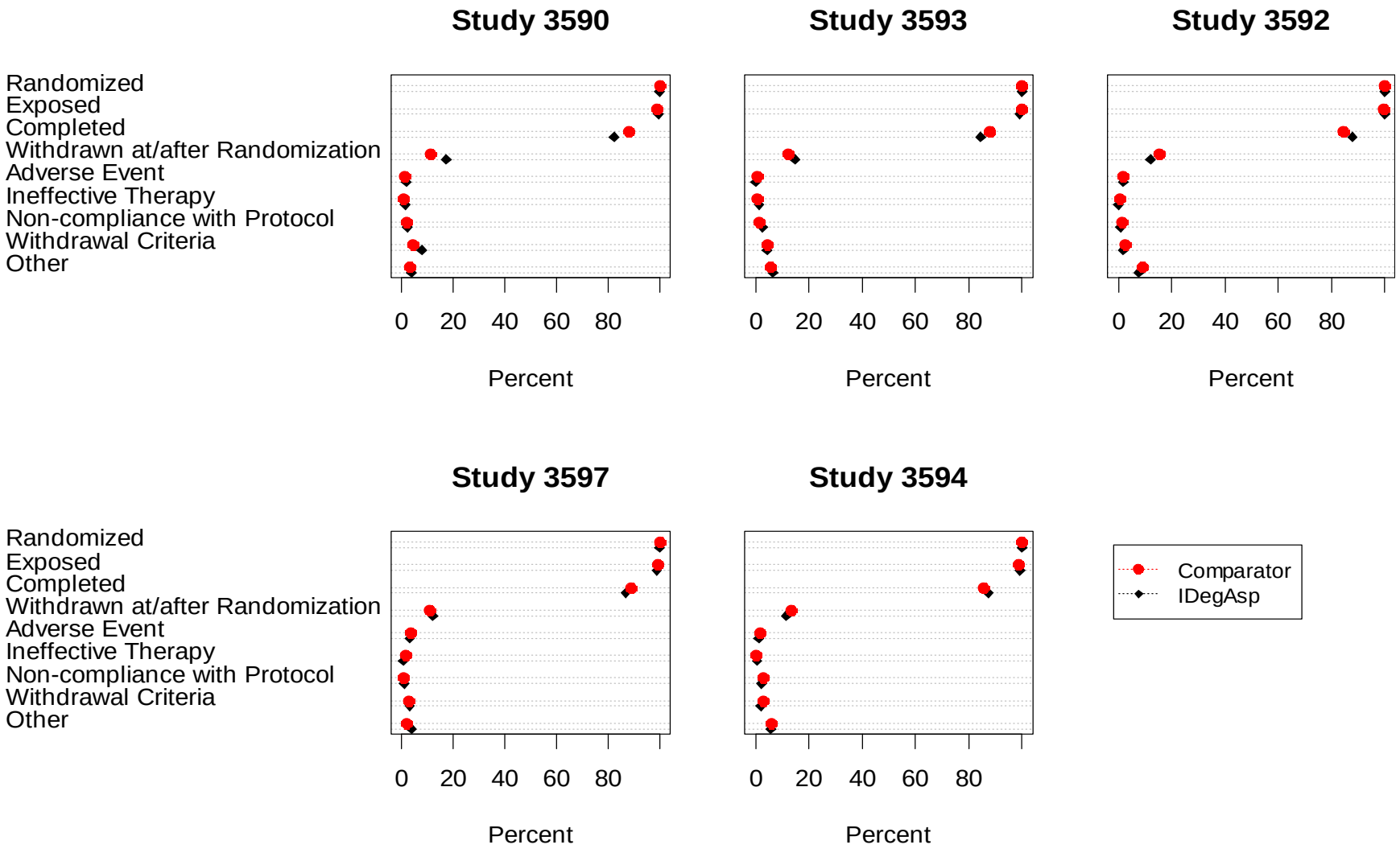

Figure 1 Summary of patient disposition.

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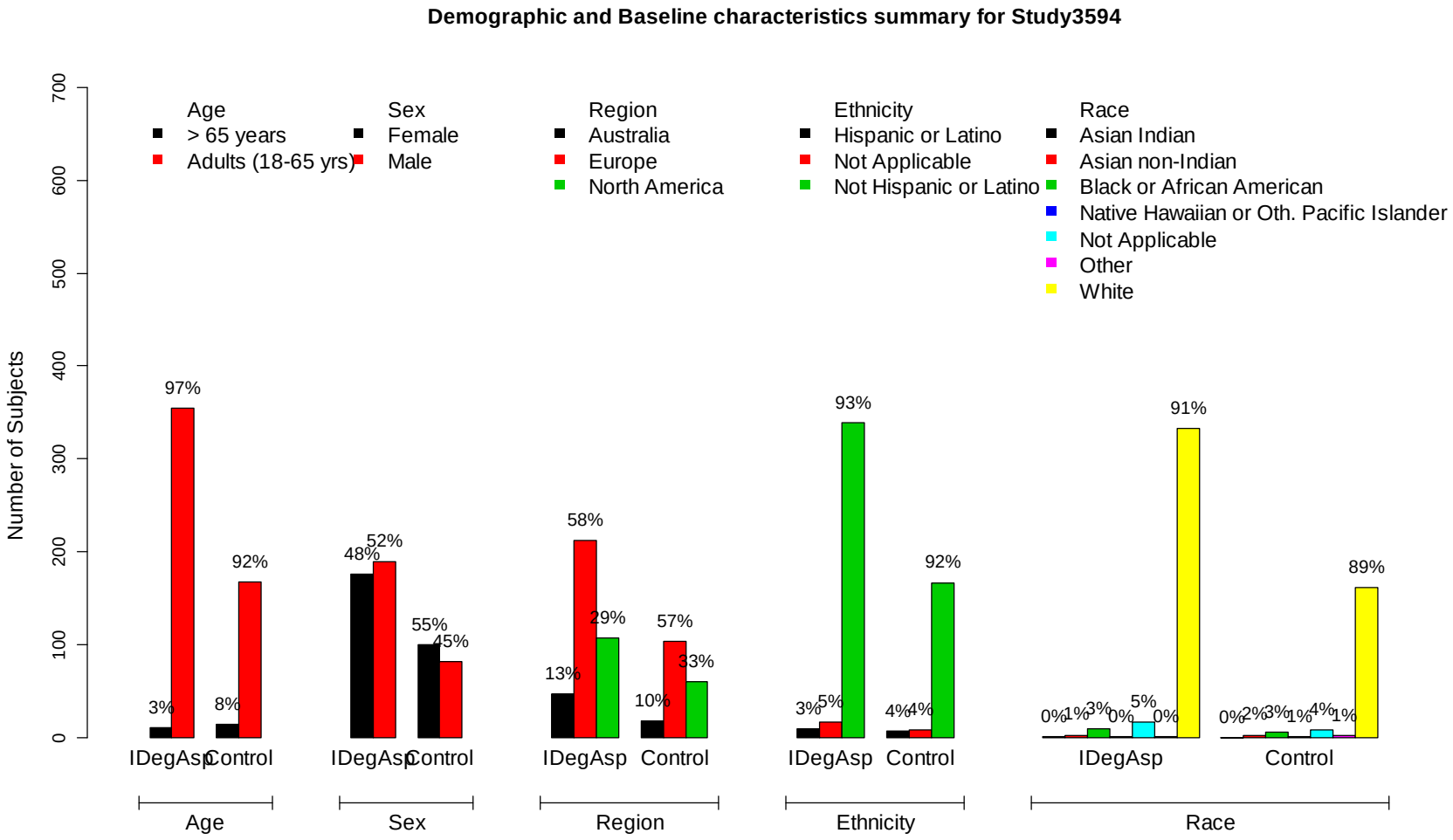

Figure 2 Demographic characteristics summary for Trial 3594.

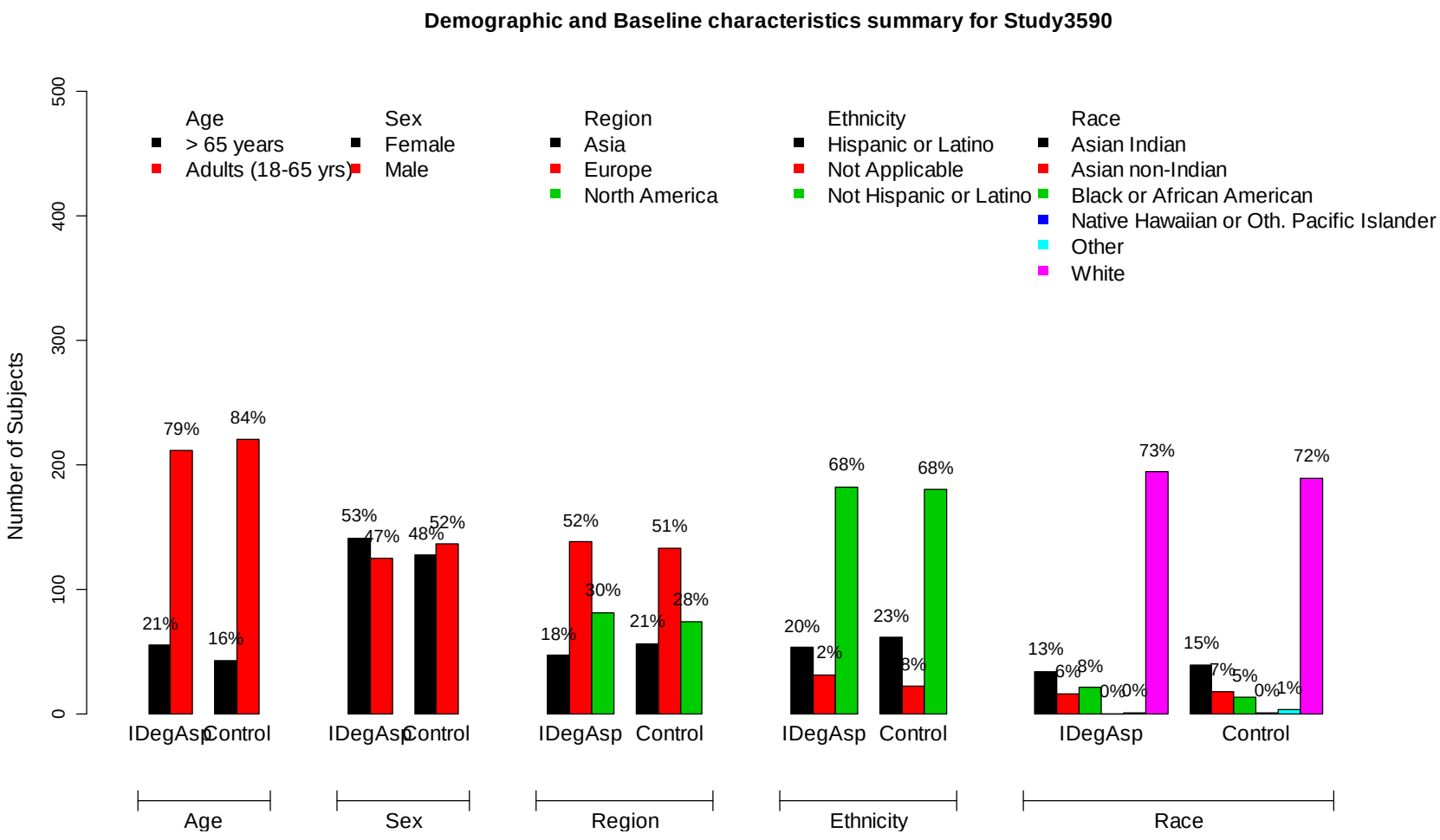

Figure 3 Demographic characteristics summary for Trial 3590.

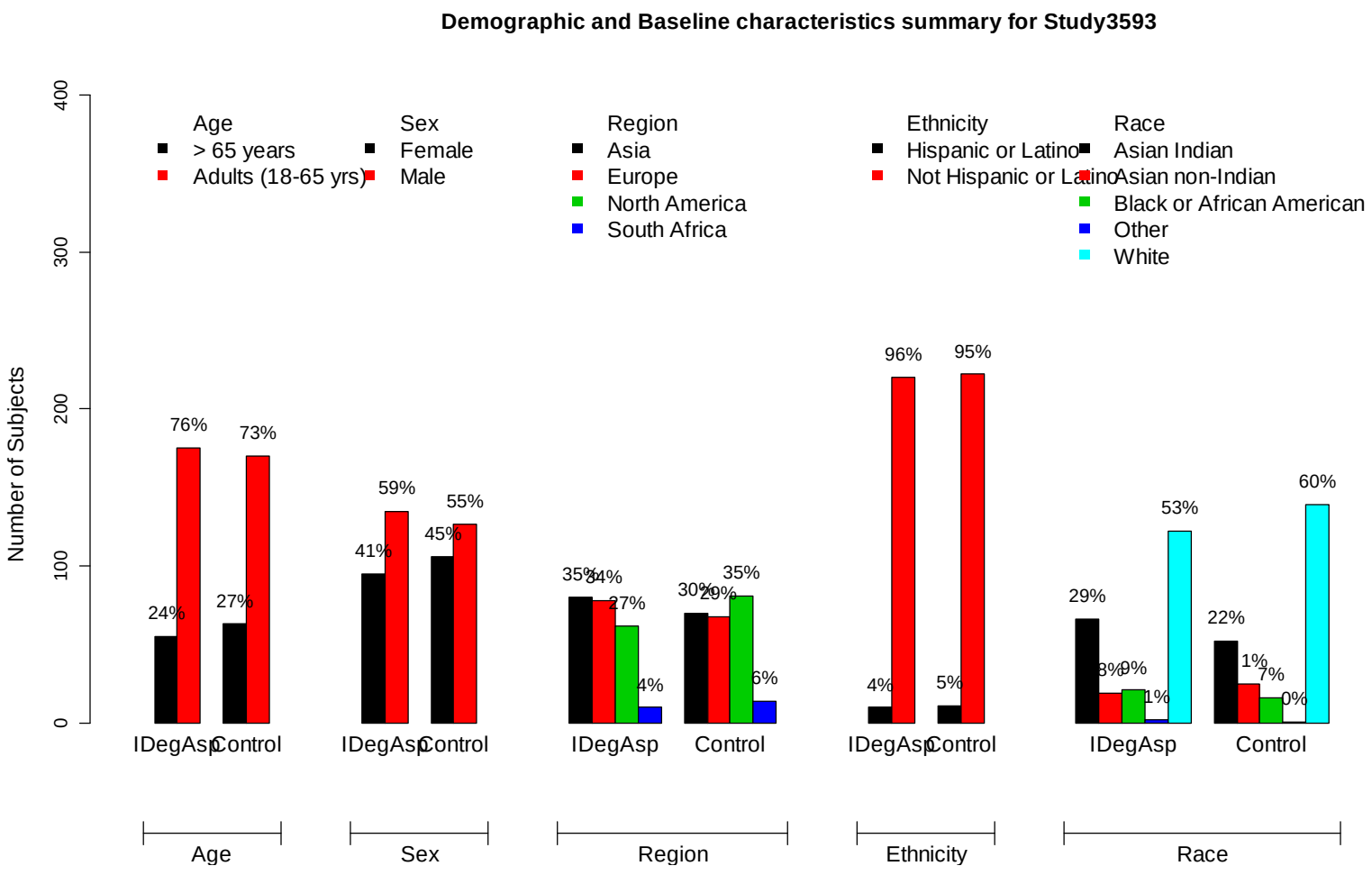

Figure 4 Demographic characteristics summary for Trial 3593.

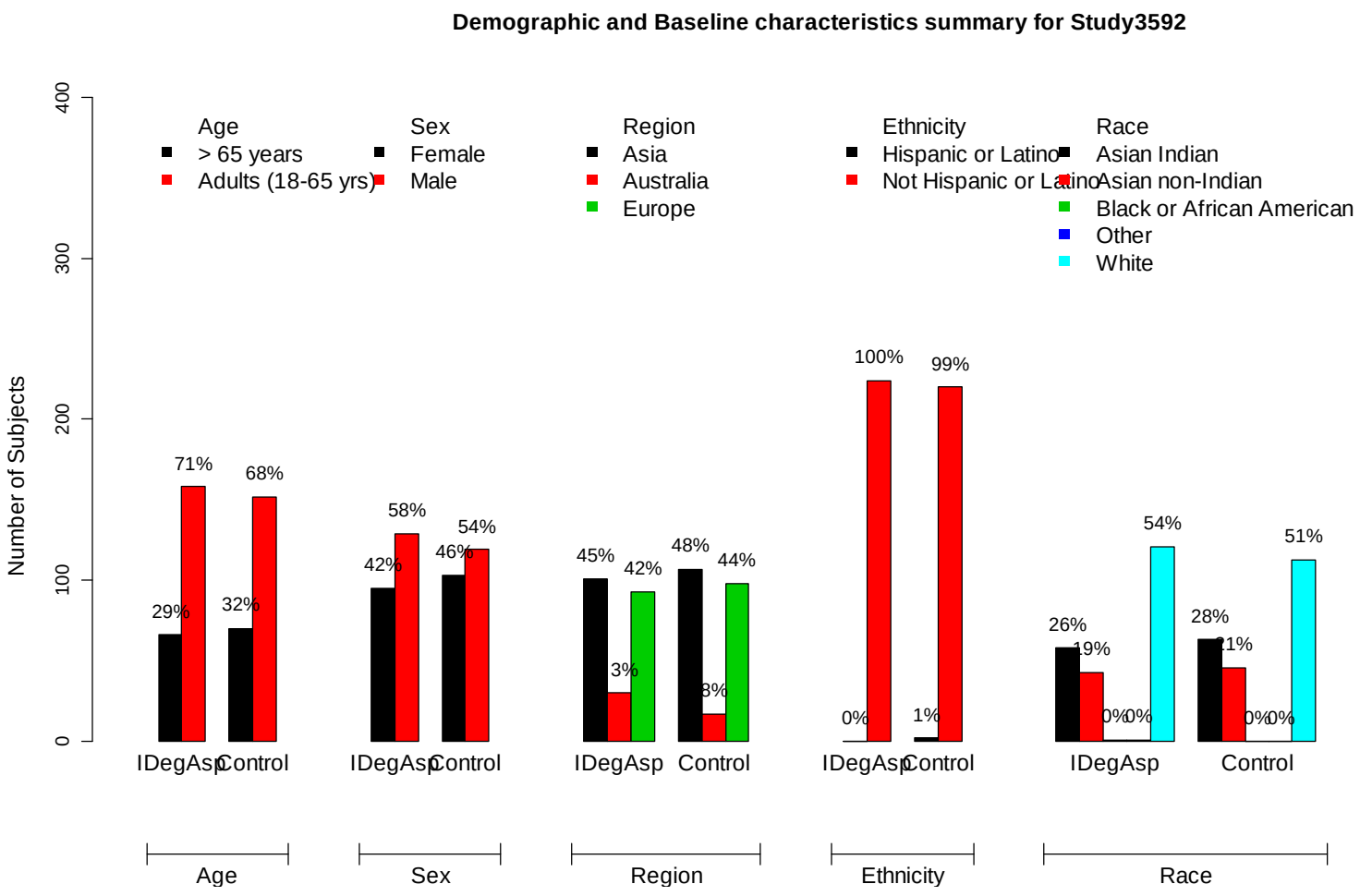

Figure 5 Demographic characteristics summary for Trial 3592.

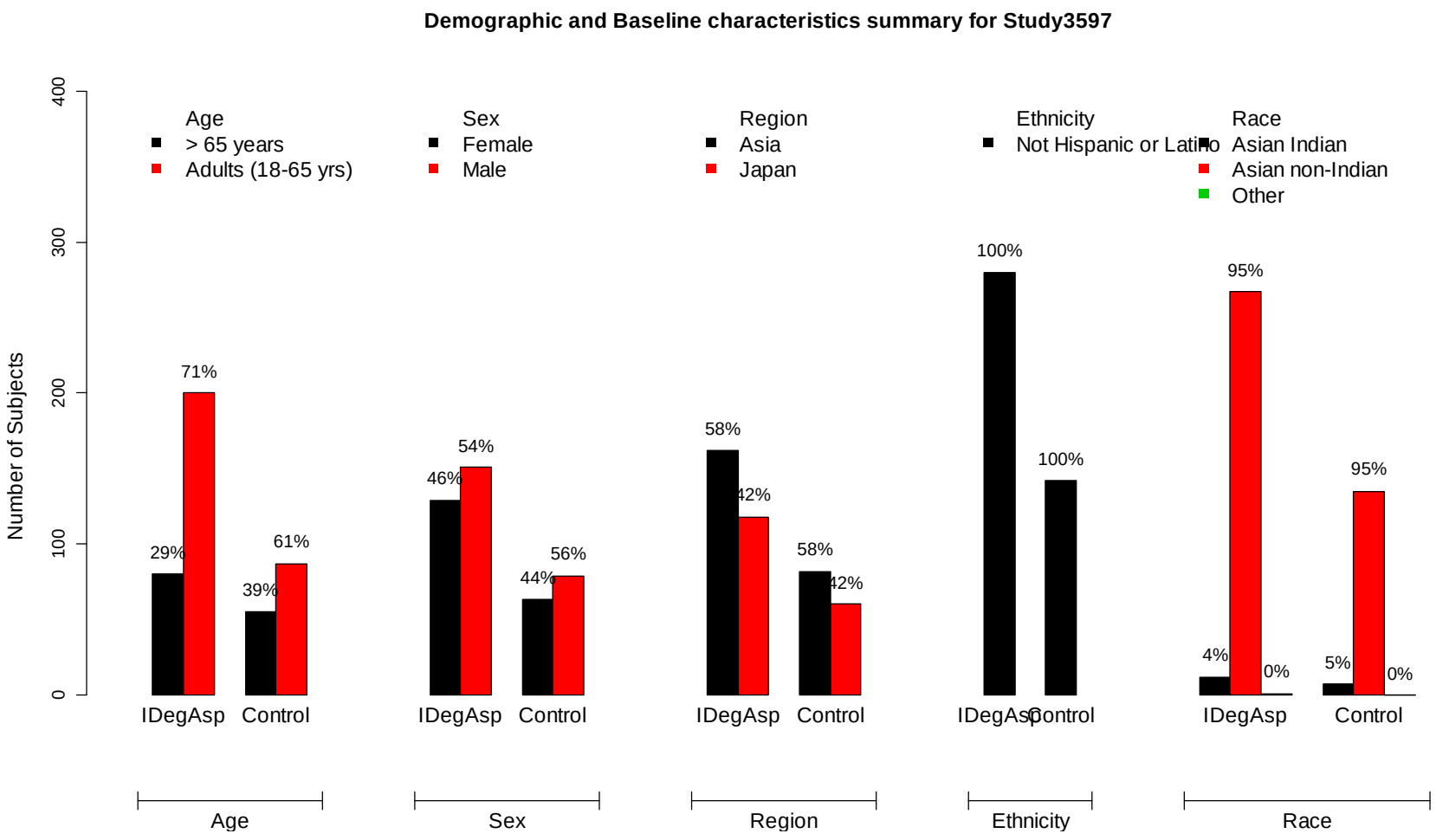

Figure 6 Demographic characteristics summary for Trial 3597.

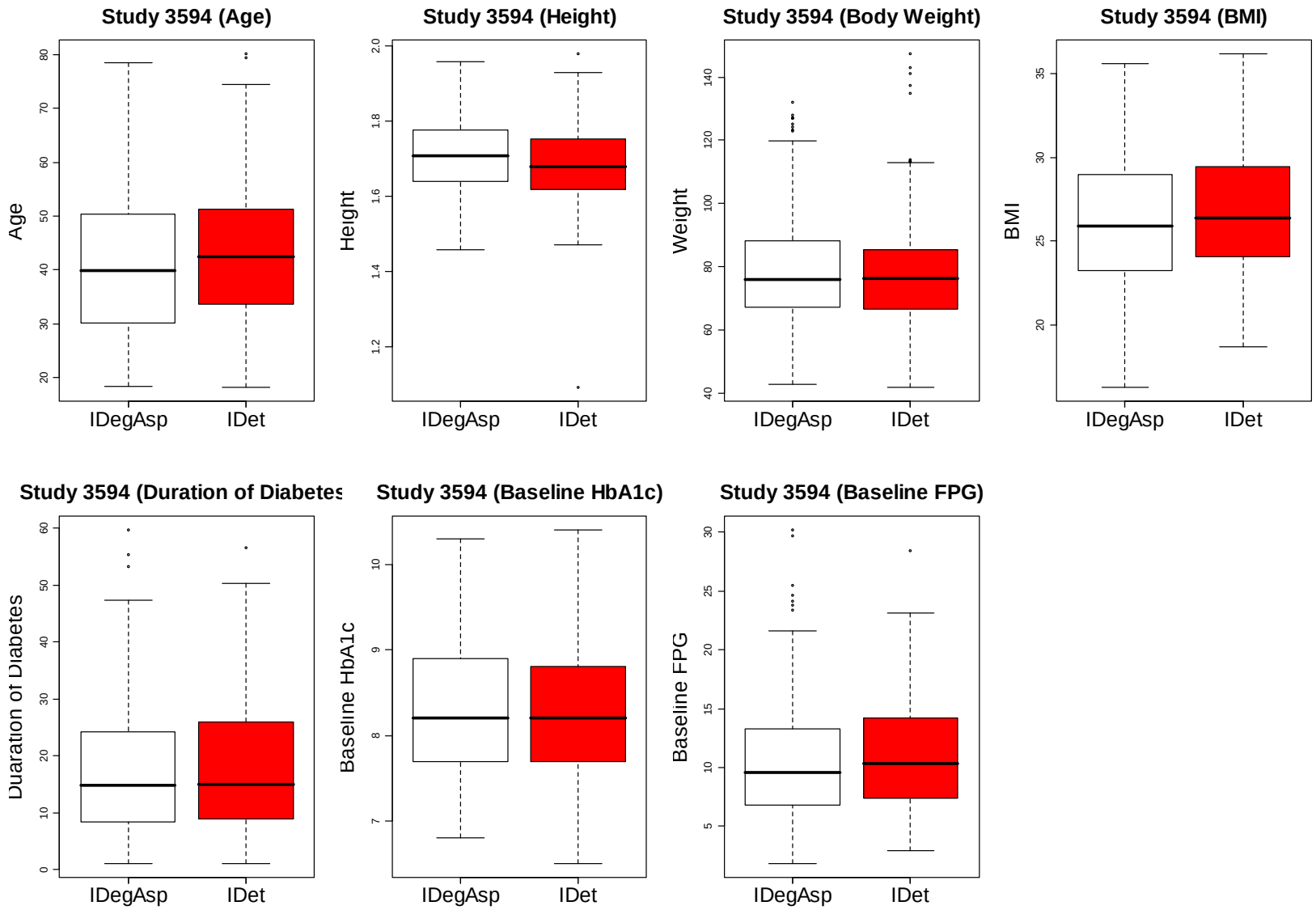

Figure 7 Baseline and diabetes characteristics for patients in Trial 3594.

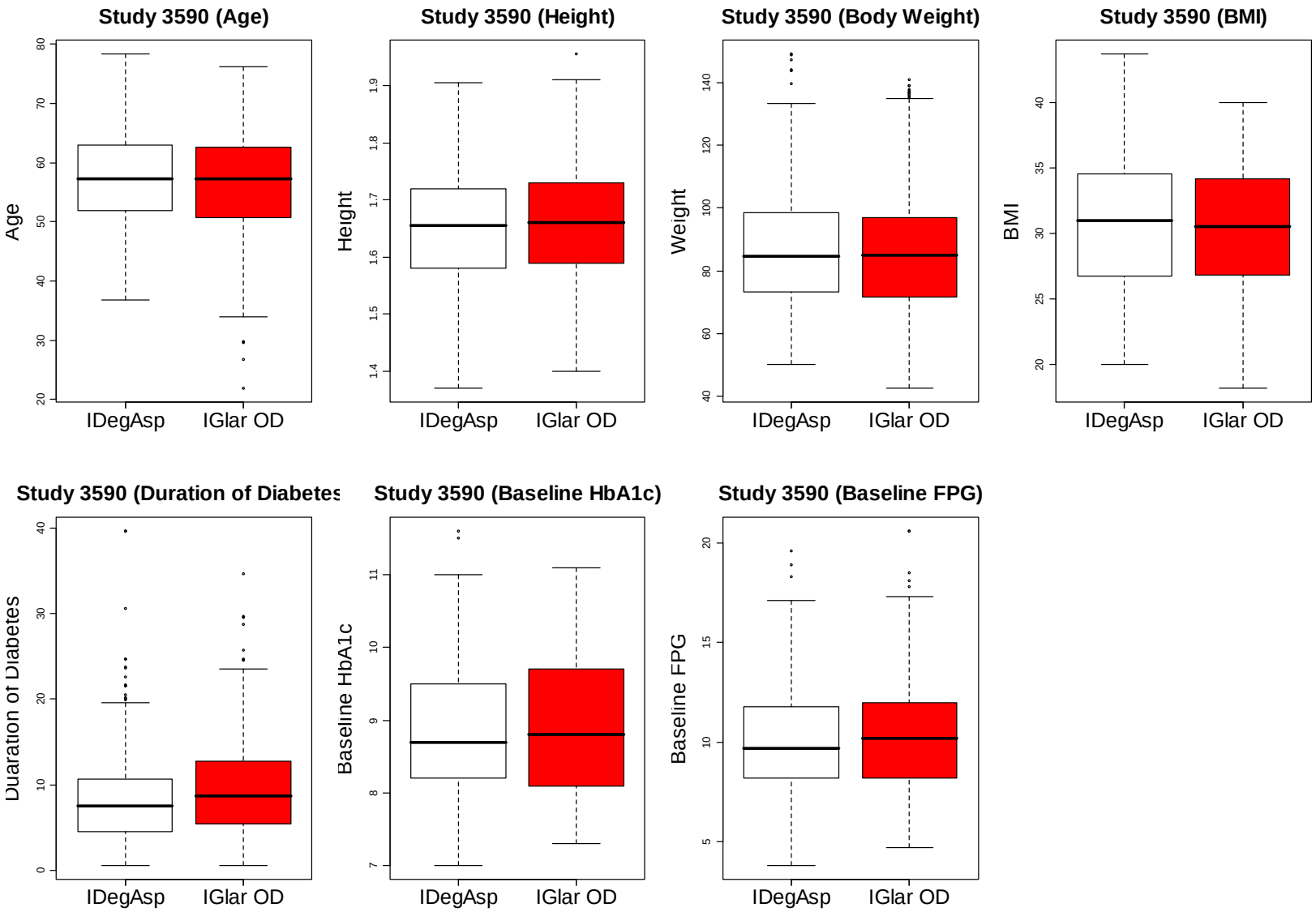

Figure 8 Baseline and diabetes characteristics for patients in Trial 3590.

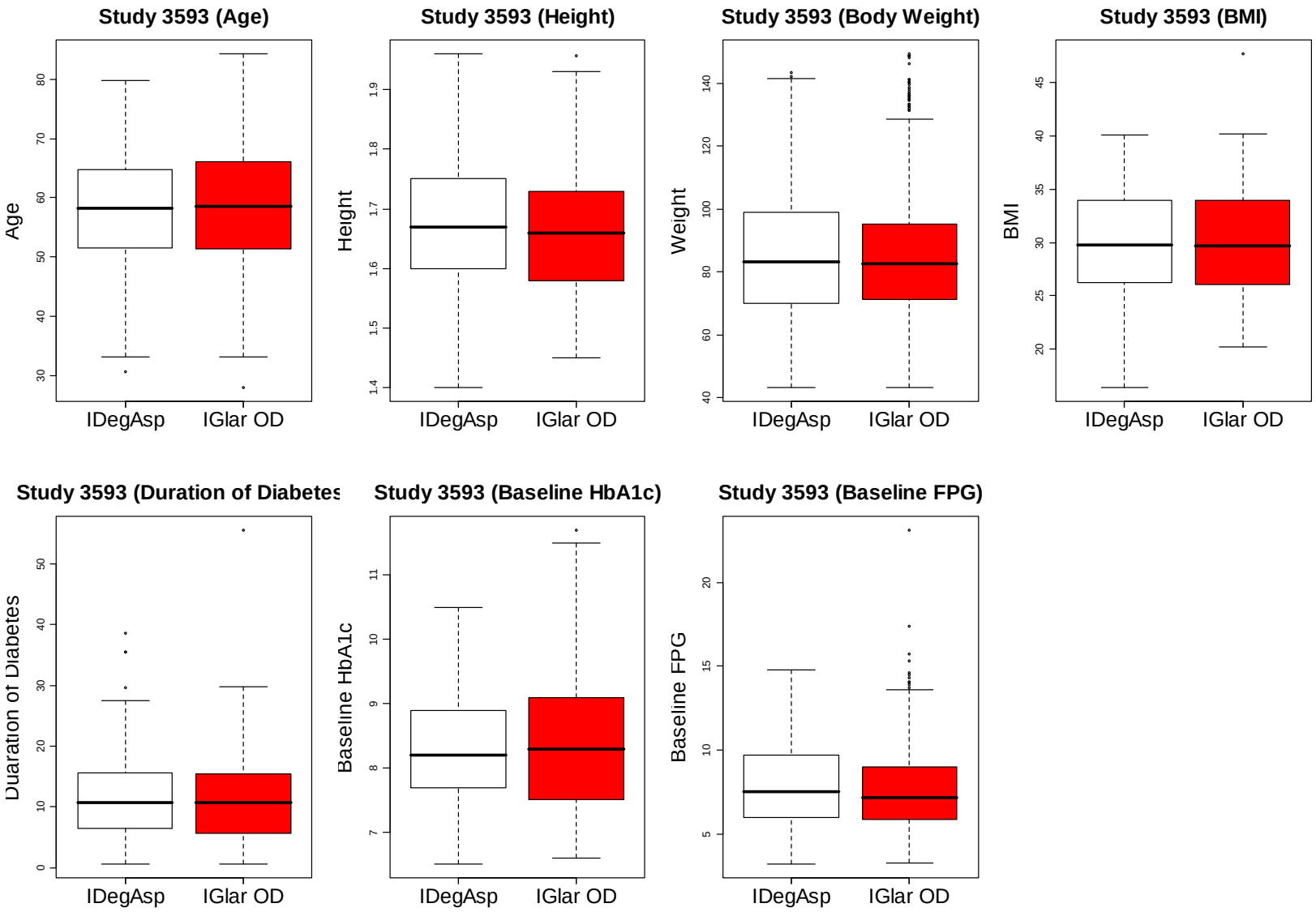

Figure 9 Baseline and diabetes characteristics for patients in Trial 3593.

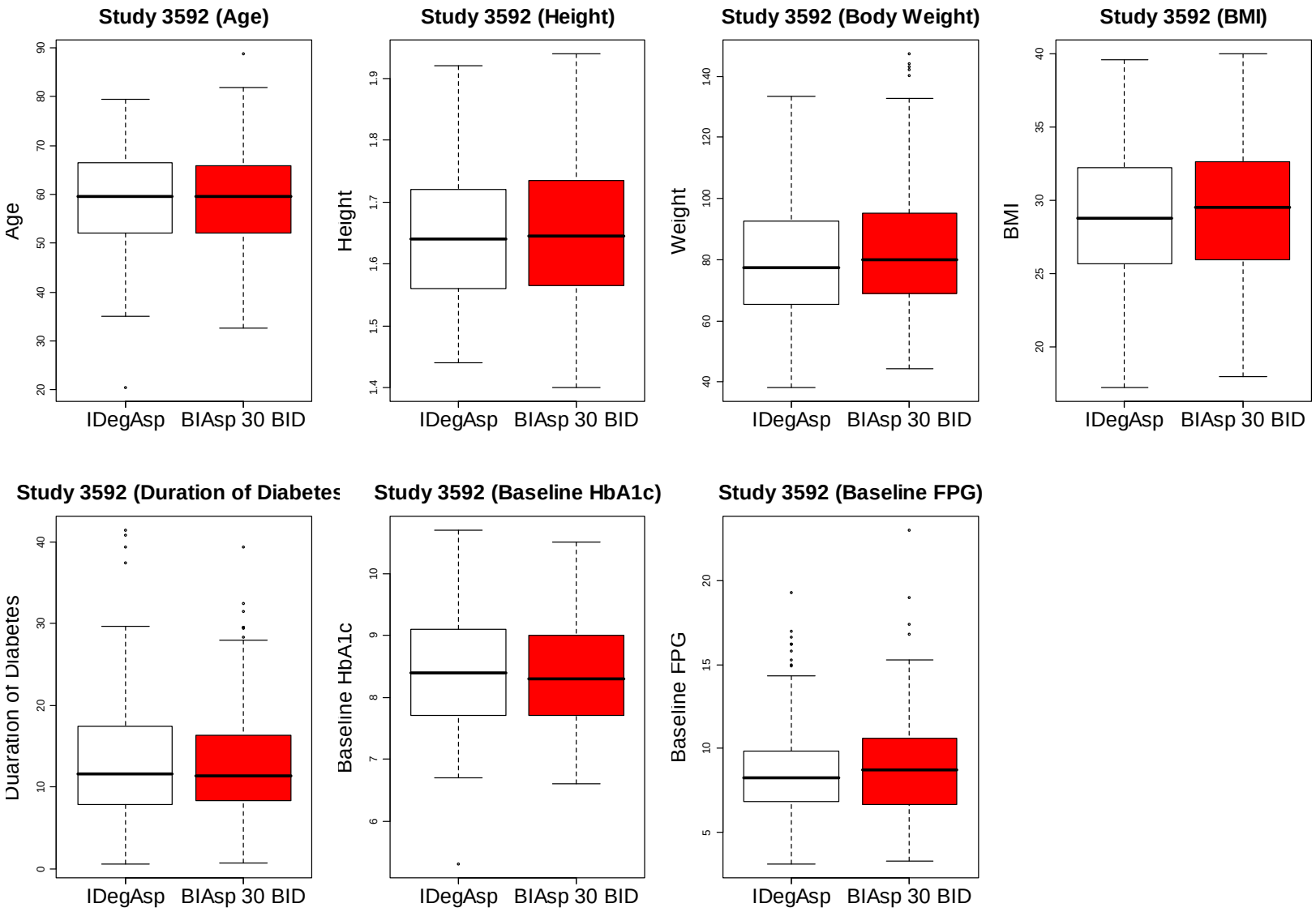

Figure 10 Baseline and diabetes characteristics for patients in Trial 3592.

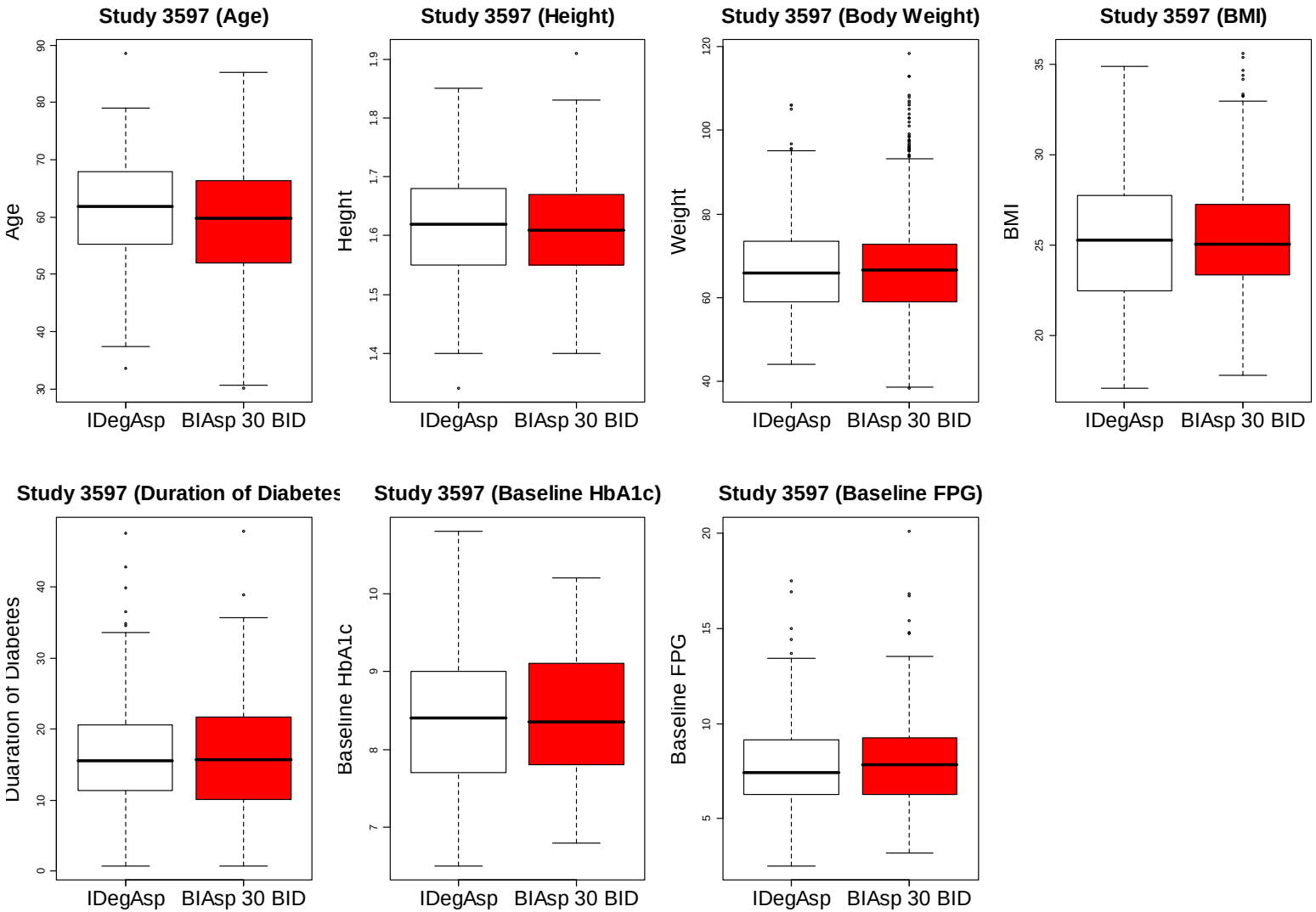

Figure 11 Baseline and diabetes characteristics for patients in Trial 3597.

3.2.3 Statistical Methodologies

Change from baseline in HbA1c, 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 HbA1c, 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 ≤ 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 HbA1c was imputed by last observation carried forward (LOCF) method. Two sensitivity analyses were performed for the primary efficacy endpoint.

All observed HbA1c 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 HbA1c as covariate to assess the sensitivity of the results to inclusion/exclusion of fixed factors and covariates.

Responder (subjects with HbA1c < 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 HbA1c.

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 HbA1c.

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.

3.2.4 Results and Conclusions

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, 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.

	IDegAsp			Comparator			IDegAsp - Comparator	
Trial	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)

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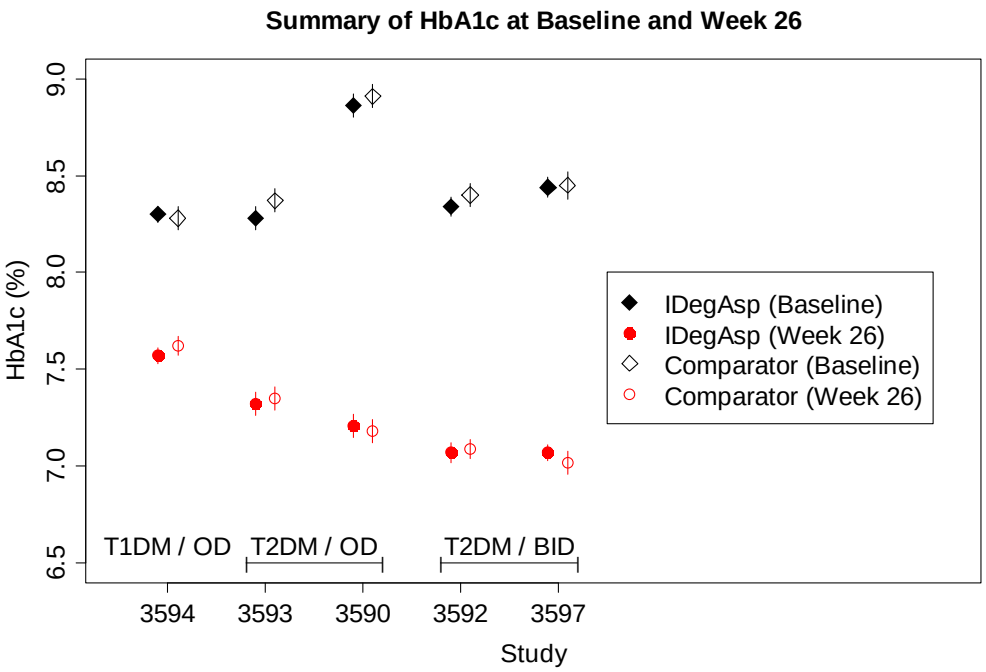

Figure 12 Summary of HbA1c at baseline and week 26.

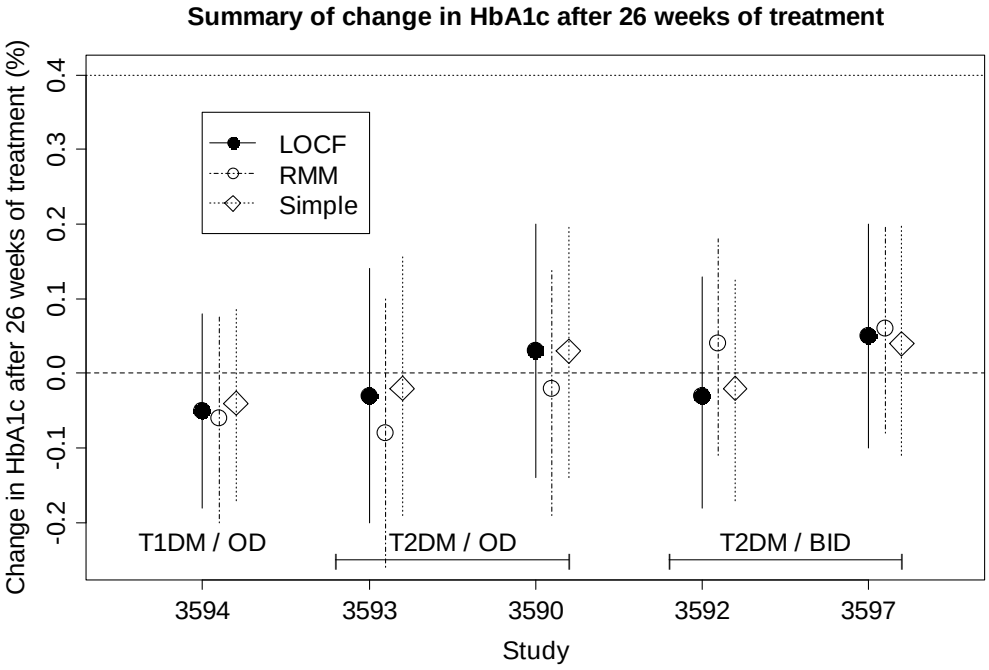

Figure 13 Summary of change in HbA1c after 26 weeks of treatment.

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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 2meeting, 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 (mean of rate ratio 0.63 with 95% CI of [0.49, 0.81]) 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 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 **Error! Reference source not found.**.

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.

Reference ID: 3218232

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 program 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.

Reference ID: 3218232

Table 5 Summary of confirmatory secondary efficacy endpoints (LOCF).

	3594 (T1DM OD)			3590 (T2DM OD)			3593 (T2DM OD)			3592 (T2DM BID)			3597 (T2DM BID)		
	Mean[3]	**95% CI**	**TO (C)**	**Mean[3]**	**95% CI**	**TO (C)**	**Mean[3]**	**95% CI**	**TO (C)**	**Mean[3]**	**95% CI**	**TO (C)**	**Mean[3]**	**95% CI**	**TO (C)**
HbA1c <7% without Hypoglycemia[1]	1.24	(0.77, 2.02)	2 (TPS)	0.61	(0.40, 0.94)	3 (TPS)	0.80	(0.50, 1.30)	2 (I)	1.60	(0.94, 2.72)	3 (I)	1.77	(0.97, 3.25)	3 (TPS)
Nocturnal Hypoglycemia[1]	0.63	(0.49, 0.81)	3 (TPS)	0.29	(0.13, 0.65)	4 (TPS)	0.80	(0.49, 1.3)	4 (TPS)	0.27	(0.18, 0.41)	5 (TPS)	0.67	(0.43, 1.06)	5 (TPS)
Confirmed Hypoglycemia[1]	0.91	(0.76, 1.09)	NIT	2.17	(1.59, 2.94)	NIT	1.43	(1.07, 1.92)	NIT	0.68	(0.52, 0.89)	2 (SC)	1.00	(0.76, 1.32)	2 (I)
Body weight[2]	1.04	(0.38, 1.69)	NIT	1.31	(0.72, 1.89)	5 (TPS)	0.33	(-0.17, 0.83)	5 (TPS)	-0.62	(-1.15, -0.10)	4 (TPS)	-0.38	(-0.96, 0.21)	4 (TPS)
FPG[2]	0.23	(-0.46, 0.91)	1 (I)	0.51	(0.09, 0.93)	NIT	0.33	(-0.11, 0.77)	NIT	-1.14	(-1.53, -0.76)	1 (SC)	-1.06	(-1.43, -0.70)	1 (SC)
Prandial PG at breakfast[2]	-0.57	(-1.36, 0.21)	NIT	-1.40	(-1.92, -0.88)	1 (SC)	-0.32	(-0.86, 0.21)	NIT	-0.54	(-1.09, 0.00)	NIT	0.06	(-0.54, 0.66)	NIT
Prandial PG at main evening meal[2]	0.12	(-0.67, 0.92)	NIT	-0.19	(-0.70, 0.31)	NIT	-1.32	(-1.93, -0.72)	1 (SC)	0.33	(-0.26, 0.92)	NIT	0.77	(-0.02, 1.55)	NIT
Fluctuation of Nocturnal IG[2]	NA	NA	NA	0.69	(0.25, 1.92)	2 (I)	0.97	(0.49, 1.3)	3 (TPS)	NA	NA	NA	NA	NA	NA

- TO (C) = Testing Order (Conclusion)
- SC = Superiority Confirmed
- I = Inconclusive
- TPS = Testing Procedure Stopped
- NIT = Not Included in Testing procedure
- NA=data were Not Available
- [1] Treatments are compared using a ratio.
- [2] Treatments are compared using a difference.
- [3] "Mean" refers to treatment ratio or treatment difference.

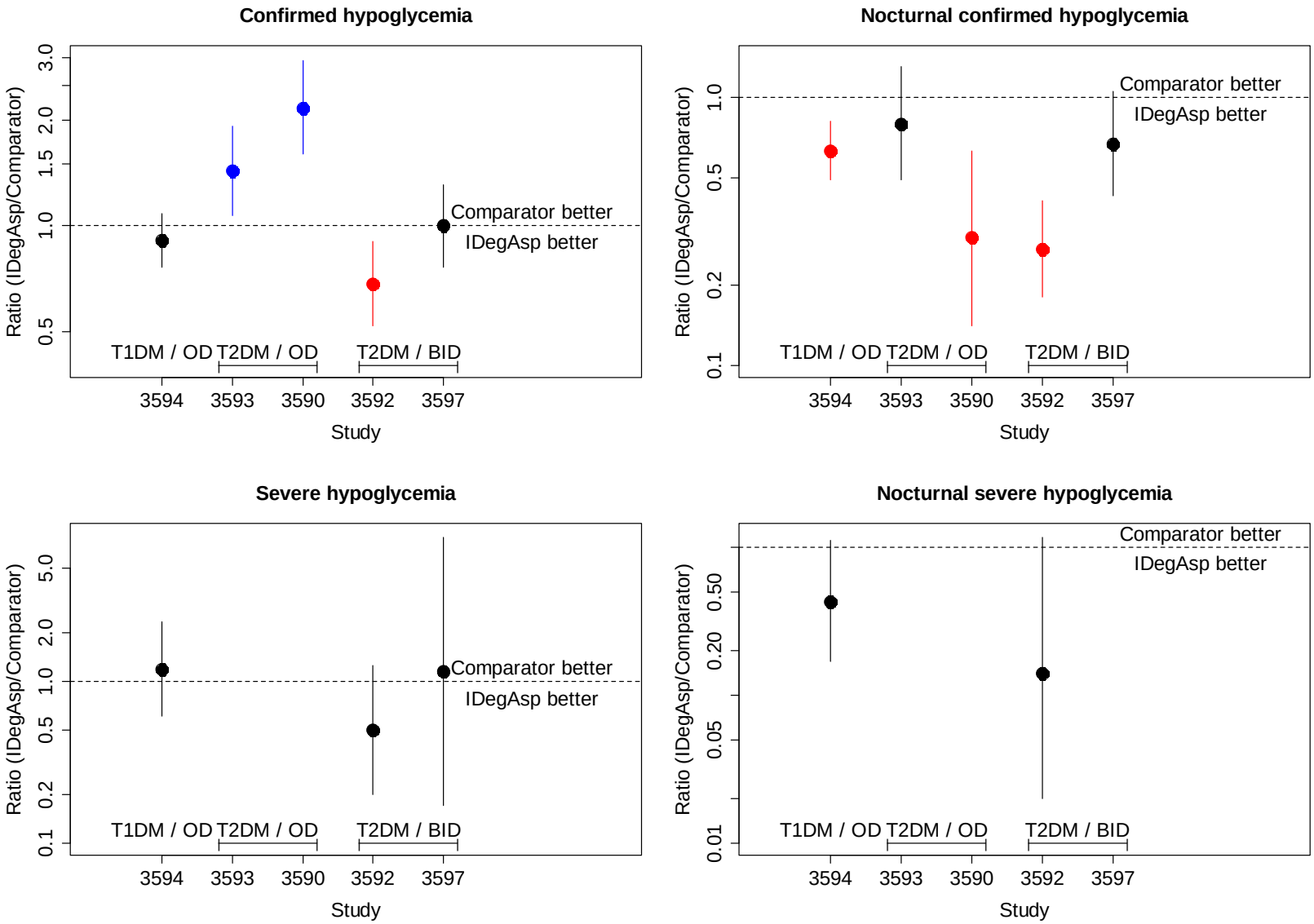

Figure 14 Ratio of hypoglycemic episodes in IDegAsp vs. Comparator.

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.

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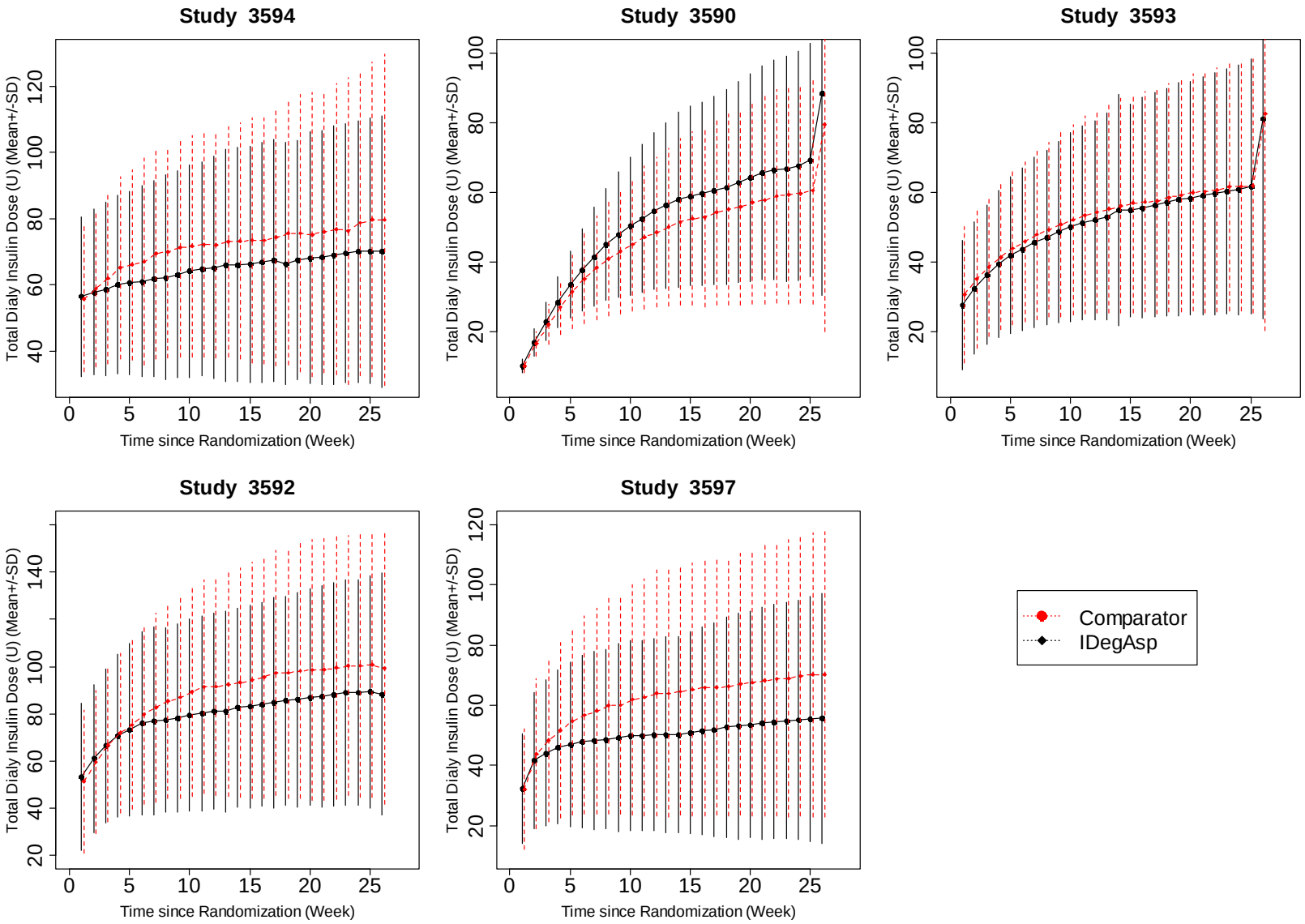

Figure 15 Summary of total daily insulin dose (Mean ± SD).

