Insulin Degludec and Insulin Degludec/Insulin Aspart Treatment to Improve Glycemic Control in Patients with Diabetes Mellitus

NDAs 203314 and 203313

Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

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List of Abbreviations and Definitions

ACS	acute coronary syndrome
ADA	American Diabetes Association
AE	adverse events
ALAT	alanine transaminase
ANOVA	analysis of variance
AUC	area under the curve
%B/T	percentage bound radioactivity (B) of the total amount of radioactivity (T)
BB	basal-bolus
BIAsp 30	biphasic insulin aspart (marketed as NovoLog® Mix 70/30)
BOT	basal-only therapy
BMI	body mass index
CHF	congestive heart failure
CI	confidence interval
CL_{CR}	creatinine clearance
C_{max}	maximum concentration
CV	cardiovascular
CV%	coefficient of variation
DCCT	Diabetes Control and Complications Trial
DPP-4I	dipeptidyl peptidase-4 inhibitors
ECG	electrocardiogram
FAS	full analysis set
FPG	fasting plasma glucose
GLP-1	glucagon-like peptide-1
GIR	glucose infusion rate
HbA_{1c}	hemoglobin A_{1c}
HDL	high density lipoprotein
IAsp	insulin aspart (marketed as NovoLog®)
IDeg	insulin degludec
IDegAsp	insulin degludec/insulin aspart
IDet	insulin detemir (marketed as Levemir®)
IGF-1	insulin-like growth factor-1
IGlar	insulin glargine (marketed as Lantus®)
ITT	intention-to-treat
i.v.	intravenous
LDL	low density lipoprotein
LOCF	last observation carried forward

MACE	major adverse cardiovascular event(s)
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NHANES	National Health and Nutrition Examination Survey
NDA	New Drug Application
NPH	Neutral Protamine Hagedorn insulin
OADs	oral antidiabetic drugs
PG	plasma glucose
PP	per protocol
PYE	patient years of exposure
SAE	serious adverse event
SAS	safety analysis set
s.c.	subcutaneous
SMPG	self-measured plasma glucose (derived from blood glucose meter measurements)
SMQ	standardized MedDRA query
SOC	system organ class
SS	steady state
SU	sulfonylurea
$t_{½}$	terminal half-life
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TEAE	treatment-emergent adverse event
TZD	thiazolidinedione
U	unit(s)
UAP	unstable angina pectoris
UKPDS	United Kingdom Prospective Diabetes Trial

1 Executive Summary

Novo Nordisk is seeking approval for insulin degludec (IDeg), a basal insulin for once-daily (OD) subcutaneous (s.c.) administration, to improve glycemic control in adults with diabetes mellitus (NDA 203314). IDeg was developed to cover basal insulin needs in patients with diabetes mellitus, either alone or in combination with bolus (mealtime) insulin and/or oral antidiabetic drugs (OADs). Novo Nordisk is also seeking approval for insulin degludec/insulin aspart (IDegAsp), a soluble coformulation of 70% IDeg and 30% of the rapid-acting insulin analogue, insulin aspart (IAsp, marketed as NovoLog®), for once- or twice-daily s.c. administration to improve glycemic control in adults with diabetes mellitus (NDA 203313).

Unmet Medical Need

Patients with type 2 diabetes mellitus (T2DM) who are unable to achieve glycemic control with OADs/glucagon-like peptide-1 (GLP-1) receptor agonists and all patients with type 1 diabetes mellitus (T1DM) require insulin therapy. Basal (long-acting) insulin therapy provides a necessary background of insulin therapy to cover 24 hours of baseline insulin requirements. Basal insulin and mealtime bolus (rapid-acting) insulin are required in T1DM and advanced T2DM. In the early stages of T2DM, treatment with basal insulin alone is sufficient to achieve and maintain glycemic control.

The goal of therapy for patients with diabetes is to safely achieve near-normal glycemic control in order to reduce the risk of developing the long-term complications associated with diabetes. Despite the availability of an abundance of antidiabetes therapies, a considerable number of patients with diabetes continue to have relatively poor glycemic control. While insulin is the most effective agent in attaining glucose control in patients with diabetes, barriers to achieving glycemic control with insulin include complicated and strict dosing regimens and suboptimal dosing due to the risk and fear of hypoglycemia, particularly nocturnal hypoglycemia.

Hypoglycemia is a barrier to achieving optimal glycemic control across the spectrum of diabetes. While rates of hypoglycemia tend to be relatively low in patients with T2DM treated with basal-only insulin therapy, hypoglycemic episodes can still interfere with achieving glycemic targets in these patients. Patients with advanced T2DM require a more complicated regimen of basal and bolus insulin and experience more hypoglycemia than T2DM patients treated with basal-only therapy, largely due to the requirement for more exogenous insulin and the effect of the bolus insulin. Patients with T1DM require full basal-bolus insulin replacement and have the highest rates of hypoglycemia.

Nocturnal hypoglycemia is of particular concern to patients with diabetes as they are less likely (or unable) to sense hypoglycemic symptoms and are therefore more prone to progress to severe hypoglycemia. It is also a societal concern because nocturnal hypoglycemia has been shown to be

associated with loss of work productivity.[1] In addition to impaired well-being and loss of work productivity, nocturnal hypoglycemia prompts increased glucose monitoring and more frequent contacts with health care providers, further adding to health care costs.[1]

Currently available basal insulin products may fail to provide consistent insulin coverage over 24 hours and from day to day for all patients. The flatter a basal insulin's pharmacokinetic (PK) profile at steady state, the more stable the glucose levels will be overnight and between meals, reducing the likelihood of blood glucose excursions that cause hypoglycemia, especially at night. IDeg either alone or in combination with bolus (mealtime) insulin (IDegAsp) was designed to have a longer half-life and less variable absorption profile than currently available basal insulin products that would translate into achievement of glycemic control with lower risk of hypoglycemia, especially at night.

Product Description and Molecule

The structure of IDeg is based on that of human insulin. Compared with human insulin, IDeg contains no amino acid substitutions, but the last amino acid residue (threonine at position B30), which does not impact receptor recognition, has been omitted. In addition, a di-carboxylic fatty acid (hexadecanedioic acid) has been coupled to the lysine at position B29 via a glutamic acid spacer. The addition of this specific di-carboxylic fatty acid via the glutamic acid spacer is what enables IDeg to form soluble and stable multi-hexamers when injected into subcutaneous tissue. In contrast, human insulin remains as hexamers. The biologically active monomers of IDeg gradually separate from the multi-hexamers in the subcutaneous depot, providing a slow, stable and continuous delivery of IDeg into the circulation resulting in the observed pharmacokinetic and pharmacodynamic (PD) profiles. Like human insulin, IDeg monomers bind to and activate insulin receptors at the target tissues, resulting in an overall lowering of blood glucose.

The molecular structure of IDeg allows it to be coformulated with IAsp with no molecular interactions between the two analogues, giving rise to an absorption profile of IDegAsp that resembles that of IDeg and IAsp injected separately. For this reason, a soluble fixed-ratio combination of IDeg and IAsp was developed to benefit patients who require prandial coverage in addition to their basal insulin.

To accommodate a wide range of insulin dose requirements in clinical practice, IDeg is being developed in two formulations: IDeg 100 U/mL (U100, 600 nmol/mL), and IDeg 200 U/mL (U200, 1200 nmol/mL). The IDeg U100 and IDeg U200 formulations were found to be bioequivalent and can therefore be used interchangeably. With IDeg U100, doses from 1-80 U per injection, in 1-U dose increments, can be administered. With IDeg U200, doses from 2-160 U per injection, in 2-U dose increments, can be administered. A dose with the U200 product is delivered in half the volume as the same dose with the U100 product. IDeg U200 will enable the 20−30% of

patients with T2DM who require more than 80 U per injection to administer the required insulin dose as a single daily injection. IDegAsp is developed in a U100 concentration only.

Nonclinical Pharmacology and Toxicology
IDeg acts specifically and gives full effect at the human insulin receptor and its mode of action is the same as that of human insulin, thus giving rise to the same metabolic effects such as cellular glucose uptake, glycogen synthesis and lipogenesis. The relative ratio between the IGF-1 and insulin receptor binding affinities was determined to be lower for IDeg than for human insulin. IDeg retains the same balance between the mitogenic and metabolic potency as human insulin. The nonclinical safety pharmacology and toxicology studies demonstrated no adverse effects apart from those related to exaggerated pharmacology (i.e., hypoglycemia). Overall, the nonclinical studies demonstrated that the modifications introduced in IDeg have not changed its metabolic or safety profile compared with human insulin. Furthermore, coformulation with IAsp does not affect the safety and efficacy of the individual components of IDegAsp.

Clinical Pharmacology
The steady-state pharmacokinetic and pharmacodynamic profiles of IDeg demonstrate continuous and slow absorption of IDeg into the circulation that results in a half-life of 25 hours, twice as long as currently available basal insulin products. The duration of glucose-lowering effect is more than 42 hours. Steady state concentration of IDeg is achieved within 3 days of once-daily dosing. Total exposure during one 24-hour dosing interval and maximum concentration of IDeg at steady state increased proportionally with increasing dose. The steady-state pharmacokinetic and pharmacodynamic profiles of IDeg were relatively peakless and evenly distributed over a 24-hour dosing interval.

IDeg was associated with a four-times-lower day-to-day variability in total glucose-lowering effect compared with insulin glargine (IGlar). The counter-regulatory response to experimentally induced hypoglycemia, patients' awareness of hypoglycemia, and their ability to recover from hypoglycemia were shown to be similar between IDeg and IGlar. IDeg demonstrated similar pharmacokinetic and pharmacodynamic properties in all populations investigated.

The pharmacokinetic profile of IDeg was not affected by coformulation with IAsp. With regard to the glucose-lowering effect of IDegAsp, the bolus component showed a rapid onset of action and a distinct peak action, whereas the basal component had a flat, stable and long action profile.

In summary, the glucose-lowering effect of IDeg (alone and coformulated with IAsp) was longer-acting and less variable than currently available basal insulin products. This long-acting, flat, and stable basal insulin profile is expected to translate into the following clinical attributes: full coverage of basal insulin requirements with once-daily dosing in all patients; the potential to achieve glycemic control with a low risk of hypoglycemia; and the potential to vary dosing intervals if doses are inadvertently missed or delayed.

Overview of the Phase 3 Trials

The NDA comprised 16 therapeutic confirmatory phase 3 trials in the IDeg and IDegAsp clinical development programs (11 IDeg and 5 IDegAsp). All trials were included in the evaluation of safety in the NDA. Extension data from one trial (IDegAsp T1DM OD basal-bolus [BB] trial) was also included in the presentation of safety in the NDA.

Of the 11 IDeg trials, 9 investigated once-daily dosing and 2 investigated three-times-weekly (3TW) dosing. The efficacy of IDeg is presented only for the 9 phase 3, randomized, controlled, open-label, multi-center, multinational trials that investigated once-daily dosing since the 3TW regimen is not being pursued in the current application. All trials were 26 or 52 weeks in duration and enrolled insulin-naïve patients with T2DM and insulin-treated patients with T2DM or T1DM.

In accordance with FDA guidance for insulin development[2], the goal was to obtain actual improvements in long-term glycemic control (HbA_{1c}) with IDeg and achieve noninferiority versus insulin comparators. Noninferiority is necessary to allow for a comparison among groups in hypoglycemia. In an effort to achieve similar glycemic control between treatment groups, a treat-to-target design was applied in which insulin doses were adjusted for each individual patient to reach a pre-breakfast self-measured plasma glucose (SMPG) target of between 70−90 mg/dL. Thus the goal was to have noninferior, not superior, HbA_{1c} reductions with IDeg or IDegAsp versus comparator insulin products, considering the fact that all insulin products are capable of lowering glucose levels.

Based on the flat and stable pharmacodynamic profile of IDeg, two phase 3 trials (one in T2DM and one in T1DM) were conducted to investigate whether it is possible to vary dosing intervals (IDeg flexible dosing arm) and compare this regimen to a standard IGlar dosing regimen. In the IDeg flexible dosing arm, the injection time was deliberately alternated between morning to evening on successive days. This resulted in dosing intervals of approximately 8 to 40 hours between injections without compromising safety and efficacy. This is not the intended dosing recommendation but rather an attempt to understand the impact of this degree of dosing variability on both glycemic control and the risk of hypoglycemia.

As mentioned previously, IDeg was also developed in a U200 formulation. Trial 3672 compared the efficacy and safety of once-daily IDeg U200 with IGlar. IDeg U200 allows for doses higher than 80 U to be administered in a single injection, which was required to achieve glycemic control in >20% of patients in this trial.

Unlike other currently available basal insulin products, the properties of the IDeg molecule allow for combination with IAsp in a soluble fixed ratio combination that does not require resuspension prior to injection. Five phase 3 trials investigated the efficacy and safety of the soluble fixed-ratio combination of IDeg and IAsp. In T2DM, two trials investigated IDegAsp versus a basal insulin

(IGlar), both dosed once-daily; and two trials investigated IDegAsp versus premixed insulin (BIAsp 30, NovoLog® Mix 70/30), both dosed twice daily. In T1DM, one trial investigated once-daily IDegAsp with IAsp at remaining meals versus a basal-bolus regimen of basal insulin detemir (IDet, Levemir®) and IAsp. While the ratio of IAsp to IDeg is most appropriate for twice-daily administration before two major meals, two of the IDegAsp trials were designed to investigate whether once-daily administration of IDegAsp could produce similar glycemic control as one injection of basal insulin only in T2DM. Similar to the IDeg trials, the IDegAsp trials tested noninferiority of IDegAsp to comparator with respect to change in HbA_{1c} from baseline.

To ensure sufficient exposure to IDeg or IDegAsp, nine of the sixteen phase 3 trials had unequal randomization (six trials had 2:1 and three trials had 3:1 randomization of IDeg or IDegAsp: comparator), including six of the seven IDeg/IDegAsp trials with extension periods.

In the IDeg and IDegAsp phase 3 trials, 5635 patients were exposed to IDeg or IDegAsp and 3306 were exposed to comparators. Of the 8941 patients in the phase 3 trials, 6830 (76.4%) had T2DM and 2111 (23.6%) had T1DM. Of the 6830 patients with T2DM, 3812 (55.8%) were insulin naïve and 3018 (44.2%) were insulin-treated prior to the trials. Patients with renal impairment (elevated creatinine), cardiovascular (CV) events occurring within 6 months, and hypoglycemia unawareness in the last 6 months or >1 severe episodes in the last 12 months were excluded. Exclusion of these patients was consistent with the ADA Standards of Care[3], which requires individualized glycemic targets and is incompatible with the treat-to-target design required by FDA guidelines.

Clinical Efficacy and Dosing

In all once-daily IDeg phase 3 trials, efficacy was established as once-daily IDeg was noninferior to insulin comparators in reducing HbA_{1c} (primary endpoint) (Table 1). This indicates that the treat-to-target design of the studies was successful in reaching the desired outcome of similar levels of glycemic control between the two treatments. Indeed, in all trials, the final HbA_{1c} reached, or approached, the ADA target of 7%. Importantly, in accordance with FDA Guidance for Industry[2], these results allow for meaningful comparisons of hypoglycemia.

Table 1 Overview of Clinical Efficacy Achieved in All Once-daily IDeg Phase 3 Trials

Trial ID	Trial Population, Insulin Regimen, Trial Length	Primary Treatment Comparison	Change in HbA_{1c} Estimated Treatment Difference IDeg - Comparator [95% CI]
3580	T2DM BOT 6m	IDeg vs. Sitagliptin	-0.43 [-0.61; -0.24]*
3579	T2DM BOT 12m	IDeg vs. IGlar	0.09 [-0.04; 0.22]
3672	T2DM BOT 6m	IDeg U200 vs. IGlar	0.04 [-0.11; 0.19]
3586	T2DM BOT 6m Asia	IDeg vs. IGlar	0.11 [-0.03; 0.24]
3668	T2DM BOT 6m	IDeg Flexible Dosing vs. IGlar	0.04 [-0.12; 0.20]
3582	T2DM BB 12m	IDeg vs. IGlar	0.08 [-0.05; 0.21]
3583	T1DM BB 12m	IDeg vs. IGlar	-0.01 [-0.14; 0.11]
3585	T1DM BB 6m	IDeg vs. IDet	-0.09 [-0.23; 0.05]
3770	T1DM BB 6m	IDeg Flexible Dosing vs. IGlar	0.17 [0.04; 0.30]†

*Statistically significant difference in favor of IDeg. Trial 3580 was designed to test the superiority of IDeg to sitagliptin, a non-insulin comparator.
†Statistically significant difference in favor of comparator with noninferiority criterion met.
IDeg: insulin degludec; IGlar: insulin glargine; IDet: insulin detemir; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; BOT: basal-only therapy; BB: basal-bolus therapy; CI: confidence interval. See Section 6.2 for a description of the IDeg flexible dosing schedule.
Noninferiority criterion: Upper confidence limit of difference ≤0.4. Full analysis set.

In the once-daily IDeg trials, consistently larger reductions in fasting plasma glucose (FPG) were achieved with IDeg than with comparator products, with a statistically significant difference in favor of IDeg in five of the nine trials. This finding was notable given the lower risk of hypoglycemia with IDeg than insulin comparators (described below). Improvements in glycemic control were achieved with similar doses of IDeg versus comparator insulin products.

In all IDegAsp phase 3 trials, efficacy was established as IDegAsp (dosed once or twice daily) was noninferior to insulin comparators in reducing HbA_{1c} (primary endpoint) (Table 2).

Table 2 Overview of Clinical Efficacy Achieved in the IDegAsp Phase 3 Trials

Trial ID	Trial Population, Insulin Regimen, Trial Length	Primary Treatment Comparison	Change in HbA_{1c} Estimated Treatment Difference IDegAsp - Comparator [95% CI]
3590	T2DM OD 6m	IDegAsp vs. IGlar	0.03 [-0.14; 0.20]
3593	T2DM OD 6m	IDegAsp vs. IGlar	-0.03 [-0.20; 0.14]
3592	T2DM BID 6m	IDegAsp vs. BIAsp 30	-0.03 [-0.18; 0.13]
3597	T2DM BID 6m	IDegAsp vs. BIAsp 30	0.05 [-0.10; 0.20]
3594	T1DM OD BB 6m	IDegAsp vs. IDet	-0.05 [-0.18; 0.08]

IDeg: insulin degludec; IGlar: insulin glargine; IDet: insulin detemir; BIAsp 30: biphasic insulin aspart; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; BOT: basal-only therapy; BB: basal-bolus therapy; CI: confidence interval. OD: once daily dosing; BID: twice-daily dosing.
Noninferiority criterion: Upper confidence limit of difference ≤0.4. Full analysis set.

IDegAsp administered twice-daily (BID) lowered FPG significantly more than BIAsp 30 BID. In one trial with IDegAsp OD, FPG was significantly lower with IGlar. Improvements in glycemic control were achieved with similar doses of IDegAsp compared with comparator insulin products.

Hypoglycemia

Per the FDA Guidance for Industry,[2] achieving similar efficacy in change in HbA_{1c} using a treat-to-target approach makes hypoglycemia a key differentiator in the comparison of IDeg/IDegAsp and other insulin products. Thus, these trials were designed to achieve noninferiority rather than superiority with regard to reductions in HbA_{1c}, so that meaningful comparisons between treatment groups in hypoglycemia could be made.

Severe hypoglycemia, confirmed hypoglycemia, and nocturnal confirmed hypoglycemia were predefined endpoints in the IDeg and IDegAsp clinical development programs. The hypoglycemic episodes were self-reported by patients in patient diaries specifically designed for collecting information on hypoglycemia.

- *Severe hypoglycemic episodes* were defined as episodes where patients were unable to treat themselves.
- *Confirmed hypoglycemic episodes* were defined as severe hypoglycemic episodes or those episodes of hypoglycemia with PG <56 mg/dL, regardless of symptoms. Confirmed hypoglycemia reflects the effect of both the basal insulin in all insulin treatment regimens and the mealtime bolus insulin used in more advanced T2DM and in T1DM. The 56 mg/dL cut-off was chosen because this is typically where counter-regulatory mechanisms begin and patients report clinical symptoms of hypoglycemia.[4]
- *Nocturnal confirmed hypoglycemic episodes* were defined as confirmed hypoglycemic episodes occurring between midnight and 6:00 a.m. Nocturnal hypoglycemia better reflects the action of basal insulin than overall confirmed hypoglycemia because it is not subject to the confounding effects of bolus insulin, meals or lifestyle. Hence, the flat and consistent pharmacodynamic profile of IDeg may best be observed during the nocturnal period. Accordingly, analyses of nocturnal hypoglycemia were expected to demonstrate the value of IDeg over other basal insulin products.

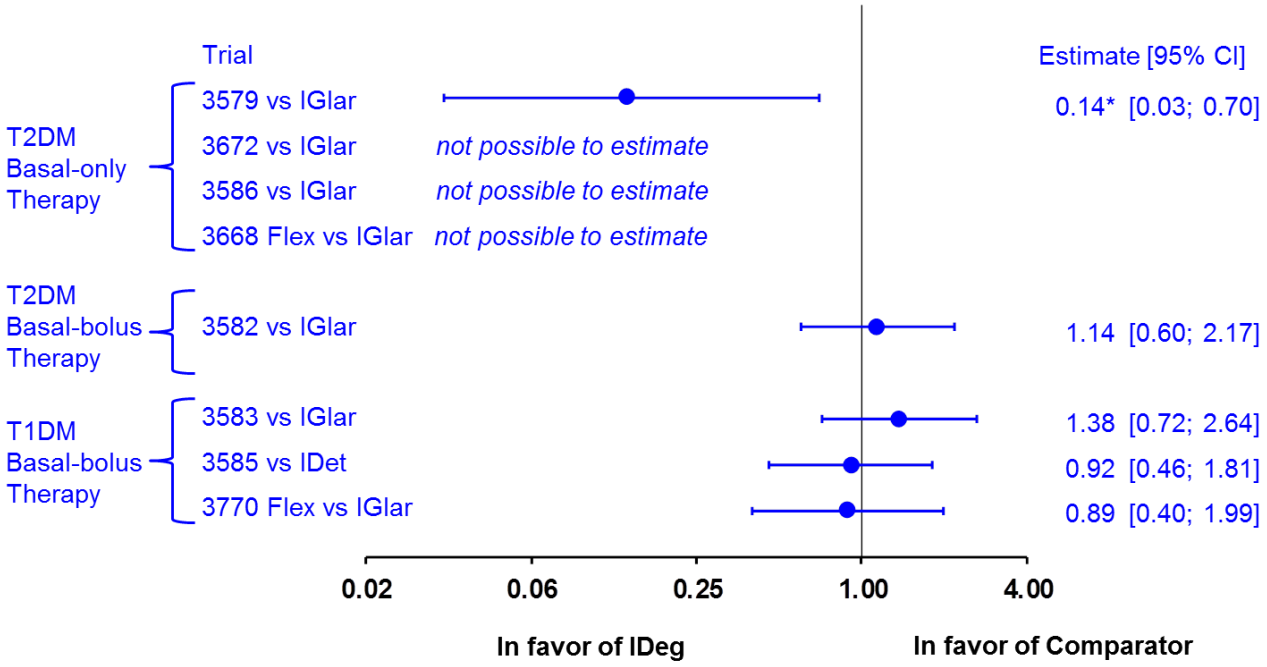
To substantiate the findings in individual trials, a prespecified meta-analysis was conducted that included all phase 3 trials in which IDeg was dosed once daily (T2DM+T1DM) and IGlar was used as comparator. In addition, the FDA had several additional requests, including an assessment of T2DM and T1DM separately and an assessment of hypoglycemia at stable doses during the maintenance phase (Novo Nordisk-defined as Week 16 to end of trial).

Severe hypoglycemia with IDeg

In T2DM basal-only therapy trials, the rates of severe hypoglycemia were low for both IDeg and comparator insulin (0–2 episodes per 100 patient-years exposure [PYE]), and were reported by a low percentage of patients (0–2%) within each treatment. In Trial 3579 with basal-only therapy, the rate of severe episodes was lower with IDeg than with IGlar (Figure 1). The addition of bolus insulin increased the occurrence of severe hypoglycemia compared with basal-only insulin therapy.

In the basal-bolus therapy trial in T2DM, severe hypoglycemia was reported for ~4.5% of the IDeg and IGlar patients. The rates of severe episodes increased from those in the basal-only trials to 6.1 and 5.2 episodes per 100 PYE with IDeg and IGlar, respectively, but were not significantly different between IDeg and IGlar (Figure 1).

In the basal-bolus trials in patients with T1DM, there were no statistically significant treatment differences between IDeg and comparators (IGlar or IDet) in the rates of severe hypoglycemia. Across trials, 10 to 12% of patients with T1DM reported one or more episode of severe hypoglycemia with IDeg or comparator, with mean rates of 21 to 34 episodes per 100 PYE with IDeg and 16 to 47 episodes per 100 PYE with comparator. The rate ratios of severe hypoglycemia in individual trials with basal-only therapy in T2DM, and with basal-bolus therapy in T2DM and T1DM are shown in Figure 1.



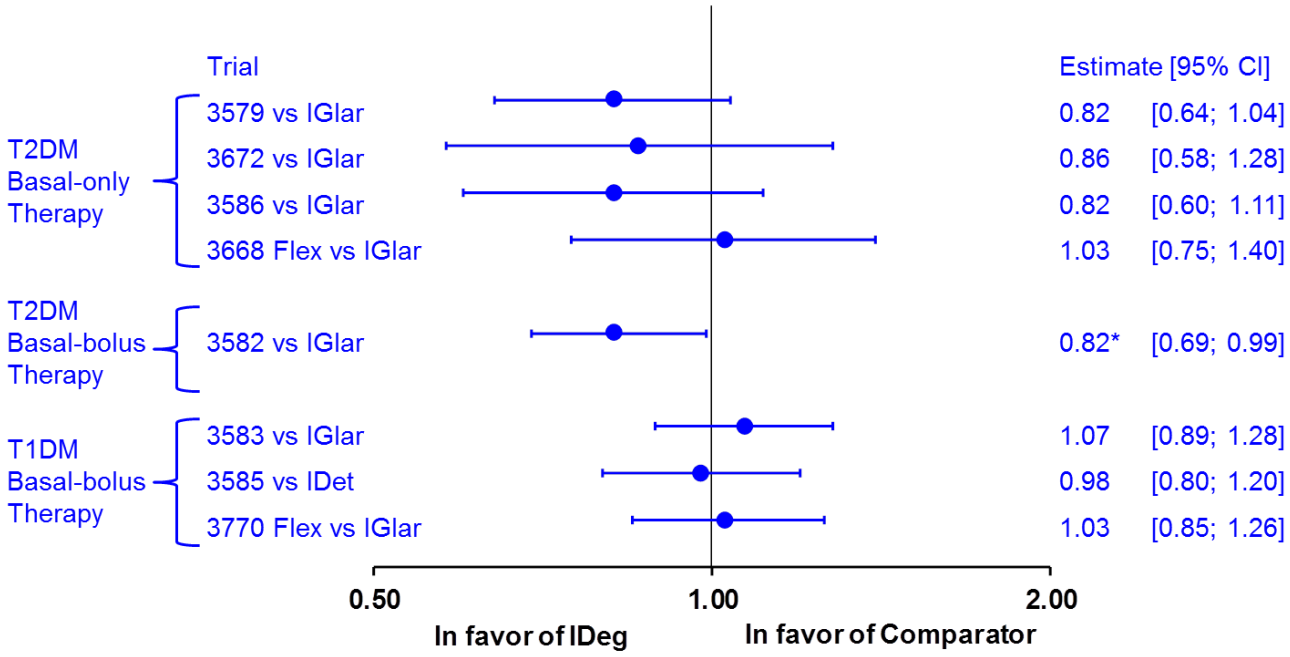
* Indicates a statistically significant difference.
IDeg: insulin degludec; IGlar: insulin glargine; IDet: insulin detemir: T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; CI: confidence interval. Not possible to determine: ≤ 2 episodes in each treatment arm. Analyses are based on a negative binomial model except for Trials 3579 and 3582 where a Poisson regression model was used. Full Analysis set.

Figure 1 Severe Hypoglycemia – IDeg Phase 3 Trials with Insulin Comparators

Episodes of nocturnal severe hypoglycemia were reported by approximately 3-4% of patients treated with IDeg (observed rate 5−9 episodes per 100 PYE) and by 2-3% of patients treated with comparator products (observed rate 2–17 episodes per 100 PYE) in T1DM trials with basal-bolus therapy. Except in Trial 3579, the rates of severe hypoglycemia or severe nocturnal hypoglycemia were not significantly different between IDeg and comparators (Figure 1).

Confirmed hypoglycemia with IDeg

In T2DM, the rates of confirmed hypoglycemia were lower with IDeg than comparator, reaching statistical significance in the basal-bolus Trial 3582. In the three IDeg T1DM trials, treatment differences between IDeg and comparator were not statistically significant (Figure 2).



* Indicates a statistically significant difference.
IDeg: insulin degludec; IGlar: insulin glargine; IDet: insulin detemir: T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; CI: confidence interval. Full Analysis set.

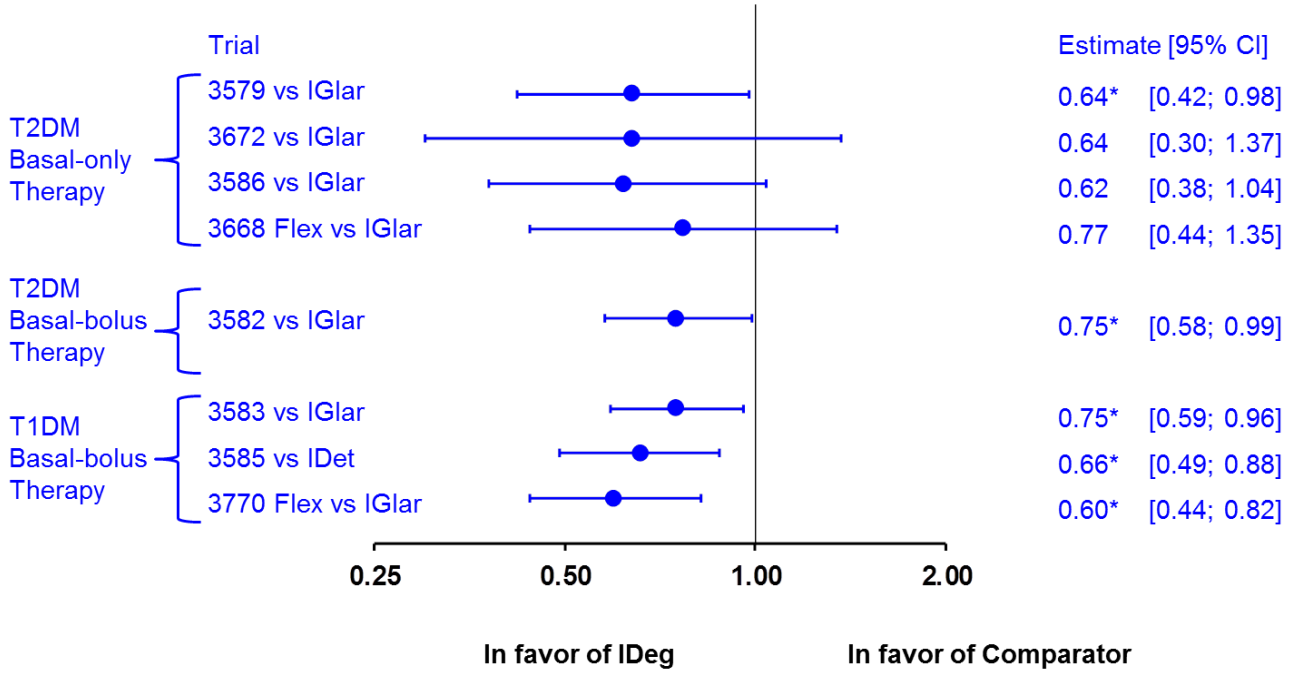
Figure 2 Confirmed Hypoglycemia – IDeg Phase 3 Trials with Insulin Comparators

Nocturnal Confirmed Hypoglycemia with IDeg

Nocturnal hypoglycemia is of clinical relevance because of the negative impact nocturnal hypoglycemic episodes can have on patients and their caregivers. Nocturnal hypoglycemia affects patients' well-being and work productivity, and is a contributing factor in the failure of patients and health care providers to optimize insulin therapy. Nocturnal hypoglycemia is particularly relevant since it may not be detected by patients who may not have adequate warning to seek treatment before they progress to severe nocturnal hypoglycemia, which can lead to unconsciousness and even death in rare cases.[5,6]

The lower rate of nocturnal confirmed hypoglycemia (episodes occurring between midnight and 6:00 a.m.) versus insulin comparators was a consistent finding across the IDeg phase 3 trials regardless of insulin regimen (basal-only therapy or basal-bolus therapy), time of dosing (once-daily

evening or flexible dosing intervals), or patient population (e.g., T1DM, T2DM, insulin-naïve). In 5 of the 8 trials with insulin comparators, the estimated rate of nocturnal confirmed hypoglycemia was significantly lower with IDeg than comparator insulin (Figure 3).



* Indicates a statistically significant difference.
IDeg: insulin degludec; IGlar: insulin glargine; IDet: insulin detemir: T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; CI: confidence interval. Nocturnal hypoglycemia: episodes occurring between midnight and 6 a.m.

Figure 3 Nocturnal Confirmed Hypoglycemia – IDeg Phase 3 Trials with Insulin Comparators

Hypoglycemia Meta-analysis of IDeg versus IGlar

The benefits related to less hypoglycemia with IDeg versus insulin comparator were further confirmed by a prespecified meta-analysis in specific populations of patients with T1DM and T2DM in which IGlar was the comparator insulin. The prospectively planned meta-analysis included all phase 3 trials in which IDeg was dosed once daily at the same time every day and IGlar used as comparator. The approach for the meta-analysis was discussed with the FDA after completing the phase 2 program and a statistical analysis plan was sent to the FDA for review prior to first database lock of the IDeg phase 3 trials.

For T2DM patients on basal-only therapy, the rate of severe episodes with IDeg therapy was significantly lower than with IGlar (rate ratio 0.14 $[0.03; 0.70]_{95\%CI}$). The rate of severe episodes with IDeg in basal-bolus therapy for T2DM was similar to that of IGlar (1.14 $[0.60; 2.17]_{95\%CI}$). For

the pooled population of T2DM patients, the rate of severe episodes with IDeg was similar to the rate of severe episodes with IGlar patients (rate ratio 0.81 [0.42; 1.56]$_{95\%CI}$).

Not unexpectedly, the rates of hypoglycemia in T1DM patients were higher generally than those of the T2DM patients. Overall, because of the influence of the bolus insulin, there was no significant treatment difference in severe hypoglycemia for the populations of T2DM+T1DM patients or T1DM patients.

IDeg was associated with a significantly lower rate of confirmed hypoglycemic episodes than IGlar for pooled T2DM+T1DM patients and T2DM patients, while the rates were not significantly different for TIDM patients. Once patients had titrated their basal insulin to a steady level they began a maintenance period where rates were significantly lower for IDeg compared with IGlar in T2DM+T1DM and T2DM patients but not in T1DM patients (Table 3).

Table 3 Meta-analysis of Confirmed Hypoglycemia during the Entire Treatment Period (from Week 0) and the Maintenance Period (from Week 16)

		Entire Treatment Period Estimated Rate-Ratio		Maintenance Treatment Period Estimated Rate-Ratio	
	Comparison	Estimate	[95% CI]	Estimate	[95% CI]
T2DM Basal-only therapy	IDeg vs. IGlar	0.83	[0.70; 0.98]*	0.72	[0.58; 0.88]*
T2DM	IDeg vs. IGlar	0.83	[0.74; 0.94]*	0.75	[0.66; 0.87]*
T1DM	IDeg vs. IGlar	1.10	[0.96; 1.26]	1.02	[0.88; 1.19]
Pooled (T2DM+T1DM)	IDeg vs. IGlar	0.91	[0.83; 0.99]*	0.84	[0.75; 0.93]*

*Ratio significantly different than 1.
IDeg: insulin degludec; IGlar: insulin glargine; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; CI: confidence interval.
T2DM: Trials 3672, 3579, 3582, 3586, and 3668 (excluding flexible dosing arm); Basal-only therapy in insulin-naive patients: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583.

Meta-analysis of Nocturnal Confirmed Hypoglycemia

The rates of nocturnal confirmed hypoglycemia with IDeg were significantly lower than those with IGlar in all populations of patients as shown below (Table 4). As with confirmed hypoglycemia, the rate ratios in the maintenance period were lower than those in the entire treatment period, suggesting that the rates of nocturnal confirmed hypoglycemia with IDeg were further improved compared with IGlar during this period when insulin doses had stabilized.

Table 4 Meta-analysis of Nocturnal Confirmed Hypoglycemia during the Entire Treatment Period (from Week 0) and Maintenance Period (from Week 16)

		Entire Treatment Period Estimated Rate-Ratio		Maintenance Treatment Period Estimated Rate-Ratio	
	Comparison	**Estimate**	**[95% CI]**	**Estimate**	**[95% CI]**
T2DM Basal-only therapy	IDeg vs. IGlar	0.64	[0.48; 0.86]*	0.51	[0.36; 0.72]*
T2DM	IDeg vs. IGlar	0.68	[0.57; 0.82]*	0.62	[0.49; 0.78]*
T1DM	IDeg vs. IGlar	0.83	[0.69; 1.00]	0.75	[0.60; 0.94]*
All (T2DM + T1DM)	IDeg vs. IGlar	0.74	[0.65; 0.85]*	0.68	[0.58; 0.80]*

*Ratio significantly different than 1.
IDeg: insulin degludec; IGlar: insulin glargine; T2DM: type 2 diabetes mellitus; T1DM: type 1 diabetes mellitus; CI: confidence interval.
T2DM: Trials 3672, 3579, 3582, 3586, and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583.

Analysis of Hypoglycemia Based on Incidence Rates

The FDA recommended an analysis using incidence rates of hypoglycemia that describes the proportion of patients who experience at least one hypoglycemic episode divided by the extent of exposure.

Consistent with the prespecified primary analysis, odds ratios for confirmed hypoglycemia in T1DM+T2DM was 0.93 $[0.79; 1.08]_{95\% CI}$ and was 0.89 $[0.75; 1.04]_{95\% CI}$ for overall T2DM and 0.91 $[0.74; 1.11]_{95\% CI}$ for insulin-naïve patients with IDeg compared with IGlar. The estimates did not reach statistical significance due to reduced power when only taking the first hypoglycemic episode into consideration. In T1DM, the analysis for the incidence of confirmed hypoglycemia is not informative because, not surprisingly, a very high proportion of patients in this population (>95% in both treatment groups) experienced at least one episode of confirmed hypoglycemia.

The analysis using incidence of nocturnal confirmed hypoglycemic episodes in the pooled population of T1DM and T2DM showed that IDeg had an incidence that was 22% lower compared with IGlar (odds ratio 0.78 $[0.67; 0.92]_{95\%CI}$). In the corresponding analysis for patients with T1DM, there was no difference in the incidence of nocturnal confirmed hypoglycemia between IDeg and IGlar (odds ratio of 1.04 $[0.76; 1.43]_{95\% CI}$). The incidence of nocturnal confirmed hypoglycemia was statistically significantly lower with IDeg compared with IGlar in patients with T2DM (odds ratio of 0.71 $[0.59; 0.85]_{95\% CI}$). Likewise, for insulin-naïve patients with T2DM, there was a lower incidence of nocturnal confirmed hypoglycemia with IDeg compared with IGlar; the difference was not statistically significant (odds ratio of 0.80 $[0.61; 1.06]_{95\% CI}$.

Hypoglycemia with IDegAsp

The rates of severe hypoglycemia with IDegAsp increased in relation to the complexity of the insulin regimen (toward more intensive insulin therapy) and to the type of diabetes. In the two trials with T2DM patients taking IDegAsp OD therapy, 1 event was reported with IDegAsp, and 5 events

with IGlar therapy. Severe hypoglycemia increased in Trial 3592 where twice-daily IDegAsp dosing was compared to twice-daily BIAsp 30 in T2DM patients (8.8 compared with 25.3 events per 100 PYE for IDegAsp and BIAsp 30, respectively). In Trial 3597 with twice-daily dosing in T2DM, the rates of severe hypoglycemia were similar for the two treatments (4.7 and 3.1 episodes per 100 PYE for IDegAsp and BIAsp 30, respectively). In the single trial where IDegAsp was compared with IDet in basal-bolus therapy in T1DM patients, the rate of severe hypoglycemia (33 vs. 42 events per 100 PYE, respectively) was slightly lower for the IDegAsp patients than the IDet patients.

The rates of confirmed hypoglycemia favored the comparator insulin in two trials where once-daily IDegAsp was compared to once-daily IGlar. The higher rate with IDegAsp is expected and reflects the contribution of the bolus component present in IDegAsp but not in the comparator. Twice-daily IDegAsp was compared with twice-daily BIAsp 30 in T2DM in two studies. The rate of confirmed hypoglycemia was significantly lower for IDegAsp than for BIAsp 30 in one study, and similar in the second study. The rate of confirmed hypoglycemia with IDegAsp in basal bolus therapy in T1DM was not different than IDet in basal bolus therapy.

In two trials with once-daily IDegAsp in T2DM patients, the rates of nocturnal confirmed hypoglycemia were 20% and 71% lower with IDegAsp OD than with IGlar OD (statistically significant for 71% in Trial 3590). In two trials with twice-daily IDegAsp in T2DM patients, the rates of nocturnal confirmed hypoglycemia were 33% and 73% lower for patients treated with IDegAsp BID than with BIAsp 30 BID (statistically significant for 73% in Trial 3592). Similarly, significantly lower rates (by 37%) of nocturnal hypoglycemia were reported for T1DM patients taking IDegAsp in basal-bolus therapy compared with IDet in basal-bolus therapy. Thus, the pharmacokinetic/pharmacodynamic profile of IDeg with regard to reducing the rate of nocturnal hypoglycemia compared with other basal insulin products was retained in the IDegAsp formulation.

Clinical Safety

In line with the *in vitro* and preclinical toxicology profile of IDeg, no new or unique adverse events were observed with this new insulin analogue. The adverse event profiles of IDeg and IDegAsp were similar in type, frequency, and time of onset to the comparator for nearly 9,000 diabetes patients in the phase 3 clinical development programs, including the subsets of both T2DM and T1DM patients. The majority of adverse events (AEs) were mild in severity and the rates of serious AEs (SAEs) were comparable for the IDeg+IDegAsp (16.1 events per 100 PYE), and comparator groups (15.0 events per 100 PYE). There were 18 deaths in the IDeg+IDegAsp groups compared with 8 deaths in the comparator groups with mortality rates of 0.6 events per 100 PYE for IDeg+IDegAsp and 0.5 events per 100 PYE for comparator. There were no apparent differences between IDeg or IDegAsp groups and comparator groups with respect to the patterns of AEs or SAEs leading to withdrawal, and these were dispersed across the entire treatment period.

Adverse events considered by Novo Nordisk to be of special medical interest included those in the categories hypoglycemia, cardiovascular, neoplasms, and allergic reactions. By protocol the reporting procedures were set to be identical to reporting procedures of SAEs in the phase 3 trials to ensure adequate information for a thorough assessment of AEs in these categories.

Rates of malignant neoplasms were similar between IDeg+IDegAsp (0.9 events per 100 PYE) and comparator (0.8 events per 100 PYE). The five most frequently reported malignant neoplasm types were skin, gastrointestinal, breast, thyroid and bladder neoplasms. There was no consistent pattern of reporting: malignant skin neoplasms and colorectal cancer, included in malignant gastrointestinal neoplasms, were reported slightly more frequently in the IDeg+IDegAsp group, whereas malignant breast, thyroid and bladder neoplasms were reported slightly more often in the comparator group. The majority of the malignant neoplasms in the IDeg+IDegAsp group (52%) were reported within 3 months after start of trial treatment, which suggests that a causal relationship is unlikely.

No differences were seen in the onset or duration of allergic reactions or injection-site reactions between IDeg+IDegAsp and the comparators. Allergic reactions were infrequent with IDeg and IDegAsp and comparator groups with corresponding rates of 1.3 and 0.9 episodes per 100 PYE, respectively. Rates of injection-site reactions were 7.0 events per 100 PYE in the IDeg+IDegAsp group and 9.0 events per 100 PYE in the comparator group.

The increase in body weight was similar with IDeg and IGlar, both in T2DM and T1DM, with no statistically significant treatment differences. In the IDegAsp phase 3 trials, the weight increase was smaller for IDegAsp BID compared with BIAsp 30 BID in patients with T2DM, whereas it was greater with IDegAsp OD than IDet in T1DM and greater with IDegAsp OD than with IGlar in T2DM (likely due to the bolus component).

Overall, there were no clinically relevant differences between IDeg, IDegAsp and the comparators in clinical laboratory findings after 26 or 52 weeks of treatment.

There was no evidence of neutralizing antibodies with IDeg in patients with either T1DM or T2DM, and there was no correlation between IDeg antibody formation and HbA_{1c}, change in HbA_{1c} at the end of the trial, or total daily dose at the end of the trial.

In conclusion, IDeg and IDegAsp were well tolerated with adverse event profiles similar to that of other marketed insulin products.

Cardiovascular Safety

NDA

The IDeg and IDegAsp phase 3 trials were not designed as cardiovascular outcome trials. The focus was on glycemic efficacy and the relationship between glycemic efficacy and the risk of hypoglycemia.

As part of the overall safety evaluation in the IDeg and IDegAsp phase 3 trials, cardiovascular safety was comprehensively assessed by collecting AEs (from first dose of randomized treatment up until 7 days after stop of randomized treatment) as well as measuring vital signs, ECG, QTc, and lipids. A follow-up visit was scheduled at least 7 days after drug discontinuation to ensure that all adverse events were captured in a systematic and rigorous manner for the complete trial period. Events occurring after this follow-up visit, and hence outside the trial period, were only reported to Novo Nordisk at the discretion of the investigator.

The prespecified plan to collect and analyze cardiovascular events was developed as per the FDA draft guideline at the time. Per protocol, in all phase 3 trials cardiovascular events suspected to be major adverse cardiovascular events (MACE) were sent to an external independent committee of experts blinded to treatment allocation for adjudication.

The prespecified MACE composite endpoint for the IDeg and IDegAsp phase 3 trials was cardiovascular (CV) death, stroke, acute coronary syndrome (myocardial infarction [MI] and unstable angina pectoris [UAP]). Inclusion of UAP in the prespecified MACE composite endpoint was done to obtain a broad assessment of cardiovascular risk in this trial population.

In the 16 phase 3 trials included in the NDA, 80 patients experienced treatment-emergent MACE (53 IDeg+IDegAsp patients and 27 comparator patients), with similar incidence rates for MACE between IDeg+IDegAsp and comparator (1.48 and 1.44 patients with MACE per 100 PYE, respectively). In the prespecified primary analysis, the overall estimated hazard ratio for IDeg+IDegAsp/comparator was 1.097 $[0.681; 1.768]_{95\%CI}$. For the prespecified primary analysis of time to first MACE, there was no consistent pattern in the estimated hazard ratios across trials, some favored IDeg+IDegAsp and some favored comparator. This estimate and confidence interval do not suggest an undue cardiovascular risk. Results from prespecified sensitivity analyses supported the results of the primary analysis. The majority of patients with MACE (76/80 patients, 95%) had T2DM. In both treatment groups, patients with prior cardiovascular disease had a higher risk of experiencing a MACE than patients without prior cardiovascular disease.

In the NDA, no clinically relevant differences in vital signs, ECG, QTc, and lipids were observed between IDeg+IDegAsp and comparator.

FDA Requested Post Hoc Analyses of MACE

As per FDA request, an additional *post hoc* analysis of MACE was conducted excluding UAP from the MACE composite endpoint definition. When UAP was excluded, the estimated hazard ratio for IDeg+IDegAsp/comparator increased to 1.393 $[0.757; 2.565]_{95\%CI}$, based on 54 MACE (39 IDeg+IDegAsp, 15 comparator).

In addition, updated MACE analyses were conducted with additional exposure per FDA request. As of the cut-off date of May 1, 2012, data from 9 additional completed trials were available: 6 extension trials (5 IDeg and 1 IDegAsp), 1 IDegAsp phase 3a trial, and 2 IDeg phase 3b trials. All additional MACE were prospectively and blindly adjudicated by the same external committee using the same procedure as outlined for the trials included in the NDA.

The nine additional trials contributed an additional 742 patients treated with IDeg+IDegAsp (1838 PYE) and 149 patients treated with comparator (689 PYE) to the MACE analyses. In the period from the NDA until the May 1, 2012 cut-off, an additional 54 patients experienced treatment-emergent MACE (44 IDeg+IDegAsp patients and 10 comparator patients). The majority of patients experiencing MACE since the original NDA were from planned extensions of a few trials.

The FDA also requested additional *post hoc* analyses including MACE reported within 30 days after drug discontinuation rather than MACE reported within the 7-day follow-up period (i.e., treatment-emergent MACE). In most trials, patients were switched from trial drug to NPH during the protocol-defined 7-day follow-up period and then switched to marketed insulin products after their last visit (i.e., the 7-day follow-up visit). As of the May 1, 2012 cut off, 7 MACE were reported during the period from 7 to 30 days post-treatment (3 in the NDA trials, 4 in trials completed after the NDA up to May 1, 2012).

Upon request of the FDA, an additional *post hoc* analysis of MACE excluding UAP from the MACE composite endpoint was conducted including MACE reported up to 30 days after drug discontinuation from all completed trials as of May 1, 2012. Incidence rates were 1.41 patients with MACE per 100 PYE with IDeg+IDegAsp and 0.90 patients with MACE per 100 PYE with comparator. Thus, the incidence rate for IDeg+IDegAsp was approximately the same as in the prespecified NDA analysis, whereas the incidence rate for the comparator group had decreased. The estimated hazard ratio was 1.614 $[0.999; 2.609]_{95\%CI}$.

The majority of patients experiencing MACE since the original NDA were from planned extensions of a few trials. Data from extensions represented only 35% of the original randomized population and provided 2-year cardiovascular outcome information on approximately 10% of the population in the IDeg+IDegAsp programs based on the design of the trials in the development programs. Therefore, the analyses including the extension data are not considered as robust as the prespecified NDA analysis.

For this reason, the prespecified analysis (treatment-emergent MACE, prespecified MACE composite endpoint [including UAP]) was repeated for all MACE based solely on data from randomized phase 3a and 3b trials as of May 1, 2012, and hence without inclusion of data from extensions. Incidence rates were 1.51 patients with MACE per 100 PYE with IDeg+IDegAsp and 1.49 patients with MACE per 100 PYE with comparator. Thus, when extensions were excluded from the May 1, 2012 data, based on 85 MACE, an estimated hazard ratio of 1.125 $[0.705; 1.797]_{95\%CI}$ was obtained, similar to the primary NDA analysis.

In conclusion, the prespecifed primary analysis in the NDA did not show an increased risk of MACE for patients treated with IDeg or IDegAsp. However, the hazard ratio increased with an alternative MACE composite endpoint definition that excluded UAP and increased with additional exposure from extensions. Hence, the totality of the data neither confirms nor excludes increased cardiovascular risk. In order to better define the cardiovascular profile, Novo Nordisk will continue to work with FDA on potential post-approval activities.

Benefit-Risk Profile and Risk Management

The long and stable action profile of IDeg results in a duration of action beyond 42 hours at clinically relevant doses and a markedly lower day-to-day and hour-to-hour variability in glucose-lowering effect. This distinct pharmacodynamic profile is associated with important clinical benefits compared to currently marketed basal insulin analogues. Most importantly, it allows patients to optimize glycemic control with less risk of overall confirmed hypoglycemia and particularly nocturnal hypoglycemia. The lower rate of nocturnal hypoglycemia was a consistent finding across the individual trials regardless of insulin regimen (basal-only therapy or basal-bolus therapy), time of dosing (once-daily evening or varying dosing intervals [~8 to ~40 hours between injections] for IDeg or largest meal for IDegAsp), type of insulin comparator (IGlar, IDet, BIAsp 30), or patient population (e.g., T1DM, T2DM, insulin-naïve, and elderly patients).

In addition, the use of IDeg enables patients who forget or for other reasons miss a scheduled dose to administer IDeg when this is discovered without undue risk of hypoglycemia or lack of short-term glycemic control. Furthermore, the availability of the U200 formulation of IDeg allows most patients with high dose requirements to administer the required daily dose of IDeg as one single injection.

The clinical benefits of IDeg are retained in the IDegAsp formulation, most notably a reduced risk of nocturnal hypoglycemia. IDegAsp will be the first soluble insulin analog coformulation of basal and bolus components that will not require resuspension before administration. The formulation of IDegAsp has been optimized such that the individual components do not interact, enabling a clear distinction of the bolus and basal components, as evidenced from the clinical pharmacology program. As supported by clinical data, the long duration of action of the basal component of

IDegAsp supports once- or twice-daily dosing with the ability to advance or delay the injection to a different main meal on the same day.

The adverse events of interest with IDeg and IDegAsp are those also observed with other insulin products and include hypoglycemia, injection-site disorders and neoplasms. There were no clinically relevant differences in the rates of these adverse events between IDeg+IDegAsp and comparator products, but Novo Nordisk will continue to collect detailed safety information for these during the phase 3b program considering their clinical importance.

The clinical development programs undertaken with IDeg and IDegAsp were the largest ever conducted with an insulin analogue and consistently substantiated the advantages of these insulin products across the range of potential use in patients with T2DM from early onset to more advanced stages of disease, as well as in patients with T1DM. It is important to note that the program was designed to evaluate the efficacy and safety profile of IDeg or IDegAsp versus comparator agents in terms of glycemic control and general safety parameters; the program was not specifically designed as a cardiovascular outcome program.

The overall estimated hazard ratio for MACE based on the prespecified analysis of the pooled IDeg+IDegAsp (T2DM+T1DM) population from the original NDA dataset was 1.097 $[0.681; 1.768]_{95\%CI}$, with no consistent pattern across individual trials. However, considering data from the additional *post hoc* analyses that redefine MACE from the prespecified definition and that include extension periods with imbalanced exposure and representing 35% of the original randomized population, Novo Nordisk cannot delineate the cardiovascular risk profile. In order to further define the relative cardiovascular profile of IDeg and IDegAsp, Novo Nordisk will continue to work with the FDA on appropriate post-approval activities.

2 Diabetes Mellitus and Challenges with Current Insulin Therapy

Summary

- Poor glycemic control increases the risk of diabetes complications.
- Patients with T2DM suboptimally controlled with oral antidiabetes drugs (OADs)/GLP-1 receptor agonists and all patients with T1DM require insulin therapy to achieve glycemic control.
- Along the spectrum of insulin treatment from basal-only therapy in T2DM, to the addition of mealtime bolus insulin in more advanced T2DM, and full basal-bolus insulin replacement in T1DM, insulin therapy becomes more complicated and the risk of hypoglycemia increases.
- Hypoglycemia is the primary limiting factor to achieving glycemic control with insulin.
- Intensive and complex insulin regimens and dosing limitations are additional barriers to achieving glycemic control with insulin.
- Currently available basal insulin products often fail to reproducibly provide insulin coverage over a full 24 hours and from day to day. A basal insulin with a long, flat, and stable profile would reduce the likelihood of blood glucose fluctuations causing both hyperglycemia and hypoglycemia.

2.1 Type 2 and Type 1 Diabetes Mellitus Treatment and Treatment Goals

In the United States, 25.8 million people (8.3% of the population) are affected by diabetes (18.8 million people diagnosed, 7.0 million people undiagnosed).[7] Unfortunately, from the perspective of the patient and the public health system, these numbers are increasing rapidly and the medical, social and economic burdens imposed by diabetes continue to rise.

Type 2 diabetes mellitus (T2DM), which accounts for more than 90% of cases of diabetes, is a progressive disorder characterized by a combination of insulin resistance and defective insulin secretion that is insufficient to compensate for that resistance. Along with lifestyle changes (diet and exercise), metformin is typically used as first-line pharmacotherapy. If glycemic control is suboptimal with metformin, combination therapy with other oral antidiabetic drugs (OADs) such as SUs, TZDs, DPP-4 inhibitors or with GLP-1 receptor agonists can be initiated.[8]

Ultimately, patients with T2DM require insulin therapy to achieve glycemic control. Typically, basal insulin therapy is added-on to OAD/GLP-1 receptor agonist therapy because of its ease of use and the fact that it is quite effective as sole insulin therapy when the HbA_{1c} is not too elevated. As beta-cell function further declines, insulin output becomes insufficient to control mealtime post-

prandial glycemia. Addition of mealtime bolus insulin to the basal insulin regimen then becomes necessary to maintain glycemic control. For some patients, a fixed-ratio combination insulin product with a basal and bolus component is an option when these individuals require mealtime glucose control along with the need for basal insulin, but they cannot deal with the complexity of bolus insulin administration and dose adjustment before each meal. Currently available premixed insulin products are dosed with meals, typically twice a day.

In patients with type 1 diabetes mellitus (T1DM), insulin-producing beta-cells in the pancreas are destroyed due to autoimmune processes, and these patients are nearly or completely deficient in insulin secretion. These patients require insulin injections for survival. This generally is accomplished with exogenous insulin replacement to cover basal as well as meal-related (bolus) insulin requirements. Hence, basal-bolus insulin therapy is required for glycemic control and is initiated upon diagnosis.

Despite the abundance of available antidiabetes therapies, a considerable number of patients with diabetes continue to have suboptimal glycemic control.[9] Data from NHANES indicate that from 2004 to 2006, only 57% of patients with diagnosed diabetes had an HbA_{1c} <7%.[10] In general, as the duration of diabetes increases and the need for complex therapy becomes greater, the percentage of patients who achieve target levels of glucose control decreases. Inadequate treatment of T2DM or T1DM over sustained periods of time results in suboptimal glycemic control that leads to long-term complications of diabetes such as eye disease (retinopathy), kidney disease (nephropathy), nerve disease (neuropathy), hypertension, heart disease and stroke .[7]

Studies have found that improved glycemic control results in long-term benefits in patients with either T2DM or T1DM. Every percentage point drop in HbA_{1c} (e.g., from 8.0% to 7.0%) decreases the risk of microvascular complications by ~40%.[7] Thus, the present goal of therapy for most patients is to reduce hemoglobin A_{1c} (HbA_{1c}) to a target (e.g., <7.0%) while minimizing side effects, although patient-specific factors like age, ability to comply with treatment, and concomitant illness and medication use should guide treatment goals for individual patients.[8]

Long-term outcome trials in diabetes (DCCT, UKPDS, ACCORD) have confirmed the necessity of good glucose control to reduce diabetes complications but also highlighted the increased frequency of hypoglycemia associated with intensive diabetes treatment.[11-13] The rise in the prevalence of diabetes (and its complications) requires new approaches to therapy including the development of improved insulin analogues to address hypoglycemia and other barriers to good glycemic control.

2.2 Challenges with Insulin Therapy – Unmet Medical Needs

While insulin is the most effective agent to achieve glucose control in patients with diabetes, it has a narrow therapeutic window. To avoid hypoglycemia, insulin is often underutilized, resulting in poor glycemic control, and thereby increasing the risk of developing diabetes complications. Other

barriers to insulin treatment include weight gain and interference with lifestyle, where complicated and strict regimens provide an additional burden to patients with diabetes.

2.2.1 The Burden of Hypoglycemia

The impact of hypoglycemia on the daily life of patients with diabetes on insulin therapy often is underestimated. The risk of hypoglycemia affects both the prescriber's and the patient's targets for glucose control.

As stated above, while insulin has unsurpassed potential efficacy, it is often initiated late in the disease or suboptimally dosed primarily due to the risk and fear of hypoglycemia.[14,15] Severe hypoglycemia can cause seizures, unconsciousness, and even death, and non-severe hypoglycemia is also concerning as it may affect cognitive function or motor control. Fear of reoccurring hypoglycemia has been shown to cause many patients to decrease their insulin dose, thereby compromising their glycemic control.[1,16] As a defensive measure against hypoglycemia, patients may consume more food causing weight gain. Recurrent hypoglycemia contributes to hypoglycemic unawareness, which affects the ability to recognize and deal with future episodes.[4]

Nocturnal hypoglycemia is of particular concern as patients are less likely or not able to sense hypoglycemic symptoms and thus cannot seek treatment and may progress to severe hypoglycemia. Signs and symptoms of nocturnal hypoglycemia include nightmares, night sweats, altered mood, headache, fatigue or high morning glucose.[17] Nocturnal hypoglycemia has been associated with loss of work productivity: 23% of patients who experience nocturnal hypoglycemia arrive late to work or fully miss work and 32% miss a meeting or do not finish a task.[1] Besides impaired well-being and loss of work productivity, hypoglycemia further adds to the treatment costs due to increased glucose monitoring and contacts to health care providers.[1]

Hypoglycemia is a barrier to achieving optimal glycemic control across the spectrum of diabetes. Rates of hypoglycemia tend to be relatively low in patients with T2DM on basal-only insulin therapy; however, hypoglycemic episodes can still interfere with achieving glycemic targets and with daily life in these patients. More advanced T2DM requires a more complicated regimen of basal insulin to control fasting glucose and bolus or rapid-acting insulin to control mealtime (prandial) hyperglycemia. This regimen is associated with a higher rate of hypoglycemia than basal-only therapy due to the requirement for more exogenous insulin and the effect of the bolus insulin. Insulin therapy in T1DM begins at diagnosis and requires full basal-bolus insulin replacement due to the almost complete absence of endogenous insulin. Patients with T1DM have the highest rates of hypoglycemia.

2.2.2 Complicated and Strict Insulin Dosing Regimens

Rigid dosing regimens can lead to patients not taking their insulin as prescribed which then increases the risk for either hypo- or hyperglycemia and hence, suboptimal treatment.[18] In one

survey, 57% of respondents reported that they had intentionally omitted an insulin injection, and 20% reported that they regularly omitted an injection.[19] Important factors underlying omission of an insulin injection included increased daily injection frequency, interference with daily activities, and pain and embarrassment associated with injections.[19]

If a patient inadvertently forgets or misses a dose or is unable to administer their dose at the recommended time of day due to traveling, varying working hours, irregular eating patterns, etc., it would be advantageous to have a basal insulin with a long and consistent action profile.

2.2.3 Limitations in Insulin Dosing

An increasing number of patients with T2DM require large doses of insulin to compensate for insulin resistance that often accompanies obesity. Not only may large injection volumes be associated with injection pain and discomfort,[18] the currently available injection devices only allow administration of a maximum of 80 U per injection. Consequently, many patients each day have to administer two or more separate injections to meet their basal insulin requirements, which may be a further barrier to achieving glycemic control.

2.3 History of Insulin Development and Rationale for Insulin Degludec and Insulin Degludec/Insulin Aspart

Each successive generation of basal insulin has allowed target glucose levels to be lowered and to be achieved more safely (i.e., with lower risk of hypoglycemia). This was true in the move from NPH insulin to insulin glargine (IGlar) and insulin detemir (IDet). However, currently available basal insulin products often fail to reproducibly provide insulin coverage over a full 24 hours and to do so from day to day.[20]

A basal insulin that would provide consistent glucose lowering over 24-hours and from day to day for all patients would be ideal. The flatter a basal insulin's pharmacokinetic profile at steady-state, the more stable the glucose lowering will be overnight and between meals. A flatter and more consistent profile would better address the challenge of insulin's narrow therapeutic window by reducing the likelihood of blood glucose fluctuations that cause hypoglycemia.

Insulin degludec (IDeg) is the result of continued advances in understanding the structure and function of insulin and how subtle modifications of the molecule can be utilized to achieve desired pharmacokinetic and pharmacodynamic properties such as a long duration of action and low variability in glucose-lowering effect that would translate into achievement of glycemic targets with lower risk of hypoglycemia for both T2DM and T1DM.

An important feature of IDeg is that it can be coformulated with other proteins; IDegAsp is a soluble coformulation of 70% IDeg with 30% rapid-acting insulin aspart (IAsp) (approved by FDA in 2000 under the tradename NovoLog®) that, unlike existing premixed insulin products, does not

require resuspension. The rapid-onset of action after dosing of the IAsp component enables effective mealtime coverage, while the long duration of action and low variability in glucose-lowering effect of the basal component (IDeg) enables glycemic improvements with lower risk of hypoglycemia relative to existing premixed insulin products.

3 Product Description and Molecule

Summary

- IDeg is a basal insulin that has no amino acid substitutions in its primary structure compared with human insulin. There are two modifications to the B chain: threonine at B30, which does not impact receptor recognition, is deleted and an amino acid linker and a di-carboxylic fatty acid are added to the lysine at position B29.
- Upon subcutaneous injection, IDeg forms a depot of soluble and stable multi-hexamers. Biologically active IDeg monomers gradually dissociate from the multi-hexamers and are slowly absorbed into the circulation. This mechanism provides a long, stable, and consistent release of IDeg.
- The molecular structure of IDeg allows it to be coformulated with IAsp in a soluble fixed-ratio combination that does not require resuspension prior to injection.
- To accommodate a wide range of insulin dose requirements, IDeg was developed as IDeg 100 U/mL and a separate low-volume IDeg 200 U/mL, which allows doses up to 160 U to be administered in a single injection.

The objective was to develop a basal insulin that was at least as safe and efficacious as human insulin that would provide at least 24 hours of action with low variability throughout the day and from day to day. Furthermore, this basal insulin should have the ability to be combined with rapid-acting insulin while still retaining the pharmacokinetic profiles of the individual components.

3.1 Structure, Molecular Design and Mechanism of IDeg

IDeg is a basal insulin that was specifically designed to provide a slow, continuous, and consistent delivery of insulin into the circulation. IDeg has retained the amino acid sequence of human insulin apart from deletion of residue B30. Thus, it contains no amino acid substitutions. To accomplish the long action profile, a fatty acid (hexadecanedioic acid) has been coupled to the lysine at position B29 via a short glutamic acid spacer (Figure 4).

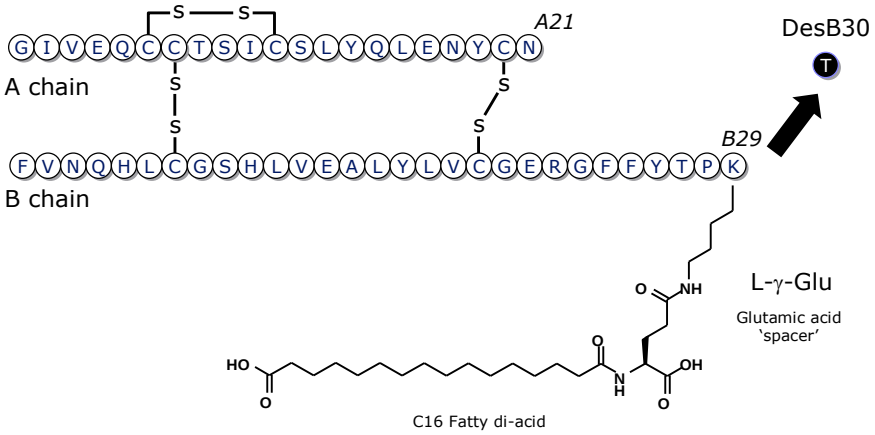


Figure 4 Structure of IDeg Molecule

The addition of the specific glutamic acid linker and fatty di-acid is what confers IDeg with its unique ability to form soluble multi-hexamers, which is the mechanistic basis for IDeg's slow absorption from the injection site. In the pharmaceutical solution that is in the pen device, IDeg adopts a stable di-hexamer structure. Upon injection into the subcutaneous tissue, there is a rapid dissipation of the pharmaceutical excipients, most importantly phenol, allowing IDeg to form soluble and stable multi-hexamers with a molecular size so large that they cannot be absorbed into the capillaries, thus creating a soluble subcutaneous depot. As zinc dissolves from the multi-hexamers, IDeg monomers gradually dissociate and are slowly absorbed into the circulation leading to its unique pharmacokinetic and pharmacodynamic profiles (25-hour half-life and >42-hour duration of action). In addition, the fatty acid part of the IDeg molecule is able to bind to albumin.

3.2 Coformulation of IDeg and IAsp (IDegAsp)

The molecular structure of IDeg allows it to be coformulated with IAsp in the presence of zinc and phenol without the occurrence of significant molecular interactions between the two analogues. The mechanism by which IDegAsp essentially retains the rapid absorption kinetics of IAsp and the slow and continuous absorption profile of IDeg can be described in the following step-wise manner: 1) In the pharmaceutical formulation the two insulin analogues exist in soluble and stable forms: IDeg as di-hexamers and IAsp as hexamers. 2) Upon subcutaneous injection, IAsp hexamers promptly separate into monomers, while IDeg di-hexamers form soluble multi-hexamers, creating a depot of IDeg; 3) IAsp monomers are rapidly absorbed into the circulation. 4) In contrast, IDeg multi-hexamers in the depot gradually separate into monomers and are slowly and continuously absorbed into the circulation. 5) At target tissues, IDeg and IAsp monomers bind to and activate insulin receptors triggering the same cellular effects as human insulin such as promoting glucose uptake. In this manner, IDegAsp is able to provide a pharmacodynamic profile with a clear distinction between the effects of the basal (IDeg) and bolus (IAsp) components.

3.3 Formulations

Insulin Degludec

To accommodate a wide range of insulin dose requirements, IDeg is developed as IDeg 100 unit (U)/mL (600 nmol/mL) and IDeg 200 U/mL (1200 nmol/mL), hereafter referred to as IDeg U100 and IDeg U200, respectively.

IDeg U100 will be provided in disposable prefilled pen injectors with a dose range of 1-80 U/injection in 1-U dose increments as well as in 3 mL cartridges for use with durable pens.

IDeg U200 will only be provided in disposable prefilled pen injectors with a dose range of 2-160 U/injection in 2-U dose increments. If a patient dials a dose of IDeg U200 it will equal the same dose of insulin dialed with IDeg U100. Only the injected volume of a given dose of insulin will differ between the two strengths (i.e., a dose of U200 is half the volume of the same dose of U100). IDeg U200 will specifically benefit the 20−30% of patients with T2DM who require more than 80 U per injection to administer the required insulin dose as a single daily injection rather than as two successive injections.

Insulin Degludec/Insulin Aspart

The proposed fixed-ratio formulation of IDegAsp is comprised of 70% IDeg and 30% IAsp (70/30). This formulation was tested in all IDegAsp phase 3 trials. Earlier in the development program, an alternative IDegAsp formulation comprised of 55% IDeg and 45% IAsp was investigated, but IDegAsp 70/30 was selected for phase 3 testing based on its more favorable benefit/risk profile. Moreover, the 70/30 ratio of IDeg/IAsp is consistent with the currently marketed premixed insulin analogue, BIAsp 30 (NovoLog® Mix 70/30).

IDegAsp is developed in a U100 concentration provided in disposable prefilled pen injectors with a dose range of 1–80 U/injection in 1-U dose increments as well as in cartridges for use with durable pens.

4 Nonclinical Pharmacology and Toxicology

Summary

- The molecular pharmacology of IDeg was demonstrated to be the same as human insulin:
  - Effects of IDeg are mediated specifically via the insulin receptor.
  - Intracellular signaling with IDeg is as expected for human insulin.
  - Metabolic effects of IDeg are the same as for human insulin.
  - IDeg (including its fatty acid side chain) is degraded in the cell via same internalization-mediated pathway as human insulin.
- IDeg nonclinical safety pharmacology studies showed no adverse effects.
- All toxicology findings were related to insulin pharmacology (e.g., hypoglycemia) and were similar between IDeg and human insulin.

The nonclinical development of IDeg and IDegAsp focused primarily on biological characterization and nonclinical safety evaluation of the new molecule, IDeg, for which a comprehensive nonclinical development program was conducted. In addition, IDegAsp was specifically examined in nonclinical primary pharmacology studies as well as in two toxicology studies in rats.

4.1 Mode of Action

A series of *in vitro* biological studies were performed, demonstrating that IDeg's mode of action is the same as that of naturally occurring human insulin. Thus, the changes introduced in the IDeg molecule are expected to affect only its absorption profile, and once absorbed into the bloodstream, IDeg should have the same efficacy and safety as human insulin.

Insulin Receptor Binding
Insulin's actions are mediated by its binding to specific insulin receptors that recognize the structure of the insulin molecule. IDeg has been shown to bind specifically to the insulin receptor and to bind equally well to the A-isoform (short form) of the insulin receptor and the B-isoform (long form) relative to human insulin. Due to the molecular modifications made to IDeg, its insulin receptor binding affinity is slightly lower than that of human insulin, but the efficacy at the receptor is the same as for human insulin.

IGF-1 Receptor Binding
IDeg was found to bind to the human IGF-1 receptor with a lower affinity than human insulin and the ratio between IGF-1 and insulin receptor affinities for IDeg relative to human insulin was consistently <1 in all species and assay systems tested (see Appendix 1, Table 1).

Insulin Receptor Activation (Signaling)

IDeg's ability to activate insulin receptors and post-receptor signaling was demonstrated to be the same as that of human insulin. IDeg elicited a typical dose-response curve (e.g., for insulin receptor and PKB phosphorylation), with the same maximum response as human insulin, indicating that IDeg has 100% efficacy compared with human insulin.

Taken together, these results indicate that the molecular mode of action of IDeg is the same as for human insulin.

Cellular Metabolic and Mitogenic Responses

In cells derived from insulin's primary pharmacological target organs (fat, liver and muscle), it has been demonstrated that IDeg activates the same pattern of metabolic effects as human insulin, including glucose uptake, lipogenesis, and inhibition of lipolysis in fat cells, as well as the stimulation of glycogen accumulation in hepatocytes and glycogen synthesis in muscle cells. Insulin can also promote an increase in cell number; thus, cell growth (mitogenicity) in response to IDeg has been tested in cells that proliferate in response to human insulin. In all cell types tested, IDeg demonstrated a low mitogenic potency similar to its *in vitro* metabolic potency and insulin receptor affinity (Appendix 1, Table 2). Taken together, these *in vitro* biological studies demonstrate that IDeg acts similarly to human insulin.

For IDegAsp, *in vitro* experiments in fat cells were conducted to examine the metabolic effects of IDeg and IAsp alone or in combination, and it was shown that the effects of IDeg and IAsp were additive, and that there were no interactions between the two at the cellular level. Although IAsp and IDeg have slightly different receptor affinities, their individual contributions to the total effect were as would be expected based on the biological response of each tested individually because both IAsp and IDeg are full agonists at the insulin receptor.

4.2 Safety Pharmacology and Effects on the Cardiovascular System

IDeg was investigated in a series of safety pharmacology studies assessing its potential effects on the cardiovascular system. IDeg had no significant effect on ECG parameters or general hemodynamics in anesthetized, mechanically ventilated, glucose-clamped male Beagle dogs dosed intravenously with 4, 8 and 12 nmol/kg (~10× human exposure).

After single s.c. administration of 24 nmol/kg IDeg (~3× human exposure) to conscious female Beagle dogs, no effects on blood pressure and ECG were observed. The heart rate tended to increase; however, this effect did not reach statistical significance as compared to control animals. The effect was assessed as a sympathetic counter-regulatory response to the significant decrease in blood glucose concentration observed in the dogs.

IDeg had no effect on the ion channel (hERG) responsible for repolarization of the heart, or on the action potential recorded from rabbit heart purkinje fibers when tested *in vitro* at 1000 nmol/L (~100× human exposure) of IDeg.

In conclusion, the nonclinical safety pharmacology program demonstrated no adverse effects of IDeg on cardiovascular function.

4.3 Nonclinical Pharmacokinetics and Absorption, Distribution, Metabolism and Excretion

The fatty di-acid side chain of IDeg allows it to bind strongly but reversibly to albumin, resulting in a plasma protein binding of >99%. As a result, the concentration of IDeg is relatively high in the bloodstream, with the majority of circulating IDeg bound to albumin, and thus unavailable for receptor binding. The distribution of IDeg was studied with radiolabeled IDeg. Following s.c. administration, absorbed IDeg was distributed mainly to the serum compartment. The results of *in vitro* protein binding studies demonstrated that common protein-bound drugs such as ibuprofen, warfarin, acetylsalicylate and salicylate, do not affect IDeg binding to human serum albumin at therapeutically relevant drug concentrations. The opposite effect, IDeg displacement of other albumin-bound drugs, is considered rather unlikely, as the concentration of IDeg is very low compared to the albumin concentration (>10,000-fold) and IDeg will occupy less than 0.01% of the albumin molecules. Therefore, the pharmacokinetic properties of IDeg would not be affected *in vivo* by other albumin-bound drugs or by even very large changes in albumin concentration.

As with any other insulin product, elimination of IDeg is primarily via insulin receptor-mediated internalization. The initial peptide cleavage of IDeg occurs within the cell and is the same as seen for human insulin. The fatty acid side chain is extensively metabolized similarly to other naturally occurring fatty acids.

4.4 Toxicology Findings

Dosing of IDeg or IDegAsp to healthy normoglycemic animals lowered blood glucose concentrations to levels below the normal physiological level and thereby induced clinical signs of hypoglycemia and hypoglycemia-related mortality, which were observed in most toxicity studies.

The changes seen with IDeg alone, or in combination with IAsp, were similar in nature and magnitude to those induced by human insulin and were therefore considered related to the pharmacological effects of insulin, with no toxicological significance.

4.5 Nonclinical Carcinogenicity Assessment

In Vivo Studies

The *in vivo* assessment of the carcinogenic potential comprises an evaluation of hyperplastic and neoplastic changes in all pivotal repeated-dose toxicity studies in both rats and dogs. Furthermore,

the carcinogenic potential was the focus of detailed investigations included in the 52-week toxicity study in Sprague Dawley rats (a strain prone to develop mammary gland tumors) and the preferred *in vivo* model for assessing carcinogenic potential of insulin analogues.[21]

In the 52-week toxicity study, IDeg showed no carcinogenic potential when dosed up to 60 nmol/kg (~5× human exposure). In the mammary gland (Appendix 1, Table 3), the tumor incidence was the same in the control group, low-dose IDeg (20 nmol/kg), and the comparator group (human insulin, 40 nmol/kg). No mammary gland tumors were observed in animals dosed with the IDeg mid (40 nmol/kg) and high (60 nmol/kg) doses. There were no treatment-related changes in mammary cell proliferation in the female mammary gland. Further, IDeg was not associated with any treatment-related changes in the occurrence of hyperplastic or neoplastic changes in dogs or rats dosed for up to 26 and 52 weeks, respectively.

Overall Assessment of Carcinogenicity
Based on this nonclinical package of *in vitro* and *in vivo* studies addressing the carcinogenic potential of IDeg, all studies support the conclusion that the carcinogenic potential of IDeg is similar to that of human insulin.

4.6 Nonclinical Pharmacology and Toxicology Conclusions

IDeg is a specific and full agonist at the human insulin receptor with the same mode of action as human insulin. The nonclinical program revealed no safety signals based on studies assessing single and repeated dose toxicity, reproductive and development toxicity, local tolerance and carcinogenic potential. The nonclinical studies have thus demonstrated that the modifications introduced in IDeg have not changed its metabolic profile or its safety profile compared with human insulin. Furthermore, coformulation with IAsp does not affect the safety and efficacy of the individual components.

5 Clinical Pharmacology

Summary

- Both the exposure and the glucose-lowering effect are more evenly distributed across a 24-hour period with IDeg than with IGlar.
- The day-to-day variability in glucose-lowering effect is four times lower with IDeg compared with IGlar. The lower day-to-day variability is seen consistently throughout a 24-hour period.
- IDeg steady-state levels are reached within 3 days after which total exposure is unchanged from day to day.
- IDeg has a half-life of 25 hours, which is twice as long as that of IGlar (12 hours).
- The glucose-lowering effect lasts more than 42 hours and duration of action is considerably longer for IDeg compared with IGlar at clinically relevant doses.
- IDeg U100 and IDeg U200 are found to be bioequivalent, elicit comparable glucose-lowering effect and thus can be used interchangeably.
- The rapid absorption characteristics of IAsp and the long pharmacokinetic and pharmacodynamic properties of IDeg are preserved when coformulated in IDegAsp.
- The glucose-lowering effects of the bolus (IAsp) and the basal (IDeg) components of IDegAsp are distinct and more clearly separated compared with BIAsp 30.
- Overall, the pharmacokinetic and pharmacodynamic properties of IDeg and IDegAsp are preserved in all sub-populations investigated.

5.1 Overview of Clinical Pharmacology Trials

IDeg has a duration of action extending beyond the 24-hour dosing interval, and steady state is reached after approximately 3 days in a once-daily dosing regimen. Therefore, the clinically relevant pharmacokinetic properties of IDeg are described with emphasis on steady state, which was achieved in the multiple-dose trials. The IDeg clinical pharmacology program included investigations of T2DM and T1DM. In addition, there were trials that studied the properties of IDeg in special populations (i.e., patients with renal or hepatic impairment, elderly patients, children and adolescents, and patients of different race/ethnicity). An overview of the key clinical pharmacology trials designed to evaluate the pharmacokinetic and pharmacodynamic properties of IDeg is presented in Appendix 2.

The IDegAsp clinical pharmacology program consists of single-dose IDegAsp trials and the multiple-dose trials in the IDeg clinical pharmacology program. The single-dose trials performed

with IDegAsp characterize the pharmacodynamic profile and support the clear distinction between the effects of the basal (IDeg) and prandial (IAsp) components of IDegAsp. The multiple-dose trials with IDeg alone are used to describe the pharmacokinetic and pharmacodynamic properties of the basal component in IDegAsp in the clinical setting, including special populations. This approach is supported by the fact that the pharmacokinetic properties of IDeg are not affected by coformulation with IAsp (see Section 5.3). Furthermore, the clear distinction between the effects of the basal and prandial components of IDegAsp also was confirmed at steady state in Trial 1979, completed after submission of the NDA.

The glucose-lowering effects of IDeg and IDegAsp were evaluated using the euglycemic clamp technique, which is a validated method regarded as the gold standard when assessing the effect of exogenous insulin. Following insulin injection, the blood glucose level will drop due to the glucose-lowering effect of the insulin. In a euglycemic clamp, this drop is counteracted by variable i.v. glucose infusion. The amount of i.v. glucose needed to maintain a stable blood glucose level after insulin injection is then a measure of the glucose-lowering effect of the insulin.

5.2 IDeg Pharmacokinetic and Pharmacodynamic Properties

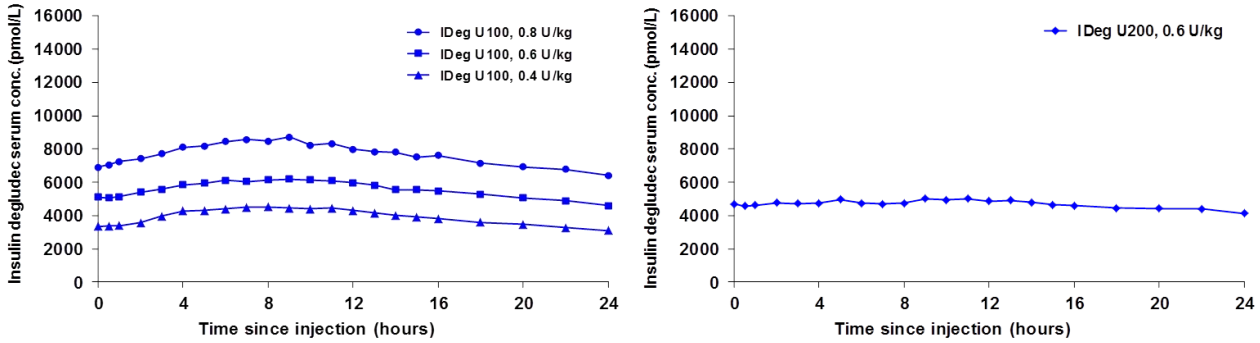
5.2.1 Distribution, Metabolism, and Excretion

Distribution, metabolism and excretion have mainly been investigated in nonclinical studies and are therefore provided in Section 4.3. One clinical pharmacology trial investigated excretion of IDeg in patients with and without renal impairment (Trial 1990). The results of this trial demonstrated negligible renal clearance of intact IDeg.

5.2.2 Steady-State Profiles, Dose Relationship and Molar Dose Ratio

The pharmacokinetic and pharmacodynamic properties of IDeg U100 were investigated at three clinically relevant dose levels (0.4, 0.6, and 0.8 U/kg) at steady state in patients with T2DM (Trial 1987) and T1DM (Trial 1993). In T2DM in Trial 1987, the pharmacokinetic and pharmacodynamic properties of IDeg U200 at a dose level of 0.6 U/kg were also investigated. In T1DM in Trial 1993, IDeg was further compared with IGlar since this basal insulin analogue currently represents the majority of basal insulin use in the U.S.

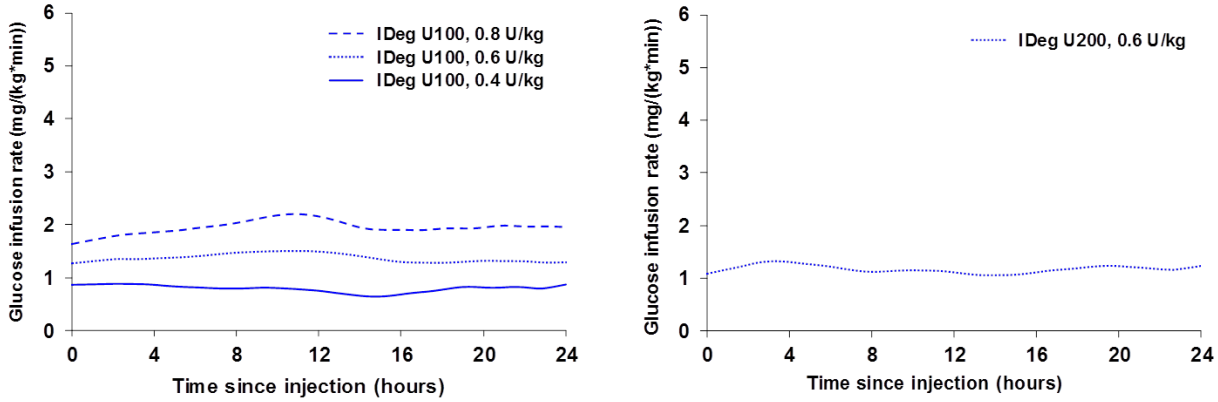
Consistent with the mechanism of protraction presented in Section 3, IDeg exposure was shown to be evenly distributed over 24 hours at steady state both for IDeg U100 and IDeg U200 in patients with T2DM (Trial 1987). Total exposure during one 24-hour dosing interval and maximum concentration of IDeg at steady state increased proportionally with increasing dose (Figure 5).



Based on 21-37 patients per dose level for IDeg U100 and 16 patients for IDeg U200.

Figure 5 24-hour Mean Concentration-Time Profiles – IDeg U100 (Left) and IDeg U200 (Right) at Steady State (Trial 1987, T2DM)

Relatively flat and stable glucose infusion rate (GIR) profiles were obtained during the entire dosing interval for all three dose levels of IDeg U100, and the dose level of IDeg U200 in patients with T2DM (Figure 6). The total glucose-lowering effect of IDeg increased linearly with increasing dose in patients with T2DM.

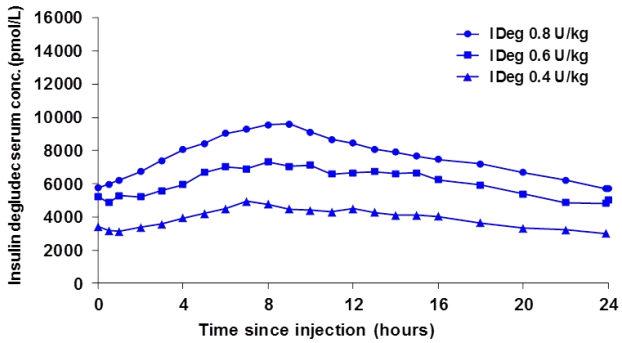


Based on 21-37 patients per dose level for IDeg U100 and 16 patients for IDeg U200.

Figure 6 24-hour Glucose Infusion Rate Mean Profiles – IDeg U100 (Left) and IDeg U200 (Right) at Steady State (Trial 1987, T2DM)

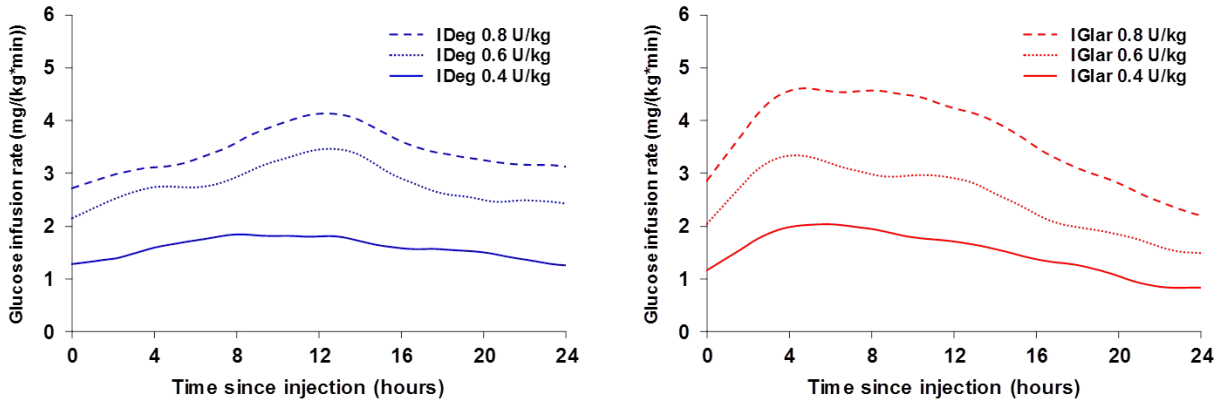
The steady-state pharmacokinetic profile of IDeg is consistent with the continuous and slow absorption of IDeg into the circulation (Figure 7), which leads to a flatter and more stable mean GIR profile for IDeg compared with IGlar over 24 hours in patients with T1DM (Figure 8). While comparisons of the GIR profiles of IDeg and IGlar are possible, it is not possible to compare the absolute serum concentrations due to the albumin binding of IDeg. Only pharmacokinetic endpoints such as terminal half-life ($t_{½}$) after s.c. administration can be compared directly between IDeg and

IGlar (see Section 5.2.5). Both the total exposure during one 24-hour dosing interval and the maximum concentration of IDeg at steady state increased proportionally with increasing dose in patients with T1DM (Trial 1993). The total glucose-lowering effect of IDeg increased proportionally with increasing dose in patients with T1DM (Trial 1993).



Based on 21-22 patients per dose level.

Figure 7 24-hour Mean Concentration-Time Profiles – IDeg at Steady State (Trial 1993, T1DM)



Based on 21-22 patients per dose level for IDeg and 22 patients per dose level for IGlar.

Figure 8 24-hour Glucose Infusion Rate Mean Profiles – IDeg (Left) and IGlar (Right) at Steady State (Trial 1993, T1DM)

The molar dose ratio between IDeg and IGlar was 1.03 $[0.95; 1.12]_{95\%CI}$ across the three dose levels (Trial 1993). Thus, the total glucose-lowering effect is similar with IDeg and IGlar when administered in identical doses.

5.2.3 Distribution of Exposure and Glucose-lowering Effect over the 24-hour Dosing Interval

As shown in Figure 5 and Figure 6, the steady-state pharmacokinetic and pharmacodynamic profiles of IDeg were relatively flat and stable in patients with T2DM. Within one 24-hour dosing interval, the glucose-lowering effects of IDeg were similar in all four 6-hour measurement intervals and very close to a 25-25-25-25% split (Trial 1987; Table 5). This type of profile can only be achieved by insulin preparations that have a duration of action longer than the dosing interval (24 hours). The fluctuations in insulin levels (and thereby in the glucose-lowering effect) are reduced when the effects of subsequent injections overlap because this, upon repeated injections, leads to establishment of a stable steady-state insulin concentration in the circulation and at the target receptors. Indeed, the slow absorption of IDeg was confirmed in this trial by demonstrating a half-life of 25 hours (see Section 5.2.5).