Table 8 Summary of change from baseline in body weight after 26 weeks of treatment.

	IDegAsp			Comparator			IDegAsp - Comparator	
Trial	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 **Error! Reference source not found.**. 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 active control arm. The only exception was Trial 3590 where the direction was reversed.

Change in body weight from baseline 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.

3.2.5 Evaluation of Safety

Meta-analyses on cardiovascular events was reviewed by Dr. Xiao Ding from Division of Biometrics VII. Other safety events were reviewed by Dr. Karim Calis from Medical Division of Metabolism and Endocrinology Products. Reader is referred to those three reviews for this section.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Comparison of primary efficacy endpoint in subpopulations were summarized in Figure 16 for patients with T1DM and Figure 17 for patients with T2DM.

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

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.

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 TL 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 27 in appendix. In T1DM subjects, no statistically significant treatment-by-subgroup interaction was found.

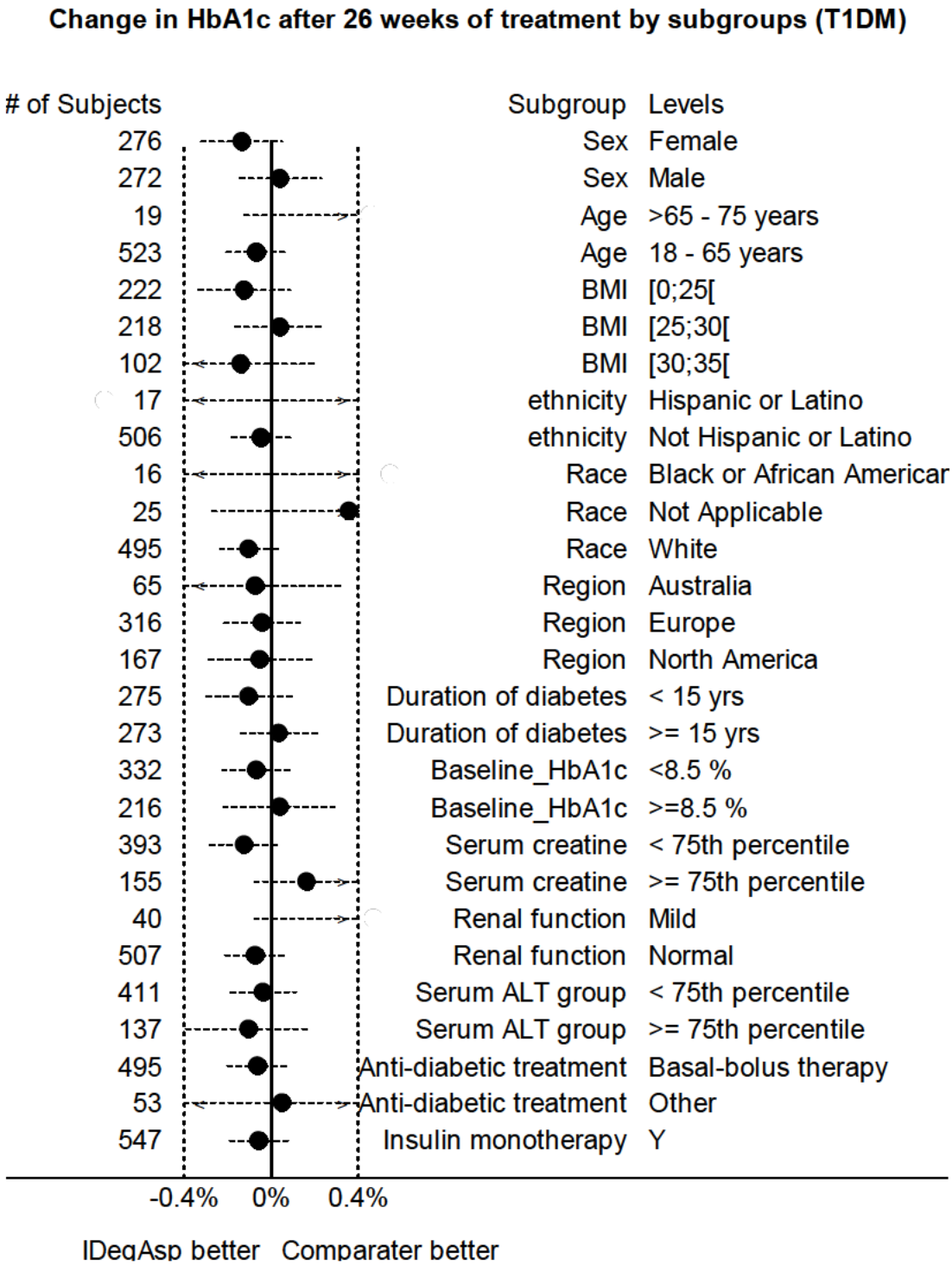

Figure 16 Change in HbA1c after 26 weeks of treatment by subgroups in T1DM subjects.

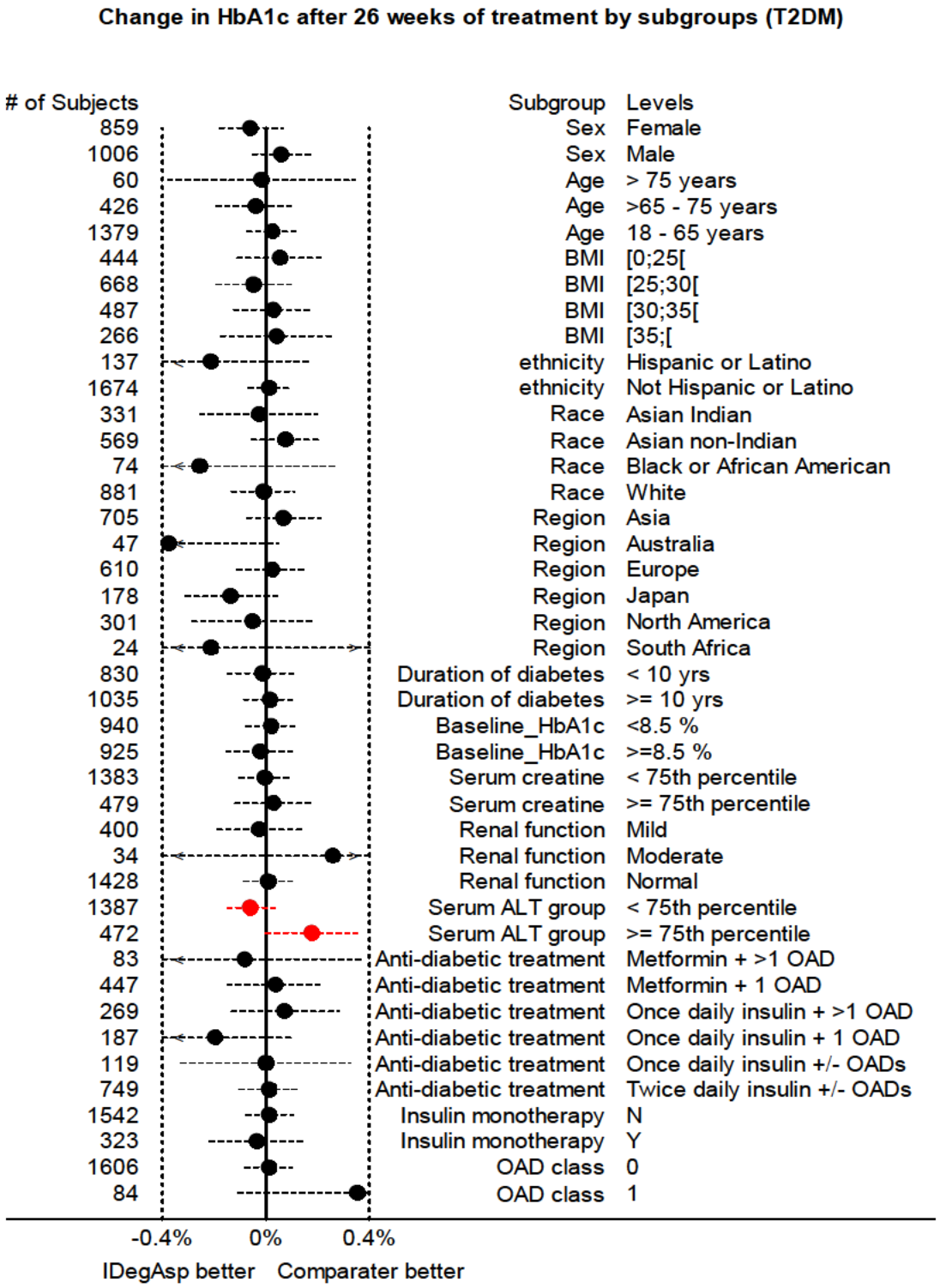

Figure 17 Change in HbA1c after 26 weeks of treatment by subgroups in T2DM subjects.

5 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 (CI) 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 everyone knew the treatment they were getting. The results on hypoglycemia episode should be interpreted carefully. Comparing patients randomized to IDegAsp arm to patients randomized to the control arm, there was no consistent weight gain or weight loss across trials. In general, patients randomized to IDegAsp arm received on average lower dose of total daily insulin comparing to patients randomized to the active 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. This NDA is approvable from statistical point of view.

APPENDICES

Table 9 Demographics and Baseline characteristics summary for Trial 3594 (quoted from CSR).

	IDegAsp OD N (%)	IDet N (%)	Total N (%)
Number of Subjects	366	182	548
Age Group			
N	366 (100.0)	182 (100.0)	548 (100.0)
> 65 years	11 (3.0)	14 (7.7)	25 (4.6)
Adults (18-65 yrs)	355 (97.0)	168 (92.3)	523 (95.4)
Sex			
N	366 (100.0)	182 (100.0)	548 (100.0)
Female	176 (48.1)	100 (54.9)	276 (50.4)
Male	190 (51.9)	82 (45.1)	272 (49.6)
Country of Residence			
N	366 (100.0)	182 (100.0)	548 (100.0)
Australia	47 (12.8)	18 (9.9)	65 (11.9)
Denmark	16 (4.4)	15 (8.2)	31 (5.7)
France	17 (4.6)	8 (4.4)	25 (4.6)
Israel	22 (6.0)	11 (6.0)	33 (6.0)
Poland	37 (10.1)	15 (8.2)	52 (9.5)
Romania	49 (13.4)	21 (11.5)	70 (12.8)
Russian Federation	47 (12.8)	22 (12.1)	69 (12.6)
United Kingdom	24 (6.6)	12 (6.6)	36 (6.6)
United States	107 (29.2)	60 (33.0)	167 (30.5)
Ethnicity			
N	366 (100.0)	182 (100.0)	548 (100.0)
Hispanic or Latino	10 (2.7)	7 (3.8)	17 (3.1)
Not Hispanic or Latino	339 (92.6)	167 (91.8)	506 (92.3)
Not Applicable	17 (4.6)	8 (4.4)	25 (4.6)
Race			
N	366 (100.0)	182 (100.0)	548 (100.0)
White	333 (91.0)	162 (89.0)	495 (90.3)
Black or African American	10 (2.7)	6 (3.3)	16 (2.9)
Asian Indian	1 (0.3)	0 (0.0)	1 (0.2)
Asian non-Indian	3 (0.8)	3 (1.6)	6 (1.1)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	1 (0.3)	1 (0.5)	2 (0.4)
Not Applicable	17 (4.6)	8 (4.4)	25 (4.6)
Other	1 (0.3)	2 (1.1)	3 (0.5)

N = Number of Subjects
Subjects from France did not report race

Reference ID: 3218232

Table 10 Baseline and diabetes characteristics summary for Trial 3594 (quoted from CSR).

	IDegAsp OD	IDet	Total
Number of Subjects	366	182	548
Age (years)			
N	366	182	548
Mean (SD)	40.7 (12.8)	42.6 (13.8)	41.3 (13.2)
Median	39.9	42.4	40.6
Min ; Max	18.3 ; 78.5	18.1 ; 80.2	18.1 ; 80.2
Height (m)			
N	366	182	548
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.7
Min ; Max	1.5 ; 2.0	1.1 ; 2.0	1.1 ; 2.0
Body Weight (kg)			
N	366	182	548
Mean (SD)	76.7 (14.6)	76.0 (14.0)	76.5 (14.4)
Median	75.0	76.0	75.3
Min ; Max	44.0 ; 123.4	42.9 ; 137.4	42.9 ; 137.4
BMI (kg/m^2)			
N	366	182	548
Mean (SD)	26.2 (4.0)	26.7 (3.9)	26.4 (4.0)
Median	25.9	26.3	26.0
Min ; Max	16.2 ; 35.6	18.7 ; 36.2	16.2 ; 36.2
Duration of Diabetes (year)			
N	366	181	547
Mean (SD)	17.2 (11.3)	17.9 (12.3)	17.4 (11.6)
Median	14.9	15.0	14.9
Min ; Max	1.1 ; 59.7	1.0 ; 56.6	1.0 ; 59.7
HbAlc (%)			
N	366	182	548
Mean (SD)	8.3 (0.8)	8.3 (0.7)	8.3 (0.8)
Median	8.2	8.2	8.2
Min ; Max	6.8 ; 10.3	6.5 ; 10.4	6.5 ; 10.4
FPG (mmol/L)			
N	365	181	546
Mean (SD)	10.3 (4.7)	11.0 (4.8)	10.5 (4.8)
Median	9.6	10.3	9.9
Min ; Max	1.8 ; 30.2	2.9 ; 28.4	1.8 ; 30.2

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Reference ID: 3218232

Table 11 Anti-diabetic treatment regimen at screening for subjects in Trial 3594 (quoted from CSR).

	IDegAsp OD		IDet		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	366		182		548	
Basal-Bolus	334	(91.3)	161	(88.5)	495	(90.3)
Basal-Bolus	334	(91.3)	161	(88.5)	495	(90.3)
Other	32	(8.7)	21	(11.5)	53	(9.7)
Basal + PreMix			1	(0.5)	1	(0.2)
Basal Only	1	(0.3)	1	(0.5)	2	(0.4)
PreMix + Bolus	11	(3.0)	7	(3.8)	18	(3.3)
PreMix Only	18	(4.9)	10	(5.5)	28	(5.1)
SelfMix	2	(0.5)	2	(1.1)	4	(0.7)

N: Number of Subjects
%: Proportion of Subjects

Reference ID: 3218232

Table 12 Demographics and Baseline Characteristics summary for Trial 3590 (quoted from CSR).

	IDegAsp OD N (%)	IGlar OD N (%)	Total N (%)
Number of Subjects	266	263	529
Age Group			
N	266 (100.0)	263 (100.0)	529 (100.0)
> 65 years	55 (20.7)	43 (16.3)	98 (18.5)
Adults (18-65 yrs)	211 (79.3)	220 (83.7)	431 (81.5)
Sex			
N	266 (100.0)	263 (100.0)	529 (100.0)
Female	141 (53.0)	127 (48.3)	268 (50.7)
Male	125 (47.0)	136 (51.7)	261 (49.3)
Country of Residence			
N	266 (100.0)	263 (100.0)	529 (100.0)
Austria	9 (3.4)	13 (4.9)	22 (4.2)
India	34 (12.8)	38 (14.4)	72 (13.6)
Poland	37 (13.9)	27 (10.3)	64 (12.1)
Russian Federation	43 (16.2)	36 (13.7)	79 (14.9)
South Korea	13 (4.9)	18 (6.8)	31 (5.9)
Spain	30 (11.3)	37 (14.1)	67 (12.7)
Turkey	19 (7.1)	20 (7.6)	39 (7.4)
United States	81 (30.5)	74 (28.1)	155 (29.3)
Ethnicity			
N	266 (100.0)	263 (100.0)	529 (100.0)
Hispanic or Latino	53 (19.9)	61 (23.2)	114 (21.6)
Not Hispanic or Latino	182 (68.4)	180 (68.4)	362 (68.4)
Not Applicable	31 (11.7)	22 (8.4)	53 (10.0)
Race			
N	266 (100.0)	263 (100.0)	529 (100.0)
White	194 (72.9)	189 (71.9)	383 (72.4)
Black or African American	21 (7.9)	13 (4.9)	34 (6.4)
Asian Indian	34 (12.8)	39 (14.8)	73 (13.8)
Asian non-Indian	16 (6.0)	18 (6.8)	34 (6.4)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Other Pacific Islander	0 (0.0)	1 (0.4)	1 (0.2)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	3 (1.1)	4 (0.8)

N = Number of Subjects

Reference ID: 3218232

Table 13 Baseline and diabetes characteristics summary for Trial 3590 (quoted from CSR).

	IDegAsp OD	IGlar OD	Total
Number of Subjects	266	263	529
Age (years)			
N	266	263	529
Mean (SD)	57.4 (9.0)	56.4 (9.2)	56.9 (9.1)
Median	57.3	57.3	57.3
Min ; Max	36.8 ; 78.4	21.8 ; 76.1	21.8 ; 78.4
Height (m)			
N	266	263	529
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.7
Min ; Max	1.4 ; 1.9	1.4 ; 2.0	1.4 ; 2.0
Body Weight (kg)			
N	266	263	529
Mean (SD)	85.0 (17.9)	85.1 (18.6)	85.0 (18.2)
Median	82.8	84.4	84.0
Min ; Max	50.0 ; 144.2	42.4 ; 139.0	42.4 ; 144.2
BMI (kg/m^2)			
N	266	263	529
Mean (SD)	30.9 (5.1)	30.5 (5.1)	30.7 (5.1)
Median	31.0	30.5	30.7
Min ; Max	20.0 ; 43.8[a]	18.1 ; 40.0	18.1 ; 43.8[a]
Duration of Diabetes (years)			
N	265	263	528
Mean (SD)	8.7 (6.1)	9.6 (6.1)	9.2 (6.1)
Median	7.5	8.8	7.7
Min ; Max	0.6 ; 39.6	0.6 ; 34.7	0.6 ; 39.6
HbA_{1c} (%)			
N	266	263	529
Mean (SD)	8.9 (1.0)	8.9 (0.9)	8.9 (0.9)
Median	8.8	8.8	8.8
Min ; Max	7.0 ; 11.6[b]	7.3 ; 11.1 [b]	7.0 ; 11.6 [b]
FPG (mmol/L)			
N	261	261	522
Mean (SD)	10.1 (2.9)	10.4 (2.8)	10.2 (2.9)
Median	9.7	10.2	9.9
Min ; Max	3.8 ; 19.6	4.7 ; 20.6	3.8 ; 20.6

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Table 14 Anti-diabetic treatment regimen at screening for subjects in Trial 3590 (quoted from CSR).

	IDegAsp OD		IGlar OD		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	266		263		529	
Metformin ± SU or Glinide + DPP4-I ± AGI	28	(10.5)	46	(17.5)	74	(14.0)
Metformin + SU or Glinide	238	(89.5)	217	(82.5)	455	(86.0)

N: Number of Subjects; %: Proportion of Subjects
DPP4 I: DPP-4 inhibitor; AGI: alphaglucosidase inhibitor; SU: sulphonylurea

Reference ID: 3218232

Table 15 Demographics and baseline characteristics summary for Trial 3593 (quoted from CSR).

	IDegAsp OD N (%)	IGlar OD N (%)	Total N (%)
Number of Subjects	230	233	463
Age Group			
18-65 yrs	175 (76.1)	170 (73.0)	345 (74.5)
> 65 yrs	55 (23.9)	63 (27.0)	118 (25.5)
Sex			
Female	95 (41.3)	106 (45.5)	201 (43.4)
Male	135 (58.7)	127 (54.5)	262 (56.6)
Country of Residence			
Croatia	11 (4.8)	11 (4.7)	22 (4.8)
France	11 (4.8)	10 (4.3)	21 (4.5)
India	61 (26.5)	47 (20.2)	108 (23.3)
Poland	21 (9.1)	11 (4.7)	32 (6.9)
South Africa	10 (4.3)	14 (6.0)	24 (5.2)
South Korea	19 (8.3)	23 (9.9)	42 (9.1)
Sweden	18 (7.8)	20 (8.6)	38 (8.2)
Turkey	17 (7.4)	16 (6.9)	33 (7.1)
United States	62 (27.0)	81 (34.8)	143 (30.9)
Ethnicity			
Hispanic or Latino	10 (4.3)	11 (4.7)	21 (4.5)
Not Hispanic or Latino	220 (95.7)	222 (95.3)	442 (95.5)
Race			
White	122 (53.0)	139 (59.7)	261 (56.4)
Black/African American	21 (9.1)	16 (6.9)	37 (8.0)
Asian Indian	66 (28.7)	52 (22.3)	118 (25.5)
Asian non-Indian	19 (8.3)	25 (10.7)	44 (9.5)
Other	2 (0.9)	1 (0.4)	3 (0.6)

N = Number of Subjects

Reference ID: 3218232

Table 16 Baseline and diabetes characteristics summary for Trial 3593 (quoted from CSR).

	IDegAsp OD	IGlar OD	Total
Number of Subjects	230	233	463
Age (years)			
N	230	233	463
Mean (SD)	57.8 (9.5)	58.4 (10.1)	58.1 (9.8)
Median	58.2	58.6	58.2
Min ; Max	30.7 ; 79.8	27.9 ; 84.3	27.9 ; 84.3
Height (m)			
N	230	233	463
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Median	1.7	1.7	1.7
Min ; Max	1.4 ; 2.0	1.5 ; 2.0	1.4 ; 2.0
Body Weight (kg)			
N	230	233	463
Mean (SD)	84.7 (19.9)	83.9 (19.2)	84.3 (19.6)
Median	83.0	82.5	83.0
Min ; Max	44.0 ; 137.5	46.1 ; 149.5	44.0 ; 149.5
BMI (kg/m^2)			
N	230	233	463
Mean (SD)	30.1 (5.1)	30.1 (5.3)	30.1 (5.2)
Median	29.7	29.7	29.7
Min ; Max	16.4 ; 40.1	20.2 ; 47.7	16.4 ; 47.7
Duration of Diabetes (years)			
N	230	233	463
Mean (SD)	11.6 (6.8)	11.4 (7.3)	11.5 (7.0)
Median	10.7	10.7	10.7
Min ; Max	0.6 ; 38.5	0.6 ; 55.6	0.6 ; 55.6
HbA1c (%)			
N	230	233	463
Mean (SD)	8.3 (0.8)	8.4 (1.0)	8.3 (0.9)
Median	8.2	8.3	8.3
Min ; Max	6.5 ; 10.5	6.6 ; 11.7	6.5 ; 11.7
FPG (mmol/L)			
N	228	231	459
Mean (SD)	8.0 (2.5)	7.8 (2.8)	7.9 (2.7)
Median	7.5	7.2	7.3
Min ; Max	3.2 ; 14.8	3.3 ; 23.1	3.2 ; 23.1

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

Table 17 Anti-diabetic treatment regimen at screening for subjects in Trial 3593 (quoted from CSR).

	IDegAsp OD		IGlar OD		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	230		233		463	
Basal insulin + metformin	94	(40.9)	96	(41.2)	190	(41.0)
Basal insulin + metformin + other OADs	109	(47.4)	108	(46.4)	217	(46.9)
Basal insulin + metformin + pioglitazone	27	(11.7)	29	(12.4)	56	(12.1)

N: Number of Subjects
%: Proportion of Subjects
Basal + metformin + other OADs does not include pioglitazone
OADs = Oral Antidiabetic Drugs

Reference ID: 3218232

Table 18 Demographics and baseline characteristics summary for Trial 3592 (quoted from CSR).

	IDegAsp BID N (%)	BIAsp 30 BID N (%)	Total N (%)
Number of Subjects	224	222	446
Age Group			
N	224 (100.0)	222 (100.0)	446 (100.0)
18-65 yrs	158 (70.5)	152 (68.5)	310 (69.5)
> 65 yrs	66 (29.5)	70 (31.5)	136 (30.5)
Sex			
N	224 (100.0)	222 (100.0)	446 (100.0)
Female	95 (42.4)	103 (46.4)	198 (44.4)
Male	129 (57.6)	119 (53.6)	248 (55.6)
Country of Residence			
N	224 (100.0)	222 (100.0)	446 (100.0)
Australia	30 (13.4)	17 (7.7)	47 (10.5)
Denmark	27 (12.1)	23 (10.4)	50 (11.2)
Finland	13 (5.8)	14 (6.3)	27 (6.1)
India	57 (25.4)	60 (27.0)	117 (26.2)
Malaysia	10 (4.5)	15 (6.8)	25 (5.6)
Poland	25 (11.2)	29 (13.1)	54 (12.1)
Sweden	15 (6.7)	19 (8.6)	34 (7.6)
Taiwan	11 (4.9)	14 (6.3)	25 (5.6)
Thailand	23 (10.3)	18 (8.1)	41 (9.2)
Turkey	13 (5.8)	13 (5.9)	26 (5.8)
Ethnicity			
N	224 (100.0)	222 (100.0)	446 (100.0)
Hispanic or Latino	0 (0.0)	2 (0.9)	2 (0.4)
Not Hispanic or Latino	224 (100.0)	220 (99.1)	444 (99.6)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Race			
N	224 (100.0)	222 (100.0)	446 (100.0)
White	121 (54.0)	113 (50.9)	234 (52.5)
Black or African American	1 (0.4)	0 (0.0)	1 (0.2)
Asian Indian	58 (25.9)	63 (28.4)	121 (27.1)
Asian non-Indian	43 (19.2)	46 (20.7)	89 (20.0)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of Subjects

Reference ID: 3218232

Table 19 Baseline and diabetes characteristics summary for Trial 3592 (quoted from CSR).

	IDegAsp BID	BIAsp 30 BID	Total
Number of Subjects	224	222	446
Age (years)			
N	224	222	446
Mean (SD)	58.7 (9.9)	58.8 (9.8)	58.7 (9.8)
Median	59.7	59.5	59.5
Min ; Max	32.7 ; 88.8	20.4 ; 79.4	20.4 ; 88.8
Height (m)			
N	224	222	446
Mean (SD)	1.7 (0.1)	1.6 (0.1)	1.6 (0.1)
Median	1.6	1.6	1.6
Min ; Max	1.4 ; 1.9	1.4 ; 1.9	1.4 ; 1.9
Body Weight (kg)			
N	224	222	446
Mean (SD)	81.5 (18.1)	78.9 (17.6)	80.2 (17.9)
Median	79.0	76.0	77.9
Min ; Max	44.9 ; 140.1	38.7 ; 127.3	38.7 ; 140.1
BMI (kg/m^2)			
N	224	222	446
Mean (SD)	29.6 (4.6)	29.0 (4.9)	29.3 (4.8)
Median	29.5	28.8	29.0
Min ; Max	18.0 ; 40.0	17.2 ; 39.6	17.2 ; 40.0
Duration of Diabetes (year)			
N	224	222	446
Mean (SD)	12.8 (6.8)	13.1 (7.4)	13.0 (7.1)
Median	11.4	11.7	11.5
Min ; Max	0.7 ; 39.4	0.6 ; 41.4	0.6 ; 41.4
HbA1c (%)			
N	224	222	446
Mean (SD)	8.3 (0.8)	8.4 (0.9)	8.4 (0.8)
Median	8.3	8.4	8.3
Min ; Max	6.6 ; 10.5	5.3 ; 10.7	5.3 ; 10.7
FPG (mmol/L)			
N	224	220	444
Mean (SD)	8.9 (2.9)	8.6 (2.6)	8.7 (2.8)
Median	8.7	8.3	8.5
Min ; Max	3.3 ; 23.0	3.1 ; 19.3	3.1 ; 23.0

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Reference ID: 3218232

Table 20 Anti-diabetic treatment regimen at screening for subjects in Trial 3592 (quoted from CSR).

	IDegAsp BID		BIAsp 30 BID		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	224		222		446	
Insulin BID with one or more OAD	155	(69.2)	168	(75.7)	323	(72.4)
Insulin BID without OAD	51	(22.8)	41	(18.5)	92	(20.6)
Insulin OD with one OAD or none	8	(3.6)	10	(4.5)	18	(4.0)
Insulin OD with two or more OADs	10	(4.5)	3	(1.4)	13	(2.9)

N: Number of Subjects
%: Proportion of Subjects

Reference ID: 3218232

Table 21 Demographics and baseline characteristics summary for Trial 3597 (quoted from CSR).

	IDegAsp BID N (%)	BIAsp 30 BID N (%)	Total N (%)
Number of Subjects	280	142	422
Age Group			
N	280 (100.0)	142 (100.0)	422 (100.0)
Adults (18-65 yrs)	200 (71.4)	87 (61.3)	287 (68.0)
> 65 years	80 (28.6)	55 (38.7)	135 (32.0)
Sex			
N	280 (100.0)	142 (100.0)	422 (100.0)
Female	129 (46.1)	63 (44.4)	192 (45.5)
Male	151 (53.9)	79 (55.6)	230 (54.5)
Country of Residence			
N	280 (100.0)	142 (100.0)	422 (100.0)
Hong Kong	22 (7.9)	12 (8.5)	34 (8.1)
Japan	118 (42.1)	60 (42.3)	178 (42.2)
Malaysia	37 (13.2)	16 (11.3)	53 (12.6)
South Korea	86 (30.7)	45 (31.7)	131 (31.0)
Taiwan	17 (6.1)	9 (6.3)	26 (6.2)
Ethnicity			
N	280 (100.0)	142 (100.0)	422 (100.0)
Hispanic or Latino	0 (0.0)	0 (0.0)	0 (0.0)
Not Hispanic or Latino	280 (100.0)	142 (100.0)	422 (100.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Race			
N	280 (100.0)	142 (100.0)	422 (100.0)
White	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	0 (0.0)	0 (0.0)	0 (0.0)
Asian Indian	12 (4.3)	7 (4.9)	19 (4.5)
Asian non-Indian	267 (95.4)	135 (95.1)	402 (95.3)
American Indian or Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian or Oth. Pacific Islander	0 (0.0)	0 (0.0)	0 (0.0)
Not Applicable	0 (0.0)	0 (0.0)	0 (0.0)
Other	1 (0.4)	0 (0.0)	1 (0.2)

N = Number of Subjects

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Table 22 Baseline and diabetes characteristics summary for Trial 3597 (quoted from CSR).

	IDegAsp BID	BIAsp 30 BID	Total
Number of Subjects	280	142	422
Age (years)			
N	280	142	422
Mean (SD)	59.1 (10.2)	61.2 (9.5)	59.8 (10.0)
Median	59.7	61.9	60.4
Min ; Max	30.0 ; 85.2	33.5 ; 88.5	30.0 ; 88.5
Height (m)			
N	280	142	422
Mean (SD)	1.6 (0.1)	1.6 (0.1)	1.6 (0.1)
Median	1.6	1.6	1.6
Min ; Max	1.4 ; 1.9	1.3 ; 1.9	1.3 ; 1.9
Body Weight (kg)			
N	280	142	422
Mean (SD)	66.1 (11.2)	66.0 (11.2)	66.0 (11.2)
Median	65.7	65.2	65.5
Min ; Max	38.2 ; 106.0	44.0 ; 95.0	38.2 ; 106.0
BMI (kg/m^2)			
N	280	142	422
Mean (SD)	25.4 (3.4)	25.4 (3.7)	25.4 (3.5)
Median	25.0	25.3	25.1
Min ; Max	17.8 ; 35.6	17.1 ; 34.9	17.1 ; 35.6
Duration of Diabetes (years)			
N	280	142	422
Mean (SD)	16.3 (7.9)	16.3 (8.2)	16.3 (8.0)
Median	15.7	15.5	15.6
Min ; Max	0.7 ; 47.8	0.7 ; 47.6	0.7 ; 47.8
HbA1c (%)			
N	280	142	422
Mean (SD)	8.4 (0.8)	8.4 (0.9)	8.4 (0.8)
Median	8.4	8.4	8.4
Min ; Max	6.8 ; 10.2	6.5 ; 10.8	6.5 ; 10.8
FPG (mmol/L)			
N	280	140	420
Mean (SD)	7.9 (2.5)	7.9 (2.5)	7.9 (2.5)
Median	7.9	7.4	7.8
Min ; Max	3.2 ; 20.1	2.5 ; 17.5	2.5 ; 20.1

BMI = Body Mass Index, N = Number of Subjects, SD = Standard Deviation

Table 23 Anti-diabetic treatment regimen at screening for subjects in Trial 3597 (quoted from CSR).

	IDegAsp BID		BIAsp 30 BID		Total	
	N	(%)	N	(%)	N	(%)
Number of Subjects	280		142		422	
Basal insulin only	31	(11.1)	13	(9.2)	44	(10.4)
Basal insulin + metformin	51	(18.2)	29	(20.4)	80	(19.0)
Premix/self-mix insulin only	81	(28.9)	44	(31.0)	125	(29.6)
Premix/self-mix insulin + metformin	117	(41.8)	56	(39.4)	173	(41.0)

N: Number of Subjects
%: Proportion of Subjects

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Table 24 Hypoglycemia in T1DM (quoted from Clinical Overview).

	IDegAsp				Comparator			
Trial (wks)	N	(%)	E	R	N	(%)	E	R
Confirmed								
3594/3645 (52)	344	(95.0)	9450	3183.1	169	(93.9)	5342	3672.6
Nocturnal confirmed								
3594/3645 (52)	221	(61.0)	918	309.2	135	(75.0)	787	541.1
Severe								
3594/3645 (52)	48	(13.3)	79	26.6	33	(18.3)	65	44.7
Nocturnal severe								
3594/3645 (52)	13	(3.6)	14	4.7	14	(7.8)	28	19.2

N: number of subjects, %: percentage of subjects, E: number of events, R: event rate per 100 exposure years

Table 25 Hypoglycemia with IDegAsp OD in T2DM (quoted from clinical overview).

	IDegAsp				Comparator			
Trial (wks)	N	(%)	E	R	N	(%)	E	R
Confirmed								
3590 (26)	132	(49.8)	500	422.8	96	(36.8)	226	185.3
3593 (26)	121	(52.6)	451	431.4	112	(48.1)	344	320.1
Nocturnel confirmed								
3590 (26)	13	(4.9)	22	18.6	30	(11.5)	56	45.9
3593 (26)	44	(19.1)	86	82.3	49	(21.0)	108	100.5
Severe								
3590 (26)	1	(0.4)	1	0.8	1	(0.4)	1	0.8
3593 (26)	0		0		3	(1.3)	4	3.7
Nocturnel severe								
3590 (26)	0		0		0		0	
3593 (26)	0		0		0		0	

N: number of subjects, %: percentage of subjects, E: number of events, R: event rate per 100 exposure years,

Table 26 Hypoglycemia with IDegAsp BID in T2DM (quoted from clinical overview).

	IDegAsp				Comparator			
Trial (wks)	N	(%)	E	R	N	(%)	E	R
Confirmed								
3592 (26)	148	(66.1)	993	971.7	153	(68.9)	1379	1396.3
3597 (26)	205	(73.5)	1227	956.0	107	(75.9)	621	952.3
Nocturnel confirmed								
3592 (26)	52	(23.2)	76	74.4	80	(36.0)	250	253.1
3597 (26)	70	(25.1)	143	111.4	44	(31.2)	101	154.9
Severe								
3592 (26)	7	(3.1)	9	8.8	16	(7.2)	25	25.3
3597 (26)	4	(1.4)	6	4.7	2	(1.4)	2	3.1
Nocturnel severe								
3592 (26)	1	(0.4)	1	1.0	8	(3.6)	9	9.1
3597 (26)	1	(0.4)	1	0.8				

N: number of subjects, %: percentage of subjects, E: number of events, R: event rate per 100 exposure years,

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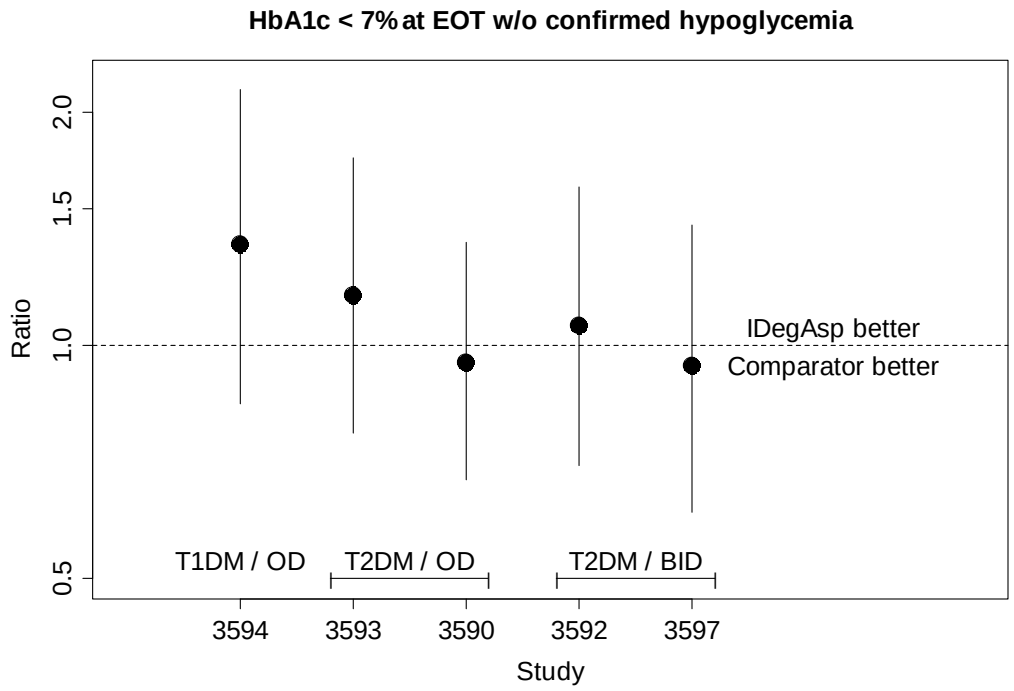

Figure 18 Summary of HbA1c responder ratio in IDegAsp vs. Comparator at week 26.

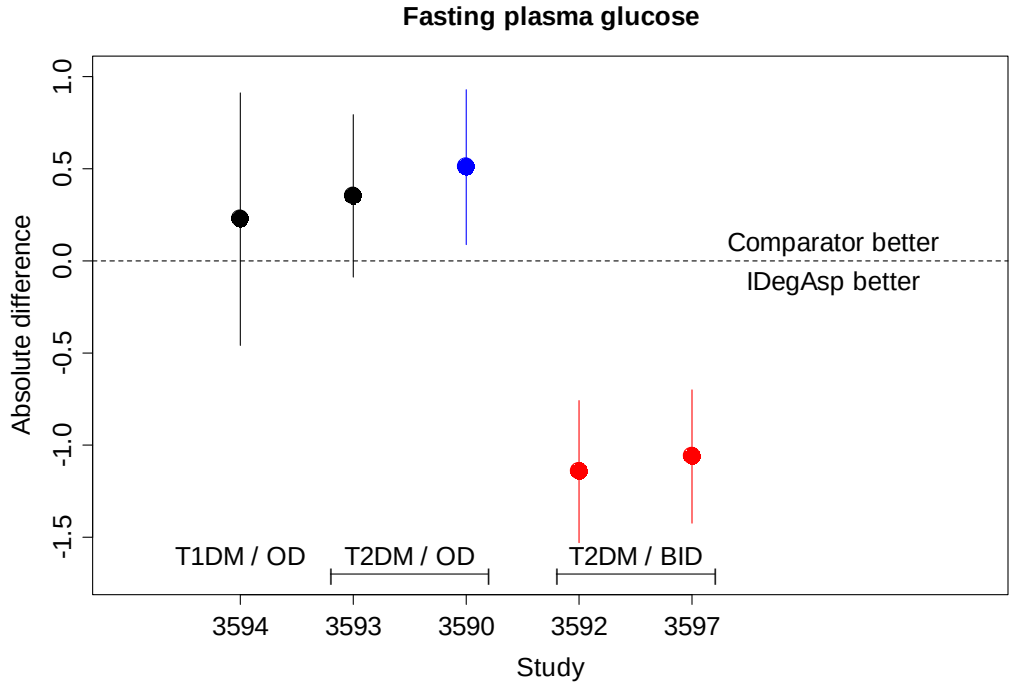

Figure 19 Summary of change in fasting plasma glucose from baseline to week 26.

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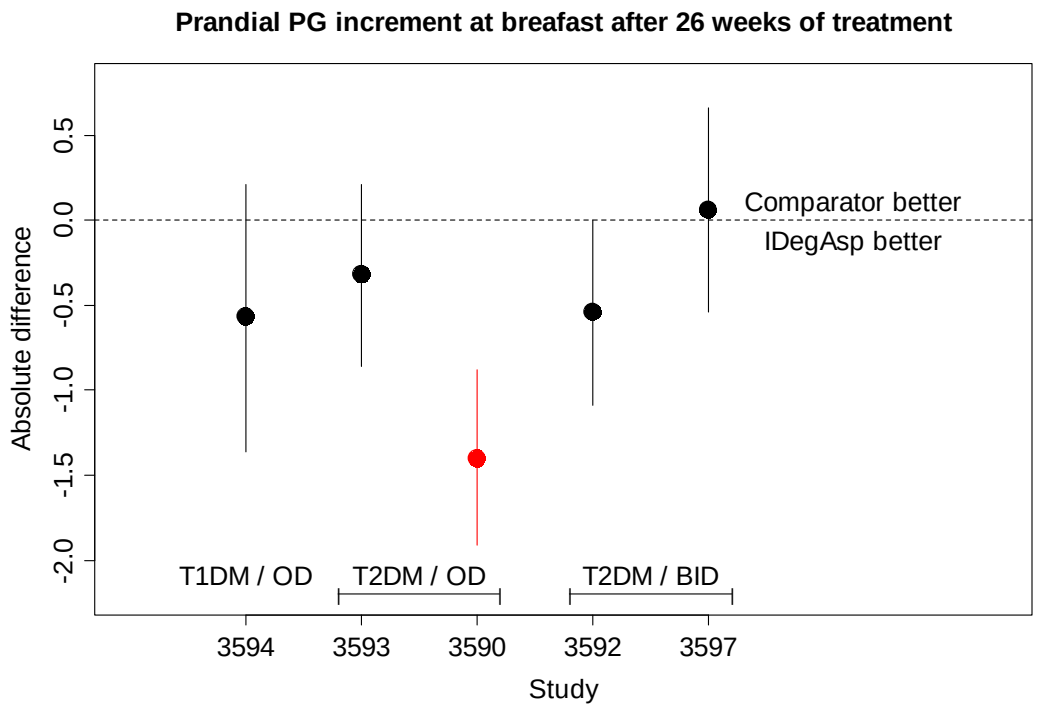

Figure 20 Summary of change in Prandial PG increment at breakfast from baseline to week 26.

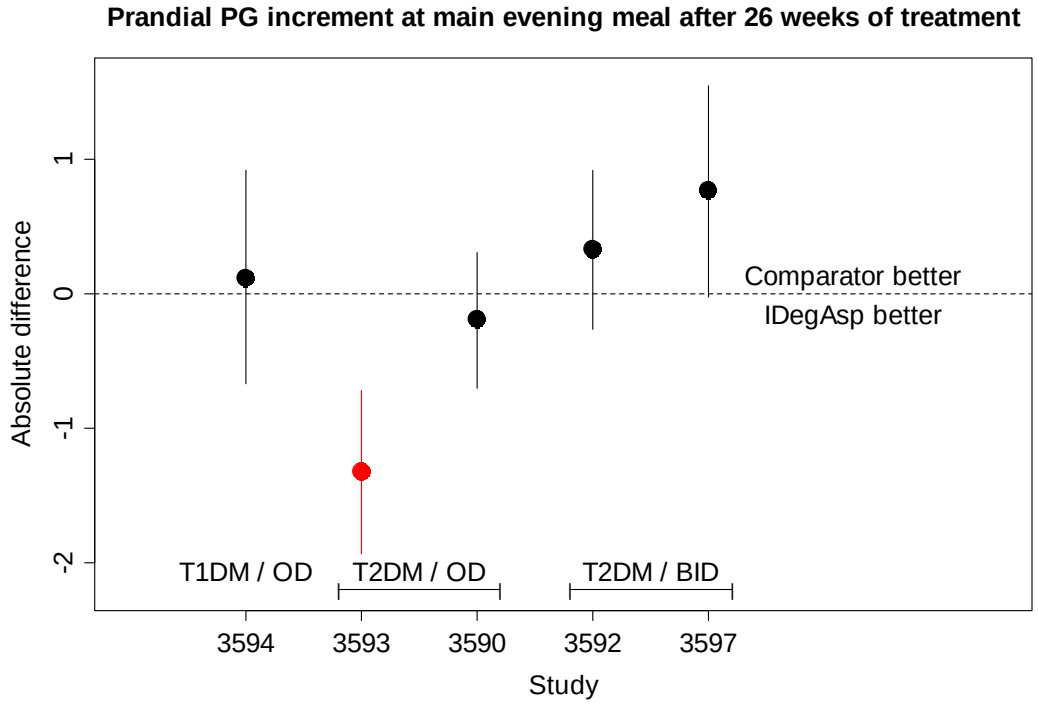

Figure 21 Summary of change in Prandial PG increment at main evening meal from baseline to week 26.

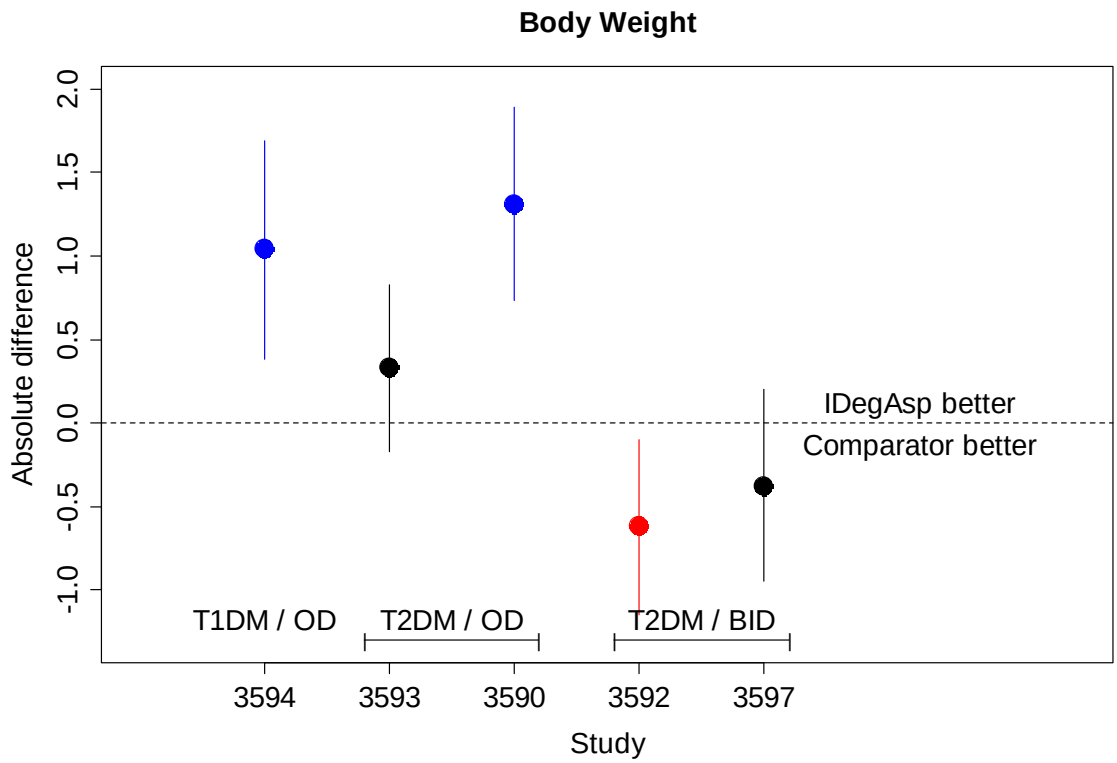

Figure 22 Summary of change in body weight from baseline to week 26.

Table 27 HbA1c at baseline and week 26 by serum ALT group - T2DM - pooling trials (quoted from CSR).

Serum ATL group	IDegAsp							Comparator						
		Baseline		Week 26		Change			Baseline		Week 26		Change	
	N	Mean	SD	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD	Mean	SD
<75th 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
≥75th 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.

Table 28 Change of HbA1c from baseline to end-of-trial (per-protocol analysis).

	IDegAsp			Comparator			IDegAsp - Comparator	
Trial	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)

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concur

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

STATISTICAL REVIEW AND EVALUATION

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
Keywords:	NDA review, clinical studies

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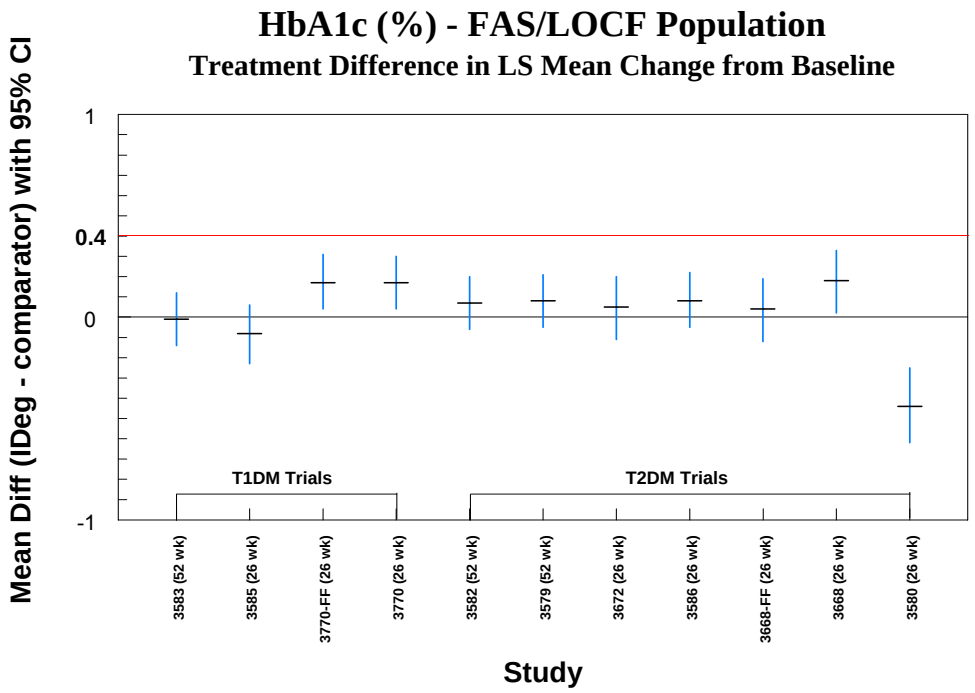
1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

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 figure 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.



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.

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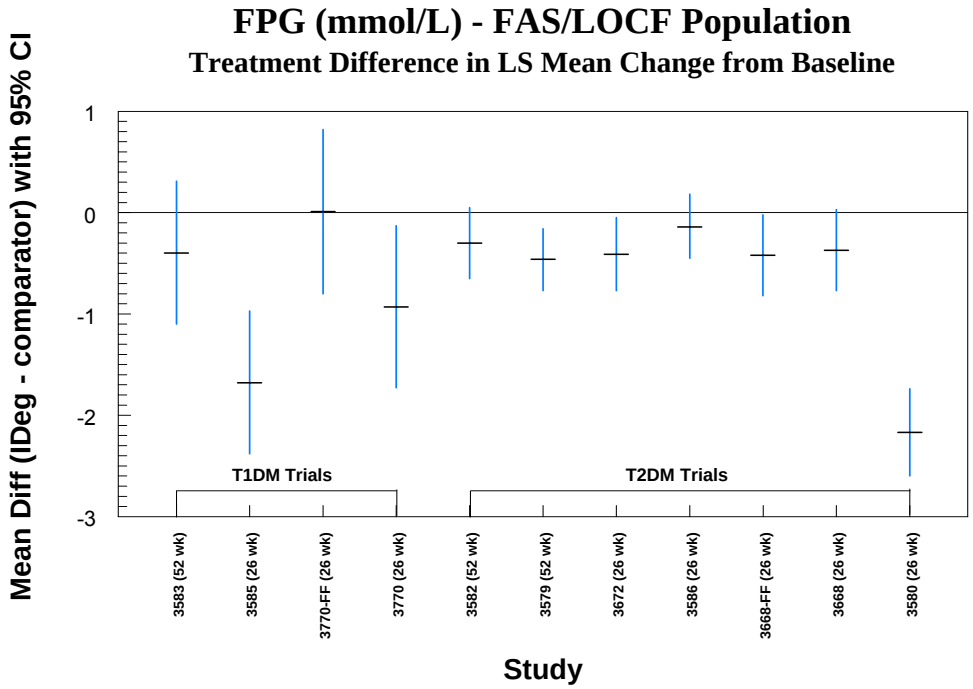
The proportion of subjects achieving HbA1c level < 7.0% at endpoint was numerically smaller, but not statistically significant, in the IDeg group than in the comparator group for all trials, except for Study 3585 (T1DM) and Study 3580 (T2DM) where the IDeg group showed a higher % of patients achieving 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 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.

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

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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.

Labeling Comments: The following bullets summarize this reviewer's comments for the sponsor's proposed labeling in the Clinical Studies section.

- There is [redacted] (b) (4) for Study 3770, only the text. In addition, [redacted] (b) (4) included for Study 3586.

- The total N (sample size) reported in Tables 8 – 13 [redacted] (b) (4), were reported for HbA1c and FPG.

- For Studies 3770 and 3668, [redacted] (b) (4). This reviewer does not think the statement is correct because the mean reductions in both IDeg and IDeg Flex groups in Study 3770 and the IDeg group in Study 3668 were actually statistically significantly less than that in the IGlar group. However, IDeg Flex was clinically non-inferior to IGlar according to the pre-specified non-inferiority margin. If the same criterion were applied, clinical non-inferiority of IDeg to IGlar could have also been shown in these two studies.

- Since hypoglycemia is a more subjective endpoint than a lab value, and there were no consistently significant findings across the open-label trials, this reviewer thinks that the results should be described descriptively.

- The testing sequence of the confirmatory secondary endpoints was prioritized differently from trial to trial and the sponsor flagged the significance for the parameters accordingly. Since the testing order is not presented in the labeling, it is confusing to understand why some significant results are not being flagged in the

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tables. Therefore, this reviewer suggests only descriptive statistics be used for the non-primary endpoints.

- [redacted] (b) (4) . It may be necessary to separate safety parameters from efficacy tables.

1.2 Brief Overview of Clinical Studies

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. Insulin degludec (IDeg) is a new molecular entity. It is intended to cover the basal insulin requirements in diabetes mellitus with once daily injection. Moreover, 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's IDeg development program comprises a total of 41 completed clinical trials. Of which, 11 are therapeutic Phase 3a confirmatory trials consisting of 9 once-daily injection and 2 thrice-weekly injection studies. Since the sponsor is not seeking the 3x weekly dosing regimen indication, this review focuses on all the 9 once-daily injection trials which are grouped by type of diabetes mellitus in the following table.