Table 5 Pharmacodynamic Distribution (%) for IDeg at Steady State (Trial 1987, T2DM)

IDeg Dose (U/kg)	$AUC_{GIR,0\text{-}6h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,6\text{-}12h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,12\text{-}18h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,18\text{-}24h,SS}$/ $AUC_{GIR,\tau,SS}$
0.4	27	22	20	31
0.6	27	26	23	24
0.8	24	26	24	26

AUC: area under the curve; SS: steady state; GIR: glucose infusion rate; Trial 1987, arithmetic means. Based on 21-37 patients per dose level.

As shown in Table 6, the even distribution of glucose-lowering effect was confirmed in patients with T1DM. Moreover, the glucose-lowering effect was more evenly distributed across a 24-hour dosing interval with IDeg than IGlar (Trial 1993), with most of the effect of IGlar occurring during the first 12-18 hours after dosing. This is in accordance with the half-life of IDeg being twice as long as for IGlar (25 hours vs. 12 hours), see Section 5.2.5.

Table 6 Pharmacodynamic Distribution (%) for IDeg and IGlar at Steady State (Trial 1993, T1DM)

Product	Dose	$AUC_{GIR,0\text{-}6h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,6\text{-}12h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,12\text{-}18h,SS}$/ $AUC_{GIR,\tau,SS}$	$AUC_{GIR,18\text{-}24h,SS}$/ $AUC_{GIR,\tau,SS}$
IDeg	0.4 U/kg	23	28	26	23
IGlar	0.4 U/kg	31	29	23	17
IDeg	0.6 U/kg	23	28	27	22
IGlar	0.6 U/kg	29	30	24	17
IDeg	0.8 U/kg	22	27	27	24
IGlar	0.8 U/kg	28	30	25	17

AUC: area under the curve; SS: steady state; GIR: glucose infusion rate. Trial 1993, arithmetic means. Based on 21-22 patients per dose level for IDeg and 22 patients per dose level for IGlar.

The difference in the absorption and glucose-lowering effect between IDeg and IGlar was further demonstrated by the relative fluctuation in the glucose infusion rate of IDeg and IGlar at steady

state ($AUCF_{GIR,\tau,SS}$). The estimated values were lower for IDeg than for IGlar at all three dose levels (Table 7), meaning that the 24-hour pharmacodynamic profiles for IDeg were more stable and consistent than the profiles for IGlar (Trial 1993), see Section 5.2.2.

Table 7 Fluctuation of Glucose-lowering Effect during One Dosing Interval for IDeg and IGlar at Steady State (Trial 1993, T1DM)

Dose U/kg	IDeg $AUCF_{GIR,\tau,SS}$ (mg/(kg*min))	IGlar $AUCF_{GIR,\tau,SS}$ (mg/(kg*min))
0.4	0.25	0.39
0.6	0.37	0.54
0.8	0.38	0.73

AUC: area under the curve; SS: steady state; GIR: glucose infusion rate
Trial 1993, geometric means. Based on 21-22 patients per dose level for IDeg and 22 patients per dose level for IGlar.

In summary, the pharmacokinetic and pharmacodynamic profiles of IDeg reflect its slow continuous rate of absorption, which provides a consistent and stable glucose-lowering effect across one dosing interval. This is an important attribute given the narrow therapeutic window of insulin and the goal of achieving nighttime and interprandial glycemic control with low risk of hypoglycemia, a goal that is challenging given the variability of absorption and lower pharmacokinetic half-lives of current basal insulin products.

5.2.4 Day-to-Day Variability in Glucose-lowering Effect

In order to facilitate insulin titration to fasting plasma glucose targets without increasing the risk of hypoglycemia, it is important that the glucose-lowering effect is consistent and stable, and that the same insulin dose elicits the same glucose-lowering effect on different days in a given patient.

Trial 1991 compared the within-patient day-to-day variability in glucose-lowering effect at steady state between IDeg and IGlar. Patients with T1DM (i.e., patients without endogenous insulin secretion) underwent a 24-hour euglycemic glucose clamp on three different days during a 12-day treatment period. Within-patient day-to-day variability was estimated as the within-patient coefficient of variation (CV%), which corresponds to the difference in the glucose-lowering effect from one insulin injection to another under comparable conditions in the same patient. This approach in patients with T1DM is considered to be state-of-the-art in determining the variability of an insulin product as the potential for confounding factors has been reduced to a minimum.[22]

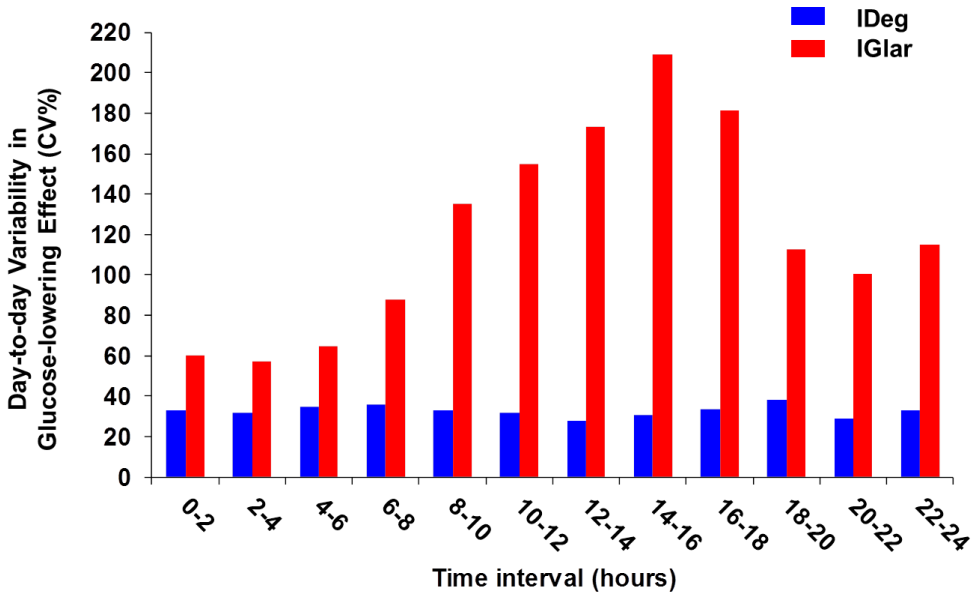
IDeg was associated with a four-times-lower day-to-day variability in total glucose-lowering effect compared with IGlar (Table 8).

Table 8 Day-to-Day Variability in Glucose-lowering Effect over 24 Hours at Steady State (Trial 1991, T1DM)

	IDeg (CV%)	IGlar (CV%)
$AUC_{GIR,\tau,SS}$	20	82
$AUC_{GIR,2\text{-}24h,SS}$	22	92
$GIR_{max,SS}$	18	60

AUC: area under the curve; SS: steady state; GIR: glucose infusion rate; CV%: coefficient of variation;
$AUC_{GIR,2\text{-}24h,SS}$: the effect in the last 22 hours of the clamp, that is, the time period in which the action is not influenced by i.v. insulin at the start of the clamp. Based on 26 patients for IDeg and 27 patients for IGlar.

Furthermore, this was consistent throughout the 24-hour period. As illustrated in Figure 9, the within-patient variability for 2-hour intervals of area under the glucose-infusion rate curve was consistently low with IDeg and significantly lower with IDeg than with IGlar over the entire 24-hour dosing interval at steady state.



Trial 1991, 0.4 U/kg. Based on 26 patients for IDeg and 27 patients for IGlar.

Figure 9 Day-to-Day Variability in Glucose-lowering Effect During a Dosing Interval – IDeg and IGlar at Steady State (Trial 1991, T1DM)

As the pharmacokinetic and pharmacodynamic properties of IDeg are similar between patients with T1DM and T2DM, it is expected that this improvement in the within-patient variability in glucose-lowering effect of IDeg is also found in patients with T2DM.

Overall, the stable pharmacodynamic profile as well as the lower day-to-day variability in glucose-lowering effect with IDeg compared to IGlar is reflected in a lower rate of hypoglycemia with IDeg, especially during the night (see Section 9).

5.2.5 Half-life and Time to Steady State

The half-life ($t_{½}$) after s.c. administration was twice as long for IDeg than for IGlar (25 vs. 12 hours, respectively) across all 3 dose levels in both T1DM (Table 9) and T2DM (Trial 1987). Furthermore, the between-patient variability in half-life in terms of the coefficient of variation (CV%) was lower with IDeg than IGlar.

Table 9 Half-life – IDeg and IGlar at Steady State (Trial 1993, T1DM)

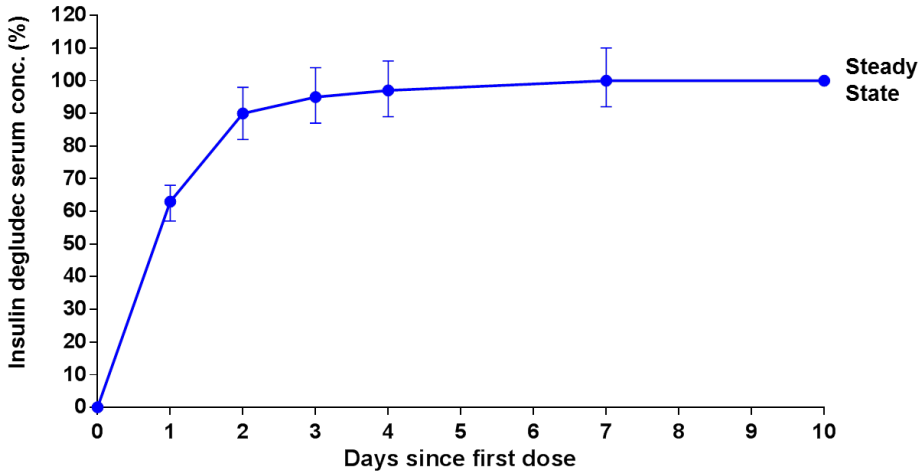
	IDeg ($t_{½,IDeg,SS}$)				IGlar ($t_{½,IGlar,SS}$)			
Dose (U/kg)	**Mean (h)**	**CV (%)**	**$Q_{25\%}$ (h)**	**$Q_{75\%}$ (h)**	**Mean (h)**	**CV (%)**	**$Q_{25\%}$ (h)**	**$Q_{75\%}$ (h)**
0.4	25.9	26	21.7	32.4	11.5	47	8.9	17.9
0.6	27.0	27	23.9	30.1	12.9	38	12.2	18.5
0.8	23.6	29	20.9	25.6	11.9	47	10.4	19.6
0.4, 0.6, 0.8[a]	25.4	28	21.5	30.4	12.1	44	9.9	19.5

[a] Combined estimate across the three dose levels.
Mean: harmonic mean; CV: Coefficient of variation. $Q_{25\%}$: 25% quartile; $Q_{75\%}$: 75% quartile. Based on 21-22 patients per dose level for IDeg and 22 patients per dose level for IGlar.

The long $t_{½}$ of IDeg after s.c. administration primarily reflects the protracted absorption process of IDeg from the injection site, implying that the rate at which IDeg is eliminated after s.c. administration is determined by the absorption rate. This is evident from the longer $t_{½}$ after s.c. than after i.v. administration of IDeg. The elimination $t_{½}$ after i.v. administration was approximately 5 hours compared with a $t_{½}$ of 25 hours after s.c. administration at steady state.

The pharmacokinetic properties of IDeg reflect its distinct protraction mechanism, resulting in a slow and continuous delivery of IDeg into the circulation in patients with both T1DM and T2DM.

For all patients, independent of dose or type of diabetes, steady state levels in plasma were reached within approximately 3 days of IDeg dosing (Figure 10). As expected, when the half-life is close to the dosing interval, the build-up factor from first dosing to the steady state level is approximately two (Trials 1993 and 1987), i.e. within a dosing interval, exposure at steady state is twice that after the first dose. At steady state, total exposure is unchanged from day to day; in other words, there is no insulin accumulation once steady-state is achieved.



Relative serum IDeg trough concentrations during initiation of once-daily dosing in patients with T1DM. Values are estimated ratios and 95% CI relative to Day 10. Trial 1991, 0.4 U/kg. Based on 26 patients.

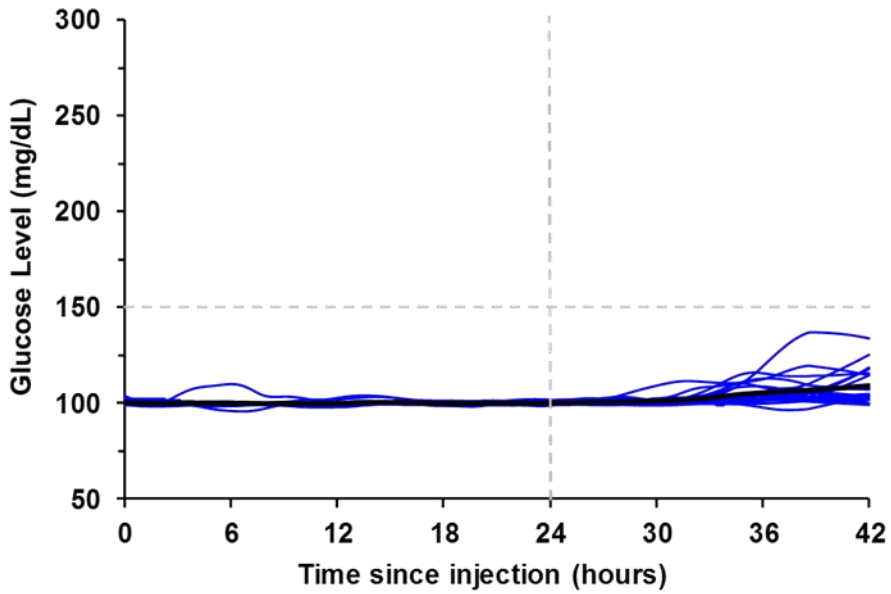
Figure 10 Relative Serum IDeg Trough Concentrations during Initiation of Once-daily Dosing (Trial 1991, T1DM)

5.2.6 Duration of Action

Duration of action was defined as the time from trial product administration until the blood glucose concentration was consistently above 150 mg/dL in the setting of a glucose clamp procedure, as this threshold is recognized as a proper measure of end of action for insulin.[23] With IDeg, blood glucose did not exceed 150 mg/dL within the 42-hour clamp period for any patient (Figure 11).

Thus, the glucose-lowering effect of IDeg extends beyond 42 hours, although an exact duration of action could not be estimated for IDeg due to the fact that the clamp procedure was terminated at 42 hours in Trial 1993. This is in line with the half-life of 25 hours for IDeg after s.c. administration and the fact that IDeg was detectable in serum for at least 120 hours for all three dose levels. For IGlar, the duration of action was significantly shorter than that for IDeg in line with the shorter half-life (12.1 hours) and the fact that IGlar was only detectable for up to 36-48 hours in the majority of patients.

Given the long duration of action due to continuous and stable absorption of IDeg monomers, IDeg would be predicted to allow flexibility in the timing of administration.



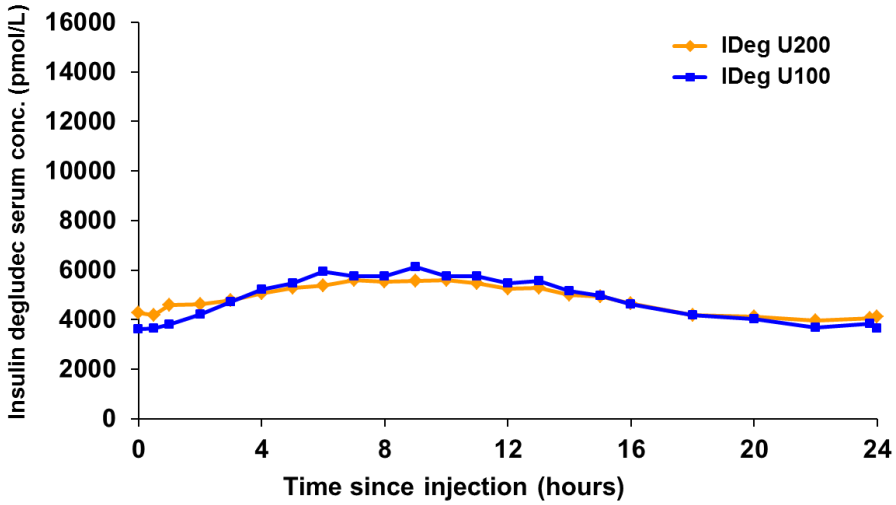
Trial 1993, 0.6 U/kg. Based on 21 patients. The 150 mg/dL blood glucose level represents the threshold for end of action.

Figure 11 42-hour Blood Glucose Mean and Compiled Individual Profiles – IDeg at Steady State (Trial 1993, T1DM)

5.2.7 IDeg U100 and IDeg U200 Interchangeability

The pharmacokinetic properties of IDeg U100 and IDeg U200 at steady state in patients with T1DM were compared in a double-blind, crossover design with 8 days of once-daily administration (0.4 U/kg) in Trial 3678.

The shape and level of the mean steady-state 24-hour concentration-time profiles were similar for IDeg U100 and IDeg U200 (Figure 12). A *post hoc* statistical analysis demonstrated that the requirements for bioequivalence at steady state between IDeg U200 and IDeg U100 were met for $AUC_{IDeg,\tau,SS}$ (0.99 $[0.91; 1.07]_{90\%CI}$) and $C_{max,IDeg,SS}$ (0.93 $[0.84; 1.02]_{90\%CI}$) as the 90% CIs were within the interval [0.80; 1.25].



Trial 3678: 0.4 U/kg. Based on 33 patients.

Figure 12 24-Hour Mean Concentration-Time Profiles – IDeg U100 and IDeg U200 at Steady State (Trial 3678, T1DM)

As observed for total exposure, IDeg U100 and IDeg U200 also provided a similar glucose-lowering effect at steady state: IDeg U200 versus IDeg U100 for $AUC_{GIR,\tau,SS}$ (0.94 [0.86; 1.03]$_{95\%CI}$).

As bioequivalence was demonstrated, and the glucose-lowering effect at steady state was similar between IDeg U100 and IDeg U200, the two products can be used interchangeably.

5.2.8 Response to Hypoglycemia

As with other insulin products, it is important to characterize the response to and awareness of experimentally induced hypoglycemia and to investigate how recovery from hypoglycemia develops. Trial 3538 was conducted to confirm that counter-regulation to controlled hypoglycemia induced by IDeg is not impaired relative to that of IGlar in patients with T1DM.

The increase in hypoglycemic symptoms score and hypoglycemic awareness observed at low plasma glucose values, together with the rise in epinephrine (the most important counter-regulatory hormone in T1DM since the glucagon response to hypoglycemia may be impaired[24]), growth hormone and cortisol levels, demonstrate an appropriate counter-regulatory response to hypoglycemia with IDeg. Clinical symptoms of hypoglycemia, vital signs and cognitive function, were generally comparable between IDeg and IGlar. There was no sign that the counter-regulatory response to hypoglycemia with IDeg was diminished in any parameter compared with that achieved with IGlar. Recovery from hypoglycemia occurred within the same time span for IDeg and IGlar and with comparable return to baseline for all hypoglycemic response assessments. During recovery, less glucose was required to alleviate hypoglycemia with IDeg compared with IGlar.

Taken together, the response to hypoglycemia is at least as robust with IDeg as with IGlar, and the ability of the patients to recover from hypoglycemia and their awareness of hypoglycemia are at least as good with IDeg as with IGlar.

5.3 IDegAsp Pharmacokinetic and Pharmacodynamic Properties

The pharmacokinetic profile of IDeg was not affected by coformulation with IAsp in the IDegAsp product (see Section 5.3.1). Therefore, IDeg dosing alone is representative of the basal component in IDegAsp. Please see IDeg Section 5.2 for a detailed description of the properties of IDeg, the basal component of IDegAsp.

5.3.1 IDegAsp versus Corresponding Separate Simultaneous Injections of IDeg and IAsp

The single-dose pharmacokinetic properties of IDegAsp were compared with corresponding separate simultaneous injections of the IDeg and IAsp products in Trial 1959. Dose levels of the two components were matched to their respective fractions in IDegAsp (70% IDeg and 30% IAsp).

While the pharmacokinetic profile of IDeg was unchanged by coformulation with IAsp, some differences were observed in the pharmacokinetic profile of IAsp when coformulated with IDeg (Table 10). However, there were no significant effects on pharmacodynamics based on $GIR_{max,SD,}$ $AUC_{GIR,0\text{-}6h,SD}$ (both reflecting the effect of the rapid-acting IAsp) and $AUC_{GIR,0\text{-}24h,SD}$ (Table 11). Furthermore, a comparable time to GIR_{max} ($tGIR_{max}$) was observed for IDegAsp and separate simultaneous IAsp and IDeg administration.

Table 10 IDeg and IAsp Pharmacokinetic Endpoints after Single-dose IDegAsp vs. IDeg+IAsp (Trial 1959, T1DM)

IDeg Pharmacokinetic Endpoint	Estimated Ratio [95% CI] (IDegAsp/IDeg)	IAsp Pharmacokinetic Endpoint	Estimated Ratio [95% CI] (IDegAsp/IAsp)
$AUC_{IDeg,0\text{-}6h,SD}$	0.91 [0.74; 1.14]	$AUC_{IAsp,0\text{-}2h,SD}$	0.68 [0.61; 0.75]
$AUC_{IDeg,0\text{-}\infty,SD}$	1.05 [0.95; 1.16]	$AUC_{IAsp,0\text{-}10h,SD}$	0.94 [0.88; 1.01]
$C_{max,IDeg,SD}$	1.03 [0.93; 1.14]	$C_{max,IAsp,SD}$	0.72 [0.64; 0.79]

AUC: area under the curve; CI: confidence interval; C_{max}: maximum concentration.
Trial 1959: 0.92 U/kg IDegAsp (equal to 0.64 U/kg IDeg and 0.28 U/kg IAsp) and 0.64 U/kg IDeg + 0.28 U/kg IAsp. Based on 23 patients for IDegAsp and 21 patients for IDeg+IAsp.

Table 11 Glucose Infusion Rate Endpoints after Single-dose IDegAsp vs. IDeg+IAsp (Trial 1959, T1DM)

Endpoint	Estimated Ratio (IDegAsp/IDeg+IAsp)	95% CI	p-value for Ratio = 1
$AUC_{GIR,0\text{-}6h,SD}$	0.97	0.88; 1.06	0.48
$AUC_{GIR,0\text{-}24h,SD}$	1.04	0.94; 1.14	0.47
$GIR_{max,SD}$	0.94	0.86; 1.03	0.20

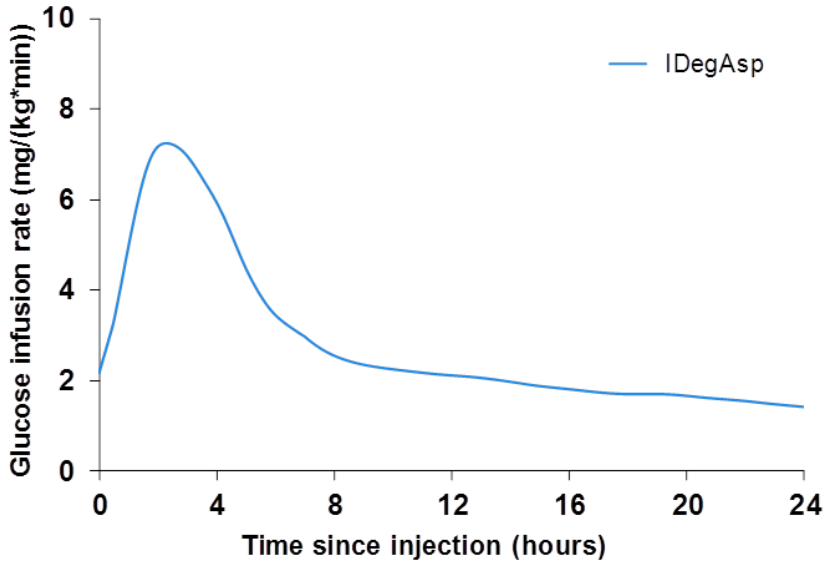
AUC: area under the curve; CI: confidence interval; GIR: glucose infusion rate
Trial 1959: 0.92 U/kg IDegAsp (equal to 0.64 U/kg IDeg and 0.28 U/kg IAsp) and 0.64 U/kg IDeg + 0.28 U/kg IAsp. Based on 23 patients for IDegAsp and 21 patients for IDeg+IAsp.

5.3.2 Difference of IDegAsp Compared to the Individual Components

The glucose-lowering effect of IDegAsp is clearly distinguished from that of both IDeg and IAsp during clinically relevant parts of the action profile. Trial 3857 demonstrated the distinctiveness of IDegAsp relative to both IDeg and IAsp when given as single doses at the same total dose level (0.5 U/kg). Both the pharmacokinetic and pharmacodynamic profiles of IDegAsp fulfill the FDA requirement of being at least 20% different from each of its single components (IDeg and IAsp).[2]

5.3.3 Profiles and Dose Relationship

At steady state (Trial 1979), the long-acting properties of IDeg are clearly preserved in IDegAsp and furthermore, the glucose-lowering effects of the prandial and basal components of IDegAsp were distinct and clearly separated, as is evident in Figure 13.



Trial 1979: 0.6 U/kg IDegAsp at steady state. Based on 22 patients.

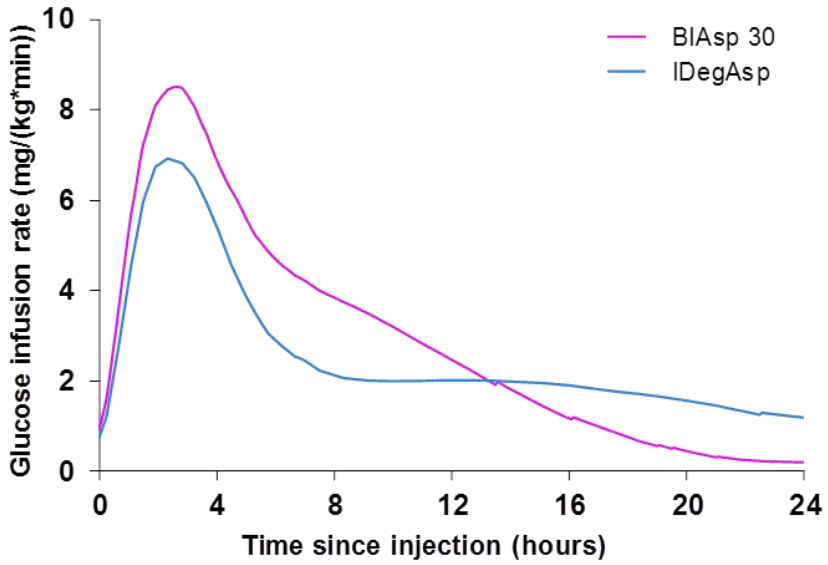
Figure 13 24-hour Glucose-Infusion Rate Mean Profile – IDegAsp at Steady State (Trial 1979, T1DM)

The single-dose pharmacokinetic and pharmacodynamic properties of the rapid-acting component (IAsp) of IDegAsp were investigated at three clinically relevant dose levels (0.4, 0.6 and 0.8 U/kg) in patients with T2DM (Trial 1978) and T1DM (Trial 3539). Please refer to Section 5.2 for the pharmacokinetic and pharmacodynamic properties of IDeg, the basal component of IDegAsp.

The peak concentration of IAsp ($C_{max,IAsp,SD}$) increased proportionally with increasing dose (estimated log-dose slope was 0.98 $[0.81; 1.14]_{95\%CI}$ in T2DM and 0.88 $[0.72; 1.04]_{95\%CI}$ in T1DM) and total exposure of IAsp ($AUC_{IAsp,0\text{-}12h,SD}$) increased essentially proportionally with increasing dose (estimated log-dose slope was 1.17 $[1.04; 1.30]_{95\%CI}$ in T2DM and 1.09 $[1.02; 1.17]_{95\%CI}$ in T1DM).

The total and maximum glucose-lowering effect of IDegAsp ($AUC_{GIR,0\text{-}24h,SD}$ and $GIR_{max,SD}$) increased with increasing dose, and linearity was demonstrated for T2DM (p=0.78 and p=0.67, respectively), whereas dose proportionality was demonstrated in patients with T1DM (estimated log-dose slope was 1.19 $[0.99; 1.40]_{95\%CI}$ for $AUC_{GIR,0\text{-}24h,SD}$ and 0.89 $[0.66; 1.13]_{95\%CI}$ for $GIR_{max,SD}$).

Compared with BIAsp 30, IDegAsp had a similar onset of glucose-lowering effect, similar time to maximum effect ($tGIR_{max,SD}$) and a similar shape of the mean GIR profiles during the first 4 hours after injection (Figure 14). However, the effect from the basal component of IDegAsp is longer and more clearly separated from the prandial component compared with BIAsp 30. This should translate to better control of FPG and a clinical advantage in regard to risk of hypoglycemia, particularly 8-12 hours after injection, compared with BIAsp 30.



Trial 3539: 0.8 U/kg. Based on 20 patients for IDegAsp and 21 patients for BIAsp 30.

Figure 14 24-hour Glucose Infusion Rate Mean Profiles − Single-dose IDegAsp and BIAsp 30 (Trial 3539, T1DM)

5.4 Clinical Pharmacology Data in Subgroups

The pharmacokinetic and pharmacodynamic properties of IDeg were preserved in all populations investigated. There were no differences in the pharmacokinetic or pharmacodynamic properties of IDeg between elderly patients and younger adult patients, between patients with or without hepatic or renal impairment, or between women and men.

The effect of race and ethnicity also was investigated in a clinical pharmacology trial. A randomized, double-blind, two-period, cross-over trial investigated the pharmacokinetic and pharmacodynamic properties of IDeg at steady-state in 63 insulin-treated patients with T2DM of different race and/or ethnicity (18 Black/African American, 23 White, 22 Hispanic/Latino). Pair-wise comparisons of total exposure ($AUC_{IDeg,\tau,SS}$) was similar between the three groups (Appendix 1, Table 4). The half-life ($t_{½,IDeg,SS}$), was also within the same range (22.8 to 28.5 hours) for Black/African American, White and Hispanic/Latino patients.

Likewise, the mean glucose infusion rate profiles at steady state were similar for the three race/ethnic groups. Pair-wise comparisons of total glucose-lowering effect of IDeg at steady state ($AUC_{GIR,\tau,SS}$) were not significantly different. Thus, the pharmacodynamic properties of IDeg are preserved across racial and ethnic groups.

In addition, the long pharmacokinetic and pharmacodynamic properties of IDeg, the rapid absorption characteristics of IAsp, and the distinctively separate glucose-lowering effect for the two components of IDegAsp were preserved across various demographic and disease factor groups.

5.5 Clinical Pharmacology Conclusions

IDeg

The IDeg exposure was shown to be evenly distributed over 24 hours at steady state in both T2DM and T1DM. Total exposure during one 24-hour dosing interval and maximum concentration of IDeg at steady state increased proportionally with increasing dose. Steady state concentration of IDeg is achieved in approximately 3 days after which total exposure is unchanged from day-to-day. The steady-state pharmacokinetic profile of IDeg demonstrates continuous and slow absorption of IDeg into the circulation that results in a half-life of 25 hours and a glucose-lowering effect lasting for more than 42 hours. Furthermore, the glucose-lowering effect was similar in all the 6-hour intervals within the 24-hour dosing interval, confirming the even distribution of IDeg exposure and glucose-lowering effect over 24 hours. IDeg was associated with a four-times-lower day-to-day variability in total glucose-lowering effect compared with IGlar in T1DM patients. The counter-regulatory response to experimentally induced hypoglycemia, the ability of the patients to recover from hypoglycemia, and their awareness of hypoglycemia were at least as good with IDeg as with IGlar. The IDeg U100 and IDeg U200 formulations were found to be bioequivalent and can therefore be used interchangeably.

IDegAsp

The glucose-lowering effect of IDegAsp was distinctively separate for the two components, the rapid-acting IAsp and the long-acting IDeg. The bolus component showed a rapid onset of action and a distinct peak action, whereas the basal component had a flat, stable and long action profile. The pharmacokinetic profile of IDeg was not affected by coformulation with IAsp in the IDegAsp product. Thus, trials with IDeg dosing alone can be used to characterize the basal component in IDegAsp. Some differences were observed in the pharmacokinetic profile of IAsp when coformulated with IDeg; however, this did not translate into statistically or clinically significant effects on the pharmacodynamic properties of IDegAsp compared with separate simultaneous injections of IDeg and IAsp. In the IDegAsp single-dose trials in T2DM and T1DM, IAsp total exposure increased essentially proportionally and maximum exposure increased proportionally with increasing dose. The pharmacokinetic and pharmacodynamic profiles of IDegAsp fulfill the FDA requirement of being at least 20% different from each of its single components.[2]

In summary, the plasma half-life of IDeg is longer and the glucose-lowering effect of IDeg is less variable over the day and from day to day compared with IGlar. The pharmacokinetic and pharmacodynamic properties of IDeg and IDegAsp are demonstrated in all populations investigated.

6 Clinical and Statistical Methods

Summary

- The 16 phase 3 trials included in the IDeg and IDegAsp NDAs covered the spectrum of patients with diabetes who require insulin treatment (insulin-naive T2DM, insulin-treated T2DM and T1DM). Using a later cut-off date of May 1, 2012 additional data beyond the NDA came from 2 new phase 3b trials, 1 new phase 3a trial, and 6 extensions to trials in the NDA.
- All IDeg and IDegAsp phase 3 trials were designed as treat-to-target trials based on a prespecified and defined target fasting glucose level that required insulin dose adjustment for each individual patient based on self-measured plasma glucose. The goal was to obtain actual reductions in glycemic control and achieve noninferiority in change in HbA_{1c} versus insulin comparators. As stated in the 2008 FDA Guidance on Developing Drugs and Therapeutic Biologics for the Treatment and Prevention of Diabetes Mellitus,[2] achieving noninferiority is necessary in order to make meaningful treatment comparisons in secondary endpoints like hypoglycemia.
- All phase 3 trials had similar design characteristics, allowing prespecified individual patient-level meta-analyses of hypoglycemia for IDeg versus IGlar. Although designed as glycemic efficacy trials and not cardiovascular outcome trials, major adverse cardiovascular events (MACE) in the IDeg and IDegAsp trials were collected, adjudicated in a blinded manner, and subjected to a meta-analysis.
- Based on the flat and stable pharmacodynamic profile of IDeg, two trials were designed to test whether IDeg dosing intervals could be varied from ~8 to ~40 hours between injections.
- To increase exposure to IDeg or IDegAsp, 9 of the 16 phase 3 trials had unequal randomization (6 trials had 2:1 and 3 trials had 3:1 randomization of IDeg or IDegAsp:comparator), including 6 of the 7 trials with extension periods.
- Key endpoints included HbA_{1c} (primary endpoint), FPG (central laboratory measured), self-measured plasma glucose profiles, insulin dose, and hypoglycemic episodes.
- Hypoglycemia was classified as:
  - Severe (in which patients were unable to treat themselves),
  - Confirmed (severe hypoglycemic episodes or episodes of hypoglycemia with confirmed PG <56 mg/dL), which reflects the action of the basal and bolus insulin.
  - Nocturnal confirmed (confirmed episodes occurring between midnight and 6:00 a.m.), which best reflects the action of a basal insulin as it is not affected by the action of bolus insulin, meals or lifestyle.

6.1 Overview of the Phase 3 Trials

Phase 3 Trials Included in the NDA

The IDeg and IDegAsp development programs consisted of 16 therapeutic confirmatory phase 3 trials (Figure 15). In all, there were 11 phase 3 trials of 26 or 52 weeks' duration investigating IDeg in T2DM (U100 and U200) and T1DM (U100) and 5 therapeutic confirmatory phase 3 trials of 26 weeks' duration investigating IDegAsp in T2DM and T1DM (Figure 15), hereafter referred to simply as "phase 3 trials."

All 16 phase 3 trials were randomized, controlled, open-label, multicenter, multinational trials. The clinical program included patients with T2DM or T1DM at different stages of the disease, from newly diagnosed patients with T2DM to high-risk patients with advanced diabetes at enrollment. Detailed descriptions of the 16 individual phase 3 trials are presented in Appendix 2.

In the IDeg program, 9 of the 11 phase 3 trials studied once-daily dosing while 2 of the 11 phase 3 trials studied three-times-weekly (3TW) dosing. In the 3TW trials, IDeg was dosed on Monday, Wednesday, and Friday. Although clinically relevant reductions in HbA_{1c} were achieved with IDeg 3TW, noninferiority of IDeg 3TW to IGlar once daily was not confirmed. Thus, Novo Nordisk is not pursuing the 3TW dosing regimen for IDeg. The 3TW trials are included in all evaluations of safety except for the evaluations of hypoglycemia and injection site reactions.

In the IDeg clinical efficacy and dosing and hypoglycemia sections, the 9 once-daily IDeg phase 3 trials are grouped according to the patient population under investigation (T2DM or T1DM) and are presented in the following order:

- T2DM
  - Insulin therapy with basal insulin only (basal-only therapy [BOT]) ± OADs (5 trials): Trials 3579, 3672, 3586, 3580 and 3668 that investigated once-daily IDeg dosing.
  - Insulin therapy with both basal insulin and bolus insulin at mealtimes (basal-bolus insulin therapy) (1 trial): Trial 3582
- T1DM
  - Basal-bolus insulin therapy (3 trials): Trials 3583, 3585, and 3770

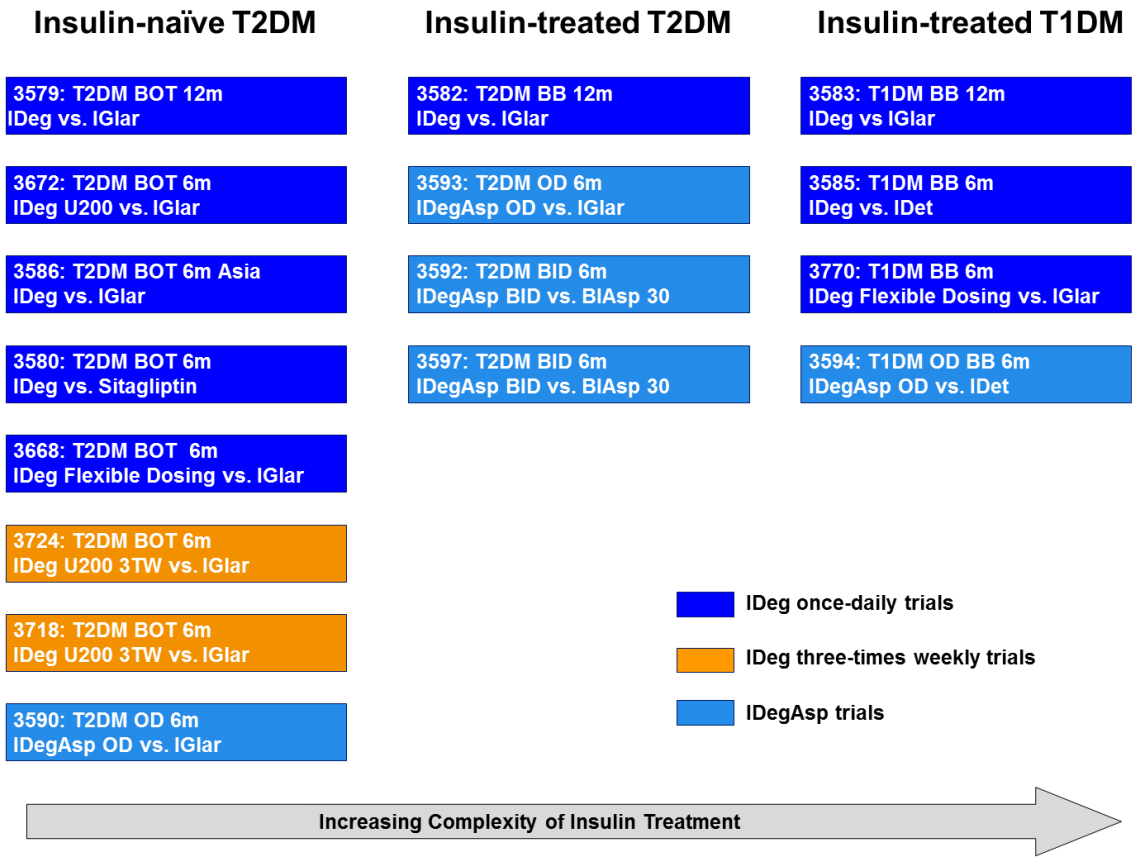
In the IDegAsp clinical efficacy and dosing and hypoglycemia sections, the five IDegAsp phase 3 trials are grouped according to the frequency of dosing and the patient population under investigation and are presented in the following order:

- T2DM
  - Once-daily IDegAsp: Trial 3590 in insulin-naïve patients and Trial 3593 in insulin-treated patients
  - Twice-daily IDegAsp: Trials 3592 and 3597 in insulin-treated patients. This regimen was tested because, while the IDeg (basal) component of IDegAsp would not necessitate more

than one dose per day, most patients who use fixed-ratio insulin products inject their insulin twice daily in order to obtain mealtime coverage at two main meals.

- T1DM
  - Basal-bolus therapy (IDegAsp dosed once daily + IAsp at remaining meals): Trial 3594

In the NDA, safety data from completed clinical trials with IDeg and IDegAsp were pooled and included for evaluation of safety (see Section 10.1). Extension data from the one completed trial (Trial 3645, the extension to IDegAsp T1DM BB Trial 3594) were included in the NDA.



IDeg: insulin degludec; IGlar: insulin glargine; IAsp: insulin aspart; IDegAsp: insulin degludec/insulin aspart; OD: once daily; BID: twice daily; See Section 6.2 for a description of the IDeg flexible dosing schedule; 3TW: three-times weekly dosing; 12m: 12-month (52-week) trial; 6m: 6-month (26-week) trial; BOT: basal-only insulin therapy; BB: basal-bolus insulin therapy. Trial 3668 enrolled 58% insulin-naïve patients and 42% insulin-treated patients. The primary comparison in Trials 3668 and 3770 was IDeg flexible dosing versus IGlar. In addition, there were IDeg once-daily arms in both of these trials that allowed secondary comparisons of IDeg and IDeg flexible dosing.

Figure 15 IDeg and IDegAsp Phase 3 Main Randomized Trials − NDA

In the T2DM trials, IDeg and IDegAsp were studied when added to one or more OADs to reflect common clinical practice (Table 12). Specifically, IDeg and IDegAsp could be used in combination with metformin in all OAD trials (as this is recommended as first line therapy), with insulin

secretagogues in Trials 3586, 3668 and 3580; with TZD (pioglitazone) in Trials 3580, 3668, 3582, 3593 and 3592; with DPP-4 inhibitors in Trials 3579, 3672, 3593 and 3592, and with α-glucosidase inhibitors in Trial 3586.

Table 12 Background Antidiabetic Treatment – IDeg and IDegAsp Phase 3 Trials – T2DM

Trial ID and Description	Metformin	SU or glinides	TZD	DPP-4 I	α-GI	Number of OADs
IDeg						
Basal-only Therapy Trials						
T2DM BOT 12m (3579)	Mandatory			Allowed		1–2
T2DM BOT 6m U200 (3672)	Mandatory			Allowed		1–2
T2DM BOT 6m Asia (3586)	Allowed	Allowed			Allowed	1–3
T2DM BOT 6m vs Sita (3580)	Allowed	Allowed	Allowed			1–2
T2DM BOT 6m Flexible Dosing (3668)	Allowed	Allowed	Allowed			0–3
Basal-bolus Therapy Trials						
T2DM BB 12m (3582)	Allowed		Allowed			0–2
IDegAsp						
OD Trials						
T2DM OD 6m (3590)	Mandatory					1
T2DM OD 6m (3593)	Mandatory		Allowed	Allowed		1–3
BID Trials						
T2DM BID 6m (3592)	Allowed		Allowed	Allowed		0–3
T2DM BID 6m (3597)	Allowed					0–1

SU: sulphonylurea; TZD: thiazolidinedione; DPP-4I: dipeptidyl peptidase-4 inhibitor; α-GI: alpha-glucosidase inhibitor; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus; BID: twice daily; BOT: basal-only therapy; BB: basal-bolus therapy; Sita: sitagliptin; See Section 6.2 for a description of the IDeg flexible dosing schedule; 12m: 12-month trial; 6m: 6-month trial.

In addition to treatment with OADs and basal insulin, patients with a longer duration of T2DM often require intensification with bolus insulin to cover mealtime glucose excursions. For this reason, IDeg was studied in T2DM as part of a basal-bolus regimen with IAsp at meals in IDeg Trial 3582. Moreover, in T1DM, IDeg was used as part of a basal-bolus regimen with IAsp at meals (all trials). IDegAsp OD also was tested as part of a basal-bolus regimen in T1DM with IAsp at remaining meals (Trial 3594).

Based on IDeg's 25-hour half-life and duration of action >42 hours (described in Section 5), extreme variation in the timing of the injection was investigated in order to determine the effect on glucose control and hypoglycemia. The IDeg phase 3 clinical trial program included two studies (IDeg flexible dosing studies: 3668 [T2DM] and 3770 [T1DM]) to look at the impact of changing the time of IDeg administration from day to day, with the goal of determining if the pharmacokinetic and pharmacodynamic properties of IDeg would allow patients to vary the timing of their insulin dose according to the requirements of daily living. This is not the intended or recommended dosing regimen, but these trials provided an opportunity to test whether the long half-

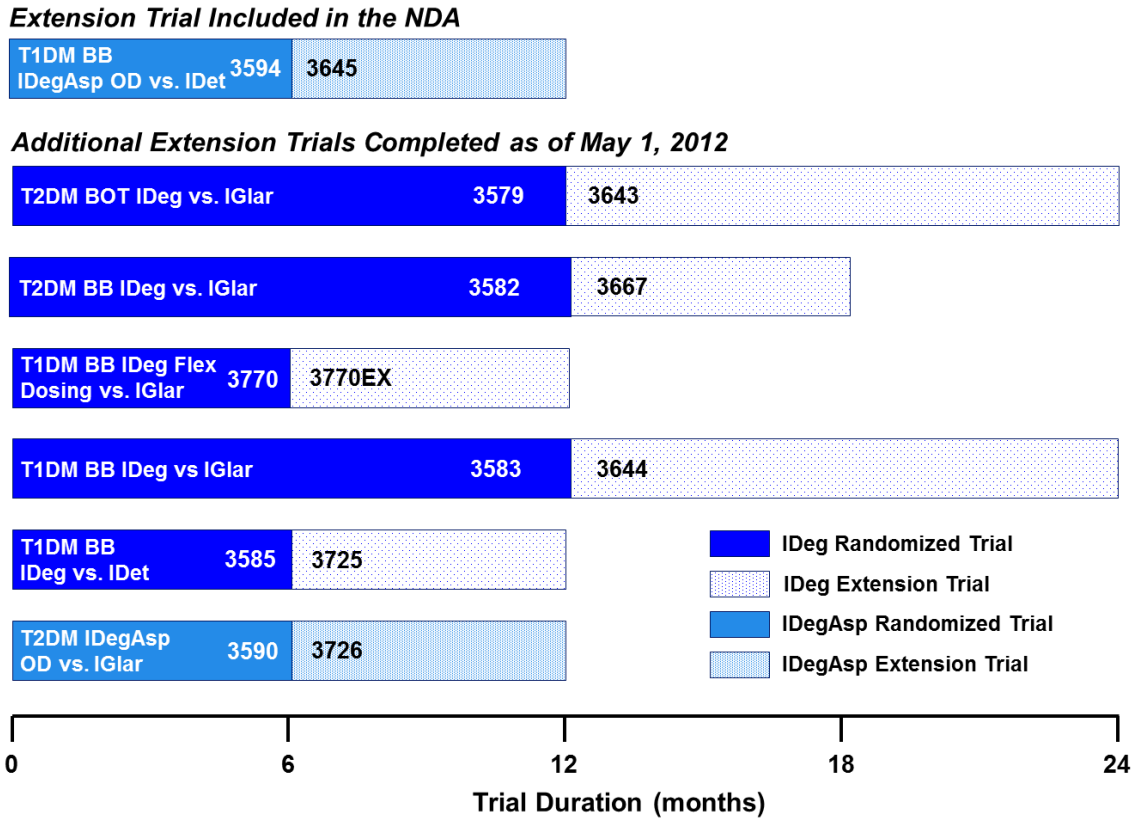
life of IDeg might allow greater flexibility of insulin administration when a patient's schedule varies.

Additional Trials Included in the FDA-requested Analyses of Safety

After submission of the NDA and 120-day Safety Update, the FDA requested additional AE data primarily for a reanalysis of major adverse cardiovascular events (MACE). A cut-off date of May 1, 2012 was chosen.

Beyond the data presented in the NDA (January 31, 2011 cut-off date), the May 1, 2012 cut-off contains additional AEs from the following nine completed phase 3 trials:

- One new completed phase 3a IDegAsp trial: Trial 3896, a 6-month, open-label, randomized phase 3a trial comparing the efficacy and safety of IDegAsp and IGlar in insulin-naïve Japanese patients with T2DM.
- Two new completed phase 3b IDeg trials:
  - Trial 3846 (6-month trial comparing IDeg simple titration to IDeg step-wise titration in T2DM)
  - Trial 3923 (6-month trial comparing IDeg U200 to IDeg U100 in T2DM)
- Five completed extensions of IDeg trials (Figure 16):
  - Trial 3667 (extension of Trial 3582)
  - Trial 3770EX (extension of Trial 3770)
  - Trial 3725 (extension Trial 3585)
  - Trial 3644 (extension of Trial 3583)
  - Trial 3643 (extension of Trial 3579)
- One completed extension of an IDegAsp trial: Trial 3726 (extension of Trial 3590) (Figure 16)



OD: once daily; See Section 6.2 for a description of the IDeg flexible dosing schedule; BOT: basal-only insulin therapy; BB: basal-bolus insulin therapy. Numbers on the bars are Trial IDs. All trials, except for Trial 3770, had different trial IDs for the main and extension periods. In all trials but 3582-3667 patients temporarily discontinued randomized treatment (switched to NPH) in the period between the main trial and the extension.

Figure 16 IDeg and IDegAsp Phase 3 Trials with Extensions Completed as of May 1, 2012

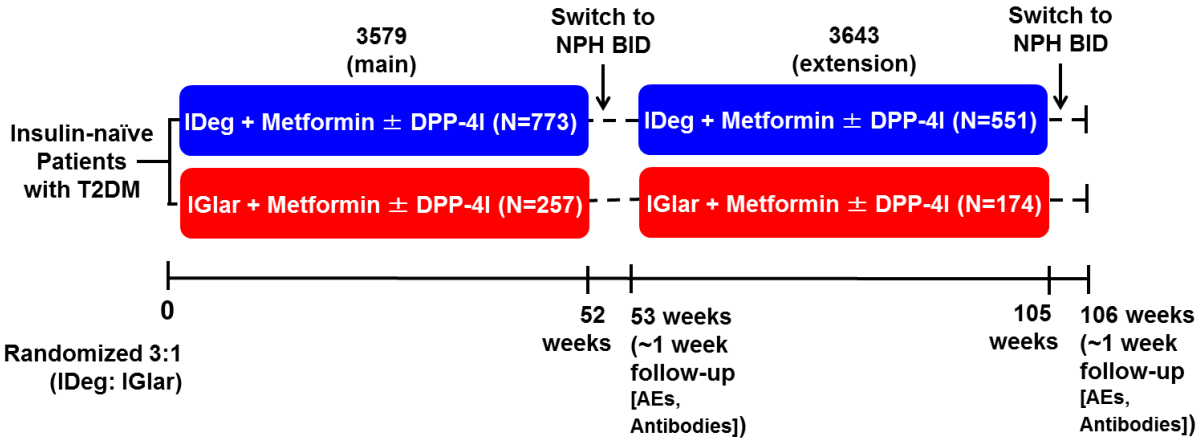
The length of the main plus extension trial periods in the IDeg and IDegAsp clinical programs, ranged from one year to two years, as shown in Figure 16.

6.2 Trial Design of Phase 3 Trials

All phase 3 trials had common trial design elements. The IDeg T2DM BOT Trial 3579-3643 is presented below as an example of the uniform phase 3 trial design used for IDeg main trials and extensions (Figure 17). Trial 3579-3643 was a randomized, controlled, open-label, multi-center, multinational trial comparing the efficacy and safety of IDeg and IGlar both injected once daily in combination with OADs in T2DM patients. As shown in (Figure 17), at the end of the main randomized trial (3579), patients switched to NPH for a ~7-day washout period prior to measurement of antibodies. At the follow-up visit 7 days after drug discontinuation, patients who chose to continue in an extension (for trials with extensions) switched back to their randomized treatment. Those not continuing in an extension trial switched from NPH to a marketed insulin (that

may have been the same as their trial treatment in the case of the comparator group). Patients also switched to a marketed insulin at the end of the extension period, after the 7-day follow-up period.

To ensure adequate exposure to IDeg, a 3:1 (IDeg:IGlar) randomization was applied in this trial and in several other phase 3 trials. Design features of the other IDeg and IDegAsp phase 3 trials are presented in Appendix 2.



DPP-4I: di-peptidyl peptidase-4 inhibitor; NPH: neutral protamine Hagedorn; BID: twice daily; AE: adverse event; N: number of randomized patients (3579) and number of patients entering the extension (3643).

Figure 17 Trial Schematic for IDeg T2DM BOT Trial 3579 (Main) and 3643 (Extension)

Noninferiority Design

The phase 3 trials were designed to adhere to the 2008 FDA guidance for insulin development, which states: "*These studies should be directed at achieving actual reductions in glycemia (as opposed to simple maintenance of pretrial levels of control) from baseline to end of study. Test and comparator groups should be treated to similar goals. Similar degrees of glycemic control (test noninferior to reference) should be achieved so that comparisons among groups in frequency and severity of hypoglycemia will be interpretable in ultimate risk-benefit assessments.*"[2] All trials were designed to achieve improvements in long-term glycemic control as measured by change in HbA_{1c} from baseline. Change in HbA_{1c} was the primary endpoint of the phase 3 trials because HbA_{1c} is considered the most widely accepted measure of long-term glucose control in T2DM and T1DM.

All phase 3 trials (except superiority Trial 3580 [vs. sitagliptin]) were powered to show noninferiority in change in HbA_{1c} from baseline at a 0.4% level. Thus, when reviewing the HbA_{1c} results, it is important to remember that these trials were designed to achieve noninferiority rather than superiority with regard to reductions in HbA_{1c} with IDeg or IDegAsp versus insulin comparators. To establish efficacy, noninferiority of IDeg or IDegAsp to insulin comparators was the goal so that meaningful comparisons between treatment groups in hypoglycemia could be made.

This is a distinctly different approach used for the evaluation of other drugs to treat diabetes and is based on the premise that all insulin products can lower glucose levels but that they do so differentially in regard to risk of hypoglycemia, weight, dose, or frequency of administration.

Treat-to-target Design

In order to achieve noninferiority with respect to change in HbA_{1c}, a treat-to-target design was applied in the phase 3 trials, in accordance with the 2008 FDA guidance.[2] This means that insulin doses were adjusted for each individual patient, with the aim of achieving the same glycemic targets for IDeg/IDegAsp and comparator insulin products based on patient self-measured blood glucose. As mentioned above, achieving noninferiority in change in HbA_{1c} using a treat-to-target approach makes hypoglycemia a key differentiator in the comparison of IDeg/IDegAsp and comparator products. This approach was first applied to comparisons between basal insulin analogues (IGlar and IDet) and NPH insulin[25,26] and has since been adopted as both a clinical trial and as a regulatory standard.

When designing the IDeg phase 3 program and based on data from the phase 2 trials, it was hypothesized that the low day-to-day variability of IDeg and its relatively flat profile (see Section 5) would allow for targets approaching normoglycemia to be reached more safely. For this reason, a pre-breakfast self-measured plasma glucose (SMPG) titration target between 70−90 mg/dL was chosen. This target was previously shown to be safe in the IDet TITRATE trial[27] and is similar to the glycemic targets used for other basal insulin products in development.

Insulin Titration

Basal insulin doses were adjusted weekly for the first six months based on a titration algorithm to ensure treatment uniformity between trial sites and across trials. The algorithm specified the self-measured plasma glucose target and the recommended dose adjustments at different plasma glucose levels. The same titration algorithm was used for IDeg and for comparator insulin products.

A titration committee monitored and reviewed the titration of insulin doses in a blinded fashion. Repeated and unsubstantiated deviations from the titration algorithm were discussed in a blinded manner with the trial site, but the final decisions regarding dose adjustments were based on clinical judgment, and were made at the discretion of the trial site investigator.

During all therapeutic confirmatory trials, basal insulin dose could be continuously adjusted, based on the mean pre-breakfast SMPG values from the two to three days prior to site visits and telephone contacts. The pre-breakfast SMPG target was between 70−90 mg/dL in all trials. The basal insulin dose was to be reduced when SMPG values were <70 mg/dL and was to be increased for SMPG values ≥90 mg/dL. Of note, individuals treated with twice-daily basal insulin before randomization were asked to reduce their dose by 20% when switching to insulin glargine (per label), but were allowed to switch to the same total dose of IDeg based on data from phase 2.

Dosing Schedules

The IDeg and IDegAsp development programs were designed to investigate a wide range of dosing times. In some trials a fixed administration time was applied, while in others, the administration time could vary from day to day. IDeg was administered with the main evening meal in T2DM Trials 3579, 3672, 3582, 3668 (IDeg arm) and T1DM Trials 3583 and 3770 (IDeg arm). IDeg could be administered from the start of the evening meal until bedtime in Trials 3586 (T2DM) and 3585 (T1DM). In Trial 3580, patients could choose to administer IDeg once daily at any time of the day, within the limits of 8 to 40 hours between doses.

IDegAsp was dosed either OD or BID. IDegAsp OD was dosed with any main meal in Trial 3594, with dinner or the largest meal in 3593, and with the option of choosing a different meal from day to day in Trial 3594. IDegAsp was administered with the morning meal in Trial 3590. IDegAsp was administered with the morning and main evening meal when dosed BID (Trials 3592 and 3597).

In all trials, comparators were dosed according to product label. In trials with IDet as comparator (IDeg Trial 3585 and IDegAsp Trial 3594), a second dose of IDet could be added in case of inadequate glycemic control after ≥8 weeks of treatment. BIAsp 30 was administered with the morning and main evening meal when dosed BID (Trials 3592 and 3597).

The fixed flexible dosing schedule (IDeg flexible dosing arms in Trials 3668 [T2DM] and 3770 [T1DM]) was employed to investigate the impact of extreme day-to-day variation in the dosing intervals. In the flexible dosing arms, IDeg was injected OD in the morning on Mondays, Wednesdays and Fridays and in the evening on Tuesdays, Thursdays, Saturdays and Sundays (Figure 18). This meant that IDeg was administered with alternating narrow (8–12 hours) and wide (36–40 hours) dosing intervals, with the exception of a 24-hour dosing interval between Saturdays and Sundays. In these trials, the primary comparison was between IDeg flexible dosing and IGlar dosed at the same time every day.

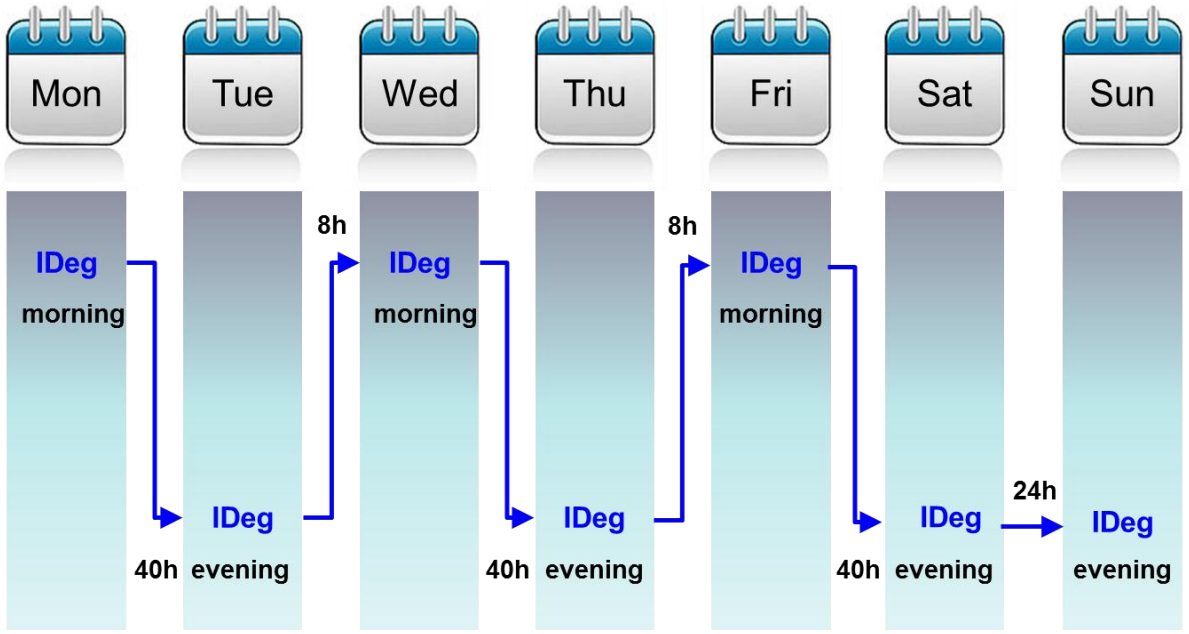


Figure 18 IDeg Flexible Dosing Schedule Used in Trials 3668 (T2DM) and 3770 (T1DM)

Open-label Design

All phase 3 trials were open label. An open-label design for insulin trials is consistent with the 2008 FDA guidance.[2] Moreover, a double-blind design was not possible to conduct due to the differences in insulin injection devices.

While the phase 3 trials were open label, all possible measures were taken to limit the influence of additional confounding factors. Most importantly, identical titration guidelines and glycemic targets were applied for both treatment arms with similar requirements for concomitant antidiabetic therapy. Furthermore, source data verification was performed in order to verify hypoglycemic episodes and AEs.

Randomization

To increase exposure to IDeg or IDegAsp, nine of the sixteen phase 3 trials had unequal randomization (six trials had 2:1 and three trials had 3:1 randomization of IDeg or IDegAsp:comparator), including six of the seven trials with extension periods. Of the 16 randomized phase 3 trials included in the NDA:

- Two of the nine once-daily IDeg phase 3 trials had 1:1 randomization to each of the treatment arms (Trials 3672 and 3580)
- Seven of the nine once-daily IDeg phase 3 trials had unequal randomization of IDeg:comparator (four trials had 2:1 randomization [Trials 3586, 3668, 3585 and 3770] and three trials had 3:1 randomization [Trials 3579, 3582 and 3583]).

- The two IDeg 3TW trials had 1:1 randomization of IDeg U200 3TW: IGlar (Trials 3718 and 3724).
- Of the five IDegAsp trials, three had 1:1 randomization (Trials 3590, 3592 and 3593) and two had 2:1 randomization of IDegAsp:comparator (Trials 3597 and 3594).

Choice of Comparator

In nine of the IDeg phase 3 trials, IDeg was compared with IGlar (Lantus®) as this is the most widely used basal insulin approved for once-daily dosing and has a well-studied safety and efficacy profile. Trial 3585 had IDet (Levemir®) administered once or twice daily (per product labeling[28]) as the comparator insulin, whereas the superiority Trial 3580 had the DPP-4 inhibitor sitagliptin (Januvia®). The rationale for the comparison with sitagliptin was to investigate the efficacy and safety of adding IDeg instead of an additional OAD (in this case, a DPP-4 inhibitor) in patients inadequately controlled on 1−2 OADs.

In the IDegAsp T2DM trials, comparators for once- and twice-daily dosing with IDegAsp were IGlar and BIAsp 30 (NovoLog®Mix 70/30), respectively. IGlar is the preferred comparator for once-daily basal dosing, but it does not have the bolus component, an important point to consider when evaluating the glycemic control and hypoglycemia results from the IDegAsp OD trials. BIAsp 30 twice daily is considered the preferred comparator for twice-daily dosing since it is the most widely used premixed insulin worldwide, and because it contains a basal component and the same rapid-acting component (IAsp) as IDegAsp. In T1DM Trial 3594, IDegAsp once-daily + IAsp at remaining meals was compared with IDet + IAsp at all meals, which is representative for basal-bolus therapy, the standard of care for patients with T1DM.

Patient Selection Criteria

Selection criteria were as uniform as possible in the phase 3 trials in order to allow comparison across trials. Key selection criteria are shown in Table 13.

Table 13 Key Inclusion, Exclusion, and Withdrawal Criteria – Phase 3 Trials

Key Inclusion Criteria

• ≥18 years of age (≥20 years for Japan)
• Diagnosed clinically with diabetes mellitus: T2DM for ≥6 months, T1DM for ≥12 months
• Current antidiabetes treatment:
  • T2DM (IDeg trials): treated with OADs (monotherapy or combination therapy) for ≥3 months (exceptions were Trial 3668: treated with OADs and/or basal insulin and Trial 3582: treated with any insulin treatment ±OADs).
  • T2DM (IDegAsp trials): insulin-naïve or previously insulin-treated (basal or mixed insulin) and/or OADs (monotherapy or combination therapy) for ≥3 months
  • T1DM (IDeg and IDegAsp trials): treated with basal-bolus insulin or other mixed insulin regimens for ≥12 months
• Baseline HbA_{1c}: IDeg T2DM and IDegAsp trials: 7.0–10.0%, both inclusive[a]; IDeg T1DM trials ≤10.0%
• Baseline BMI: ≤40 kg/m^2 (T2DM trials with IDeg U100 and IDegAsp T2DM trials), ≤45 kg/m^2 (IDeg T2DM Trial 3672, IDeg U200), ≤35 kg/m^2 (T1DM and Trials 3586 and 3597)

Key Exclusion Criteria
• Use within the last 3 months prior to screening of certain OADs and GLP-1 • Cardiovascular disease within the last 6 months prior to visit 1, defined as: stroke; decompensated heart failure New York Heart Association class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty • Uncontrolled treated/untreated severe hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg) • Impaired liver function, defined as alanine transaminase (ALAT) ≥2.5 times upper limit of normal range • Impaired renal function defined as serum-creatinine ≥125 µmol/l (≥1.4 mg/dL) for males and ≥110 µmol/L (≥1.3 mg/dL) for females in T2DM; serum-creatinine ≥180 µmol/L (≥2.0 mg/dL) in T1DM • Recurrent severe hypoglycemia (more than 1 severe hypoglycemic episode during the last 12 months) or hypoglycemic unawareness or hospitalization for diabetic ketoacidosis during the previous 6 months • Cancer and medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)
Key Withdrawal Criteria
• Hypoglycemia during the treatment period posing a safety problem as judged by the investigator • Protocol deviation having influence on efficacy or safety data as judged by the investigator • Lack of effect: after Week 12[b] the patient has not had reduction in HbA_{1c} and has a prebreakfast SMPG reading >240 mg/dL on 3 consecutive days despite appropriate dose adjustments. The patient should come in for an unscheduled visit as soon as possible. An FPG should be obtained and analyzed by the central laboratory. If this FPG exceeds 240 mg/dL and no treatable intercurrent cause for the hyperglycemia has been diagnosed, the patient must be withdrawn.

[a]Exceptions were Trial 3590 and Trial 3580: 7.5–11% (both inclusive) and Trial 3668: 7.0–11.0% (both inclusive) for the insulin-naïve patients.

[b] Trial 3580 has an additional checkpoint after Week 6, in which lack of HbA_{1c} reduction, combined with prebreakfast SMPG + laboratory-measured FPG >270 mg/dL, entailed withdrawal.

Inclusion and exclusion criteria for T2DM were set to enroll a population of patients requiring additional therapy. Note that high upper HbA_{1c} limits were set because patients with T2DM or T1DM in poor glycemic control are likely to benefit from intensified insulin therapy. Very high baseline HbA_{1c} levels are often indicative of patient noncompliance to treatment and individuals

with very high levels were excluded for this reason. In addition, high upper BMI limits in a few trials (≤45 kg/m^2) ensured a broad representation of the global T2DM population.

Patients with significant concomitant illnesses were excluded, including patients with significant acute cardiovascular disease (see Table 13), as they may require different treatment goals and be prone to early withdrawal. Current treatment guidelines from the ADA do not recommend intensive insulin treatment and ambitious glycemic targets in individuals with recent cardiovascular history due to the risk of hypoglycemia and its adverse effects in these individuals.[3] Patients with prior cardiovascular events occurring up to 6 months before inclusion in the trial, as well as patients with mild or moderate renal impairment, were included.

To ensure patient safety, patients with hypoglycemia unawareness or >1 severe episode in the last year were excluded in the IDeg and IDegAsp phase 3 trials.

The exclusion criterion for impaired renal function was consistent with metformin labeling since metformin was allowed as background therapy in T2DM trials.

Extension Trial Design Features

Enrollment in extension trials was offered to all randomized patients in seven of the main trials, and 74% chose to continue. Patients who entered extension trials signed a separate informed consent form from the main trials at the time of extension period initiation. Patients remained in their randomized treatment groups in the main and extension trials, except for Trials 3770 [T1DM], in which the IDeg once-daily arm (dosed at the same time every day) and IDeg flexible dosing arms were merged.

In the extensions, visits, titration contacts and assessments occurred less frequently than in the main randomized trial periods. Clinic and phone visits occurred one week apart during the main trials and 2 weeks apart during extension trials. Titration contacts between the investigator and the patient occurred on a weekly basis during main trials and on a biweekly basis during extension trials. Efficacy assessments (HbA_{1c}, fasting plasma glucose, 4- and 9-point self-measured plasma glucose [SMPG] profiles) were taken less frequently during extensions than during the main trials.

In extension trials in which insulin antibodies were measured (Trials 3643 [extension to 3579], 3644 [extension to 3583], 3645 [extension to 3594], 3725 [extension to 3585], 3726 [extension to 3590], and 3770EX [extension to 3770]), patients switched basal insulin treatment at the end-of-treatment visit (main trial) to twice-daily NPH insulin for approximately one week until the follow-up visit. The dose of NPH insulin taken during the washout period was approximately 80% of the total daily basal dose at the end of treatment. The follow-up visit (main trial) and the screening visit (extension trial) occurred on the same day that patients resumed trial drug. In most cases, a sharp increase in mean FPG values in both treatment groups was observed after switching to NPH; FPG decreased

after resuming trial drug and renewing titration. In Trial 3667 (extension to 3582), insulin antibodies were not measured; therefore, patients started the extension trial on the same day as the end-of-treatment visit for the main trial and did not change basal insulin treatment.

6.3 Objectives and Endpoints

The main objective of the phase 3 trials was to confirm the long-term glycemic improvements with IDeg or IDegAsp as measured by HbA_{1c} either in combination with OADs (T2DM only) or in combination with rapid-acting bolus insulin (T2DM and T1DM). This was done by demonstrating noninferiority of IDeg to comparator insulin in reducing HbA_{1c} at a 0.4% level (see Section 6.4). The treat-to-target trial designs allowed detection of possible differences in other endpoints, such as hypoglycemia, which was a key secondary endpoint.

Main efficacy measures were:

- HbA_{1c} (consistent with 2008 FDA regulatory guidance,[2] change in HbA_{1c} from baseline was the primary endpoint in all trials)
- FPG (central-laboratory measured): According to the FDA guidance,[2] changes in FPG can be used as a secondary, supportive measure of efficacy in phase 3 trials.
- Confirmed hypoglycemia and nocturnal confirmed hypoglycemia—which more clearly reflects the action of the basal insulin— were assessed in accordance with the ADA working group report, "Defining and Reporting Hypoglycemia in Diabetes." Confirmed hypoglycemia was included as an efficacy endpoint because of the recognized challenges of achieving glycemic control in the absence of hypoglycemia. FDA guidance recommends evaluating hypoglycemia relative to approved insulin products when both groups achieve similar HbA_{1c} levels and HbA_{1c} improvements.[2]

In addition, insulin doses were evaluated because of the recognized correlation with glycemic control, hypoglycemia, and weight gain.

To adhere to regulatory guidance,[2] and to ensure consistency across trials, prespecified, standardized definitions of hypoglycemia were used across the IDeg and IDegAsp phase 3 development programs (Figure 19).

Severe hypoglycemia was defined as episodes requiring assistance from another person. The definition of severe hypoglycemia used in the IDeg and IDegAsp trials was identical to the one used by the ADA.[29]

Confirmed hypoglycemic episodes were defined as severe hypoglycemic episodes (patient not able to treat self), or episodes of hypoglycemia with PG <56 mg/dL, regardless of symptoms (Figure 19). Novo Nordisk has historically used the cut-off level of 56 mg/dL to define hypoglycemia, rather than the ADA criteria (<70 mg/dL), because <56 mg/dL is typically where counter-regulatory

mechanisms begin and patients report clinical symptoms of hypoglycemia.[30] Furthermore, the cut-off of 56 mg/dL is sufficiently below the target pre-breakfast self-measured PG of between 70−90 mg/dL to avoid a high incidence of clinically irrelevant hypoglycemic episodes with self-measured PG values just below the target.

Nocturnal hypoglycemia was prospectively defined as episodes occurring between midnight and 6:00 a.m. to allow consistent evaluation across trials. Although episodes of hypoglycemia may go unnoticed and therefore be unreported, especially at night when patients are asleep, this is less likely for hypoglycemic episodes with a PG < 56 mg/dL, as such episodes are more often associated with symptoms. Separation of hypoglycemic episodes into nocturnal hypoglycemia is consistent with ADA guidance for hypoglycemia reporting.[29] As no specific timeframe for defining nocturnal hypoglycemia was recommended by the ADA,[29] the interval between midnight and 6:00 a.m. was chosen in order to isolate the effect of the basal insulin by avoiding the effects of bolus insulin dosing associated with late meals or breakfast.

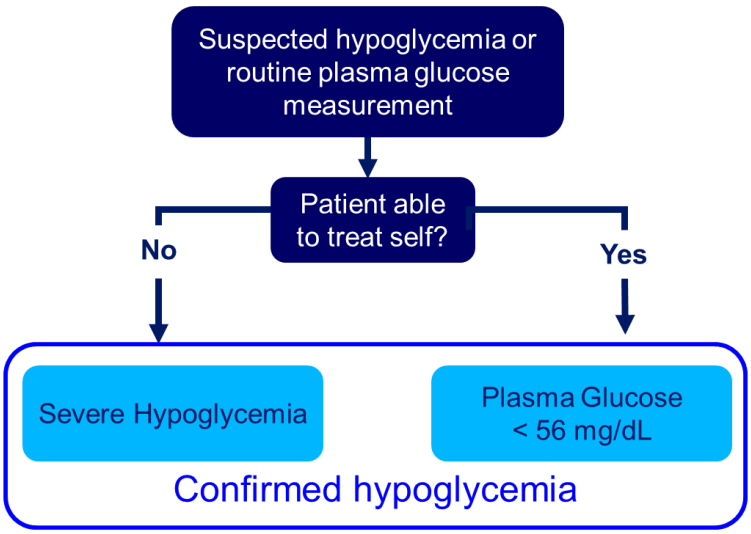


Figure 19 Prespecified Definitions of Hypoglycemia in the IDeg and IDegAsp Phase 3 Trials

All episodes of hypoglycemia were recorded in the patient diaries.

Hypoglycemic episodes that were judged by the investigator as fulfilling the regulatory definition of an SAE, or the ADA definition of severe hypoglycemia, were also reported as AEs, with the purpose of capturing additional information on the precipitating factors (e.g., exercise, skipped meals).

6.4 Statistical Analyses

6.4.1 Individual Trials

All statistical analyses of efficacy in the IDeg and IDegAsp phase 3 trials were made on the full analysis set (FAS), defined as all randomized patients. In exceptional cases, patients could be excluded from the FAS, as justified and documented in the individual trial reports. The statistical evaluation of the FAS follows the intention-to-treat (ITT) principle and patients contributed to the evaluation "as randomized." All descriptive statistics on safety endpoints, hypoglycemia, and dose used the safety analysis set (SAS), which included all patients receiving at least one dose of the investigational product or its comparator.

Missing values were imputed using the Last Observation Carried Forward (LOCF) method as a transparent and robust method in the context of treat-to-target trials, where patients typically continue their therapy using a commercially available insulin preparation after withdrawal, and are thereby expected, to some degree, to maintain the glycemic control achieved using the allocated trial insulin.

If noninferiority was confirmed for the primary endpoint (or superiority in IDeg Trial 3580), a number of confirmatory secondary endpoints were tested in a hierarchical manner. The secondary endpoints were ordered in the different trials on the basis of their clinical relevance within the respective treatment regimens and populations investigated. Superiority was only confirmed for endpoints in which all previous hypotheses had been confirmed, thereby allowing for the overall control of type 1 error within the given trial. The term "superior" is solely used if statistical superiority was confirmed based on this procedure. The terms "statistically significant" or "significant" are used either for non-confirmatory endpoints or for confirmatory secondary endpoints where previous hypotheses in the hierarchical testing order were not confirmed.

HbA_{1c}

The primary objective of the phase 3 trials was to confirm the efficacy of IDeg or IDegAsp in terms of glycemic control as assessed by the primary endpoint, change in HbA_{1c} from baseline. The primary statistical analysis was an analysis of variance (ANOVA) method with treatment, antidiabetic therapy at screening, sex and region as fixed factors and age and baseline HbA_{1c} as covariates. With the exception of Trial 3580, all trials were noninferiority trials, and efficacy was confirmed if the upper bound of the two-sided 95% confidence interval (CI) for the estimated treatment difference (IDeg or IDegAsp minus comparator) was below or equal to the noninferiority limit of 0.4%. This limit, which is in agreement with the FDA Guidance on Diabetes,[2] has been used in previous submissions for other insulin products (e.g., NovoLog®, Levemir®). In Trial 3580, which compared IDeg to sitagliptin, efficacy was confirmed if a statistically significant difference in change in HbA_{1c} was observed (superiority). In three-arm trials (Trials 3668 [T2DM] and 3770 [T1DM]), the primary analysis was IDeg flexible dosing vs. IGlar.

The robustness of the primary analyses was confirmed by sensitivity analyses, wherein missing data were handled by various alternatives to the LOCF method. Among these sensitivity analyses were an analysis of the data from patients completing the trials, as well as a repeated measures model, where missing values were accounted for, through the pattern over time for the values actually observed. For all trials the point estimates and confidence intervals for the treatment difference were well matched with no systematic difference between the various methods to handle missing data.

FPG (Assessed by a Central Laboratory)
Change from baseline FPG values were analyzed using the same model as for HbA_{1c} where baseline HbA_{1c} was replaced by baseline FPG.

Hypoglycemia
The number of treatment-emergent 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 treatment, antidiabetic therapy at screening, sex and region as fixed factors, and age as covariate. The treatment-emergent period was defined as on or after the first day of trial drug administration and up to and including 7 days after last trial drug administration.

The treatment-emergent severe hypoglycemia in Trials 3579 and 3582 were subject to a simpler Poisson regression model with the same covariates as the negative binomial model that could not be fitted to the sparse data.

Body Weight
Change in body weight from baseline to end of treatment was analyzed using the same model as for HbA_{1c} where baseline HbA_{1c} was replaced by baseline weight.

QTc

Change from baseline in QTc was analyzed using the same model as for HbA_{1c} where baseline HbA_{1c} was replaced by baseline QTc.

6.4.2 Hypoglycemia Meta-analysis of IDeg Trials

A prospectively planned meta-analysis was conducted based on pooled individual patient data from all trials in both T2DM and T1DM comparing IDeg with IGlar. The primary objective was to demonstrate superiority of treatment with IDeg to IGlar in terms of a lower rate of confirmed hypoglycemic episodes. A secondary confirmatory objective of the meta-analysis was to demonstrate superiority of treatment with IDeg to IGlar in terms of a lower rate of nocturnal confirmed hypoglycemic episodes. These objectives were addressed by analyzing the number of treatment-emergent confirmed and nocturnal confirmed hypoglycemic episodes 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 trial, treatment, antidiabetic therapy at screening, sex and region as fixed factors and age as a covariate. As a sensitivity analysis, the incidence of confirmed and nocturnal confirmed hypoglycemia (defined as the proportion of patients who experienced at least one hypoglycemic episode) were investigated separately by analyzing a binary endpoint indicating whether a patient had experienced at least one episode using a logistic regression model with logit link and with the fixed factors and covariate as in the primary analysis model. Severe hypoglycemic episodes and confirmed hypoglycemic episodes in elderly patients (≥65 years at the time of screening) were analyzed using the same model as was used for the primary meta-analysis. For severe hypoglycemia in overall T2DM and for basal-only therapy, the simpler Poisson regression model was used as the negative binomial model could not be fitted to the sparse data.

6.4.3 Cardiovascular Meta-analysis of IDeg+IDegAsp Trials

A prespecified meta-analysis of events categorized as MACE was conducted. The primary endpoint in the prespecified meta-analysis was the time until first MACE (or exposure time for patients with no MACE) and was analyzed for the full analysis set using Cox Regression stratified by trial and with treatment (IDeg+IDegAsp and comparators) as explanatory variable. The statistical analysis plan for the meta-analysis was finalized before locking the database for the first trial included in the analysis, and included the following MACE composite endpoint: cardiovascular death, stroke, and acute coronary syndrome (including myocardial infarction and unstable angina pectoris). The predefined meta-analysis was based on all phase 3 trials in the IDeg and IDegAsp programs included in the NDA data set. Additional exploratory analyses were conducted on all trials including extension periods, based on a cut-off date of May 1, 2012.

The primary analysis was repeated on the safety analysis set as a sensitivity analysis. Furthermore, the primary analysis was repeated without stratification by trials (stratified by type of diabetes [T2DM and T1DM]) and with inclusion of treatment, sex, and race as fixed factors and age as a covariate. The additional analyses on alternative composite endpoints of MACE were performed using Cox Regression as described above.

To investigate the robustness of the Cox Regression estimate when there were a large number of trials with no events in one or both treatment arms, a sensitivity analysis was made using a stratified (by trial) Mantel-Haenszel approach, correcting for treatment arms with zero events by adding a small number in the calculations. To account for the fact that many trials were randomized 2:1 or 3:1, the small number added to zero was determined as the ratio of number of patients in the full analysis set in each treatment group divided by the total number of patients. So, for instance, in trials with 3:1 randomization, approximately 0.75 was added if the IDeg+IDegAsp had zero events, and only 0.25 was added if comparator arm had zero events.

7 Trial Population

Summary

- Overall, 5654 patients (4076 with T2DM and 1578 with T1DM) were randomized in IDeg phase 3 trials and 2414 patients (1866 with T2DM and 548 with T1DM) were randomized in the IDegAsp phase 3 trials.
- In the T2DM trials, 84% of patients randomized to IDeg+IDegAsp and 86% of patients randomized to comparator completed the trials. In the T1DM trials, 86% of patients randomized to IDeg+IDegAsp and 87% of patients randomized to comparator completed the trials. A small percentage of patients withdrew from the trials because of adverse events (T2DM: 2.2% with IDeg+IDegAsp and 1.5% with comparator; T1DM: 2.1% and 1.1%, respectively).
- The IDeg and IDegAsp clinical programs were global and included patients from all major regions in order to represent patients across various race and ethnic groups. Trial sites were selected in geographical regions where the populations of special interest were represented.
- In the IDeg+IDegAsp phase 3 trials 15% of patients from North America were Black or African American.
- The demographic and baseline characteristics were not unusual for the T2DM and T1DM patients enrolled in these types of studies, and were similar across treatment groups.

This section will review the disposition and characteristics of patients in the IDeg and IDegAsp phase 3 trials.

7.1 IDeg and IDegAsp Phase 3 Trial Population − NDA

The IDeg phase 3 clinical trials included in the NDA randomized 5654 patients (4076 with T2DM and 1578 with T1DM). The IDeg patient population was selected to represent populations with either T1DM or T2DM with insufficient glycemic control on current treatment (both insulin-naïve and previously insulin-treated), who would benefit from intensified treatment.

The IDegAsp phase 3 clinical trials randomized 2414 patients (1866 with T2DM and 548 with T1DM). The IDeg and IDegAsp phase 3 trial population included an adequate number of elderly patients with diabetes to assess efficacy and safety and allow treatment recommendation in this age group.

To ensure adequate exposure of patients across race and ethnicity, trial sites were selected in geographical regions where the populations of special interest were represented. The IDeg clinical program was global and included patients from all major regions; 41% of patients were from North

America (U.S. and Canada). All IDegAsp trials were conducted at sites across different continents except Trial 3597, which included sites in Japan, South Korea, Hong Kong, Malaysia and Taiwan only.

In the IDeg+IDegAsp phase 3 trials, 15% of patients from North America were Black or African American.

7.1.1 T2DM Trial Population

Patient disposition for the IDeg+IDegAsp T2DM trials is summarized in Table 14. Overall, 84% of patients randomized to IDeg+IDegAsp and 86% of patients randomized to comparator completed the T2DM trials. A small percentage of patients withdrew because of adverse events.

Table 14 Patient Disposition – IDeg+IDegAsp T2DM Trials

	IDeg+IDegAsp		Comparator		Total	
	N	%	N	%	N	%
Randomized	4200	100	2669	100	6869	100
Withdrawn at or after Randomization	679	16.2	381	14.3	1060	15.4
Withdrawn due to Adverse Event	92	2.2	39	1.5	131	1.9
Full Analysis Set	4178	99.5	2656	99.5	6834	99.5

N: Number of patients; %: Proportion of randomized patients
Comparator: IGlar (3582, 3579, 3672, 3586, 3668, 3590, 3593), BIAsp 30 (3592, 3597) and Sitagliptin (3580).

Key baseline characteristics are shown in Table 15 for the 6834 patients in the full analysis set population from the IDeg+IDegAsp T2DM phase 3 trials. In this population, 1675 patients (24.5%) were >65 years, consistent with the later onset of disease in T2DM. Mean BMI was similar between groups at baseline.

Table 15 Key Demographics and Baseline Characteristics – IDeg+IDegAsp T2DM Trials

	IDeg+IDegAsp N = 4178			Comparator N = 2656			Total N = 6834		
	Mean (SD)	**N**	**(%)**	**Mean (SD)**	**N**	**(%)**	**Mean (SD)**	**N**	**(%)**
Age (years)	58.3 (9.7)			57.7 (10.0)			58.0 (9.8)		
Age Group: ≤ 65 years		3139	75.1		2020	76.1		5159	75.5
Age Group: > 65 years		1039	24.9		636	23.9		1675	24.5
Sex: Females		1829	43.8		1192	44.9		3021	44.2
BMI (kg/m^2)	30.2 (5.3)			30.6 (5.3)			30.4 (5.3)		
Duration of Diabetes (years)	10.9 (7.1)			10.4 (6.8)			10.7 (7.0)		
HbA_{1C} (%)	8.4 (0.9)			8.4 (0.9)			8.4 (0.9)		
FPG (mg/dL)	165.0 (49.3)			167.0 (50.4)			165.8 (49.7)		
Race									
White		2749	65.8		1758	66.2		4507	65.9
Black or African American		265	6.3		156	5.9		421	6.2
Asian		1096	26.2		701	26.4		1797	26.3
Other #		68	1.6		41	1.5		109	1.6
Ethnicity									
Hispanic or Latino		434	10.4		293	11.0		727	10.6
Not Hispanic or Latino		3671	87.9		2310	87.0		5981	87.5
Not Applicable		73	1.7		53	2.0		126	1.8

Other #: Primarily American Indian or Alaska Native, Native Hawaiian or Pacific Islander
N: Number of Patients, %: Percentage of patients; SD: Standard deviation; Comparator: IGlar, BIAsp 30 and Sitagliptin. Full analysis set.

The mean duration of diabetes for T2DM patients in the IDeg trials (10.5 years) was slightly shorter than those in the IDegAsp trials (12.3 years). However, the mean duration of diabetes was similar across treatment groups (IDegAsp, 12.4 vs. comparator, 12.1 years; IDeg, 10.8 vs. comparator, 9.9 years).

For IDeg+IDegAsp T2DM trials, approximately 97% of all patients were reported to have a medical history/concomitant illness at the time of screening and the most frequent were hypertension (~69%), hyperlipidemia (~28%) and dyslipidemia (~22%). Medical history/concomitant illness was generally similar for IDeg or IDegAsp and comparator and was expected for a population of patients with T2DM.

Diabetes complications at the beginning of the T2DM trials were reported by 22% of patients in the IDeg trials and by 31% of patients in the IDegAsp trials. The proportions and types of these were generally similar for IDeg or IDegAsp versus comparator. Ophthalmic complications (mainly diabetic retinopathy) and neurological complications (mainly diabetic neuropathy) were the most frequently reported diabetes complications.

Patients in the five IDeg T2DM basal-only therapy trials were primarily insulin-naïve patients (except for a subgroup of patients in Trial 3668) who were treated with a wide range of OADs pretrial. The IDegAsp T2DM trials represented a spectrum of patients from insulin-naïve to insulin-treated. Overall, prior to the IDegAsp trials, the majority of T2DM patients were treated with insulin in addition to one or two OADs. For all IDeg and IDegAsp T2DM trials, pre-trial regimens were similar between IDeg or IDegAsp and comparator.

7.1.2 T1DM Trial Population

Patient disposition for the IDeg+IDegAsp T1DM trials is summarized in Table 16. In the T1DM trials, 86% of patients randomized to IDeg+IDegAsp and 87% of patients randomized to comparator completed the trials.

Table 16 Patient Disposition – IDeg+IDegAsp Phase 3 T1DM Trials

	IDeg+IDegAsp		Comparator		Total	
	N	%	N	%	N	%
Randomized	1470	100.0	656	100	2126	100.0
Withdrawn at or after Randomization	207	14.1	82	12.5	289	13.6
Withdrawn due to Adverse Event	31	2.1	7	1.1	38	1.8
Full Analysis Set	1469	99.9	656	100	2125	100.0

N: Number of patients; %: Proportion of randomized patients; Comparator: IDet and IGlar.

Key baseline characteristics are shown in Table 17 for the 2125 patients in the full analysis set population for the IDeg+IDegAsp T1DM trials.

Table 17 Key Demographics and Baseline Characteristics – IDeg+IDegAsp Phase 3 T1DM Trials

	IDeg+IDegAsp N = 1469			Comparator N = 656			Total N = 2125		
	Mean (SD)	**N**	**%**	**Mean (SD)**	**N**	**%**	**Mean (SD)**	**N**	**%**
Age (years)	42.1 (13.7)			43.0 (13.6)			42.4 (13.6)		
Age Group: ≤ 65 years		1381	94.0		612	93.3		1993	93.8
Age Group: > 65 years		88	6.0		44	6.7		132	6.2
Sex: Females		655	44.6		310	47.3		965	45.4
BMI (kg/m^2)	25.9 (3.9)			25.9 (4.1)			25.9 (4.0)		
Duration of Diabetes (years)	17.4 (11.9)			17.2 (11.5)			17.4 (11.7)		
HbA_{1C} (%)	7.9 (1.0)			7.9 (0.9)			7.9 (0.9)		
FPG (mg/dL)	175.2 (76.1)			180.4 (79.6)			176.8 (77.2)		
Race									
White		1222	83.2		542	82.6		1764	83
Black or African American		29	2.0		10	1.5		39	1.8
Asian		176	12.0		89	13.6		265	12.5
Other #		42	2.9		15	2.3		57	2.7
Ethnicity									
Hispanic or Latino		56	3.8		30	4.6		86	4.0
Not Hispanic or Latino		1396	95.0		618	94.2		2014	94.8
Not Applicable ¤		17	1.2		8	1.2		25	1.2

Other #: Primarily American Indian or Alaska Native, Native Hawaiian or Pacific Islander
N: Number of patients; %: Proportion of full analysis set. Comparator: IDet and IGlar; SD: Standard deviation. Full analysis set.