Text Table 1 – Study Designs

Study	WK	Treatment groups	Background medication	Randomized patients	Stratifying factor
Table 1 Diabetes Mellitus (T1DM)					
3583 (09/09 – 11/10)	52	IDeg 100 vs. IGlar 100	IAsp	629 (472:157)	None
3585 (02/10 – 12/10)	26	IDeg 100 vs. IDet 100	IAsp	456 (303:153)	Region (Europe, South America, Japan, India)
3770 (11/09 – 09/10)	26	IDeg 100 Flex vs. IDeg 100 vs. IGlar 100	IAsp	493 (164:165:164)	None
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)
3579 (09/09 – 01/11)	52	IDeg 100 vs. IGlar 100	OAD(s)	1030 (773:257)	None
3672 (03/10	26	IDeg 200 vs. IGlar 100	OAD(s)	460 (230:230)	None

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– 11/10)					
3586 (02/10 – 12/10)	26	IDeg 100 vs. IGlar 100	OAD(s)	435 (289:146)	Region (Japan, Asia w/o Japan)
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))
3580 (01/10 – 11/10)	26	IDeg 100 Flex vs. Sitagliptin	OAD(s)	458 (229:229)	Use of pioglitazone at screening
The OAD(s) for Study 3582 were ± metformin ± pioglitazone. The OAD(s) for Studies 3579 and 3672 were + metformin ± DPP-4 inhibitor. The OAD(s) for Study 3586 were ± metformin ± SU/glinide ± α-GI. The OAD(s) for Studies 3668 and 3580 were ± metformin ± SU/glinide ± pioglitazone.					

The 9 studies were all multinational, muticenter, randomized, open-label, parallel-group, active-controlled, treat-to-target trials. 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.

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.

The inclusion criterion for HbA1c at entry was in the range of 7.0% to 11.0% across the T2DM trials, with the upper limit set at 10.0% for most of the trials. For the T1DM trials, the inclusion criterion for HbA1c was ≤ 10.0% with no lower limit restriction. HbA1c was collected at Weeks -1, 0, 12, 16, and 26 for all the 26-week trials, with additional Weeks 40 and 52 for the three 52-week trials.

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

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change in HbA1c from baseline to end of treatment for all trials. The confirmatory secondary endpoints (nocturnal confirmed hypoglycemia, confirmed hypoglycemia, FPG, within-subject variability in SMPG, HbA1c < 7.0% without confirmed hypoglycemia, and HbA1c < 7.0%) were prioritized for the purpose of statistical testing and were different in each trial. 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.

In general, the subject dispositions were comparable between the study groups for most of the trials. 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. The mean BMI at entry was < 30 kg/m^2 for the T1DM trials, but was > 30 kg/m^2 for the T2DM trials (except for Study 3586 a Pan-Asian trial). As expected, the mean duration of diabetes in years was longer in the T1DM trials than in the T2DM trials.

1.3 Statistical Issues and Findings

The primary efficacy endpoint 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. 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. Several sensitivity analyses were performed by the sponsor and/or this reviewer (e.g., using the completer cohort, MMRM analysis method, etc.) to examine the robustness of the primary analysis method based on the FAS population with the LOCF technique for missing data. The results from the sensitivity analyses were all similar to the results from the primary analyses. 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. The collective evidence here is summarized across the 9 Phase 3a efficacy trials.

HbA1c. Text Table 2 below shows the mean HbA1c at baseline and endpoint as well as the mean changes from baseline for all trials. Text Table 3 shows the statistical hypothesis testing results for HbA1c for all trials using the FAS population (randomized and exposed) with LOCF. As shown in Text Table 2, 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%).

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As depicted graphically in Appendix III, 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 (note: due to low dropout rates, the presentations based on the ITT/LOCF populations here as opposed to completers are adequate). 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 <u>less</u>, but not statistically significant, in the IDeg group than in the IGlar 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 <u>greater</u>, but not statistically significant, in the IDeg group than in the IGlar 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 <u>less</u> in the IDeg Flex group than in the IGlar 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 IGlar 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

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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 IGlar 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 IGlar group in both studies. However, if the same NI criterion was applied, IDeg could be shown to be clinically non-inferior to IGlar 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%.

Note that flexible dosing regimen was investigated in Studies 3770, 3668, and 3580. Studies 3770 and 3668 used fixed-flexible method, while Study 3580 used free-flexible method. The fixed-flexible dose was injected in the morning on Mondays, Wednesdays, and Fridays, and in the evening on Tuesdays, Thursdays, Saturdays, and Sundays. The free-flexible dose was injected at *any time* of the day and at varying times from day to day. Either method required a minimum of 8 hours and a maximum of 40 hours interval between doses.

As shown in Text Table 4, 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 sitaglitpin 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.

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Text Table 2 – 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.

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Text Table 3 – 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	• IDeg + IAsp (472) • IGlar + IAsp (154)	Non-inferiority	-0.01 (0.07)	(-0.14, 0.12)	0.8800	➢ NI
3585	26-week	• IDeg + IAsp (301) • IDet + IAsp (152)	Non-inferiority	-0.08 (0.07)	(-0.23, 0.06)	0.2546	➢ NI
3770	26-week	• IDeg Flex + IAsp (164) • IDeg + IAsp (165) • IGlar + IAsp (161)	Non-inferiority	IDeg Flex vs. IGlar (*primary*): +0.17 (0.07) IDeg vs. IGlar (additional): +0.17 (0.07)	(0.04, 0.31) (0.04, 0.30)	0.0102 0.0119	➢ NI for both endpoints ➢ Statistically worse for both IDeg Flex and IDeg
Type 2 Diabetes Mellitus (T2DM)							
3582	52-week	• 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	• IDeg + OAD(s) (766) • IGlar + OAD(s) (257)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.21)	0.2293	➢ NI
3672	26-week	• 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	• IDeg + OAD(s) (284) • IGlar + OAD(s) (146)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.22)	0.2177	➢ NI
3668	26-week	• IDeg Flex + OAD(s) (228) • IDeg + OAD(s) (228) • IGlar + OAD(s) (229)	Non-inferiority	IDeg Flex vs. IGlar (*primary*): +0.04 (0.08) IDeg vs. IGlar (additional): +0.18 (0.08)	(-0.12, 0.19) (0.02, 0.33)	0.6421 0.0244	➢ NI for both endpoints ➢ Statistically worse for IDeg, but not for IDeg Flex
3580	26-week	• 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.

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Text Table 4 – 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] 61/165 (37.0%)	65/161 (40.4%)	-3.2% -3.4%	(-13.8%, 7.4%) (-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] 93/228 (40.8%)	101/229 (44.1%)	-5.1% -3.3%	(-14.1%, 4.0%) (-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. As depicted in Appendix IV, 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. Text Table 5 below summarizes the statistical results of mean change from baseline in FPG at endpoint, favoring the treatment with IDeg.

Text Table 5 – Efficacy Results for FPG (mmol/L) across Trials

DM[b]	Study	LS Mean Chang from Baseline ± SE (n)		Treatment Diff		
		IDeg	Comparator	LS Mean ± SE	95% CI	p-value
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] -2.34 ± 0.30 (164)	-1.41 ± 0.30 (160)	+0.01 ± 0.41 -0.93 ± 0.41	(-0.80, 0.82) (-1.73, -0.13)	0.98 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] -3.01 ± 0.19 (228)	-2.64 ± 0.20 (225)	-0.42 ± 0.20 -0.37 ± 0.20	(-0.82, -0.02) (-0.77, 0.03)	0.04 0.07
T2	3580	-3.42 ± 0.24 (220)	-1.25 ± 0.23 (218)	-2.17 ± 0.22	(-2.60, -1.74)	< 0.0001

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

Body Weight. As depicted in Appendix V, 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 Text Table 6 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).

Text Table 6 – Results for Body Weight (kg) across Trials

DM[b]	Study	LS Mean Chang from Baseline ± SE (n)		Treatment Diff		
		IDeg	Comparator	LS Mean ± SE	95% CI	p-value
T1	3583	2.13 ± 0.30 (472)	1.98 ± 0.40 (154)	+0.15 ± 0.37	(-0.58, 0.88)	0.69
T1	3585	1.51 ± 0.20 (301)	0.43 ± 0.24 (152)	+1.08 ± 0.25	(0.58, 1.58)	< 0.0001
T1	3770	1.27 ± 0.26 (164) [a]	1.72 ± 0.27 (161)	-0.46 ± 0.36	(-1.17, 0.25)	0.21
		0.94 ± 0.26 (165)		-0.79 ± 0.36	(-1.49, -0.08)	0.03
T2	3582	3.24 ± 0.33 (742)	3.54 ± 0.41 (248)	-0.30 ± 0.34	(-0.97, 0.38)	0.39
T2	3579	2.59 ± 0.17 (766)	2.29 ± 0.27 (257)	+0.30 ± 0.31	(-0.30, 0.90)	0.33
T2	3672	2.30 ± 0.36 (228)	1.86 ± 0.35 (228)	+0.44 ± 0.33	(-0.21, 1.08)	0.18
T2	3586	1.57 ± 0.18 (284)	1.71 ± 0.21 (146)	-0.14 ± 0.22	(-0.57, 0.29)	0.51
T2	3668	1.87 ± 0.27 (228) [a]	1.59 ± 0.26 (229)	+0.27 ± 0.27	(-0.25, 0.80)	0.31
		1.87 ± 0.26 (228)		+0.27 ± 0.27	(-0.25, 0.80)	0.31
T2	3580	2.72 ± 0.44 (222)	-0.06 ± 0.43 (221)	+2.78 ± 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 (Text Table 7).

Text Table 7 – Results for Confirmed Hypoglycemic Episodes across Trials

		IDeg	Comparator

Reference ID: 3216499

DM[b]	Study	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 Text Table 8, 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.

Text Table 8 – 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

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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 (Text Table 9).

Text Table 9 – 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] 121/165 (73.3%)	453/72.7 (6.23) [a] 732/76.2 (9.61)	117/161 (72.7%)	782/78.5 (9.96)
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] 24/228 (10.5%)	67/105.8 (0.63) [a] 58/104.9 (0.55)	49/229 (21.4%)	79/105.6 (0.75)
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 VI, the mean daily basal insulin doses were consistently lower in the IDeg group than in the IGlar 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 (IGlar 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 IGlar 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 IGlar, 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

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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.

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2. INTRODUCTION

2.1 Overview

Novo Nordisk is developing a novel, ultra-long-acting human insulin analog, called Tresiba™ (insulin degludec, NN1250), to improve glycemic control in adults with diabetes mellitus. The sponsor submitted the original NDA on 09/29/2011, including the results from 9 Phase 3a confirmatory trials (3 for type 1 diabetes mellitus [T1DM] and 6 for type 2 diabetes mellitus [T2DM], see the bullets below). Insulin degludec (IDeg) is a new molecular entity. It is expected that the timing of the injection can vary from day to day (about 8-40 hours between injections), depending on the needs of the individual patient.

- T1DM – once daily 100 U/mL – basal-bolus therapy (3583, 3585, 3770)
- T2DM – once daily 100 U/mL – basal-bolus therapy (3582)
- T2DM – once daily 100 U/mL – OAD insulin combination (3579, 3586, 3668, 3580)
- T2DM – once daily 200 U/mL – OAD insulin combination (3672)

The 9 studies were all multinational, muticenter, randomized, open-label, parallel-group, active-controlled, treat-to-target trials. 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 for these trials was change in HbA1c from baseline to end of treatment (varying from study to study). The key secondary endpoints were prioritized for the purpose of statistical testing and were different in each trial.

(b) (4) .

Nevertheless, this review discusses the results from all trials (see the study highlights below, sponsor's table).

Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of Subjects (FAS) (M/F)	Healthy, T1DM or T2DM	Duration of treatment
NN1250-3579 AT, BE, CA, CZ, DK, FI, FR, DE, NO, RS, ES, US	Efficacy and safety	Multi-centre, multi-national randomised (3:1), three arm, open-label, parallel group, treat-to-target trial. Active control (IGlar)	IDeg (M): OD s.c. IGlar: OD s.c. + met p.o. ± DPP-4I p.o. + NPH s.c. in the follow-up period	1030 (638/392) IDeg (M): 773 IGlar: 257	T2DM	52 weeks
NN1250-3580 AR, CA, IN, MX, ZA, TR, US	Efficacy and safety	Multi-centre, multi-national randomised (1:1), open-label, two arm, parallel group, treat-to-target trial. Active control (Sitagliptin)	IDeg (M): OD s.c. Sitagliptin OD p.o. + 1 or 2 of the following p.o.: met, SU/glin, pio	447 (262/185) IDeg (M): 225 Sitagliptin: 222	T2DM	26 weeks
NN1250-3582 BG, DE, HK, IE, IT, RO, SK, RU, ZA, ES, TR, US	Efficacy and safety	Multi-centre, multi-national randomised (3:1), open-label, two-arm, parallel group, treat-to-target trial. Active control (IGlar)	IDeg (M): OD s.c. IGlar: OD s.c. + IAsp s.c. at main meals ± met p.o. ± pio p.o.	992 (538/454) IDeg (M): 744 IGlar: 248	T2DM	52 weeks

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Trial ID Country	Type of study	Trial design and type of control	Test drugs and route of administration	Number of Subjects (FAS) (M/F)	Healthy, T1DM or T2DM	Duration of treatment
NN1250-3583 FR, DE, RU, GB, ZA, US	Efficacy and safety	Multi-centre, multi-national randomised (3:1), open-label, two-arm, parallel group, treat-to-target trial. Active control (IGlar)	IDeg (M): OD s.c. IGlar: OD s.c. + IAsp s.c. at main meals + NPH s.c. in the follow-up period	629 (368/261) IDeg (M): 472 IGlar: 157	T1DM	52 weeks
NN1250-3585 BR, FI, IN, IT, JP, GB, MK	Efficacy and safety	Multi-centre, multi-national randomised (2:1), open-label, two arm, parallel group, treat-to-target trial. Active control (IDet)	IDeg (M): OD s.c. IDet: OD (or BID if required) s.c. + IAsp s.c. at main meals	455 (236/219) IDeg (M): 302 IDet: 153	T1DM	26 weeks
NN1250-3586 HK, JP, MY, KR, TH, TW	Efficacy and safety	Multi-centre, multi-national randomised (2:1), open-label, two arm, treat-to-target trial. Active control (IGlar)	IDeg (M): OD s.c. IGlar: OD s.c. ± met p.o. ± SU/glin p.o. ± α-GI p.o. + NPH s.c. in the follow-up period.	435 (233/202) IDeg (M): 289 IGlar: 146	T2DM	26 weeks
NN1250-3668 IN, MY, TW, HU, MK, RS, FI, NO, GB, AR, MX, ZA, RU, IL	Efficacy and safety	Multi-centre, multi-national randomised (1:1:1), open-label, three arm, treat-to-target trial. Active control (IGlar)	IDeg (M): Flex s.c. (administered OD according to a flexible dosing schedule with 8 to 40h intervals between doses) IDeg (M): OD s.c. IGlar: OD s.c. ± met p.o., ± SU/glin p.o., ± pio p.o. + NPH s.c. in the follow-up period.	687 (370/317) IDeg (M) Flex: 229 IDeg (M): OD 228 IGlar: 230	T2DM	26 weeks
NN1250-3672 CA, FR, IE, RU, ZA, UA, GB, US	Efficacy and safety	Multi-centre, multi-national randomised (1:1), open-label, parallel group, treat-to-target trial. Active control (IGlar)	IDeg (P): OD s.c. IGlar: OD s.c. + met p.o. ± DPP-4I p.o. + NPH s.c. in the follow-up period.	457 (243/214) IDeg (P): 228 IGlar: 229	T2DM	26 weeks
NN1250-3770 BE, DE, NO, PL, GB, US	Efficacy and safety	Multi-centre, multi-national randomised (1:1:1), three arm, open-label, parallel group, treat-to-target trial. Active control (IGlar)	IDeg (M): Flex s.c. (administered OD according to a flexible dosing schedule with 8 to 40h intervals between doses) IDeg (M): OD s.c. IGlar: OD s.c. + IAsp s.c. at main meals + NPH s.c. in the follow-up period.	493 (284/209) IDeg (M) Flex: 164 IDeg (M) OD: 165 IGlar: 164	T1DM	26 weeks

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.

2.2 Data Sources

The original clinical study reports and electronic data files are located in the sub-folders of EDR **\\CDSESUB5\EVSPROD\NDA203314\0000**. In general, the quality of the electronic data sets and integrity of the study reports are satisfactory.

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3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study Design and Endpoints

All the 9 efficacy trials 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 (see the sponsor's rationale in the next paragraph), 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. IDeg, IGlar, and IDet were administered once daily (OD) subcutaneously in these trials. However, in case of inadequate glycemic control after 8 weeks of treatment, a second dose of IDet may be added based on the investigator's discretion. Unless otherwise noted, IDeg was injected at the main evening meal or in the evening (from the start of main evening meal to bedtime). The 3 T1DM trials all had insulin aspart (IAsp, NovoRapid®/NovoLog®) 100 U/mL as the bolus therapy. The 6 T2DM trials each had different OAD(s) as the background medication (see footnotes in Table 1).

The 200 U/mL formulation of IDeg contains the same amount of units of insulin in half the volume compared to a 100 U/mL formulation, thus permitting insulin doses to be administered in a smaller volume than when using a 100 U/mL formulation. This will be particularly beneficial for very insulin resistant subjects requiring large doses of insulin that cannot be administered with a single injection due to a limited volume of delivery of available pen devices. By using IDeg 200 U/mL these subjects will be able to administer their total insulin dose in a single injection rather than multiple injections.

Both Study 3770 (T1DM) and Study 3668 (T2DM) had 3 treatment arms (1:1:1 randomization ratio): IDeg Flex (flexible dosing), IDeg OD (referred as IDeg in this report), and IGlar OD (referred as IGlar in this report). The flexible dosing 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 (see the diagram below). The primary objective for these 2 studies was to confirm the efficacy of IDeg administered in a fixed-flexible (FF) dosing schedule in controlling glycemia when compared with IGlar. The comparison between IDeg Flex and IDeg in terms of HbA1c lowering was a secondary objective.

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 with a minimum of 8 hours and a maximum of 40 hours interval between injections.

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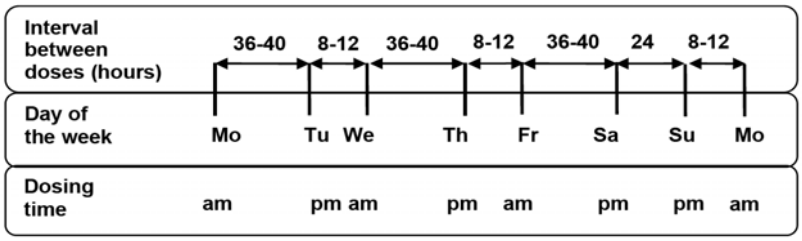

am: morning (defined as time period from waking up to first meal of the day)
pm: evening (defined as time period from start of evening meal to bedtime)

For each of the three 1-year trials (Studies 3583, 3582, and 3579), the randomization ratio was 3:1 for IDeg vs. IGlar. For Studies 3585 and 3586, the randomization ratio was 2:1 for IDeg vs. comparator. For Studies 3672 and 3580, the randomization ratio was 1:1 for IDeg vs. comparator.

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. Studies 3579, 3672, 3586, and 3580 were conducted in insulin-naïve patients only. Subjects in Study 3580 also had to be DPP-4 inhibitor naïve at entry.

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							
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							
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

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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

The OAD(s) for Study 3582 were ± metformin ± pioglitazone.

The OAD(s) for Studies 3579 and 3672 were + metformin ± DPP-4 inhibitor.

The OAD(s) for Study 3586 were ± metformin ± SU/glinide ± α-GI.

The OAD(s) for Studies 3668 and 3580 were ± metformin ± SU/glinide ± pioglitazone.

[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).

[b] For patients from Argentina, HbA1c at entry was 7.5% - 10.0%.

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 and were different from trial to trial (Table 2). There were also supportive secondary endpoints such as HbA1c < 7.0% responder rate, self measured plasma glucose (SMPG), etc., in each trial. Since not all the statistically significant endpoints will be of interest and 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	1st	2nd	3rd	4th	--	--
3585	1st	2nd	3rd	4th	--	--
3770	--	--	--	--	--	--
Table 2 Diabetes Mellitus						
3582	--	1st	2nd	3rd	4th	--
3579	--	1st	2nd	3rd	4th	--
3672	--	1st	2nd	3rd	4th	--
3586	2nd	1st	3rd	4th	5th	--

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3668	--	--	--	--	--	--
3580	--	--	1st	--	3rd	2nd

For the sample size calculation, the sponsor used SD of 1.1% for subjects with T1DM and 1.3% for subjects with T2DM generally. The sample size was powered to the PP analysis set with an assumption that between 15% and 25% (depending on trial design) of the randomized subjects were excluded from the PP analysis set. For the non-inferiority trials, the sample size was determined under the assumption of no difference between the two treatment arms. For the superiority trial, the sample size was determined to detect a treatment difference of 0.4% in HbA1c at the end of the treatment. All the Phase 3a trials have 85 – 95% power.

3.1.2 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, Table 3). 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%. In addition, the sponsor tested the prioritized confirmatory secondary endpoints sequentially for superiority after the non-inferiority/superiority was confirmed for the primary efficacy endpoint so that the overall 1-sided type 1 error at the 2.5% level was preserved. Some of the sponsor's confirmatory secondary endpoints were defined as shown below.

<u>Responder (HbA1c < 7.0% at end of trial)</u>

Responder analysis was based on a logistic regression model using treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline HbA1c as covariates. Superiority was considered confirmed if the 95% confidence interval for the odds ratio (IDeg / comparator) was entirely above one.

<u>Responder without hypoglycemic episodes (HbA1c < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment including only subjects exposed for at least 12 weeks)</u>

Analysis method was the same as HbA1c < 7.0% at end of trial above.

<u>Change from baseline in FPG at end of trial (analyzed at central laboratory)</u>

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Change from baseline in FPG at endpoint was analyzed using an ANCOVA model with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline FPG as covariates. Superiority was considered confirmed if the 95% confidence interval for the treatment difference (IDeg – comparator) was entirely below zero.

Number of treatment emergent nocturnal (00:01-05:59 a.m.) severe and/or minor hypoglycemic episodes

Severe (need assistance) and/or minor (no need for assistance, but PG < 3.1 mmol/L) hypoglycemia together was classified as confirmed hypoglycemic episodes by the sponsor. The number of nocturnal confirmed hypoglycemic episodes was analyzed using a negative binominal 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 was to include treatment, antidiabetic therapy at screening, sex, region as fixed factors and age as covariate. Superiority was considered confirmed if the 95% confidence interval for the relative risk (IDeg / comparator) was entirely below one.

Number of treatment emergent severe and/or minor hypoglycemic episodes

Analysis method was the same as nocturnal confirmed hypoglycemic episodes above.

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). Body weight data were analyzed using the method similar to the primary efficacy endpoint.

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 primary analysis was repeated based on the PP analysis set.
- The primary analysis was repeated based on the completer cohort.

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- 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.

The results from the above sensitivity analyses were all similar to the results from the primary analyses.

Table 3 – Levels of Factors Used in Statistical Model

Study	Antidiabetic therapy at screening category	Region category
Table 1 Diabetes Mellitus		
3583	(1) Twice daily basal injections, (2) Once daily basal injection	European Union, North America, South Africa
3585	(1) Twice daily basal injections, (2) Once daily basal injection	Europe, South America, Japan, India
3770	(1) Twice daily basal injections, (2) Once daily basal injection	Europe, North America
Table 2 Diabetes Mellitus		
3582	(1) Basal-bolus insulin regimen (basal at least 1/day and bolus at least 2/day) or pump, (2) Basal only (basal at least 1/day and no bolus), (3) Other (any other insulin regimen not mentioned above, including regimen with premixed insulin preparation)	Europe, North America, South Africa, Asia
3579	(1) Metformin monotherapy, (2) Metformin ± SU or glinides ± Acarbose, (3) Metformin + DPP-4 inhibitor ± SU or glinides ± Acarbose	European Union, North America
3672	(1) Metformin monotherapy, (2) Metformin ± SU or glinides ± Acarbose, (3) Metformin + DPP-4 inhibitor ± SU or glinides ± Acarbose	Europe, North America, South Africa
3586	(1) Monotherapy, (2) Combination therapy	Japan, Asia w/o Japan
3668	(1) Treatment with one OAD, (2) Combination of two OADs, (3) Combination of three OADs, (4) basal insulin alone, (5) basal insulin and at least one OAD	Europe, South America, South Africa, Asia

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3580	(1) Pioglitazone ± (SU or glinides) or metformin, (2) SU or glinides ± metformin, (3) Metformin monotherapy	Europe, North America, South America, South Africa, Asia

No interim analyses were planned and performed for these trials by the sponsor.

3.1.3 Subject Disposition

Table 4 presents the subject disposition for the 9 trials reviewed. Except for Studies 3579 and 3580 (both T2DM), at least 80% of the randomized subjects in each study completed their treatment periods. 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 IGlar group was much smaller than that in the IDeg group. The most frequently recorded category for withdrawal in each trial was 'Other', which included many miscellaneous reasons such as withdrawal of consent, randomization in error, moving away, lost to follow-up, etc. According to the sponsor, Site 109 (11 IDeg, 3 IGlar) 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.

In general, the overall reasons for withdrawal and time of discontinuation (Appendix I) were comparable between the study groups for most of the trials.

3.1.4 Demographic and Baseline Characteristics

Table 5 presents the demographic and baseline characteristics for the 9 trials reviewed. In each trial, there were more male subjects enrolled than female ones. For both 3-arm trials (Studies 3770 and 3668), the IDeg Flex group enrolled the greatest number of males and the IGlar group enrolled the fewest. Except for Study 3586 a Pan-Asian trial and Study 3585, the majority of patients in each trial were White. Study 3585 did not enroll any subjects from the US and slightly more than half of the population was from Asia (Japan and India together). Studies 3668 and 3580 also had at least 25% of the population from Asia.

There were a total of 2698 patients exposed to IDeg and 1329 patients exposed to IGlar or sitaglipitin across the 6 T2DM trials. Among them, 1500 IDeg-treated and 852 comparator-treated patients were insulin-naïve.

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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/m^2 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. There was no lower limit for baseline HbA1c inclusion for type 1 diabetic subjects (see Table 1 above). Study 3580 had the largest mean HbA1c at baseline when compared to the other T2DM trials, which was a result of higher HbA1c inclusion criterion for this superiority trial. 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.

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.

Reference ID: 3216499

Table 4 – 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.

Reference ID: 3216499

Table 4 – 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.

Reference ID: 3216499

Table 5 – 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 **Sponsor FAS**	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)
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

Reference ID: 3216499

Table 5 – 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 **Sponsor FAS**	IDeg (n = 773)	IGlar (n = 257)	IDeg (n = 228)	IGlar (n = 229)	IDeg (n = 289)	IGlar (n = 146)	IDeg Flex (n = 229)	IDeg (n = 228)	IGlar (n = 230)	IDeg Flex (n = 225)	DPP-4 (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)
Race:											
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

Reference ID: 3216499

3.1.5 Efficacy Results and Discussion

In general, this reviewer's results were similar to the sponsor's findings. Unless otherwise stated, the following results and discussions are based on this reviewer's analyses on the FAS population consisting of subjects who were randomized and exposed to study treatment. The sponsor's results based on all the randomized subjects (including the unexposed ones) are presented in Appendices I – VII. The graphs in this review report were copied from the sponsor's clinical study reports, unless otherwise noted.

TYPE 1 DIABETES MELLITUS (T1DM)

Study 3583

HbA1c (%). After 52 weeks of treatment, both IDeg and IGlar groups showed raw mean decreases in HbA1c from baseline (-0.40% for both groups). The HbA1c reductions in the 2 study groups at Week 52 were not statistically significantly different from each other (treatment difference = -0.01%, p = 0.88, Table 6). The non-inferiority of IDeg to IGlar in patients with T1DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.12% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 6 – Study 3583 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + IAsp vs. IGlar + IAsp (FAS w/ LOCF)			-0.01 (0.07)	(-0.14, **0.12**)	0.88
IDeg + IAsp vs. IGlar + IAsp (Completers)			-0.05 (0.07)	(-0.18, **0.09**)	0.50
IDeg + IAsp vs. IGlar + IAsp (FAS using MMRM with UN option for variance-covariance structure)			-0.02 (0.07)	(-0.16, **0.11**)	0.73

The percentages of responders defined as patients with Week 52 HbA1c value < 7.0% or ≤ 6.5% were numerically smaller, but not statistically significant, in the IDeg group when compared with the IGlar group (Table 7). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

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Table 7 – Study 3583 – Responder Rates for HbA1c at Week 52

FAS with LOCF	IDeg + IAsp (n = 472)	IGlar + IAsp (n = 154)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	188 (39.8%)	66 (42.9%)	-3.0%	(-12.0%, 5.9%)
HbA1c < 7.0% [1]	167 (35.4%)	59 (38.3%)	-2.9%	(-11.7%, 5.9%)
HbA1c ≤ 6.5%	113 (23.9%)	38 (24.7%)	-0.7%	(-8.6%, 7.1%)
[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%				

FPG (mmol/L). The mean reductions at Week 52 in the 2 study groups were not statistically significantly different from each other (treatment difference = -0.40 mmol/L, p = 0.27, Table 8), although the reduction was numerically greater in the IDeg group than in the IGlar group.

Table 8 – Study 3583 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + IAsp	465	9.13 (4.00)	7.86 (3.77)	-1.27 (5.04)	-1.56 (0.29)
IGlar + IAsp	152	9.77 (4.37)	8.35 (4.17)	-1.42 (5.38)	-1.16 (0.39)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + IAsp vs. IGlar + IAsp (FAS w/ LOCF)			-0.40 (0.36)	(-1.10, 0.31)	0.27

Study 3585

HbA1c (%). After 26 weeks of treatment, both IDeg and IDet groups showed raw mean decreases in HbA1c from baseline (-0.73% and -0.65%, respectively). The HbA1c reductions in the 2 study groups at Week 26 were not statistically significantly different from each other (treatment difference = -0.08%, p = 0.25, Table 9). The non-inferiority of IDeg to IDet in patients with T1DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.06% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 9 – Study 3585 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)

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Treatment Comparison	Treatment Difference		
	LS Mean (SE)	95% CI	p-value
IDeg + IAsp vs. IDet + IAsp (FAS w/ LOCF)	-0.08 (0.07)	(-0.23, **0.06**)	0.25
IDeg + IAsp vs. IDet + IAsp (Completers)	-0.06 (0.07)	(-0.20, **0.08**)	0.44
IDeg + IAsp vs. IDet + IAsp (FAS using MMRM with UN option for variance-covariance structure)	-0.07 (0.08)	(-0.22, **0.08**)	0.37

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were numerically larger, but not statistically significant, in the IDeg group when compared with the IDet group (Table 10). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

Table 10 – Study 3585 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg + IAsp (n = 301)	IDet + IAsp (n = 152)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	124 (41.2%)	57 (37.5%)	3.7%	(-5.8%, 13.2%)
HbA1c < 7.0% [1]	116 (38.5%)	54 (35.5%)	3.0%	(-6.4%, 12.4%)
HbA1c ≤ 6.5%	73 (24.3%)	33 (21.7%)	2.5%	(-5.6%, 10.7%)

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%

FPG (mmol/L). The mean reduction at Week 26 was significantly greater in the IDeg group than in the IDet group (treatment difference = -1.68 mmol/L, p < 0.0001, Table 11).

Table 11 – Study 3585 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + IAsp	300	9.86 (3.98)	7.26 (3.36)	-2.61 (4.88)	-2.42 (0.28)
IDet + IAsp	148	9.48 (4.02)	8.85 (4.13)	-0.63 (4.49)	-0.74 (0.35)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
IDeg + IAsp vs. Idet + Iasp (FAS w/ LOCF)			-1.68 (0.36)	(-2.38, -0.97)	< 0.0001

Study 3770

HbA1c (%). After 26 weeks of treatment, the IDeg Flex, IDeg, and IGlar groups all showed raw mean decreases in HbA1c from baseline (-0.40%, -0.41%, and -0.59%, respectively). However, the HbA1c reduction in the IDeg Flex and IDeg groups at Week 26 were both

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statistically significantly less than that in the IGlar group (treatment difference = +0.17%, p = 0.01, Table 12). The non-inferiority of IDeg Flex to IGlar in patients with T1DM (primary objective) was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.31% (less than the pre-defined NI margin 0.4%, but greater than 0%). Similarly, although it was neither a primary nor a secondary objective, the non-inferiority of IDeg to IGlar in patients with T1DM could also be established if the same NI criterion was applied, since the upper bound of the 95% CI of the treatment difference was +0.30% (< 0.4%). There was no significant difference in mean change from baseline in HbA1c at Week 26 between the IDeg Flex and IDeg groups (treatment difference = +0.005%, p = 0.94). All other supportive analyses also showed similar results.

Table 12 – Study 3770 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + IAsp vs. IGlar + Iasp (FAS w/ LOCF)			0.17 (0.07)	(0.04, **0.31**)	0.010
IDeg Flex + IAsp vs. IGlar + Iasp (Completers)			0.13 (0.07)	(-0.004, **0.27**)	0.058
IDeg Flex + IAsp vs. IGlar + IAsp (FAS using MMRM with UN option for variance-covariance structure)			0.15 (0.07)	(0.01, **0.29**)	0.038
IDeg + IAsp vs. IGlar + IAsp (FAS w/ LOCF)			0.17 (0.07)	(0.04, **0.30**)	0.012
IDeg + IAsp vs. IGlar + IAsp (Completers)			0.16 (0.07)	(0.02, **0.29**)	0.027
IDeg + IAsp vs. IGlar + IAsp (FAS using MMRM with UN option for variance-covariance structure)			0.17 (0.07)	(0.03, **0.31**)	0.015
IDeg Flex + IAsp vs. IDeg + IAsp (FAS w/ LOCF)			0.005 (0.07)	(-0.13, 0.14)	0.944

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were all numerically smaller, but not statistically significant, in the IDeg Flex and IDeg groups when compared with the IGlar group (Table 13). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between either of the two IDeg groups and the IGlar group. The responder rates in the IDeg Flex and IDeg groups were also comparable in all the cases.

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Table 13 – Study 3770 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg Flex + IAsp (n = 164)	IDeg + IAsp (n = 165)	IGlar + IAsp (n = 161)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	61 (37.2%)	61 (37.0%)	65 (40.4%)	-3.2% [2] -3.4% [3]	(-13.8%, 7.4%) [2] (-14.0%, 7.2%) [3]
HbA1c < 7.0% [1]	57 (34.8%)	59 (35.8%)	63 (39.1%)	-4.4% [2] -3.4% [3]	(-14.9%, 6.1%) [2] (-13.9%, 7.1%) [3]
HbA1c ≤ 6.5%	33 (20.1%)	35 (21.2%)	37 (23.0%)	-2.9% [2] -1.8% [3]	(-11.8%, 6.1%) [2] (-10.8%, 7.2%) [3]

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%
[2] For IDeg Flex + IAsp vs. IGlar + IAsp comparison
[3] For IDeg + IAsp vs. IGlar + IAsp comparison

FPG (mmol/L). There was no significant difference in mean change from baseline in FPG at Week 26 between the IDeg Flex and IGlar groups (treatment difference = +0.01 mmol/L, p = 0.98, Table 14). However, a nominally significantly greater mean reduction in FPG at Week 26 was observed in the IDeg group (-2.34 mmol/L) when compared with the IGlar group (-1.41 mmol/L) or IDeg Flex group (-1.40 mmol/L).

Table 14 – Study 3770 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg Flex + IAsp	161	9.59 (4.05)	8.31 (4.02)	-1.28 (5.03)	-1.40 (0.30)
IDeg + IAsp	164	9.96 (4.04)	7.42 (3.47)	-2.54 (5.11)	-2.34 (0.30)
IGlar + IAsp	160	9.77 (4.21)	8.34 (3.57)	-1.43 (5.16)	-1.41 (0.30)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + IAsp vs. IGlar + IAsp (FAS w/ LOCF)			0.01 (0.41)	(-0.80, 0.82)	0.98
IDeg + IAsp vs. IGlar + IAsp (FAS w/ LOCF)			-0.93 (0.41)	(-1.73, -0.13)	0.02
IDeg Flex + IAsp vs. IDeg + IAsp (FAS w/ LOCF)			0.95 (0.41)	(0.14, 1.75)	0.02

TYPE 2 DIABETES MELLITUS (T2DM)

Study 3582

HbA1c (%). After 52 weeks of treatment, both IDeg and IGlar groups showed raw mean decreases in HbA1c from baseline (-1.17% and -1.29%, respectively). Although the mean

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reductions at Week 52 were not statistically different between the 2 study groups (treatment difference = +0.07%, p = 0.27, Table 15), reductions were numerically smaller in the IDeg group than in the IGlar group. The non-inferiority of IDeg to IGlar in patients with T2DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.20% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 15 – Study 3582 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg group vs. IGlar group (FAS w/ LOCF)			0.07 (0.07)	(-0.06, **0.20**)	0.27
IDeg group vs. IGlar group (Completers)			-0.007 (0.07)	(-0.14, **0.13**)	0.91
IDeg group vs. IGlar group (FAS using MMRM with UN option for variance-covariance structure)			0.01 (0.07)	(-0.12, **0.14**)	0.87

The percentages of responders defined as patients with Week 52 HbA1c value < 7.0% or ≤ 6.5% were numerically smaller, but not statistically significant, in the IDeg group when compared with the IGlar group (Table 16). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

Table 16 – Study 3582 – Responder Rates for HbA1c at Week 52

FAS with LOCF	IDeg + IAsp ± OAD(s) (n = 742)	IGlar + IAsp ± OAD(s) (n = 248)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	368 (49.6%)	124 (50.0%)	-0.4%	(-7.6%, 6.8%)
HbA1c < 7.0% [1]	338 (45.6%)	112 (45.2%)	0.4%	(-6.8%, 7.5%)
HbA1c ≤ 6.5%	229 (30.9%)	82 (33.1%)	-2.2%	(-8.9%, 4.5%)

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%

FPG (mmol/L). The mean reductions at Week 52 in the 2 study groups were not statistically significantly different from each other (treatment difference = -0.30 mmol/L, p = 0.10, Table 17), although the reduction was numerically greater in the IDeg group than in the IGlar group.

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Table 17 – Study 3582 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + IAsp ± OAD(s)	739	9.19 (3.05)	6.75 (2.45)	-2.44 (3.53)	-2.26 (0.17)
IGlar + IAsp ± OAD(s)	248	9.20 (3.24)	7.06 (2.71)	-2.14 (3.62)	-1.96 (0.22)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg group vs. Iglar group (FAS w/ LOCF)			-0.30 (0.18)	(-0.65, 0.05)	0.10

Study 3579

HbA1c (%). After 52 weeks of treatment, both IDeg and IGlar groups showed raw mean decreases in HbA1c from baseline (-1.07% and -1.19%, respectively). Although the mean reductions at Week 52 were not statistically different between the 2 study groups (treatment difference = +0.08%, p = 0.23, Table 18), reductions were numerically smaller in the IDeg group than in the IGlar group. The non-inferiority of IDeg to IGlar in patients with T2DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.21% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 18 – Study 3579 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			0.08 (0.07)	(-0.05, **0.21**)	0.23
IDeg + OAD(s) vs. IGlar + OAD(s) (Completers)			0.06 (0.07)	(-0.07, **0.19**)	0.39
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)			0.10 (0.07)	(-0.04, **0.23**)	0.16

The percentages of responders defined as patients with Week 52 HbA1c value < 7.0% or ≤ 6.5% were numerically smaller, but not statistically significant, in the IDeg group when compared with the IGlar group (Table 19). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

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Table 19 – Study 3579 – Responder Rates for HbA1c at Week 52

FAS with LOCF	IDeg + OAD(s) (n = 766)	IGlar + OAD(s) (n = 257)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	400 (52.2%)	139 (54.1%)	-1.9%	(-8.9%, 5.2%)
HbA1c < 7.0% [1]	357 (46.6%)	120 (46.7%)	-0.1%	(-7.1%, 7.0%)
HbA1c ≤ 6.5%	238 (31.1%)	90 (35.0%)	-3.9%	(-10.6%, 2.7%)
[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%				

FPG (mmol/L). The mean reduction at Week 52 was significantly greater in the IDeg group than in the IGlar group (treatment difference = -0.46 mmol/L, p = 0.003, Table 20).

Table 20 – Study 3579 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 52 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + OAD(s)	758	9.64 (2.56)	5.86 (2.14)	-3.78 (3.04)	-3.80 (0.08)
IGlar + OAD(s)	256	9.66 (2.57)	6.36 (2.33)	-3.30 (2.87)	-3.33 (0.14)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			-0.46 (0.15)	(-0.77, -0.16)	0.003

Study 3672

HbA1c (%). After 26 weeks of treatment, both IDeg (200 U/mL) and IGlar groups showed raw mean decreases in HbA1c from baseline (-1.30% and -1.32%, respectively). Although the mean reductions at Week 26 were not statistically different between the 2 study groups (treatment difference = +0.05%, p = 0.55, Table 21), reductions were numerically smaller in the IDeg group than in the IGlar group. The non-inferiority of IDeg to IGlar in patients with T2DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.20% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 21 – Study 3672 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + 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)

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Treatment Comparison	Treatment Difference		
	LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)	0.05 (0.08)	(-0.11, **0.20**)	0.55
IDeg + OAD(s) vs. IGlar + OAD(s) (Completers)	0.06 (0.07)	(-0.08, **0.21**)	0.40
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)	0.03 (0.07)	(-0.11, **0.18**)	0.67

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were numerically smaller, but not statistically significant, in the IDeg group when compared with the IGlar group (Table 22). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

Table 22 – Study 3672 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg + OAD(s) (n = 228)	IGlar + OAD(s) (n = 228)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	119 (52.2%)	128 (56.1%)	-3.9%	(-13.1%, 5.2%)
HbA1c < 7.0% [1]	112 (49.1%)	121 (53.1%)	-3.9%	(-13.1%, 5.2%)
HbA1c ≤ 6.5%	86 (37.7%)	98 (43.0%)	-5.3%	(-14.3%, 3.7%)

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%

FPG (mmol/L). The mean reduction at Week 26 was significantly greater in the IDeg group than in the IGlar group (treatment difference = -0.41 mmol/L, p = 0.03, Table 23).

Table 23 – Study 3672 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + OAD(s)	228	9.57 (2.87)	5.86 (1.87)	-3.70 (3.06)	-3.95 (0.20)
IGlar + OAD(s)	225	9.67 (2.60)	6.27 (2.19)	-3.40 (2.96)	-3.53 (0.20)
Treatment Comparison			Treatment Difference		
			LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			-0.41 (0.18)	(-0.77, -0.05)	0.03

Study 3586

HbA1c (%). After 26 weeks of treatment, both IDeg and IGlar groups showed raw mean decreases in HbA1c from baseline (-1.26% and -1.35%, respectively). Although the mean reductions at Week 26 were not statistically different between the 2 study groups (treatment

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difference = +0.08%, p = 0.22, Table 24), reductions were numerically smaller in the IDeg group than in the IGlar group. The non-inferiority of IDeg to IGlar in patients with T2DM was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.22% (less than the pre-defined NI margin 0.4%, but greater than 0%). All other supportive analyses also showed similar results.

Table 24 – Study 3586 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			0.08 (0.07)	(-0.05, **0.22**)	0.22
IDeg + OAD(s) vs. IGlar + OAD(s) (Completers)			0.08 (0.07)	(-0.05, **0.22**)	0.23
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)			0.09 (0.07)	(-0.05, **0.22**)	0.21

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were numerically smaller, but not statistically significant, in the IDeg group when compared with the IGlar group (Table 25). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between the 2 study groups.

Table 25 – Study 3586 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg + OAD(s) (n = 284)	IGlar + OAD(s) (n = 146)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	118 (41.5%)	71 (48.6%)	-7.1%	(-17.0%, 2.8%)
HbA1c < 7.0% [1]	112 (39.4%)	68 (46.6%)	-7.1%	(-17.0%, 2.7%)
HbA1c ≤ 6.5%	52 (18.3%)	36 (24.7%)	-6.3%	(-14.7%, 2.0%)

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%

FPG (mmol/L). The mean reductions at Week 26 in the 2 study groups were not statistically significantly different from each other (treatment difference = -0.14 mmol/L, p = 0.40, Table 26), although the reduction was numerically greater in the IDeg group than in the IGlar group.

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Table 26 – Study 3586 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg + OAD(s)	283	8.43 (2.08)	5.50 (1.61)	-2.92 (2.48)	-3.08 (0.13)
IGlar + OAD(s)	145	8.63 (1.93)	5.67 (1.54)	-2.97 (2.28)	-2.95 (0.16)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			-0.14 (0.16)	(-0.45, 0.18)	0.40

Study 3668

HbA1c (%). After 26 weeks of treatment, the IDeg Flex, IDeg, and IGlar groups all showed raw mean decreases in HbA1c from baseline (-1.29%, -1.07%, and -1.27%, respectively). The HbA1c reduction at Week 26 was significantly less in the IDeg group when compared with the IGlar group (treatment difference = +0.18%, p = 0.02, Table 27). The mean reduction in the IDeg Flex group was, however, similar to that in the IGlar group (treatment difference = +0.04%, p = 0.64, Table 27). The non-inferiority of IDeg Flex to IGlar in patients with T2DM (primary objective) was established in this study, but not superiority, since the upper bound of the 95% CI of the treatment difference was +0.19% (less than the pre-defined NI margin 0.4%, but greater than 0%). Similarly, although it was neither a primary nor a secondary objective, the non-inferiority of IDeg to IGlar in patients with T2DM could also be established if the same NI criterion was applied, since the upper bound of the 95% CI of the treatment difference was +0.33% (< 0.4%). There was no significant difference in mean change from baseline in HbA1c at Week 26 between the IDeg Flex and IDeg groups (treatment difference = -0.14%, p = 0.08). All other supportive analyses also showed similar results.

Table 27 – Study 3668 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
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)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			0.04 (0.08)	(-0.12, **0.19**)	0.64
IDeg Flex + OAD(s) vs. IGlar + OAD(s) (Completers)			0.07 (0.07)	(-0.07, **0.21**)	0.34

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IDeg Flex + OAD(s) vs. IGlar + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)	0.06 (0.08)	(-0.09, **0.20**)	0.46
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)	0.18 (0.08)	(0.02, **0.33**)	0.02
IDeg + OAD(s) vs. IGlar + OAD(s) (Completers)	0.14 (0.07)	(0.00, **0.29**)	0.05
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)	0.14 (0.08)	(-0.01, **0.28**)	0.07
IDeg Flex + OAD(s) vs. IDeg + OAD(s) (FAS w/ LOCF)	-0.14 (0.08)	(-0.30, 0.01)	0.08

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were all numerically smaller, but not statistically significant, in the IDeg Flex and IDeg groups when compared with the IGlar group (Table 28). In addition, the % of patients achieving the target of HbA1c < 7.0% without confirmed or severe hypoglycemic episodes during the last 12 weeks of treatment were also similar between either of the two IDeg groups and the IGlar group. The responder rates in the IDeg Flex and IDeg groups were also comparable in all the cases.

Table 28 – Study 3668 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg Flex + OAD(s) (n = 228)	IDeg + OAD(s) (n = 228)	IGlar + OAD(s) (n = 229)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	89 (39.0%)	93 (40.8%)	101 (44.1%)	-5.1% [2] -3.3% [3]	(-14.1%, 4.0%) [2] (-12.4%, 5.7%) [3]
HbA1c < 7.0% [1]	84 (36.8%)	92 (40.4%)	97 (42.4%)	-5.5% [2] -2.0% [3]	(-14.5%, 3.4%) [2] (-11.0%, 7.0%) [3]
HbA1c ≤ 6.5%	55 (24.1%)	52 (22.8%)	59 (25.8%)	-1.6% [2] -3.0% [3]	(-9.6%, 6.3%) [2] (-10.8%, 4.9%) [3]

[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%
[2] For IDeg Flex + OAD(s) vs. IGlar + OAD(s) comparison
[3] For IDeg + OAD(s) vs. IGlar + OAD(s) comparison

FPG (mmol/L). A significantly greater reduction in mean FPG from baseline to Week 26 was observed in the IDeg Flex group, but not in the IDeg group, when compared with the IGlar group (treatment difference = -0.42 mmol/L, p = 0.04). There was no statistical difference between the IDeg Flex and IDeg groups in mean change from baseline in FPG at Week 26 (Table 29).

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Table 29 – Study 3668 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg Flex + OAD(s)	226	9.00 (2.57)	5.85 (1.98)	-3.15 (2.91)	-3.05 (0.20)
IDeg + OAD(s)	228	8.75 (2.83)	5.84 (2.41)	-2.91 (3.05)	-3.01 (0.19)
IGlar + OAD(s)	225	9.02 (2.75)	6.24 (2.36)	-2.78 (3.08)	-2.64 (0.20)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			-0.42 (0.20)	(-0.82, -0.02)	0.04
IDeg + OAD(s) vs. IGlar + OAD(s) (FAS w/ LOCF)			-0.37 (0.20)	(-0.77, 0.03)	0.07
IDeg Flex + OAD(s) vs. IDeg + OAD(s) (FAS w/ LOCF)			-0.05 (0.20)	(-0.45, 0.35)	0.81

Study 3580

HbA1c (%). After 26 weeks of treatment, both IDeg and sitagliptin groups showed raw mean decreases in HbA1c from baseline (-1.58% and -1.23%, respectively). The HbA1c reduction at Week 26 was significantly greater in the IDeg group than in the sitagliptin group (treatment difference = -0.44%, $p < 0.0001$, Table 30). The superiority of IDeg to sitagliptin in patients with T2DM was established in this study since the upper bound of the 95% CI of the treatment difference was -0.25% (less than 0%). All other supportive analyses also showed similar results.

Table 30 – Study 3580 – Efficacy Results for HbA1c (%)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg Flex + OAD(s)	222	8.78 (1.01)	7.20 (1.01)	-1.58 (1.08)	-1.53 (0.10)
DPP-4 + OAD(s)	221	8.97 (1.01)	7.74 (1.19)	-1.23 (1.16)	-1.09 (0.10)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + OAD(s) vs. DPP-4 + OAD(s) (FAS w/ LOCF)			-0.44 (0.09)	(-0.62, -0.25)	< 0.0001
IDeg Flex + OAD(s) vs. DPP-4 + OAD(s) (Completers) [1]			-0.38 (0.09)	(-0.56, -0.19)	< 0.0001
IDeg Flex + OAD(s) vs. DPP-4 + OAD(s) (FAS using MMRM with UN option for variance-covariance structure)			-0.43 (0.10)	(-0.62, -0.24)	< 0.0001

The percentages of responders defined as patients with Week 26 HbA1c value < 7.0% or ≤ 6.5% were also significantly greater in the IDeg group than in the sitagliptin group (Table 31). However, there was no statistical difference between the 2 study groups in the % of

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patients achieving the target of HbA1c < 7.0% without confirmed hypoglycemic episodes during the last 12 weeks of treatment (24.9% vs. 22.9%).

Table 31 – Study 3580 – Responder Rates for HbA1c at Week 26

FAS with LOCF	IDeg Flex + OAD(s) (n = 222)	DPP-4 + OAD(s) (n = 221)	Difference in Proportion	Asymptotic 95% CI
HbA1c < 7.0%	92 (41.4%)	62 (28.1%)	13.4%	(4.6%, 22.2%)
HbA1c < 7.0% [1]	80 (36.0%)	56 (25.3%)	10.7%	(2.2%, 19.2%)
HbA1c ≤ 6.5%	63 (28.4%)	33 (14.9%)	13.4%	(5.9%, 21.0%)
[1] Worse case scenario: Treating subjects with missing HbA1c at endpoint (due to early dropout, for example) as non-responders even though their LOCF value could be < 7.0%				

FPG (mmol/L). A significantly greater reduction in mean FPG from baseline to Week 26 was observed in the IDeg group when compared with the sitagliptin group (treatment difference = -2.17 mmol/L, p < 0.0001, Table 32).

Table 32 – Study 3580 – Efficacy Results for FPG (mmol/L)

Treatment Group (FAS with LOCF)	N	Baseline (Week 0) Mean (SD)	Week 26 Mean (SD)	Change From Baseline	
				Mean (SD)	LS Mean (SE)
IDeg Flex + OAD(s)	220	9.45 (2.62)	6.22 (2.12)	-3.24 (3.17)	-3.42 (0.24)
DPP-4 + OAD(s)	218	9.92 (3.10)	8.53 (2.53)	-1.39 (3.11)	-1.25 (0.23)
			Treatment Difference		
Treatment Comparison			LS Mean (SE)	95% CI	p-value
IDeg Flex + OAD(s) vs. DPP-4 + OAD(s) (FAS w/ LOCF)			-2.17 (0.22)	(-2.60, -1.74)	< 0.0001

3.2 Evaluation of Safety

This reviewer's analysis results of hypoglycemic episodes, body weight, and insulin dose for each trial are summarized briefly in this section. Dr. Eugenio Andraca-Carrera from Division VII, Office of Biometrics, conducted meta-analyses for hypoglycemic episodes. See Drs. Jean-Marc Guettier and Karim Calis's medical reviews for complete safety evaluations for this NDA submission.

TYPE 1 DIABETES MELLITUS (T1DM)

Study 3583

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IGlar groups (0.92 and 0.94 years, respectively, p = 0.31). As shown in Table 33, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study

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groups were almost the same (95.6% in the IDeg group and 95.5% in the IGlar group). The number of confirmed events per subject and the event rate per year per subject between the 2 study groups were also not significantly different (p = 0.94 and 0.62, respectively, according to the Wilcoxon test). In addition, there was no significant difference in the rate of severe or nocturnal confirmed hypoglycemic episodes between the 2 study groups after 52 weeks of treatment according to either Fisher's exact test or Wilcoxon test.

Table 33 – Study 3583 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + IAsp	451/472 (95.6%)	18389/432.3 (42.5)
	IGlar + IAsp	147/154 (95.5%)	5796/144.3 (40.2)
Severe	IDeg + IAsp	58/472 (12.3%)	90/432.3 (0.21)
	IGlar + IAsp	16/154 (10.4%)	23/144.3 (0.16)
Nocturnal Confirmed	IDeg + IAsp	341/472 (72.2%)	1905/432.3 (4.41)
	IGlar + IAsp	114/154 (74.0%)	845/144.3 (5.86)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, IDeg was superior to IGlar in terms of a lower estimated rate of nocturnal confirmed hypoglycemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg / IGlar) was < 1 (estimated rate ratio = 0.75, 95% CI = [0.59, 0.96]).

Body Weight (kg). The raw mean weight gain at Week 52 was 1.79 ± 3.96 kg (n = 472) for the IDeg group and 1.62 ± 4.29 kg (n = 154) for the IGlar group. Although the gain was numerically greater in the IDeg group than in the IGlar group, the difference was not statistically significant (treatment difference = +0.15 kg, p = 0.69).

Insulin Dose (U). At the end of Week 52, the mean total daily insulin dose was increased by 4.2 U from baseline to 61.4 U in the IDeg group and by 10.5 U from baseline to 66.2 U in the IGlar group (Table 34).

Table 34 – Study 3583 – Dose (U)

	IDeg + IAsp (n = 470)			IGlar + IAsp (n = 154)		
	Week 1	Week 52	Change	Week 1	Week 52	Change
Basal Insulin	28.1 ± 13.9	29.2 ± 17.0	1.2 ± 11.2	26.3 ± 13.0	31.4 ± 17.7	5.1 ± 12.6
Bolus Insulin	29.2 ± 17.1	32.4 ± 21.4	3.2 ± 17.7	29.4 ± 15.1	34.9 ± 21.4	5.5 ± 16.5
Total Insulin	57.2 ± 26.0	61.4 ± 33.8	4.2 ± 21.3	55.7 ± 23.1	66.2 ± 34.4	10.5 ± 22.2

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Study 3585

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IDet groups (0.48 and 0.47 years, respectively, p = 0.24). As shown in Table 35, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study groups were comparable (93.0% in the IDeg group and 91.4% in the IDet group, p = 0.57 according to the Fisher's Exact test). The number of confirmed events per subject and the event rate per year per subject between the 2 study groups were also not statistically different (p = 0.27 and 0.40, respectively, according to the Wilcoxon test). In addition, there was no significant difference in the rate of severe or nocturnal confirmed hypoglycemic episodes between the 2 study groups after 26 weeks of treatment according to either Fisher's exact test or Wilcoxon test.

Table 35 – Study 3585 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + IAsp	280/301 (93.0%)	6673/145.6 (45.8)
	IDet + IAsp	139/152 (91.4%)	3295/72.1 (45.7)
Severe	IDeg + IAsp	32/301 (10.6%)	45/145.6 (0.31)
	IDet + IAsp	16/152 (10.5%)	28/72.1 (0.39)
Nocturnal Confirmed	IDeg + IAsp	176/301 (58.5%)	603/145.6 (4.14)
	IDet + IAsp	89/152 (58.6%)	428/72.1 (5.94)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, IDeg was superior to IDet in terms of a lower estimated rate of nocturnal confirmed hypoglycemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg / IGlar) was < 1 (estimated rate ratio = 0.66, 95% CI = [0.49, 0.88]).

Body Weight (kg). The raw mean weight gain at Week 26 was 1.51 ± 2.66 kg (n = 301) for the IDeg group and 0.43 ± 2.36 kg (n = 152) for the IDet group. The gain at Week 26 in the IDeg group was significantly greater than that in the IDet group (treatment difference = +1.08 kg, p < 0.0001).

Insulin Dose (U). At the end of Week 26, the mean total daily insulin dose was increased by 10.0 U from baseline to 60.2 U in the IDeg group and by 16.2 U from baseline to 68.2 U in the IDet group (Table 36).

Table 36 – Study 3585 – Dose (U)

	IDeg + IAsp (n = 298)	IDet + IAsp (n = 149)

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	Week 1	Week 26	Change	Week 1	Week 26	Change
Basal Insulin	22.3 ± 12.2	24.9 ± 15.6	2.7 ± 11.1	21.6 ± 11.9	28.7 ± 19.8	7.1 ± 11.9
Bolus Insulin	28.1 ± 14.5	35.6 ± 25.1	7.5 ± 19.6	30.5 ± 15.4	40.4 ± 23.8	9.9 ± 21.8
Total Insulin	50.2 ± 21.7	60.2 ± 35.4	10.0 ± 25.7	52.0 ± 22.7	68.2 ± 37.4	16.2 ± 27.2

Study 3770

Hypoglycemic Episodes. The mean duration of exposure in years were statistically different among the IDeg Flex, IDeg, and IGlar groups (0.44, 0.46, and 0.49 years, respectively, p = 0.0015). As shown in Table 37, the % of subjects experiencing at least 1 confirmed hypoglycemic episode were comparable between either of the two IDeg groups and the IGlar group, but not when the IDeg Flex group (93.9%) was compared with the IDeg group (99.4%, p = 0.006 according to the Fisher's Exact test). However, the number of confirmed events per subject and the event rate per year per subject were comparable among the 3 study groups (all p > 0.05 according to the Wilcoxon test). In addition, there were also no significant differences in the rate of severe hypoglycemic episodes among the 3 study groups after 26 weeks of treatment. A significantly lower number of nocturnal confirmed events was observed in the IDeg Flex group when compared with the IGlar group according to the Wilcoxon test, although the % of subjects experiencing at least 1 episode were similar among the 3 study groups.

Table 37 – Study 3770 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg Flex + IAsp	154/164 (93.9%)	5988/72.7 (82.4)
	IDeg + IAsp	164/165 (99.4%)	6724/76.2 (88.2)
	IGlar + IAsp	156/161 (96.9%)	6263/78.5 (79.8)
Severe	IDeg Flex + IAsp	17/164 (10.4%)	25/72.7 (0.34)
	IDeg + IAsp	21/165 (12.7%)	28/76.2 (0.37)
	IGlar + IAsp	16/161 (9.9%)	37/78.5 (0.47)
Nocturnal Confirmed	IDeg Flex + IAsp	111/164 (67.7%)	453/72.7 (6.23)
	IDeg + IAsp	121/165 (73.3%)	732/76.2 (9.61)
	IGlar + IAsp	117/161 (72.7%)	782/78.5 (9.96)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, IDeg Flex was superior to IGlar in terms of a lower estimated rate of nocturnal confirmed hypoglycemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg / IGlar) was < 1 (estimated rate ratio = 0.60, 95% CI = [0.44, 0.82]). Similarly, IDeg Flex was

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also superior to IDeg in terms of a lower rate of nocturnal confirmed hypoglycemia since the estimated rate ratio was 0.63 with 95% CI = (0.46, 0.86).

Body Weight (kg). The raw mean weight gain at Week 26 was 1.16 ± 3.47 kg (n = 164) for the IDeg Flex group, 0.79 ± 2.53 kg (n = 165) for the IDeg group, and 1.64 ± 3.69 kg (n = 161) for the IGlar group. The gain at Week 26 in the IDeg Flex group was not significantly different from that in the IGlar group (treatment difference = -0.46 kg, p = 0.21) or in the IDeg group (treatment difference = +0.33 kg, p = 0.36). However, the gain at Week 26 in the IDeg group was significantly less than that in the IGlar group (treatment difference = -0.79 kg, p = 0.03).

Insulin Dose (U). At the end of Week 26, the mean total daily insulin dose was increased by 3.7 U from baseline to 65.2 U in the IDeg Flex group, by 1.7 U from baseline to 58.5 U in the IDeg group, and by 8.6 U from baseline to 69.9 U in the IGlar group (Table 38).

Table 38 – Study 3770 – Dose (U)

	IDeg Flex + IAsp (n = 159)			IDeg + IAsp (n = 165)			IGlar + IAsp (n = 160)		
	Week 1	Week 26	Change	Week 1	Week 26	Change	Week 1	Week 26	Change
Basal Insulin	28.9 ± 18.5	35.6 ± 26.2	6.6 ± 14.3	27.9 ± 14.4	31.9 ± 25.1	4.0 ± 17.8	28.8 ± 14.1	35.0 ± 21.3	6.2 ± 15.3
Bolus Insulin	32.8 ± 25.1	29.4 ± 15.6	-3.4 ± 23.1	29.3 ± 21.2	26.8 ± 22.1	-2.5 ± 17.8	32.5 ± 16.5	35.0 ± 35.9	2.5 ± 35.6
Total Insulin	61.6 ± 35.4	65.2 ± 36.2	3.7 ± 27.4	56.8 ± 28.5	58.5 ± 41.3	1.7 ± 27.8	61.3 ± 24.9	69.9 ± 51.0	8.6 ± 46.3

TYPE 2 DIABETES MELLITUS (T2DM)

Study 3582

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IGlar groups (0.89 and 0.92 years, respectively, p = 0.23). As shown in Table 39, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study groups were comparable (81.9% in the IDeg group and 83.1% in the IGlar group, p = 0.77 according to the Fisher's Exact test). The number of confirmed events per subject and the event rate per year per subject between the 2 study groups were also not significantly different (both p = 0.11 according to the Wilcoxon test). In addition, there was no significant difference in the rate of severe hypoglycemic episodes between the 2 study groups after 52 weeks of treatment. A significantly lower % of subjects experiencing at least 1 nocturnal confirmed hypoglycemic episode was observed in the IDeg group (40.2%) when compared with the IGlar group (48.0%, p = 0.03 according to the Fisher's Exact test). The number of

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nocturnal confirmed events per subject and the event rate per year per subject were also significantly lower in the IDeg group when compared with the IGlar group ($p < 0.05$ according to the Wilcoxon test).

Table 39 – Study 3582 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + IAsp ± OAD(s)	608/742 (81.9%)	7436/664.0 (11.2)
	IGlar + IAsp ± OAD(s)	206/248 (83.1%)	3120/227.3 (13.7)
Severe	IDeg + IAsp ± OAD(s)	34/742 (4.6%)	41/664.0 (0.06)
	IGlar + IAsp ± OAD(s)	11/248 (4.4%)	12/227.3 (0.05)
Nocturnal Confirmed	IDeg + IAsp ± OAD(s)	298/742 (40.2%)	930/664.0 (1.40)
	IGlar + IAsp ± OAD(s)	119/248 (48.0%)	422/227.3 (1.86)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, IDeg was superior to IGlar in terms of a lower estimated rate of confirmed hypoglycemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg / IGlar) was < 1 (estimated rate ratio = 0.82, 95% CI = [0.69, 0.99]). Similarly, IDeg was also superior to IGlar in terms of a lower rate of nocturnal confirmed hypoglycemia since the estimated rate ratio was 0.75 with 95% CI = (0.58, 0.99).

Body Weight (kg). The raw mean weight gain at Week 52 was 3.62 ± 4.86 kg (n = 742) for the IDeg group and 3.97 ± 4.57 kg (n = 248) for the IGlar group. Although the gain was numerically less in the IDeg group than in the IGlar group, the difference was not statistically significant (treatment difference = -0.30 kg, p = 0.39).

Insulin Dose (U). At the end of Week 52, the mean total daily insulin dose was increased by 67.2 U from baseline to 141.3 U in the IDeg group and by 64.6 U from baseline to 137.8 U in the IGlar group (Table 40).

Table 40 – Study 3582 – Dose (U)

	IDeg + IAsp ± OAD(s) (n = 740)			IGlar + IAsp ± OAD(s) (n = 246)		
	Week 1	Week 52	Change	Week 1	Week 52	Change
Basal Insulin	41.3 ± 26.4	72.5 ± 45.8	31.1 ± 33.4	40.2 ± 27.1	66.2 ± 41.8	25.9 ± 29.9
Bolus Insulin	33.0 ± 28.8	69.2 ± 55.7	36.2 ± 50.4	33.2 ± 30.7	72.5 ± 62.6	39.3 ± 51.6
Total Insulin	74.1 ± 45.6	141.3 ± 93.1	67.2 ± 73.3	73.2 ± 49.2	137.8 ± 98.2	64.6 ± 73.3

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Study 3579

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IGlar groups (0.87 and 0.85 years, respectively, p = 0.27). As shown in Table 41, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study groups were almost the same (46.5% in the IDeg group and 46.3% in the IGlar group). The number of confirmed events per subject and the event rate per year per subject between the 2 study groups were also not significantly different (p = 0.9 and 1.0, respectively, according to the Wilcoxon test). There were very few severe hypoglycemic episodes reported in this trial, 2 events by 2 subjects in the IDeg group and 5 events by 5 subjects in the IGlar groups. However, since this was a 3:1 randomization trial, the rate of severe hypoglycemic episodes in the IDeg group appeared to be much smaller than that in the IGlar group. There was no significant difference in the rate of nocturnal confirmed hypoglycemic episodes between the 2 study groups after 52 weeks of treatment according to either Fisher's exact test or Wilcoxon test.

Table 41 – Study 3579 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + OAD(s)	356/766 (46.5%)	1014/667.2 (1.52)
	IGlar + OAD(s)	119/257 (46.3%)	403/217.9 (1.85)
Severe	IDeg + OAD(s)	2/766 (0.3%)	2/667.2 (0.003)
	IGlar + OAD(s)	5/257 (1.9%)	5/217.9 (0.023)
Nocturnal Confirmed	IDeg + OAD(s)	106/766 (13.8%)	169/667.2 (0.25)
	IGlar + OAD(s)	39/257 (15.2%)	84/217.9 (0.39)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, IDeg was superior to IGlar in terms of a lower estimated rate of nocturnal confirmed hypoglycemic episodes as the upper limit of the 95% CI for the estimated rate ratio (IDeg / IGlar) was < 1 (estimated rate ratio = 0.64, 95% CI = [0.42, 0.98]).

Body Weight (kg). The raw mean weight gain at Week 52 was 2.35 ± 4.32 kg (n = 766) for the IDeg group and 2.12 ± 4.09 kg (n = 257) for the IGlar group. Although the gain was numerically greater in the IDeg group than in the IGlar group, the difference was not statistically significant (treatment difference = +0.30 kg, p = 0.33).

Insulin Dose (U). At the end of Week 52, the mean daily basal insulin dose was increased by 45.8 U from baseline to 55.9 U in the IDeg group and by 47.8 U from baseline to 57.8 U in the IGlar group.

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Study 3672

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IGlar groups (0.46 and 0.47 years, respectively, p = 0.57). As shown in Table 42, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study groups were comparable (28.5% in the IDeg group and 30.7% in the IGlar group, p = 0.68 according to the Fisher's Exact test). The number of confirmed events per subject and the event rate per year per subject between the 2 study groups were also not significantly different (both p = 0.6 according to the Wilcoxon test). No severe hypoglycemic episode was reported in either treatment group. There was no significant difference in the rate of nocturnal confirmed hypoglycemic episodes between the 2 study groups after 26 weeks of treatment.

Table 42 – Study 3672 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + OAD(s)	65/228 (28.5%)	129/105.7 (1.22)
	IGlar + OAD(s)	70/228 (30.7%)	152/106.9 (1.42)
Severe	IDeg + OAD(s)	0/228 (0%)	0/105.7 (0)
	IGlar + OAD(s)	0/228 (0%)	0/106.9 (0)
Nocturnal Confirmed	IDeg + OAD(s)	14/228 (6.1%)	19/105.7 (0.18)
	IGlar + OAD(s)	20/228 (8.8%)	30/106.9 (0.28)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Body Weight (kg). The raw mean weight gain at Week 26 was 1.87 ± 3.47 kg (n = 228) for the IDeg group and 1.48 ± 3.49 kg (n = 228) for the IGlar group. Although the gain was numerically greater in the IDeg group than in the IGlar group, the difference was not statistically significant (treatment difference = +0.44 kg, p = 0.18).

Insulin Dose (U). At the end of Week 26, the mean daily basal insulin dose was increased by 49.4 U from baseline to 59.5 U in the IDeg group and by 52.6 U from baseline to 62.7 U in the IGlar group.

Study 3586

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and IGlar groups (0.47 and 0.48 years, respectively, p = 0.22). As shown in Table 43, the % of subjects experiencing at least 1 confirmed hypoglycemic episode in the 2 study groups were comparable (50.0% in the IDeg group and 53.4% in the IGlar group, p = 0.54 according to the Fisher's Exact test). The number of confirmed events per subject and the

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event rate per year per subject between the 2 study groups were also not significantly different (both p = 0.2 according to the Wilcoxon test). There was no significant difference in the rate of severe or nocturnal confirmed hypoglycemic episodes between the 2 study groups after 26 weeks of treatment.

Table 43 – Study 3586 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg + OAD(s)	142/284 (50.0%)	397/133.4 (2.98)
	IGlar + OAD(s)	78/146 (53.4%)	260/70.3 (3.70)
Severe	IDeg + OAD(s)	0/284 (0%)	0/133.4 (0)
	IGlar + OAD(s)	1/146 (0.7%)	1/70.3 (0.01)
Nocturnal Confirmed	IDeg + OAD(s)	58/284 (20.4%)	104/133.4 (0.78)
	IGlar + OAD(s)	35/146 (24.0%)	87/70.3 (1.24)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Body Weight (kg). The raw mean weight gain at Week 26 was 1.31 ± 2.20 kg (n = 284) for the IDeg group and 1.41 ± 2.15 kg (n = 146) for the IGlar group. Although the gain was numerically less in the IDeg group than in the IGlar group, the difference was not statistically significant (treatment difference = -0.14 kg, p = 0.51).

Insulin Dose (U). At the end of Week 26, the mean daily basal insulin dose was increased by 10.0 U from baseline to 18.9 U in the IDeg group and by 15.3 U from baseline to 24.2 U in the IGlar group.

Study 3668

Hypoglycemic Episodes. The mean duration of exposure in years were similar among the IDeg Flex, IDeg, and IGlar groups (0.46 years in each group, p = 0.93). There were no statistically significant differences in the rate of confirmed hypoglycemic episodes among the 3 study groups after 26 weeks of treatment (Table 44, all p > 0.05 for either Fisher's Exact test or Wilcoxon test). The numbers of severe hypoglycemic episodes were too few in each study group to have any valid comparison. The rates of nocturnal confirmed hypoglycemic episodes in the two IDeg groups were significantly lower than that in the IGlar group, but were similar with each other.

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Table 44 – Study 3668 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg Flex + OAD(s)	117/228 (51.3%)	388/105.8 (3.67)
	IDeg + OAD(s)	99/228 (43.4%)	378/104.9 (3.60)
	IGlar + OAD(s)	113/229 (49.3%)	368/105.6 (3.48)
Severe	IDeg Flex + OAD(s)	1/228 (0.44%)	2/105.8 (0.02)
	IDeg + OAD(s)	2/228 (0.88%)	2/104.9 (0.02)
	IGlar + OAD(s)	2/229 (0.87%)	2/105.6 (0.02)
Nocturnal Confirmed	IDeg Flex + OAD(s)	31/228 (13.6%)	67/105.8 (0.63)
	IDeg + OAD(s)	24/228 (10.5%)	58/104.9 (0.55)
	IGlar + OAD(s)	49/229 (21.4%)	79/105.6 (0.75)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, the estimated rate of nocturnal confirmed hypoglycemic episodes in the IDeg Flex group was similar to that in the IGlar (estimated rate ratio = 0.77, 95% CI = [0.44, 1.35]) and IDeg (estimated rate ratio = 1.18, 95% CI = [0.66, 2.12]) groups.

Body Weight (kg). The raw mean weight gain at Week 26 was 1.52 ± 3.04 kg (n = 228) for the IDeg Flex group, 1.56 ± 2.77 kg (n = 228) for the IDeg group, and 1.27 ± 2.80 kg (n = 229) for the IGlar group. Although the mean gains at Week 26 were numerically higher in the two IDeg groups when compared with the IGlar group, they were all statistically comparable among each other.

Insulin Dose (U). At the end of Week 26, the mean daily basal insulin dose was increased by 27.1 U from baseline to 45.6 U in the IDeg Flex group, by 24.1 U from baseline to 45.5 U in the IDeg group, and by 26.0 U from baseline to 44.6 U in the IGlar group.

Study 3580

Hypoglycemic Episodes. The mean duration of exposure in years were similar between the IDeg and sitagliptin groups (0.45 and 0.43 years, respectively, p = 0.11). As shown in Table 45, the IDeg group had significantly higher incidence/event rates of confirmed and nocturnal confirmed hypoglycemic episodes than the sitagliptin group. There was only 1 severe hypoglycemic episode reported in the study and it occurred in the IDeg group.

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Table 45 – Study 3580 – Hypoglycemic Episodes

Hypoglycemia	Treatment Group	Incidence Rate [1]	Event Rate [2]
Confirmed	IDeg Flex + OAD(s)	96/222 (43.2%)	311/99.5 (3.13)
	DPP-4 + OAD(s)	29/221 (13.1%)	123/94.9 (1.30)
Severe	IDeg Flex + OAD(s)	1/222 (0.5%)	1/99.5 (0.01)
	DPP-4 + OAD(s)	0/221 (0%)	0/94.9 (0)
Nocturnal Confirmed	IDeg Flex + OAD(s)	29/222 (13.1%)	53/99.5 (0.53)
	DPP-4 + OAD(s)	13/221 (5.9%)	29/94.9 (0.31)

[1] Simple crude rate (# of pts with events / total # of pts)
[2] Calculated as total # of events / total exposure in year

Note that based on the sponsor's analysis using a negative binominal regression model, no statistically significant difference was observed in the estimated rate of nocturnal confirmed hypoglycemic episodes between the IDeg Flex and sitagliptin groups. The estimated rate ratio was = 1.93 with 95% CI = (0.90, 4.10).

Body Weight (kg). The raw mean body weight at Week 26 was increased from baseline in the IDeg group (2.32 ± 4.45 kg (n = 222)), while it was decreased in the sitagliptin group (-0.35 ± 3.92 kg (n = 221)). The difference in mean change at Week 26 between the 2 study groups was statistically significant ($p < 0.0001$).

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4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, and Age

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 $p > 0.10$).

4.2 Other Special/Subgroup Populations

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.

In response to the medical reviewer's request, subgroup analyses for baseline HbA1c (≤ 7%, 7 – 10%, ≥ 10%) were also conducted. No significant treatment-by-baseline HbA1c interactions were observed in all trials ($p > 0.10$), except for Studies 3579 and 3668 where the interaction terms were $p = 0.03$ and 0.06, respectively. As shown in Table 46, the differences in treatment effect on mean change in HbA1c in Study 3579 were quantitative, not qualitative among the 3 subgroups. However, in study 3668, the differences in treatment effect were more a qualitative issue, meaning that the treatment effects were in different direction among the 3 subgroups. Nevertheless, in both studies, the higher the baseline HbA1c was, the greater was the reduction in HbA1c at endpoint.

Table 46 – LS Mean Change ± SE from Baseline in HbA1c at Endpoint by Baseline HbA1c Subgroup

Baseline HbA1c	Study 3579 (52-week)			Study 3668 (26-week)		
	≤ 7%	7% – 10%	≥ 10%	≤ 7%	7% – 10%	≥ 10%
IDeg Flex	--	--	--	0.08 ± 0.33 (n = 8)	-1.09 ± 0.09 (n = 204)	-2.98 ± 0.23 (n = 16)
IDeg	-0.24 ± 0.15 (n = 44)	-1.10 ± 0.04 (n = 709)	-1.45 ± 0.27 (n = 13)	-0.30 ± 0.34 (n = 7)	-0.93 ± 0.08 (n = 207)	-1.92 ± 0.25 (n = 14)
IGlar	-0.53 ± 0.33 (n = 9)	-1.17 ± 0.06 (n = 245)	-3.16 ± 0.57 (n = 3)	-0.01 ± 0.28 (n = 11)	-1.12 ± 0.09 (n = 205)	-2.68 ± 0.26 (n = 13)
IDeg Flex vs. IGlar	--	--	--	0.09 ± 0.42	0.04 ± 0.09	-0.30 ± 0.34
IDeg vs. IGlar	0.29 ± 0.36	0.07 ± 0.07	1.72 ± 0.63	-0.30 ± 0.44	0.19 ± 0.09	0.76 ± 0.35

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5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

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

HbA1c. Table 47 below shows the mean HbA1c at baseline and endpoint as well as the mean changes from baseline for all trials. Table 48 shows the statistical hypothesis testing results for HbA1c for all trials using the FAS population (randomized and exposed) with LOCF.

As shown in Table 47, 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%).

As depicted graphically in Appendix III, 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 (note: due to low dropout rates, the presentations based on the ITT/LOCF populations here as opposed to completers are adequate). 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 <u>less</u>, but not statistically significant, in the IDeg group than in the IGlar 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 <u>greater</u>, but not statistically significant, in the IDeg group than in the IGlar or IDet groups. Non-inferiority of IDeg in lowering HbA1c was established in these trials since the upper

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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 IGlar 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 IGlar 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 IGlar 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 IGlar group in both studies. However, if the same NI criterion was applied, IDeg could be shown to be clinically non-inferior to IGlar 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%.

Note that flexible dosing regimen was investigated in Studies 3770, 3668, and 3580. Studies 3770 and 3668 used fixed-flexible method, while Study 3580 used free-flexible method. The fixed-flexible dose was injected in the morning on Mondays, Wednesdays, and Fridays, and in the evening on Tuesdays, Thursdays, Saturdays, and Sundays. The free-flexible dose was injected at *any time* of the day and at varying times from day to day. Either method required a minimum of 8 hours and a maximum of 40 hours interval between doses.

As shown in Table 49, 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 sitaglitpin group. The findings from

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responders across trials were somewhat in line with the findings from the continuous HbA1c variable discussed above.

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Table 47 – 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.

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Table 48 – 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	• IDeg + IAsp (472) • IGlar + IAsp (154)	Non-inferiority	-0.01 (0.07)	(-0.14, 0.12)	0.8800	➢ NI
3585	26-week	• IDeg + IAsp (301) • IDet + IAsp (152)	Non-inferiority	-0.08 (0.07)	(-0.23, 0.06)	0.2546	➢ NI
3770	26-week	• IDeg Flex + IAsp (164) • IDeg + IAsp (165) • IGlar + IAsp (161)	Non-inferiority	IDeg Flex vs. IGlar (*primary*): +0.17 (0.07) IDeg vs. IGlar (additional): +0.17 (0.07)	(0.04, 0.31) (0.04, 0.30)	0.0102 0.0119	➢ NI for both endpoints ➢ Statistically worse for both IDeg Flex and IDeg
Type 2 Diabetes Mellitus (T2DM)							
3582	52-week	• 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	• IDeg + OAD(s) (766) • IGlar + OAD(s) (257)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.21)	0.2293	➢ NI
3672	26-week	• 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	• IDeg + OAD(s) (284) • IGlar + OAD(s) (146)	Non-inferiority	+0.08 (0.07)	(-0.05, 0.22)	0.2177	➢ NI
3668	26-week	• IDeg Flex + OAD(s) (228) • IDeg + OAD(s) (228) • IGlar + OAD(s) (229)	Non-inferiority	IDeg Flex vs. IGlar (*primary*): +0.04 (0.08) IDeg vs. IGlar (additional): +0.18 (0.08)	(-0.12, 0.19) (0.02, 0.33)	0.6421 0.0244	➢ NI for both endpoints ➢ Statistically worse for IDeg, but not for IDeg Flex
3580	26-week	• 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.

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Table 49 – 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] 61/165 (37.0%)	65/161 (40.4%)	-3.2% -3.4%	(-13.8%, 7.4%) (-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] 93/228 (40.8%)	101/229 (44.1%)	-5.1% -3.3%	(-14.1%, 4.0%) (-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. As depicted in Appendix IV, 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 50 below summarizes the statistical results of mean change from baseline in FPG at endpoint, favoring the treatment with IDeg.

Table 50 – Efficacy Results for FPG (mmol/L) across Trials

DM[b]	Study	LS Mean Chang from Baseline ± SE (n)		Treatment Diff		
		IDeg	Comparator	LS Mean ± SE	95% CI	p-value
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] -2.34 ± 0.30 (164)	-1.41 ± 0.30 (160)	+0.01 ± 0.41 -0.93 ± 0.41	(-0.80, 0.82) (-1.73, -0.13)	0.98 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] -3.01 ± 0.19 (228)	-2.64 ± 0.20 (225)	-0.42 ± 0.20 -0.37 ± 0.20	(-0.82, -0.02) (-0.77, 0.03)	0.04 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

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Body Weight. As depicted in Appendix V, 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 51 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 51 – Results for Body Weight (kg) across Trials

DM[b]	Study	LS Mean Chang from Baseline ± SE (n)		Treatment Diff		
		IDeg	Comparator	LS Mean ± SE	95% CI	p-value
T1	3583	2.13 ± 0.30 (472)	1.98 ± 0.40 (154)	+0.15 ± 0.37	(-0.58, 0.88)	0.69
T1	3585	1.51 ± 0.20 (301)	0.43 ± 0.24 (152)	+1.08 ± 0.25	(0.58, 1.58)	< 0.0001
T1	3770	1.27 ± 0.26 (164) [a]	1.72 ± 0.27 (161)	-0.46 ± 0.36	(-1.17, 0.25)	0.21
		0.94 ± 0.26 (165)		-0.79 ± 0.36	(-1.49, -0.08)	0.03
T2	3582	3.24 ± 0.33 (742)	3.54 ± 0.41 (248)	-0.30 ± 0.34	(-0.97, 0.38)	0.39
T2	3579	2.59 ± 0.17 (766)	2.29 ± 0.27 (257)	+0.30 ± 0.31	(-0.30, 0.90)	0.33
T2	3672	2.30 ± 0.36 (228)	1.86 ± 0.35 (228)	+0.44 ± 0.33	(-0.21, 1.08)	0.18
T2	3586	1.57 ± 0.18 (284)	1.71 ± 0.21 (146)	-0.14 ± 0.22	(-0.57, 0.29)	0.51
T2	3668	1.87 ± 0.27 (228) [a]	1.59 ± 0.26 (229)	+0.27 ± 0.27	(-0.25, 0.80)	0.31
		1.87 ± 0.26 (228)		+0.27 ± 0.27	(-0.25, 0.80)	0.31
T2	3580	2.72 ± 0.44 (222)	-0.06 ± 0.43 (221)	+2.78 ± 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 studies ($p > 0.05$ 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 52).

Table 52 – Results for Confirmed Hypoglycemic Episodes across Trials

DM[b]	Study	IDeg		Comparator	
		Incidence Rate [c]	Event Rate [d]	Incidence Rate [c]	Event Rate [d]

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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 53, 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 53 – 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

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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 54).

Table 54 – 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] 121/165 (73.3%)	453/72.7 (6.23) [a] 732/76.2 (9.61)	117/161 (72.7%)	782/78.5 (9.96)
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] 24/228 (10.5%)	67/105.8 (0.63) [a] 58/104.9 (0.55)	49/229 (21.4%)	79/105.6 (0.75)
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 VI, the mean daily basal insulin doses were consistently lower in the IDeg group than in the IGlar 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 (IGlar 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 IGlar 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 IGlar, and consequently the total daily insulin doses, throughout the trial.

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

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FAS/LOCF population, indicating that the dropouts in each study did not have any major impact on the reduction of HbA1c.

5.2 Conclusions and Recommendations

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.

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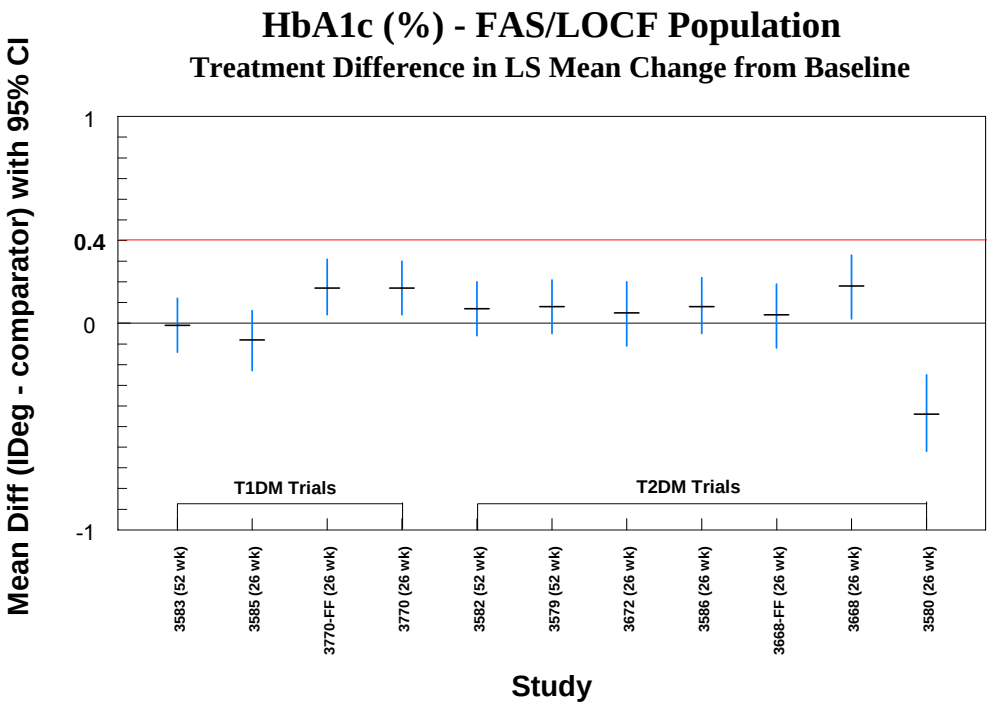
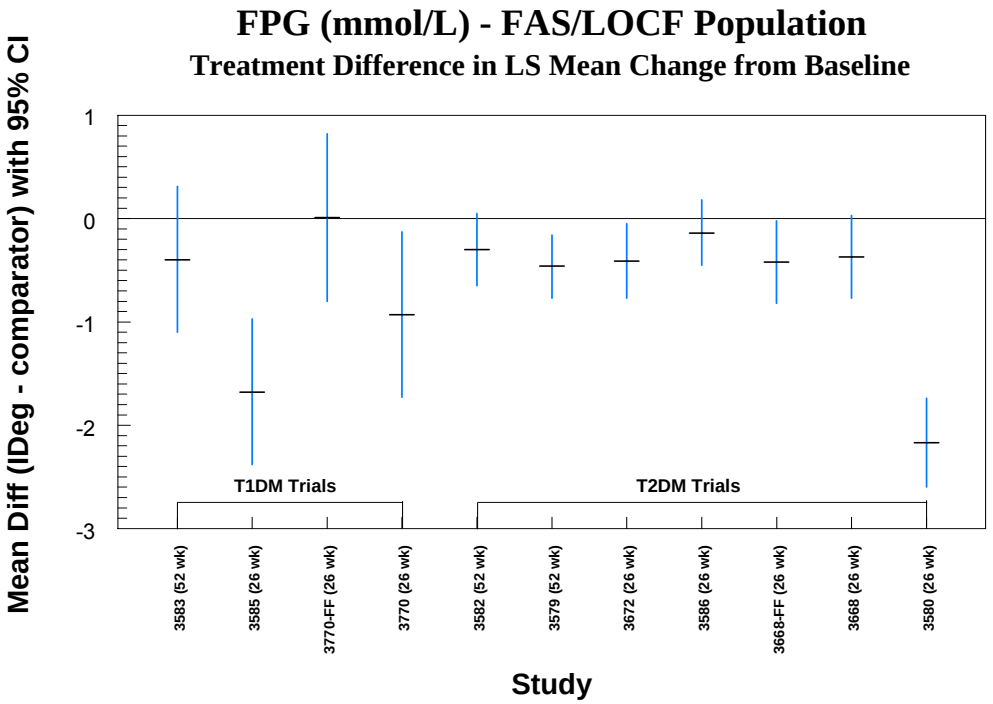


Note 1 Except that 3770-FF, 3668-FF, and 3580 were IDeg flexible dosing, all others were fixed dosing.
Note 2 Except for 3580 a superiority trial, all others were NI trials.
Note 3 Treatment difference above 0 favored the comparator.



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.

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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.

5.3 Labeling Comments

The following bullets summarize this reviewer's comments for the sponsor's proposed labeling in the Clinical Studies section.

- There is [redacted] (b) (4) for Study 3770, only the text. In addition, [redacted] (b) (4) was included for Study 3586.

- The total N (sample size) reported in Tables 8 – 13 [redacted] (b) (4) were reported for HbA1c and FPG.

- For Studies 3770 and 3668, [redacted] (b) (4). This reviewer does not think the statement is correct because the mean reductions in both IDeg and IDeg Flex groups in Study 3770 and the IDeg group in Study 3668 were actually statistically significantly less than that in the IGlar group. However, IDeg Flex was clinically non-inferior to IGlar according to the pre-specified non-inferiority margin. If the

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same criterion were applied, clinical non-inferiority of IDeg to IGlar could have also been shown in these two studies.

- Since hypoglycemia is a more subjective endpoint than a lab value, and there were no consistently significant findings across the open-label trials, this reviewer thinks that the results should be described descriptively.

- The testing sequence of the confirmatory secondary endpoints was prioritized differently from trial to trial and the sponsor flagged the significance for the parameters accordingly. Since the testing order is not presented in the labeling, it is confusing to understand why some significant results are not being flagged in the tables. Therefore, this reviewer suggests only descriptive statistics be used for the non-primary endpoints.

- (b) (4) . It may be necessary to separate safety parameters from efficacy tables.

Primary Statistical Reviewer: Cynthia Liu, MA

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

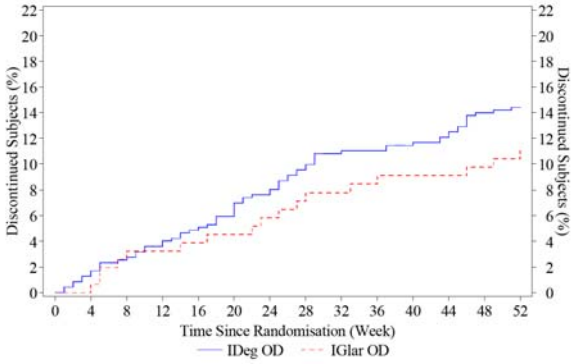
CC: HFD-510/RHartford, MParks, JMGuettier, KCalis
HFD-715/TPermutt, TSahlroot, CLiu
HFD-700/LPatrician

Reference ID: 3216499

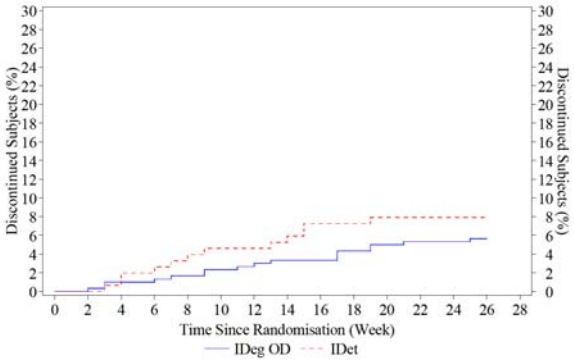
6. APPENDIX I

Time to Discontinuation – Full Analysis Set (Sponsor's Graphs)

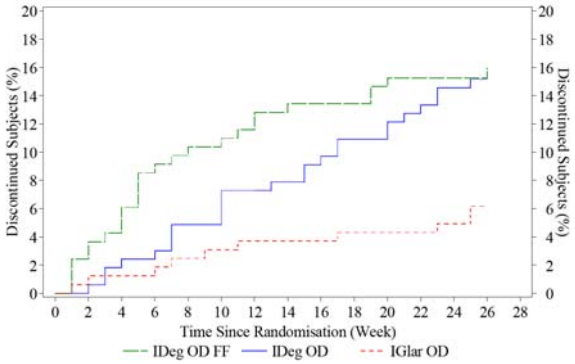
Study 3583 (T1DM)



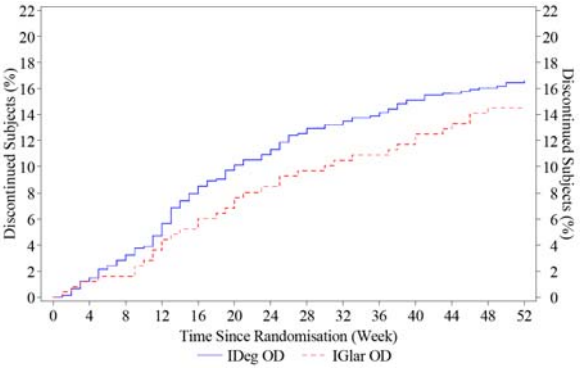
Study 3585 (T1DM)



Study 3770 (T1DM)

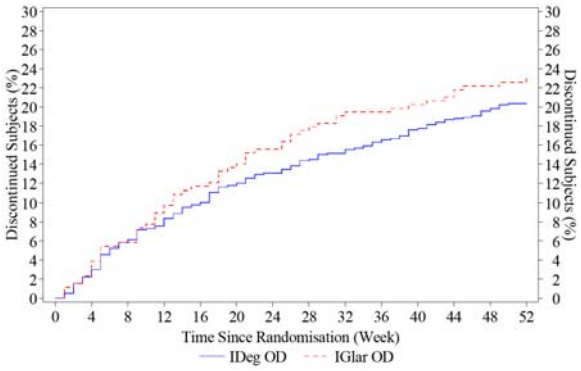


Study 3582 (T2DM)

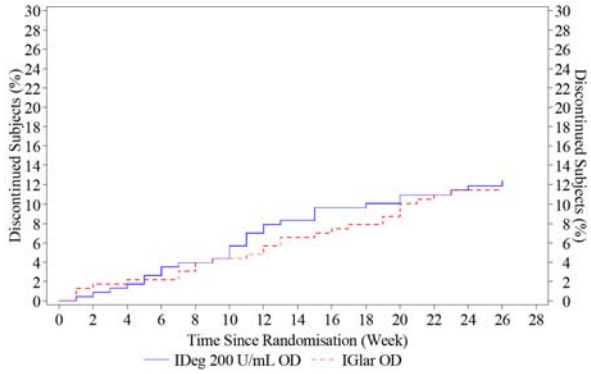


Site 109 (11 IDeg, 3 IGlar) was excluded due to data quality issue.

Study 3579 (T2DM)



Study 3672 (T2DM)



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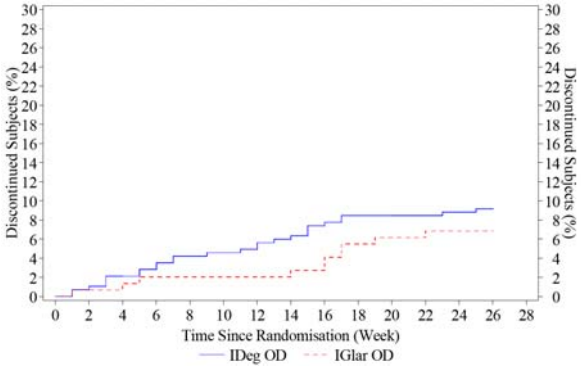
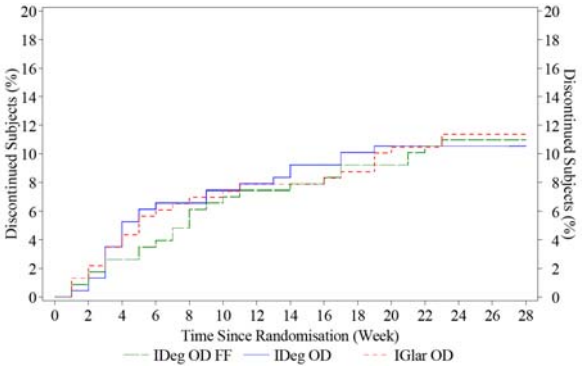
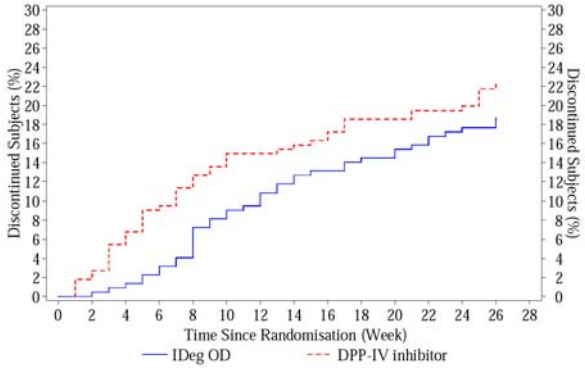
Study 3586 (T2DM)



Study 3668 (T2DM)



Study 3580 (T2DM)



Site 704 (4 IDeg, 7 sita) was excluded due to data quality issue.

Reference ID: 3216499

7. APPENDIX II

Sponsor's Results Summary

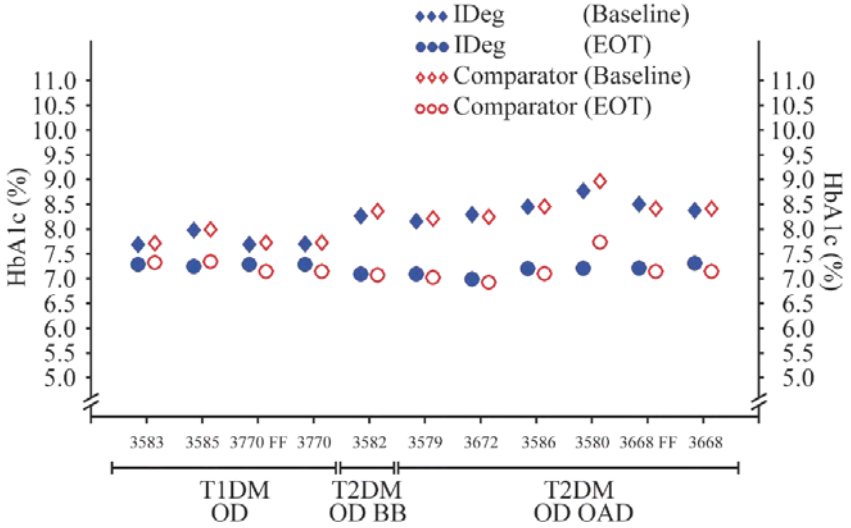
Sponsor's Table 4-2 in Clinical Overview
HbA1c (%) Change from Baseline at End-of-trial – IDeg OD – Statistical Analysis - FAS

	IDeg		Comparator		IDeg - Comparator	
Trial (wks)	N	LSMEAN (SE)	N	LSMEAN (SE)	Contrast	95% CI
T1DM						
3583 (52)	472	-0.36 (0.05)	157	-0.34 (0.07)	-0.01	[-0.14; 0.11]
3585 (26)	302	-0.71 (0.06)	153	-0.61 (0.07)	-0.09	[-0.23; 0.05]
3770 (26) IDeg FF - IGlar	164	-0.40 (0.05)	164	-0.57 (0.05)	0.17	[0.04; 0.30]*
3770 (26) IDeg FF - IDeg			165	-0.41 (0.05)	0.01	[-0.13; 0.14]
T2DM						
Basal-bolus therapy ± OADs						
3582 (52)	744	-1.10 (0.06)	248	-1.18 (0.08)	0.08	[-0.05; 0.21]
OAD-insulin combination therapy						
3579 (52)	773	-1.06 (0.04)	257	-1.15 (0.06)	0.09	[-0.04; 0.22]
3672 (26)	228	-1.18 (0.09)	229	-1.22 (0.08)	0.04	[-0.11; 0.19]
3586 (26)	289	-1.42 (0.06)	146	-1.52 (0.07)	0.11	[-0.03; 0.24]
3580 (26)	225	-1.52 (0.10)	222	-1.09 (0.10)	-0.43	[-0.61; -0.24]*
3668 (26) IDeg FF - IGlar	229	-1.17 (0.08)	230	-1.21 (0.08)	0.04	[-0.12; 0.20]
3668 (26) IDeg FF - IDeg			228	-1.03 (0.08)	-0.13	[-0.29; 0.03]

N: Number of subjects contributing to analysis; FF: Fixed Flexible, subjects treated with a rotating dosing schedule; LSmean: least-square mean; SE: standard error

*Difference statistically significantly different from 0; Endpoint was analysed by an ANOVA model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors and age and baseline HbA1c as covariates; Non-inferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%); The primary treatment contrast of interest in 3770 and 3668 was IDeg FF – IGlar, the comparison IDeg OD vs. IGlar was not specified in the protocol, End of Trial: a subject's last trial visit excluding the follow-up visit; Comparator: IDet (3585), IGlar (3583, 3770, 3582, 3579, 3672, 3586, 3668), and Sita (3580); Missing values are imputed by LOCF.

Sponsor's Figure 3-1 in Clinical Summary
HbA1c (%) at Baseline and End of Trial – Plot of Mean Values - FAS



FF: Fixed Flexible, subjects treated with a rotating dosing schedule;
Comparator: IGlar, except IDet (3585) and Sita (3580); LSMeans with 95%CI; missing values are imputed by LOCF

Reference ID: 3216499

Sponsor's Table 4-3 in Clinical Overview

Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – T1DM – Statistical Analysis - FAS

	Confirmed Hypoglycaemia Estimated Rate-Ratio IDeg / Comparator		**Nocturnal confirmed Hypoglycaemia** Estimated Rate-Ratio IDeg / Comparator	
Trial (wks)	RR	95% CI	RR	95% CI
3583 (52)	1.07	[0.89 ; 1.28]	0.75	[0.59 ; 0.96]*
3585 (26)	0.98	[0.80 ; 1.20]	0.66	[0.49 ; 0.88]*
3770 (26) IDeg Flex - IGlar	1.03	[0.85 ; 1.26]	0.60	[0.44 ; 0.82]*
3770 (26) IDeg Flex - IDeg	0.92	[0.76 ; 1.12]	0.63	[0.46 ; 0.86]*

*Ratio statistically significantly different from 1;

Estimated rate: Estimated rate per 100 exposure years; The endpoint was analysed using a negative binomial model with log link and log of the treatment emergent period as offset. The model included treatment, sex, anti-diabetic treatment at screening and region as fixed factors and age as covariate; Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L (56 mg/dL); The primary treatment contrast of interest in 3770 was IDeg FF – IGlar, the comparison IDeg OD vs. IGlar was not specified in the protocol; Comparator: IDet (3585) and IGlar (3583, 3770); Nocturnal period: the period between 00:01 and 05:59 (both included).