The duration of diabetes for T1DM patients (17.4 years) was longer than that seen in the T2DM patient population (10.7 years).

Approximately 90% of all patients with T1DM in both the IDeg and IDegAsp phase 3 trials were reported to have a medical history/concomitant illness at the time of screening. The most frequent were hypertension (28%), hyperlipidemia (18%) and diabetic retinopathy (17%) in the IDeg phase 3 trials, and hypertension (35%), diabetic retinopathy (27%), and diabetic neuropathy (18%) in the IDegAsp trial. Medical history/concomitant illness was generally similar across treatment groups in the IDeg and IDegAsp trials for T1DM patients and was not unusual for a population of patients with T1DM.

Diabetes complications at screening were reported by approximately 24% of T1DM patients in the IDeg trials and by approximately 35% of all patients in IDegAsp trial. Ophthalmic complications (mainly diabetic retinopathy) and neurological complications (mainly diabetic neuropathy) were most frequently reported, and were generally similar between treatment groups.

Almost all of the T1DM patients who entered the IDeg and IDegAsp trials were treated with basal-bolus therapy at screening. In the IDeg trials, IGlar was the basal insulin used most frequently (62%), followed by IDet (27%); IAsp was the bolus insulin most frequently used (53%), followed by insulin lispro (34%). Pre-trial insulin usage by T1DM patients in the IDegAsp trials was generally similar to that of the IDeg trials with the exception of premixed insulin that was used by 0.4% of patients in the IDeg trials and by 9.4% of patients in the IDegAsp trial. The treatment groups were well balanced with respect to the use of pretrial insulin products.

Relevant to interpretation of the trial results are the proportions of patients who were randomized to treatment with the same insulin product they were taking prior to the trials. As shown in Table 18, in IDeg Trials 3583 and 3770, the majority of patients randomized to comparator treatment with IGlar were already treated with IGlar prior to trial entry.

Table 18 Proportion of Patients Treated with Comparator Basal Insulin Pre-Trial – IDeg+IDegAsp T1DM Trials

Trials	Primary Treatment Comparison	Pre-Trial Insulin	IDeg or IDegAsp (%)	Comparator (%)
IDeg Trials				
T1DM BB 12m (3583)	IDeg vs. IGlar	IGlar	71.2	68.8
T1DM BB 6m (3585)	IDeg vs. IDet	IDet	37.1	34.6
T1DM BB 6m (3770)	IDeg Flexible Dosing vs. IGlar	IGlar	65.2	61.0
IDegAsp Trial				
T1DM BB 6m (3594)	IDegAsp vs. IDet	IDet	15.6	13.2

BB: basal bolus insulin treatment. Full Analysis Set.

7.2 IDeg and IDegAsp Phase 3 Trial Population – Including Additional Phase 3 Trials Completed as of May 1, 2012

As described in Section 6.1, an additional cut off of May 1, 2012 was used to provide additional exposure for AEs and MACE analyses as requested by the FDA. The May 1, 2012 cut off contained an additional nine completed phase 3 trials (of which six were extensions of ongoing trials). Table 19 shows the patient disposition of all individual trials included in the May 1, 2012 dataset. Approximately 35% of the randomized patients in the trials completed as of May 1, 2012 entered an extension period.

Table 19 Randomized Patient Disposition − IDeg+IDegAsp Phase 3 Trials Completed as of May 1, 2012

	IDeg+IDegAsp		Comparator		Total	
	N	%	N	%	N	%
Randomized	6412	100.0	3474	100.0	9886	100.0
Completed the main trial	5477	85.4	3008	86.6	8485	85.8
Started the extension	2401	37.4	1081	31.1	3482	35.2
Completed the extension	2251	35.1	1009	29.0	3260	33.0

N= Number of patients; %: proportion of randomized patients.

When only the 7 trials with extension periods were considered, a total of 3264 patients were randomized to IDeg or IDegAsp and 1428 to comparator, with 69% and 71% completing the extensions, respectively (Table 20).

Table 20 Randomized Patient Disposition − IDeg+IDegAsp Phase 3 Trials with Extensions Completed as of May 1, 2012

	IDeg+IDegAsp		Comparator		Total	
	N	%	N	%	N	%
Randomized	3264	100.0	1428	100.0	4692	100.0
Completed the main trial	2728	83.6	1223	85.6	3951	84.2
Started the extension	2401	73.6	1081	75.7	3482	74.2
Completed the extension	2251	69.0	1009	70.7	3260	69.5

N= Number of patients; %: proportion of randomized patients.

Patient disposition of all IDeg and IDegAsp phase 3 trials completed as of May 1, 2012 (including extensions) is summarized by individual trial in Appendix 1, Table 14.

8 Clinical Efficacy and Dosing

Summary

- In all IDeg phase 3 trials, the efficacy of once-daily IDeg was established as IDeg was noninferior to insulin comparators in reducing HbA_{1c} (the measure of long-term glycemic control) in all patient populations tested (insulin-naïve T2DM, insulin-treated T2DM, and T1DM). IDeg was noninferior to insulin comparators as basal-only therapy and as part of a basal-bolus regimen (i.e., in combination with rapid-acting mealtime insulin).
- In both T2DM and T1DM, HbA_{1c} reductions at end of trial were noninferior between IGlar dosed once daily at the same time from day to day and IDeg dosed once daily in a flexible schedule where the injection time was deliberately alternated from morning to evening on successive days resulting in dosing intervals of ~8 to ~40 hours between injections.
- In all IDegAsp phase 3 trials, efficacy was established as IDegAsp (once-or twice daily) was noninferior to insulin comparators in reducing HbA_{1c}.
- Noninferiority in change in HbA_{1c}, the primary endpoint of all trials, indicates that the treat-to-target design of the studies was successful in reaching the desired outcome of similar levels of glycemic control between IDeg/IDegAsp and comparator treatment. More importantly, noninferiority in glycemic control allows for meaningful comparisons of hypoglycemia between IDeg and comparators.
- In the IDeg phase 3 trials, consistently larger reductions in FPG were achieved with once-daily IDeg than with comparator products, with a statistically significant difference in favor of IDeg in five of the nine trials.
- IDegAsp administered twice daily lowered FPG significantly more than twice-daily BIAsp 30.
- Improvements in glycemic control were achieved with similar doses of IDeg or with IDegAsp versus comparator insulin products.

In this section, key efficacy results (HbA_{1c}, FPG, and dosing) for IDeg are presented across the spectrum of diabetes beginning with insulin initiation in T2DM and finishing with a discussion of its use with IAsp as part of basal bolus therapy in both T2DM and T1DM. IDegAsp results are presented according to the frequency of dosing (once daily and then twice daily) in T2DM and then as part of a basal-bolus regimen in T1DM.

8.1 HbA_{1c}

HbA_{1c} is the most widely accepted measure of overall, long-term glycemic control and is predictive of diabetes complications. The primary endpoint (change in HbA_{1c} from baseline to end of trial)

was subject to a noninferiority analysis in all trials except Trial 3580 (superiority vs. sitagliptin). In these treat-to-target IDeg and IDegAsp trials, noninferiority of IDeg/IDegAsp versus comparator with respect to change in HbA_{1c} was confirmed, as the upper limit of the 95% CI for the estimated treatment difference (IDeg/IDegAsp − comparator) was well below the predefined noninferiority limit of 0.4%.

8.1.1 HbA_{1c} with IDeg Therapy

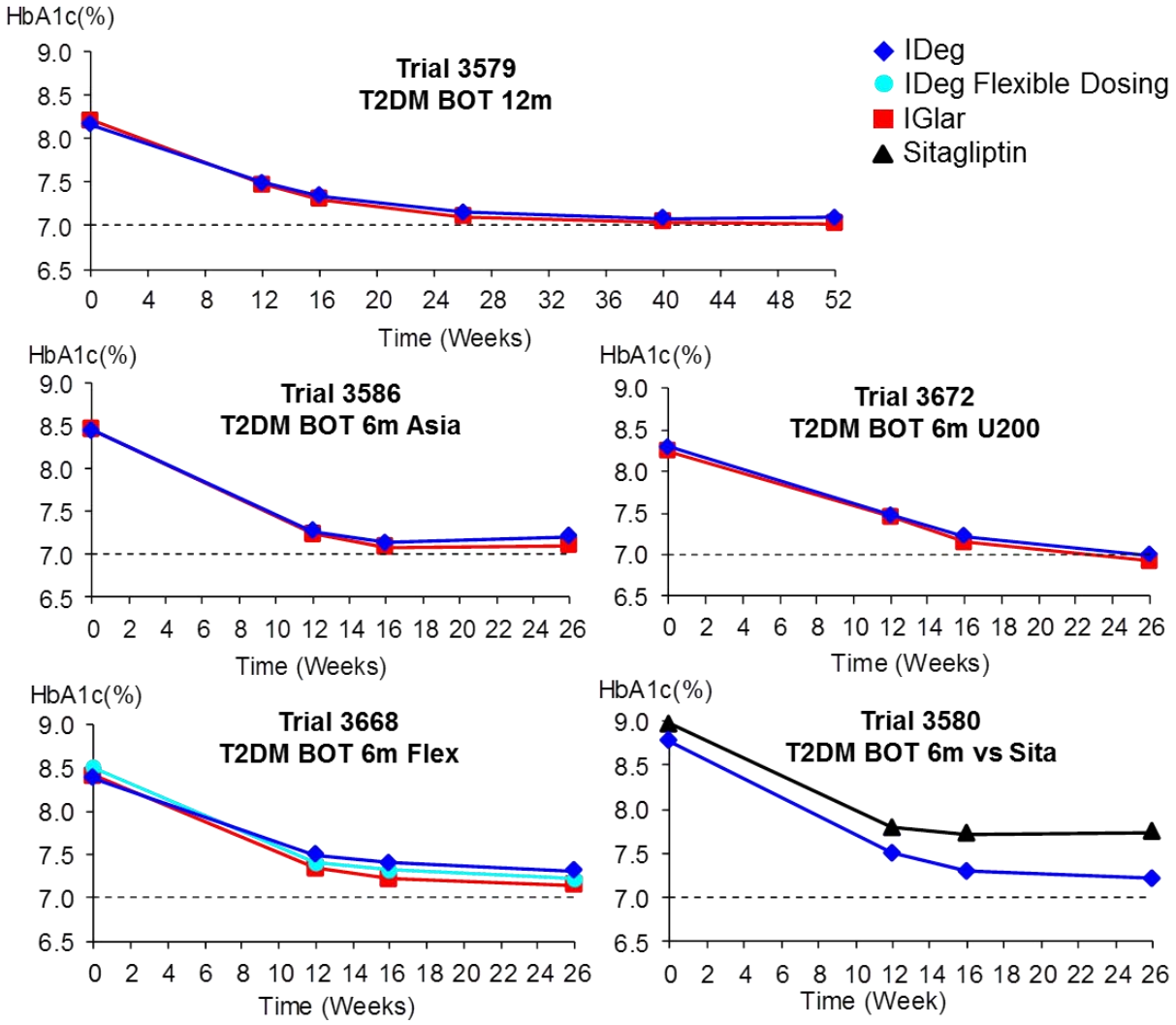
8.1.1.1 HbA_{1c} with IDeg Therapy in T2DM

Basal-only Therapy in T2DM

In all five trials in which IDeg was used as basal-only therapy + OADs, IDeg effectively improved long-term glycemic control in insulin-naïve patients with T2DM (Figure 20). The observed reductions in HbA_{1c} ranged from approximately 1.1−1.6%-points with IDeg and 1.2−1.4 %-points with comparator products. HbA_{1c} decreased primarily during the first 12−16 weeks (Figure 20), the period in which basal insulin dose was adjusted the most. Modest decreases were observed in HbA_{1c} during the remaining part of the trials and improved glycemic control was sustained up to 52 weeks of treatment. The mean observed HbA_{1c} at end of trial was between 7.0 and 7.3% with IDeg and between 6.9 and 7.1% with IGlar (7.7% with sitagliptin).

In Trial 3668, observed mean HbA_{1c} at end of trial was comparable between IDeg dosed once daily in the evening (7.3%) and IDeg dosed in a flexible schedule with alternating morning and evening injections, thus alternating wide and narrow dosing intervals (7.2%) (Figure 20). The observed mean HbA_{1c} at end of trial with IDeg dosed any time of day in Trial 3580 (7.2%) was comparable to the other trials in which IDeg was dosed at a fixed time (Figure 20).

Overall, good glycemic control was achieved with IDeg in all five T2DM basal-only therapy trials, with end of trial HbA_{1c} close to 7%.



Flexible dosing schedule (see Section 6.2). Missing data are imputed by LOCF. Full analysis set.

Figure 20 Mean HbA_{1c} (%) by Treatment Week – IDeg Basal-only Therapy T2DM Trials

The noninferiority of IDeg versus insulin comparators with respect to change in HbA_{1c} was confirmed since the upper limit of the 95% CI for the estimated treatment difference (IDeg−comparator) was well below the predefined noninferiority limit of 0.4% (Table 21). This included Trial 3668, in which IDeg was dosed with alternating short (8−12 hours) and long (36−40 hours) intervals.

In superiority Trial 3580, superiority of IDeg compared with sitagliptin with respect to change in HbA_{1c} was confirmed in Trial 3580 as the upper limit of the 95% CI for the estimated treatment difference was <0 (Table 21).

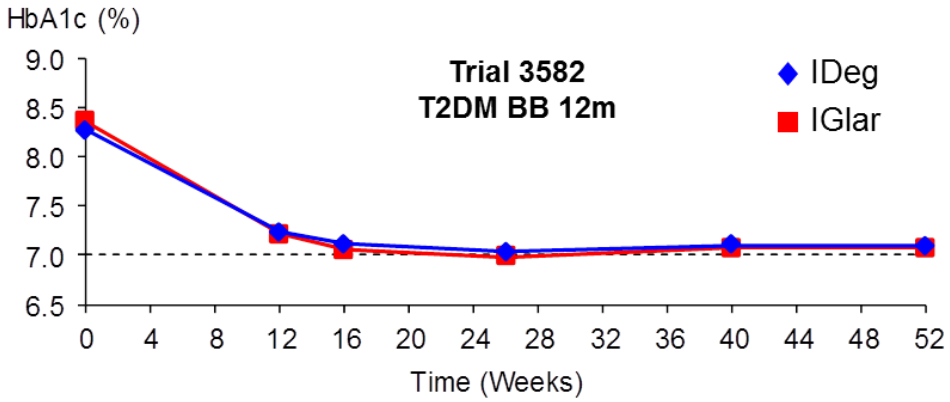
Table 21 HbA_{1c} (%) Change from Baseline at End-of-trial – Statistical Analysis – IDeg Basal-only Therapy – T2DM

		IDeg		Comparator		IDeg - Comparator
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BOT 12m (3579)	IDeg vs. IGlar	773	-1.06 (0.04)	257	-1.15 (0.06)	0.09 [-0.04; 0.22]
T2DM BOT 6m U200 (3672)	IDeg vs. IGlar	228	-1.18 (0.09)	229	-1.22 (0.08)	0.04 [-0.11; 0.19]
T2DM BOT 6m Asia (3586)	IDeg vs. IGlar	289	-1.42 (0.06)	146	-1.52 (0.07)	0.11 [-0.03; 0.24]
T2DM BOT 6m (3668)	IDeg Flexible Dosing vs. IGlar	229	-1.17 (0.08)	230	-1.21 (0.08)	0.04 [-0.12; 0.20]
T2DM BOT 6m (3580)	IDeg vs. Sitagliptin	225	-1.52 (0.10)	222	-1.09 (0.10)	-0.43 [-0.61; -0.24]*

*Difference significantly different from 0.
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). The primary treatment comparison of interest in Trial 3668 was IDeg Flexible Dosing – IGlar (shown in this table); a secondary treatment comparison was IDeg Flexible Dosing – IDeg (estimated treatment difference -0.13 $[-0.29; 0.03]_{95\%CI}$). See Section 6.2 for a description of the IDeg flexible dosing schedule. Full analysis set.

Basal-bolus Therapy in T2DM

In Trial 3582, the T2DM trial in which IDeg was used as part of a basal-bolus insulin regimen with IAsp, substantial improvements in HbA_{1c} from baseline to the end of trial were observed (Figure 21). Observed reductions were 1.2%-points with IDeg and 1.3%-points with IGlar. HbA_{1c} decreased primarily during the first 12 weeks of the 52-week trial. After 52 weeks, the mean observed HbA_{1c} was close to 7.1% in both treatment groups.



Missing values are imputed by LOCF. Full analysis set.

Figure 21 Mean HbA_{1c} (%) by Treatment Week – IDeg Basal-bolus T2DM Trial 3582

In basal-bolus T2DM Trial 3582, noninferiority of IDeg versus IGlar with respect to change in HbA_{1c} was confirmed, as the upper limit of the 95% CI for the estimated treatment difference (IDeg−IGlar) was below 0.4% (Table 22).

Table 22 HbA_{1c} (%) Change from Baseline at End-of-trial – Statistical Analysis – IDeg Basal-bolus T2DM Trial 3582

		IDeg		IGlar		IDeg – IGlar
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BB 12m (3582)	IDeg vs. IGlar	744	-1.10 (0.06)	248	-1.18 (0.08)	0.08 [-0.05; 0.21]

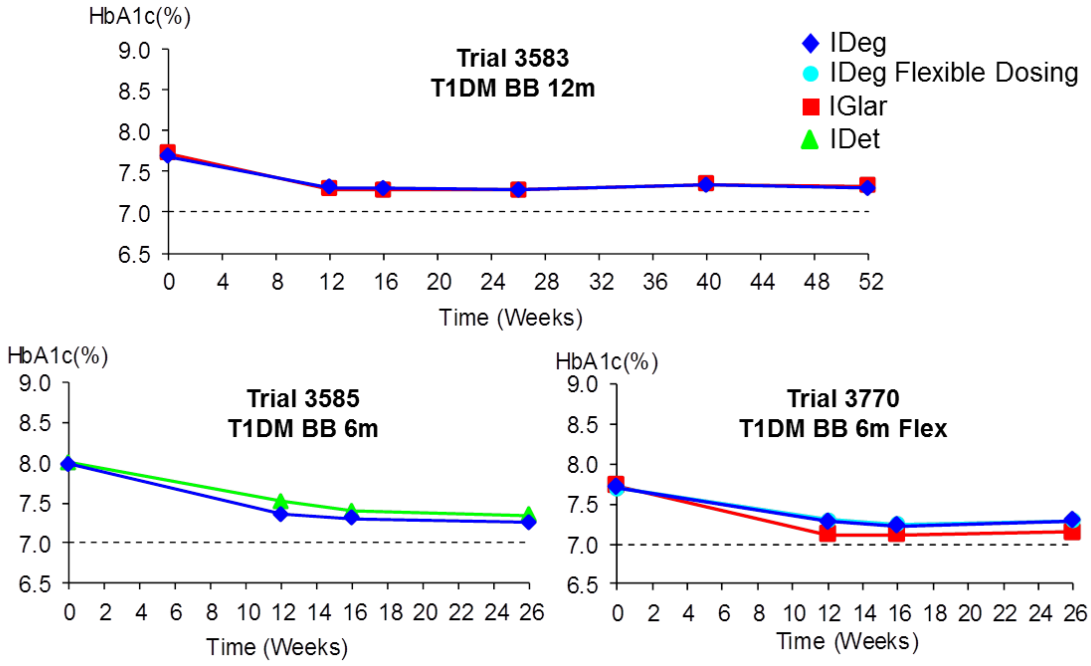
N: Number of patients contributing to analysis; LS mean: least-square mean; SE: standard error. Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). Full analysis set.

8.1.1.2 HbA_{1c} with IDeg Therapy in T1DM

Basal-bolus Therapy in T1DM

IDeg was compared with IGlar (Trials 3583 and 3770) or IDet (Trial 3585), both with mealtime IAsp as part of a basal-bolus regimen in T1DM where basal and bolus insulin is required therapy.

In all three T1DM trials in which IDeg was used OD in a basal-bolus treatment regimen with mealtime IAsp, clinically relevant improvements in HbA_{1c} from baseline to the end of the trial were observed with both IDeg and comparator (observed reductions ranged from 0.4 to 0.7%-points) (Figure 22). Similar to the T2DM trials, the reduction in mean HbA_{1c} was evident after the first 12 weeks of treatment, and the lower HbA_{1c} level was maintained for at least 52 weeks based on the results from Trial 3583. A mean HbA_{1c} of 7.2−7.4% at end of trial was obtained with both IDeg and comparator products in the T1DM trials.



See Section 6.2 for a description of the IDeg flexible dosing schedule; LOCF-imputed data; full analysis set.

Figure 22 Mean HbA_{1c} (%) by Treatment Week – IDeg T1DM Trials

Noninferiority of IDeg to IGlar was confirmed in Trial 3583; noninferiority of the IDeg flexible dosing arm to IGlar was confirmed in Trial 3770; and noninferiority of IDeg to IDet was confirmed in Trial 3585, as the upper limits of the 95% CIs were ≤0.4% for all the estimated treatment differences of change in HbA_{1c}. In Trial 3770, noninferiority of the IDeg flexible dosing arm to IGlar was confirmed although the 95% CI lower limit for the change in HbA_{1c} was >0 (Table 23).

Table 23 HbA_{1c} (%) Change from Baseline at End of Trial – Statistical Analysis – IDeg T1DM Trials

		IDeg		Comparator		IDeg - Comparator
Trial	Comparison	N	LS Mean (SE)	N	LS Mean (SE)	Difference [95% CI]
T1DM BB 12m (3583)	IDeg vs. IGlar	472	-0.36 (0.05)	157	-0.34 (0.07)	-0.01 [-0.14; 0.11]
T1DM BB 6m (3585)	IDeg vs. IDet	302	-0.71 (0.06)	153	-0.61 (0.07)	-0.09 [-0.23; 0.05]
T1DM BB 6m (3770)	IDeg Flexible Dosing vs. IGlar	164	-0.40 (0.05)	164	-0.57 (0.05)	0.17 [0.04; 0.30]*

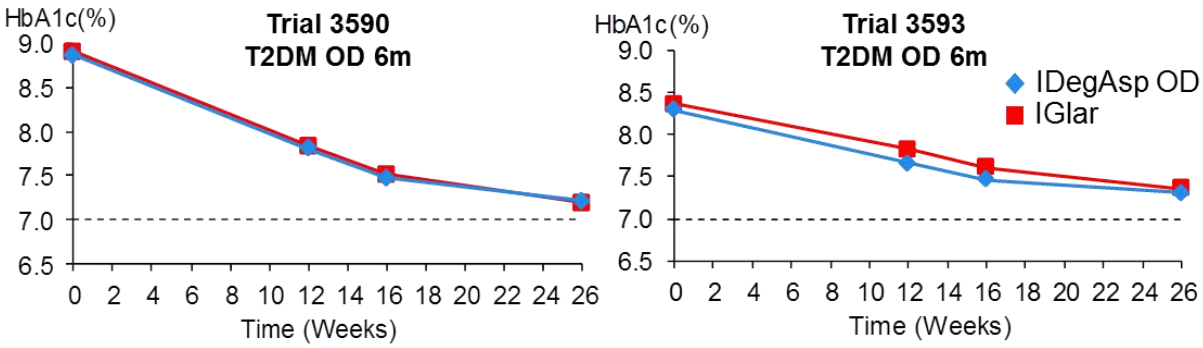
*Difference significantly different from 0;
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). The primary treatment contrast of interest in Trial 3770 was IDeg flexible dosing – IGlar (shown in this table); a secondary treatment comparison was IDeg Flexible Dosing – IDeg (estimated treatment difference 0.01 $[-0.13; 0.14]_{95\%CI}$). See Section 6.2 for a description of the IDeg flexible dosing schedule. Full analysis set.

8.1.2 HbA_{1c} with IDegAsp Therapy

8.1.2.1 HbA_{1c} with IDegAsp Therapy in T2DM

Once-daily IDegAsp Therapy in T2DM

IDegAsp OD effectively improved long-term glycemic control in both insulin-naïve patients (Trial 3590) and patients treated with insulin pretrial (Trial 3593) (Figure 23). The observed mean reduction from baseline to end of trial in the IDegAsp group was 1.65 %-point in Trial 3590 and 0.98 %-point in Trial 3593, similar to the reductions after IGlar OD treatment. A mean HbA_{1c} of 7.2−7.4% at end of trial was obtained with both IDegAsp and IGlar in the two trials.



LOCF-imputed data. Full analysis set.

Figure 23 Mean HbA_{1c} (%) by Treatment Week – IDegAsp OD T2DM Trials

IDegAsp OD was noninferior (95% CI for the estimated mean treatment difference ≤0.4%) to IGlar OD in terms of lowering HbA_{1c} after 26 weeks in both insulin-naïve patients (Trial 3590) and patients treated with insulin pretrial (Trial 3593).

Table 24 HbA_{1c} (%) Change from Baseline at End of Trial – Statistical Analysis – IDegAsp OD T2DM Trials

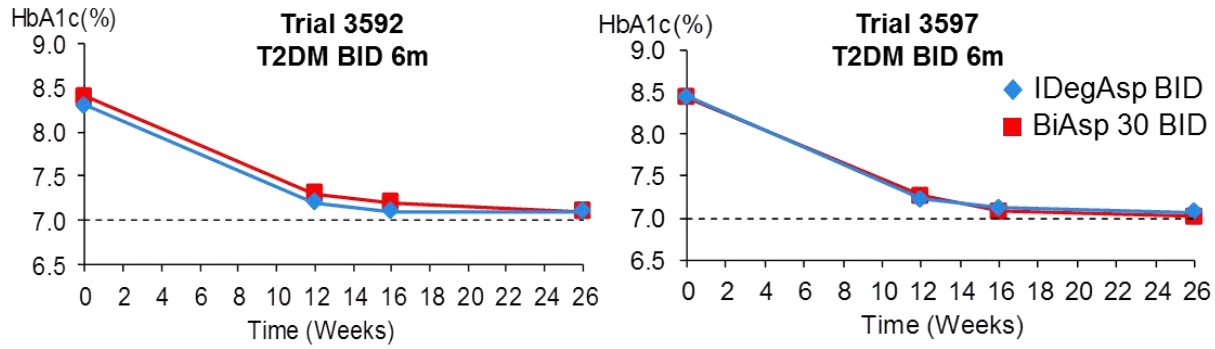
		IDeg		IGlar		IDeg – IGlar
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM OD 6m (3590)	IDegAsp vs. IGlar	266	-1.72 (0.08)	263	-1.75 (0.08)	0.03 [-0.14; 0.20]
T2DM OD 6m (3593)	IDegAsp vs. IGlar	230	-1.00 (0.08)	233	-0.97 (0.08)	-0.03 [-0.20; 0.14]

N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). Full analysis set.

Twice-daily IDegAsp Therapy in T2DM

As was observed in the OD trials, IDegAsp BID effectively improved long-term glycemic control in patients with T2DM (Figure 24). The observed mean reduction from baseline to end of trial in the

IDegAsp group was 1.28 %-point in Trial 3592 and 1.38 %-point in Trial 3597, similar to the reduction after BIAsp 30 BID treatment. Treatment with IDegAsp BID for 26 weeks led to an observed mean HbA_{1c} of 7.0% and 7.1% in Trials 3592 and 3597, respectively.



LOCF-imputed data. Based on Full Analysis Set.

Figure 24 Mean HbA_{1c} (%) by Treatment Week – IDegAsp BID T2DM Trials

Noninferiority of IDegAsp BID compared with BIAsp 30 was confirmed in Trials 3592 and 3597 as the upper limits of the 95% CIs were ≤0.4 % for all comparisons of estimated change in HbA_{1c} (Table 25).

Table 25 HbA_{1c} (%) Change from Baseline at End of Trial – Statistical Analysis – IDegAsp BID T2DM Trials

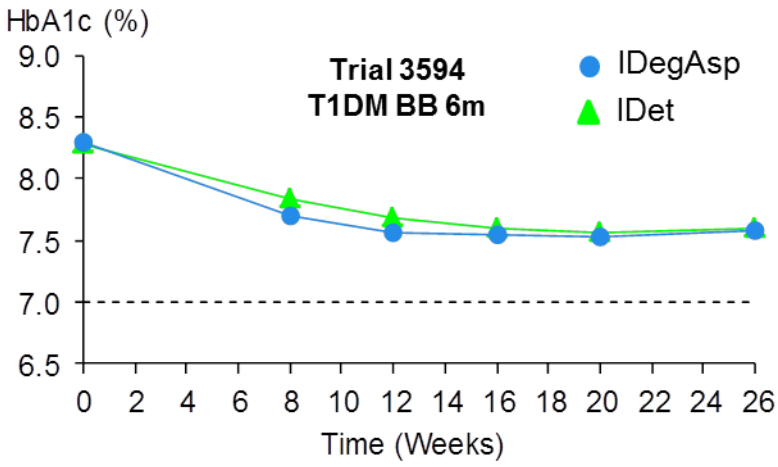
		IDegAsp BID		BIAsp 30		IDegAsp BID – BIAsp 30
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BID 6m (3592)	IDegAsp BID vs. BIAsp 30	224	-1.31 (0.09)	222	-1.29 (0.10)	-0.03 [-0.18; 0.13]
T2DM BID 6m (3597)	IDegAsp BID vs. BIAsp 30	280	-1.39 (0.05)	142	-1.44 (0.07)	0.05 [-0.10; 0.20]

N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error; BID: twice daily.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). Full analysis set.

8.1.2.2 HbA_{1c} with IDegAsp Therapy in T1DM

Basal-bolus Therapy in T1DM

In Trial 3594, patients with T1DM treated with IDegAsp OD in combination with IAsp at remaining meals effectively improved long-term glycemic control (Figure 25). After 26 weeks, the observed HbA_{1c} reduction was 0.73 %-point in the IDegAsp group, comparable to the 0.68 %-point reduction in the IDet group. A mean HbA_{1c} of 7.6% at end of trial was obtained with both IDegAsp and IDet.



LOCF imputed data. Full Analysis Set.

Figure 25 Mean HbA_{1c} (%) by Treatment Week – IDegAsp OD T1DM Trial 3594

IDegAsp OD was noninferior to IDet in terms of lowering HbA_{1c} after 26 weeks of treatment as the upper limit of the 95% CI for the estimated mean treatment difference was 0.08%, well below the noninferiority limit set to ≤0.4% (Table 26).

Table 26 HbA_{1c} (%) Change from Baseline at End of Trial – Statistical Analysis – IDegAsp T1DM Trial 3594

		IDeg Asp OD		IDet		IDeg Asp OD – IDet
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T1DM OD BB 6m (3594)	IDegAsp OD vs. IDet	366	-0.75 (0.06)	182	-0.70 (0.08)	-0.05 [-0.18; 0.08]

N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error; OD: once daily.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Noninferiority criterion: Upper confidence limit of difference less than or equal to 0.4 (%). Full analysis set.

8.1.3 HbA_{1c} in Subgroups

As shown in Appendix 1, Table 5 (pooled IDeg T2DM trials), Appendix 1, Table 6 (pooled IDeg T1DM trials), Appendix 1, Table 7 (pooled IDegAsp T2DM trials) and Appendix 1, Table 8 (IDegAsp T1DM Trial 3594) in the phase 3 trials, there was no consistent pattern in HbA_{1c} reductions by age group, ethnicity, race, or baseline renal function for the IDeg/IDegAsp or comparator treatment groups. Moreover, there was no consistent pattern in HbA_{1c} reductions by other key demographic or disease characteristics such as sex, BMI, or duration of diabetes for the IDeg/IDegAsp or comparator treatment groups.

8.2 Fasting Plasma Glucose

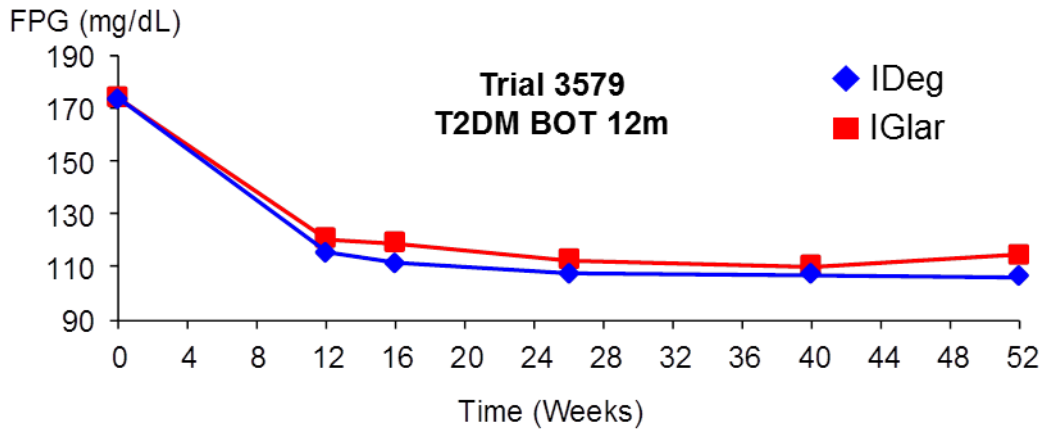
In all IDeg and IDegAsp trials, FPG was measured at selected timepoints and at end of trial, and analyzed at a central laboratory.

8.2.1 FPG with IDeg Therapy

8.2.1.1 FPG with IDeg Therapy in T2DM

Basal-only Therapy in T2DM

In the five basal-only T2DM trials, FPG decreased with both IDeg and comparator, and the observed mean FPG at end of trial was slightly lower with IDeg than with comparator products. As shown in a representative plot of FPG over time from T2DM BOT 12m Trial 3579, reductions in FPG were evident after 12 weeks of treatment (first postbaseline assessment) and were maintained. FPG reductions occurred earlier than the HbA_{1c} reductions (shown in Figure 20). Thus, the FPG reductions contributed to the improvements in long-term glycemic control as measured by HbA_{1c}.



FPG: fasting plasma glucose; BOT: basal-only therapy. Missing values are imputed by LOCF. Full analysis set.

Figure 26 Mean FPG by Treatment Week – IDeg Basal-only Therapy – T2DM

IDeg was associated with a consistently larger reduction in FPG (central laboratory) than comparator products in the five basal-only therapy T2DM trials, with a statistically significant difference in favor of IDeg in four of the five trials (Table 27).

Table 27 FPG (mg/dL) – Change from Baseline at End of Trial – Statistical Analysis – IDeg Basal-only Therapy – T2DM

		IDeg		Comparator		IDeg - Comparator
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BOT 12m (3579)	IDeg vs. IGlar	762	-68.01 (1.55)	256	-60.18 (2.50)	-7.83 [-13.34; -2.31]*
T2DM BOT 6m U200 (3672)	IDeg vs. IGlar	228	-71.08 (3.68)	226	-63.49 (3.60)	-7.59 [-14.09; -1.09]*
T2DM BOT 6m Asia (3586)	IDeg vs. IGlar	288	-54.60 (2.35)	145	-53.04 (2.91)	-1.57 [-7.31; 4.18]
T2DM BOT 6m (3580)	IDeg vs. Sita	221	-61.42 (4.25)	218	-22.35 (4.15)	-39.07 [-46.75;-31.39]*
T2DM BOT 6m (3668)	IDeg Flexible Dosing vs. IGlar	226	-55.04 (3.66)	225	-47.51 (3.55)	-7.53 [-14.72; -0.35]*

*Difference significantly different from 0;
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. The primary treatment contrast of interest in Trial 3668 was IDeg flexible dosing – IGlar (shown in this table); a secondary treatment comparison was IDeg Flexible Dosing – IDeg (estimated treatment difference -0.88 $[-8.07; 6.32]_{95\%CI}$). See Section 6.2 for a description of the IDeg flexible dosing schedule. Full analysis set.

The lower laboratory-measured FPG observed with IDeg was not counteracted by higher plasma glucose values at other times of the day relative to comparator insulin products since both groups had similar self-measured plasma glucose values at end of study for all nine timepoints measured (before and after meals, at bedtime, and during the night).

Basal-bolus Therapy in T2DM

In patients with advanced T2DM studied in basal-bolus Trial 3582, the observed reductions in FPG (central laboratory) over 52 weeks were substantial: 44 mg/dL with IDeg and 39 mg/dL with IGlar. However, the estimated treatment differences were not significantly different (Table 28).

Table 28 FPG (mg/dL) – Change from Baseline at End of Trial – Statistical Analysis – IDeg Basal-bolus T2DM Trial 3582

		IDeg		IGlar		IDeg - IGlar
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BB 12m (3582)	IDeg vs. IGlar	740	-40.57 (3.12)	248	-35.32 (3.89)	-5.24 [-11.62; 1.14]

N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Full analysis set.

8.2.1.2 FPG with IDeg Therapy in T1DM

Basal-bolus therapy in T1DM

In patients with T1DM, FPG decreased substantially both with IDeg and comparator products in a basal-bolus regimen. With IDeg, the reduction in FPG was evident at the first postbaseline

assessment (12 weeks), and the lower FPG was generally maintained until end of trial. The observed reductions in mean FPG ranged from 22.9 to 46.8 mg/dL with IDeg and from 11.3 to 25.1 mg/dL with comparator.

The estimated reduction in FPG was larger with IDeg than with comparator products (Table 29), which was statistically significant in Trial 3585 (IDeg versus IDet). In Trial 3770, 26 weeks of treatment with IDeg (dosed in the evening) resulted in a larger reduction in estimated FPG compared with the IDeg flexible dosing arm which involved dosing at alternating narrow and wide dosing intervals (statistically significant).

Table 29 FPG (mg/dL) – Change from Baseline to End of Trial – Statistical Analysis – IDeg T1DM Trials

		IDeg		Comparator		IDeg - Comparator
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T1DM BB 12m (3583)	IDeg vs. IGlar	465	-27.60 (5.16)	155	-21.63 (6.91)	-5.97 [-18.50; 6.56]
T1DM BB 6m (3585)	IDeg vs. IDet	301	-43.31 (4.98)	148	-13.47 (6.26)	-29.84 [-42.64;-17.05]*
T1DM BB 6m (3770)	IDeg Flexible Dosing vs. IGlar	161	-24.74 (5.39)	162	-23.91 (5.41)	-0.83 [-15.35; 13.70]

*Difference significantly different from 0;
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. The primary treatment contrast of interest in Trial 3770 was IDeg flexible dosing – IGlar (shown in this table); a secondary treatment comparison was IDeg Flexible Dosing – IDeg (estimated treatment difference 17.09 [2.63; 31.55]$_{95\%CI}$*). See Section 6.2 for a description of the IDeg flexible dosing schedule. Full analysis set.

8.2.2 FPG with IDegAsp Therapy

8.2.2.1 FPG with IDegAsp Therapy in T2DM

Once-daily IDegAsp Therapy in T2DM

FPG decreased during the IDegAsp OD trials (Trial 3590 and 3593) in both the IDegAsp OD and comparator treatment groups. The decrease was 60 mg/dL for IDegAsp OD and 72 mg/dL for IGlar OD in pretrial insulin-naïve patients (Trial 3590) and 30 mg/dL for IDegAsp OD and 34 mg/dL for IGlar OD in patients treated with insulin pretrial (Trial 3593).

FPG reductions were significantly greater with IGlar OD compared with IDegAsp OD in Trial 3590, but not Trial 3593 (Table 30). It should be noted that the basal component of total insulin in the IDegAsp formulation was 70%.

Table 30 FPG (mg/dL) – Change from Baseline to End of Trial – Statistical Analysis – IDegAsp OD T2DM Trials

		IDegAsp OD		IGlar		IDegAsp OD - IGlar
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM OD 6m (3590)	IDegAsp vs. IGlar	261	-63.26 (3.62)	261	-72.50 (3.36)	9.24 [1.68; 16.80]*
T2DM OD 6m (3593)	IDegAsp vs. IGlar	228	-28.90 (3.74)	231	-34.86 (3.63)	5.96 [-1.97; 13.89]

*Difference significantly different from 0;
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed using LOCF. Full analysis set.

Twice-daily IDegAsp Therapy in T2DM

FPG decreased during the IDegAsp BID trials (Trial 3592 and 3597) and in both the IDegAsp BID and comparator treatment groups. The observed mean FPG reduction in Trial 3592 was 56 mg/dL for IDegAsp BID and 32 mg/dL for BIAsp 30 BID. In Trial 3597 the observed mean FPG reduction was 46 mg/dL for IDegAsp BID and 27 mg/dL for BIAsp. IDegAsp BID was superior to BIAsp 30 BID in terms of lowering FPG in Trials 3592 and 3597 (Table 31).

Table 31 FPG (mg/dL) – Change from Baseline to End of Trial – Statistical Analysis – IDegAsp BID T2DM Trials

		IDegAsp BID		BIAsp 30		IDegAsp BID–BIAsp 30
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T2DM BID 6m (3592)	IDegAsp BID vs. BIAsp 30	224	-50.38 (4.10)	220	-29.81 (4.40)	-20.57 [-27.51;-13.63]*
T2DM BID 6m (3597)	IDegAsp BID vs. BIAsp 30	280	-45.31 (2.10)	140	-26.15 (2.85)	-19.15 [-25.69;-12.62]*

*Difference significantly different from 0;
N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Full analysis set.

8.2.2.2 FPG with IDegAsp Therapy in T1DM

Basal-bolus Therapy in T1DM

FPG decreased in both the IDegAsp OD and IDet treatment groups during Trial 3594. The mean decrease in FPG was smaller for IDegAsp OD compared with IDet after 26 weeks likely due to the lower mean baseline value for IDegAsp OD (186 mg/dL) compared with IDet (198 mg/dL). There were no statistically significant differences between IDegAsp OD and IDet following 26 weeks of treatment (Table 32).

Table 32 FPG (mg/dL) – Change from Baseline to End of Trial – Statistical Analysis – IDegAsp OD T1DM Trial 3594

		IDegAsp OD		IDet		IDegAsp OD–IDet
Trial	**Comparison**	**N**	**LS Mean (SE)**	**N**	**LS Mean (SE)**	**Difference [95% CI]**
T1DM OD BB 6m (3594)	IDegAsp OD vs. IDet	365	-29.74 (6.04)	181	-33.84 (7.04)	4.09 [-8.25; 16.43]

N: Number of patients contributing to analysis; LS Mean: least-square mean; SE: standard error.
Endpoint was analyzed by an ANOVA model (see Section 6.4.1). Missing values are imputed by LOCF. Full analysis set.

8.3 Insulin Dose

Insulin dosing guidelines for IDeg and IDegAsp specified the starting dose, the self-monitored plasma glucose target and the recommended dose adjustments at different plasma glucose levels, all to ensure uniformity between trials and across trial sites. (See Section 6.2 for details on basal insulin titration). In an effort to achieve glycemic targets, doses were adjusted individually based on SMPG measurements, taking into consideration diet, activity level, and other lifestyle factors. Because IDeg and IGlar have the same molar potency, the same titration algorithm was used by both treatment groups.

8.3.1 IDeg Insulin Doses

Within IDeg trials, insulin dose variations between trials were attributed to differences in treatment regimens, differences in insulin requirements between patients with T1DM or T2DM, and baseline characteristics of the patients.

8.3.1.1 Insulin Doses in IDeg T2DM Trials

Overall, in the basal-only T2DM trials, in order to achieve comparable glycemic control, patients treated with IDeg required similar doses of basal insulin compared with patients treated with IGlar as demonstrated by a dose ratio close to 1 (Table 33).

Doses were individualized and hence varied between individuals. The main adjustments of basal insulin dose took place early in the trials, whereafter the basal insulin dose stabilized.

Table 33 Mean Daily Basal Insulin Dose (U) at End of Trial – IDeg Basal-only Therapy T2DM Trials

Trial	**IDeg Dose Mean (U)**	**IGlar Dose Mean (U)**	**Dose Ratio IDeg/IGlar**
T2DM BOT 12m (3579)	56.0	57.8	0.97
T2DM BOT 6m U200 (3672)	59.5	62.7	0.95
T2DM BOT 6m (3668) IDeg Flexible Dosing	46.4	44.5	1.04
T2DM BOT 6m Asia (3586)	19.0	24.2	0.79

BOT: basal-only therapy; 12m: 12-month trial; 6m: 6-month trial; U: units; See Section 6.2 for a description of the IDeg flexible dosing schedule.

In basal-bolus therapy in T2DM, the basal, bolus, and total insulin dose at end of trial varied greatly between individuals, which reflected the differences in the individual dose requirements in a population of patients with advanced T2DM.

Overall, patients in the IDeg group in Trial 3582 required a similar total daily insulin dose compared to patients treated with IGlar in order to achieve comparable glycemic control (Table 34).

Table 34 Mean Daily Basal-Bolus Insulin Doses (U) at End of Trial – IDeg T2DM Trial 3582

	IDeg Mean (U)	IGlar Mean (U)	Dose Ratio IDeg/IGlar
Basal Insulin Dose	73.5	67.2	1.09
Bolus Insulin Dose (IAsp)	70.3	72.6	0.97
Total Insulin Dose	143.1	139.0	1.03

U: units.

8.3.1.2 Insulin Doses in IDeg T1DM Trials

The mean daily basal insulin doses were similar with IDeg and comparators at end of trial, whereas the total daily insulin dose was consistently lower in the IDeg groups than in the comparator groups (Table 35).

In Trials 3583 and 3585 in T1DM, the mean bolus dose increased during the initial weeks of the trials in both groups. In Trial 3770, the mean bolus dose was reduced during the initial weeks in the IDeg groups while it remained approximately the same in the comparator group during the trial. The self-titration algorithm with frequent blood glucose measurements that was implemented in Trial 3770 may have caused more precaution in the adjustment of bolus insulin dose.

Mean total insulin dose and specifically, the basal dose remained close to the baseline level in the IDeg groups throughout Trial 3583 and Trial 3770, while the total insulin dose increased during the first weeks of treatment in the comparator groups. This is due to the fact that per protocol and product label, patients in the IGlar group decreased their dose of IGlar by 20% when transferring from other insulin products if those products were administered twice daily. This was not the case for the transfer to IDeg.