Sponsor's Table 4-4 in Clinical Overview

Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – T2DM – Statistical Analysis - FAS

	Confirmed Hypoglycaemia Estimated Rate-Ratio IDeg / Comparator		**Nocturnal Confirmed Hypoglycaemia** Estimated Rate-Ratio IDeg / Comparator	
Trial (wks)	RR	95% CI	RR	95% CI
Basal-bolus therapy ±OADs				
3582 (52)	0.82	[0.69 ; 0.99]*	0.75	[0.58 ; 0.99]*
OAD-insulin combination therapy				
3579 (52)	0.82	[0.64 ; 1.04]	0.64	[0.42 ; 0.98]*
3672 (26)	0.86	[0.58 ; 1.28]	0.64	[0.30 ; 1.37]
3586 (26)	0.82	[0.60 ; 1.11]	0.62	[0.38 ; 1.04]
3580 (26)	3.81	[2.40 ; 6.05]*	1.93	[0.90 ; 4.10]
3668 (26) IDeg FF - IGlar	1.03	[0.75 ; 1.40]	0.77	[0.44 ; 1.35]
3668 (26) IDeg FF - IDeg	1.10	[0.79 ; 1.52]	1.18	[0.66 ; 2.12]

FF: Fixed Flexible, subjects treated with a rotating dosing schedule

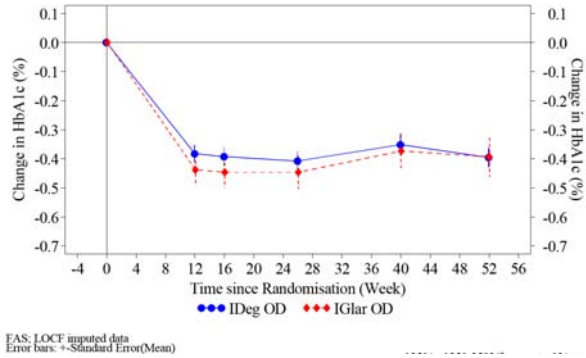
*Ratio statistically significantly different from 1; Estimated rate: Estimated rate per 100 exposure years; The endpoint was analysed using a negative binomial model with log link and log of the treatment emergent period as offset. The model included treatment, sex, anti-diabetic treatment at screening and region as fixed factors and age as covariate; The primary treatment contrast of interest in 3668 was IDeg FF – IGlar, the comparison IDeg OD vs. IGlar was not specified in the protocol. Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG <3.1 mmol/L (56 mg/dL); Comparator: IGlar (3582, 3579, 3672, 3586, 3668) and Sita (3580); Nocturnal period: the period between 00:01 and 05:59 (both included)

Reference ID: 3216499

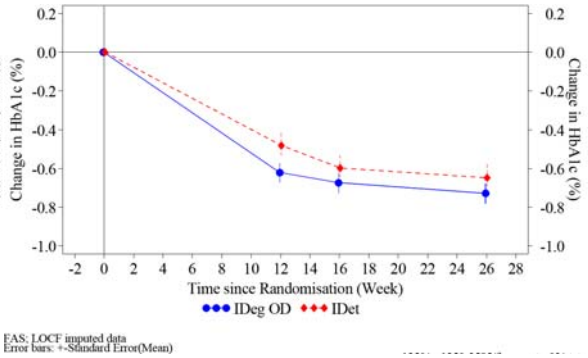
8. APPENDIX III

Change in HbA1c Profile Over Time (Sponsor's Graphs)

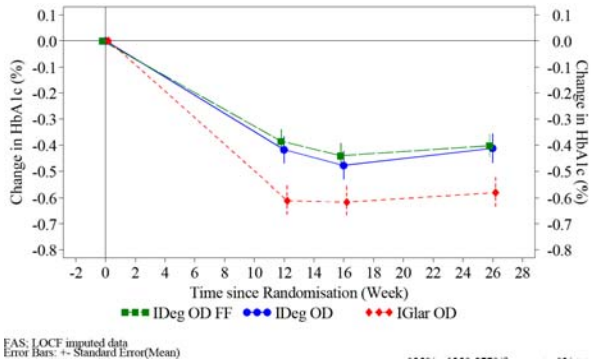
Study 3583 (T1DM)



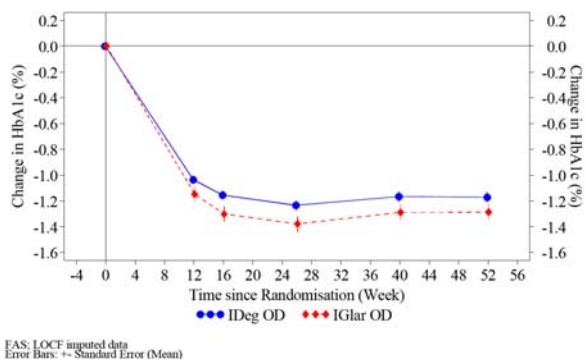
Study 3585 (T1DM)



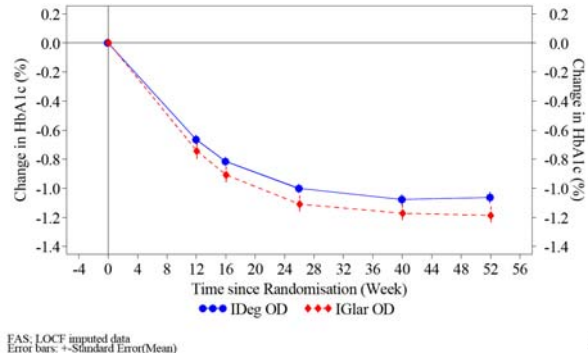
Study 3770 (T1DM)



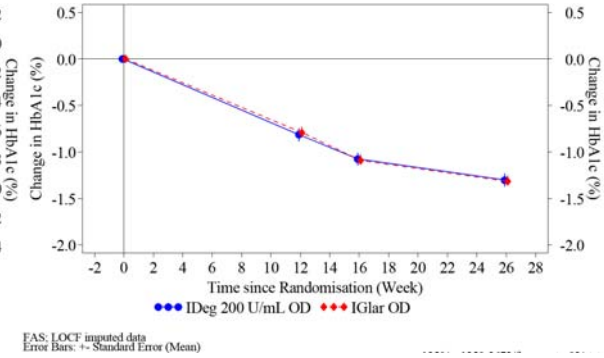
Study 3582 (T2DM)



Study 3579 (T2DM)

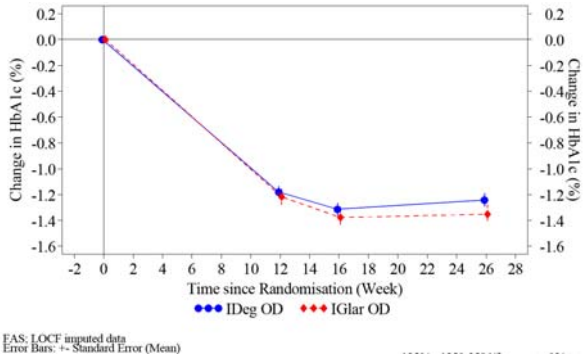


Study 3672 (T2DM)

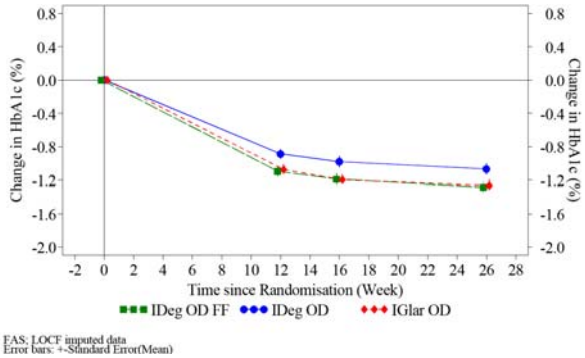


Reference ID: 3216499

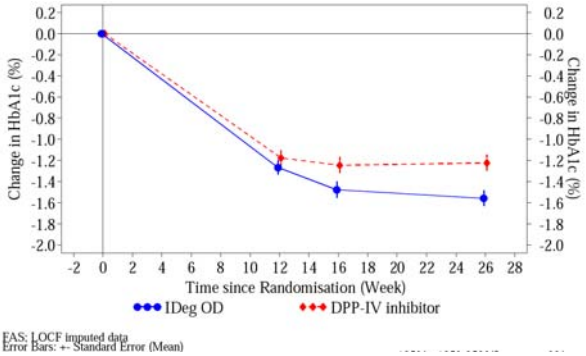
Study 3586 (T2DM)



Study 3668 (T2DM)



Study 3580 (T2DM)

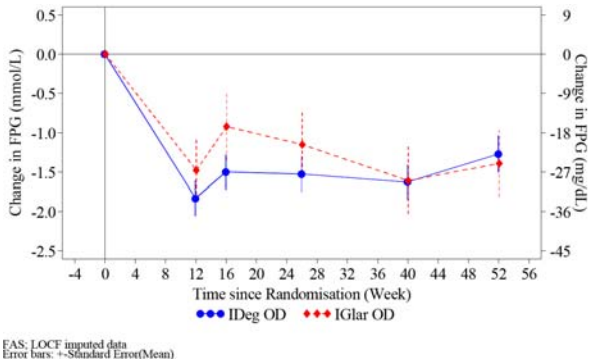


Reference ID: 3216499

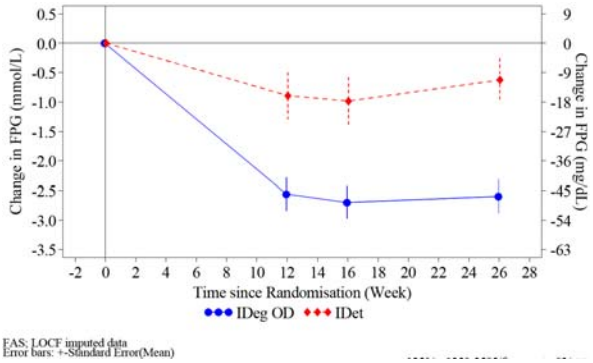
9. APPENDIX IV

Change in FPG Profile Over Time (Sponsor's Graphs)

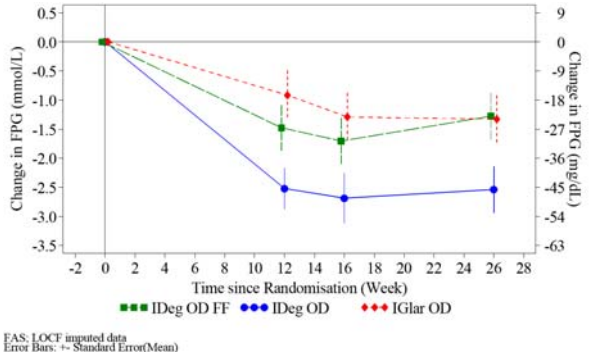
Study 3583 (T1DM)



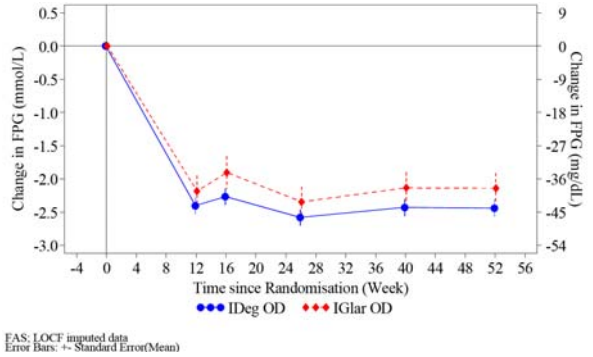
Study 3585 (T1DM)



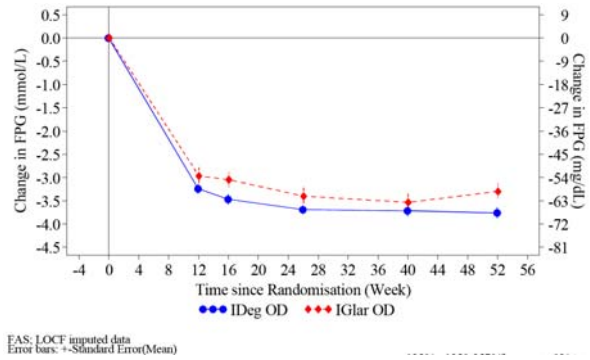
Study 3770 (T1DM)



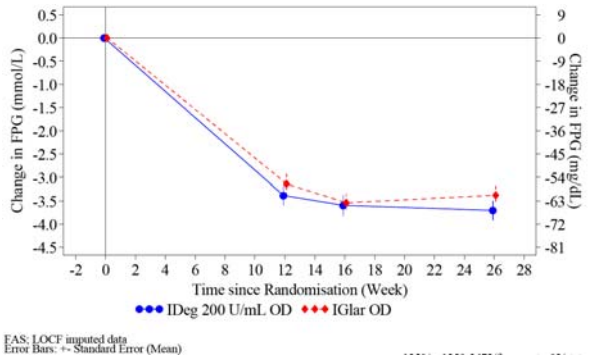
Study 3582 (T2DM)



Study 3579 (T2DM)

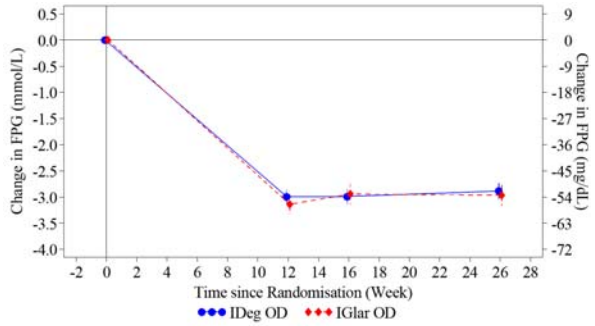


Study 3672 (T2DM)



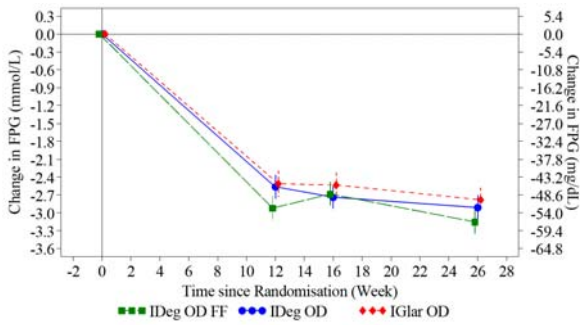
Reference ID: 3216499

Study 3586 (T2DM)



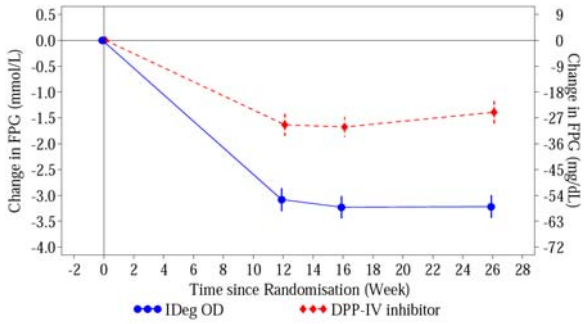
FAS; LOCF imputed data
Error Bars: +- Standard Error (Mean)

Study 3668 (T2DM)



FAS; LOCF imputed data
Error bars: +-Standard Error(Mean)

Study 3580 (T2DM)



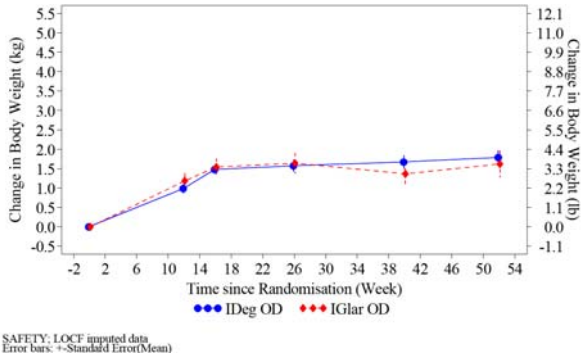
FAS; LOCF imputed data
Error Bars: +- Standard Error (Mean)

Reference ID: 3216499

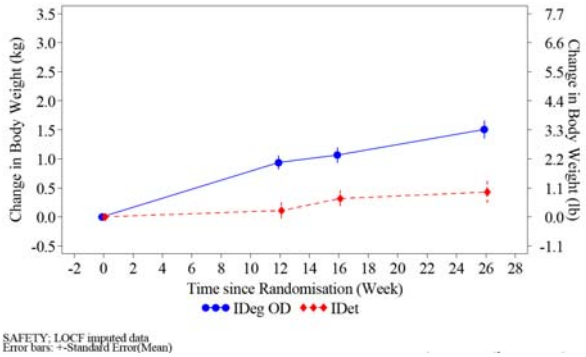
10. APPENDIX V

Change in Body Weight Profile Over Time (Sponsor's Graphs)

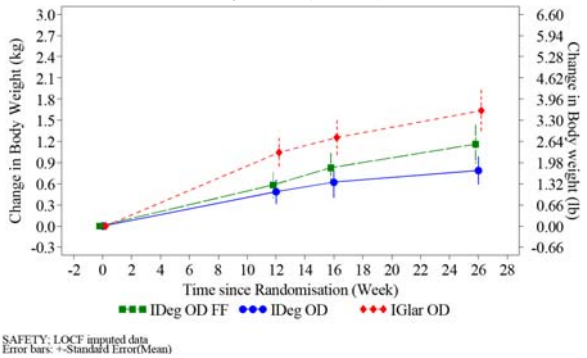
Study 3583 (T1DM)



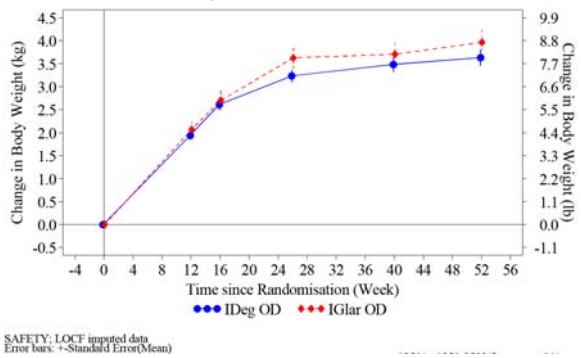
Study 3585 (T1DM)



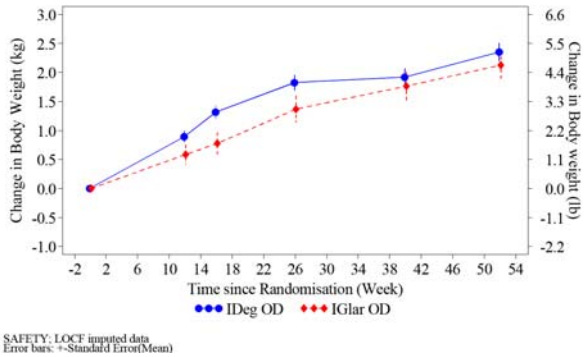
Study 3770 (T1DM)



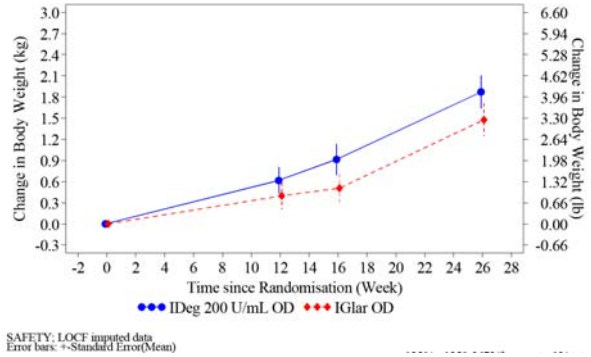
Study 3582 (T2DM)



Study 3579 (T2DM)

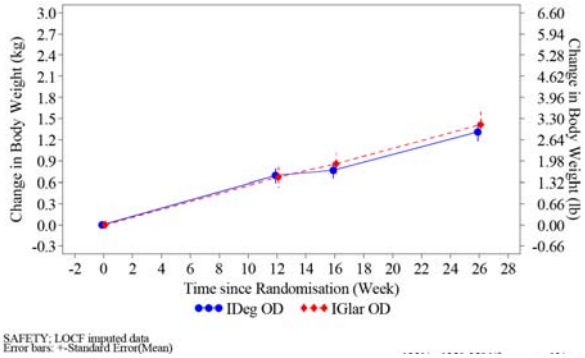


Study 3672 (T2DM)

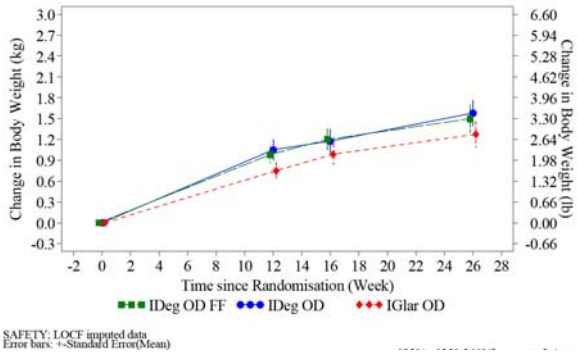


Reference ID: 3216499

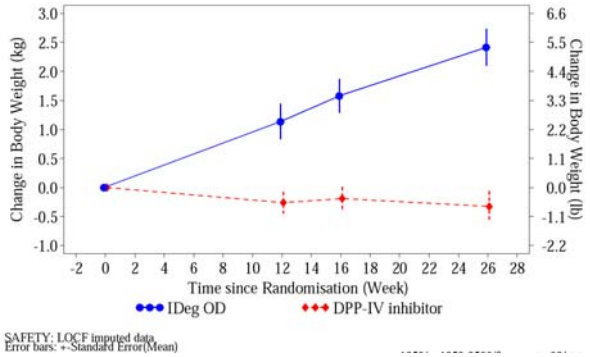
Study 3586 (T2DM)



Study 3668 (T2DM)



Study 3580 (T2DM)

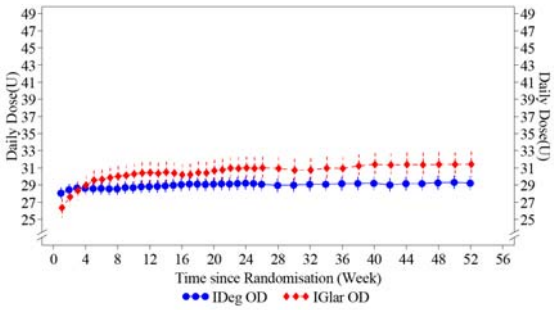


Reference ID: 3216499

11. APPENDIX VI

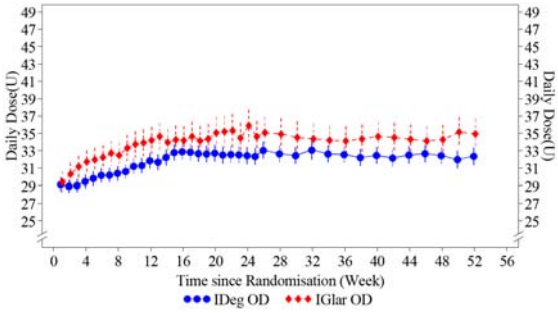
Insulin Dose Over Time (Sponsor's Graphs)

Study 3583: Daily Basal Insulin Dose (U)



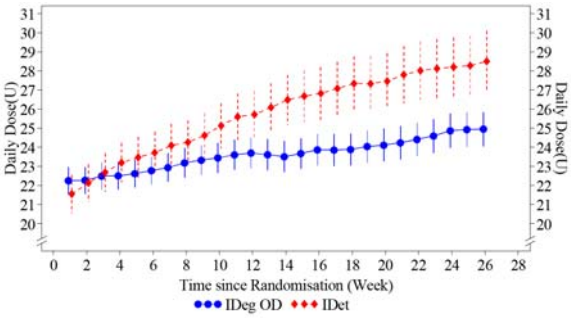
SAFETY; LOCF imputed data
Error bars: +- Standard Error (Mean)

Study 3583: Daily Bolus Insulin Dose (U)



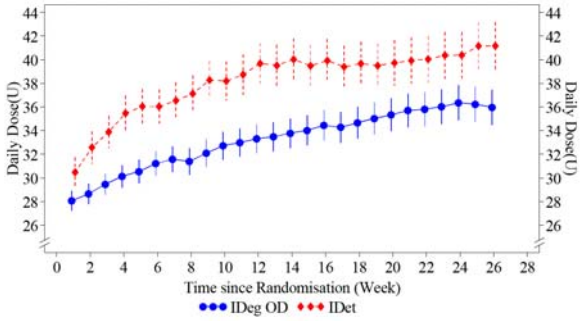
SAFETY; LOCF imputed data
Error bars: +- Standard Error (Mean)

Study 3585: Daily Basal Insulin Dose (U)



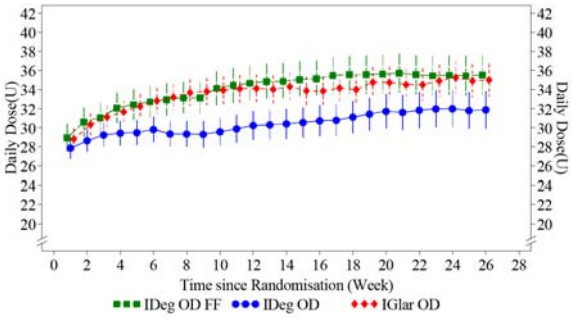
SAFETY; LOCF imputed data
Error bars: +-Standard Error(Mean)

Study 3585: Daily Bolus Insulin Dose (U)



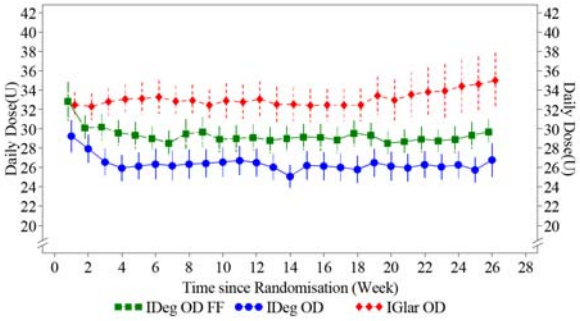
SAFETY; LOCF imputed data
Error bars: +-Standard Error(Mean)

Study 3770: Daily Basal Insulin Dose (U)



SAFETY; LOCF imputed data
Error bars: +-Standard Error(Mean)

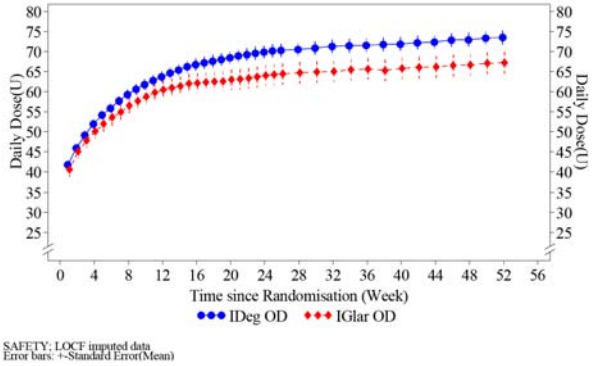
Study 3770: Daily Bolus Insulin Dose (U)



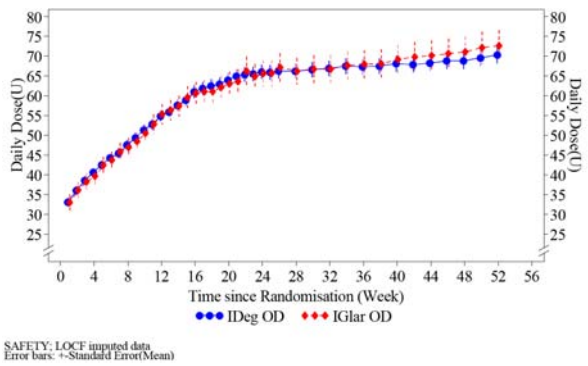
SAFETY; LOCF imputed data
Error bars: +-Standard Error(Mean)

Reference ID: 3216499

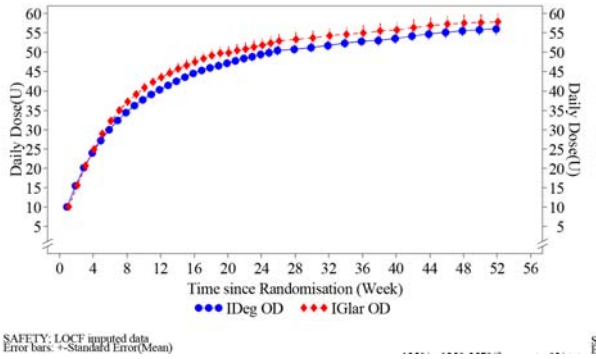
Study 3582: Daily Basal Insulin Dose (U)



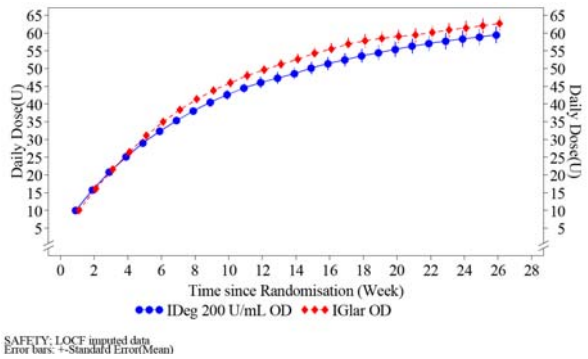
Study 3582: Daily Bolus Insulin Dose (U)



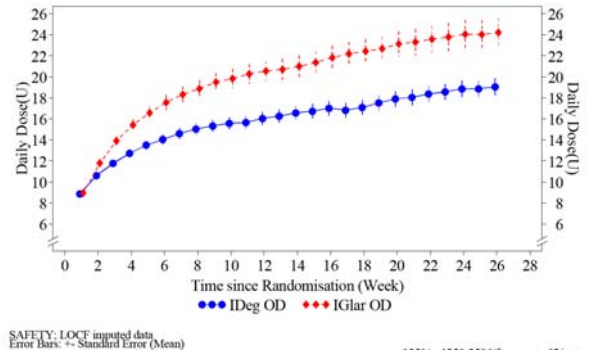
Study 3579: Daily Basal Insulin Dose (U)



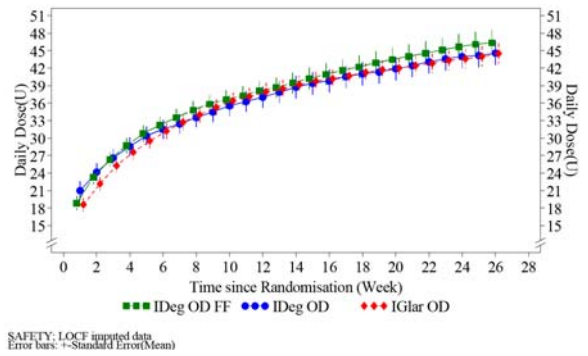
Study 3672: Daily Basal Insulin Dose (U)



Study 3586: Daily Basal Insulin Dose (U)



Study 3668: Daily Basal Insulin Dose (U)



Reference ID: 3216499

12. APPENDIX VII

115: Conclusion of Confirmatory Statistical Analysis – T1DM – IDeg OD – FAS

Trial (wks)	HbA1c (%) (IDeg-Comp)	Nocturnal confirmed hypoglycaemia (IDeg/Comp)	Confirmed hypoglycaemia (IDeg/Comp)	FPG (mmol/L) (central lab) (IDeg-Comp)	Within-subject variability in SMPG (%) (IDeg/Comp)
3583 (52)	Non-inferiority -0.01 [-0.14;0.11]	Superiority 0.75 [0.59;0.96]	Inconclusive 1.07 [0.89;1.28]	Testing Proc. Stopped -0.33 [-1.03;0.36]	Testing Proc. Stopped 0.96 [0.86;1.05]
3585 (26)	Non-inferiority -0.09 [-0.23;0.05]	Superiority 0.66 [0.49;0.88]	Inconclusive 0.98 [0.80;1.20]	Testing Proc. Stopped -1.66 [-2.37;-0.95]*	Testing Proc. Stopped 1.02 [0.91;1.12]
3770** (26)	Non-inferiority 0.17 [0.04;0.30]	-	-	-	-

Columns appear in the order of the test priority.
*Difference significant, but testing procedure was stopped
**The confirmatory analysis was with respect to the IDeg FF vs IGlar comparison
Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L (56 mg/dL)
Nocturnal: the period between 00:01 and 05:59 a.m. (both included)
SMPG: Self measured plasma glucose
- : Endpoint was not a confirmatory endpoint in that specific trial
Comp: Comparator IDet (3585) and IGlar (3583, 3770)

116: Conclusion of Confirmatory Statistical Analysis – T2DM – IDeg OD – Basal-bolus Therapy – FAS

Trial (wks)	HbA1c (%) (IDeg-Comp)	Confirmed hypoglycaemia (IDeg/Comp)	FPG (mmol/L) (central lab) (IDeg-Comp)	Within-subject variability in SMPG (%) (IDeg/Comp)	HbA1c<7.0% without conf. hypoglycaemia (IDeg/Comp)
3582 (52)	Non-inferiority 0.08 [-0.05;0.21]	Superiority 0.82 [0.69;0.99]	Inconclusive -0.29 [-0.65;0.06]	Testing Proc. Stopped 0.94 [0.87;1.01]	Testing Proc. Stopped 1.02 [0.72;1.47]

Columns appear in the order of the test priority
HbA1c<7.0% without conf. hypoglycaemia: A subject exposed for at least 12 weeks, who meets the HbA1c target without confirmed hypoglycaemia during the last 12 weeks of treatment or within 7 days after last randomised treatment
Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L (56 mg/dL)
SMPG: Self measured plasma glucose
Comp: Comparator IGlar

Reference ID: 3216499

117: Conclusion of Confirmatory Statistical Analysis – T2DM – IDeg OD – OAD-insulin Combination – FAS

Trial (wks)	HbA1c (%) (IDeg-Comp)	Confirmed hypoglycaemia (IDeg/Comp)	Nocturnal confirmed hypoglycaemia (IDeg/Comp)	FPG (mmol/L) (central lab) (IDeg-Comp)	Within-subject variability in SMPG (%) (IDeg/Comp)	HbA1c<7.0% (IDeg/Comp)	HbA1c<7.0% without conf. hypoglycaemia (IDeg/Comp)
3579 (52)	Non-inferiority 0.09 [-0.04;0.22]	Inconclusive 0.82 [0.64;1.04]	-	Testing Stopped -0.43 [-0.74;-0.13]*	Testing Stopped 0.99 [0.92;1.06]	-	Testing Stopped 0.86 [0.63;1.17]
3672 (26)	Non-inferiority 0.04 [-0.11;0.19]	Inconclusive 0.86 [0.58;1.28]	-	Testing Stopped -0.42 [-0.78;-0.06]*	Testing Stopped 0.92 [0.84;1.01]	-	Testing Stopped 1.05 [0.69;1.61]
3586 (26)	Non-inferiority 0.11 [-0.03;0.24]	Inconclusive 0.82 [0.60;1.11]	Testing Stopped 0.62 [0.38;1.04]	Testing Stopped -0.09 [-0.41;0.23]	Testing Stopped 0.89 [0.80;0.99]*	-	Testing Stopped 0.89 [0.56;1.42]
3580 (26)	Superiority -0.43 [-0.61;-0.24]	-	-	Superiority -2.17 [-2.59;-1.74]	-	Superiority 1.60 [1.04;2.47]	Inconclusive 0.92 [0.55;1.53]
3668** (26)	Non-inferiority 0.04 [-0.12;0.20]	-	-	-	-	-	-

Columns appear in the order of the test priority.
*Difference significant, but testing procedure was stopped
**The confirmatory analysis was with respect to the IDeg FF vs IGlar comparison
Confirmed hypoglycaemia: subject unable to treat himself/herself and/or has a recorded PG < 3.1 mmol/L (56 mg/dL)
HbA1c<7.0% without hypoglycaemia: A subject exposed for at least 12 weeks, who meets the HbA1c target without confirmed hypoglycaemia during the last 12 weeks of treatment or within 7 days after last randomised treatment.
SMPG: Self measured plasma glucose
- : Endpoint was not a confirmatory endpoint in that specific trial
Comp: Comparator IGlar (3579, 3672, 3586, 3668) and Sita (3580)

Note that when the hierarchical testing procedure was stopped, superiority could not be confirmed for the remaining confirmatory secondary endpoints.

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/s/

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11/14/2012
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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 AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	203314
Drug Name:	Tresiba (insulin degludec)
Indication(s):	Control of hyperglycemia in subjects with diabetes mellitus.
Applicant:	Novo Nordisk
Date(s):	Submitted: 09/29/2011 PDUFA Goal Date: 07/27/2012
Review Priority:	Standard
Biometrics Division:	Division of Biometrics VII
Statistical Reviewer:	Eugenio Andraca-Carrera, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer (efficacy): Jean Marc Guettier, M.D. Medical Officer (safety): Karim Calis, M.D.
Project Manager:	Rachel Hartford (DMEP)

Keywords: safety, meta-analysis, diabetes mellitus, hypoglycemia

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List of Abbreviations

ADA	American Diabetes Association
IDeg	Insulin degludec (formerly known as (b) (4)
IDet	Insulin detemir
IGlar	Insulin glargine
OD	Once daily
HbA1c	Glycosylated haemoglobin
IAsp	Insulin aspart
TID	Three times a day
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
OAD	Oral antidiabetic drug
DPP-4I	Dipeptyl peptidase-4 inhibitor
BMI	Body mass index
RR	Rate ratio
SAP	Statistical Analysis Plan

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1 Executive Summary

The proposed indication of Insulin degludec (IDeg) is the treatment of patients with (b) (4) diabetes mellitus (b) (4). The proposed dosages are 100 U/mL and 200 U/mL administered through subcutaneous injection once a day (OD). Per the request of the Division of Metabolism and Endocrinology Products this statistical review evaluates the rate of hypoglycemia, comparing IDeg with Insulin glargine OD (IGlar OD) in 9 Phase 3a randomized clinical trials (trials 3583, 3770, 3582, 3579, 3672, 3586, 3668, 3718 and 3724). This review focuses on the pre-marketing evaluation of hypoglycemia only. A separate statistical review addressing efficacy is being conducted by Dr. Dongmei Liu. An evaluation of cardiovascular safety is being conducted by Dr. Xiao Ding.

1.1 Conclusions and Recommendations

Novo Nordisk compared the rate ratio (RR) of confirmed hypoglycemia between IDeg OD and IGlar OD in 7 trials: 5 trials for T2DM and 2 trials for T1DM. Sensitivity analyses were conducted in 2 additional trials with an IDeg 3TW randomized treatment arm and an IGlar OD comparator arm. The Statistical Analysis Plan (SAP) was submitted by the Sponsor on 04 June 2010 and revised on 16 August 2011 to incorporate comments from the FDA review team.

The agreed upon population of interest consisted of all subjects randomized in these 9 Phase 3a trials, except for subjects randomized to an IDeg fixed-flexible dosing scheme alternating morning and night, because this dosing scheme does not correspond to clinical practice. The primary endpoint was confirmed hypoglycemia, defined as hypoglycemia events with plasma glucose <3.1 mmol/L and/or requiring assistance from another person to actively administer carbohydrate, glucagons or resuscitative actions. Secondary endpoints included severe hypoglycemia, American Diabetes Association (ADA) documented hypoglycemia and nocturnal confirmed hypoglycemia. These endpoints are defined in Section 3.2.

The primary analysis compared IDeg OD to IGlar OD in the 7 trials with an IDeg OD treatment arm. In these 7 trials, 4330 subjects contributed information to the analysis: 2899 randomized to IDeg OD and 1431 randomized to IGlar OD. The two trials with an IDeg *3TW* are excluded from the primary analysis and are only used in sensitivity analyses.

The observed rate of confirmed hypoglycemia varied considerably by trial. Among subjects with T1DM, the observed annual rate of confirmed hypoglycemia events was as high as 87 events per year among subjects randomized to IDeg OD in trial 3770 and as low as 39 events per year among subjects randomized to IGlar OD in trial 3583. The annual rate of confirmed hypoglycemia was much lower among subjects with T2DM and ranged between approximately 1 event per year and 13 events per year.

The pre-specified primary model was a negative binomial model comparing the rate of confirmed hypoglycemia between IDeg OD and IGlar OD controlling for trial and baseline covariates. The estimated RR and 95% CI from this model were ***0.91 (0.83, 0.99)***, implying a borderline statistically significant reduction in the rate of confirmed hypoglycemia associated

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with IDeg OD. The primary model assumes that the RR of confirmed hypoglycemia between IDeg OD and IGlar OD is the same whether a subject has type 1 or type 2 diabetes. Secondary analyses included an interaction term for randomized treatment by type of diabetes. The interaction term was statistically significant, p-value 0.0057, and suggests that the rate ratio comparing IDeg to IGlar is different in subjects with different types of diabetes. Among subjects with T1DM, IDeg OD was not different from IGlar OD, with an estimated RR and 95% CI of ***1.11 (0.94, 1.31)***. 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)***. These results are summarized in Table 1.

Table 1. Summary of results: RR of confirmed hypoglycemia comparing IDeg OD vs. IGlar

Overall Rate Ratio (95% CI) (pre-specified primary analysis)	***0.91 (0.83, 0.99)***
T1DM Rate Ratio (95% CI)	***1.11 (0.94, 1.31)***
T2DM Rate Ratio (95% CI)	***0.84 (0.76, 0.93)***

Source: Created by reviewer. Dataset: hypo.xpt

Based on these results, we recommend treating the effect of IDeg OD on hypoglycemia differently for subjects with type I and type II diabetes. There is 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.

Subgroup analyses were consistent with the primary analysis except for subgroups defined by country of randomization (USA vs. non-USA). Among subjects with T1DM, 64% were randomized in the USA, and among subjects with T2DM, 33% were randomized in the USA. There was no observed difference between IDeg and IGlar among subjects randomized in the USA with either type of diabetes. The rate ratio of confirmed hypoglycemia comparing IDeg OD to IGlar OD among subjects with T1DM was ***0.99 (0.81, 1.20)*** in the USA, and ***1.28 (0.96, 1.71)*** outside the USA. Among subjects with T2DM, the estimated RR was ***0.97 (0.81, 1.15)*** among subjects randomized in the USA, and ***0.79 (0.69, 0.90)*** outside the USA. Among subjects with T2DM randomized in the USA, two of three studies showed a trend for lower risk of confirmed hypoglycemia associated with IDeg (trials 3572 and 3582), but a third study (trial 3579) showed higher risk associated with IDeg (see Figure 2 on page 37). These results are summarized in Table 2.

Table 2. RR of confirmed hypoglycemia by place of randomization

Subjects randomized in the USA	
T1DM Rate Ratio (95% CI)	***0.99 (0.81, 1.20)***
T2DM Rate Ratio (95% CI)	***0.97 (0.81, 1.15)***
Subjects randomized outside the USA	
T1DM Rate Ratio (95% CI)	***1.28 (0.96, 1.71)***
T2DM Rate Ratio (95% CI	***0.79 (0.69, 0.90)***

Source: Dataset: hypo.xpt.

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Overall, the results of the primary analysis, as well as sensitivity and subgroup analysis were consistent and showed that IDeg OD was associated with a statistically significant reduction in the rate of confirmed hypoglycemia, compared to IGlar OD, among subjects with T2DM only, except among subjects randomized in the USA. Among secondary endpoints, only the estimated rate ratio of confirmed nocturnal hypoglycemia was statistically significant at $\alpha = 0.05$.Among subjects with T1DM, there was no statistically significant difference in the rate of hypoglycemia between IDeg OD and IGlar OD in either the primary or secondary endpoints.

1.2 Brief Overview of Clinical Studies

In this NDA application, Novo Nordisk submitted data for 9 trials. All trials were Phase 3a, open-label, randomized, multicenter, active-controlled with IGlar OD comparator. The primary efficacy endpoint in all trials was the change from baseline in HbA1c comparing IDeg to IGlar. Two trials were conducted in subjects with T1DM, and 7 were conducted in subjects with T2DM. All 9 trials have been completed and their databases have been locked. A detailed discussion of these trials is provided in Section 3.1.

1.3 Statistical Issues and Findings

Secondary analyses looked at endpoints such as confirmed nocturnal hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia. These analyses were mostly consistent with the primary analysis: IDeg appears to be no better than IGlar at reducing the rate of hypoglycemia in subjects with T1DM, but there is some evidence that IDeg may reduce the rate in subjects with T2DM. The estimated rate ratios of confirmed nocturnal hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia were all lower than 1 among subjects with T2DM, suggesting a possible protective effect associated with IDeg; however only nocturnal confirmed hypoglycemia reached statistical significance ***RR 0.69 (0.59, 0.81).*** The estimated benefit of IDeg in T2DM was not statistically significant for severe hypoglycemia ***RR 0.74 (0.40, 1.36)*** and there was no evidence of benefit (or harm) for ADA documented hypoglycemia ***RR 1.01 (0.94, 1.10).***

The analysis of the binary endpoint of having experienced at least one episode of confirmed hypoglycemia was consistent with the primary analysis. This analysis showed no difference between IDeg and IGlar among subjects with T1DM. Among subjects with T2DM, subjects randomized to IDeg were less likely to experience at least one episode of confirmed hypoglycemia than subjects randomized to IGlar ***OR 0.72 (0.59, 0.86).***

A sensitivity analysis was fit based on an alternative statistical model: a zero-inflated negative binomial model (ZINB). The ZINB model fit the data better than the pre-specified Negative Binomial, according to the Akaike information criterion, The interaction between treatment and type of diabetes was also statistically significant in the ZINB model and led to the same conclusions as the pre-specified Negative Binomial model: IDeg OD reduces the rate of confirmed hypoglycemia in subjects with T2DM but not subjects with T1DM. It is worth noting that all statistical models (Negative Binomial, ZINB, and Wilcoxon rank-sum test) in this review

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reached consistent conclusions. In future applications involving event counts with a high probability of zero events, the use of zero-inflated models could be considered as either the primary analysis method or sensitivity analysis method.

2 Introduction

2.1 Product Description and Regulatory Background

This review addresses Novo Nordisk submission of NDA 203314 on December 02, 2011.

Insulin degludec is a long acting soluble insulin analogue. The proposed indication of IDeg is the treatment of patients with diabetes mellitus [redacted] (b) (4). The proposed dosages are 100 U/mL and 200 U/mL administered through subcutaneous injection once a day. Novo [redacted] (b) (4)

2.2 Clinical Trial Overview

Novo Nordisk assessed the risk of hypoglycemia associated with the use of IDeg, compared to Insulin glargine, through a primary meta-analysis of 7 randomized, controlled, Phase 3 clinical trials with at least one IDeg once daily (IDeg OD) randomized treatment arm and one IGlar OD randomized treatment arm. A secondary analysis was conducted in two additional trials with a randomized IDeg 3 times weekly (IDeg 3TW) treatment arm. All 9 trials have been completed and their databases have been locked. Table 3 summarizes the design, duration and sample size of these trials.

The SAP for the primary meta-analysis of the 7 trials with an IDeg OD randomized treatment arm, as well as the secondary analyses including the 2 trials with an IDeg 3TW randomized treatment arm, was submitted to the FDA on June 11, 2010 and revised on 16 August 2011. A detailed discussion of the methodology used to analyze these trials can be found in the Statistical Methodologies section of this review.

2.3 Data Sources

The applicant submitted electronic documents and datasets individually for 9 trials: 3583, 3770, 3582, 3579, 3672, 3586, 3668, 3718 and 3724. In addition, the applicant submitted pooled analysis datasets for episodes of hypoglycemia (filename "HYPO") and subject level demographics and trial disposition (filename "S"). Clinical study reports (CSRs) of each individual trial were reviewed to evaluate trial protocols.

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The following file folder available within the CDER Electronic Document Room (EDR) was used in this review:

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Reference ID: 3139787

Table 3. Trials included in meta-analysis

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. IGlar OD *(+ IAsp TID)*	T1DM Insulin-treated	Any basal–bolus regimen	52	3:1	IDeg: 472 IGlar: 157
3770	IDeg Flex vs. IGlar 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. IGlar 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. IGlar 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. IGlar 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. IGlar 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 IGlar 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
T2DM IDeg 3TW OAD–Insulin Combination Therapy						
3718	IDeg 200 U/mL 3TW (evening) vs. IGlar OD *(+ met ± DPP-4I)*	T2DM Insulin-naïve	met monotherapy met + [SU/glin ± DPP-4I ± α-GI] in any combination	26	1:1	IDeg: 233 IGlar: 234
3724	IDeg 200 U/mL 3TW (morning) vs. IGlar OD *+ met ± DPP-4I)*	T2DM Insulin-naïve	met monotherapy met + [SU/glin ± DPP-4I ± α-GI] in any combination	26	1:1	IDeg: 229 IGlar: 230

Source: 5.3.5.3 Meta-analysis of Hypoglycaemic Episodes. Table 4-1.

Abbreviations: α-GI: alpha-glucosidase inhibitor, 3TW: three times weekly, BID: twice daily; DPP-4I: dipeptidyl peptidase-4 inhibitor, FAS: full analysis set, FF: fixed flexible, Glin: glinides, IAsp: insulin aspart, IGlar: insulin glargine, met: metformin, OAD: oral antidiabetic drug,, OD: once daily, PIO: pioglitazone, SU: sulphonylurea, TID: three times daily, U: unit(s).

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3 Statistical Evaluation

This review evaluates the risk of hypoglycemia in the 9 trials listed in Table 3. For a statistical review of cardiovascular risk, please refer to the review authored by Dr. Xiao Ding. For a statistical evaluation of efficacy results, please refer to the review authored by Dr. Dongmei Lui.

3.1 Trial Designs

Nine trials were submitted to evaluate the association between IDeg and hypoglycemia, compared with IGlar. All nine trials were Phase 3a, open-label, randomized, multicenter, active-controlled with IGlar. The primary efficacy endpoint in all trials was the change from baseline in HbA1c comparing IDeg to IGlar.

Five of these nine trials included an extension trial. According to the Sponsor, the databases for these extension trials had not been cleaned or locked prior to the present submission. Therefore, the extension parts of these trials were not submitted, are not reviewed in this document and are not included in any analyses.

The following 7 trials included randomized subjects to IDeg OD (100u/mL or 200 U/mL) and IGlar OD: 3583, 3770, 3582, 3579, 3672, 3586 and 3668. Two of these trials, 3770 and 3668, additionally randomized subjects to IDeg fixed-flexible dosing, where IDeg OD was dosed in an alternating morning/evening schedule. Subjects randomized to IDeg fixed-flexible dosing in these two trials are not included in any analyses because, according to the Sponsor: "the constantly shifting morning-evening injection scheme does not correspond to the typical use of IDeg in clinical practice".

Two trials, 3718 and 3724, randomized subjects to either IDeg 200 U/mL 3TW or to IGlar OD. These two trials are not included in the primary analysis of IDeg OD vs. IGlar OD and are analyzed separately.

The design of the 9 submitted trials is discussed below:

Trial 3583 was a Phase 3a trial. According to the Sponsor this was a: "52-week randomised, controlled, open-label, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of NN12501 and insulin glargine both administered once daily in a basal-bolus regimen with insulin as part as mealtime insulin in subjects with type 1 diabetes". The primary efficacy endpoint was the change in glycosylated haemoglobin (HbA1c) from baseline to week 52. Subjects were randomized on a 3:1 ratio to IDeg 100U/mL OD (472 subjects) and IGlar OD (157 subjects). All randomized subjects also received injected IAsp TID.

This trial had the following inclusion criteria: men or women over 18 years of age with T1DM diagnosed clinically at least 12 months before Visit 1 (screening), treatment with any basal-bolus insulin regimen for at least 12 months prior to Visit 1, HbA1c $\leq$ 10.0% by central laboratory analysis, BMI $\leq$ 35.0 kg/m^2. This trial was conducted between September 2009 and November 2010. This trial enrolled 70% of all subjects in the United States.

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Trial 3770 was a Phase 3a trial. According to the Sponsor this was a: "A 26-week trial investigating the dosing flexibility, efficacy and safety of NN1250 in subjects with type 1 diabetes with a 26-week extension". This was an open-label trial conducted in 71 sites in 6 countries. The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized on a 1:1:1 ratio to IDeg Flex (164 subjects), IDeg 100U/mL OD (165 subjects) or IGlar OD (164 subjects). All randomized subjects were also injected with IAsp at meal times (TID). Subjects randomized to IDeg Flex are not included in this meta-analysis, as discussed earlier.

This trial had the following inclusion criteria: men or women over 18 years of age with T1DM diagnosed clinically at least 12 months before Visit 1 (screening), treatment with any basal-bolus insulin regimen for at least 12 months prior to Visit 1, HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 35.0 kg/m^2, and current treatment with any basal insulin (e.g. IGlar, IDet, NPH insulin) using 1 or 2 daily injections and no less than 3 injections with bolus insulin as meal-time bolus insulin therapy. This trial was conducted between March 2010 and November 2010. This trial enrolled 52% of all subjects in the United States.

Trial 3582 was a Phase 3a trial titled: "Comparison of NN12501 With Insulin Glargine Plus Insulin Aspart With/Without Metformin and With/Without Pioglitazone in Type 2 Diabetes (BEGIN™)". This was an open-label trial conducted in 123 sites in 12 countries. The primary efficacy endpoint was the change from baseline in HbA1c after 52 weeks of treatment. Subjects were randomized in a 3:1 ratio to IDeg 100U/mL OD (744 subjects) or IGlar OD (248 subjects). All randomized subjects were also injected with IAsp TID, and continued treatment with metformin and/or pioglitazone, if the treatment started prior to this trial.

This trial had the following inclusion criteria: men or women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 40.0 kg/m^2, and current treatment with any insulin regimen (premix, self-mix, basal only, basal-bolus (one or more boluses), bolus only, pump) for at least 3 months ± OADs prior to Visit 1 (screening). This trial was conducted between September 2009 and October 2010. This trial enrolled 50% of all subjects in the United States.

Trial 3579 was a Phase 3a trial. According to the Sponsor this was a: "52-week Randomised, Controlled, Open Label, Multicentre, Multinational Treat-to-target Trial Comparing the Efficacy and Safety of NN1250 and Insulin Glargine, Both Injected Daily in Combination With Oral Anti-diabetic Drugs (OADs), in Subjects With Type 2 Diabetes Mellitus Currently Treated With OADs and Qualifying for More Intensified Treatment (BEGIN™: Once Long)". The primary efficacy endpoint was the change from baseline in HbA1c after 52 weeks of treatment. Subjects were randomized in a 3:1 ratio to IDeg 100U/mL OD (773 subjects) or IGlar OD (248 subjects). All randomized subjects continued their pre-randomization treatment, described in the inclusion criteria.

This trial had the following inclusion criteria: insulin naïve men and women over 18 years with age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 40.0 kg/m^2, and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues

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(sulphonylurea [SU] or glinide), DPP-4 inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1. This trial was conducted between September 2009 and December 2010. This trial enrolled 37% of all subjects in the United States.

Trial 3672 was a Phase 3a trial. According to the Sponsor this was a: "confirmatory 26-week randomised, controlled, open-labelled, multicentre, multinational, parallel, treat-to-target trial comparing efficacy and safety of IDeg 200 U/mL and IGlar both administered OD in combination with metformin ± DPP-4 inhibitor in insulin-naïve subjects diagnosed with type 2 diabetes mellitus currently treated with oral antidiabetic drugs (OADs) qualifying for intensified treatment." The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized in a 1:1 ratio to IDeg 200U/mL OD (228 subjects) or IGlar OD (229 subjects). All randomized subjects continued their pre-randomization treatment, described in the inclusion criteria.

This trial had the following inclusion criteria: insulin naïve men and women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 45.0 kg/m^2, and with current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues (sulphonylurea [SU] or glinide), DPP-4 inhibitor, α-glucosidase-inhibitor (acarbose) with unchanged dosing for at least 3 months prior to Visit 1. This trial was conducted between March 2010 and November 2010. This trial enrolled 48% of all subjects in the United States.

Trial 3586 was a Phase 3a trial. According to the Sponsor this was a: "26-week randomised, confirmatory, controlled, open-label, multicentre, multinational treat-to-target trial comparing the efficacy and safety of IDeg and IGlar, both injected once daily in combination with OAD(s) in a population of insulin naïve subjects with type 2 diabetes mellitus currently treated with OADs qualifying for intensified treatment." The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized in a 2:1 ratio to IDeg 100U/mL OD (289 subjects) or IGlar OD (146 subjects). All randomized subjects continued their pre-randomization treatment, described in the inclusion criteria.

This trial had the following inclusion criteria: insulin naïve men and women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 35.0 kg/m^2, and current treatment with monotherapy or combination of an insulin secretagogue and metformin, with or without addition of α-glucosidase-inhibitors or a DPP-4 inhibitor with unchanged dosing for at least 3 months prior to Visit 1. This trial was conducted between February 2010 and December 2010. This trial did not enroll subjects in the United States.

Trial 3668 was a Phase 3a trial. According to the Sponsor this was a: "26 week randomised, controlled, open-label, multicentre, multinational, three-arm, treat-to-target trial comparing efficacy and safety of three different dosing regimens of either NN1250 1 or insulin glargine with or without combination with OAD treatment, in subjects with type 2 diabetes mellitus (BEGIN™ FLEX)". The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized in a 1:1:1 ratio to IDeg Flex (229 subjects), IDeg 100U/mL OD (228 subjects) or IGlar OD (230 subjects). All randomized subjects

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continued their pre-randomization treatment, described in the inclusion criteria. Subjects randomized to IDeg Flex are not included in this meta-analysis, as discussed earlier.

This trial had the following inclusion criteria: men and women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 40.0 kg/m^2, and current treatment with OAD(s) alone, basal insulin alone or the combination of OAD(s) and basal insulin for at least 3 months prior to Visit 1. The following OADs were allowed with unchanged dosing for at least 3 months prior to visit 1: metformin, insulin secretagogues (sulphonylureas (SU) or glinides), and pioglitazone. This trial was conducted between November 2009 and September 2010. This trial did not enroll subjects in the United States.

Trial 3718 was a Phase 3a trial. According to the Sponsor this was a: "26-week randomised, confirmatory, controlled, open-label, multicentre, multinational treat-to-target trial comparing efficacy and safety of IDeg three times weekly (3TW) injected in the evening (with the evening meal) on Mondays, Wednesdays and Fridays, and IGlar once daily (OD) (injected at the same time each day according to local labelling), both in a population of insulin-naïve subjects with type 2 diabetes mellitus currently treated with oral antidiabetic drugs (OADs) and qualifying for intensified treatment." The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized in a 1:1 ratio to IDeg 200U/mL 3TW (233 subjects) or IGlar OD (234 subjects). One week after randomization, subjects' current antidiabetic treatment was to be discontinued except for metformin and DPP4-inhibitor, if applicable.

This trial had the following inclusion criteria: insulin naïve men and women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤ HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 45.0 kg/m^2, and with current treatment: metformin as monotherapy or in any combination with insulin secretagogues (sulphonylurea or glinide), DPP-4 inhibitor (minimum half daily max dose), α-glucosidase-inhibitor (acarbose) (minimum half daily max dose) with unchanged dosing for at least 3 months prior to Visit 1. This trial was conducted between March 2010 and December 2010. This trial enrolled 42% of all subjects in the United States

Trial 3724 was a Phase 3a trial. According to the Sponsor this was a: "26-week randomised, confirmatory, controlled, open-label, multicentre, multinational treat-to-target trial comparing efficacy and safety of IDeg 3TW injected in the morning (from wake-up to before first meal of the day) and IGlar OD (same time each day according to local labelling), both in a population of insulin-naïve subjects with type 2 diabetes mellitus currently treated with OADs and qualifying for intensified treatment." The primary efficacy endpoint was the change from baseline in HbA1c after 26 weeks of treatment. Subjects were randomized in a 1:1 ratio to IDeg 200U/mL 3TW (230 subjects) or IGlar OD (230 subjects). One week after randomization, subjects' current antidiabetic treatment was to be discontinued except for metformin and DPP4-inhibitor, if applicable.

The trial had the following inclusion criteria: insulin naïve men and women over 18 years of age with T2DM diagnosed clinically at least 6 months prior to the start of the trial, with 7.0% ≤

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HbA1c ≤ 10.0% by central laboratory analysis, BMI ≤ 45.0 kg/m^2, and with current treatment: metformin as monotherapy or in any combination with insulin secretagogues (sulphonylurea or glinide), DPP-4 inhibitor (minimum half daily max dose), α-glucosidase-inhibitor (acarbose) (minimum half daily max dose) with unchanged dosing for at least 3 months prior to Visit 1. This trial was conducted between February 2010 and December 2010. This trial enrolled 45% of all subjects in the United States.

Reviewer's comment:
The 2 trials with an IDeg 200U/mL 3TW treatment arm (trials 3718 and 3724) have similar designs, endpoints, duration, and sample size. These 2 trials are analyzed separately from other trials.

The 7 trials included in the primary meta-analysis have the same primary efficacy endpoint, similar duration, inclusion criteria, and treatment arms. There are two important differences between these 7 trials:

1. *Trials 3583 and 3770 enrolled subjects with T1DM, whereas trials 3582, 3579, 3672, 3586 and 3668 enrolled subjects with T2DM.*
2. *Some trials enrolled insulin-treated subjects only (trials 3583, 3770, 3582); while other trials enrolled insulin-naïve subjects (trials 3579, 3672, 3586). Trial 3668 enrolled both.*

The meta-analysis conducted by the sponsor controls for these two factors (type of diabetes and anti-diabetic treatment at baseline) in the statistical model. The details of the model are discussed in Section 3.3.1.

It is also worth noting that 2 of the trials included in the primary analysis, 3586 and 3668, did not enroll any subjects in the United States.

The clinical review team at the FDA agreed with the excluding subjects randomized to IDeg fixed-flexible dosing from analyses of hypoglycemia.

3.2 Endpoints

3.2.1 Primary Endpoint

The agreed upon primary endpoint is: "the total number of confirmed hypoglycaemic episodes during the time where hypoglycaemic episodes are considered treatment emergent". Episodes are considered treatment emergent if they occur on or after the date of first exposure to trial insulin until 7 days after the last exposure of trial insulin.

A hypoglycemic episode is classified as ***confirmed*** if it meets one of the following two criteria:

- An episode requiring assistance of another person to actively administer carbohydrate, glucagons or resuscitative actions. These episodes are also called '***severe hypoglycemic episodes***'.
- An episode with or without symptoms of hypoglycemia confirmed by plasma glucose < 3.1 mmol/L and which is handled by the subject himself/herself.

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The agreed upon primary comparison is between subjects randomized to IDeg once daily and IGlar once daily.

3.2.2 Secondary Endpoints

The following secondary endpoints are defined by the Sponsor:

- ***Nocturnal confirmed hypoglycemia*** is a confirmed hypoglycemic episode with time of onset between 00:01 and 05:59 hours.

- ***Daytime confirmed hypoglycemia*** is a confirmed hypoglycemic episode with time of onset between 06:00 and 24:00 hours.

- ***ADA Documented symptomatic hypoglycemia*** is an episode during which typical symptoms of hypoglycemia are accompanied by a measured PG concentration < 3.9 mmol/L.

Upon request from the review team at DMEP, a binary endpoint for the occurrence of at least one confirmed hypoglycemia event during the treatment emergent period was defined post-hoc as a secondary endpoint. This endpoint will be referred to as "***At least one episode of confirmed hypoglycemia".***

3.2.3 Adjudication Methods

Only severe hypoglycemic episodes and episodes classified as serious adverse events (SAEs) and medical events of special interest were adjudicated by an independent, blinded, external consultant. Adjudication was done retrospectively. Case narratives were classified as 'severe hypoglycemia', 'not severe hypoglycemia', 'not possible to classify (contradiction)' or 'not possible to classify (missing information)'.

3.3 Statistical Methodologies

This section describes the statistical models used to evaluate the endpoints listed in Section 3.2.

3.3.1 Primary Analysis of the Primary Endpoint

The agreed upon primary analysis compares the rate ratio (RR) of confirmed hypoglycemia episodes between subjects randomized to IDeg OD 100U/mL or IDeg OD 200U/mL and subjects randomized to IGlar OD in trials 3583, 3770, 3582, 3579, 3672, 3586 and 3668. The null hypothesis is H_0: RR $\geq$ 1 vs. the alternative H_A: RR < 1. The null hypothesis will be rejected if the upper bound of the 95% confidence interval for the RR is smaller than 1 (i.e. the hypothesis is tested at the one-sided α=0.025 level).