Table 35 Mean Daily Basal-Bolus Insulin Doses (U) at End of Trial – IDeg T1DM Trials

Trial Dose Type	IDeg Mean (U)	Comparator Mean (U)	Dose Ratio IDeg/Comparator
T1DM BB 12m vs. IGlar (3583)			
Basal Insulin Dose	29.2	31.4	0.93
Bolus Insulin Dose (IAsp)	32.4	34.9	0.93
Total Insulin Dose	61.4	66.2	0.93
T1DM BB 6m vs. IDet (3585)			
Basal Insulin Dose	24.9	28.5	0.88
Bolus Insulin Dose (IAsp)	36.0	41.2	0.87
Total Insulin Dose	60.6	68.9	0.88
T1DM BB 6m (3770) IDeg Flexible Dosing vs. IGlar			
Basal Insulin Dose	35.5	35.0	1.02
Bolus Insulin Dose (IAsp)	29.7	35.0	0.85
Total Insulin Dose	65.2	69.9	0.93

12m: 12-month trial; 6m: 6-month trial; IDet: insulin detemir; U: units; See Section 6.2 for a description of the IDeg flexible dosing schedule.

8.3.2 IDegAsp Insulin Doses

Within the IDegAsp trials, insulin dose variations between trials were mainly due to differences in treatment regimens, differences in insulin requirements between patients with T1DM or T2DM, and baseline characteristics of the patients.

8.3.2.1 Insulin Doses in IDegAsp T2DM Trials

The mean daily doses of IDegAsp OD and comparator (IGlar OD) were similar within and between Trials 3590 and 3593. The mean daily dose of IDegAsp and comparator (BIAsp30) were lower in Trial 3597 than Trial 3592 (both BID trials), due to the high proportion of Asian patients having lower BMI in Trial 3597. In Trial 3597, the mean daily IDegAsp dose was lower than comparator (BIAsp30).

Table 36 Total Mean Daily Insulin Doses at End of Trial – IDegAsp T2DM Trials

Trial		IDegAsp Mean (U)	Comparator Mean (U)	Dose Ratio IDegAsp/Comparator
IDegAsp OD vs IGlar OD				
T2DM OD 6m (3590)	Total Daily Insulin Dose	65.6	58.6	1.12
T2DM OD 6m (3593)	Total Daily Insulin Dose	60.2	59.8	1.01
IDegAsp BID vs BIAsp 30 BID				
T2DM BID 6m (3592)	Total Daily Insulin Dose	90.3	97.7	0.92
T2DM BID 6m (3597)	Total Daily Insulin Dose	55.0	68.3	0.81

OD: once daily dosing; BID: twice daily dosing; 6m: 6-month trial; U: units.

8.3.2.2 Insulin Doses in IDegAsp T1DM Trial 3594

At the end of T1DM Trial 3594, the basal component of IDegAsp was lower (29 U) than with IDet (36 U). The total daily bolus component in patients randomized to IDegAsp consisted of IAsp + 30% IDegAsp and was 39 U compared to 43 U in the patients receiving IDet + IAsp. At end of trial, the mean total daily insulin dose was lower for IDegAsp + IAsp (69 U) than for IDet + IAsp (79 U).

8.4 Clinical Efficacy and Dosing Conclusions

IDeg and IDegAsp effectively improved long-term glycemic control as noninferiority to basal insulin comparators in reducing HbA_{1c} (primary endpoint) was established across all phase 3 treat-to-target trials in T2DM and T1DM. These findings were consistent across all patient populations including insulin-naïve T2DM patients initiated on basal insulin therapy, patients with advanced T2DM diabetes requiring basal-bolus therapy, as well as patients with T1DM diabetes requiring basal-bolus therapy. In addition, IDeg and IDegAsp were in most trials associated with larger reductions in FPG than comparator products. Improvements in glycemic control were achieved with similar doses of insulin.

9 Hypoglycemia

Summary

Hypoglycemia Assessment in Trials with IDeg

- In T2DM trials, rates of severe hypoglycemia were low for both IDeg and IGlar in basal-only therapy and in basal-bolus therapy. Rates of confirmed and nocturnal confirmed hypoglycemia tended to be lower with IDeg compared with IGlar in basal-only therapy (significant for nocturnal hypoglycemia in one trial) and were both significantly lower with IDeg in a basal-bolus trial.
- In T1DM trials with basal-bolus therapy, the rates of severe or confirmed hypoglycemia were not significantly different between IDeg and comparators (IGlar or IDet), while IDeg was associated with a 25–40% lower risk of nocturnal confirmed hypoglycemia, consistent with the lower rates of nocturnal confirmed hypoglycemia in T2DM.
- A flexible dosing regimen of IDeg in both T2DM and T1DM was associated with a lower rate of nocturnal confirmed hypoglycemia compared with IGlar, which is consistent with the long, stable glucose-lowering effect of IDeg and despite the marked variation in time between doses.

Meta-analysis of Hypoglycemia when IDeg is Compared with IGlar

- In a prespecified meta-analysis, IDeg was associated with significantly lower rates of confirmed hypoglycemic episodes (9 versus 17%) than IGlar for combined T2DM+T1DM patients and T2DM patients, while the rates were not significantly different for T1DM patients. IDeg had significantly lower rates of nocturnal confirmed hypoglycemic episodes (26–36%) than IGlar for the T2DM+T1DM, T2DM, and T1DM populations.

Hypoglycemia Assessment in Trials with IDegAsp

- In T2DM patients, the rates of confirmed hypoglycemia were significantly greater for IDegAsp OD than for IGlar OD. The rates of nocturnal confirmed hypoglycemia were significantly lower for IDegAsp OD in one trial, and trended lower in the other trial. Very few events of severe hypoglycemia were reported with IDegAsp OD.
- In T2DM patients, the rates of confirmed and nocturnal confirmed hypoglycemia in two twice-daily IDegAsp trials were significantly lower for IDegAsp (by 32% and 73%, respectively) compared with BIAsp 30 BID in Trial 3592, but rates were similar in Trial 3597.
- In T1DM patients, the rate of confirmed hypoglycemia with once-daily IDegAsp used in basal-bolus therapy was similar to IDet while the rate of nocturnal confirmed hypoglycemic episodes was significantly lower (by 37%) with IDegAsp than with IDet. The rate of severe hypoglycemia with once-daily IDegAsp was similar to that of once-daily IDet in basal-bolus therapy.

Hypoglycemia, or even fear of hypoglycemia, may limit the initiation and/or titration of insulin and lead to suboptimal dosing and inadequate glycemic control. Hypoglycemia is recognized as the limiting factor in achieving recommended targets of glycemic control with insulin.[14] Nocturnal hypoglycemia is particularly relevant since it is often not detected by patients who may not have adequate warning to seek treatment before they progress to severe nocturnal hypoglycemia which can lead to unconsciousness and even death in rare cases.[5,6]

The pharmacokinetics and pharmacodynamics of a basal insulin are best reflected by nocturnal hypoglycemia since this time period is least affected by the use of bolus insulin and other factors such as diet and exercise. The stable pharmacokinetic/pharmacodynamic profiles of IDeg predict that long-term insulin therapy with IDeg would be associated with a reduced risk of hypoglycemia, particularly nocturnal hypoglycemia, compared with treatment with currently available basal insulin comparators. In the following sections, severe, confirmed, and nocturnal confirmed hypoglycemia in the individual IDeg phase 3 trials will be presented for IDeg treatment in T1DM and T2DM patients in which a consistent pattern of a decrease in nocturnal confirmed hypoglycemia will be presented.

A prespecified hypoglycemia meta-analysis was performed to compare IDeg with IGlar at the individual patient level. The objective was to demonstrate superiority of treatment with IDeg versus IGlar in terms of a lower rate of confirmed and nocturnal confirmed hypoglycemic episodes. The nocturnal period was prespecified to be between midnight and 6 a.m. Hypoglycemia event rates were used in the meta-analysis. At the suggestion of the FDA (see Section 9.2.1 for a summary of interactions with the FDA), an analysis was conducted on the incidence of confirmed and nocturnal confirmed hypoglycemia (defined as the proportion of patients who experienced at least one hypoglycemic episode). As almost all T1DM patients would be expected to have at least one hypoglycemic episode in a long-term trial, an analysis using incidence rate would limit the assessment of hypoglycemia for T1DM. The analysis using event rates was performed as it would be informative, particularly for providing information about recurrent hypoglycemia.

Hypoglycemia in the individual IDegAsp phase 3 trials was also assessed in T2DM patients for once- and twice-daily use and as a component of basal-bolus therapy in T1DM patients. The comparison of IDegAsp to BIAsp 30 in two trials is particularly relevant as both formulations contain a 30% rapid-acting insulin component (insulin aspart) and a 70% basal insulin component, (IDeg) in the case of IDegAsp, and protaminated insulin aspart in the case of BIAsp 30 (a currently marketed biphasic insulin formulation).

Please refer to Section 6.3 for the hypoglycemia definitions used in the IDeg and IDegAsp phase 3 trials and Sections 6.4.1 and 6.4.2 for details on the statistical analyses of hypoglycemia for the individual trials and the meta-analysis, respectively.

9.1 Hypoglycemia in IDeg Trials

9.1.1 Hypoglycemia with IDeg Therapy in T2DM

Basal-only Therapy in T2DM

Severe Hypoglycemia

As recurrent severe hypoglycemia was a trial exclusion criterion for safety reasons, the total number of severe hypoglycemic episodes were generally low. In patients with T2DM treated with the basal-only therapy, the number of severe hypoglycemic episodes was also low, ranging from 0−2 episodes with IDeg and from 0−5 episodes with IGlar (Table 37). The rate of severe hypoglycemia in Trial 3579, the longest and largest trial with basal-only therapy, was significantly lower for IDeg than for IGlar (rate ratio 0.14 $[0.03; 0.70]_{95\% CI}$). The proportion of patients reporting severe hypoglycemia ranged from 0−0.3% with IDeg and from 0−1.9% with comparator.

The low rate of severe hypoglycemia in T2DM patients reflects the relative disease state of these patients treated with basal-only insulin therapy, i.e., they do not require basal-bolus therapy, the bolus component of which would likely increase the occurrence of severe hypoglycemia. As such, this patient population may best demonstrate the benefits of IDeg in minimizing severe hypoglycemia where the basal-only insulin regimen is not confounded with the use of a bolus insulin component.

Confirmed and Nocturnal Confirmed Hypoglycemia

In the once-daily IDeg basal-only therapy trials in T2DM with insulin comparators, between 29% and 51% of patients experienced at least one episode of confirmed hypoglycemia (Table 37). Rates of confirmed hypoglycemia were lower (by 14–18%) with IDeg than with IGlar in Trials 3579, 3672 and 3586 (not statistically significant, Table 38). Rates of confirmed hypoglycemia and nocturnal confirmed hypoglycemia were similar to IGlar when IDeg was dosed at alternating time intervals (i.e., flexible dosing in Trial 3668, Table 38).

Table 37 Hypoglycemic Episodes by Classification – IDeg Basal-only Therapy T2DM Trials

Trial	IDeg				Comparator			
Classification	N	(%)	E	R	N	(%)	E	R
T2DM BOT 12m vs. IGlar (Trial 3579)								
Number of patients	766				257			
Severe	2	0.3	2	0.3	5	1.9	5	2.3
Confirmed	356	46.5	1014	152.0	119	46.3	403	184.9
Nocturnal confirmed	106	13.8	169	25.3	39	15.2	84	38.5
T2DM BOT 6m U200 vs. IGlar (Trial 3672)								
Number of patients	228				228			
Severe	0				0			
Confirmed	65	28.5	129	122.1	70	30.7	152	142.1
Nocturnal confirmed	14	6.1	19	18.0	20	8.8	30	28.1
T2DM BOT 6m Asia vs. IGlar (Trial 3586)								
Number of patients	284				146			
Severe	0				1	0.7	1	1.4
Confirmed	142	50.0	397	297.6	78	53.4	260	369.9
Nocturnal confirmed	58	20.4	104	78.0	35	24.0	87	123.8
T2DM BOT 6m IDeg Flexible dosing[a] vs. IGlar (Trial 3668)								
Number of patients	230				229			
Severe	1	0.4	2	1.9	2	0.9	2	1.9
Confirmed	117	50.9	388	364.3	113	49.3	368	348.4
Nocturnal confirmed	31	13.5	67	62.9	49	21.4	79	74.8
T2DM BOT 6m vs. Sitagliptin (Trial 3580) [insulin vs. Non-insulin comparison]								
Number of patients	226				228			
Severe	1	0.4	1	1.0	0			
Confirmed	96	42.5	311	307	29	12.7	123	126.1
Nocturnal confirmed	29	12.8	53	52.3	13	5.7	29	29.7

[a] Data for the IDeg Flexible dosing group is shown for Trial 3668.
N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years; BOT: basal-only therapy. See Section 6.2 for a description of the IDeg flexible dosing schedule. For definition of hypoglycemia classification, see Section 6.3. Safety analysis set.

As expected, the only trial in which IDeg had higher rates of confirmed hypoglycemia was Trial 3580; the comparator was the DPP-4 inhibitor sitagliptin (an oral agent associated with very low rates of hypoglycemia), and IDeg was superior in lowering HbA_{1c} (Table 21).

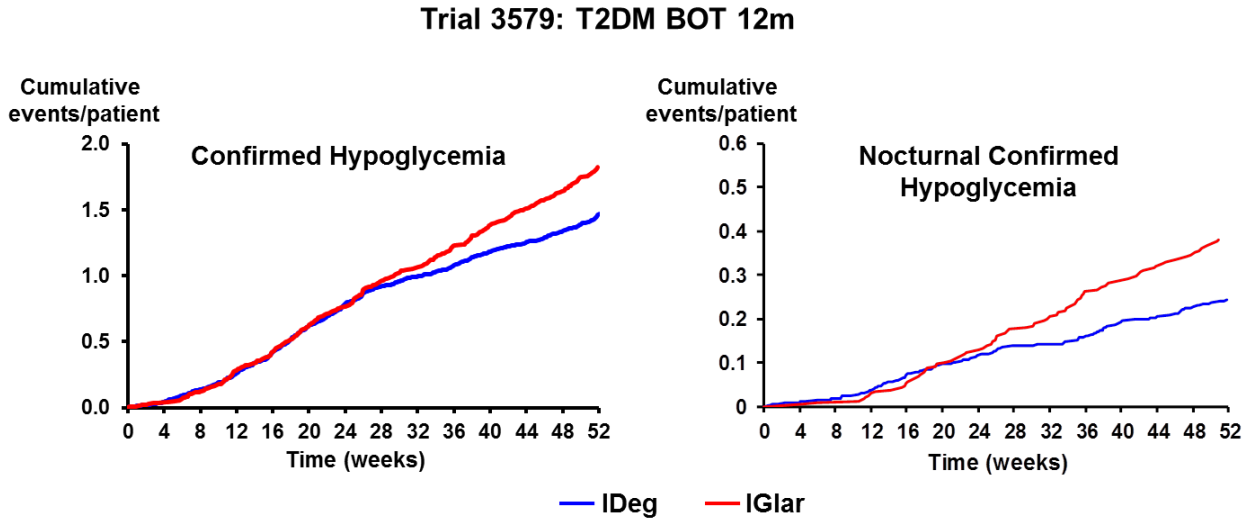
Table 38 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes in Non-inferiority Trials – Statistical Analysis – IDeg Basal-only Therapy T2DM Trials

Trial	Comparison	Confirmed Hypoglycemia Estimated Rate Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate Ratio [95% CI]
T2DM BOT 12m (Trial 3579)	IDeg vs. IGlar	0.82 [0.64 ; 1.04]	0.64 [0.42 ; 0.98]*
T2DM BOT 6m U200 (Trial 3672)	IDeg vs. IGlar	0.86 [0.58 ; 1.28]	0.64 [0.30 ; 1.37]
T2DM BOT 6m Asia (Trial 3586)	IDeg vs. IGlar	0.82 [0.60 ; 1.11]	0.62 [0.38 ; 1.04]
T2DM BOT 6m (Trial 3668)	IDeg Flexible Dosing vs. IGlar	1.03 [0.75 ; 1.40]	0.77 [0.44 ; 1.35]

*Ratio statistically significantly different from 1.
The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1). The primary treatment contrast in Trial 3668 was IDeg flexible dosing – IGlar. See Section 6.2 for a description of the IDeg flexible dosing schedule; estimated rate: estimated rate per 100 exposure years. See Section 6.3 for hypoglycemia definitions. Full analysis set.

Based on results from Trials 3579, 3672, 3586 and 3668, the rates of nocturnal confirmed hypoglycemic episodes were 23–38% lower with IDeg than with IGlar and the treatment difference was statistically significant in Trial 3579 (Table 38). In Trial 3580, the rate of nocturnal confirmed hypoglycemia was lower with sitagliptin than with IDeg; however, this was not statistically significant. Consistently lower rates of nocturnal hypoglycemia with IDeg were observed in all 4 trials with IGlar as a comparator despite the fact that FPG levels were lower with IDeg than with IGlar.

A clear pattern in the development of hypoglycemic events over time was seen in all trials (with the exception of the trial vs. sitagliptin), where the advantage of IDeg began to appear after insulin titration was largely complete. For example, in Trial 3579, rates of confirmed and nocturnal confirmed hypoglycemia were similar with IDeg and IGlar early in the trial, but later in the trial, the rate of hypoglycemia in the IDeg group was lower than that of the IGlar group (Figure 27).



Nocturnal period: the period between midnight and 6 a.m. Safety analysis set.
Note that the scales are different to accommodate differences in the number of hypoglycemic episodes.

Figure 27 Mean Cumulative Confirmed and Nocturnal Confirmed Hypoglycemic Episodes for Basal-only Therapy – IDeg T2DM Trial 3579

In conclusion, lower rates of confirmed (by 14–18%) and nocturnal confirmed (by 23–38%) hypoglycemic episodes were observed with IDeg compared with IGlar in basal-only therapy T2DM trials; and were statistically significant for nocturnal hypoglycemia in Trial 3579. These differences become more apparent during the maintenance phase (i.e., after Week 16). Compared with IGlar, a flexible dosing regimen of IDeg was associated with a 23% lower rate of nocturnal confirmed hypoglycemia, although not statistically significant (Trial 3668, Table 38).

Basal-bolus Therapy in T2DM

For most patients with T2DM, disease progression ultimately leads to intensive therapy. For some T2DM patients, basal-bolus insulin therapy will be required to control mealtime glycemia. The administration of a bolus insulin component of basal-bolus therapy demands additional consideration because of the rapid-acting nature of the bolus insulin component, the injection timing and dose adjustment to the meal, and the daytime activity level of the patient. Because of the disease progression associated with diabetes and the complexities of the bolus insulin component, basal-bolus insulin therapy is associated with higher rates of hypoglycemia than basal-only insulin therapy in T2DM.

Severe Hypoglycemia

Severe hypoglycemia becomes an increasingly urgent factor in T2DM as the disease progresses and more intensive therapy is required,[31] resulting in the addition of bolus insulin before meals to the basal insulin regimen. In Trial 3582, 4.5% of IDeg and 4.4% of IGlar patients experienced one or

more episodes of severe hypoglycemia during the 52-week trial period. However, the rates of severe episodes were low, 6.1 episodes per 100 PYE with IDeg and 5.2 episodes per 100 PYE with IGlar (Table 39). For Trial 3582, the rate of severe hypoglycemia with IDeg was similar to that of IGlar (rate ratio 1.14 [0.60; 2.17]$_{95\% CI}$).

Overall Confirmed and Nocturnal Confirmed Hypoglycemia

In Trial 3582, episodes of confirmed hypoglycemia were reported by approximately 80% of patients (Table 39). After 52 weeks of treatment, the superiority of IDeg was demonstrated as the rate of confirmed hypoglycemia was 18% lower with IDeg than with IGlar (see Table 40).

Table 39 Hypoglycemic Episodes by Classification – IDeg Basal-bolus T2DM Trial 3582

Trial	IDeg				IGlar			
Classification	N	%	E	R	N	%	E	R
T2DM BB 12m (Trial 3582)								
Number of patients	753				251			
Severe	34	4.5	41	6.1	11	4.4	12	5.2
Confirmed	609	80.9	7437	1108.9	206	82.1	3120	1363.4
Nocturnal confirmed	298	39.6	930	138.7	119	47.4	422	184.4

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years. See Section 6.3 for definition of hypoglycemia classification. Safety analysis set.

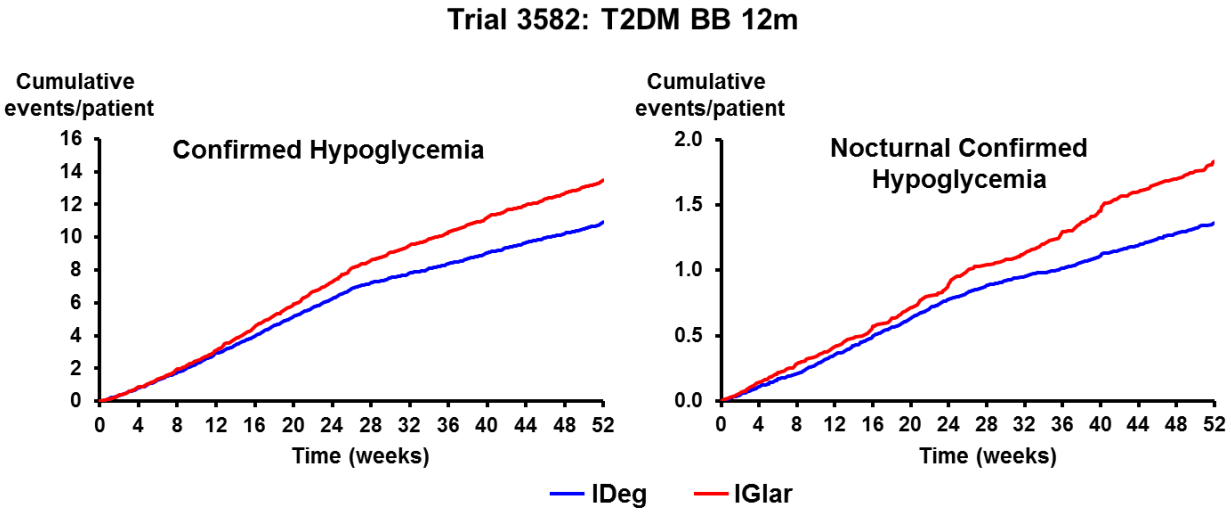
Table 40 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – Statistical Analysis – IDeg Basal-bolus T2DM Trial 3582

Trial	Comparison	Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]
T2DM BB 12m (Trial 3582)	IDeg vs. IGlar	0.82 [0.69 ; 0.99]*	0.75 [0.58 ; 0.99]*

*Ratio statistically significantly different from 1.
The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1).
Estimated rate: Estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia classification. Full analysis set.

With basal-bolus therapy, the nocturnal period best reflects the effect of basal insulin because the impact of meals, exercise, and mealtime bolus insulin effect is minimal. In Trial 3582, episodes of nocturnal confirmed hypoglycemia were reported by 40% of the patients treated with IDeg and 47% treated with IGlar (Table 39). After 52 weeks of treatment, the rate of nocturnal confirmed hypoglycemia was 25% lower with IDeg than with IGlar (statistically significant, see Table 40).

In Trial 3582, rates of confirmed and nocturnal confirmed hypoglycemia were lower with IDeg than IGlar after Weeks 16−20 (Figure 28). During this period in the trial, glycemic control and insulin dose were at a stable level.



Nocturnal period: the period between midnight and 6:00 a.m. Safety analysis set.
Note that the scales are different to accommodate differences in the number of confirmed and nocturnal confirmed hypoglycemic episodes.

Figure 28 Mean Cumulative Confirmed and Nocturnal Confirmed Hypoglycemic Episodes for Basal-bolus Therapy – IDeg T2DM Trial 3582

9.1.2 Hypoglycemia with IDeg Therapy in T1DM

Basal-bolus Therapy in T1DM

Severe Hypoglycemia

As shown in Table 41, between 10% and 12% of patients with T1DM reported one or more episodes of severe hypoglycemia with IDeg or comparator. The absolute number of episodes of severe hypoglycemia was low. Observed rates of severe episodes ranged from approximately 21 to 34 episodes per 100 PYE with IDeg and from approximately 16 to 47 episodes per 100 PYE with comparator. Nocturnal severe episodes were reported by approximately 3–4% of patients treated with IDeg (observed rate 5−9 episodes per 100 PYE) and by 2–3% of patients treated with comparator products (observed rate 2-17 episodes per 100 PYE). There were no statistically significant treatment differences between IDeg and comparator in the rates of severe or nocturnal severe hypoglycemia (Table 42).

Table 41 Severe and Nocturnal Severe Hypoglycemic Episodes – IDeg T1DM Trials

Trial	IDeg				Comparator			
Classification	N	(%)	E	R	N	(%)	E	R
T1DM BB 12m vs. IGlar (3583)								
Number of patients	472				154			
Severe	58	12.3	90	20.8	16	10.4	23	15.9
Nocturnal severe	18	3.8	23	5.3	3	1.9	3	2.1
T1DM BB 6m vs. IDet (3585)								
Number of patients	301				152			
Severe	32	10.6	45	30.9	16	10.5	28	38.8
Nocturnal severe	12	4.0	13	8.9	5	3.3	6	8.3
T1DM BB 6m (3770) IDeg Flexible Dosing vs. IGlar								
Number of patients	164				161			
Severe	17	10.4	25	34.4	16	9.9	37	47.1
Nocturnal severe	5	3.0	5	6.6	5	3.1	13	16.6

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years; Data for the IDeg Flexible dosing group is shown for Trial 3770. See Section 6.2 for a description of the IDeg flexible dosing schedule. For definition of hypoglycemia classification, see Section 6.3. Safety analysis set.

Table 42 Severe and Nocturnal Severe Hypoglycemic Episodes – Statistical Analysis – IDeg T1DM Trials

Trial	Comparison	Severe Episodes Estimated Rate-Ratio [95% CI]	Nocturnal Severe Episodes Estimated Rate-Ratio [95% CI]
T1DM BB 12m (3583)	IDeg vs. IGlar	1.38 [0.72 ; 2.64]	1.11 [0.82 ; 1.51]
T1DM BB 6m (3585)	IDeg vs. IDet	0.92 [0.46 ; 1.81]	1.02 [0.72 ; 1.45]
T1DM BB 6m (3770)	IDeg Flexible Dosing vs. IGlar	0.89 [0.40 ; 1.99]	0.48 [0.11 ; 2.07]

BB: basal-bolus dosing. The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1). The primary treatment contrast of interest in Trial 3770 was IDeg flexible dosing – IGlar. See Section 6.2 for a description of the IDeg flexible dosing schedule; estimated rate: estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia classification. Full analysis set.

The duration of severe hypoglycemia was similar with IDeg and comparator products. This was supported by the results from a clinical pharmacology trial (Trial 3538) investigating time of recovery from hypoglycemia as well as counter-regulatory response to hypoglycemia (see Section 5.2.8).

Confirmed and Nocturnal Confirmed Hypoglycemia

Between 91% and 97% of patients with T1DM experienced at least one episode of confirmed hypoglycemia (see Table 43), suggesting that hypoglycemia is inherent for most individuals with T1DM on basal-bolus insulin therapy. The high percentage of patients with hypoglycemia reflects

the underlying disease state and the effect of the mealtime bolus insulin, as illustrated by the fact that the majority of episodes (~90%) occurred during the daytime (Table 43).

Table 43 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – IDeg T1DM Trials

Trial	IDeg				Comparator			
Classification	N	(%)	E	R	N	(%)	E	R
T1DM BB 12m vs. IGlar (3583)								
Number of patients	472				154			
Confirmed	451	95.6	18389	4254	147	95.5	5796	4018
Nocturnal confirmed	341	72.2	1905	441	114	74.0	845	586
T1DM BB 6m vs. IDet (3585)								
Number of patients	301				152			
Confirmed	280	93.0	6673	4583	139	91.4	3295	4569
Nocturnal confirmed	176	58.5	603	414	89	58.6	428	594
T1DM BB 6m (3770) IDeg Flexible Dosing vs. IGlar								
Number of patients	164				161			
Confirmed	154	93.9	5988	8238	156	96.9	6263	7973
Nocturnal confirmed	111	67.7	453	623	117	72.7	782	996

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years; BB: basal-bolus dosing. See Section 6.2 for a description of the IDeg flexible dosing schedule. For definition of hypoglycemia classification, see Section 6.3. Safety analysis set.

The rate ratios (IDeg/comparator) for confirmed hypoglycemia ranged from 0.98 to 1.07 with no significant treatment difference between IDeg and comparator (Table 44). There was no significant difference in terms of rates of confirmed hypoglycemia between IDeg dosed at alternating narrow and wide time intervals (i.e., IDeg flexible dosing) and IDeg dosed in the evening (Trial 3770).

Table 44 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – Statistical Analysis – IDeg T1DM Trials

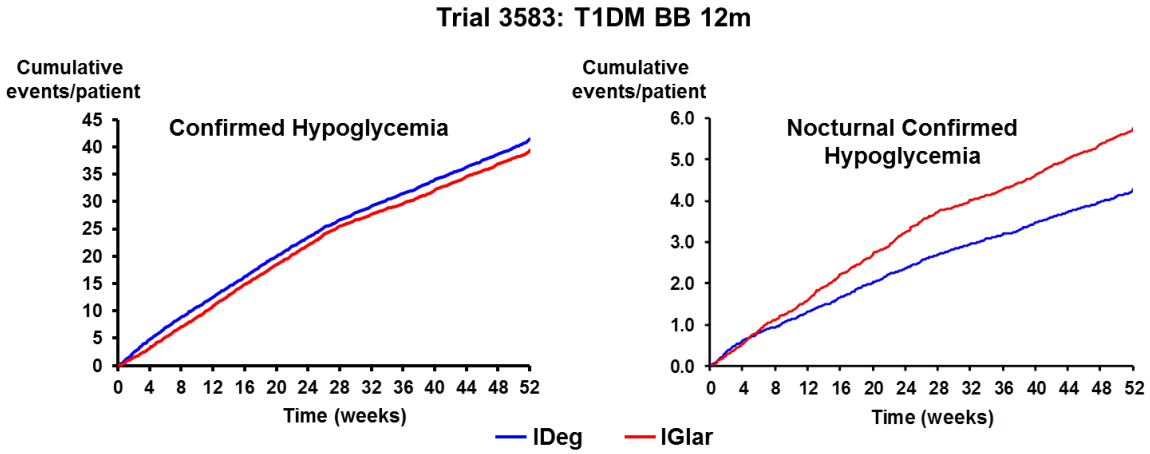
Trial	Comparison	Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]
T1DM BB 12m (3583)	IDeg vs. IGlar	1.07 [0.89 ; 1.28]	0.75 [0.59 ; 0.96]*
T1DM BB 6m (3585)	IDeg vs. IDet	0.98 [0.80 ; 1.20]	0.66 [0.49 ; 0.88]*
T1DM BB 6m (3770)	IDeg Flexible Dosing vs. IGlar	1.03 [0.85 ; 1.26]	0.60 [0.44 ; 0.82]*

*Ratio statistically significantly different from 1.
The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1). The primary treatment contrast of interest in Trial 3770 was IDeg flexible dosing – IGlar. See Section 6.2 for a description of the IDeg flexible dosing schedule; estimated rate: estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia classification. Full analysis set.

Between 59 and 74% of patients with T1DM reported nocturnal confirmed hypoglycemia (see Table 43). While the reductions in FPG were greater for IDeg than comparator products (Section 8.2), the observed rates of nocturnal confirmed hypoglycemia were consistently lower with IDeg

than with comparator products. Overall, IDeg was associated with a 25-40% significantly lower risk of nocturnal confirmed hypoglycemic episodes than IDet or IGlar. Superiority of IDeg over comparator products was confirmed in Trials 3583 and 3585 (Table 44). In Trial 3770, the rate of nocturnal confirmed hypoglycemia was significantly lower with IDeg than with IGlar (Table 44).

As shown in the 52-week Trial 3583 (Figure 29), the cumulative number of confirmed hypoglycemic episodes was similar for IDeg and IGlar, both in the titration period (Week 0−15) and in the maintenance period (Week 16 to end of trial). The lower rate of nocturnal confirmed hypoglycemia became increasingly apparent over time. A similar pattern was seen in Trial 3585 and Trial 3770 where the rate of nocturnal hypoglycemia was lower with IDeg than with IGlar.



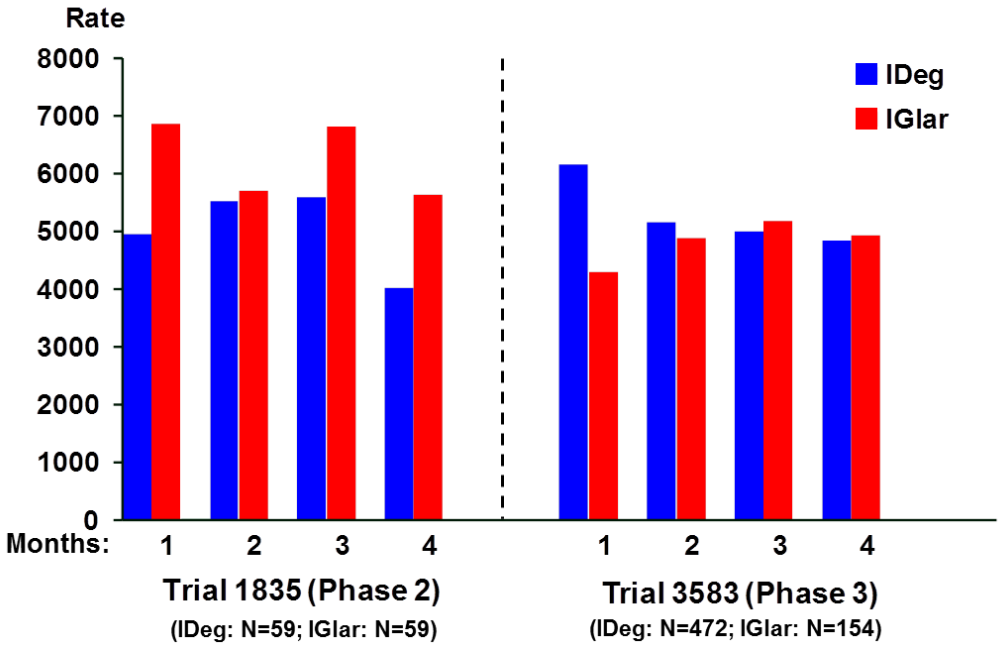
Nocturnal period: the period between midnight and 6:00 a.m. Safety analysis set.
Note that the scales are different to accommodate differences in the number of hypoglycemic episodes.

Figure 29 Mean Cumulative Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – IDeg T1DM Trial 3583

The switch from pre-trial basal insulin to trial basal insulin was different for patients randomized to IDeg and IGlar in the trials. Patients randomized from treatment with twice-daily basal insulin to IDeg were instructed to do so on a unit-to-unit basis, whereas patients transferring to IGlar were instructed to reduce their starting insulin dose by 20% (according to protocol and product label) compared to their pre-trial twice-daily basal insulin dose. The higher rate of confirmed hypoglycemia during the first month of treatment in the IDeg group was most pronounced in patients with T1DM transferring from twice-daily basal insulin (Figure 30). Therefore, part of the initial difference in the rates of confirmed hypoglycemia between IDeg and comparator could be explained by the initial starting dose.

In contrast, rates of confirmed hypoglycemia were lower with IDeg than IGlar during the first month of treatment in Trial 1835 (phase 2), in which patients in both treatment groups reduced their dose by 20% if they were transferring from BID basal insulin to trial insulin (Figure 30). Taken

together, these factors may explain the trend toward a higher rate of confirmed hypoglycemia in the titration phase with IDeg compared with IGlar for patients with T1DM.



Rate: event rate per 100 exposure years. Results from all patients treated with IDeg and IGlar in Trial 1835 and 3583.

Figure 30 Confirmed Hypoglycemia in T1DM with (Trial 1835) or without (Trial 3583) 20% Basal Insulin Dose Reduction from BID Basal Insulin

In conclusion, in patients with T1DM, IDeg was associated with similar rates of both severe and confirmed hypoglycemic episodes as comparator products. Based on the temporal pattern of hypoglycemia, most episodes of confirmed hypoglycemia occurred during daytime hours and were related to mealtime bolus insulin administration. IDeg was superior to both IGlar and IDet with respect to a lower rate of nocturnal confirmed hypoglycemic episodes. Across trials, similar results were observed even with a flexible dosing regimen (Trial 3770) and with different comparators and doses of basal insulin (see Section 8.3.1.2).

9.2 Prespecified Meta-analysis of Hypoglycemic Episodes with IDeg

9.2.1 Interactions with FDA

The prospectively planned meta-analysis included all phase 3 trials in which IDeg was dosed once daily and IGlar was used as the comparator; the meta-analysis substantiated the results for the individual trials. The approach for the meta-analysis of hypoglycemic episodes was discussed with

regulatory authorities after completing the phase 2 program. A statistical analysis plan was sent to the FDA for review prior to first database lock of the IDeg phase 3 trials.

Shortly after first database lock, the FDA provided feedback on the statistical analysis plan (see Section 9), and the FDA's comments were incorporated into the meta-analysis. The FDA recommended adding:

- Separate assessments of T2DM and T1DM to account for trial and patient heterogeneity
- An assessment of hypoglycemia during the titration period, during the period when the insulin dose had stabilized, and when the patients had achieved glycemic target ($HbA_{1c} < 7\%$). The period in which the insulin dose had stabilized is referred to as the maintenance phase (defined by Novo Nordisk as Week 16 to the end of the trial).
- An analysis of daytime hypoglycemia
- An analysis of symptomatic and asymptomatic hypoglycemia.

The FDA recommended a blinded retrospective independent classification of all cases of treatment emergent severe hypoglycemia and hypoglycemia reported as serious adverse events, as severe hypoglycemia may be least subject to bias and is more clinically concerning than minor hypoglycemia. The independent, blinded classification of hypoglycemia was done retrospectively by an external consultant who reviewed the blinded case narrative and 'hypoglycemic episode form' for each of the episodes and assigned the episode to one of the categories 'severe hypoglycemia', 'not severe hypoglycemia', 'not possible to classify (contradiction)' or 'not possible to classify (missing information)'.

The FDA recommended an analysis using incident cases of hypoglycemia (total number of patients with at least one hypoglycemic event divided by the total extent of exposure in patient-years), as well as analyses using the total number of hypoglycemic events per patient-year of exposure (PYE) and using total number of hypoglycemic events without adjustment for patient-year exposure. These additional analyses were discussed with the FDA at the pre-NDA meeting, at which time the FDA agreed that some of their methodological concerns had been addressed. Novo Nordisk also complied with the FDA's request for several additional analyses, which were submitted in the NDA.

The meta-analyses were based on hypoglycemic episodes collected in 7 phase 3 trials comparing IDeg once daily with IGlar once daily: 5 trials in patients with T2DM (Trials 3582, 3579, 3672, 3586, and 3668) and 2 trials in patients with T1DM (Trials 3583 and 3770). These trials consisted of 4 trials with basal-only therapy (Trials 3579, 3672, 3586, and 3668) and three trials with basal-bolus therapy (Trials 3582[T2DM], 3583 and 3770 [T1DM]). The IDeg flexible dosing arms of Trials 3770 and 3668 were excluded from the meta-analysis as the flexible dosing intervals investigated the extremes of once-daily dosing and do not reflect the intended use of IDeg in clinical practice.

The prespecified primary and confirmatory secondary analyses were based on the total number of confirmed hypoglycemic episodes in the pooled population of patients with T1DM and T2DM, as IDeg is expected to have the same influence on hypoglycemia regardless of diabetes type, and pooling T1DM or T2DM trials would increase the power of the analysis. Pooling did not specifically take into account the differences between basal-only insulin therapy and basal-bolus insulin therapy, and in view of the impact of bolus insulin, tended to decrease the overall potential impact of IDeg as a basal insulin on overall confirmed hypoglycemia.

9.2.2 Meta-analysis of Confirmed Hypoglycemia during the Entire Treatment Period and the Maintenance Period

Meta-analysis of Confirmed Hypoglycemia Based on Rate of Hypoglycemic Events

The primary meta-analysis demonstrated that IDeg was superior to IGlar with a 9% lower rate of confirmed hypoglycemic episodes in the pooled analysis of patients with T1DM and T2DM (estimated rate ratio IDeg/IGlar: 0.91 $[0.83; 0.99]_{95\%CI}$); please see Table 45.

The meta-analysis in T2DM extended the outcome of the primary pooled analysis of confirmed hypoglycemia (estimated rate ratio: 0.83 $[0.74; 0.94]_{95\%CI}$) (Table 45). For the subset of insulin-naïve patients with T2DM treated with basal-only therapy, the rate of confirmed hypoglycemia was 17% lower with IDeg than with IGlar (estimated rate ratio: 0.83 $[0.70; 0.98]_{95\%CI}$).

In T1DM, the estimated rate ratio for confirmed hypoglycemia was 1.10 $[0.96; 1.26]_{95\%CI}$ (Table 45). However, the analysis of the rates of confirmed hypoglycemia may be confounded by the use of a bolus insulin component that is required for T1DM patients treated with basal-bolus insulin therapy, and by the algorithm with which patients were switched from pre-trial basal insulin to their assigned basal insulin in the trial, especially if patients' pre-trial basal regimen was IGlar twice daily (as described in Section 9.1.2).

Rate ratios decreased during the maintenance period compared with the entire treatment period. In the maintenance period, the rate ratios were significantly lower for IDeg compared with IGlar in the pooled, basal-only therapy T2DM trials (28% lower); in all T2DM trials (25% lower;, and in pooled T2DM+T1DM trials (16% lower); (see (Table 45). For T1DM, the rate ratio of confirmed hypoglycemia during the maintenance period decreased slightly from the entire treatment period to approach unity (Table 45).

Table 45 Meta-analysis of Confirmed Hypoglycemia during the Entire Treatment Period (from Week 0) and Maintenance Period (from Week 16)

		Entire Treatment Period Estimated Rate-Ratio	Maintenance Treatment Period Estimated Rate-Ratio
	Comparison	Estimate [95% CI]	Estimate [95% CI]
T2DM Basal-only therapy	IDeg vs. IGlar	0.83 [0.70; 0.98]*	0.72 [0.58; 0.88]*
T2DM	IDeg vs. IGlar	0.83 [0.74; 0.94]*	0.75 [0.66; 0.87]*
T1DM	IDeg vs. IGlar	1.10 [0.96; 1.26]	1.02 [0.88; 1.19]
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.91 [0.83; 0.99]*	0.84 [0.75; 0.93]*

*Ratio significantly different from 1.
T2DM: Trials 3672, 3579, 3582, 3586 and 3668 (excluding flexible dosing arm); Basal-only therapy in insulin-naive patients: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583. Full analysis set.

9.2.3 Meta-analysis of Nocturnal Confirmed Hypoglycemia during the Entire Treatment Period and the Maintenance Period

Meta-analysis of Nocturnal Confirmed Hypoglycemia Based on Rate of Hypoglycemic Events

IDeg was superior to IGlar in terms of a 26% lower rate of nocturnal confirmed hypoglycemic episodes in the pooled analysis of patients with T1DM and T2DM; (estimated rate ratio: 0.74 [0.65; 0.85]$_{95\%CI}$); see Table 46.

The rate of nocturnal confirmed hypoglycemia was 32% lower with IDeg than with IGlar in the pooled population of patients with T2DM (estimated rate ratio: 0.68 [0.57; 0.82]$_{95\%CI}$) and 36% lower in the subset of insulin-naïve patients with T2DM treated with basal-only therapy (estimated rate ratio: 0.64 [0.48; 0.86]$_{95\%CI}$) (Table 46). The rate of nocturnal confirmed hypoglycemia in the T1DM trials was lower by 17% with IDeg than with IGlar for T1DM patients (estimated rate ratio: 0.83 [0.69; 1.00]$_{95\%CI}$).

Additional analyses were conducted for the maintenance phase (Week 16 to end of trial) when insulin titration was largely complete and insulin doses were stable. As shown in Table 46, the rate of nocturnal confirmed hypoglycemia during the maintenance period was significantly lower with IDeg compared with IGlar in pooled T1DM+T2DM trials (32% lower), all T2DM trials (38% lower), basal-only therapy T2DM trials (49% lower), and T1DM trials (25% lower).

Table 46 Meta-analysis of Nocturnal Confirmed Hypoglycemia during the Entire Treatment Period (from Week 0) and Maintenance Period (from Week 16)

		Entire Treatment Period Estimated Rate-Ratio	Maintenance Treatment Period Estimated Rate-Ratio
	Comparison	Estimate [95% CI]	Estimate [95% CI]
T2DM Basal-only therapy	IDeg vs. IGlar	0.64 [0.48; 0.86]*	0.51 [0.36; 0.72]*
T2DM	IDeg vs. IGlar	0.68 [0.57; 0.82]*	0.62 [0.49; 0.78]*
T1DM	IDeg vs. IGlar	0.83 [0.69; 1.00]	0.75 [0.60; 0.94]*
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.74 [0.65; 0.85]*	0.68 [0.58; 0.80]*

*Ratio significantly different from 1.

T2DM: Trials 3672, 3579, 3582, 3586 and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583. Full analysis set.

9.2.4 Meta-analysis of Confirmed and Nocturnal Confirmed Hypoglycemia in Elderly Patients

Elderly patients are generally more susceptible to hypoglycemia due to longstanding disease, higher incidence of comorbidities and reduced hypoglycemic awareness and are more vulnerable if living alone.[32] Therefore, the overall hypoglycemia meta-analyses were repeated in elderly patients ≥65 years.

IDeg was associated with an 18% lower risk of confirmed hypoglycemia (estimated rate ratio: 0.82 $[0.66; 1.00]_{95\%CI}$) and a significantly lower (35%) risk of nocturnal confirmed hypoglycemia (estimated rate ratio: 0.65 $[0.46; 0.93]_{95\%CI}$) compared with IGlar, indicating that the advantages seen with IDeg in relation to hypoglycemia are also present in the elderly.