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The primary analysis includes trials for both T1DM and T2DM and assumes that the RR of confirmed hypoglycemia is the same for all trials. A sensitivity analysis including the interaction between treatment and type of diabetes is discussed in the next section. If this interaction term is statistically significant, then sensitivity and subgroup analyses in this review will adjust for type of diabetes.

The primary endpoint is defined as the total number of confirmed hypoglycaemic episodes for each subject. Subjects may have multiple recorded episodes. In order to analyze this type of count data, the sponsor proposed a negative binomial regression model with a log-link function and the logarithm of the time where episodes were considered treatment-emergent as an offset. This time is calculated as extent of exposure + 7 days. The model can be written as follows:

$$\log \mu_i = \log t_i + \alpha_i + \delta_i + \gamma_i + \eta_i + \tau_i + \omega \cdot x_i$$

where:

- μ_i is the expected number of confirmed hypoglycemia episodes for subject *i*,
- t_i denotes the length of the time period where episodes are considered treatment emergent for subject *i*,
- α_i is a categorical variable with 7 levels denoting the trial the subject was randomized in,
- δ_i denotes randomized treatment (IDeg OD vs. IGlar OD),
- γ_i denotes whether the subject was treated with insulin at baseline,
- η_i denotes gender,
- τ_i denotes geographic region of randomization (six levels: Europe, North America, South America, Africa, Asia excluding Japan, and Japan),
- x_i denotes the subject's age, and
- ω denotes the effect of age on the rate of confirmed hypoglycemia.

<u>Reviewer's comment:</u>
The proposed negative binomial model is one of many possible statistical models for count data. The model can vary by the covariates it includes, such as the sensitivity analysis discussed in the next section, which includes the interaction of treatment and type of diabetes. Models can also vary by the statistical distribution chosen to fit the data; in this review we estimate the goodness of fit of the proposed negative binomial model and compare it to a zero-inflated negative binomial model that may more adequately capture data with a high proportion of subjects with no events. The appendix includes a detailed discussion of these models' goodness of fit. The zero-inflated negative binomial model discussed in the appendix was not proposed by the Sponsor but included by this reviewer to assess the robustness of the study findings.

3.3.2 Sensitivity Analysis of the Primary Endpoint

The following sensitivity analyses are discussed in this review. These sensitivity analyses were pre-specified in the SAP:

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- A negative binomial model similar to the primary model discussed in the previous section, which also includes a term for the interaction of treatment by type of diabetes. This model allows for a different RR of confirmed hypoglycemia, comparing IDeg OD vs. IGlar OD, in subjects with T1DM and T2DM.
- A random effects model will be fit with a random intercept for each trial to estimate the RR of confirmed hypoglycemia comparing IDeg OD vs. IGlar OD. This model will be compared to the primary fixed effects model to evaluate whether the estimated RR are sensitive to the choice of fixed or random effects. The random effects model will include an interaction term of treatment by type of diabetes if this interaction was statistically significant in the fixed effects model.
- A negative binomial model similar to the primary model discussed previously, which also includes terms for the interaction between treatment and trial. This model is fit for the purpose of producing forest plots of the estimated RR of confirmed hypoglycemia, and corresponding 95% confidence interval, for each of the 7 trials in the primary analysis. This model allows for a different RR of confirmed hypoglycemia in each trial. The purpose of this model is to estimate a RR for each trial controlling for other covariates.
- A non-parametric, Wilcoxon rank-sum test, comparing IDeg OD vs. IGlar OD on the rate of confirmed hypoglycemia stratified by trial. This analysis will be done across all 7 trials in the primary analysis, and separately for the 2 T1DM trials and the 5 T2DM trials. Non-parametric models are more robust to subjects with large number of events, but can control for covariates through stratification only.

3.3.3 Analysis of Secondary Endpoints

A negative binomial model similar to the primary model described in Section 3.3.1 will be fit to estimate the RR of the secondary endpoints: confirmed nocturnal hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia, comparing IDeg OD vs. IGlar OD. The model will be fit with and without an interaction term for randomized treatment and type of diabetes.

For the analysis of the binary outcome of at least one episode of confirmed hypoglycemia, a logistic model will be fit to estimate the odds ratio of experiencing at least one confirmed hypoglycemia event comparing IDeg to IGlar. The logistic model will include log(time) as an offset and the same covariates as the primary negative binomial model: region, treatment, insulin use at baseline, age, gender, and the interaction of treatment by type of diabetes.

3.3.4 Additional Sensitivity Analyses

A negative binomial model, again similar to the model described in Section 3.1.1, will be fit to estimate the RR of confirmed hypoglycemia comparing IDeg 3TW vs. IGlar OD in the 2 trials with an IDeg 3TW treatment arm: 3718 and 3724.

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3.3.4 Subgroup Analyses

Rate ratios for the primary endpoint will be calculated by subgroups of gender, age, race, country of randomization, BMI at baseline, and duration of diabetes at baseline. Within each subgroup, rate ratios will be estimated separately by type of diabetes. In order to be consistent with the analysis of the primary endpoint in Section 3.3.1, subgroup rate ratios are calculated based on a negative binomial model with a fixed effect for each trial and controlling for covariates: log(time), region, treatment, insulin use at baseline, age, gender, and the interaction of treatment by type of diabetes. In each case, the covariate corresponding to the subgroup of interest is excluded from the negative binomial model: for example, the negative binomial model for the subgroup analysis among females does not include gender in the model.

3.4 Populations

According to Novo Nordisk, the primary meta-analysis of hypoglycaemic episodes was conducted on the Full analysis set (FAS), consisting of all randomized subjects. A Safety analysis set (SAS) was defined as all subjects receiving at least one dose of either IDeg OD or IGlar OD. In the datasets submitted by the sponsor, the number of subjects eligible to contribute information to the primary analysis is 4330 in the FAS and 4308 in the SAS, a difference of 22. However, 20 of these subjects are excluded from all analyses because their time on treatment is zero. The remaining 2 subjects (1 on IDeg, 1 on IGlar) had no observed hypoglycaemic events and contributed a total of 27 days to the denominator of the meta-analysis. Therefore, analyses conducted on the FAS and SAS are equivalent for all practical purposes. This review makes no further distinction between the two populations and uses the FAS in all analyses.

The FAS population for the primary analysis consists of 4330 subjects: 1431 randomized to IGlar OD (321 with T1DM, 1110 with T2DM), and 2899 randomized to IDeg OD (637 with T1DM, 2262 with T2DM).

Upon request from the review team at DMEP, secondary analyses will be conducted on the subset of trials 3582, 3586 and 3668. These are trials for T2DM which include subjects treated with insulin (trial 3583) and a sulfonylurea (trials 3586 and 3668). Subjects in these trials are expected to be at higher risk of hypoglycemia than subjects in other trials for T2DM.

3.5 Subject Disposition, Demographics and Baseline Characteristics

Demographic characteristics for subjects in the seven trials included in the primary analysis are shown separately by type of diabetes in Table 4 (T1DM) and Table 5 (T2DM).

A larger percentage of females were randomized to IGlar than IDeg: 44.5% vs. 41.6% in T1DM and 45.1% vs. 43.6% in T2DM. There was practically no difference between both treatment groups in terms of age and BMI. In both types of diabetes, subjects randomized to IDeg tended to have slightly longer duration of diabetes at baseline than subjects randomized to IGlar. There was a slightly higher percentage of White subjects randomized to IGlar (96.6%) than IDeg

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(93.9%) among subjects with T1DM. Small imbalances such as these are expected by chance due to randomization.

Appendix 2 shows the rate of study discontinuation by time and randomized treatment group for each of the seven trials in the primary analysis. In the two trials for T1DM, subjects randomized to IDeg had a higher study discontinuation rate at all times than subjects randomized to IGlar. Among trials for T2DM there is some heterogeneity in terms of study discontinuation rate: in trials 3582 and 3586 subjects randomized to IDeg dropped out of the study at a higher rate than subjects randomized to IGlar; in trial 3579 subjects randomized to IGlar had a higher discontinuation rate; there was no clear difference in trials 3672 and 3668.

Reviewer Comment:
The analyses in this review assume that a subject's probability to drop out from the study is independent of his/her rate of hypoglycemia.

Table 4. Baseline characteristics of subjects with T1DM in the primary analysis

	IDeg OD (*N =637*)	**IGlar OD** (*N =321*)
Total patient-years	508.5	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/m^2)	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. Datasets: hypo.xpt, S.xpt. Trials: 3583, 3770.

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Table 5. Baseline characteristics of subjects with T2DM in the primary analysis

	IDeg OD (*N =2262*)	IGlar OD (*N =1110*)
Total patient-years	1675.1	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/m^2)	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. Datasets: hypo.xpt, S.xpt.
Trials: 3582, 3579, 3672, 3586 and 3668.

3.6 Analysis Results

3.6.1 Descriptive Statistics

Appendix 1 shows plots of the average number of confirmed hypoglycemia events through time, by treatment group, in each of the 7 trials in the primary analysis. Figure 6 shows that subjects with T1DM, in trials 3583 and 3770, randomized to IDeg OD tended to experience more events than subjects randomized to IGlar OD throughout the duration of the trials. Figure 7 shows that among subjects with T2DM, those randomized to IGlar OD tended to experience more events, particularly after 15 or 20 weeks, except in trial 3668, where subjects on IDeg OD seemed to experience slightly more events than subjects on IGlar OD.

The time of follow-up varied by trial and subject, therefore descriptive statistics of the raw counts of confirmed hypoglycemia events are not easily comparable across studies. In order to produce meaningful descriptive statistics, the standardized annual rate of events, and not the raw event count, is presented and discussed in the following tables. Table 6 shows the annual rate of confirmed hypoglycemia for the 9 trials submitted by the sponsor. There is clear heterogeneity in the rate of confirmed hypoglycemia by type of diabetes, with a much higher rate in subjects with

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T1DM, and by type of therapy within subjects with T2DM, with a higher rate of hypoglycemia in subjects with basal-bolus therapy. The proposed statistical models account for these two factors.

Table 6. Observed rate of confirmed hypoglycemia events by trial

			Annual rate of confirmed hypoglycemia. Mean (SD)		
	Trial	weeks	IGlar OD	IDeg OD	IDeg 3TW
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)	-
T2DM IDeg 3TW OAD-Insulin Combination Therapy	3718	26	0.9 (2.5)	-	1.5 (3.4)
	3724	26	1.1 (2.6)	-	1.2 (3.0)

Source: Created by reviewer. Dataset: hypo.xpt

Table 7 shows the observed distribution of confirmed hypoglycemia by type of diabetes in the 7 trials included in the primary meta-analysis. It shows that a large proportion of subjects with T2DM had no confirmed hypoglycemia events: 43.3% in the IDeg group and 47% in IGlar. The negative binomial models proposed by the sponsor may underestimate the probability of having no events among subjects with T2DM and as such, this review presents results from a zero-inflated negative binomial model which adequately captures the probability of no events. Appendix 5 discusses model fit of the negative binomial model and the post-hoc zero-inflated negative binomial model.

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

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

Datasets: hypo.xpt

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3.6.2 Primary Endpoint

3.6.2.1 Primary Analysis of Primary Endpoint

Table 8 shows the estimated rate ratio 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). There is evidence with borderline statistical significance that IDeg OD reduces the rate of confirmed hypoglycemia compared to IGlar OD. Full parameter estimates from the primary model are given in Appendix 3.

Table 8. 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: MA Report Table 7-2. Confirmed by reviewer. Dataset: hypo.xpt

The primary model assumes that the RR of confirmed hypoglycemia comparing IDeg to IGlar is constant across trials. Table 5 and Table 6 show that there is heterogeneity in the rate of hypoglycemia by trial and type of diabetes. Therefore, it is reasonable to evaluate whether the RR of hypoglycemia also varies by type of diabetes. This topic will be discussed in the following sections.

3.6.2.2 Sensitivity Analysis of Primary Endpoint

Figure 1 shows a forest plot of the estimated RR of confirmed hypoglycemia comparing IDeg OD vs. IGlar OD for each of the 7 trials with an IDeg OD arm, controlling for all other covariates included in the primary model. The plot shows that IDeg appears to 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.

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Figure 1. IDeg OD vs. IGlar OD by trial

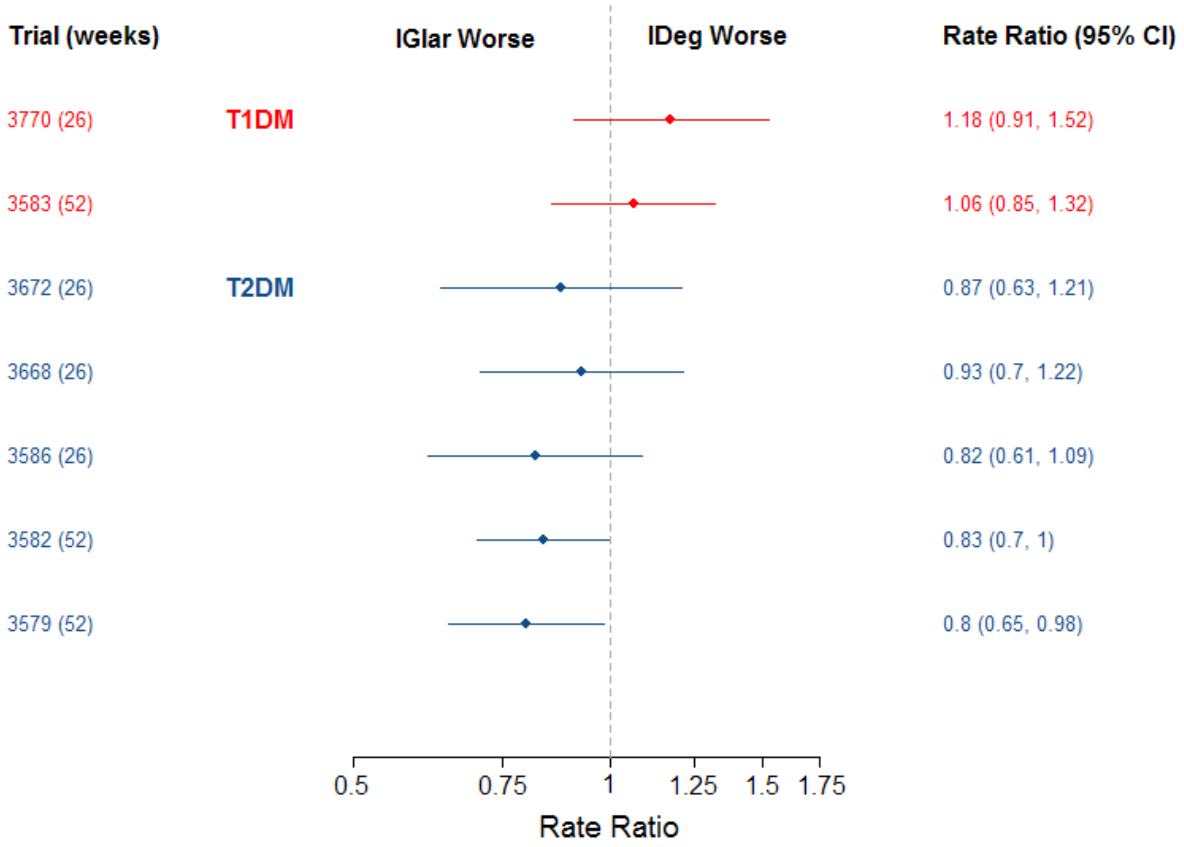

Table 9 shows parameter estimates and corresponding 95% confidence intervals for the RR of confirmed hypoglycemia in the model with a term for the interaction between randomized treatment and type of diabetes. Full parameter estimates from this model are shown in Appendix 4. The test of H_0: Interaction = 0 vs. the alternative H_A: Interaction ≠ 0 has a p-value of 0.0057, showing statistically significant evidence that the RR of confirmed hypoglycemia associated with IDeg vs. IGlar is different among subjects with T1DM and subjects with T2DM.

Primary endpoint results by diabetes type (T1DM and T2DM) are provided in Table 10. The estimated RR of 1.11 (0.94, 1.31) among subjects with T1DM shows no statistically significant difference between IDeg and IGlar. Among subjects with T2DM, the model shows a statistically significant decrease in the rate of confirmed hypoglycemia associated with IDeg: RR 0.84 (0.76, 0.93).

Reviewer Comment:
Appendix 5 shows that the model with a treatment by type of diabetes interaction fits the data better than the proposed primary model without an interaction. Therefore, in this review all sensitivity and subgroup analyses include a treatment by type of diabetes interaction.

Appendix 6 discusses a post-hoc sensitivity analysis: a zero-inflated negative binomial (ZINB) model. Fit statistics discussed in the appendix show that the ZINB model fits the data better than the negative binomial models with or without an interaction term. Based on results shown in Table 8 and Appendix 6, the ZINB model reaches the same conclusion as the sensitivity analysis discussed in the previous paragraph: IDeg is associated with a decrease in the rate of confirmed hypoglycemia in subjects with T2DM and with a non-statistically significant numerical increase in the rate of confirmed hypoglycemia among subjects with T1DM. A complete discussion of the ZINB model is found in the appendix.

Table 9. Sensitivity analysis: primary model + interaction term

Parameter	log RR	SE
IDeg	0.102	0.085
(IDeg * T2DM) Interaction	-0.278	0.101
T1DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	637	321
Subjects used in analysis	637	316
Rate Ratio (95% CI)	***1.11 (0.94, 1.31)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	2262	1110
Subjects used in analysis	2249	1105
Rate Ratio (95% CI)	***0.84 (0.76, 0.93)***	

Source: MA Report Table 7-3. Confirmed by reviewer. Dataset: hypo.xpt

Table 10 shows estimated RR and 95% confidence intervals for a model with random intercepts for each trial, instead of the fixed effects used in the models discussed above. The random effects model produced very similar RR estimates and slightly larger confidence intervals. There were no important differences between the fixed effects and random effects models.

Table 10. Sensitivity analysis: random effects model

Rate Ratio (95% CI) in **T1DM**	***1.12 (0.93, 1.35)***
Rate Ratio (95% CI) in **T2DM**	***0.84 (0.75, 0.94)***

Dataset: hypo.xpt

3.6.2.3 Non-Parametric Analysis of Primary Endpoint

Table 11 shows p-values for a Wilcoxon rank-sum test comparing IDeg OD vs. IGlar OD on the number of episodes and the rate of confirmed hypoglycemia, stratified by trial. Overall, this test showed no statistically significant difference between IDeg and IGlar. However, when this test is conducted among subjects with T1DM and T2DM separately, the test was statistically significant for T2DM but not so for T1DM. These results are consistent with the sensitivity analyses discussed in the previous section.

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Table 11. IDeg OD vs. IGlar OD stratified Wilcoxon test

	p-value
Number of Episodes (not adjusting for trial duration)	0.1698
Rate of Episodes	0.2928

Source: MA Report Table 98. Confirmed by reviewer. Dataset: hypo.xpt

Table 12. IDeg OD vs. IGlar OD stratified Wilcoxon test by type of diabetes

	p-value
T1DM: Rate of Episodes	0.1493
T2DM: Rate of Episodes	0.0416

Dataset: hypo.xpt

3.6.3 Secondary Endpoints

3.6.3.1 Nocturnal, severe and ADA documented hypoglycemia

Table 13, Table 14 and Table 15 show RR estimates for nocturnal confirmed hypoglycemia, severe hypoglycemia and ADA documented hypoglycemia comparing IDeg OD vs IGlar OD. These tables are mostly consistent with the analyses discussed in previous sections: IDeg appears to be no better than IGlar at reducing the rate of hypoglycemia in subjects with T1DM, but there is some evidence suggesting that IDeg may reduce the rate of hypoglycemia in subjects with T2DM. However, only nocturnal confirmed hypoglycemia reached statistical significance among subjects with T2DM: RR 0.69 (0.59, 0.81). The estimated benefit of IDeg was not statistically significant for severe hypoglycemia: RR 0.74 (0.40, 1.36), and there was no difference between treatments for ADA documented hypoglycemia: RR 1.01 (0.94, 1.10).

Nocturnal Confirmed Hypoglycemia

Table 13. IDeg OD vs. IGlar OD, nocturnal confirmed hypoglycemia

Model without an Interaction term:	
Rate Ratio (95% CI)	***0.74 (0.65, 0.85)***
Model with an (IDeg x T2DM) Interaction term:	
Rate Ratio (95% CI) in **T1DM**	***0.85 (0.68, 1.06)***
Rate Ratio (95% CI) in **T2DM**	***0.69 (0.59, 0.81)***

Source: MA Report Table 7-4. Confirmed by reviewer. Dataset: hypo.xpt

Severe Hypoglycemia

Table 14. IDeg OD vs. IGlar OD, severe hypoglycemia

Model without an Interaction term:	
Rate Ratio (95% CI)	***0.92 (0.63, 1.36)***
Model with an (IDeg x T2DM) Interaction term:	
Rate Ratio (95% CI) in **T1DM**	***1.06 (0.65, 1.73)***
Rate Ratio (95% CI) in **T2DM**	***0.74 (0.40, 1.36)***

ADA documented Hypoglycemia

Table 15. IDeg OD vs. IGlar OD, documented symptomatic hypoglycemia

Model without an Interaction term:	
Rate Ratio (95% CI)	***1.04 (0.97, 1.11)***
Model with an (IDeg x T2DM) Interaction term:	
Rate Ratio (95% CI) in **T1DM**	***1.12 (0.98, 1.29)***
Rate Ratio (95% CI) in **T2DM**	***1.01 (0.94, 1.10)***

Source: Dataset: hypo.xpt.

3.6.3.2 Binary endpoint

Table 16 shows estimated odds ratios for the binary outcome of experiencing at least one confirmed hypoglycemia event. Among subjects with T1DM, there was no difference between IDeg OD and IGlar OD. Among subjects with T2DM, those randomized to IDeg were less likely to experience at least one event than those randomized to IGlar OR 0.72 (0.59, 0.86). In other words, among subjects with T2DM, subjects randomized to IDeg were more likely to be hypoglycemia free. These results are consistent with the primary analysis and show a lower probability of hypoglycemia among subjects with T2DM randomized to IDeg; and show no difference between IDeg and IGlar among subjects with T1DM.

Table 16. IDeg OD vs. IGlar OD, odds ratio of at least one confirmed hypoglycemia events

Odds Ratio (95% CI) in **T1DM**	***1.04 (0.75, 1.43)***
Odds Ratio (95% CI) in **T2DM**	***0.72 (0.59, 0.86)***

Reference ID: 3139787

3.6.4 Additional Sensitivity Analyses

3.6.4.1 Confirmed Hypoglycemia in Trials with IDeg 3TW

Table 17 shows RR estimates comparing IDeg 3TW vs. IGlar OD in trials 3718 and 3724. Both trials were conducted in subjects with T2DM. The estimated RR in these trials is 1.34 with 95% CI (1.00, 1.81). The estimated RR and confidence interval show a possible increase in the rate of confirmed hypoglycemia associated with IDeg 3TW compared to IGlar OD among subjects with T2DM.

It is unclear whether this result is concerning given that the sponsor does not seek approval of the IDeg 3TW regimen, and that the observed rate of confirmed hypoglycemia in these two trials was the lowest among all 9 trials: lower than 1.5 events per year in any treatment arm, such that the observed RR of 1.34 may be less clinically worrisome than a similar rate ratio in a population with a higher background rate of events.

Table 17. IDeg 3TW vs. IGlar OD, confirmed hypoglycemia

Rate Ratio (95% CI)	***1.34 (1.00, 1.81)***

Source: Dataset: hypo.xpt. Analysis conducted in studies 3718 and 3724 only.

3.6.4.2 Primary and Secondary Hypoglycemia Endpoints in T2DM Trials with Subjects at High Risk of Hypoglycemia (3582, 3586 and 3668)

Upon request from the review team at DMEP, secondary analyses were conducted on the subset of trials 3582, 3586 and 3668. These are trials for T2DM which include subjects treated with insulin (trial 3583) and a sulfonylurea (trials 3586 and 3668). Subjects in these trials are expected to be at higher risk of hypoglycemia than subjects in other trials for T2DM.

Table 18 - Table 21 show RR estimates for confirmed hypoglycemia, nocturnal confirmed hypoglycemia, severe hypoglycemia and ADA documented hypoglycemia among subjects randomized in trials 3582, 3586 and 3668. These tables suggest that IDeg might be associated with a statistically significant decrease in the rate of confirmed hypoglycemia (RR 0.84, 95% CI 0.73-0.96) and nocturnal confirmed hypoglycemia (RR 0.70, 95% CI 0.56-0.87). There was no statistically significant difference between IDeg and IGlar in the rate of severe hypoglycemia (RR 1.03, 95% CI 0.58-1.89) and ADA documented hypoglycemia (RR 0.96, 95% CI 0.86-1.06).

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Primary endpoint: confirmed hypoglycemia

Table 18. IDeg OD vs. IGlar OD, confirmed hypoglycemia in trials 3582, 3586 and 3668

Rate Ratio (95% CI)	***0.84 (0.73, 0.96)***

Source: Dataset: hypo.xpt. Analysis conducted in studies 3582, 3586 and 3668 only.

Nocturnal confirmed hypoglycemia

Table 19. IDeg OD vs. IGlar OD, nocturnal confirmed hypoglycemia in trials 3582, 3586 and 3668

Rate Ratio (95% CI)	***0.70 (0.56, 0.87)***

Source: Dataset: hypo.xpt. Analysis conducted in studies 3582, 3586 and 3668 only.

Severe hypoglycemia

Table 20. IDeg OD vs. IGlar OD, severe hypoglycemia in trials 3582, 3586 and 3668

Rate Ratio (95% CI)	***1.03 (0.58, 1.89)***

Source: Dataset: hypo.xpt. Analysis conducted in studies 3582, 3586 and 3668 only.

ADA documented hypoglycemia

Table 21. IDeg OD vs. IGlar OD, documented symptomatic hypoglycemia in trials 3582, 3586 and 3668

Rate Ratio (95% CI)	***0.96 (0.86, 1.06)***

Source: Dataset: hypo.xpt. Analysis conducted in studies 3582, 3586 and 3668 only.

4 Findings in special/subgroup populations

4.1 Gender, Race, Age and Country

Evaluations for gender, race, age and country are presented in the paragraphs that follow for the primary endpoint – confirmed hypoglycemia. Forest plots combining all results are presented in Figure 4 and Figure 5. There were no protocol-defined multiplicity corrections for subgroup analyses and as such results are presented using unadjusted 95% confidence intervals for each of the subgroup analyses according to the methodology described in Section 3.3.4.

Reference ID: 3139787

Gender

The percentage of females was 42.6% among randomized subjects with T1DM and 44% among subjects with T2DM. Table 22 shows the estimated rate ratio of confirmed hypoglycemia associated with IDeg by type of diabetes among females. Table 23 shows the same information for males. Results are consistent between males and females, and with previous analyses: IDeg OD is associated with a decrease in the RR of confirmed hypoglycemia in subjects with T2DM; IDeg OD is associated with a numerically higher, but not statistically significant increase in the RR of confirmed hypoglycemia in subjects with T1DM.

Table 22. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Females

T1DM	IDeg OD	IGlar OD
Total subjects randomized	265	143
Rate Ratio (95% CI)	***1.14 (0.90, 1.46)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	985	500
Rate Ratio (95% CI)	***0.83 (0.71, 0.96)***	

Source: Dataset: hypo.xpt.

Table 23. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Males

T1DM	IDeg OD	IGlar OD
Total subjects randomized	372	178
Rate Ratio (95% CI)	***1.07 (0.86, 1.35)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1277	610
Rate Ratio (95% CI)	***0.84 (0.73, 0.97)***	

Source: Dataset: hypo.xpt.

Race

Among subjects with T1DM, 94.8% had their race recorded as “White”, 1.7% as “Black or African American”, and the remaining 3.5% as multiracial or other races. Due to the small number of subjects of races other than White, subgroup analyses for subjects with T1DM will be conducted among White subjects only.

Among subjects with T2DM, 71.1% had their race recorded as “White”, 19.9% as “Asian”, 7.2% as “Black or African American”, and the remaining 1.8% as multiracial or other.

Table 24 shows the RR of confirmed hypoglycemia in White subjects by type of diabetes. The results are consistent with the primary analysis: White subjects with T1DM show a non-statistically significant increase in the rate of hypoglycemia associated with IDeg, RR 1.12 (0.95, 1.32); while subjects with T2DM show a statistically significant decrease RR 0.81 (0.72, 0.92).

Table 25 and Table 26 show results for Black and Asian subjects with T2DM. Due to the small number of randomized Black subjects, the estimated RR has a wide confidence interval: RR 1.15 (0.75, 1.77). Among Asian subjects, the estimated RR 0.85 (0.66, 1.09) is consistent with the RR estimated among White subjects.

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Table 24. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Race=White

T1DM	IDeg OD	IGlar OD
Total subjects randomized	598	310
Rate Ratio (95% CI)	***1.12 (0.95, 1.32)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1632	766
Rate Ratio (95% CI)	***0.81 (0.72, 0.92)***	

Source: Dataset: hypo.xpt.

Table 25. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Race=Black

T2DM	IDeg OD	IGlar OD
Total subjects randomized	163	81
Rate Ratio (95% CI)	***1.15 (0.75, 1.77)***	

Source: Dataset: hypo.xpt.

Table 26. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Race=Asian

T2DM	IDeg OD	IGlar OD
Total subjects randomized	431	241
Rate Ratio (95% CI)	***0.85 (0.66, 1.09)***	

Source: Dataset: hypo.xpt.

Age

Among subjects with T1DM, 93.6% were under 65 years of age. Among subjects with T2DM, 75% were under 65 years of age. Table 27 and Table 28 show that in both age groups IDeg OD was associated with a small increase in the rate of confirmed hypoglycemia in subjects with T1DM. IDeg OD was associated with a decrease in the rate of confirmed hypoglycemia in both age groups among subjects with T2DM. These results are consistent with the primary analysis.

Table 27. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Age < 65

T1DM	IDeg OD	IGlar OD
Total subjects randomized	594	303
Rate Ratio (95% CI)	***1.09 (0.92, 1.30)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1673	845
Rate Ratio (95% CI)	***0.86 (0.76, 0.97)***	

Source: Dataset: hypo.xpt.

Reference ID: 3139787

Table 28. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Age ≥ 65

T1DM	IDeg OD	IGlar OD
Total subjects randomized	43	18
Rate Ratio (95% CI)	***1.46 (0.75, 2.86)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	589	265
Rate Ratio (95% CI)	***0.77 (0.62, 0.96)***	

Source: Dataset: hypo.xpt.

Since 'Age' was a pre-specified subgroup of special interest in the SAP, we estimated the rate ratio of the secondary endpoints nocturnal confirmed hypoglycemia and severe hypoglycemia by age subgroups. The results are shown in Table 29 - Table 32. These tables show that IDeg appears to be associated with a decrease in the rate of nocturnal confirmed hypoglycemia in both age groups, with more narrow confidence intervals for T2DM.

There were large differences between age categories in the estimated RR of severe hypoglycemia. Among subjects under age 65, IDeg was associated with an increase in the rate of severe hypoglycemia in subjects with both types of diabetes. Among subjects age 65 and older, IDeg was associated with a small decrease in the rate of severe hypoglycemia. These results suggest a possible interaction between IDeg and Age in the rate ratio of severe hypoglycemia. We fit a model for the rate of severe hypoglycemia with both treatment by type of diabetes, and treatment by age interaction terms. In this exploratory model, the interaction between treatment and age, measured as a continuous variable has a p-value of 0.1160, suggesting that perhaps the differences between Table 31 and Table 32 are due to chance, or to the categorization of age as under 65, or 65 and older.

Table 29. IDeg OD vs. IGlar OD, nocturnal confirmed hypoglycemia, Age < 65

Rate Ratio (95% CI) in **T1DM**	***0.84 (0.68, 1.05)***
Rate Ratio (95% CI) in **T2DM**	***0.70 (0.59, 0.85)***

Source: Dataset: hypo.xpt.

Table 30. IDeg OD vs. IGlar OD, nocturnal confirmed hypoglycemia, Age ≥ 65

Rate Ratio (95% CI) in **T1DM**	***0.81 (0.29, 2.24)***
Rate Ratio (95% CI) in **T2DM**	***0.64 (0.44, 0.93)***

Source: Dataset: hypo.xpt.

Table 31. IDeg OD vs. IGlar OD, severe hypoglycemia, Age < 65

Rate Ratio (95% CI) in **T1DM**	***1.11 (0.66, 1.86)***
Rate Ratio (95% CI) in **T2DM**	***1.10 (0.46, 2.63)***

Source: Dataset: hypo.xpt.

Table 32. IDeg OD vs. IGlar OD, severe hypoglycemia, Age ≥ 65

Rate Ratio (95% CI) in **T1DM**	***0.58 (0.11, 2.99)***
Rate Ratio (95% CI) in **T2DM**	***0.57 (0.26, 1.24)***

Source: Dataset: hypo.xpt.

Reference ID: 3139787

Country

Among subjects with T1DM, 63.8% were randomized in the USA. Among subjects with T2DM, 32.7% were randomized in the USA. Table 33 and Table 34 show the estimated RR of confirmed hypoglycemia by place of randomization (USA vs. non-USA) and type of diabetes. Table 33 shows that among subjects randomized in the USA, there was almost no difference in overall rate of confirmed hypoglycemia between IDeg and IGlar in either type of diabetes: T1DM RR 0.99 (0.81, 1.20), and T2DM RR 0.97 (0.81, 1.15).
Table 34 shows that subjects randomized outside of the USA experienced a non-statistically significant higher rate of confirmed hypoglycemia associated with IDeg in T1DM, RR 1.28 (0.96, 1.71), and a statistically significant decrease in confirmed hypoglycemia in T2DM, RR 0.79 (0.69, 0.90).

Figure 2 shows a forest plot of the RR of confirmed hypoglycemia comparing IDeg OD to IGlar OD among subjects randomized in the USA, while Figure 3 shows the forest plot for subjects randomized outside the USA. In these plots trials 3770 and 3579 show large differences in RR of confirmed hypoglycemia between subjects randomized in the USA and outside the USA. In trial 3770 for T1DM, subjects randomized in the USA have an estimated RR of 0.87 (0.63, 0.21), while subjects randomized outside the USA have an estimated RR of 1.54 (1.03, 2.31). In trial 3579 for T2DM, subjects randomized in the USA have an estimated RR of 1.27 (0.89, 1.83), while subjects randomized outside the USA have an estimated RR of 0.70 (0.53, 0.91). It is unclear why these two trials show such large differences in estimated RR of confirmed hypoglycemia comparing IDeg to IGlar between subjects randomized in the USA and outside the USA.

Overall, these tables show that there is no evidence of lower risk of confirmed hypoglycemia associated with IDeg OD in subjects randomized in the USA with either type of diabetes. There is evidence of a statistically significant decrease in confirmed hypoglycemia among subjects with T2DM randomized outside of the USA.

Table 33. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Country = USA

T1DM	IDeg OD	IGlar OD
Total subjects randomized	416	195
Rate Ratio (95% CI)	***0.99 (0.81, 1.20)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	787	316
Rate Ratio (95% CI)	***0.97 (0.81, 1.15)***	

Source: Dataset: hypo.xpt.

Table 34. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Country ≠ USA

T1DM	IDeg OD	IGlar OD
Total subjects randomized	221	126
Rate Ratio (95% CI)	***1.28 (0.96, 1.71)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1475	794
Rate Ratio (95% CI)	***0.79 (0.69, 0.90)***	

Source: Dataset: hypo.xpt.

Reference ID: 3139787

Figure 2. IDeg OD vs. IGlar OD by trial, among subjects randomized in the USA

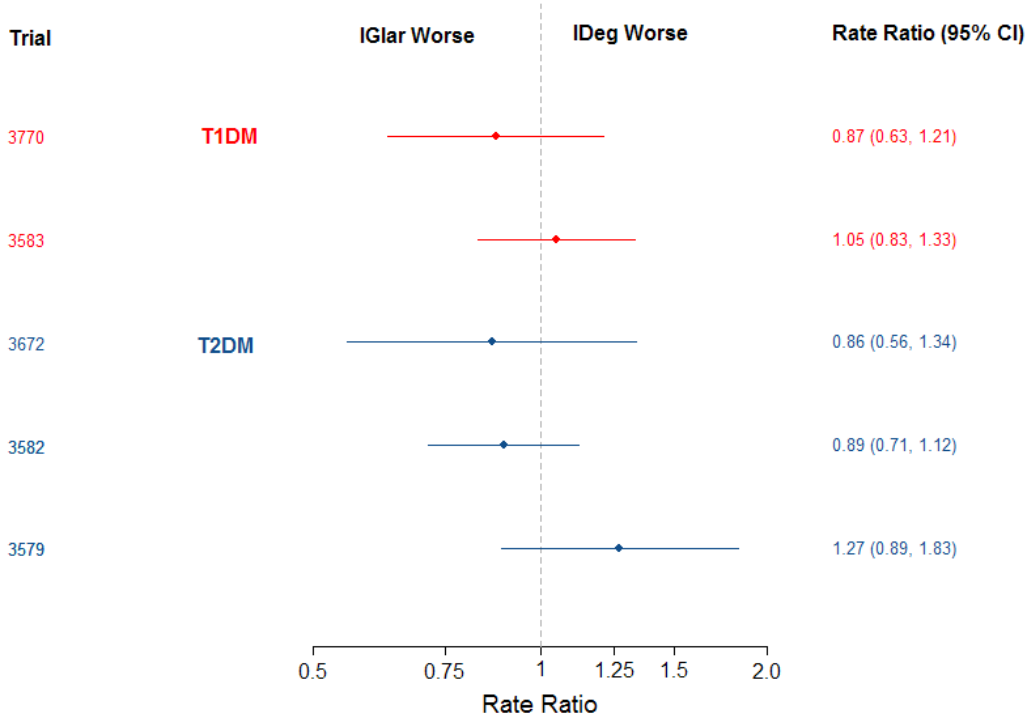
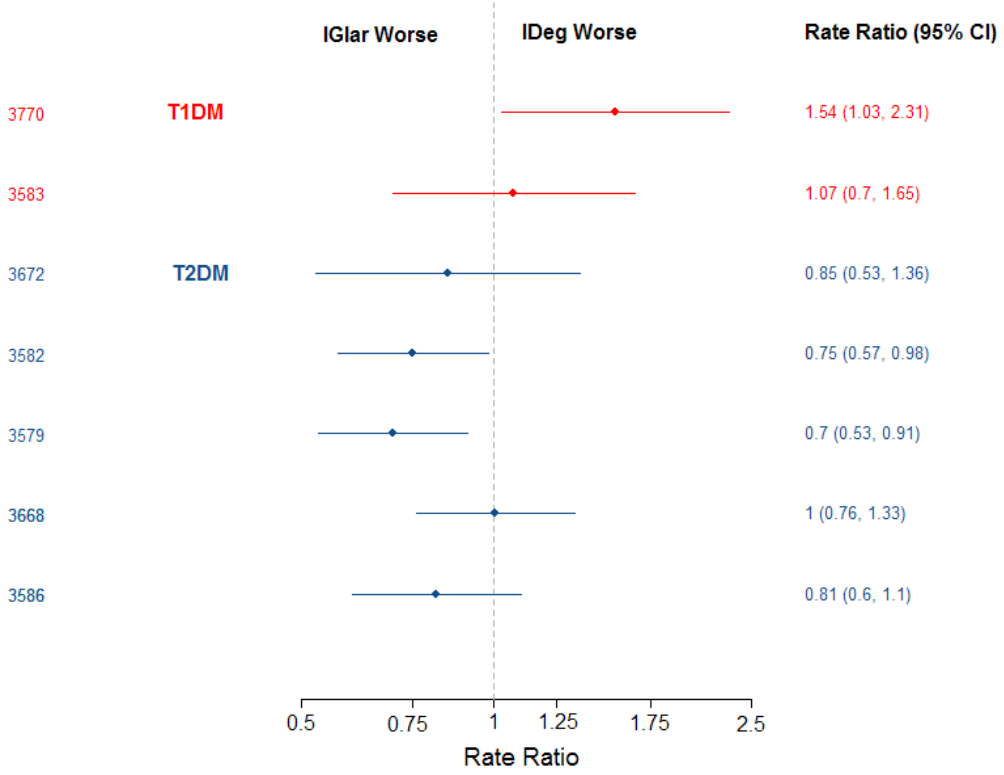


Figure 3. IDeg OD vs. IGlar OD by trial, among subjects randomized outside the USA



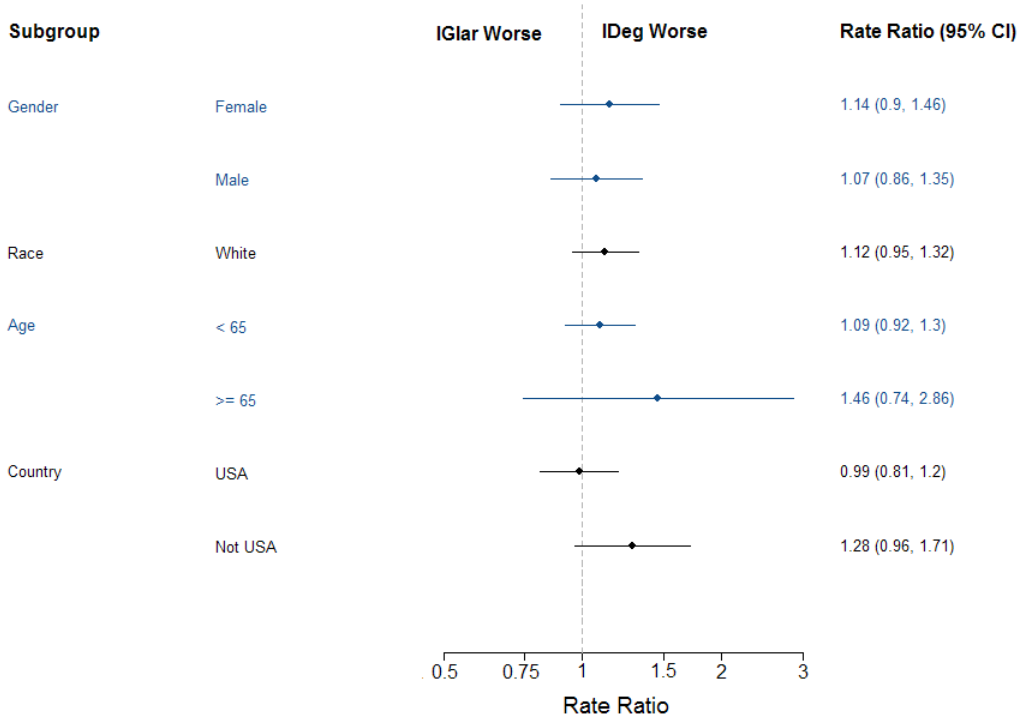
Summary of Subgroup Analyses

Figure 4 and Figure 5 show forest plots of the RR of confirmed hypoglycemia comparing IDeg OD vs. IGlar OD, by type of diabetes and subgroups of gender, race, age and country of randomization. Results are consistent for subgroups by gender, race and age: IDeg appears to be no different from IGlar among subjects with T1DM, and IDeg appears to be associated with a statistically significant decrease in the rate of confirmed hypoglycemia among subjects with T2DM. Subjects with T2DM and race recorded as Black or African American showed a numerically higher rate of confirmed hypoglycemia with IDeg, but the confidence interval was very wide due to the small subgroup sample size.

Analyses of nocturnal confirmed hypoglycemia by age category showed a lower rate of hypoglycemia associated with IDeg in subjects with T2DM, and a slightly lower rate in T1DM. Subjects under age 65 showed a slightly higher rate of severe hypoglycemia associated with IDeg, while subjects age 65 and older showed a slightly lower rate of severe hypoglycemia with IDeg.

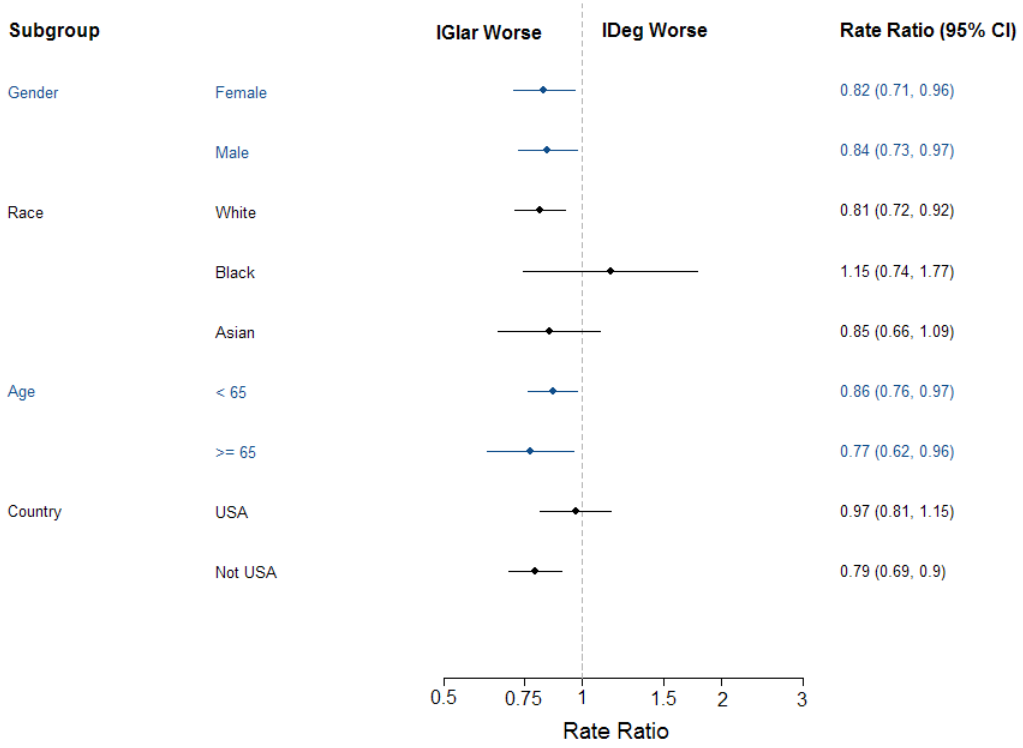
The analysis of subgroups by country showed differences between subjects randomized in the USA and subjects randomized outside the USA, as discussed previously. There was no difference in the rate of confirmed hypoglycemia between IDeg and IGlar in both T1DM and T2DM among subjects randomized in the USA.

Figure 4. IDeg OD vs. IGlar OD in subjects with T1DM



Reference ID: 3139787

Figure 5. IDeg OD vs. IGlar OD in subjects with T2DM



4.2 Other Special/Subgroup Populations

4.2.1 Baseline BMI and Diabetes Duration

BMI

Among subjects with T1DM, 81% had BMI ≤ 30. Among subjects with T2DM this proportion was 47%. The RR of confirmed hypoglycemia comparing IDeg OD to IGlar OD was not significantly different by BMI subgroups, after controlling for type of diabetes, as shown in Table 35 and Table 36. These analyses are consistent with the primary analysis and show a lower rate of confirmed hypoglycemia associated with IDeg OD among subjects with T2DM.

Table 35. IDeg OD vs. IGlar OD, confirmed hypoglycemia, BMI ≤ 30

T1DM	IDeg OD	IGlar OD
Total subjects randomized	527	249
Rate Ratio (95% CI)	***1.14 (0.96, 1.36)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1067	516
Rate Ratio (95% CI)	***0.86 (0.74, 0.99)***	

Datasets: hypo.xpt, S.xpt.

Table 36. IDeg OD vs. IGlar OD, confirmed hypoglycemia, BMI > 30

T1DM	IDeg OD	IGlar OD
Total subjects randomized	110	72
Rate Ratio (95% CI)	***1.21 (0.85, 1.71)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1203	596
Rate Ratio (95% CI)	***0.76 (0.65, 0.88)***	

Datasets: hypo.xpt, S.xpt.

Diabetes Duration

Among subjects with T1DM, 43.3% had had diabetes for 15 years or less at the time of randomization. Among subjects with T2DM this proportion was 76.6%. The estimated RR of confirmed hypoglycemia comparing IDeg OD to IGlar OD in subjects with T1DM did not change by duration of diabetes: RR 1.20 (0.94, 1.52) for subjects with 15 or fewer years of diabetes, and RR 1.17 (0.95, 1.42) for subjects with more than 15 years of diabetes. Among subjects with T2DM, both subgroups suggest a smaller rate of confirmed hypoglycemia associated with IDeg, but numerically this effect was slightly larger in subjects with more than 15 years of diabetes RR 0.70 (0.58, 0.85) than in subjects with 15 or fewer years of diabetes RR 0.87 (0.77, 0.99).

Table 37. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Diabetes Duration ≤ 15 years

T1DM	IDeg OD	IGlar OD
Total subjects randomized	266	149
Rate Ratio (95% CI)	***1.20 (0.94, 1.52)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	1713	879
Rate Ratio (95% CI)	***0.87 (0.77, 0.99)***	

Datasets: hypo.xpt, S.xpt.

Table 38. IDeg OD vs. IGlar OD, confirmed hypoglycemia, Diabetes Duration > 15 years

T1DM	IDeg OD	IGlar OD
Total subjects randomized	371	172
Rate Ratio (95% CI)	***1.17 (0.96, 1.42)***	
T2DM	**IDeg OD**	**IGlar OD**
Total subjects randomized	557	233
Rate Ratio (95% CI)	***0.70 (0.58, 0.85)***	

Datasets: hypo.xpt, S.xpt.

Reference ID: 3139787

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The SAP submitted on 04 June 2010 and revised on 16 August 2011 details the plan to compare the rate of hypoglycemia between IDeg OD and IGlar OD in 7 trials, and IDeg 3TW vs. IGlar OD in 2 additional trials. The agreed upon population of interest consists of all subjects randomized in these 9 trials, except for subjects randomized to IDeg fixed-flexible dosing, because this dosing scheme does not correspond to clinical practice. The primary endpoint of interest is the rate of confirmed hypoglycaemic episodes. Secondary endpoints include nocturnal confirmed hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia. These endpoints are defined in Section 3.2.

The observed rate of confirmed hypoglycemia varied significantly by trial. Among subjects with T1DM, the observed annual rate of events was as high as 87 events per year among subjects randomized to IDeg in trial 3770 and as low as 39 events per year among subjects randomized to IGlar in trial 3583. The annual rate of confirmed hypoglycemia was much lower among subjects with T2DM and ranged between approximately 1 event per year and 13 events per year.

The pre-specified primary analysis of the primary endpoint used a negative binomial model to estimate the rate ratio of confirmed hypoglycemia between IDeg OD and IGlar OD. The estimated RR in the primary model was ***0.91 (0.83, 0.99)*** and showed borderline statistically significant evidence that IDeg reduces the rate of confirmed hypoglycemia. This primary model assumes that the RR between IDeg and IGlar was constant between all trials. A sensitivity analysis fit a model with an interaction term between treatment and type of diabetes to test whether the RR is different for subjects with T1DM and T2DM. This model fit the data better than the primary model and showed that among subjects with T1DM, IDeg OD was not statistically different from IGlar OD in terms of confirmed hypoglycemia: ***RR 1.11 (0.94, 1.31)***. Among subjects with T2DM, IDeg OD was associated with a statistically significant decrease in the rate of confirmed hypoglycemia: ***RR 0.84 (0.76, 0.93).*** Sensitivity analyses of the primary endpoint included a random effects model, a zero-inflated negative binomial model, and a stratified, nonparametric Wilcoxon test. Results from these sensitivity analyses were consistent with the results from the primary analysis method.

Sensitivity analyses also looked at secondary endpoints such as confirmed nocturnal hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia. These analyses were mostly consistent with the primary endpoint analysis: IDeg appears to be no better than IGlar at reducing the rate of hypoglycemia in subjects with T1DM, but there is some evidence suggesting that IDeg may reduce the rate in subjects with T2DM. The estimated rate ratio of confirmed nocturnal hypoglycemia, ADA documented hypoglycemia and severe hypoglycemia was lower than 1 among subjects with T2DM, suggesting a possible protective effect associated with IDeg; however only nocturnal confirmed hypoglycemia reached statistical significance ***RR 0.69 (0.59-0.81).*** The estimated benefit of IDeg in T2DM was not statistically significant for severe hypoglycemia and the effect was very small and non-statistically significant for ADA documented hypoglycemia.

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Subgroup analyses by gender, age, race, BMI and duration of diabetes at baseline were consistent with the analyses discussed above: IDeg OD was associated with a decrease in the rate of confirmed hypoglycemia among subjects with T2DM, but was no different from IGlar OD among subjects with T1DM. Subgroup analyses by country showed considerable differences: among subjects randomized in the USA, IDeg OD was no different from IGlar OD in terms of the rate of confirmed hypoglycemia in either T1DM, ***RR 0.99 (0.81, 1.20)***, or T2DM, ***RR 0.97 (0.81, 1.15)***. However, among subjects randomized outside of the USA, IDeg OD had a higher rate of confirmed hypoglycemia than IGlar OD among subjects with T1DM: ***RR 1.28 (0.96, 1.71)*** and a lower rate among subjects with T2DM: ***0.79 (0.69, 0.90)***. Among subjects with T2DM randomized in the USA, two of three studies showed a trend for lower risk of confirmed hypoglycemia associated with IDeg (trials 3572 and 3582), but a third study (trial 3579) showed higher risk associated with IDeg.

Overall, the results of the primary analysis, as well as sensitivity and subgroup analysis were consistent and showed that IDeg OD was associated with a statistically significant reduction in the rate of confirmed hypoglycemia, compared to IGlar OD, among subjects with T2DM only, except among subjects randomized in the USA. Among secondary endpoints, only the estimated rate ratio of confirmed nocturnal hypoglycemia was statistically significant at $\alpha = 0.05$.Among subjects with T1DM, there was no statistically significant difference in the rate of hypoglycemia between IDeg OD and IGlar OD in either the primary or secondary endpoints.

5.2 Conclusions and Recommendations

Novo Nordisk compared the rate ratio of confirmed hypoglycemia between IDeg OD and IGlar OD through a negative binomial model combining 5 trials for T2DM and 2 trials for T1DM. Sensitivity analyses were conducted in two additional trials with an IDeg 3TW randomized treatment arm. These analyses were pre-specified and agreed upon on a SAP dated 04 June 2010.

Seven trials were used in the primary analysis: 3583, 3770, 3582, 3579, 3672, 3586 and 3668. A total of 4330 subjects contributed information to this analysis: 1431 randomized to IGlar OD (321 with T1DM, 1110 with T2DM), and 2899 randomized to IDeg OD (637 with T1DM, 2262 with T2DM).

Error! Reference source not found. shows a summary of the primary analysis for the overall RR of confirmed hypoglycemia comparing IDeg OD to IGlar OD, and an analysis for this RR by type of diabetes. The overall primary analysis shows a RR and 95% CI of ***0.91 (0.83, 0.99)*** and implies a borderline statistically significant reduction in the rate of confirmed hypoglycemia events associated with IDeg OD. The primary model assumes that the RR of confirmed hypoglycemia between IDeg OD and IGlar OD is the same whether a subject had type 1 or type 2 diabetes. The secondary analysis included an interaction term for randomized treatment by type of diabetes. The interaction term was statistically significant, p-value 0.0057, and suggests the rate ratio comparing IDeg to IGlar is different in subjects with different types of diabetes. Among subjects with T1DM, IDeg OD was not different from IGlar OD, with an estimated RR and 95% CI of ***1.11 (0.94, 1.31)***. Among subjects with T2DM, IDeg OD was associated with a

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statistically significant reduction in the rate of confirmed hypoglycemia, compared to IGlar OD, with an estimated RR and 95% CI of ***0.84 (0.76, 0.93)***.

Table 39. Summary of results: RR of confirmed hypoglycemia comparing IDeg OD vs. IGlar OD

Overall Rate Ratio (95% CI) (pre-specified primary analysis)	***0.91 (0.83, 0.99)***
T1DM Rate Ratio (95% CI)	***1.11 (0.94, 1.31)***
T2DM Rate Ratio (95% CI)	***0.84 (0.76, 0.93)***

A post-hoc Zero Inflated Negative Binomial Model was shown to fit the data better than any of the pre-specified Negative Binomial models based on the AIC fit criterion and the plots in Appendix 5. Both the ZINB and the negative binomials models reached similar conclusions for these data regarding the risk of confirmed hypoglycemia. The zero-inflated negative binomial model might be considered as either a primary or sensitivity analyses in SAPs for count data with a large proportion of subjects with zero events.