9.2.5 Meta-analysis of Severe Hypoglycemia

All severe hypoglycemic episodes, hypoglycemic episodes reported as SAEs and hypoglycemic episodes reported as medical events of special interest were adjudicated by a blinded independent external consultant to evaluate the number of treatment-emergent severe hypoglycemic episodes. Slight differences were present between the severe hypoglycemic episodes reported by the investigator and the severe hypoglycemic episodes identified by the external adjudication process. Only a few episodes changed in status after the external evaluation: in total, 1 severe hypoglycemic episode was added to the IDeg group, whereas 4 episodes originally classified as severe hypoglycemic episodes were removed from the IGlar group. Overall, a total of 12.4% of patients with T1DM and 1.7% of patients with T2DM reported severe hypoglycemia during the trial period (Table 47).

The rate of severe episodes with IDeg in the overall T2DM patient population was lower than the rate of severe episodes with IGlar patients (0.81 $[0.42; 1.56]_{95\%CI}$). The rate of severe episodes with IDeg in basal-bolus therapy for T2DM was also similar to that with IGlar (1.14 $[0.60; 2.17]_{95\%CI}$).

The rate of severe episodes with IDeg in basal-only therapy for T2DM was significantly lower than that with IGlar (0.14 [0.03; 0.70]$_{95\%CI}$).

Not unexpectedly, the rates of severe hypoglycemia for T1DM patients were higher than those for the T2DM patients (Table 47). The rates of severe episodes for the T1DM patients were not significantly different between IDeg and IGlar (1.12 [0.68; 1.86]$_{95\%CI}$). Overall, there was no significant treatment difference for the population of T2DM+T1DM patients (IDeg–IGlar) (estimated rate ratio 0.98 [0.66; 1.45]$_{95\%CI}$). Please refer to Section 9.1.2 for further discussions of severe hypoglycemia and severe nocturnal hypoglycemia in T1DM patients.

Table 47 Severe Hypoglycemic Episodes in Phase 3 Trials with Once-daily IDeg

	IDeg				IGlar				Total			
	N	%	E	R	N	%	E	R	N	%	E	R
T2DM Basal-only therapy	4	0.3	4	0.40	8	0.9	8	1.60	12	0.5	12	0.79
T2DM	38	1.7	45	2.68	19	1.7	20	2.74	57	1.7	65	2.70
T1DM	79	12.4	118	23.21	32	10.2	60	26.93	111	11.7	178	24.34
Pooled T2DM+T1DM	117	4.0	163	7.44	51	3.6	80	8.40	168	3.9	243	7.73

N: Number of patients with at least one episode. %: Proportion of patients in analysis set with at least one episode. E: Number of episodes,
R: Number of episodes divided by patient years of exposure multiplied by 100.
T2DM trials: 3582, 3579, 3672, 3586, and 3668; T1DM trials: 3583 and 3770.

9.2.6 Meta-analysis of Hypoglycemia Based on Incidence Cases

Meta-analysis of Confirmed Hypoglycemia Based on Incidence Cases

The FDA recommended an analysis using incidence rates of hypoglycemia that describes the proportion of patients who experienced at least one hypoglycemic episode. Therefore, the measure is not driven by an increased hypoglycemic sensitivity by some patients. The incidence rate, defined as the number of patients with at least one hypoglycemic episode divided by the extent of exposure, describes the incidence in relation to the trial drug exposure.

The results of the logistic regression indicated that the incidence of confirmed hypoglycemic episodes in the pooled population of T1DM and T2DM was 7% lower with IDeg compared with IGlar (odds ratio of 0.93 [0.79; 1.08]$_{95\%\ CI}$). The difference was not statistically significant in the incidence analysis due to the low power of the logistic regression (as illustrated by the wider confidence interval) which only utilizes information on whether patients reported at least one hypoglycemic episode.

In T2DM, the odds ratio for confirmed hypoglycemia was 0.89 [0.75; 1.04]$_{95\%\ CI}$ for overall T2DM and 0.91 [0.74; 1.11]$_{95\%\ CI}$ for insulin-naïve patients with IDeg compared with IGlar. These findings were consistent with the results of rate ratios (Table 45) and were in line with the incidence analysis for the pooled population.

In T1DM, this analysis was not informative because of the very high proportion of patients (>95%) who experienced at least one episode of hypoglycemia.

Meta-analysis of Nocturnal Confirmed Hypoglycemia Based on Incidence Cases

The results from the logistic regression indicate that the incidence of nocturnal confirmed hypoglycemic episodes in the pooled population of T1DM and T2DM was 22% lower with IDeg compared with IGlar (odds ratio 0.78 $[0.67; 0.92]_{95\%CI}$). The incidence of nocturnal confirmed hypoglycemia was statistically significantly lower with IDeg compared with IGlar in patients with T2DM (odds ratio of 0.71 $[0.59; 0.85]_{95\% CI}$. Likewise, for insulin-naïve patients with T2DM, there was a lower incidence of nocturnal confirmed hypoglycemia with IDeg compared with IGlar; the difference was not statistically significant (odds ratio of 0.80 $[0.61; 1.06]_{95\% CI}$). In the analysis of confirmed nocturnal hypoglycemia for patients with T1DM, there was no difference in the incidence of nocturnal confirmed hypoglycemia between IDeg and IGlar (odds ratio of 1.04 [0.76; $1.43]_{95\% CI}$).

As for confirmed hypoglycemia, the incidence of nocturnal confirmed hypoglycemia was consistent with the lower rate of nocturnal confirmed hypoglycemia.

9.2.7 Meta-analysis of Hypoglycemia for Patients with HbA_{1c} <7%

Confirmed Hypoglycemic Episodes by HbA_{1c}

The rate of confirmed hypoglycemia was significantly lower for patients (T1DM+T2DM) who reached HbA_{1c} <7% when treated with IDeg as compared with IGlar (Table 48). Hence, patients treated with IDeg experienced a 14% lower rate of hypoglycemic episodes compared with IGlar. In the maintenance period, the rate of confirmed hypoglycemia was 21% lower for IDeg compared with IGlar (Table 48).

For T2DM patients and insulin-naïve T2DM patients on basal-only therapy, the rate of confirmed hypoglycemic episodes was significantly lower with IDeg than with IGlar, both in the entire treatment period and in the maintenance period (Table 48). The rate of confirmed hypoglycemic episodes in T2DM patients on basal-only therapy was significantly lower with IDeg than with IGlar in the maintenance period but not in the in the entire treatment period (Table 48). There were no statistically significant treatment differences for patients with T1DM who achieved HbA_{1c} <7% in either the entire treatment period or the maintenance period (Table 48). The rate ratios for the four subgroups were lower during the maintenance phase than during the entire treatment period.

Hypoglycemia generally increases as patients approach glycemic goals (e.g., HbA_{1c} <7%) using insulin therapy. However, IDeg treatment in patients with T2DM generally resulted in lower rates of confirmed hypoglycemia compared with IGlar treatment, and this lower rate was even more pronounced during the maintenance phase of the trials. Therefore, patients with T2DM using IDeg

obtain the benefit of a lowered confirmed hypoglycemia rate compared with IGlar, even when they achieve their glycemic goals.

Table 48 Meta-analysis of Confirmed Hypoglycemic Episodes during the Entire Treatment Period (from Week 0) and Maintenance Period (from Week 16) for Patients with HbA_{1c} < 7% at End of Trial

		Entire Treatment Period Estimated Rate-Ratio	Maintenance Treatment Period Estimated Rate-Ratio
	Comparison	Estimate [95% CI]	Estimate [95% CI]
T2DM Basal-only therapy	IDeg vs. IGlar	0.88 [0.69; 1.10]	0.77 [0.58; 1.02]
T2DM	IDeg vs. IGlar	0.80 [0.68; 0.93]*	0.74 [0.61; 0.89]*
T1DM	IDeg vs. IGlar	1.12 [0.89; 1.39]	1.00 [0.78; 1.30]
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.86 [0.76; 0.98]*	0.79 [0.68; 0.92]*

*Ratio significantly different than 1.

T2DM: Trials 3672, 3579, 3582, 3586 and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583. Full analysis set.

Nocturnal Confirmed Hypoglycemic Episodes by HbA_{1c}

For patients who reached HbA_{1c} <7%, the rates of nocturnal confirmed hypoglycemia were significantly lower for pooled patients (T1DM+T2DM), T2DM patients, and insulin-naïve T2DM patients on basal-only therapy, when treated with IDeg as compared with IGlar (Table 49). The rates of nocturnal confirmed hypoglycemia were to 37-51% lower with IDeg compared with IGlar for these groups. There were no statistically significant treatment differences observed in T1DM patients over the entire trial period (Table 49); in the maintenance period the rate of nocturnal confirmed hypoglycemia was significantly lower (by 33%) with IDeg compared with IGlar.

Table 49 Meta-analysis of Nocturnal Confirmed Hypoglycemic Episodes during the Entire Treatment Period (from Week 0) and Maintenance Period (from Week 16) for Patients with HbA_{1c} <7% at End of Trial

		Entire Treatment Period Estimated Rate-Ratio	Maintenance Treatment Period Estimated Rate-Ratio
	Comparison	Estimate [95% CI]	Estimate [95% CI]
T2DM Basal-only therapy	IDeg vs. IGlar	0.56 [0.38; 0.84]*	0.49 [0.30; 0.81]*
T2DM	IDeg vs. IGlar	0.56 [0.44; 0.72]*	0.53 [0.39; 0.72]*
T1DM	IDeg vs. IGlar	0.81 [0.59; 1.10]	0.67 [0.47; 0.95]*
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.63 [0.52; 0.77]*	0.57 [0.45; 0.72]*

*Ratio significantly different than 1.

T2DM: Trials 3672, 3579, 3582, 3586, and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583.

9.2.8 Meta-analysis of Daytime Hypoglycemia

Daytime hypoglycemia is defined as the non-nocturnal period between 6:00 a.m. to midnight. For the combined T1DM+T2DM patients, the rate of daytime confirmed hypoglycemia for IDeg treatment was not significantly different to that of IGlar treatment (rate ratio of 0.95 [0.86; 1.04]$_{95\%CI}$). When the analysis was repeated for patients with T1DM the result pointed towards a lower rate of daytime confirmed hypoglycemia with IGlar (estimated rate ratio of 1.14 [0.99; 1.31]$_{95\%\ CI}$). For patients with T2DM, the rate of daytime confirmed hypoglycemia for IDeg was significantly lower compared to IGlar (rate ratio of 0.88 [0.78; 0.99]$_{95\%\ CI}$). This was supported by the analysis of insulin-naïve patients with T2DM, although the result was not statistically significant (rate ratio of 0.88 [0.74; 1.06]$_{95\%\ CI}$).

9.2.9 Meta-analysis of Nocturnal Hypoglycemia with Alternate Nocturnal Time Periods

The global trial program included patients with very different lifestyles, including sleeping and eating habits. The prespecified nocturnal period (between midnight and 6 a.m.) was selected to reflect the time in which most patients were asleep, not eating, and not taking bolus insulin. This period was determined to be least likely to be influenced by confounding factors. The FDA also requested additional analyses defining the nocturnal period to be between midnight and 8 a.m., and between 10 PM and 6 a.m., which was provided.

In the midnight to 8 a.m. interval, the tendency towards a benefit for IDeg over comparator was maintained (Table 50). In the time period between 10 PM and 6 a.m., the result of the meta-analysis was almost identical to that obtained using the prespecified definition between midnight and 6 a.m. The cross-trial meta-analysis demonstrated that IDeg provides a benefit in terms of a lower risk of nocturnal confirmed hypoglycemia versus comparator when using the alternative definitions of nocturnal confirmed hypoglycemia. These analyses further support the robustness of the observations derived from the prespecified definition of nocturnal confirmed hypoglycemia used in the NDA.

Table 50 Meta-analysis of Nocturnal Confirmed Hypoglycemia by Different Nocturnal Time Periods

	Prespecified Nocturnal Period	**---------- FDA specified Nocturnal Period ----------**	
	Midnight to 6 a.m.	**Midnight to 8 a.m.**	**10 p.m. to 6 a.m.**
Pooled (T2DM + T1DM)	0.74 [0.65; 0.85]*	0.91 [0.82; 1.02]	0.74 [0.66; 0.83]*

*Ratio significantly different than 1.
Trials included: 3583, 3770 (excl. flexible dosing arm), 3582, 3579, 3586, 3672, and 3668. Comparator: IGlar

9.2.10 Meta-analysis of Symptomatic and Asymptomatic Hypoglycemia

Confirmed hypoglycemia and nocturnal confirmed hypoglycemia were further investigated by categorizing the episodes into symptomatic and asymptomatic episodes. Overall, the majority (74.3%) of the confirmed hypoglycemic episodes were symptomatic, as were most (82.2%) of the nocturnal confirmed episodes.

Symptomatic and Asymptomatic Confirmed Hypoglycemia

The rate of symptomatic confirmed hypoglycemia for pooled T2DM+T1DM patients was statistically significantly lower (by 13%) with IDeg compared to IGlar (Table 51). The rates of symptomatic confirmed hypoglycemia in patients with T2DM and patients with T2DM taking basal-only therapy were statistically significantly lower (by 25% and 28%, respectively) with IDeg than with IGlar, consistent with the results of the primary analysis. There was no difference in the rates of either symptomatic or asymptomatic confirmed hypoglycemic episodes for patients with T1DM (Table 51). For asymptomatic episodes, all estimated rate ratios were below or equal to 1, with no statistically significant differences between IDeg and IGlar. The results supported the primary analysis and importantly, point to the fact that the lower rates of symptomatic episodes were not achieved at the expense of higher rates of asymptomatic episodes.

Table 51 Meta-analysis of Symptomatic and Asymptomatic Confirmed Hypoglycemia

		Symptomatic Hypoglycemia	Asymptomatic Hypoglycemia
	Comparison	**Estimate [95% CI]**	**Estimate [95% CI]**
T2DM Basal-only therapy	IDeg vs. IGlar	0.72 [0.58; 0.90]*	0.93 [0.75; 1.17]
T2DM	IDeg vs. IGlar	0.75 [0.66; 0.86]*	0.96 [0.81; 1.13]
T1DM	IDeg vs. IGlar	1.14 [0.97; 1.32]	1.00 [0.79; 1.26]
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.87 [0.78; 0.96]*	0.97 [0.85; 1.11]

*Ratio significantly different than 1.
T2DM: Trials 3672, 3579, 3582, 3586, and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583

Symptomatic and Asymptomatic Nocturnal Confirmed Hypoglycemia

The rate of symptomatic nocturnal confirmed hypoglycemia for pooled T2DM+T1DM patients was statistically significantly lower (by 28%) with IDeg compared to IGlar (Table 52). In T2DM and T2DM patients on basal-only therapy, the rates of symptomatic nocturnal confirmed hypoglycemia were statistically significantly lower (by 38% and 44%, respectively) with IDeg compared to IGlar, consistent with the confirmatory analysis of nocturnal confirmed hypoglycemia in the pooled population. The lower rates of symptomatic nocturnal confirmed hypoglycemic episodes were not seen at the expense of a higher rate of asymptomatic hypoglycemia, as all estimated treatment ratios for asymptomatic hypoglycemia were below 1, and were in favor of IDeg. There was no statistically

significant treatment difference in the rate of symptomatic or asymptomatic nocturnal confirmed hypoglycemia for patients with T1DM (Table 52).

Table 52 Meta-analysis of Symptomatic and Asymptomatic Nocturnal Confirmed Hypoglycemia

		Symptomatic Hypoglycemia		Asymptomatic Hypoglycemia	
	Comparison	**Estimate**	**[95% CI]**	**Estimate**	**[95% CI]**
T2DM Basal-only therapy	IDeg vs. IGlar	0.56	[0.39; 0.80]*	0.76	[0.48; 1.19]
T2DM	IDeg vs. IGlar	0.62	[0.50; 0.76]*	0.91	[0.67; 1.24]
T1DM	IDeg vs. IGlar	0.88	[0.72; 1.08]	0.77	[0.53; 1.12]
Pooled (T2DM + T1DM)	IDeg vs. IGlar	0.72	[0.62; 0.84]*	0.83	[0.66; 1.05]

*Ratio significantly different than 1.
T2DM: Trials 3672, 3579, 3582, 3586 and 3668 (excluding flexible dosing arm); basal-only therapy: Trials 3672, 3579 and 3586; T1DM: Trials 3770 (excluding flexible dosing arm) and 3583.

9.3 Hypoglycemia in IDegAsp Trials

9.3.1 Hypoglycemia with IDegAsp Therapy in T2DM

Once-daily IDegAsp Therapy in T2DM

A confounding factor to the comparison of hypoglycemia in Trials 3593 and 3590 is the fact that these trials used a fixed-ratio combination insulin (IDegAsp), containing both basal and rapid-acting components, compared with a basal insulin (IGlar) that did not have a bolus component. When evaluating confirmed hypoglycemia, basal insulin is not the most relevant comparator for a coformulation product although insights still can be gained from the rates of nocturnal confirmed hypoglycemia in which the impact of the bolus insulin is less apparent.

In the IDegAsp Trial 3593, a similar proportion of patients (~50%) in the two treatment groups experienced confirmed hypoglycemic episodes (Table 53). In Trial 3590, the proportion of patients experiencing confirmed hypoglycemic episodes was higher in the IDegAsp once-daily group compared with the IGlar once-daily group. The rate of confirmed hypoglycemia was significantly higher with IDegAsp than with IGlar in Trials 3590 and 3593 (Table 54).

Patients treated with IDegAsp OD experienced fewer episodes of nocturnal confirmed hypoglycemia compared to patients treated with IGlar in both Trials 3593 and 3590 (Table 53). The rate of nocturnal hypoglycemia was 20% lower with IDegAsp than with IGlar in Trial 3593 and 71% lower than IGlar in Trial 3590 (statistically significant) (Table 54).

In trials with IDegAsp OD therapy, very few events of severe hypoglycemia were reported; no events occurred in Trial 3593 and 1 event occurred in Trial 3590. Once-daily IGlar therapy resulted in 4 events of severe hypoglycemia in Trial 3593 and 1 event in Trial 3590 (Table 53).

Table 53 Confirmed, Nocturnal Confirmed and Severe Hypoglycemic Episodes – IDegAsp Once Daily T2DM Trials

Trial	IDegAsp OD				IGlar			
Classification	N	%	E	R	N	%	E	R
T2DM OD 6m (Trial 3593)								
Number of patients	230				233			
Confirmed	121	52.6	451	431.4	112	48.1	344	320.1
Nocturnal confirmed	44	19.1	86	82.3	49	21.0	108	100.5
Severe	0		0		3	1.3	4	3.7
T2DM OD 6m (Trial 3590)								
Number of patients	265				261			
Confirmed	132	49.8	500	422.8	96	36.8	226	185.3
Nocturnal confirmed	13	4.9	22	18.6	30	11.5	56	45.9
Severe	1	0.4	1	0.8	1	0.4	1	0.8

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years. For definition of hypoglycemia, see Section 6.3, Safety analysis set.

Table 54 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – Statistical Analysis – IDegAsp Once Daily T2DM Trials

Trial	Comparison	Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]
T2DM OD 6m (3593)	IDegAsp vs. IGlar	1.43 [1.07; 1.92]	0.80 [0.49 ; 1.30]
T2DM OD 6m (3590)	IDegAsp vs. IGlar	2.17 [1.59; 2.94]	0.29 [0.13 ; 0.65]*

*Ratio significantly different from 1.
The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1).
Estimated rate: estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia. Full analysis set.

Twice-daily IDegAsp Therapy in T2DM

The rate of severe hypoglycemia was lower with IDegAsp BID than BIAsp 30 BID in Trial 3592, and was similar in Trial 3597.

The rate of confirmed hypoglycemic episodes in Trial 3592 was significantly lower by 32% for the IDegAsp BID group compared to the BIAsp 30 BID (Table 56). The rates of confirmed hypoglycemia in the IDegAsp BID groups were comparable across Trials 3592 and 3597 (Table 55).

In Trials 3592 and 3597, patients treated with IDegAsp BID experienced fewer episodes of nocturnal confirmed hypoglycemia than with BIAsp 30 BID (Table 55). The 73% lower rate of nocturnal confirmed hypoglycemia with IDegAsp BID treatment was significantly lower than with BIAsp 30 BID in Trial 3592 (Table 56). Trial 3597, in which Asian patients were studied, yielded an estimated rate ratio that was 33% lower for IDegAsp BID compared with BIAsp 30 BID; however, the difference was not statistically significant (Table 56).

Table 55 Confirmed, Nocturnal Confirmed, and Severe Hypoglycemic Episodes – IDegAsp Twice Daily T2DM Trials

Trial	IDegAsp BID				BIAsp 30			
Classification	N	%	E	R	N	%	E	R
T2DM BID 6m (Trial 3592)								
Number of patients	224				222			
Confirmed	148	66.1	993	971.7	153	68.9	1379	1396
Nocturnal confirmed	52	23.2	76	74.4	80	36.0	250	253.1
Severe	7	3.1	9	8.8	16	7.2	25	25.3
T2DM BID 6m (Trial 3597)								
Number of patients	279				141			
Confirmed	205	73.5	1227	956.0	107	75.9	621	952.3
Nocturnal confirmed	70	25.1	143	111.4	44	31.2	101	154.9
Severe	4	1.4	6	4.7	2	1.4	2	3.1

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years. For definition of hypoglycemia, see Section 6.3. Safety analysis set.

Table 56 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – Statistical Analysis IDegAsp Twice Daily T2DM Trials

Trial	Comparison	Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]
T2DM BID 6m (3592)	IDegAsp vs. BIAsp 30	0.68 [0.52; 0.89]*	0.27 [0.18 ; 0.41]*
T2DM BID 6m (3597)	IDegAsp vs. BIAsp 30	1.00 [0.76; 1.32]	0.67 [0.43 ; 1.06]

*Ratio significantly different from 1.
The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1).
Estimated rate: Estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia. Full analysis set.

9.3.2 Hypoglycemia with IDegAsp Therapy in T1DM

Basal-bolus Therapy in T1DM

Severe, Confirmed, and Nocturnal Confirmed Hypoglycemia

In Trial 3594, severe hypoglycemia was reported by 10% of the patients taking IDegAsp and 12% of the patients taking IDet. The rate of severe hypoglycemia was 33 episodes per 100 PYE for the patients in the IDegAsp group, and was 42 episodes per 100 PYE for patients in the IDet group.

The majority of T1DM patients (approximately 94%) treated with once-daily IDegAsp or IDet, both in combination with mealtime IAsp for 26 weeks, experienced at least one episode of confirmed hypoglycemia (Table 57). The rate of confirmed hypoglycemic episodes was similar between treatment groups in Trial 3594 (Table 57). There was no statistically significant difference for confirmed hypoglycemia between treatment groups (Table 58).

In Trial 3594, the rate of nocturnal confirmed hypoglycemic episodes was 37% lower with IDegAsp than with IDet. This difference was statistically significant (Table 58).

Table 57 Confirmed, Nocturnal Confirmed and Severe Hypoglycemic Episodes – IDegAsp Once Daily T1DM Trials

Trial	IDegAsp OD				IDet OD			
Classification	N	%	E	R	N	%	E	R
T1DM OD BB 6m (Trial 3594)								
Number of patients	362				180			
Confirmed	341	94.2	6634	3917	168	93.3	3720	4434
Nocturnal confirmed	192	53.0	629	371	125	69.4	480	572
Severe	35	9.7	56	33	22	12.2	35	42

N: number of patients; %: percentage of patients, E: number of events, R: event rate per 100 exposure years. For definition of hypoglycemia classification, see Section 6.3. Safety analysis set.

Table 58 Confirmed and Nocturnal Confirmed Hypoglycemic Episodes – Statistical Analysis – IDegAsp Once Daily T1DM Trials

Trial	Comparison	Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]	Nocturnal Confirmed Hypoglycemia Estimated Rate-Ratio [95% CI]
T1DM OD BB 6m (3594)	IDegAsp OD vs. IDet OD	0.91 [0.76; 1.09]	0.63 [0.49 ; 0.81]*

*Ratio statistically significantly different from 1.

The endpoint was analyzed using a negative binomial model with log link and log of the treatment emergent period as offset (see Section 6.4.1). Estimated rate: estimated rate per 100 exposure years; See Section 6.3 for definition of hypoglycemia classification. Full analysis set.

9.4 Hypoglycemia in Subgroups

As shown in Appendix 1, Table 9 (T2DM) and Appendix 1, Table 10 (T1DM), in the pooled IDeg phase 3 trials, there was no consistent pattern of confirmed hypoglycemia event rate by age group, ethnicity, or race. In addition, there was no consistent pattern of confirmed hypoglycemia event rate for sex, BMI, duration of diabetes, or renal function for the IDeg or comparator treatment groups.

Confirmed hypoglycemia is presented by age group, ethnicity and race for the pooled T2DM IDegAsp trials in Appendix 1, Table 11.

9.5 Hypoglycemia Conclusions

To conclude, comparable improvement in glycemic control was achieved with similar doses of insulin and was accompanied by a lower rate of hypoglycemia with IDeg, especially during the night, reflecting the stable profile and the lower day-to-day variability in glucose-lowering action with IDeg compared to IGlar. The lower rate of nocturnal hypoglycemia was a consistent finding across the individual trials regardless of insulin regimen (basal-only therapy or basal-bolus therapy), time of dosing (once-daily evening or varying dosing intervals [8-12 or 36-40 hours between

injections] for IDeg or largest meal for IDegAsp), type of insulin comparator (IGlar, IDet, BIAsp 30), or patient population (e.g., T1DM, T2DM, insulin-naïve, and elderly patients).

The benefits related to less hypoglycemia with IDeg versus IGlar were further substantiated by a prespecified meta-analysis in the combined T2DM and T1DM patient populations, showing that IDeg was superior to IGlar with 9% and 26% lower rates of confirmed and nocturnal confirmed hypoglycemic episodes, respectively. The lower rate of hypoglycemia compared to IGlar were even more apparent in the maintenance phase when patients were on a stable dose of basal insulin. Lower rates of hypoglycemia with IDeg were demonstrated as patients achieved the target HbA_{1c} <7%.

The clinical benefits of IDeg are retained in the IDegAsp formulation, most notably a reduced risk of nocturnal hypoglycemia. In T2DM patients, improvement in glycemic control with IDegAsp was achieved with a lower rate of nocturnal confirmed hypoglycemia relative to comparator. In T1DM patients, a lower rate of nocturnal confirmed hypoglycemia was achieved with IDegAsp relative to IDet in basal-bolus therapy.

10 Clinical Safety

Summary

Adverse Event Profile

- Safety data in the NDA (cut-off date: January 31, 2011) included 16 therapeutic confirmatory phase 3 trials and 1 extension. The FDA requested additional exposure data. A May 1, 2012 cut-off date was chosen that comprised 9 additional completed phase 3 trials (6 new completed extensions, 2 new phase 3b trials, and 1 new phase 3a trial).
- Total exposure to IDeg+IDegAsp as of May 1, 2012 was 5416.2 patient-years and to comparator was 2566.8 patient-years. Based on data from all completed phase 3 trials as of May 1, 2012, 841 (13.2%) patients were exposed to IDeg or IDegAsp and 269 (7.8%) were exposed to comparator for ≥24 months.
- The AE profile for IDeg+IDegAsp was similar in type, frequency, and severity to comparator. Overall there were no unexpected AEs, and no unique safety issue was identified for IDeg+IDegAsp versus comparators in the NDA, or using a May 1, 2012 cut-off date.
- Serious adverse event rates were similar in the NDA for IDeg+IDegAsp (16.1 events per 100 PYE), and comparator (15.0 events per 100 PYE). The rates for deaths were similar in the IDeg+IDegAsp and comparator groups, 0.6 and 0.5 events per 100 PYE, respectively.
- In the phase 3 trials, rates of AEs leading to withdrawal were 4.5 events per 100 PYE for IDeg+IDegAsp and 3.0 events per 100 PYE for the comparator group. For patients with T2DM or T1DM, there were no apparent differences between the IDeg+IDegAsp group and comparators with respect to the patterns of AEs or SAEs leading to withdrawal.
- The rate of malignant neoplasms with IDeg+IDegAsp (0.9 events per 100 PYE) was similar to that of comparator (0.8 events per 100 PYE). No notable differences were seen between IDeg or IDegAsp and the comparators with regard to allergic reactions, or injection-site reactions.

Cardiovascular Safety

- The IDeg and IDegAsp trials were not designed as cardiovascular outcome trials. However, as part of the overall assessment of safety, cardiovascular events suspected to be major adverse cardiovascular events (MACE) were sent to an independent committee of experts blinded to treatment allocation for adjudication.
- The prespecified MACE composite endpoint for the IDeg and IDegAsp phase 3 trials was cardiovascular death, stroke, and acute coronary syndrome (myocardial infarction [MI] and unstable angina pectoris [UAP]).

- In the IDeg and IDegAsp phase 3 trials included in the NDA, incidence rates were similar between IDeg+IDegAsp (1.48 patients with MACE per 100 PYE [53 patients with MACE]) and comparator (1.44 patients with MACE per 100 PYE [27 patients with MACE]). In the preplanned meta-analysis of time to first MACE, the overall estimated hazard ratio for IDeg+IDegAsp/comparator was 1.097 $[0.681; 1.768]_{95\%CI}$.
- The FDA requested a *post hoc* analysis of the NDA data, excluding UAP from the prespecified MACE composite endpoint. When UAP was excluded, the estimated hazard ratio increased to 1.393 $[0.757; 2.565]_{95\%CI}$, based on 54 MACE.
- The FDA requested an updated MACE analysis with additional exposure and including events up to 30 days (rather than 7 days) after drug discontinuation. Using a May 1, 2012 cut-off, additional data from 9 trials (6 were extensions) were included in the analysis. A May 1, 2012 analysis of MACE up to 30 days after drug discontinuation, excluding UAP, gave an estimated hazard ratio of 1.614 $[0.999; 2.609]_{95\%CI}$.
- The majority of new MACE in the May 1, 2012 analysis set occurred during long-term extensions of randomized trials included in the NDA, which had imbalanced exposure and represented only 35% of the original randomized population. When data from all extensions were excluded, and UAP was included, an analysis of all randomized trials completed as of May 1, 2012 gave a hazard ratio of 1.125 $[0.705; 1.797]_{95\%CI}$, similar to the primary NDA analysis.
- The totality of the MACE data neither confirms nor excludes increased cardiovascular risk.
- No clinically relevant differences in vital signs, ECG, QTc, and lipids were observed between IDeg+IDegAsp and comparator.

Other Safety

- Overall, there were no clinically relevant differences between IDeg+IDegAsp and comparators in terms of weight gain, vital signs, clinical laboratory findings, ECG or antibody formation after 26 or 52 weeks of treatment.

The IDeg and IDegAsp programs included a large number of adults across the spectrum of both T2DM and T1DM, with overall exposures more than meeting current regulatory guidance. As discussed in Section 7, these programs included a substantial number of patients aged ≥65 years and a large percentage of patients with a long duration of diabetes.

IDeg and IDegAsp have a safety profile consistent with currently marketed insulin products. The most common side effects of insulin use include hypoglycemia, injection site reactions, allergic reactions, weight gain, and medication errors.

This section presents data on the adverse events reported in the IDeg+IDegAsp phase 3 trials, with a focus on cardiovascular safety. As IDeg is the major component in IDegAsp, adverse event data from the IDeg and IDegAsp groups were pooled, with the exception of medication errors.

10.1 Safety Methodology

Descriptive safety data were based on the safety analysis set. Statistical analyses of body weight and QTc were based on the full analysis set. In addition, the MACE meta-analysis was based on the full analysis set.

10.1.1 Description of the Trials Included in Evaluations of Safety

Data from the NDA

As of January 31, 2011, 16 therapeutic confirmatory phase 3 trials were conducted to evaluate the efficacy and safety of IDeg (U100 and U200) and IDegAsp (U100). These trials included patients with early onset T2DM, those in the more advanced stages of T2DM, and patients with T1DM (Figure 15). No unique safety concerns were observed for patients treated with IDeg 3TW, or in patients treated in Trial 3580 (IDeg vs. sitagliptin), and for completeness, safety data from these trials (apart from hypoglycemia and injection-site reactions) were included in the safety analysis set. As of the January 31, 2011 cut-off date, only one extension trial (IDegAsp Trial 3645) was completed. This trial was included in the analysis of safety by joining the extension data with the main trial data. The trial ID from the main trial, IDegAsp Trial 3594, was used as the identifier.

Supportive Data Based on Additional Exposure (May 1, 2012 Cut-off Date)

Beyond the data presented in the NDA (January 31, 2011 cut-off date), the May 1, 2012 cut-off contains additional AEs from nine completed phase 3 trials, including 6 completed extensions (5 IDeg and 1 IDegAsp), two new phase 3b trials and one new phase 3a trial. See Section 6.1 for a more detailed summary of these trials. The percentage of patients who completed 52 and 104 weeks of treatment was substantially lower than those who completed 26 weeks of treatment. In addition, the three longest trials with the extension periods (Trials 3579-3643, 3582-3667, and 3583-3644) utilized a 3:1 randomization ratio of IDeg to comparator.

The methods for pooling adverse event data in the May 1, 2012 dataset were the same as those used in the NDA.

Treatment Arms

Two treatment arms were defined for safety analyses:

- IDeg+IDegAsp treatment arm that comprised the two investigational products (OD and 3TW trials for IDeg and OD and BID trials for IDegAsp)
- Comparator treatment arm that comprised all the therapeutic confirmatory phase 3 comparators (BIAsp 30, sitagliptin, IDet, and IGlar)

10.1.2 Exposure

Exposure Data from the NDA

As mentioned in Section 6.2, in order to increase exposure to IDeg or IDegAsp, the randomization of IDeg or IDegAsp versus comparator was either 2:1 or 3:1 in several of the trials, particularly those trials in which extension periods were added.

The number of patients exposed to IDeg or IDegAsp (Table 59) exceeded current regulatory guidelines. A total of 4939 patients were exposed to IDeg or IDegAsp ≥6 months, and 1870 patients were exposed to IDeg or IDegAsp for ≥12 months (Table 60).

Table 59 Patient Exposure by Treatment – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg N	IDegAsp N	IDeg+IDegAsp N	Comparator N	Total N
Phase 3 Trials	4275	1360	5635	3306	8941
Patients with T2DM	3173	998	4171	2659	6830
Insulin-naïve Patients with T2DM	1964	265	2229	1583	3812
Insulin-treated Patients with T2DM	1209	733	1942	1076	3018
Patients with T1DM	1102	362	1464	647	2111

N: number of patients. The comparator column includes pooled comparator data from all IDeg+IDegAsp phase 3 trials. Safety analysis set.

Table 60 Exposure Time (months) – IDeg+IDegAsp Phase 3 Trials – NDA

	Any Exposure		≥ 6 months		≥ 9 months		≥ 12 months		Total Exposure in Patient Years
	N	%	N	%	N	%	N	%	
All Patients									
IDeg+IDegAsp	5635	100.0	4939	87.6	1931	34.3	1870	33.2	3578.4
Comparator	3306	100.0	2920	88.3	684	20.7	662	20.0	1878.0
Patients with T2DM									
IDeg+IDegAsp	4171	100.0	3626	86.9	1268	30.4	1231	29.5	2554.7
Comparator	2659	100.0	2327	87.5	425	16.0	411	15.5	1437.6
Insulin-naïve Patients with T2DM									
IDeg+IDegAsp	2229	100.0	1922	86.2	633	28.4	611	27.4	1338.2
Comparator	1583	100.0	1376	86.9	205	13.0	199	12.6	831.7
Insulin-treated Patients with T2DM									
IDeg+IDegAsp	1942	100.0	1704	87.7	635	32.7	620	31.9	1216.5
Comparator	1076	100.0	951	88.4	220	20.4	212	19.7	605.9
Patients with T1DM									
IDeg+IDegAsp	1464	100.0	1313	89.7	663	45.3	639	43.6	1023.7
Comparator	647	100.0	593	91.7	259	40.0	251	38.8	440.4

N: Number of patients. %: percentage of patients; A month is defined as 30 days. Completers in 26 weeks and 52 weeks trials count as having 6 months and 12 months exposure respectively. Safety analysis set.

Data Based on Extended Exposure up to May 1, 2012

Using a May 1, 2012 cut-off, a total of 6374 patients were exposed to IDeg or IDegAsp and 3455 to comparator in all completed phase 3 clinical trials (Table 61). Compared with the NDA, there were an additional 739 patients exposed to IDeg+IDegAsp and 149 exposed to comparator using the May

1, 2012 cut-off. The two phase 3b trials in which different regimens of IDeg were compared, Trials 3846 and 3923, contributed to the unbalanced exposure. These trials do not provide comparative safety information.

Total exposure to IDeg+IDegAsp is 5416.2 patient-years and to comparator is 2566.8 patient-years (Table 62). Based on data from all completed phase 3 trials as of May 1, 2012, 841 (13.2%) patients were exposed to IDeg or IDegAsp and 269 (7.8%) were exposed to comparator for ≥24 months (Table 62).

Table 61 Patient Exposure by Treatment – IDeg+IDegAsp Phase 3 Trials – May 1, 2012

	IDeg N	IDegAsp N	IDeg+IDegAsp N	Comparator N	Total N
Phase 3 Trials	4867	1507	6374	3455	9829
Patients with T2DM	3765	1145	4910	2808	7718
Insulin-naïve Patients with T2DM	2185	412	2597	1732	4329
Insulin-treated Patients with T2DM	1580	733	2313	1076	3389
Patients with T1DM	1102	362	1464	647	2111

N: number of patients. The comparator column includes pooled comparator data from all IDeg+IDegAsp phase 3 trials up to May 1, 2012. Safety analysis set.

Table 62 Exposure Time (months) – IDeg+IDegAsp Phase 3 Trials – May 1, 2012

	Any Exposure		≥ 6 months		≥ 12 months		≥ 18 months		≥ 24 months		Total Exposure in Patient Years
	N	%	N	%	N	%	N	%	N	%	
All Patients											
IDeg+IDegAsp	6374	100	5276	82.8	2518	39.5	1419	22.3	841	13.2	5416.2
Comparator	3455	100	3057	88.5	1113	32.2	465	13.5	269	7.8	2566.8
Patients with T2DM											
IDeg+IDegAsp	4910	100	3963	80.7	1412	28.8	1073	21.9	510	10.4	3795.8
Comparator	2808	100	2464	87.7	624	22.2	350	12.5	156	5.6	1881.5
Insulin-naïve Patients with T2DM											
IDeg+IDegAsp	2597	100	2259	87.0	792	30.5	532	20.5	510	19.6	2152.0
Comparator	1732	100	1513	87.4	412	23.8	166	9.6	156	9.0	1182.0
Insulin-treated Patients with T2DM											
IDeg+IDegAsp	2313	100	1704	73.7	620	26.8	541	23.4	0		1643.8
Comparator	1076	100	951	88.4	212	19.7	184	17.1	0		699.5
Patients with T1DM											
IDeg+IDegAsp	1464	100	1313	89.7	1106	75.5	346	23.6	331	22.6	1620.4
Comparator	647	100	593	91.7	489	75.6	115	17.8	113	17.5	685.3

N = Number of patients; %: Percentage of patients. A month is defined as 30 days. Completers in 26-week, 52-week, 78-week and 104-week trials count as having 6, 12, 18 and 24 months of exposure respectively. Safety analysis set.

10.2 Adverse Event Profile

The AE profile for IDeg+IDegAsp was similar in type, frequency, and severity to comparator; this includes the subsets of both T2DM and/or T1DM patients.

Per protocol, in the phase 3 trials, a treatment-emergent AE is defined as an event that has an onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment. A follow-up visit was scheduled at least 7 days after drug discontinuation to ensure that all adverse events were captured in a systematic and rigorous manner for the complete trial period. Events occurring after this follow-up visit, and hence outside the trial period, were only reported to Novo Nordisk at the discretion of the investigator. The adverse events described in this document are treatment-emergent unless otherwise specified.

The AE evaluation focused on the rate of AEs because it takes into account the number of events, the number of patients, and the exposure time.

Overall, there were no unexpected AEs and no unique safety issue was identified for IDeg+IDegAsp versus comparators in the NDA or using the later cut-off date of May 1, 2012. The distribution and rate of AEs were similar between treatment groups in the clinical trials. The majority of AEs were mild in severity and the rates of severe AEs were low and comparable between groups.

10.2.1 Common Adverse Events

In the NDA, the proportions of all patients who reported AEs and the rates of AEs were similar for IDeg+IDegAsp and comparators (Table 63). In both groups, the majority of AEs were of mild or moderate severity. Rates of severe AEs were similar between IDeg+IDegAsp (20.1 events per 100 PYE) and comparator (22.3 events per 100 PYE). The most frequent treatment-emergent AEs, reported by ≥5% of patients, are summarized by treatment in Table 64.

Table 63 Treatment-emergent Adverse Events – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp				Comparator			
	N	%	E	R	N	%	E	R
Safety Analysis Set	5635				3306			
All Adverse Events	3904	69.3	15012	419.5	2172	65.7	7719	411.0
Serious Adverse Events	452	8.0	576	16.1	227	6.9	282	15.0
Adverse Events Leading to Death	18	0.3	21	0.6	8	0.2	9	0.5
Adverse Events Possibly or Probably Related to IMP	817	14.5	1340	37.4	438	13.2	707	37.6
Severity								
Mild	3410	60.5	10794	301.6	1882	56.9	5490	292.3
Moderate	1629	28.9	3496	97.7	907	27.4	1808	96.3
Severe	513	9.1	721	20.1	259	7.8	419	22.3
Unknown	1	0.0	1	0.0	2	0.1	2	0.1
Adverse Event Withdrawals	123	2.2	160	4.5	46	1.4	56	3.0

N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events, R: Number of events divided by patient years of exposure multiplied by 100; IMP = Investigational Medicinal Product. Safety analysis set.

Table 64 Treatment-emergent Adverse Events in ≥5% of Patients by System Organ Class and Preferred Term – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp				Comparator			
	N	%	E	R	N	%	E	R
Safety Analysis Set	5635				3306			
Total Exposure (years)	3578.4				1878.0			
All Adverse Events	3904	69.3	15012	419.5	2172	65.7	7719	411.0
Infections and infestations								
Nasopharyngitis	842	14.9	1121	31.3	397	12.0	535	28.5
Upper respiratory tract infection	463	8.2	611	17.1	243	7.4	315	16.8
Gastrointestinal disorders								
Diarrhea	297	5.3	375	10.5	198	6.0	236	12.6
Nervous system disorders								
Headache	499	8.9	868	24.3	237	7.2	350	18.6

N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Patient years of exposure multiplied by 100. Total Exposure (years): Total exposure in years for safety analysis set.

In patients with T2DM, AE rates were similar for IDeg+IDegAsp (406.0 events per 100 PYE) and comparators (395.8 events per 100 PYE). In the T2DM population, the most frequently reported AEs for both IDeg+IDegAsp and comparators were nasopharyngitis, headache, upper respiratory tract infection, and diarrhea.

In patients with T1DM, AE rates were similar for IDeg+IDegAsp (453.3 events per 100 PYE) and comparators (460.7 events per 100 PYE). In T1DM, the most frequently reported AEs for both IDeg+IDegAsp and comparators were the same as those reported in T2DM, with the addition of hypoglycemia.

10.2.2 Serious Adverse Events and Deaths

Serious adverse events in all patients in the phase 3 trials are summarized in Table 65. SAE rates were similar for IDeg+IDegAsp (16.1 events per 100 PYE), and comparators (15.0 events per 100 PYE).

Table 65 Treatment-emergent Serious Adverse Events – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp				Comparator			
	N	%	E	R	N	%	E	R
Safety Analysis Set	5635				3306			
Serious Adverse Events	452	8.0	576	16.1	227	6.9	282	15.0
Serious Adverse Events Leading to Death*	18	0.3	21	0.6	8	0.2	9	0.5
Serious Adverse Events Possibly or Probably Related to IMP	108	1.9	139	3.9	45	1.4	55	2.9
Severity								
Mild	40	0.7	44	1.2	24	0.7	26	1.4
Moderate	147	2.6	168	4.7	85	2.6	93	5.0
Severe	293	5.2	364	10.2	134	4.1	163	8.7
Serious Adverse Event Withdrawals	75	1.3	87	2.4	32	1.0	36	1.9

*The number of AEs with fatal outcome exceeds the number of patients who died because a patient can have more than one AE with fatal outcome.
N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by patient years of exposure multiplied by 100; IMP = Investigational Medicinal Product. Safety analysis set.

In T2DM, the rates of SAEs were similar for IDeg+IDegAsp (15.3 events per 100 PYE), and the comparators (14.6 events per 100 PYE). In the T2DM trials, ≥1% of patients in the IDeg+IDegAsp and comparator groups reported SAEs in the system-organ-classes (SOC) Cardiac disorders and Infections and infestations. SAE rates in the Cardiac disorders SOC were 3.2 and 2.9 events per 100 PYE for IDeg+IDegAsp and comparator, respectively. SAE rates in the Infections and infestations SOC were 2.3 and 1.8 events per 100 PYE for IDeg+IDegAsp and comparator, respectively.

In T1DM, the rates of SAEs were similar for IDeg+IDegAsp (18.1 events per 100 PYE) and comparators (16.3 events per 100 PYE). In the T1DM trials, ≥1% of patients in the IDeg+IDegAsp and comparator groups reported SAEs in the SOC Metabolism and nutrition disorders. SAE rates in the Metabolism and nutrition disorders SOC were 10.2 events per 100 PYE for both IDeg+IDegAsp and comparator.

In the phase 3 trials in the NDA, the rates for deaths were similar in the IDeg+IDegAsp and comparator groups, 0.6 and 0.5 events per 100 PYE, with 18 deaths in the IDeg+IDegAsp group and 8 deaths in the comparator group (see Table 65 and Table 66). Ten (10) of the 18 deaths in the IDeg+IDegAsp arm and 5 of the 8 deaths in the comparator arm were due to cardiovascular events. Nine (9) deaths in the IDeg+IDegAsp arm and 5 in the comparator arm were adjudicated as MACE (Table 66).