Subgroup analyses and sensitivity analyses were consistent with the results above, except for subgroups defined by country of randomization. The rate ratio of confirmed hypoglycemia comparing IDeg OD to IGlar OD among subjects with T1DM was 0.99 (0.81, 1.20) among subjects randomized in the USA, and 1.28 (0.96, 1.71) among subjects randomized outside the USA. Among subjects with T2DM, the estimated RR was 0.97 (0.81, 1.15) among subjects randomized in the USA, and 0.79 (0.69, 0.90) among subjects randomized outside the USA.

We recommend treating the effect of IDeg OD on hypoglycemia differently for subjects with Type I and Type II diabetes. In general, the event rates of hypoglycemia were higher in subjects with Type 1 diabetes than in subjects with Type 2 diabetes. There is 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. This treatment by type of diabetes interaction was highly statistically significant and was also observed in analyses of secondary endpoints, sensitivity analyses and subgroup analyses.

Based on the evidence reviewed in this document, we conclude that IDeg OD was associated with a reduction in the rate of confirmed hypoglycemia, compared to IGlar OD, in subjects with T2DM only. This reduction in the rate of confirmed hypoglycemia was not observed among subjects randomized in the USA.

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6 Appendix

Appendix 1. Average cumulative confirmed hypoglycemia events, by time and Study

The following plots show the average cumulative count of confirmed hypoglycemia events observed in each trial by randomized treatment. Note that since trials had different duration and patient populations, the rate of events varied considerably across trials. **These plots use different scales according to each trial's duration and rate of events; the scale was chosen for readability within each trial and not for comparability across trials. See Table 6 for a comparison of annual rates of events across trials.**

Figure 6. Cumulative confirmed hypoglycemia events in subjects with T1DM

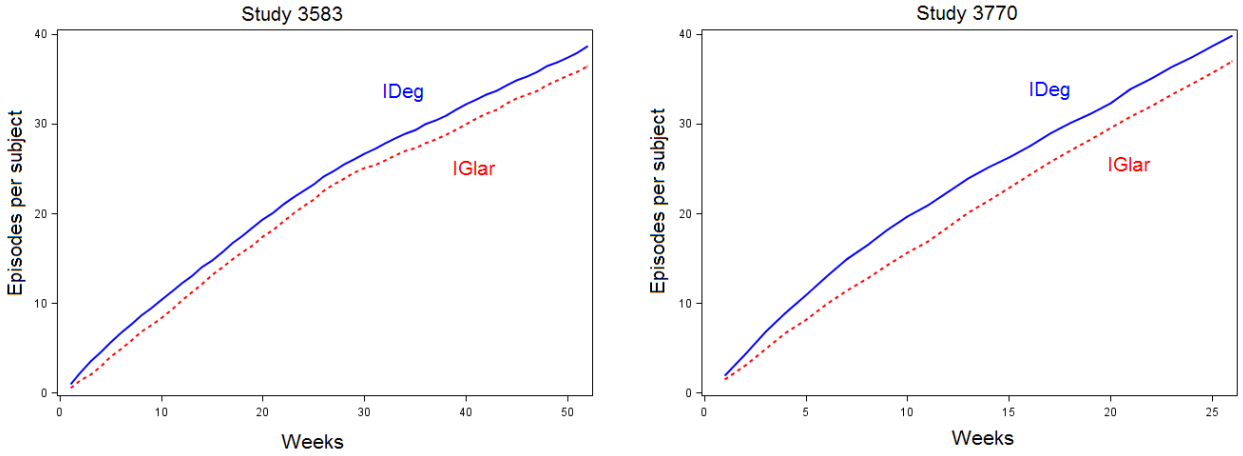
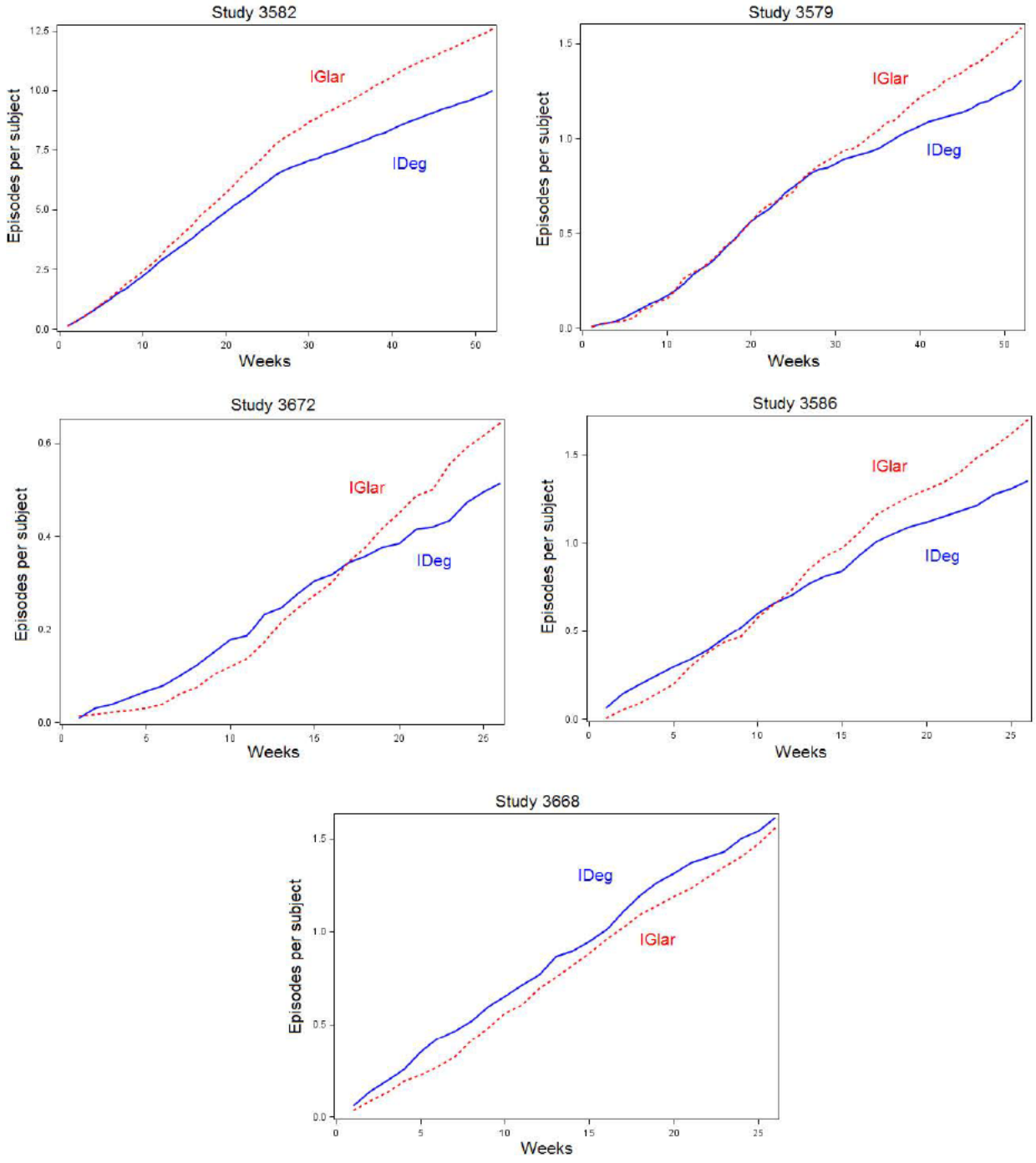


Figure 7. Cumulative confirmed hypoglycemia events in subjects with T2DM



Appendix 2. Study discontinuation rate by study

Figure 8. Study discontinuation rate in studies for T1DM

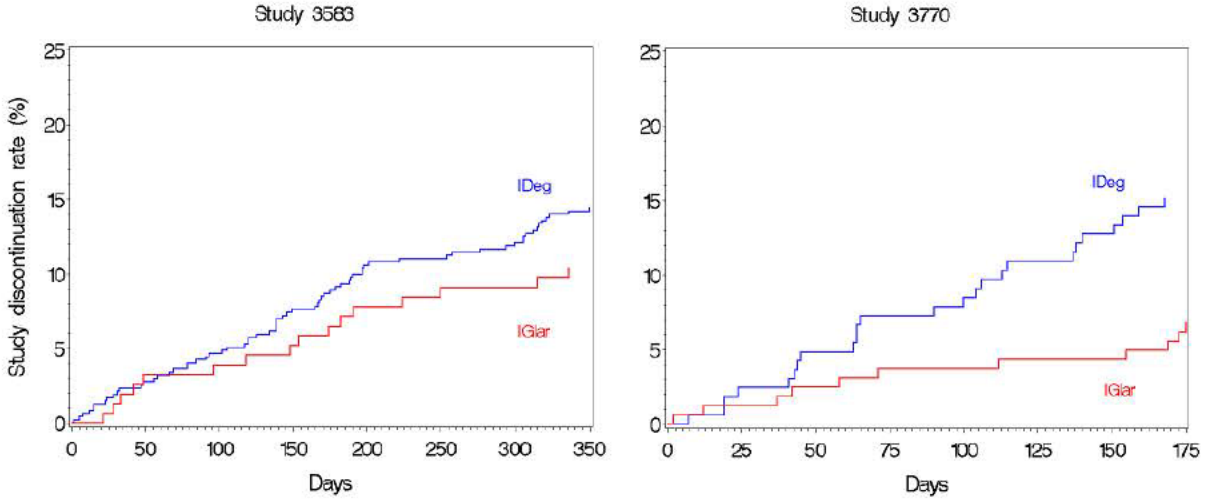
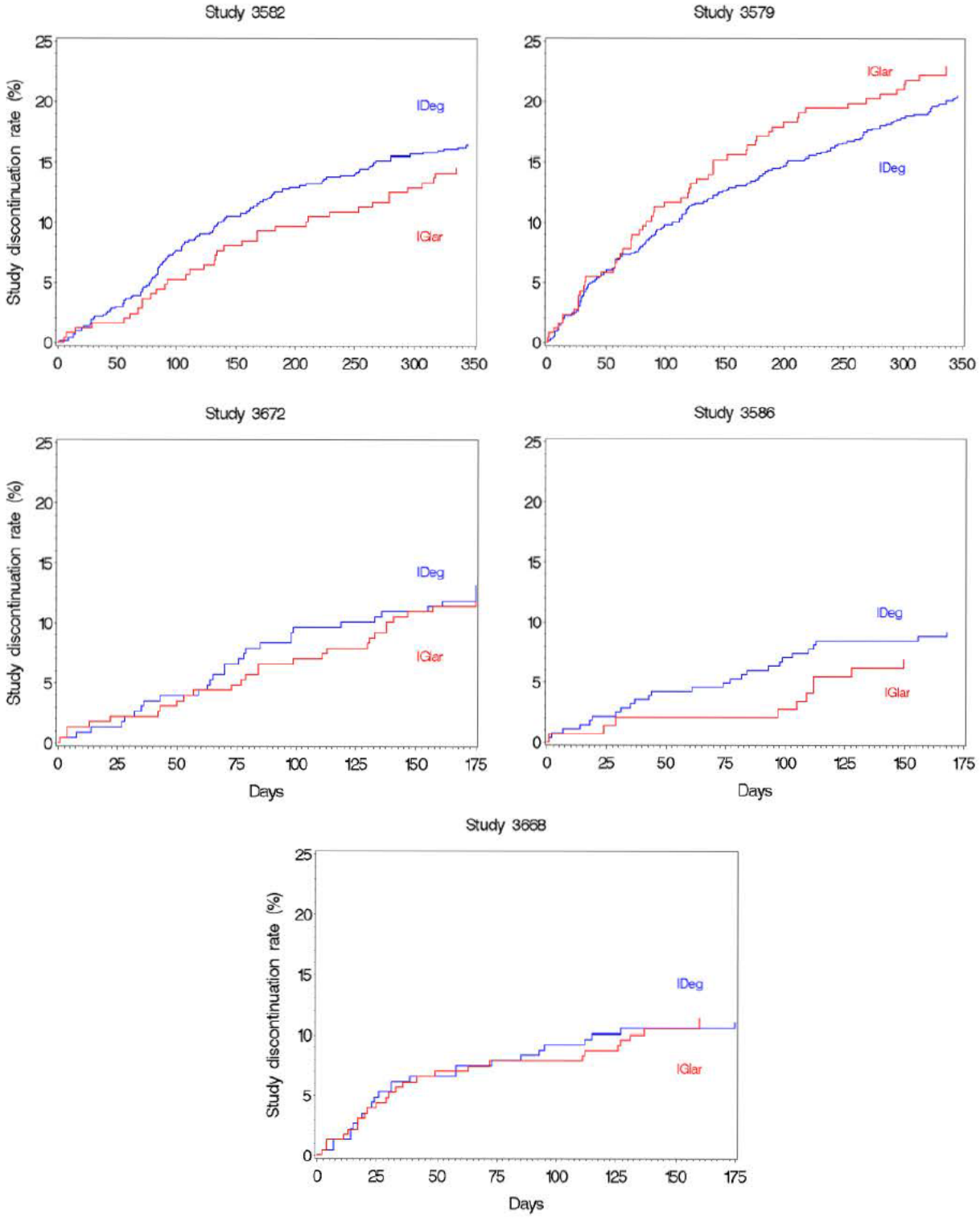


Figure 9. Study discontinuation rate in studies for T2DM



Appendix 3. The parameter estimates shown in this Table 40 correspond to the primary model in Section 3.6.2.1 and Table 8. The model estimates a RR of confirmed hypoglycemia of 0.91 (0.83, 0.99) associated with IDeg.

Table 40. Full parameter estimates from primary negative binomial model

	Estimate	SE	RR	RR 95% CI	P-value
Intercept	5.279	0.315	-		<.0001
log(offset)	0.975	0.051	2.652	(2.399, 2.931)	<.0001
Trial = 3582	1.351	0.155	3.861	(2.851, 5.228)	<.0001
Trial = 3583	2.714	0.161	15.090	(10.997, 20.706)	<.0001
Trial = 3586	0.206	0.181	1.229	(0.862, 1.750)	0.2541
Trial = 3668	0.336	0.131	1.400	(1.082, 1.810)	0.0104
Trial = 3672	-0.292	0.101	0.747	(0.613, 0.910)	0.0038
Trial = 3770	3.422	0.168	30.625	(22.022, 42.589)	<.0001
Region =Asia	0.240	0.153	1.271	(0.941, 1.716)	0.118
Region = Japan	0.486	0.214	1.625	(1.069, 2.472)	0.0231
Region = Europe	-0.280	0.048	0.755	(0.687, 0.831)	<.0001
Region = SAfrica	-0.108	0.126	0.897	(0.701, 1.148)	0.3891
Region = SAmerica	0.623	0.216	1.864	(1.222, 2.845)	0.0039
IDeg	**-0.098**	**0.046**	**0.906**	(0.829, 0.991)	**0.031**
Baseline Insulin	-0.594	0.141	0.552	(0.419, 0.728)	<.0001
Female	0.086	0.042	1.090	(1.004, 1.184)	0.04
Age	0.007	0.002	1.007	(1.003, 1.011)	0.0002

Reference levels: Trial = 3579; Region = North America

Appendix 4. The parameter estimates shown in Table 41correspond to the negative binomial model with a treatment by type of diabetes interaction in Section 3.6.2.2 and Table 9. The model estimates a RR of confirmed hypoglycemia associated with IDeg of 1.11 (0.94, 1.31) among subjects with T1DM and a RR of 0.84 (0.76, 0.93) among subjects with T2DM.

Table 41. Full parameter estimates from sensitivity analysis: primary model + interaction

	Estimate	SE	P-value
Intercept	5.367	0.317	<.0001
log(offset)	0.978	0.051	<.0001
Trial = 3582	1.341	0.155	<.0001
Trial = 3583	2.493	0.180	<.0001
Trial = 3586	0.198	0.180	0.273
Trial = 3668	0.317	0.131	0.016
Trial = 3672	-0.311	0.101	0.0021
Trial = 3770	3.249	0.179	<.0001
Region =Asia	0.238	0.153	0.1204
Region = Japan	0.485	0.214	0.0233
Region = Europe	-0.288	0.048	<.0001
Region = SAfrica	-0.118	0.126	0.3473
Region = SAmerica	0.629	0.216	0.0035
IDeg	**0.102**	**0.085**	**0.2287**
Baseline Insulin	-0.603	0.141	<.0001
Female	0.087	0.042	0.0395

Age	0.007	0.002	0.0003
IDeg * T2DM Interaction	**-0.278**	**0.101**	**0.0057**
Covariance (IDeg, Interaction) = -0.0072			
Reference levels: Trial = 3579; Region = North America			

Appendix 5. Model goodness of fit for the primary endpoint

The Akaike information criterion (AIC) is a measure of the goodness of fit of a statistical model to a given set of data. It is an increasing function of the number of parameters in the model (k) and a decreasing function of the maximized likelihood function (L): AIC = 2k – 2log (L). A smaller AIC implies a better model fit. Table 42 shows the AIC for three models considered in this review: the primary Negative Binomial (NB) Model described in Section 3.3.1, the model with an (IDeg x T2DM) Interaction described in 3.3.2, and a third post-hoc Zero-Inflated Negative Binomial (ZINB) model proposed after seeing the distribution of the observed rate of confirmed hypoglycemia by type of diabetes in Table 7. Table 42 shows that the ZINB best fits the data, followed by the NB model with an IDeg x T2DM interaction, and by the primary model in last place. The advantage of zero inflated models is that they account for a large proportion of subjects with zero events. The ZINB models the probability of zero hypoglycemia events and the probability of a positive number of hypoglycemia events separately as functions of the covariates. The ZINB model is described in more detail in Appendix 6.

Table 42. AIC model fit statistic

	AIC
Primary NB Model	22390
Primary NB Model + Interaction	22385
ZINB Model	22303

Figure 10 through Figure 13 show the observed cumulative distribution of the rate of confirmed hypoglycemia events by treatment and type of diabetes, plotted against the cumulative distribution predicted by the Primary NB model + Interaction, and the ZINB model. Figure 10 and Figure 12 show that the ZINB fits the data slightly better than the NB model in subjects with T1DM. Figure 11 shows that the NB model does not adequately model the observed high probability of zero events in subjects with T2DM: there is a large separation between the observed and predicted cumulative distributions at 0. Figure 13 shows that the ZINB adequately models the probability of zero events in subjects with T2DM. This strongly suggests that the ZINB model is preferable to describe these data than the NB model.

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Figure 10. (NB model + interaction) vs. (observed) in subjects with T1DM

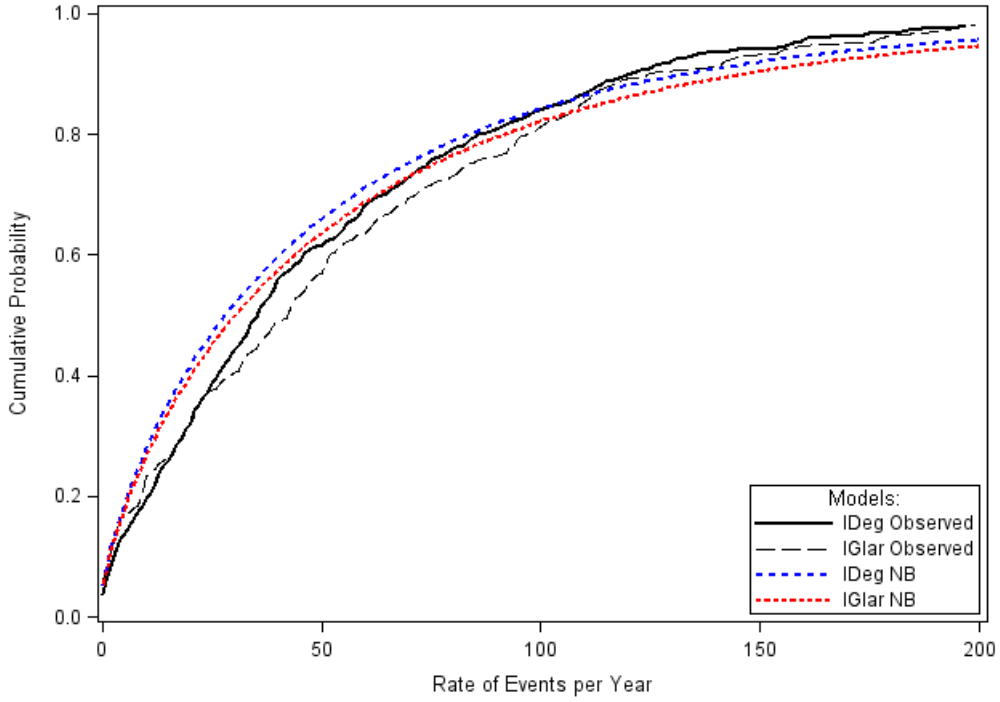


Figure 11. (NB model + interaction) vs. (observed) in subjects with T2DM

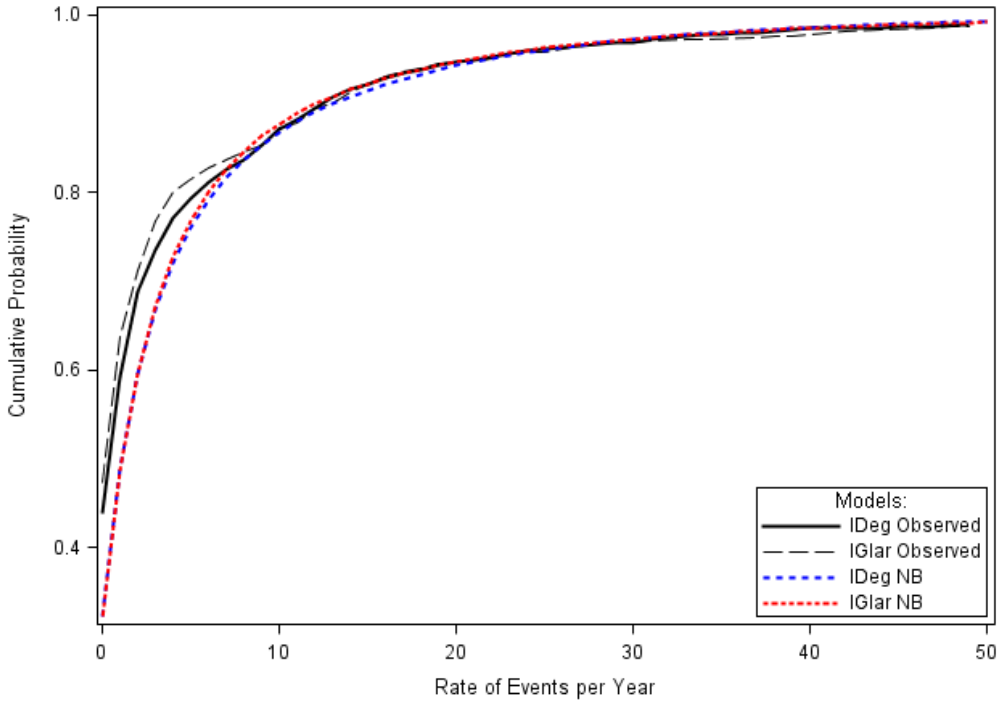


Figure 12. (ZINB model) vs. (observed) in subjects with T1DM

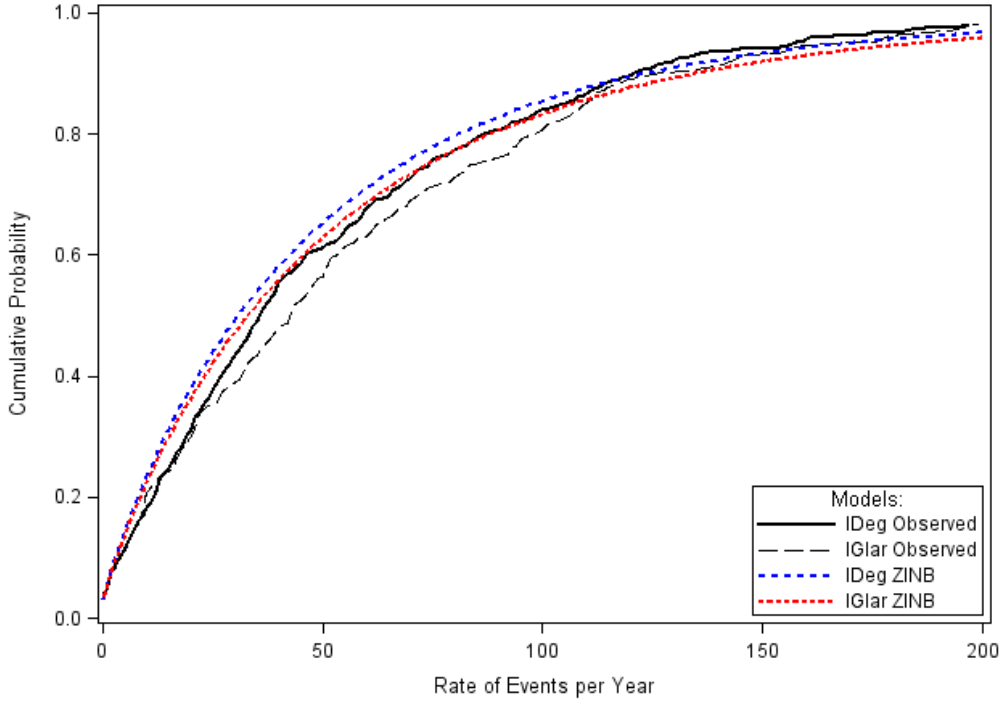
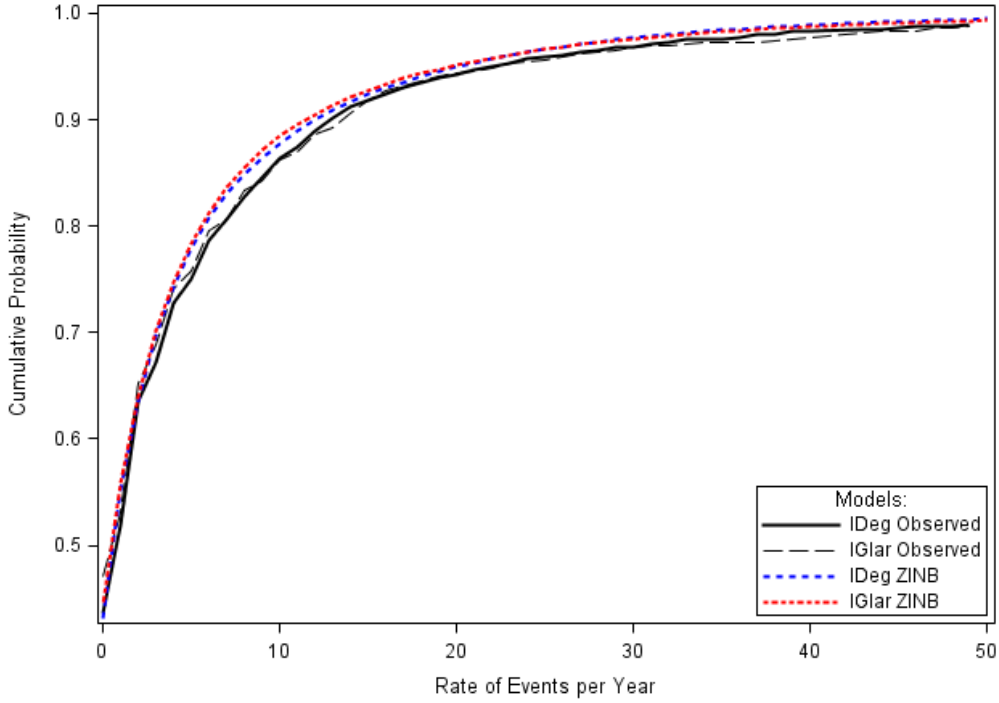


Figure 13. (ZINB model) vs. (observed) in subjects with T2DM



Appendix 6. Zero-inflated negative binomial model

A zero-inflated negative binomial was fit to model the rate of confirmed hypoglycemia and to account for the large proportion of subjects with T2DM with no observed events. Appendix 5 shows that this model fits the data better than the NB models proposed by the sponsor. The model can be written as:

$$P(Y_i = y_i \mid \mathbf{X}_i, \mathbf{Z}_i) = \begin{cases} \text{logit}(\gamma'\mathbf{Z}_i) + \{1 - \text{logit}(\gamma'\mathbf{Z}_i)\} g(0 \mid \mathbf{X}_i) & \text{if } y_i = 0 \\ \{1 - \text{logit}(\gamma'\mathbf{Z}_i)\} g(y_i \mid \mathbf{X}_i) & \text{if } y_i > 0 \end{cases}$$

Where Y_i represents the number of confirmed hypoglycemia events.

$\mathbf{Z}_i$ is a vector of the following covariates: log(offset), Treatment, Type of diabetes, Baseline Insulin, Gender, Age, and Treatment x Type of Diabetes Interaction.

$\mathbf{X}_i$ is a vector of the following covariates: Trial, Region, Gender, Age, Baseline Insulin, Treatment, Type of diabetes, and Treatment x Type of Diabetes Interaction.

The function $g(\cdot)$ is the log regression function used in the Negative Binomial models.

Parameter estimates of this model lead to similar conclusions to those of the Negative Binomial Model with an Interaction term and are shown in Table 43. Figure 14 shows the predicted cumulative distribution for the rate of confirmed hypoglycemia by treatment and type of diabetes, based on the parameter estimates of the NB + Interaction Model and the ZINB model, and assuming that all subjects in the 7 trials were to take IDeg (blue curve) or IGlar (red curve). Both models estimate that use of IGlar would result in fewer confirmed hypoglycemia events in subjects with T1DM, shown by a higher distribution function for IGlar than for IDeg. The opposite conclusion is true for T2DM: both models suggest that IDeg would be expected to result in fewer confirmed hypoglycemia events.

The Zero Inflated Negative Binomial Model was shown to fit the data better than the Negative Binomial Model with an interaction, based on the AIC fit criterion and the plots discussed in Appendix 5. Even though both models reached similar conclusions for these data, and thus the ZINB model appears to provide no additional insight to compare IDeg and IGlar, we believe the discussion in Appendices 5 and 6 may help inform the choice of statistical models for future reviews involving event counts with a high probability of zero events. The zero-inflated negative binomial model might be considered as either a primary or sensitivity analyses in SAPs for count data with a large proportion of subjects with zero events.

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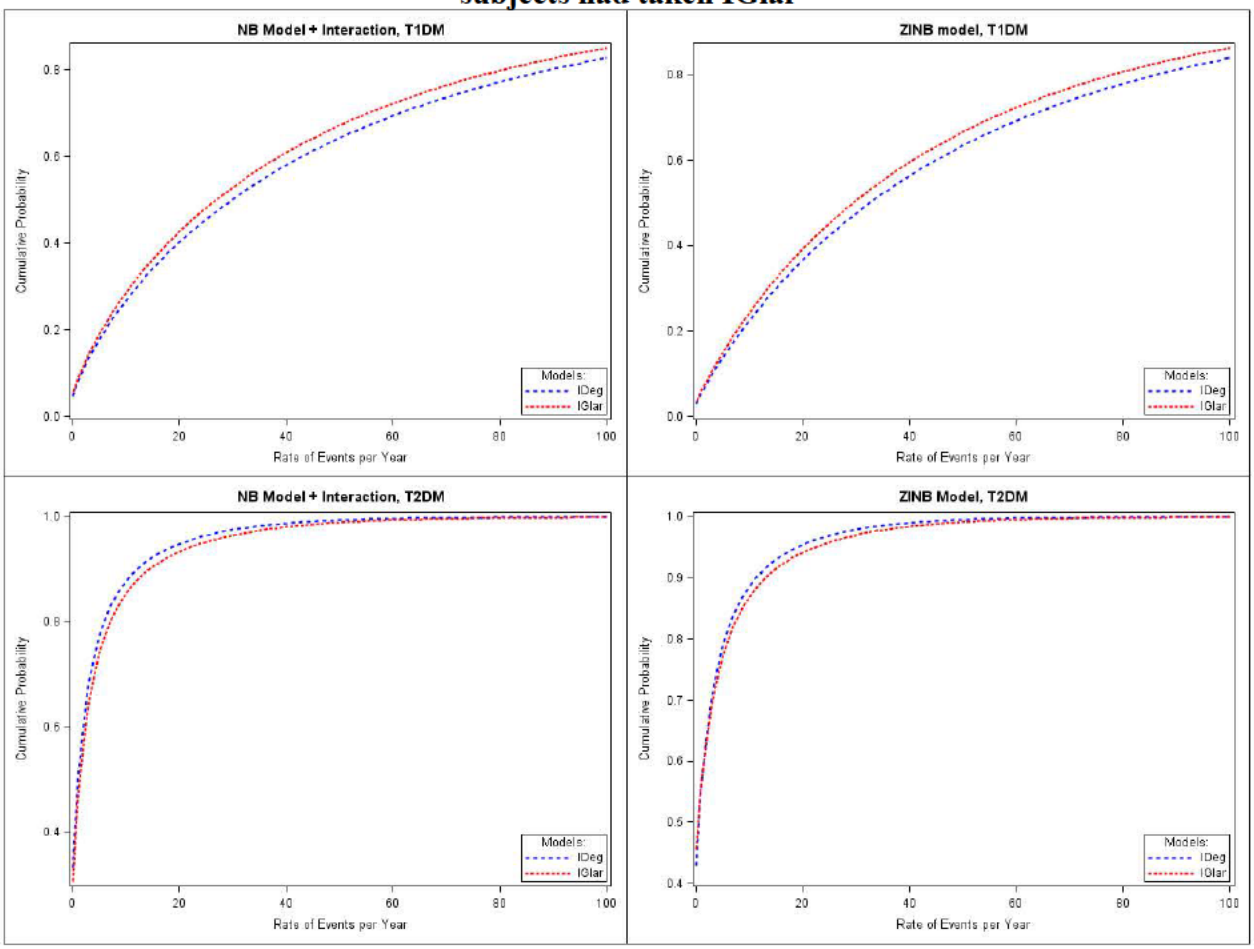
Table 43. Parameter estimates of the Zero-inflated negative binomial (ZINB) model

Vector $\mathbf{Z}_i$	Estimate	SE	P-value
Intercept	-7.807	0.304	<.0001
log(offset)	-0.378	0.106	0.000
IDeg	-0.338	0.057	<.0001
T2DM	6.033	0.304	<.0001
Baseline Insulin	0.614	0.124	<.0001
Female	-0.098	0.114	0.393
Age	-0.024	0.006	<.0001
IDeg * T2DM Interaction	0.253	0.057	<.0001

Vector $\mathbf{X}_i$	Estimate	SE	P-value
Intercept	5.301	0.349	<.0001
log(offset)	0.905	0.058	<.0001
Trial = 3582	1.387	0.164	<.0001
Trial = 3583	2.383	0.187	<.0001
Trial = 3586	0.295	0.191	0.122
Trial = 3668	0.394	0.143	0.006
Trial = 3672	-0.247	0.109	0.024
Trial = 3770	3.101	0.187	<.0001
Region =Asia	0.154	0.160	0.337
Region = Japan	0.383	0.226	0.090
Region = Europe	-0.293	0.047	<.0001
Region = SAfrica	-0.090	0.124	0.471
Region = SAmerica	0.657	0.234	0.005
IDeg	0.099	0.077	0.195
Baseline Insulin	-0.408	0.155	0.008
Female	0.063	0.044	0.155
Age	0.004	0.002	0.077
IDeg * T2DM Interaction	-0.301	0.098	0.002

Reference levels: Trial = 3579; Region = North America

Figure 14. Predicted cumulative distribution function if all subjects had taken IDeg, or all subjects had taken IGlar



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Food and Drug Administration
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	203-314 / SN 000 203-313/ SN 000
Drug Name:	Tresiba (insulin degludec, IDeg, NN1250) Ryzodeg (insulin degludec/insulin aspart, IDegAsp, NN5401)
Indication(s):	Treatment of patients with diabetes mellitus (b) (4)
Applicant:	Novo Nordisk
Date(s):	Submitted September 29, 2011
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Statistical Reviewer:	Xiao Ding, Ph.D.
Concurring Reviewers:	Mat Soukup, Ph.D. Aloka Chakravarty, Ph.D.
Medical Division:	Division of Metabolism and Endocrinology Products (DMEP)
Clinical Team:	Medical Officer: Jean-Marc Guettier, M.D. Medical Team Leader: Hylton Joffe, M. D.
Project Manager:	Rachel Hartford, M.S. (DMEP)

Keywords: clinical studies, meta-analysis, diabetes mellitus, cardiovascular safety, major adverse cardiovascular event (MACE)

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1 Executive Summary

This statistical review and evaluation was performed in response to a consultation from the Division of Biometrics 2 (DB2) for New Drug Application (NDA) 203-314/000 for IDeg and New Drug Application (NDA) 203-313/000 for IDegAsp. This statistical review assesses cardiovascular (CV) related safety endpoints in the randomized phase 3 clinical development program of IDeg (Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770) as well as IDegAsp (Studies 3590, 3592, 3593, 3594/3645, and 3597). This review focuses solely on CV safety evaluation.

Based on the meta-analysis of these 16 randomized phase 3 trials, the risk of developing major adverse cardiovascular event (MACE, composite of CV death, acute coronary syndrome including unstable angina pectoris and myocardial infarction, and stroke) tends to be slightly higher in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) than in the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Compared to the pooled all comparator group, the hazard ratio of IDeg/IDegAsp is 1.17 with a 95% CI of (0.73, 1.87). The difference of on-set time of MACE between IDeg/IDegAsp and all comparator is not statistically significant with a p-value of 0.52.

Similarly, the incidence rate of MACE was similar in the pooled IDeg/IDegAsp group as in the pooled all comparator group. The difference of MACE incidence rate between IDeg/IDegAsp and all comparator was 2.20 per 1,000 patient-years, with a 95% CI of (-4.75, 9.16) per 1,000 patient-years.

2 Introduction

2.1 Overview

Insulin degludec (IDeg) is an ultra-long-acting basal insulin modified such that the amino acid (b) (4) threonine in position B30 of human insulin has been omitted and the ε-amino group of lysine in position B29 has been coupled to hexadecanedioic acid via a glutamic acid spacer. The proposed indication of IDeg is to improve glycemic control in adults with diabetes mellitus as a once daily, (b) (4) human insulin analog.

Insulin degludec/insulin aspart (IDegAsp) is composed of IDeg and insulin aspart, a rapid-acting human insulin analog. Insulin aspart (trade name: NovoLog) was approved by the Agency on June 7, 2000 under NDA 20-986. The proposed indication of this coformulated product is to improve glycemic control in adults with diabetes mellitus with once or twice-daily dosing at any main meal.

A total of 16 phase 3 randomized active-controlled trials were submitted by the applicant for cardiovascular (CV) related safety analyses. These include 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). The summary of design characteristics of these 16 trials is presented in Table 1.

Table 1: Summary of Design Characteristics for Randomized Phase 3 Trials

Study Name	Treatment Arms	Study Size	Duration	Population
3579	**IDeg**, IGlar	1,030	52 weeks	Type 2 DM
3580	**IDeg**, sitagliptin	458	26 weeks	Type 2 DM
3582	**IDeg**, IGlar	1,006	52 weeks	Type 2 DM
3583	**IDeg**, IGlar	629	52 weeks	*Type 1 DM*
3585	**IDeg**, IDet	456	26 weeks	*Type 1 DM*
3586	**IDeg**, IGlar	435	26 weeks	Type 2 DM
3668	**IDeg**, **IDeg flex**, IGlar	687	26 weeks	Type 2 DM
3672	**IDeg**, IGlar	460	26 weeks	Type 2 DM
3718	**IDeg**, IGlar	467	26 weeks	Type 2 DM
3724	**IDeg**, IGlar	460	26 weeks	Type 2 DM
3770	**IDeg**, **IDeg flex**, IGlar	493	26 weeks	*Type 1 DM*
3590	***IDegAsp***, IGlar	530	26 weeks	Type 2 DM
3592	***IDegAsp***, BIAsp	447	26 weeks	Type 2 DM
3593	***IDegAsp***, IGlar	465	26 weeks	Type 2 DM
3594/3645	***IDegAsp***, IDet	548	26/52 weeks*	*Type 1 DM*
3597	***IDegAsp***, IGlar	424	26 weeks	Type 2 DM

IGlar= insuline glargine, IDet= insuline detemir, BIAsp= biphasic insulin aspart
* The duration of Study 3594 was 26 weeks. Study 3645 was a 26-week treatment extension to 3594.
Source: Created by reviewer.

2.2 Data Sources

The applicant submitted electronic documents and datasets for Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770 for IDeg, as well as Studies 3590, 3592, 3593, 3594/3645, and 3597 for IDegAsp. The following files available within the CDER Electronic Document Room (EDR) were utilized in this review.

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3 Statistical Evaluation

This review is focused on the meta-analysis of cardiovascular (CV) risk. A separate safety evaluation focused on hypoglycemia is being reviewed by Dr. Eugenio Andraca-Carrera. For a complete statistical evaluation of efficacy results, please refer to the review authored by Cynthia Liu for IDeg and the review authored by Dr. Dongmei Liu for IDegAsp.

3.1 Data and Analysis Quality

Data and reports of this submission were submitted electronically. The applicant submitted data for both studies as well as the related SAS programs for analysis. The reviewer was able to perform all analyses using the submitted data. No additional data submission was requested.

3.2 Evaluation of Safety

The review of CV safety comprises data from 11 randomized Phase 3 trials for IDeg (Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770) and 5 randomized Phase trials for IDegAsp (Studies 3590, 3592, 3593, 3594/3645, and 3597). All comparative analyses are between the randomized treatment groups, all IDeg regimens as well as IDegAsp regimens are combined into the pooled IDeg/IDegAsp group, and all the comparator groups are combined into the pooled all comparator group.

3.2.1 Study Design and Endpoints

3.2.1.1 Study Design

The applicant submitted the results of 11 Phase 3 randomized active-controlled trials (Studies 3579, 3580, 3582, 3583, 3585, 3586, 3668, 3672, 3718, 3724, and 3770) in support of the safety and efficacy of IDeg for treatment of type 1 and type 2 diabetes mellitus.

Study NN1250-3579 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3579 was conducted at 166 sites in 12 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 1,030 subjects were randomized in a 3:1 fashion to IDeg or insuline glargine (IGlar), both in combination with oral anti-diabetic drugs. Study NN1250-3579 was powered to provide 95% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 52.

Study NN1250-3580 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3580 was conducted at 78 sites in 7 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of 1-2 oral anti-diabetic drugs (metformin, sulphonylurea, glinides, or pioglitazone). A total of 458 subjects were randomized in a

1:1 fashion to IDeg or sitagliptin, both in combination with oral anti-diabetic drugs. The randomization was stratified by prior pioglitazone use. All 11 randomized subjects from Site 704 in the U.S. were excluded from the efficacy analysis sets (but not from the safety analysis set) after the site was closed as a result of major data quality issues reported by the monitor. Study NN1250-3580 was powered to provide 95% or greater power to demonstrate the superiority of IDeg compared to sitagliptin in HbA1c change from baseline to week 26.

Study NN1250-3582 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3582 was conducted at 123 sites in 12 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of insulin regimen. A total of 1,006 subjects were randomized in a 3:1 fashion to IDeg or IGlar, both in combination with insulin aspart (IAsp) and oral antidiabetic drugs. The randomization was stratified by prior insulin regimen (basal-bolus, basal only, or other). Study NN1250-3582 was powered to provide 95% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 52.

Study NN1250-3583 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3583 was conducted at 79 sites in 6 countries including the United States, in male and female subjects ≥ 18 years of age with *type 1 diabetes* with insufficient glycemic control despite treatment of basal-bolus insulin regimen. A total of 629 subjects were randomized in a 3:1 fashion to IDeg or IGlar, both in combination with insulin aspart (IAsp). Study NN1250-3583 was powered to provide 95% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 52.

Study NN1250-3585 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3585 was conducted at 55 sites in 7 countries outside the United States, in male and female subjects ≥ 18 years of age (≥ 20 years for Japan) with *type 1 diabetes* with insufficient glycemic control despite treatment of basal/bolus insulin regimen. A total of 456 subjects were randomized in a 2:1 fashion to IDeg or insuline detemir (IDet), both in combination with IAsp. The randomization was stratified by region (Europe, Japan, India, or South America). Study NN1250-3585 was powered to provide 90% or greater power to .demonstrate the non-inferiority of IDeg compared to IDet with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN1250-3586 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3586 was conducted at 52 sites in 6 countries outside the United States, in male and female subjects ≥ 18 years of age (≥ 20 years for Japan) with *type 2 diabetes* with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 435 subjects were randomized in a 2:1 fashion to IDeg or IGlar, both in combination with oral anti-diabetic drugs. The randomization was stratified by region (Japan or Asia without Japan). Study NN1250-3586 was powered to provide 90% or

greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN1250-3668 was a phase 3 multicenter, randomized, open-labeled, three-arm parallel study. Study NN1250-3668 was conducted at 69 sites in 14 countries outside the United States, in male and female subjects ≥ 18 years of age (≥ 20 years for Japan) with *type 2 diabetes* with insufficient glycemic control despite treatment of basal insulin alone, oral anti-diabetic drugs alone, or the combination of basal insulin and oral anti-diabetic drugs. A total of 687 subjects were randomized in a 1:1:1 fashion to IDeg, IDeg flexible dosing regimen, or IGlar, both in combination with oral anti-diabetic drugs. The randomization was stratified by previous treatment (basal insulin, oral anti-diabetic drugs, or both). The primary comparison is between IDeg flexible dosing regimen and IGlar. Study NN1250-3668 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDeg flexible dosing regimen compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26. The comparison between IDeg flexiable dosing regimen and IDeg is considered as secondary.

Study NN1250-3672 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3672 was conducted at 106 sites in 8 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 460 subjects were randomized in a 1:1 fashion to IDeg or IGlar, both in combination with metformin and/or DPP-4 inhibitor. Study NN1250-3672 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN1250-3718 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3718 was conducted at 89 sites in 7 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of, oral anti-diabetic drugs. A total of 467 subjects were randomized in a 1:1 fashion to IDeg or IGlar, both in combination with metformin and/or DPP-4 inhibitor. Study NN1250-3718 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN1250-3724 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN1250-3724 was conducted at 94 sites in 7 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of oral anti-diabetic drugs. A total of 460 subjects were randomized in a 1:1 fashion to IDeg or IGlar, both in combination with metformin and/or DPP-4 inhibitor. Study NN1250-3724 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDeg compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN1250-3770 was a phase 3 multicenter, randomized, open-labeled, three-arm parallel study. Study NN1250-3770 was conducted at 71 sites in 6 countries including the

United States, in male and female subjects ≥ 18 years of age with *type 1 diabetes* with insufficient glycemic control despite treatment of basal insulin and bolus insulin. A total of 493 subjects were randomized in a 1:1:1 fashion to IDeg, IDeg flexible dosing regimen, or IGlar, both in combination with IAsp. The primary comparison is between IDeg flexible dosing regimen and IGlar. Study NN1250-3770 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDeg flexible dosing regimen compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26. The comparison between IDeg flexiable dosing regimen and IDeg is considered as secondary.

In addition, the applicant submitted the results of 5 additional phase 3 randomized active-controlled trials (Studies 3590, 3592, 3593, 3594/3645, and 3597) in support of the safety and efficacy of IDegAsp for treatment of type 1 and type 2 diabetes mellitus.

Study NN5401-3590 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN5401-3590 was conducted at 88 sites in 8 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control. A total of 530 subjects were randomized in a 1:1 fashion to IDegAsp or insuline glargine (IGlar), both in combination with metformin. One subject was randomized in error (not fulfilling inclusion criteria) to the IGlar group and was later withdrawn from the trial before being exposed to the trial drug. Therefore this subject was excluded from the analysis. Study NN5401-3590 was powered to provide 90% or greater power to demonstrate the non-inferiority of IDegAsp compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN5401-3592 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN5401-3592 was conducted at 50 sites in 10 countries outside the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of premixed or self-mixed insulin regimen. A total of 447 subjects were randomized in a 1:1 fashion to IDegAsp or biphasic insulin aspart (BIAsp), both in combination with oral antidiabetic drugs (metformin, pioglitazone, or DPP-4 inhibitors). Randomization was stratified by the number of daily injections at screening (1 insulin injection a day, or 2 insulin injections a day). Study NN5401-3592 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDegAsp compared to BIAsp with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN5401-3593 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN5401-3593 was conducted at 61 sites in 9 countries including the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of oral antidiabetic drugs. A total of 465 subjects were randomized in a 1:1 fashion to IDegAsp or insuline glargine (IGlar), both in combination with oral antidiabetic drugs. Randomization was stratified by prior pioglitazone use. Study NN5401-3593 was powered to provide 85% or greater power to demonstrate the non-inferiority of IDegAsp compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

Study NN5401-3594 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN5401-3594 was conducted at 79 sites in 9 countries including the United States, in male and female subjects ≥ 18 years of age with *type 1 diabetes*. A total of 548 subjects were randomized in a 2:1 fashion to IDegAsp or insuline detemir (IDet), both in combination with meal-time insulin aspart (IAsp). Randomisation was stratified with respect to previous insulin regimen (basal-bolus regimen, or other insulin regimen). Study NN5401-3594 was powered to provide 95% or greater power to demonstrate the non-inferiority of IDegAsp compared to IGlar with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26. Study NN5401-3645 is a 26-week extension trial for Study NN5401-3594. All subjects who completed Study NN5401-3594 were eligible to participate in the extension trial and continued to receive treatment with either IDegAsp or IAsp as previously randomly allocated in the main trial. A total of 376 subjects were included in Study NN5401-3645.

Study NN5401-3597 was a phase 3 multicenter, randomized, open-labeled, two-arm parallel study. Study NN5401-3597 was conducted at 45 sites in 5 countries outside the United States, in male and female subjects ≥ 18 years of age with *type 2 diabetes* with insufficient glycemic control despite treatment of basal insulin, premixed or self-mixed insulin, and/or metformin. A total of 424 subjects were randomized in a 2:1 fashion to IDegAsp or biphasic insulin aspart (BIAsp), both with or without metformin. Randomization was stratified by previous insulin regimen and metformin treatment (basal insulin without metformin, basal insulin with metformin, premix/self-mix insulin without metformin, or premix/self-mix regimen with metformin). Study NN5401-3597 was powered to provide 90% or greater power to demonstrate the non-inferiority of IDegAsp compared to BIAsp with a non-inferiority margin of 0.4% in HbA1c change from baseline to week 26.

3.2.1.2 Endpoints

The primary endpoint for CV safety analysis is major adverse cardiovascular event (MACE), which is pre-specified as a composite endpoint consisting of acute coronary syndrome (ACS) including unstable angina pectoris (UAS) and myocardial infarction, stroke, and CV death.

Reviewer's comment: *The applicant's definition of MACE is different from the traditional definition of MACE which includes CV death, non-fatal MI, and non-fatal stroke. Since it is pre-specified in the protocol and was previously agreed by the Agency, this definition is used in this review.*

3.2.2 Patient Disposition, Demographic and Baseline Characteristics

As shown in Table 2, among the 8,995 randomized subjects in the Intern-to-Treat (ITT) population from the 16 randomized phase 3 trials, 4,300 (47.8%) subjects were randomized to receive IDeg (3,907 (43.4%) to IDeg once daily regimen and 393 (4.4%) to IDeg flexible dosing regimen), while 1,370 (15.2%) subjects were randomized to

receive IDegAsp, and 3,325 (37.0%) subjects were randomized to receive active comparator drugs.

Table 2: Summary of Treatment Distribution in the ITT Population by Trial

Study	Number of Subjects, N (%)			
	IDeg	**IDeg Flex**	**IDegAsp**	**Comparator**
3579 (N=1,030)	773 (75.0)	-	-	257 (25.0)
3580 (N=458)	229 (50.0)	-	-	229 (50.0)
3582 (N=1,006)	755 (75.0)	-	-	251 (25.0)
3583 (N=629)	472 (75.0)	-	-	157 (25.0)
3585 (N=456)	303 (66.5)	-	-	153 (33.5)
3586 (N=435)	289 (66.4)	-	-	146 (33.6)
3668 (N=687)	228 (33.2)	229 (33.3)	-	230 (33.5)
3672 (N=460)	230 (50.0)	-	-	230 (50.0)
3718 (N=467)	233 (49.9)	-	-	234 (50.1)
3724 (N=460)	230 (50.0)	-	-	230 (50.0)
3770 (N=493)	165 (33.4)	164 (33.3)	-	164 (33.3)
3590 (N=530)	-	-	266 (50.1)	264 (49.9)
3592 (N=447)	-	-	224 (50.1)	223 (49.9)
3593 (N=465)	-	-	232 (49.9)	233 (50.1)
3594/3645 (N=548)	-	-	366 (66.8)	182 (33.2)
3597 (N=424)	-	-	282 (66.5)	142 (33.5)
Total (N=8995)	3907 (43.4)	393 (4.4)	1370 (15.2)	3325 (37.0)

Source: Created by reviewer.

The protocol defined full analysis set (FAS) was a modified intent-to-treat population, which included all randomized subjects with some justified and documented elimination. For example, one trial site was closed due to data quality issues (discovered before the database was locked). 25 subjects from this site were excluded from the FAS. The safety population included all randomized subjects who received at least one dose of the randomized study treatment. As shown in Table 3, among the 8,995 randomized subjects in the ITT population, a total of 8,959 (99.6%) subjects were included in the FAS population, while 8,941 (99.4%) subjects were included in the safety population.

It was pre-specified that analyses based on the FAS population will be considered as primary, while analyses based on the safety population will be used as sensitivity analyses.

Table 3: Treatment Distribution in FAS Population and Safety Population

	IDeg	IDeg Flex	IDegAsp	Comparator
Randomized Subjects (ITT Population)	3907	393	1370	3325
FAS Population	3888 (99.5)	393 (100.0)	1366 (99.7)	3312 (99.6)
Safety Population	3883 (99.4)	392 (99.7)	1360 (99.3)	3306 (99.4)

Source: Created by reviewer.

As shown in Table 4, in the FAS population, baseline demographics were similar among the treatment groups. In the FAS population, there were slightly more male subjects than female subjects (56% versus 44%). Approximately 70% of subjects were White and about 23% were Asian, while 5% of subjects were Black or African American. Furthermore, about 9% subjects in the FAS population were with Hispanic or Latino ethnicity. More than 20% of subjects in the safety population were above 65 years of age, while the mean age was about 54. More than 42% of subjects had body mass index (BMI) greater than 30 kg/m^2, while the mean BMI was about 29 kg/m^2.

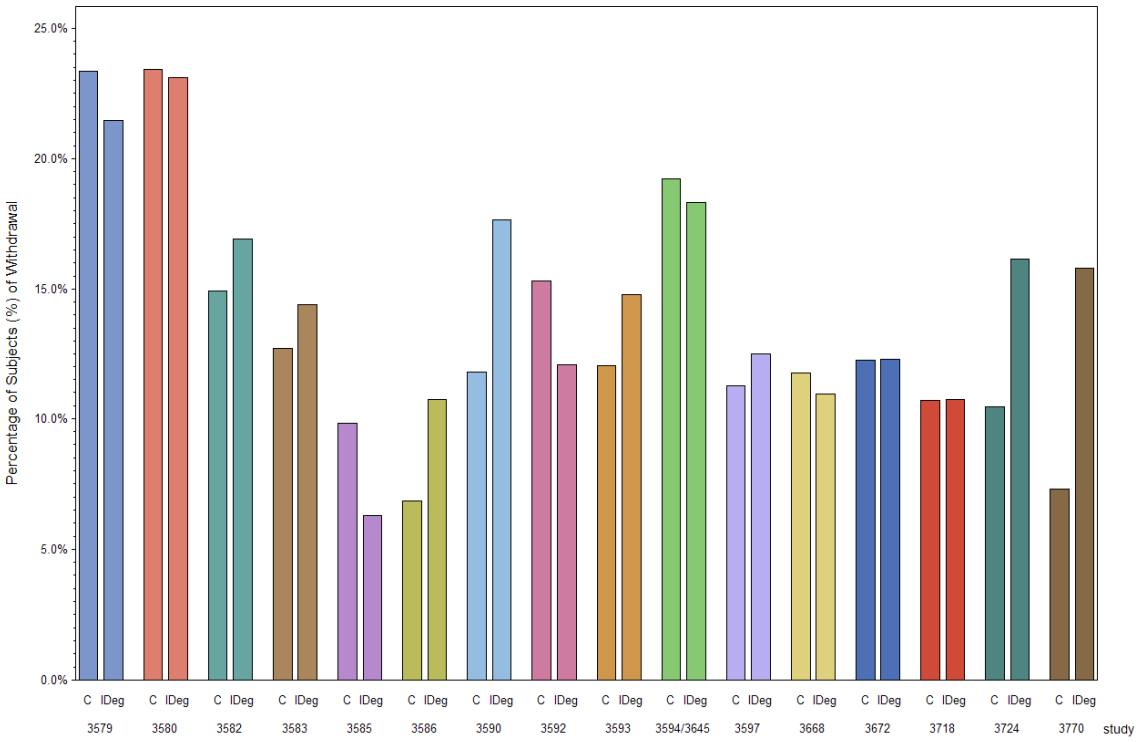
Table 4: Baseline Demographics by Treatment Group (FAS Population)

	IDeg/IDeg Flex/IDegAsp	Comparator
Total number of subjects	5647	3312
Gender		
Male	56.0%	54.6%
Female	44.0%	45.4%
Age (years)	54±13	55±12
18-65	80.0%	79.5%
65-75	17.5%	17.7%
>75	2.5%	2.8%
Race		
White	70.3%	69.4%
Black	5.2%	5.0%
Asian	22.5%	23.8%
Other	2.0%	1.8%
Ethnicity		
Hispanic or Latino	8.7%	9.8%
Not Hispanic or Latino	89.7%	88.4%
Not Applicable	1.6%	1.8%
Diabetes		
Type 1	26.0%	19.8%
Type 2	74.0%	80.2%
BMI (kg/m^2)	29.1±5.3	29.7±5.4
<25	24.0%	21.2%
25-30	35.1%	34.0%
30-35	25.8%	27.6%
>35	15.1%	17.2%

Source: Created by reviewer.

Among the 8,959 subjects in the FAS population from the 16 randomized phase 3 trials, approximately 14.7% of them (1318/8959) did not complete the trial. As presented in Figure 1, the percentage of subjects with premature discontinuation of study medication tended to be lower in the comparator groups than in the IDeg or IDegAsp groups. On average, 15.3% of the subjects in the combined IDeg/IDegAsp group discontinued study medication, which was not statistically significantly higher than the combined comparator group (13.7%) with p-value=0.12 (CMH test stratified by studies).

Figure 1: Percentage of Subjects with Discontinuation by Study and Treatment Group (FAS Population)



C=combined comparator group; IDeg=combined IDeg/IDegAsp group
Source: Created by reviewer.

3.2.3 Statistical Methodologies

All the 16 completed Phase 3 trials in the clinical development program of IDeg and IDegAsp in subjects with type 1 and type 2 diabetes mellitus as of the cut-off date (January 31, 2011) are included in the meta-analysis of CV safety evaluation. It was specified in the protocol that 6 Phase 2 trials should not be included in the meta-analysis.

3.2.3.1 Methods of Imputing Missing

As specified in the statistical analysis plan (SAP), If a subject has no adjudicated MACE at the time of database lock then the primary endpoint will be censored at the subject's latest visit date reported in Case Report Form (CRF).

3.2.3.2 Time-to-Event Analysis

The sponsor proposed to use Cox proportional hazards regression model stratified by trial with a fixed effect for treatment for the time-to-event analysis. In this review, for the time-to-event analysis of the primary composite endpoint, the stratified log-rank test was applied to compare the pooled IDeg/IDegAsp group and the pooled all comparator group, and the stratified Cox proportional hazard regression model was applied to test the hazard ratio of IDeg/IDegAsp versus all comparator. For the time-to-event analysis, only the event occurred first will be included in the analysis, if a subject experiences multiple events of interest.

3.2.3.3 Analysis of Incidence Rate

In this review, as a sensitivity analysis, Mantel-Haenszel incidence rate difference and the associated 95% confidence interval was applied to compare the incidence rate of primary CV safety event between the pooled IDeg/IDegAsp group and the pooled all comparator group. This method makes use of all trials including trials with no events of interest. The unit of analysis was a subject-year of follow-up and the stratification factor was the trial. Confidence interval of the incidence rate for individual trials is based on exact method. For the incidence rate analysis, all events reported for the same subject will be included in the analysis, not only the first event.

3.2.3.4 Handling of trials with zero events

For the primary analysis method (stratified Cox regression) used in this review, trials with zero events were excluded from the analysis. The sensitivity analysis method (M-H incidence rate difference) does not require special handling of trials with zero events.

3.2.4 Results and Conclusions

3.2.4.1 The Applicant's Results

The applicant's summary of the primary composite endpoint (MACE) is presented in Table 5. Among the 8,959 subjects in the FAS population, 80 subjects experienced at least one event that was adjudicated as MACE (3 subjects had two events of MACE while the rest had one event). The applicant reported a total of 53 events of MACE (incidence rate of 14.8 per 1,000 patient-years) in the pooled IDeg/IDegAsp group, and 27 events of MACE (incidence rate of 14.4 per 1,000 patient-years) in the pooled all comparator group. It is reported that the overall incidence of MACE was higher in subjects with type 2 diabetes mellitus (19.1 events per 1,000 patient-years) than in subjects with type 1 diabetes mellitus (2.7 events per 1,000 patient-years).

Table 5: Applicant's Summary of MACE Incidences by Treatment (FAS Population)

	N	PYE	Subjects With MACE	Incidence (Subj w MACE/N)*100	Incidence Rate (Subj w MACE/PYE)*100
All trials					
IDeg+IDegAsp	5647	(3569.9)	53	0.94	1.48
Comparator	3312	(1873.9)	27	0.82	1.44
Total	8959	(5443.8)	80	0.89	1.47
Subjects with T1DM					
IDeg+IDegAsp	1469	(1023.7)	3	0.20	0.29
Comparator	656	(440.4)	1	0.15	0.23
Total	2125	(1464.1)	4	0.19	0.27
Subjects with T2DM					
IDeg+IDegAsp	4178	(2546.2)	50	1.20	1.96
Comparator	2656	(1433.5)	26	0.98	1.81
Total	6834	(3979.7)	76	1.11	1.91

Source: Table 8-1 in the submitted report "Analysis of Cardiovascular Events across the NN1250 and NN5401 Phase 3a Trials".

The applicant's summary of the MACE events by subcategory is presented in Table 6. Among the 80 subjects experienced MACE events, a total of 53, 15, and 12 subjects were reported to have ACS, stroke, and CV death, respectively.

Table 6: Applicant's Summary of MACE Incidences by Subcategory (FAS Population)

	IDeg+IDegAsp			Comparator			Total		
	N	(%)	IR	N	(%)	IR	N	(%)	IR
Total All Trials									
FAS	5647			3312			8959		
PYE	3569.9			1873.9			5443.8		
Acute Coronary Syndrome	34	(0.60)	0.95	19	(0.57)	1.01	53	(0.59)	0.97
UAP	14	(0.25)	0.39	12	(0.36)	0.64	26	(0.29)	0.48
MI	20	(0.35)	0.56	7	(0.21)	0.37	27	(0.30)	0.50
MI - STEMI	12	(0.21)	0.34	2	(0.06)	0.11	14	(0.16)	0.26
MI - NSTEMI	8	(0.14)	0.22	5	(0.15)	0.27	13	(0.15)	0.24
Stroke	11	(0.19)	0.31	4	(0.12)	0.21	15	(0.17)	0.28
CV Death	8	(0.14)	0.22	4	(0.12)	0.21	12	(0.13)	0.22
Total MACE	53	(0.94)	1.48	27	(0.82)	1.44	80	(0.89)	1.47

Source: Table 8-2 in the submitted report "Analysis of Cardiovascular Events across the NN1250 and NN5401 Phase 3a Trials".

The applicant's primary analysis was conducted using a Cox proportional hazard model stratified by trial and with treatment as a fixed effect. No statistically significant treatment difference in risk of MACE was found between the pooled IDeg/IDegAsp group and the pooled all comparator group. The estimated hazard ratio for IDeg/IDegAsp versus all comparator was 1.10, with a 95% CI of (0.68, 1.77). As shown in Table 7, several sensitivity analyses provided results very similar to the primary analysis.

Table 7: Applicant's Results for Time-to-event Analysis (FAS Population)

Analysis	Estimated Hazard Ratio [95% CI]
Primary Analysis Stratified by trial (Full Analysis Set)	1.10 [0.68 – 1.77]
Sensitivity Analysis 1 Stratified by trial (Safety Analysis Set)	1.10 [0.68 – 1.77]
Sensitivity Analysis 2 Not stratified by trial (Full Analysis Set)	1.13 [0.71 – 1.80]
Sensitivity Analysis 3 Additional Explanatory Variables (Full Analysis Set)	1.11 [0.70 – 1.77]

Source: Table 8-5 in the submitted report "Analysis of Cardiovascular Events across the NN1250 and NN5401 Phase 3a Trials".

Reviewer's comment: *The reviewer is able to re-produce the results of the applicant's analyses using the applicant's settings. Please see Section 3.2.4.2 for the results of the reviewer's analyses.*

3.2.4.2 Reviewer Additional Analyses

The reviewer's summary of the primary composite endpoint for CV safety analysis is presented in Table 8. Among the 8,959 subjects in the FAS population, 83 subjects have at least one event that was adjudicated as MACE. A total of 56 subjects in the pooled IDeg/IDegAsp group experienced MACE event, and a total of 27 subjects in the pooled all comparator group experienced MACE event. To be more specific, a total of 54, 16, and 13 subjects were reported to have ACS, stroke, and CV death, respectively. A total of 86 events were reported for these 83 subjects, with 3 subjects each experienced two MACE events (all experienced two ACS events).

Reviewer's comment: *One subject in Study 3672 had a MACE event (ACS) during an angiography planned prior to trial entry. The applicant and the Agency had agreement that this event should be excluded from the analyses for CV safety evaluation.*

Reviewer's comment: *The applicant included only 80 subjects with MACE events in their primary analysis. Three subjects were not considered because their MACE events occurred more than 7 days after the last day of randomized treatment. The applicant did not pre-specify in the protocol or the statistical analysis plan (SAP) that the primary analysis should only focus on treatment-emergent (defined as an event with onset date on or after the first day of exposure of randomized treatment and no later than 7 days after the last day of randomized treatment) MACE events. The three MACE events occurred 9 days, 11 days, and 18 days after the last day of treatment, respectively. All three events were within the typical follow-up window of 4 weeks or 30 days after treatment used in CV safety evaluation. Therefore, the reviewer includes all 83 subjects with MACE events in the analyses that follow.*

Table 8: Summary of Subjects with MACE Event by Study and Treatment Group (FAS Population)

Study	Arms	Sample Size	MACE n (%)	*ACS* n (%)	*Stroke* n (%)	*CV Death* n (%)
3579	**IDeg**	773	12 (1.6)	9 (1.2)	2 (0.3)	1 (0.1)
	Comparator	257	2 (0.8)	1 (0.4)	1 (0.4)	-
3580	**IDeg**	225	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)
	Comparator	222	3 (1.3)	2 (0.9)	1 (0.5)	-
3582	**IDeg**	744	18 (2.4)	11 (1.5)	3 (0.4)	4 (0.5)
	Comparator	248	4 (1.6)	3 (1.2)	-	1 (0.4)
3583	**IDeg**	472	3 (0.6)	1 (0.2)	-	2 (0.4)
	Comparator	157	1 (0.6)	-	-	1 (0.6)
3585	**IDeg**	302	0 (0.0)	-	-	-
	Comparator	153	0 (0.0)	-	-	-
3586	**IDeg**	289	2 (0.7)	1 (0.4)	1 (0.4)	-
	Comparator	146	0 (0.0)	-	-	-
3668	**IDeg/IDeg Flex**	457	2 (0.4)	1 (0.2)	1 (0.2)	-
	Comparator	230	2 (0.9)	1 (0.4)	-	1 (0.4)
3672	**IDeg**	228	3 (1.3)	3 (1.3)	-	-
	Comparator	229	3 (1.3)	1 (0.4)	1 (0.4)	1 (0.4)
3718	**IDeg**	233	1 (0.4)	1 (0.4)	-	-
	Comparator	234	2 (0.9)	2 (0.9)	-	-
3724	**IDeg**	229	3 (1.3)	2 (0.9)	1 (0.4)	-
	Comparator	230	2 (0.9)	2 (0.9)	-	-
3770	**IDeg/IDeg Flex**	329	0 (0.0)	-	-	-
	Comparator	164	0 (0.0)	-	-	-
3590	**IDegAsp**	266	3 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)
	Comparator	263	0 (0.0)	-	-	-
3592	**IDegAsp**	224	3 (1.3)	2 (0.9)	1 (0.5)	-
	Comparator	222	2 (0.9)	2 (0.9)	-	-
3593	**IDegAsp**	230	2 (0.9)	2 (0.9)	-	-
	Comparator	233	1 (0.4)	1 (0.4)	-	-
3594/3645	**IDegAsp**	366	0 (0.0)	-	-	-
	Comparator	182	0 (0.0)	-	-	-
3597	**IDegAsp**	280	1 (0.4)	-	1 (0.4)	-
	Comparator	142	5 (3.5)	4 (2.8)	1 (0.7)	-

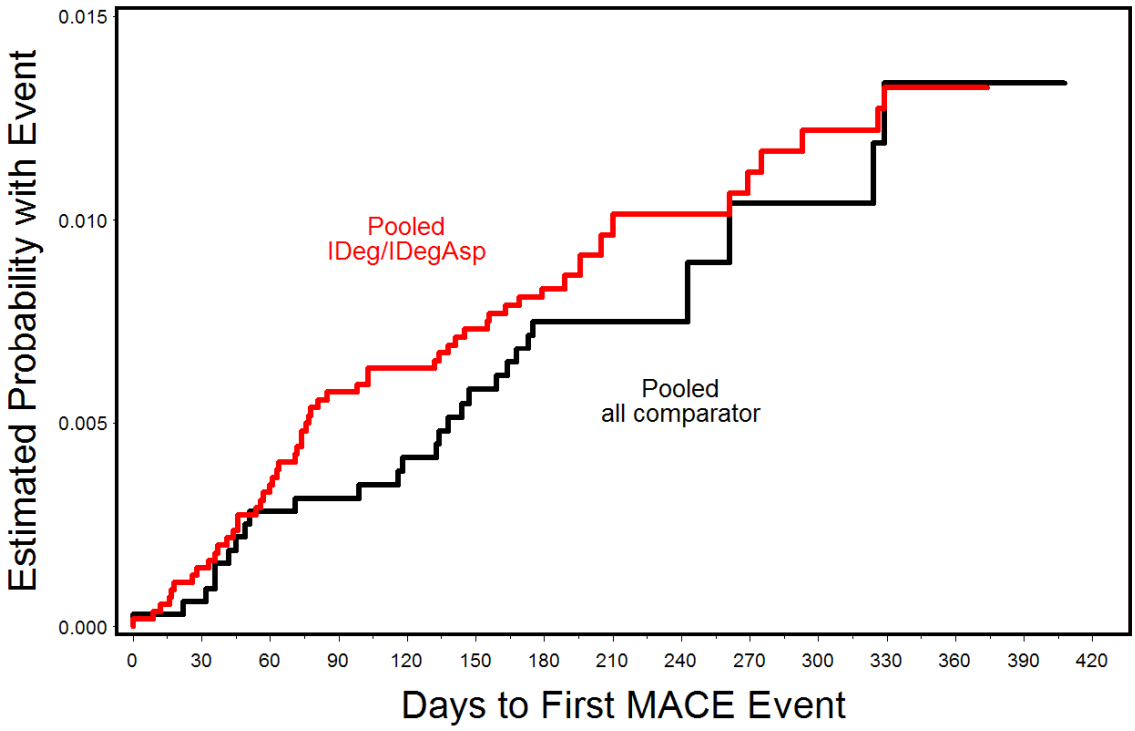
Source: Created by reviewer.

3.2.4.2.1 Time-to-Event Analysis

Based on the Kaplan Meier method, the cumulative probability of developing a CV related event as measured by the primary composite endpoint is shown in Figure 1. In the pooled IDeg/IDegAsp group, MACE event occurred earlier and more often than in the pooled all comparator group. Based on the stratified log-rank test stratified by trial, the onset time of event was not statistically significantly different between the IDeg/IDegAsp group and the comparator group (p-value=0.52). Based on the stratified Cox proportional hazard model, the hazard ratio (HR) of IDeg/IDegAsp compared to comparator was 1.166 with a 95% CI of (0.727, 1.870).

Reviewer's comment: *Because no MACE event occurred in Study 3585, Study 3770, and Study 3594, these three trials would not contribute to the stratified Cox regression model at all. The stratified HR result was based on the other 13 randomized phase 3 trials with at least one event.*

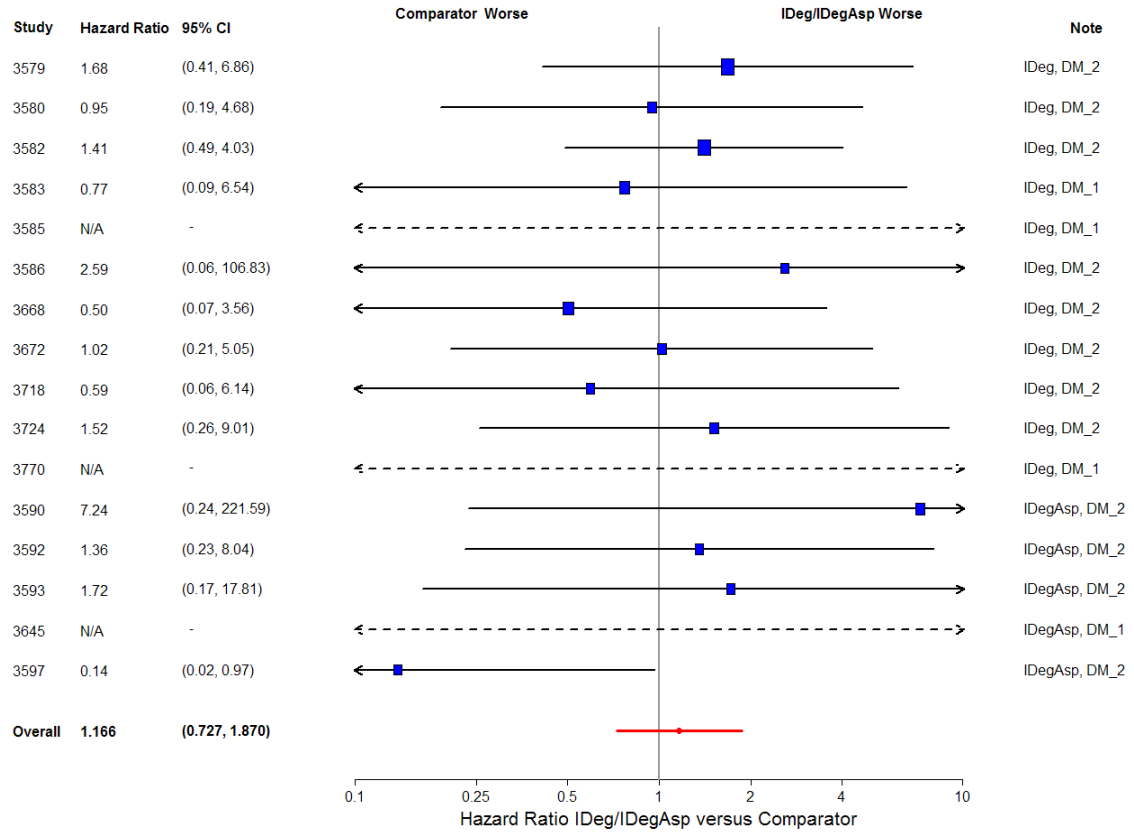
Figure 2: Time to Event Analysis of MACE (Safety Population)



Source: Created by reviewer.

The forest plot of the reviewer's analysis results of the primary composite endpoint is presented in Figure 3. Both the individual hazard ratio and the corresponding 95% CIs of each trial, and the meta-analysis result based on stratified Cox regression are included in the forest plot. Among all the 16 randomized phase 3 trials, Study 3597 was the only one showing statistically significant difference between IDeg/IDegAsp and comparator. In Study 3597, the individual HR of IDeg/IDegAsp compared to comparator was 0.14 with a 95% CI of (0.02, 0.97).

Figure 3: Forest Plot of Time-to-event Analysis Results of MACE (Safety Population)



DM_1: Trial was conducted in the population of subjects with type 1 diabetes.
DM_2: Trial was conducted in the population of subjects with type 2 diabetes.
Source: Created by reviewer.

3.2.4.2.2 Analyses of Incidence Rate

A total of 58 MACE events occurred in the pooled IDeg/IDegAsp group (incidence rate of 15.82 per 1,000 patient-years), and a total of 28 MACE events occurred in the pooled all comparator group (14.47 events per 1,000 patient-years). The overall incidence of MACE was higher in subjects with type 2 diabetes mellitus (20.02 events per 1,000 patient-years) than in subjects with type 1 diabetes mellitus (2.66 events per 1,000 patient-years). To be more specific, a total of 57 ACS events, 16 stroke events, and 13 CV death events were reported (three subjects each experienced 2 ACS events). The corresponding incidence rates are 10.18 ACS events per 1,000 patient-years, 2.86 Stroke events per 1,000 patient-years, and 2.32 CV death events per 1,000 patient-years. The detailed summary is presented in Table 9.

Table 9: Summary of Incidence Rate of MACE Events (FAS Population)

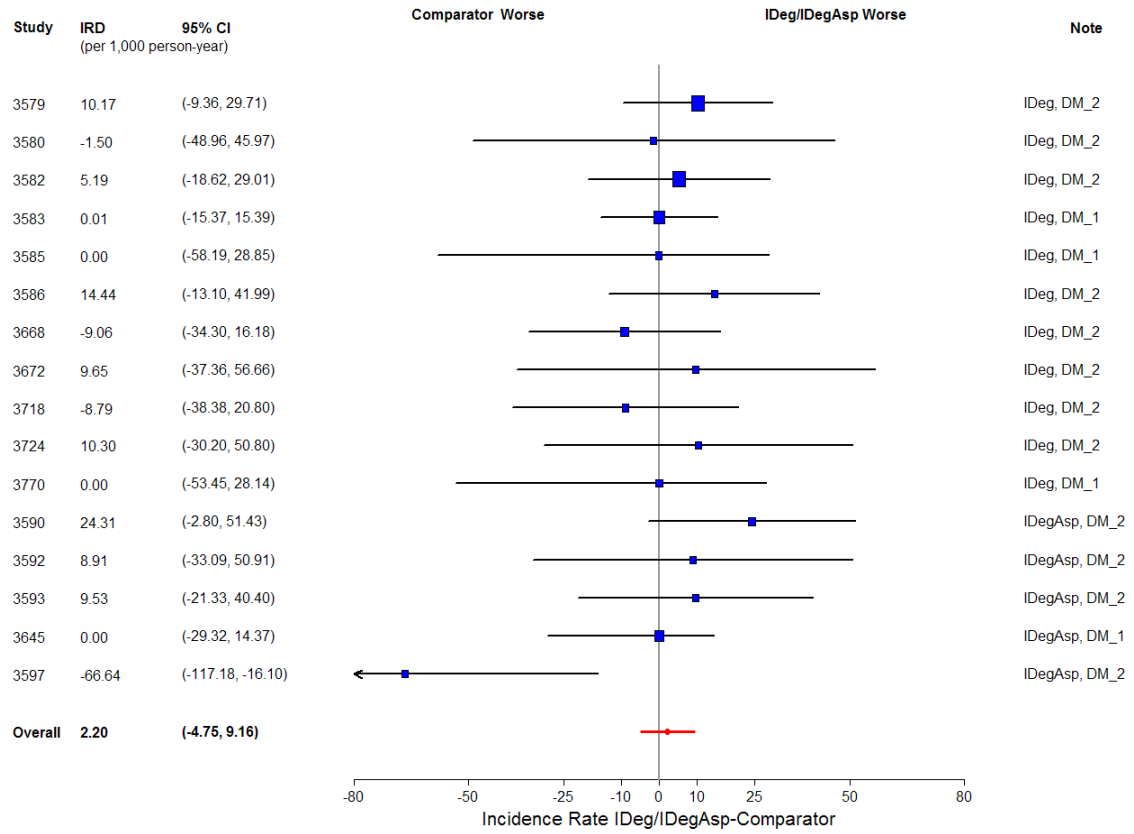
	Number of Subjects	**Total follow up in patient years**	**MACE** n (IR*)	***ACS*** n (IR*)	***Stroke*** n (IR*)	***CV Death*** n (IR*)
Pooled IDeg/IDegAsp	5647	3665.55	58 (15.82)	37 (10.09)	12 (3.27)	9 (2.46)
All comparator	3285	1934.80	28 (14.47)	20 (10.34)	4 (2.07)	4 (2.07)
Total	8959	5600.35	86 (15.36)	57 (10.18)	16 (2.86)	13 (2.32)
Type 1 Diabetes Mellitus						
Pooled IDeg/IDegAsp	1469	1051.94	3 (2.85)	1 (0.95)	0	2 (1.90)
All comparator	656	453.13	1 (2.21)	0	0	1 (2.21)
Total	2125	1505.07	4 (2.66)	1 (0.66)	0	3 (1.99)
Type 2 Diabetes Mellitus						
Pooled IDeg/IDegAsp	4178	2613.61	55 (21.04)	36 (13.77)	12 (4.59)	7 (2.68)
All comparator	2656	1481.67	27 (18.22)	20 (13.50)	4 (2.70)	3 (2.02)
Total	6834	4095.28	82 (20.02)	56 (13.67)	16 (3.91)	10 (2.44)

* Incidence rate per 1,000 patient-years.
Source: Created by reviewer.

Based on the Mantel-Haenszel approach stratified by study, the incidence rate difference between IDeg/IDegAsp and comparator was 2.20 MACE events per 1,000 person-years of follow-up, with a 95% CI of (-4.75, 9.16).

The forest plot of the reviewer's analysis results using incidence rates of the primary composite endpoint is presented in Figure 4. Both the individual incidence rate difference and the corresponding 95% CIs of each trial, and the meta-analysis result are included in the forest plot. Among all the 16 randomized phase 3 trials, Study 3597 was the only one showing statistically significant difference between IDeg/IDegAsp and comparator. In Study 3597, the individual incidence rate difference between IDeg/IDegAsp and comparator was -66.64 per 1,000 person-years, with a 95% CI of (-117.18, -16.10).

Figure 4: Forest Plot of Incidence Rate Differences of MACE (FAS Population)



Source: Created by reviewer.

3.2.4.2.3 Additional Sensitivity Analyses

As presented in Section 3.2.4.1, the hazard ratio of the pooled IDeg/IDegAsp group compared to the pooled all comparator group was 1.166 with a 95% CI of (0.727, 1.870). If only considering the 11 Phase 3 trials for IDeg, the hazard ratio of IDeg compared to comparators was 1.268 with a 95% CI (0.733, 2.193). Similarly, based on 5 Phase 3 trials for IDegAsp, the hazard ratio of IDegAsp compared to comparators was 0.891 with a 95% CI of (0.340, 2.339).

The results based on the sensitivity analyses using the safety population are consistent with the primary analysis results using the FAS population.

4 Findings in Special/Subgroup Populations

In the following sections, analysis results for CV related safety endpoints are presented for specific subgroups. It should be noted that these analyses are exploratory in nature to assess general trends. No protocol-defined multiplicity adjustments were provided and as such the statistical analysis does not include a multiplicity adjustment in the results that follow.

4.1 Gender, Race, and Age

Gender

Among the 8,959 subjects in the FAS population, 4,973 (55.5%) were male subjects and 3,986 (44.5%) were female subjects. Among the 83 subjects reported with MACE events, 56 were male subjects and 27 were female subjects.

Among male subjects, the risk of developing a CV related event as measured by the primary composite endpoint was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group but the difference was not statistically significant. The stratified hazard ratio of IDeg/IDegAsp compared to all comparator among male subjects was 1.451 with a 95% CI of (0.796, 2.644). In contrast, among female subjects, the risk appeared to be slightly lower in the IDeg/IDegAsp group while the difference was also not statistically significant.The stratified hazard ratio of IDeg/IDegAsp compared to comparator among female subjects was 0.796 with a 95% CI of (0.360, 1.760).

Race

Among the 8,959 subjects in the FAS population, 6,271 (70.0%) were White subjects, 460 (5.1%) were Black subjects, 2,062 (23.0%) were Asian subjects (including both Asian Indian and Asian non-Indian), and 166 (1.9%) were subjects with other races. Among the 83 subjects reported with MACE events, 61 were White subjects, 4 were Black subjects, 17 were Asian subjects, and 1 was of other race.

Among White subjects, the risk of developing a CV related event as measured by the primary composite endpoint was slightly higher in the pooled IDeg/IDegAsp group than in the pooled all comparator group but the difference was not statistically significant. The stratified hazard ratio of IDeg/IDegAsp compared to comparator among White subjects was 1.583 with a 95% CI of (0.879, 2.850). Similarly, among Black subjects, the risk was also higher in the IDeg/IDegAsp group than in the comparator group, the stratified hazard ratio was 2.051 with a 95% CI of (0.199, 21.106). In contrast, among Asian subjects, the risk appeared to lower in the IDeg/IDegAsp group while the difference was marginally statistically significant. The stratified hazard ratio of IDeg/IDegAsp compared to comparator among Asian subjects was 0.384 with a 95% CI of (0.143. 1.033).

Reviewer's comment: *In the subgroup of Black subjects, only 4 events of primary composite endpoint occurred. Because of the very small number of events, caution is needed when interpreting the results for the subgroup of Black subjects. Similarly, only 1 event occurred in the subgroup of other race, no formal analysis was done for this subgroup.*

Age

Among the 8,959 subjects in the safety population, 7,152 (79.8%) aged 65 years or younger, and 1,807 (20.2%) were older than 65. Among the 83 subjects reported with MACE events, 54 aged 65 years or younger, while 29 were older than 65.

Among subjects aged 65 years or younger, the risk of developing a CV related event as measured by the primary composite endpoint was slightly lower in the pooled IDeg/IDegAsp group than in the pooled all comparator group but the difference was not statistically significant. The stratified hazard ratio of IDeg/IDegAsp compared to comparator was 0.887 with a 95% CI of (0.502, 1.568). In contrast, among subjects older than 65, the risk appeared to higher in the IDeg/IDegAsp group but the difference was not statistically significant.The stratified hazard ratio of IDeg/IDegAsp compared to comparator was 1.961 with a 95% CI of (0.821. 4.683).

4.2 Other Special/Subgroup Populations

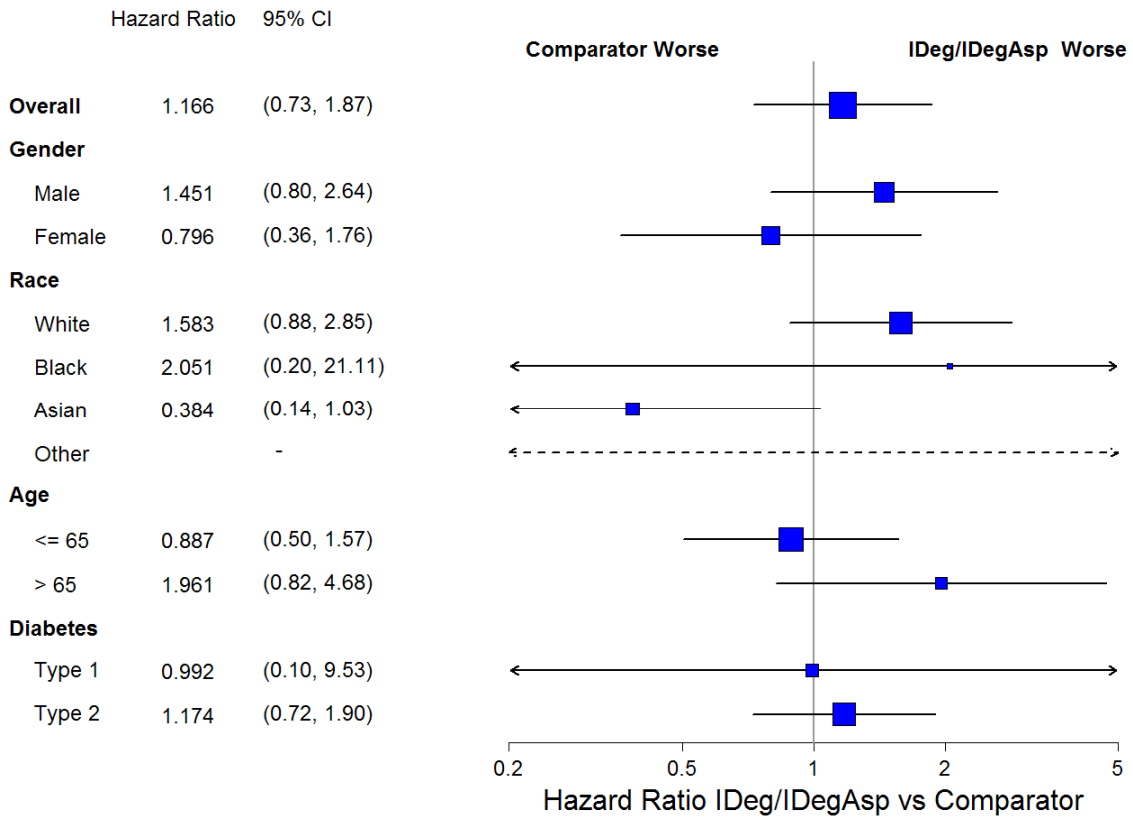
Type of Diabetes

Among the 8,959 subjects in the safety population, 2,125 (23.7%) were subjects with type 1 diabetes mellitus, and 6,834 (76.3%) were with type 2 diabetes mellitus. Among the 83 subjects reported with MACE events, 4 had type 1 diabetes mellitus while 79 had type 2 diabetes mellitus.

Among subjects with type 1 diabetes mellitus, the risk of developing a CV related event as measured by the primary composite endpoint was similar between the pooled IDeg/IDegAsp group and the pooled all comparator group. The stratified hazard ratio of IDeg/IDegAsp compared to comparator was 0.992 with a 95% CI of (0.103, 9.534). In addition, among subjects with type 2 diabetes mellitus, the risk tends to be slightly higher in the IDeg/IDegAsp group than in the comparator group. The stratified hazard ratio of IDeg/IDegAsp compared to comparator was 1.174 with a 95% CI of (0.725, 1.902).

The forest plot of reviewer's subgroup analysis results based on hazard ratio is presented in Figure 5. Most of the subgroup analysis results were in the same direction as the overall result for the primary composite endpoint.

Figure 5: Forest Plot of Subgroup Time-to-event Analyses for MACE (FAS Population)



Source: Created by reviewer.

5 Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The primary agreed upon composite endpoint for CV safety evaluation is major adverse cardiovascular event (MACE), defined as a composite endpoint consisting of acute coronary syndrome (ACS) including unstable angina pectoris (UAS) and myocardial infarction, stroke, and CV death.

Phase 3 data from the 16 randomized Phase 3 trials were pooled to evaluate the risk of developing a CV related event as measured by the primary composite endpoint. In this review, the comparison between the pooled IDeg/IDegAsp group (including both IDeg and IDegAsp) and the pooled all comparator group (including comparators of IGlar, sitagliption, IDet, or BIAsp) was performed using the stratified Cox proportional hazards regression model and the stratified log-rank test with study as stratification factor. The M-H incidence rate difference approach was also applied to evaluate the MACE incidence rate of IDeg/IDeg. More details for the statistical methodologies used in this review are provided in Section 3.2.3.

Based on the pooled data of all 16 randomized phase 3 trials, a total of 83 subjects experienced at least one adjudicated MACE event, with 56 subjects in the pooled IDeg/IDegAsp group and 27 subjects in the pooled all comparator group. MACE events tend to occur earlier and more often in the pooled IDeg/IDegAsp group than in the pooled all comparator group. The difference of MACE onset time between the two groups was not statistically significant, with a stratified log-rank test p-value of 0.52. The stratified hazard ratio of IDeg/IDegASp compared to all comparator was 1.166 with a 95% CI of (0.727, 1.870). Detailed analysis results are provided in Section 3.2.4.2.1.

A total of 86 adjudicated MACE events were reported in these 16 Phase 3 trials for 83 subjects, with 3 subjects experienced two MACE events. Among these MACE events, 58 occurred in the pooled IDeg/IDegAsp group and 28 occurred in the pooled all comparator group. The incidence rate of MACE was 15.82 per 1,000 patient-years in the pooled IDeg/IDegAsp group, as compared to 14.47 per 1,000 patient-years in the pooled all comparator group. The M-H incidence rate difference between IDeg/IDegAsp and all comparator was 2.20 per 1,000 patient-years, with a 95% CI of (-4.75, 9.16) per 1,000 patient-years. The difference between the two groups was not statistically significant. Detailed analysis results are provided in Section 3.2.4.2.2.

The difference between IDeg/IDegAsp and all comparator in developing a CV related event as measured by MACE was also evaluated in several subgroups. Most of the subgroup analysis results were in the same direction as the overall result, and no statistically significant difference was found between IDeg/IDegAsp and all comparator in these subgroups. Detailed results for subgroup analyses are provided in Section 4.

5.2 Conclusions and Recommendations

Based on the meta-analysis of these 16 randomized phase 3 trials, the risk of developing major adverse cardiovascular event (MACE, composite of CV death, acute coronary syndrome including unstable angina pectoris and myocardial infarction, and stroke) was found to be slightly higher in the pooled IDeg/IDegAsp group (IDeg or IDegAsp) than in the pooled all comparator group (IGlar, sitagliption, IDet, or BIAsp). Compared to the pooled all comparator group, the hazard ratio of IDeg/IDegAsp is 1.17 with a 95% CI of (0.73, 1.87). The difference of on-set time of MACE between IDeg/IDegAsp and all comparator is not statistically significant with a p-value of 0.52.

Similarly, the incidence rate of MACE was similar in the pooled IDeg/IDegAsp group as in the pooled all comparator group. The difference of MACE incidence rate between IDeg/IDegAsp and all comparator was 2.20 per 1,000 patient-years, with a 95% CI of (-4.75, 9.16) per 1,000 patient-years.

6 Signatures/Distribution List

Primary Statistical Reviewer: Xiao Ding, PhD
Date: 04/16/2012

Concurring Reviewer(s):

Statistical Team Leader: Mat Soukup, PhD
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Archival NDA 203314
Archival NDA 203313
DMEP (HFD-510)/ Rachel Hartford
DMEP (HFD-510)/ Jean-Marc Guettier, M.D.
DMEP (HFD-510)/ Hylton Joffe, M. D.
DMEP (HFD-510)/ Mary Parks, M. D.
DB7 (HFD-700)/Xiao Ding, PhD
DB7 (HFD-700)/Mat Soukup, PhD
DB7 (HFD-700)/Mark Levenson, PhD
DB7 (HFD-700)/Aloka Chakravarty, PhD
OB/IO (HFD-700)/Lillian Patrician, MS

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/s/

XIAO DING
04/16/2012

MATTHEW J SOUKUP
04/16/2012
Concur with review

ALOKA G CHAKRAVARTY
04/16/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

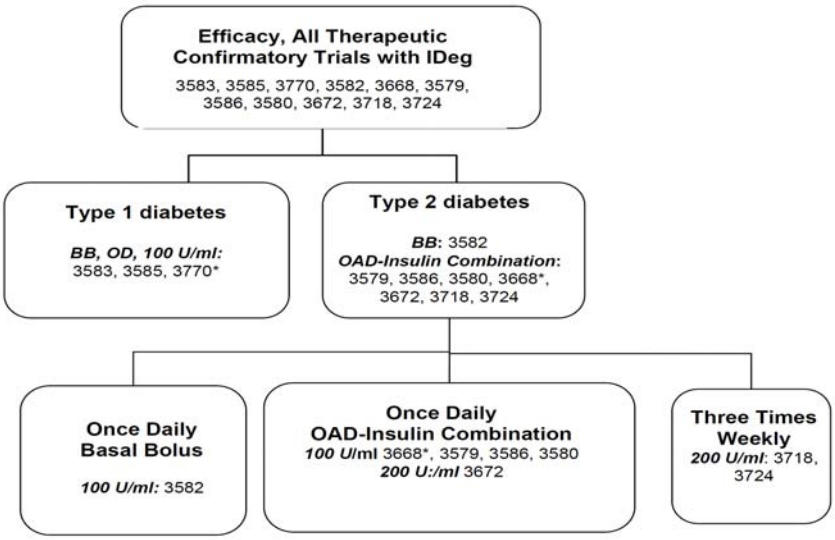
NDA No.: 203314	Applicant: Novo Nordisk	Stamp Date: 09/29/2011
Drug Name: Tresiba™ (insulin degludec)	Indication: Treatment of Diabetes Mellitus	NDA Type: Standard
Filing Meeting Date: 11/18/2011	PDUFA goal date: 07/29/2012	Statistical Reviewer: Cynthia Liu
Link to location of original submission in EDR \\CDSESUB5\EVSPROD\NDA203314\203314.enx		

Background

This is an original NDA submission. Insulin degludec (Ideg, NN1250, formally called (b) (4)) is a new molecular entity. It is a once daily, ultra-long-acting human insulin analog indicated to improve glycemic control in adults with diabetes mellitus. The timing of Ideg injection can vary from day to day (8-40 hours apart), depending on the needs of the individual patient.

At the pre-NDA meeting, the sponsor indicated that the IDeg Phase 3a development program has studied the following regimens with a total of 11 confirmatory trials:

- T1DM – IDeg once daily treatment – basal-bolus therapy
- T2DM – IDeg once daily treatment – basal-bolus therapy
- T2DM – IDeg once daily treatment – OAD insulin combination
- T2DM – IDeg three-times weekly – OAD insulin combination



* Fixed Flexible Dosing Trials

Figure 3 Grouping of IDeg Therapeutic Confirmatory Trials

In the NDA submission, the sponsor is **not** seeking the 3x weekly dosing regimen indication (Studies 3718 and 3724). (b) (4) Nevertheless, the review will focus on all the once-daily (OD) studies (9 in total).

Reference ID: 3047322

The 9 studies are all Phase 3a, multinational, muticenter, randomized, open-label, parallel-group, active-controlled, treat-to-target trials. Except Study 3580 (a superiority trial), the other 8 studies are all designed to show non-inferiority of Ideg to their comparator, with the NI margin of 0.4%. The primary endpoint for all trials is change in HbA1c from baseline to end of treatment (varies from study to study). The key secondary endpoints are prioritized for the purpose of statistical testing and are different in each trial.

For the sample size calculation, the sponsor used SD of 1.3% for subjects with T2DM and 1.1% for subjects with T1DM. The sample size was powered to the PP analysis set with an assumption that between 15% and 25% (depending on trial design) of the randomized subjects were excluded from the PP analysis set. For non-inferiority trials, the sample size was determined under the assumption of no difference between the two treatment arms (i.e., D = 0%). All the Phase 3a trials have 85 – 95% power.

DM Type	Study	WK	Treatment Groups	Background medication	Population	Randomized patients
T1	3583 (A)	52	IDeg 100 vs. IGar	IAsp		629 (472:157)
T1	3585 (B)	26	IDeg 100 vs. IDet (od / bid)	IAsp	Pan-Asian	455 (302:153)
T1	3770 (C)	26	IDeg 100 fixed dosing vs. IDeg 100 flexible dosing vs. IGar	IAsp		493 (165:164:164)
T2	3582 (G)	52	IDeg 100 vs. IGlar	IAsp ± OAD(s)		992 (744:248)
T2	3579 (D)	52	IDeg 100 vs. IGar	OAD(s)	Insulin-naive	1030 (773:257)
T2	3672 (E)	26	IDeg 200 vs. IGar	OAD(s)	Insulin-naive	457 (228:229)
T2	3586 (?)	26	IDeg 100 vs. IGlar	OAD(s)	Pan-Asian, Insulin-naive	435 (289:146)
T2	3668 (F)	26	IDeg 100 fixed dosing vs. IDeg 100 flexible dosing vs. IGar	OAD(s)	Insulin-naïve / basal insulin treated	687 (228:229:230)
T2	3580 (H)	26	IDeg 100 vs. sitagliptin	OAD(s)	Insulin-naive	447 (225:222)

The OAD(s) for Study 3582 were ± metformin ± pioglitazone.

The OAD(s) for Studies 3579 and 3672 were + metformin ± DPP-4 inhibitor.

The OAD(s) for Study 3586 were ± metformin ± SU/glinide ± α-GI.

The OAD(s) for Studies 3668 and 3580 were ± metformin ± SU/glinide ± pioglitazone.

Study 3672 is the only study to support IDeg 200 U/mL dosing regimen. Studies 3770 and 3668 are intended to support type 1 and 2 diabetic patients, respectively, with fixed

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flexible dosing regimen of IDeg 100 U/mL using the following schedule (8-40 hours between injections):

- Tuesdays, Thursdays, Saturdays and Sundays: inject SIBA 100 U/ml in the evening
- Mondays, Wednesdays and Fridays: inject SIBA 100 U/ml in the morning
  - Morning defined as: Time period from waking up to before 1st meal of the day
  - Evening defined as: Time period from start of main evening meal to bedtime

Table 8 below provides the general common key inclusion criteria used for the confirmatory trials.

Table 8 Key Selection Criteria – Common for the Therapeutic Confirmatory Trials

Key Inclusion Criteria
• Informed consent obtained before any trial-related activities. (Trial related activities are defined as any procedure that would not have been performed during normal management of the subject)
• Males or females, ≥ 18 years of age (≥ 20 years for Japan)
• Diagnosed with diabetes mellitus:
– T1DM (diagnosed clinically) for ≥ 12 months
– T2DM (diagnosed clinically) for ≥ 6 months
• Current antidiabetic treatment:
– T1DM: treated with basal -bolus insulin for ≥ 12 months
– T2DM: treated with OADs (monotherapy or combination therapy) for ≥ 3 months[a]
• Baseline HbA_{1c}:
– ≤10.0% (T1DM)
– 7.0–10.0%, both inclusive (T2DM)[b]
• Baseline BMI:
– ≤35 kg/m^2 (mainly T1DM)
– ≤40 kg/m^2 (T2DM, trials with IDeg 100 U/mL)
– ≤45 kg/m^2 (T2DM, trials with IDeg 200 U/mL)
• Ability and willingness to adhere to the protocol including performance of self measured plasma glucose (SMPG) profiles according to the protocol

For the primary endpoint, an ANCOVA model with treatment, antidiabetic therapy at screening, sex, and country/region as fixed factors, and age and baseline HbA1c as covariates was utilized. If non-inferiority/superiority was confirmed for the primary efficacy endpoint, the prioritized key secondary endpoints were to be tested sequentially for superiority.

Efficacy of IDeg is summarized in Table 15 and Figure 4-2.

The sponsor also performed meta-analyses for CV and hypoglycemia.

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STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

File-ability Checklist

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc.	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
Data sets in EDR are accessible and include adequate files for describing the data (e.g., define.pdf files).	X			
Data listings and intermediate analysis tables were sufficient to permit a statistical review.	X			
Safety and efficacy were investigated for subgroups based on gender, race, and age (including a subgroup for 65 and older) (if applicable).	X			Not for individual study, but for overall. See Clinical Summary 2.7.3.
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans and followed in the study reports.	X			
Designs utilized are appropriate for the indications requested.	X			
Intention-to-treat analysis was performed.	X			
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			Datasets for ISS submitted
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	
Appropriate references for novel statistical methodology (if present) are included.			X	
Effects of dropouts on primary analyses were investigated.	X			Completers; LOCF; MMRM

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ____YES____

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant. NA

Identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
None at this moment.

Identify and list any potential review issues.
None at this moment.

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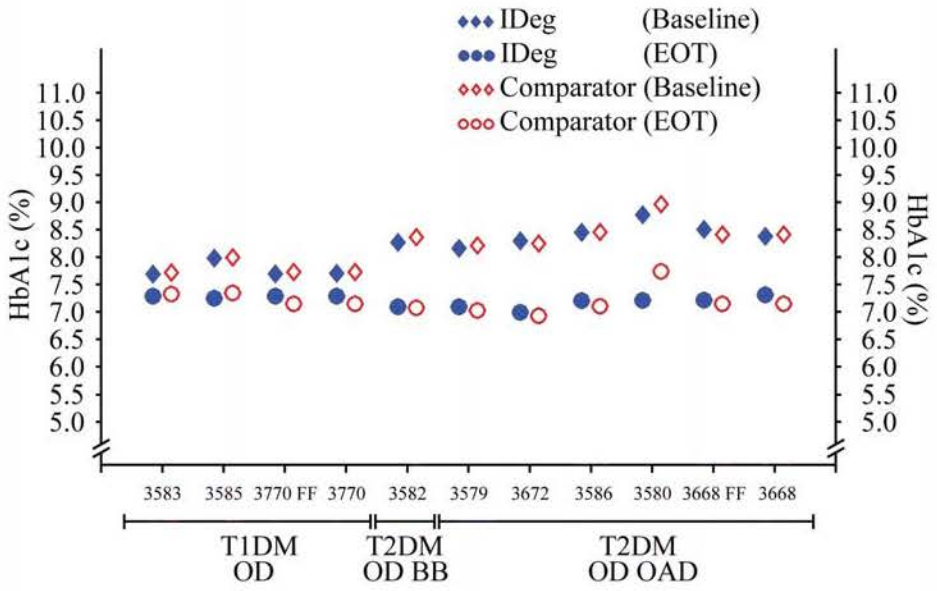
Table 15 HbA_{1c} (%) Change from Baseline at End of Trial – IDeg OD – Statistical Analysis – FAS

Trial (wks)	IDeg N	IDeg LSMEAN (SE)	Comparator N	Comparator LSMEAN (SE)	IDeg - Comparator Contrast	95% CI
T1DM						
3583 (52)	472	-0.36 (0.05)	157	-0.34 (0.07)	-0.01	[-0.14; 0.11]
3585 (26)	302	-0.71 (0.06)	153	-0.61 (0.07)	-0.09	[-0.23; 0.05]
3770 (26) FF	164	-0.40 (0.05)	164	-0.57 (0.0)	0.17	[0.04; 0.30]*
3770 (26) (IDeg FF - IDeg)					0.01	[-0.13; 0.14]
T2DM Basal-bolus Therapy						
3582 (52)	744	-1.10 (0.06)	248	-1.18 (0.08)	0.08	[-0.05; 0.21]
T2DM OAD-Insulin Combination						
3579 (52)	773	-1.06 (0.04)	257	-1.15 (0.06)	0.09	[-0.04; 0.22]
3672 (26)	228	-1.18 (0.09)	229	-1.22 (0.08)	0.04	[-0.11; 0.19]
3586 (26)	289	-1.42 (0.06)	146	-1.52 (0.07)	0.11	[-0.03; 0.24]
3580 (26)	225	-1.52 (0.10)	222	-1.09 (0.10)	-0.43	[-0.61; -0.24]*
3668 (26) FF	229	-1.17 (0.08)	230	-1.21 (0.08)	0.04	[-0.12; 0.20]
3668 (26) (IDeg FF - IDeg)					-0.13	[-0.29; 0.03]

N: Number of subjects contributing to analysis, *: Statistically significant
Endpoint was analysed by an ANOVA model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors and age and baseline HbA1c as covariates.
Non-inferiority criterion: Upper confidence limit of difference less than 0.4 (%)
End of Trial: a subject's last trial visit excluding the follow-up visit
FF: Fixed Flexible, subjects treated with a rotating dosing schedule
Comparator: IDet (3585), IGlar (3583, 3770, 3582, 3579, 3672, 3586, 3668) and Sita (3580)
Missing values are imputed by LOCF



FF: Fixed Flexible, subjects treated with a rotating dosing schedule; Comparator: IGlar, except IDet (3585) and Sita (3580); missing values are imputed by LOCF.

Cross-reference: Summary 2.7.3, Figure 3-1

Figure 4–2 HbA_{1c} (%) at Baseline and End-of-trial – Plot of Mean Values – FAS

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/s/

CYNTHIA Y LIU
11/18/2011

JON T SAHLROOT
11/21/2011

STATISTICS FINLING CHECKLIST FOR NDA 203313
Ryzodeg (insulin degludec/insulin aspart)

Filing meeting, Nov. 18, 2011
Dongmei Liu, statistical reviewer

NDA Number: 203313 **Applicant: Novo Nordisk** **Stamp Date: Sep. 29, 2011**

Drug Name: Ryzodeg **NDA/BLA Type: NDA**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	X			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	X			
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	X			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of define.pdf file for data sets).	X			

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? ___Yes_____

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter. --- None at this time.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	X			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	X			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.			X	No interim analysis.
Appropriate references for novel statistical methodology (if present) are included.			X	Analysis used standard method.
Safety data organized to permit analyses across clinical trials in the NDA/BLA.	X			
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	X			

1. Drug information

- Proposed trade name: Ryzodeg
- Generic name (components): 70% insulin degludec and 30% insulin aspart
- Proposed indication: improve glycaemic control in adult patients with diabetes mellitus
- Dosage form: 100 Units/mL (U-100)
- Route of administration: subcutaneous injection
- Applicant: Novo Nordisk
- Stamp date: September 29, 2011
- PDUFA date: July 29, 2012

2. Clinical studies

All 5 trials were 26-week, multi-center, multi-national, open-label, randomized, 2-arm parallel group, active-controlled, treat-to-target trial. Stratification was carried out according to previous insulin regimen.

Trial ID (in label)	Treatment arms	Number of subjects	Study population
NN5401-3594 (study A)	IDegAsp: QD s.c. at any meal + IAsp s.c. for the remaining meals	366	T1DM
	IDet: QD or BID s.c. + IAsp s.c. at main meals	182	
NN5401-3590 (study B)	IDegAsp: QD s.c. at any meal + met p.o. + NPH s.c. in follow-up	266	T2DM
	IGlar: QD s.c. + met p.o. + NPH s.c. in follow-up	263	
NN5401-3593 (study C)	IDegAsp: QD s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	230	T2DM
	IGlar: QD s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	233	
NN5401-3592 (study D)	IDegAsp: BID s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	224	T2DM
	BIAsp 30: BID s.c. + met p.o. ± pio p.o. ± DPP-41 p.o.	222	
NN5401-3597 (study E)	IDegAsp: BID s.c. ± met p.o. + BHI 30 s.c. in follow-up	280	T2DM
	BIAsp 30: BID s.c. ± met p.o. + BHI 30 s.c. in follow-up	142	

3. Efficacy endpoints

- Primary efficacy endpoint:
  - Change from baseline in HbA1c after 26 weeks of treatment
- Secondary efficacy endpoints (with some variation among trials)
  - Change from baseline in FPG after 26 weeks of treatment
  - HbA1c < 7% at end of trial without severe hypoglycemia
  - Number of nocturnal confirmed hypoglycemic episodes
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in body weight after 26 weeks of treatment
  - Total daily insulin dose after 26 weeks of treatment

4. Statistical methods

- Change from baseline in HbA1c, FPG and body weight at the end of treatment
  - was analyzed using an analysis of variance (ANOVA) model with treatment, anti-diabetic therapy at screening, sex and region as fixed factors, and age and baseline variable of interest at covariates.
- Subjects reaching HbA1c < 7%
  - was based on logistic regression model using the same factors and covariates for the analysis of the primary endpoint
- 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 the primary endpoint, except no baseline hypoglycemic episodes included.
- Non inferiority test on the primary efficacy endpoint
  - Efficacy was considered confirmed if the upper bound of the 2-sided 95% CI for the estimated treatment difference (IDegAsp-control) for the mean change in HbA1c was below or equal to 0.4%.
- Superiority test on secondary efficacy endpoints
  - It was done only if non-inferiority was confirmed for the primary efficacy endpoint.
  - The superiority tests on secondary efficacy endpoints were carried out in a pre-specified hierarchical procedure.
- Missing data on HbA1c was imputed by last observation carried forward (LOCF) method. Sensitivity analysis was done for primary efficacy endpoint. It included analysis by repeated measurement model and PP analysis.

5. Data quality

Datasets were provided as SAS XPORT transport files version 5. I only had chance to test out one analysis dataset from trial NN5401-3594. No problem has been detected so far. No program was submitted.

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/s/

DONGMEI LIU
11/18/2011

JON T SAHLROOT
11/18/2011