Table 66 Patients Who Died in IDeg+IDegAsp Phase 3 Trials − NDA

Trial ID	Trial Product	Age (yrs)/ Sex	Type of Diabetes	Treatment-emergent AE (Preferred Term)
IDeg+IDegAsp				
3770	IDeg	46/F	T1DM	Completed suicide, Hypoglycemic coma
3583	IDeg	67/M	T1DM	Myocardial infarction*
3583	IDeg	60/M	T1DM	Myocardial infarction*
3668	IDeg	72/F	Insulin-treated T2DM	Anemia Myelo-dysplastic syndrome
3582	IDeg	65/M	Insulin-treated T2DM	Arteriosclerosis*, Hypertensive heart disease
3582	IDeg	58/M	Insulin-treated T2DM	Myocardial infarction*
3582	IDeg	69/M	Insulin-treated T2DM	Hemorrhage intracranial*
3582	IDeg	63/M	Insulin-treated T2DM	Cardio-respiratory arrest*
3582	IDeg	69/M	Insulin-treated T2DM	Hematemesis
3582	IDeg	67/F	Insulin-treated T2DM	Cardiac arrest*
3582	IDeg	53/M	Insulin-treated T2DM	Myocardial infarction†
3582	IDeg	57/M	Insulin-treated T2DM	Road traffic accident
3580	IDeg	49/M	Insulin-naïve T2DM	Myocardial infarction*
3586	IDeg	69/M	Insulin-naïve T2DM	Drowning
3592	IDegAsp	41/M	Insulin-treated T2DM	Interstitial lung disease
3597	IDegAsp	85/F	Insulin-treated T2DM	Interstitial lung disease
3590	IDegAsp	62/M	Insulin-naïve T2DM	Hepatic cancer metastatic
3590	IDegAsp	60/M	Insulin-naïve T2DM	Death*
Comparator				
3583	IGlar	26/F	T1DM	Sudden death*
3582	IGlar	61/M	Insulin-treated T2DM	Metastatic neoplasm
3582	IGlar	49/M	Insulin-treated T2DM	Myocardial infarction*
3668	IGlar	63/M	Insulin-treated T2DM	Death*
3579	IGlar	73/M	Insulin-naïve T2DM	Urosepsis
3672	IGlar	64/M	Insulin-naïve T2DM	Myocardial ischemia*
3672	IGlar	55/M	Insulin-naïve T2DM	Pneumonia, Acute myocardial infarction*
3592	BIAsp 30	71/M	Insulin-treated T2DM	Head injury

* Fatal events in these patients were also adjudicated Major Adverse Cardiovascular Events (MACE)
† Event was not adjudicated as MACE because the patient died from hemodynamic collapse following prostatectomy.
One fatal event was considered non-treatment-emergent and was not included in the above table: Trial ID = 3579, SRC Reported Term = Sudden cardiac death (IDeg). Another death occurred in a therapeutic exploratory trial: Trial ID = 1792; Preferred term: cardiac failure (BIAsp 30).

Using the May 1, 2012 cut-off, SAE rates were 16.2 and 15.0 events per 100 PYE with IDeg+IDegAsp and comparator, similar to the NDA.

Using a May 1, 2012 cut-off, 30 patients in the IDeg+IDegAsp group (0.5%) and 13 patients in the comparator group (0.4%) died (Appendix 1, Table 12). As of May 1, 2012, 15 of the 30 (50%) deaths in the IDeg+IDegAsp arm and 8 of the 13 (62%) deaths in the comparator arm were adjudicated as MACE (Appendix 1, Table 12).

10.2.3 Withdrawals Due to Adverse Events

In the phase 3 trials, rates of AEs leading to withdrawal were 4.5 events per 100 PYE for IDeg+IDegAsp, and 3.0 events per 100 PYE for the comparators.

For patients with T2DM, the rates of AEs leading to withdrawal were 4.4 events per 100 PYE for IDeg+IDegAsp and 3.1 events per 100 PYE for comparators. The reason for withdrawal due to AEs varied, with no specific patterns between IDeg+IDegAsp and comparator. The single most common AE leading to withdrawal was "weight increased" (7 patients (0.2%) with IDeg+IDegAsp and 3 patients (0.1%) with comparator). In patients with T2DM, 4 patients (0.1%) treated with IDeg+IDegAsp withdrew due to AEs related to hypoglycemia compared with 3 patients (0.1%) treated with comparators. AEs related to hypoglycemia are AEs where the preferred term included "hypoglycemia."

In patients with T1DM, the rates of AEs leading to withdrawal were higher for IDeg+IDegAsp (4.6 events per 100 PYE) than comparators (2.5 events per 100 PYE). The most frequent AEs leading to withdrawal were related to hypoglycemia, accounting for about one-third of the withdrawals due to AEs. In patients with T1DM, a total of 14 patients (1.0%) (9 IDeg and 5 IDegAsp) withdrew due to hypoglycemic adverse events compared with 1 patient (0.2%) treated with comparator products.

It is possible that the higher rate of withdrawal due to hypoglycemia in the IDeg+IDegAsp group was related to the lack of experience with this new insulin formulation by both investigator and patient and the lack of dose reduction when switching from pre-trial insulin to IDeg or IDegAsp. Moreover, for patients treated with comparator insulin products, withdrawal may be less attractive since there is no available alternative therapy associated with lower risk of hypoglycemia.

10.2.4 Adverse Events of Special Interest

Apart from hypoglycemia, side effects of insulin include injection site reactions, allergic reactions, and medication errors. These events, along with neoplasms, were considered to be events of special interest in the IDeg and IDegAsp phase 3 programs. Hypoglycemia is presented in Section 9.

Neoplasms

A possible association between diabetes, antidiabetic therapy, and cancer has become a topic of considerable interest in the medical literature, as the incidence of cancer is higher in patients with diabetes than in patients without diabetes. The potential role of increased IGF-1 receptor activation or sustained signaling by the insulin receptor in the development or progression of cancer is debated. To date, no firm association has been established between insulin and increased cancer risk.

The cases of neoplasms reported in the phase 3 trials and captured by a SMQ search plus additional cases of neoplasms reported by the investigator as Medical Events of Special Interest (but not captured by the SMQs) were reviewed by an external independent consultant in a blinded manner for classification into three categories: malignant, benign and unclassifiable.

In all, 211 events were identified and reviewed (149 IDeg+IDegAsp, 62 comparator): 46 events were classified as malignant neoplasms, 140 events as benign neoplasms, and 25 events as unclassifiable (Table 67). The remainder of this section will focus on the events classified as malignant neoplasms.

Table 67 Outcome of External Classification of Neoplasms in the IDeg+IDegAsp Phase 3 Trials − NDA

	IDeg+IDegAsp				Comparator			
	N	%	E	R	N	%	E	R
Safety Analysis Set	5635				3306			
Total Exposure (years)	3578.4				1878.0			
Malignant Neoplasms	30	0.5	31	0.9	15	0.5	15	0.8
Benign Neoplasms	88	1.6	98	2.7	40	1.2	42	2.2
Unclassifiable events	20	0.4	20	0.6	5	0.2	5	0.3

All Neoplasms occurring post randomization are considered, including non-treatment-emergent events.
N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Patient years of exposure multiplied by 100. Safety analysis set.

Malignant Neoplasms

Events categorized as malignant neoplasms are summarized by SOC and preferred terms in Appendix 1, Table 13. An equal proportion of patients in both groups (0.5%) experienced a malignant neoplasm and rates of malignant neoplasms were similar between IDeg+IDegAsp (0.9 events per 100 PYE) and comparator (0.8 events per 100 PYE) (Table 67). The five most frequently reported malignant neoplasm types were skin, gastrointestinal, breast, thyroid and bladder neoplasms. The majority of the malignant neoplasms in the IDeg+IDegAsp group (52%) were reported within 3 months after start of trial treatment, which suggests that a causal relationship is unlikely.

Table 68 Malignant Neoplasms by Body System in the IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp				Comparator			
	N	%	E	R	N	%	E	R
Safety Analysis Set	5635				3306			
Total Exposure (years)	3578.4				1878.0			
All malignant neoplasms	30	0.5	31	0.9	15	0.5	15	0.8
Skin	11	0.2	11	0.3	2	0.1	2	0.1
Basal cell carcinoma	5	0.1	5	0.1	1	0.0	1	0.1
Squamous cell carcinoma	5	0.1	5	0.1	1	0.0	1	0.1
Malignant melanoma	1	0.0	1	0.0	0			
Gastrointestinal	8	0.1	8	0.2	3	0.1	3	0.2
Colorectal	7	0.1	7	0.2	1	0.0	1	0.1
GI other	1	0.0	1	0.0	2	0.1	2	0.1
Other	8	0.1	8	0.2	2	0.1	2	0.1
Breast	2	0.0	2	0.1	3	0.1	3	0.2
Thyroid	1	0.0	1	0.0	3	0.1	3	0.2
Bladder	1	0.0	1	0.0	2	0.1	2	0.1

All malignant neoplasms occurring post randomization are considered, including non-treatment emergent events. There was one non-treatment emergent malignant neoplasm: basal cell carcinoma that occurred 47 days after last dose of IDeg; this event is included in the table.
One IDeg patient had 2 malignant neoplasm adverse events within different body systems (gastrointestinal [colon cancer] and other [lung neoplasm]).
The 'other' category (IDeg+IDegAsp: single events of prostate cancer, bone neoplasm malignant, uterine cancer, renal cancer, laryngeal cancer, metastasis to liver and 2 events of lung neoplasm; Comparator: single events of metastatic neoplasm and endometrial cancer). N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Patient years of exposure multiplied by 100. Total Exposure (years): Total Exposure in years for safety analysis set.

The trial exclusion criteria for cancer did not exclude patients with a prior history of basal cell and squamous cell carcinoma. Based on medical review, 5 of 11 IDeg+IDegAsp patients and 1 of 2 comparator patients had symptoms present at baseline and/or a medical history of skin cancer.

Allergic Reactions

Like other insulin products, IDeg and IDegAsp are protein-based drugs and are therefore associated with a potential risk of allergic reactions, such as local reactions and immune-related reactions.

Investigators were to report events that, in their opinion, may be related to immune reactions to the trial product. Furthermore, a search was performed to identify all potential cases of allergic reactions based on standardized MedDRA queries (SMQ search).

For the IDeg+IDegAsp phase 3 trials, the SMQ search for allergic reactions captured a total of 45 allergic reactions reported by 44 patients (0.8%) in the IDeg+IDegAsp group, compared with 17 allergic reactions reported by 16 patients (0.5%) in the comparator group. The corresponding rates were 1.3 and 0.9 events per 100 PYE, respectively. Urticaria was the most common event in both treatment groups. In addition, there were 16 events (10 IDeg+IDegAsp, 6 comparator) not captured

by the allergic reaction SMQ search, but reported by the investigator to be related to an allergic reaction.

Following a medical review of allergic reaction AEs by medically qualified personnel at Novo Nordisk, 7 events in 7 patients were identified in which a potential allergic reaction to IDeg or IDegAsp could not be ruled out.

- 2 events of hypersensitivity (IDeg) and 1 event of drug hypersensitivity (IDeg): frequency of 0.04%
- 4 events of urticaria (3 IDeg, 1 IDegAsp): frequency of 0.05%

Three (3) events in 2 patients were identified in which a potential allergic reaction to comparator could not be ruled out:

- 1 event of pruritus (IGlar) and 1 event of pruritus generalized (IGlar): frequency of 0.05%
- 1 event of abdominal discomfort (IGlar); frequency of 0.02%

In conclusion, allergic reactions were infrequent with IDeg and IDegAsp.

Injection-site Reactions and Lipodystrophy

In the phase 3 trials, 3.3% of IDeg+IDegAsp patients and 3.1% of comparator patients experienced injection-site reactions. Rates of injection-site reactions were 7.0 events per 100 PYE in the IDeg+IDegAsp group and 9.0 events per 100 PYE in the comparator group. Rates were 7.9 and 7.2 events per 100 PYE in T2DM and 5.2 and 13.4 events per 100 PYE in T1DM for IDeg+IDegAsp and comparator, respectively.

The rates of lipodystrophy in the phase 3 trials were lower for IDeg+IDegAsp (0.4 events per 100 PYE) than comparators (1.0 events per 100 PYE).

Medication Errors

A high-level group term search was performed on all possible cases of medication errors.

In the IDeg phase 3 trials, medication errors were reported in 4.4% of patients (7.3 events per 100 PYE) with IDeg and 2.2% of patients (4.2 events per 100 PYE) with comparator. Mix-ups were evaluated in the four basal-bolus trials, in which IAsp was administered as bolus insulin in both treatment groups (Trials 3582 [T2DM] and 3583, 3585 and 3770 [T1DM]). In T1DM, a total of 5.1% patients treated with IDeg and 3.2% of patients treated with comparator insulin products reported mix-ups between basal and bolus insulin at rates of 8.1 and 5.1 episodes per 100 PYE, respectively. In T2DM, 8.2% of patients on IDeg and 3.6% of patients on comparator reported such mix-ups at rates of 10 and 3.9 episodes per 100 PYE. In the majority of cases, bolus insulin was injected instead of basal insulin, while administration of basal insulin instead of bolus insulin was less pronounced.

In the IDegAsp phase 3 trials, medication errors were reported in 2.4% of patients (5.2 events per 100 PYE) with IDegAsp and 1.5% of patients (3.2 events per 100 PYE) with comparator. In basal-bolus Trial 3594 (T1DM), the majority of medication errors were due to mix-ups and in BID Trial 3592 (T2DM), most medication errors were "incorrect dose administration."

In the IDeg and IDegAsp basal-bolus trials, IDeg, IDegAsp, IDet, and IAsp were administered with the FlexPen® device labeled for trial use (different from the marketed or to be marketed products) and IGlar was administered with the SoloSTAR® Pen device. Approximately 40-50% of all mix-ups led to a hypoglycemic episode, but in most cases, the patients managed their low blood glucose themselves by monitoring it more often and/or by oral intake of carbohydrates.

The final packaging and labeling for the IDeg and IDegAsp marketed products has been developed and optimized to minimize the potential risk for product mix-up. Therefore, the number of mix-ups in the clinical trials does not reflect potential mix-ups of pen-injectors with the final labeling for the marketed products.

10.3 Cardiovascular Safety

The IDeg and IDegAsp programs evaluated cardiovascular risk by collecting AEs as well as measuring vital signs, ECG, QTc, and lipids. This section will focus on the prespecified analysis of adjudicated MACE.

10.3.1 Major Adverse Cardiovascular Events (MACE)

During the End of Phase 2 Meeting, the FDA indicated to Novo Nordisk that although the Agency is not currently holding injectable insulin products to the 95% upper confidence intervals (CIs) of 1.8 and 1.3 for cardiovascular safety assessment, the sponsor should collect, analyze and report cardiovascular data in the NDA as outlined in FDA 2008 CV Risk Guidance document.[33]

The MACE statistical analysis plan was reviewed by the FDA, and a standardized approach for collecting, adjudicating, and analyzing cardiovascular outcomes was used in the phase 3 clinical program. As stated in Section 6.4.3, the primary endpoint in the prespecified MACE meta-analysis was the time until first MACE (or exposure time for patients with no MACE) and was analyzed for the full analysis set using Cox Regression stratified by trial and with treatment (IDeg+IDegAsp and comparators) as explanatory variable. The safety analysis set was used for sensitivity analysis only. Unless otherwise noted, tables and figures in this section are based on the full analysis set.

Exposure time could not be derived for 41 patients with no information on the date of drug discontinuation in the 16 trials included in the prespecified analysis. As none of these patients had any MACE recorded, the patients were excluded from analyses relying on exposure time.

10.3.1.1 Prespecified MACE Composite Endpoint

The MACE composite endpoint for all IDeg and IDegAsp phase 3 trials was prespecified in the phase 3a protocols and in the statistical analysis plan reviewed by the FDA. MACE included the following events:

- Cardiovascular death
- Stroke
- Acute coronary syndrome (ACS)
  - Myocardial infarction (MI)
    - non-ST-elevation MI (NSTEMI)
    - ST-elevation MI (STEMI)
  - Unstable angina pectoris (UAP)

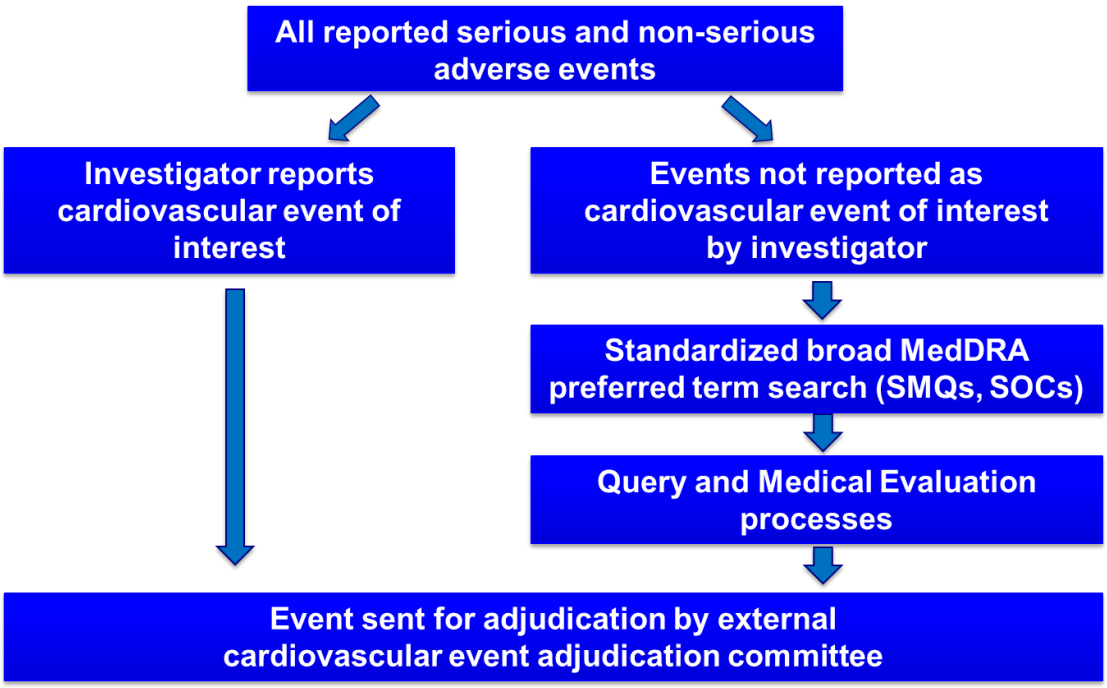
The prespecified MACE composite endpoint definition used in the IDeg and IDegAsp development programs was the same as that used in other large CV outcome trials such as TECOS[34] and CAROLINA[35] for the evaluation of CV safety with DPP-4 inhibitor. These trials were initiated around the same time as the IDeg and IDegAsp phase 3 programs.

All MACE subcategories included in the prespecified MACE composite endpoint were rigorously defined, and were adjudicated in a blinded manner by an external independent adjudication committee. The adjudication criteria used to classify events into the different MACE categories are provided in Appendix 3.

10.3.1.2 MACE Adjudication Process

In all phase 3 trials, the investigators were asked to report cardiovascular events suspected to be related to ACS, stroke or cardiovascular death, and to provide additional information as for SAEs and within the same timeline. In addition, a standardized and broad Medical Dictionary for Regulatory Activities (MedDRA) preferred term search (SMQ, SOCs) on cardiovascular events (MI, other ischemic heart disease, ischemic cerebrovascular conditions, and hemorrhagic cerebrovascular conditions) was performed by a project-independent, internal Novo Nordisk Cardiovascular Events Evaluation Group to ensure identification of all possible cardiovascular events that may have been related to cardiovascular death, stroke, or ACS that were not initially reported as such by the investigator. The broad MedDRA set of terms used was based on FDA draft recommendations outlined in the Endpoints and Standardized Data Collection for Cardiovascular Outcome Trials.[36]

All potential MACE were adjudicated by a blinded, independent external committee in accordance with a predefined set of diagnostic criteria specified in the Event Adjudication Charter (definitions and classifications of ACS, stroke, and cardiovascular death are in Appendix 3). A schematic of the process used for identifying events to be sent for adjudication in all the phase 3 trials is shown in Figure 31.



MedDRA: Medical Dictionary for Regulatory Activities; SMQ: standardized MedDRA query; SOC: system organ class.

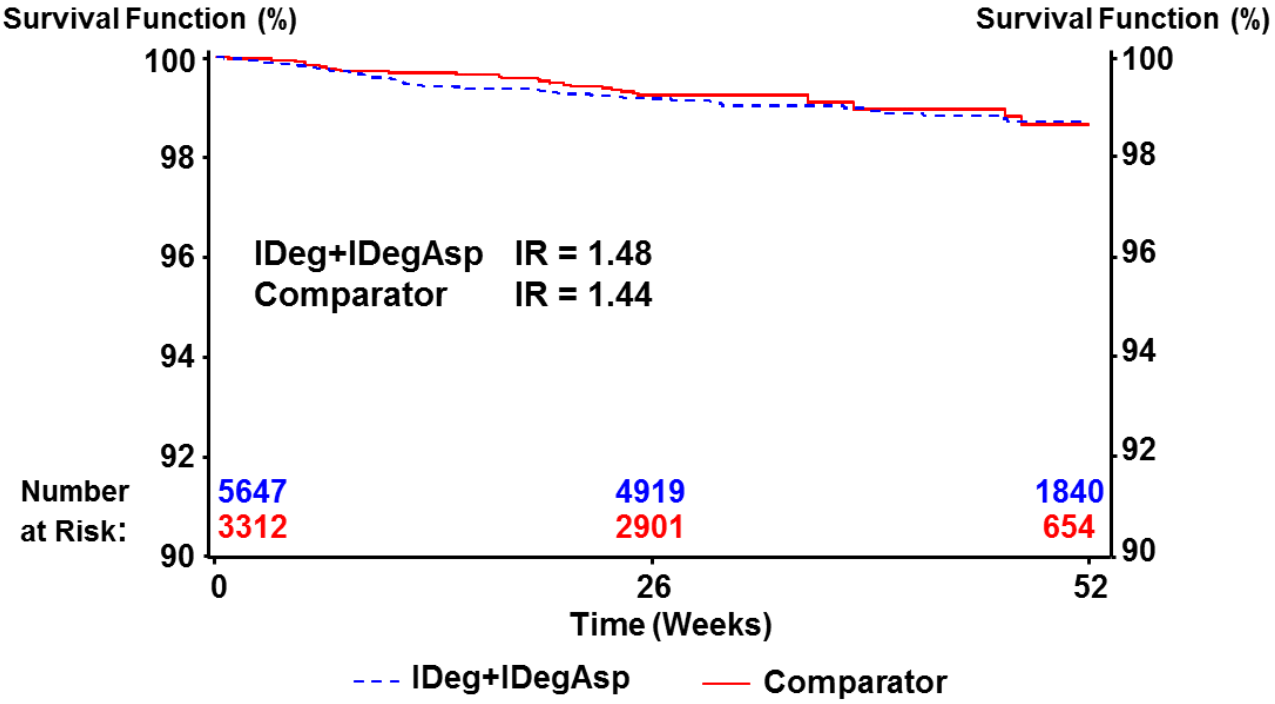
Figure 31 Cardiovascular Event Adjudication Process in the IDeg and IDegAsp Phase 3a Trials

10.3.1.3 Cardiovascular Events Sent for Adjudication − NDA

The rates of reported cardiovascular events that were sent for external adjudication in the phase 3 trials were similar for IDeg+IDegAsp (4.0 events per 100 PYE) and comparators (3.9 events per 100 PYE). A total of 218 events were sent for adjudication of which 38% were adjudicated as MACE in both treatment groups.

10.3.1.4 Prespecified Primary MACE Meta-analysis − NDA

A Kaplan-Meier plot of time to first MACE over 52 weeks shows similar incidence rates for MACE between IDeg+IDegAsp and comparator (1.48 and 1.44 patients with MACE per 100 PYE, respectively) (Figure 32). The numbers of patients at risk decreased substantially with comparator, and the ratio of IDeg+IDegAsp to comparator increased to close to 3:1.



Incidence rate (IR): number of patients with MACE per 100 PYE. Number at risk: number of patients available with no prior events at the given time-point, IDeg+IDegAsp (first row) and comparator (second row). Full analysis set.

Figure 32 Kaplan-Meier Plot of Time to First MACE within 7 Days of Treatment – Prespecified Primary Analysis – IDeg+IDegAsp Phase 3 Trials – NDA

In the 16 phase 3 trials included in the NDA, 80 patients experienced treatment-emergent MACE (53 IDeg+IDegAsp patients and 27 comparator patients); see Table 69 for the classification of these events.

Most patients with stroke experienced ischemic stroke: 9 of the 11 patients in the IDeg+IDegAsp group and all 4 patients in the comparator group. Two of the 11 patients in the IDeg+IDegAsp group had hemorrhagic stroke.

A total of 8 and 4 MACE were adjudicated as cardiovascular death in the IDeg+IDegAsp and comparator groups, respectively, corresponding to 0.1% of patients in both groups (Table 69).

For the majority of patients with UAP, the events were medically significant, not only as indicated by the need for hospitalization, but also by the fact that they led to unplanned coronary revascularization in 19 of 26 cases (11 IDeg+IDegAsp and 8 comparator).

Table 69 Treatment-emergent MACE Included in the Prespecified Primary Meta-analysis – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp			Comparator		
	N	%	Incidence Rate	N	%	Incidence Rate
Total patients	5647			3312		
Patient years of exposure	3569.9			1873.9		
Total patients with MACE	53	0.94	1.48	27	0.82	1.44
Acute coronary syndrome	34	0.60	0.95	19	0.57	1.01
Unstable angina pectoris	14	0.25	0.39	12	0.36	0.64
Myocardial infarction	20	0.35	0.56	7	0.21	0.37
STEMI	12	0.21	0.34	2	0.06	0.11
NSTEMI	8	0.14	0.22	5	0.15	0.27
Stroke	11	0.19	0.31	4	0.12	0.21
CV death	8	0.14	0.22	4	0.12	0.21

N: number of patients with at least 1 event; %: proportion of patients in analysis set with at least 1 event; Incidence rate: number of patients with event divided by patient years of exposure multiplied by 100. In addition to the treatment-emergent MACE summarized in this table, there were 3 non-treatment emergent MACE that occurred more than 7 days after drug discontinuation: sudden cardiac death that occurred 11 days after drug discontinuation (IDeg), non S-T elevation myocardial infarction that occurred 9 days after drug discontinuation (IDeg) and acute pontine stroke that occurred 18 days after drug discontinuation (IDeg). Treatment-emergent MACE (occurring within 7 days of randomized treatment).Full analysis set.

Two patients in the IDeg+IDegAsp group and one patient in the comparator group experienced two MACE each, for a total of 83 treatment-emergent MACE in 80 patients. In addition to the treatment-emergent MACE, there were 3 patients with non-treatment-emergent MACE that occurred beyond the 7-day AE follow-up window: sudden cardiac death that occurred 11 days after stopping treatment (IDeg), non S-T elevation myocardial infarction that occurred nine days after stopping treatment (IDeg) and acute pontine stroke that occurred 18 days after stopping treatment (IDeg). Furthermore, one patient in the IDeg+IDegAsp group had a MACE during an angiography planned prior to trial entry. It was recognized by the FDA that patients with peri-procedural events of MACE should be analyzed separately[36], therefore, the patient experiencing this event was excluded from the primary meta-analysis, and therefore is not included in Table 69.

Baseline and diabetes characteristics of patients with MACE in the IDeg+IDegAsp and comparator groups are summarized beside those of all patients in Table 70. Information on smoking and family history of cardiovascular disease was not recorded at trial entry in the IDeg and IDegAsp phase 3 trials. Patients with cardiovascular disease within the last 6 months prior to screening (defined as: stroke; decompensated heart failure New York Heart Association class III or IV; myocardial infarction; unstable angina pectoris; or coronary arterial bypass graft or angioplasty), or patients with uncontrolled treated/untreated severe hypertension (systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg), were excluded from the trials.

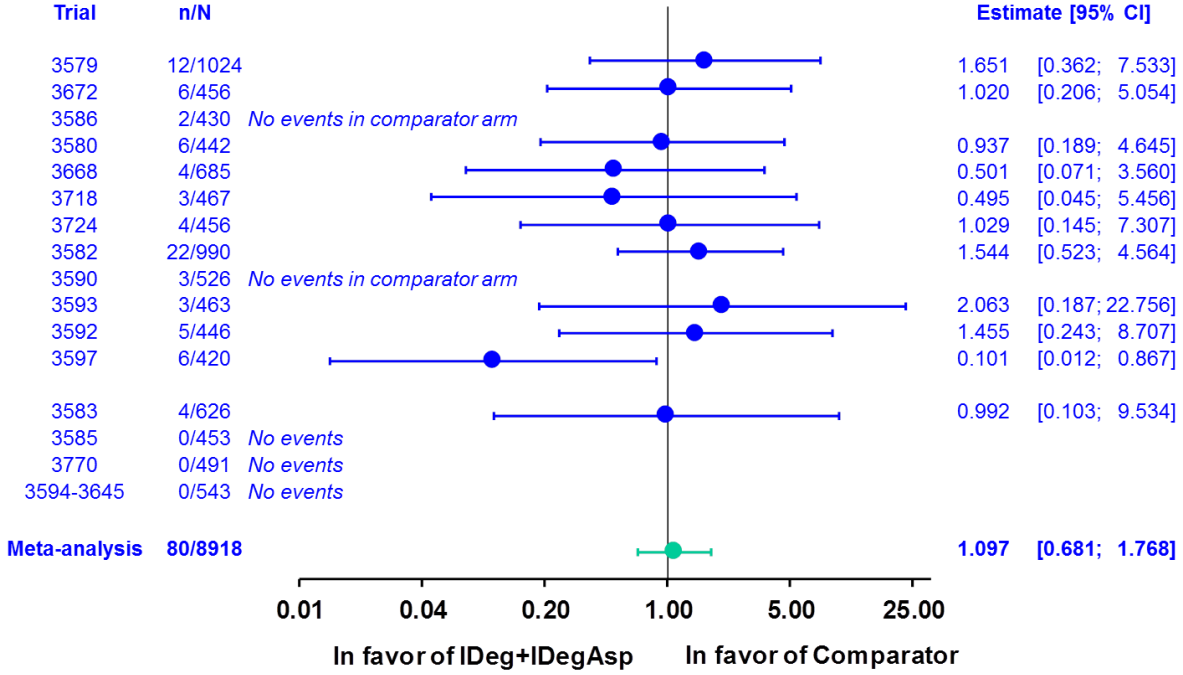
Baseline cardiovascular risk factors were similar between the IDeg+IDegAsp and comparator populations. Compared with the entire population, patients who had MACE were older and had a longer duration of diabetes, had higher BMI, and a higher proportion of patients had prior cardiovascular disease and administered medications for cardiovascular protection.

Table 70 Baseline Characteristics of Patients with MACE − NDA

	IDeg+IDegAsp		Comparator	
	All Patients (N=5647) %	Patients with MACE (N=53) %	All Patients (N=3312) %	Patients with MACE (N=27) %
Prior cardiovascular disease	16.0	37.7	15.0	44.4
Age >65 and diabetes duration >10 years	13.4	24.5	13.4	14.8
Male	56.0	71.7	54.6	59.3
Hypertension	59.6	81.1	62.5	77.8
Mild or moderate renal impairment	15.8	11.3	15.2	29.6
BMI >30 mg/kg^2	40.9	56.6	44.9	55.6
Concomitant medications				
Lipid-lowering drug	52.3	67.9	55.0	66.7
Aspirin	30.9	50.9	33.2	51.9
Beta-blocker	17.8	26.4	17.5	37.0
Renin-angiotensin system inhibitors	53.7	75.5	55.7	77.8

Full analysis set. %: proportion of patients.

Estimated hazard ratios and corresponding 95% CIs are presented for the individual trials and for the pool of all trials in Figure 33 for the prespecified primary analysis, time to first MACE. There was no consistent pattern in the estimated hazard ratios across individual trials; some favored IDeg+IDegAsp and others favored comparator. The overall estimated hazard ratio for IDeg+IDegAsp/comparator was 1.097 $[0.681; 1.768]_{95\%CI}$.



n/N: number of patients with a MACE/number of patients contributing to the analysis.
Cox regression hazard ratios with 95% CI and comparator as reference. Full analysis set.

Figure 33 Prespecified Primary Analysis − Time to First MACE within 7 Days of Treatment – IDeg+IDegAsp Phase 3 Trials – Cox Regression – Forest Plot – NDA

Estimated overall hazard ratios of the three prespecified sensitivity analyses of MACE were similar to those obtained for the primary analysis (Table 71).

Table 71 Prespecified Sensitivity Analyses – Cox Proportional Hazard Analyses of Time to First MACE – IDeg+IDegAsp Phase 3 Trials − NDA

Analysis	Estimated Hazard Ratio [95% CI]
Primary Analysis: Stratified by trial (Full Analysis Set)	1.097 [0.681; 1.768]
Sensitivity Analysis 1: Stratified by trial (Safety Analysis Set)	1.097 [0.681; 1.768]
Sensitivity Analysis 2: Not stratified by trial (Full Analysis Set)	1.128 [0.708; 1.798]
Sensitivity Analysis 3: Additional Explanatory Variables (Full Analysis Set)	1.109 [0.696; 1.767]

The incidence of MACE was also summarized descriptively by type of diabetes, sex, age, and cardiovascular history (Table 72).

As expected, the incidence rate of MACE was higher in patients with T2DM than T1DM (Table 72). In T2DM, the estimated hazard ratio was 1.102 [0.677; 1.795]$_{95\%CI}$, consistent with the primary analysis. The confidence interval for the estimated hazard ratio in T1DM was wide: 0.992 [0.103;

9.534]$_{95\%CI}$. This was a consequence of the fact that only four patients with T1DM experienced a MACE (Table 72).

The incidence rate of MACE (patients with MACE per 100 PYE) tended to be higher in males than females, and higher in elderly patients (>65 years of age) than younger patients (≤65 years of age) (Table 72).

In both treatment groups, patients with prior cardiovascular disease had a higher risk of experiencing a MACE than patients without prior cardiovascular disease (Table 72).

Table 72 Incidence of MACE by Diabetes Type, Sex, Age, Race, and Prior Cardiovascular Disease − IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp		Comparator	
	N with MACE/ N in FAS	Incidence Rate	N with MACE/ N in FAS	Incidence Rate
Type of diabetes				
T2DM	50/4178	1.96	26/2656	1.81
T1DM	3/1469	0.29	1/656	0.23
Sex				
Male	38/3163	1.88	16/1810	1.55
Female	15/2484	0.97	11/1502	1.31
Age				
≤65 years	33/4520	1.15	20/2632	1.33
>65 years	20/1127	2.87	7/680	1.87
Prior cardiovascular disease				
Yes	20/905	3.50	12/496	4.26
No	33/4742	1.10	15/2816	0.94

MACE: Major adverse cardiovascular events; FAS: Full analysis set; N: Number of patients in FAS. Patients with MACE: Number of patients with at least one MACE, Incidence rate: number of patients with event divided by patient years of exposure multiplied by 100.
Prior CV disease was assessed based on a list of preferred terms characterizing non-fatal myocardial infarction and non-fatal stroke.

In conclusion, the number of MACE was low and the incidence rates were similar between IDeg+IDegAsp and comparator treatment in the prespecified primary analysis of MACE presented in the NDA.

10.3.1.5 Additional Analyses Using Alternate MACE Composite Endpoint Definitions

As described in Section 10.3.1.1, the prespecified MACE composite endpoint for the IDeg and IDegAsp phase 3 trials was cardiovascular (CV) death, stroke, acute coronary syndrome (myocardial infarction [MI] and unstable angina pectoris [UAP]).

Sensitivity analyses of the NDA data using the following three alternate MACE composite endpoint definitions were performed:

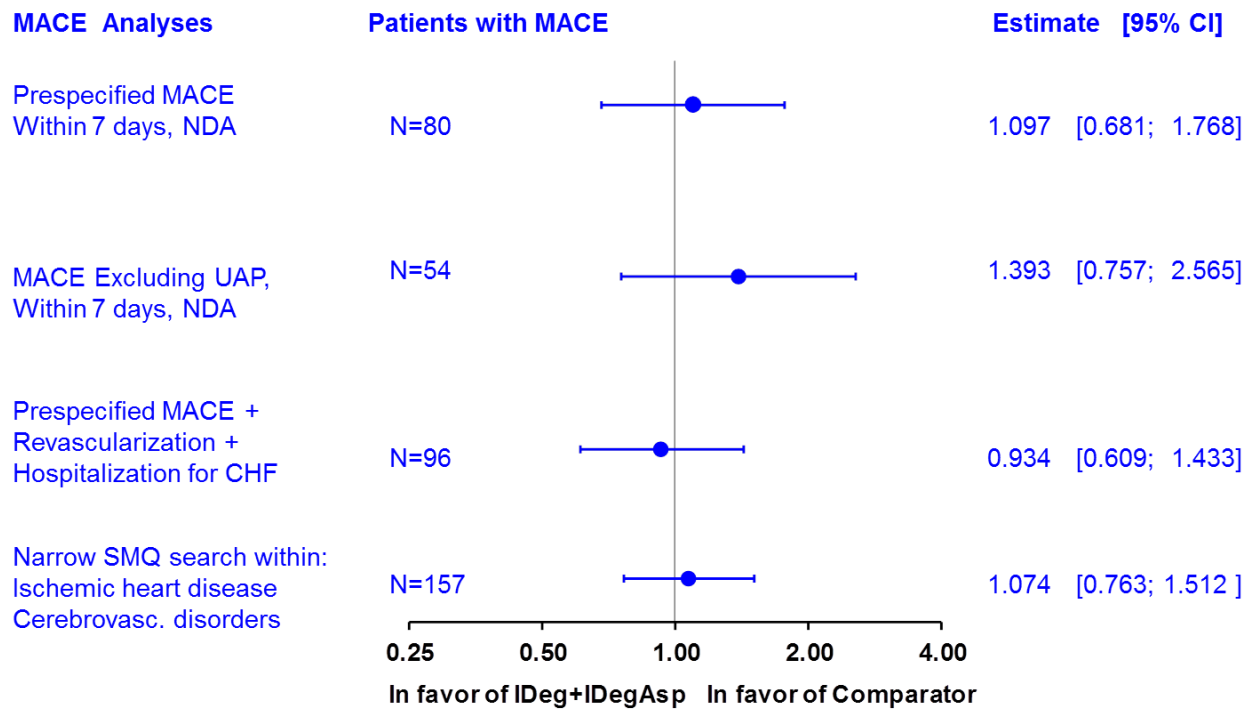
- CV death, stroke, MI (as requested by FDA; referred to as "MACE excluding UAP")
- CV death, stroke, MI, UAP, revascularization and hospitalization due to congestive heart failure (CHF)
- AEs in the narrow scope SMQs for ischemic heart disease and cerebrovascular disorders

It is important to note that not all events in the last two broader categories were adjudicated.

The first composite endpoint definition was narrower than the primary prespecified definition because it excluded events of UAP, whereas, the second was broader as it included revascularization and congestive heart failure (CHF). The first and second definitions are commonly used composite endpoints; with first definition commonly used for cardiovascular outcome trials with enriched patient populations.[36] The third definition was comprised of narrow scope SMQs for ischemic heart disease and cerebrovascular disorders as specified by the FDA in a May 2012 addendum to their briefing document for the obesity drug lorcaserin.[37] This definition was the broadest, and was used in order to capture a greater number of events.

Exclusion of UAP in the MACE analysis reduced the overall number of patients with MACE by 33% from 80 to 54 (39 IDeg+IDegAsp, 15 comparator) (Figure 34). When the primary analysis was repeated excluding UAP, the estimated hazard ratio was 1.393 $[0.757; 2.565]_{95\%CI}$ and resulted in a wider confidence interval around the point estimate compared with the original primary analysis.

The alternate expanded MACE composite endpoint definition that included revascularization and hospitalization due to CHF, and a definition that included all AEs in the narrow scope SMQs for ischemic heart disease and cerebrovascular disorders, increased the number of patients with MACE to 96 and 157, respectively (Figure 34). Repeating the primary analysis using these expanded definitions resulted in hazard ratio point estimates close to 1 with narrower 95% confidence intervals.



MACE: major adverse cardiovascular event: NDA: new drug application; SMQ: standardized MedDRA query; CHF: congestive heart failure. Treatment-emergent adverse events. Full analysis set.

Figure 34 Time to First MACE within 7 Days of Treatment Using Different MACE Composite Endpoint Definitions – IDeg+IDegAsp Phase 3 Trials – Cox Regression – Forest Plot – NDA

10.3.1.6 MACE Analyses as of May 1, 2012

Per the FDA request, updated MACE analyses using all available data from completed phase 3 trials since the NDA cut off of January 31, 2011 were performed. In order to include the largest number of completed IDeg and IDegAsp trials, May 1, 2012 was chosen as the cut-off date for the updated analyses. All additional MACE that were reported to Novo Nordisk were included in the datasets from the locked databases as of May 1, 2012 and were prospectively adjudicated by blinded external reviewers using the same procedure as outlined for the trials included in the NDA (see Section 10.3.1.2).

As first stated in Section 10.1, the May 1, 2012 dataset included 9 additional completed trials: 6 new extensions (5 IDeg and 1 IDegAsp), 1 new IDegAsp phase 3a trial (Trial 3896), and 2 new IDeg phase 3b trials (Trials 3846 and 3923).

A summary of patient years of exposure in the NDA and in additional individual trials (including extensions) included in the May 1, 2012 analyses is shown in Table 73. The nine additional trials

included an unbalanced additional exposure with 742 patients treated with IDeg+IDegAsp and 149 patients treated with comparator products. This added 1837.8 PYE for IDeg+IDegAsp and 688.9 PYE for comparator to the MACE analyses, an imbalance inherited from the extension of the 3:1 randomized trials.

In the period between the NDA and May 1, 2012 cut-off, a total of 54 additional patients experienced at least one treatment-emergent MACE (44 IDeg+IDegAsp patients and 10 comparator patients) (Table 73). When the additional patients with MACE were added to the 80 patients from the NDA with MACE, a total of 134 patients had treatment-emergent MACE (97 treated with IDeg+IDegAsp and 37 treated with comparator) as of the May 1, 2012 cut-off.

The majority of patients experiencing MACE since the original NDA were from planned extensions of a few trials, which represented 35% of the original randomized population (Table 73 and Table 20). Of note, only a small proportion of patients were followed for two years. Of all patients enrolled in the phase 3 program, the cardiovascular status was known for 12.7% of patients in the IDeg+IDegAsp group but only 7.7% of patients in the comparator group (calculated as the proportion of patients at risk for treatment-emergent MACE at 2 years' follow-up in the full analysis set for completed IDeg+IDegAsp trials as of May 1, 2012).

Table 73 Overview of Treatment-emergent MACE in Completed IDeg+IDegAsp Phase 3 Trials in the NDA and the Additional Phase 3 Trials Completed up to May 1, 2012 (Extension Trials, Phase 3b Trials, Trial 3896)

	IDeg+IDegAsp			Comparator		
	N	PYE	MACE	N	PYE	MACE
NDA	5647	3569.9	53	3312	1873.9	27
Additional extension trials*						
IDeg T2DM BOT (3643, extension to 3579)		542.2	19		167.3	2
IDeg T2DM BB (3667, extension to3582)		277.4	10		93.6	3
IDeg T1DM BB (3644, extension to 3583)		349.3	5		117.5	1
IDeg T1DM BB (3725, extension to 3585)		127.7	1		62.1	0
IDeg T1DM BB Flexible Dosing (3770EX, extension to 3770)		119.8	1		65.3	2
IDegAsp T2DM OD (3726, extension to 3590)		97.3	4		112.9	1
Total, additional extension trials		1513.7	40		618.7	9
Additional randomized (main) trials						
IDegAsp T2DM Japan (3896, phase 3a)	147	70.0	2	149	70.2	1
IDeg T2DM titration (3846, phase 3b)	222	104.3	2	NA	NA	NA
IDeg T2DM U100 vs U200 (3923, phase 3b)	373	149.8	0	NA	NA	NA
Total, additional randomized (main) trials	742	324.1	4	149	70.2	1
Total, all additional trials	**742**	**1837.8**	**44**	**149**	**688.9**	**10**
All trials	**6389**	**5407.8**	**97**	**3461**	**2562.7**	**37**

MACE: Number of patients with major adverse cardiovascular events. PYE: Patient years of exposure (One patient year of exposure: 365.25 days). Non-treatment emergent events (NDA): IDeg+IDegAsp: Trial 3579 (2 events), Trial 3724 (1 event). Non-treatment emergent events (additional trials) IDeg+IDegAsp: Trial 3582-3667 (1 event) Trial 3923 (1 event); Comparator: Trial 3579-3643 (1 event), Trial 3590-3726 (1 event). NA: not applicable, as there was no comparator group in these trials.
*Patients that completed main phase 3 trials continued into the extension trials; therefore, extension trials contribute additional patient years' exposure but not additional patients to May 1, 2012 analyses. Treatment-emergent adverse events. Full analysis set.

In addition to the 134 patients with treatment-emergent MACE up to 7 days after drug discontinuation (80 in the NDA and 54 from the NDA to May 1, 2012), there were a total of 7 patients with non-treatment-emergent MACE up to 30 days after drug discontinuation (3 in the NDA and 4 from the NDA to May 1, 2012). The 141 patients with treatment-emergent MACE or non-treatment-emergent MACE up to 30 days after drug discontinuation as of the May 1, 2012 cut-off are summarized by MACE category in Table 74.

Table 74 MACE Up to 30 Days after Drug Discontinuation – IDeg+IDegAsp Phase 3 Trials – May 1, 2012

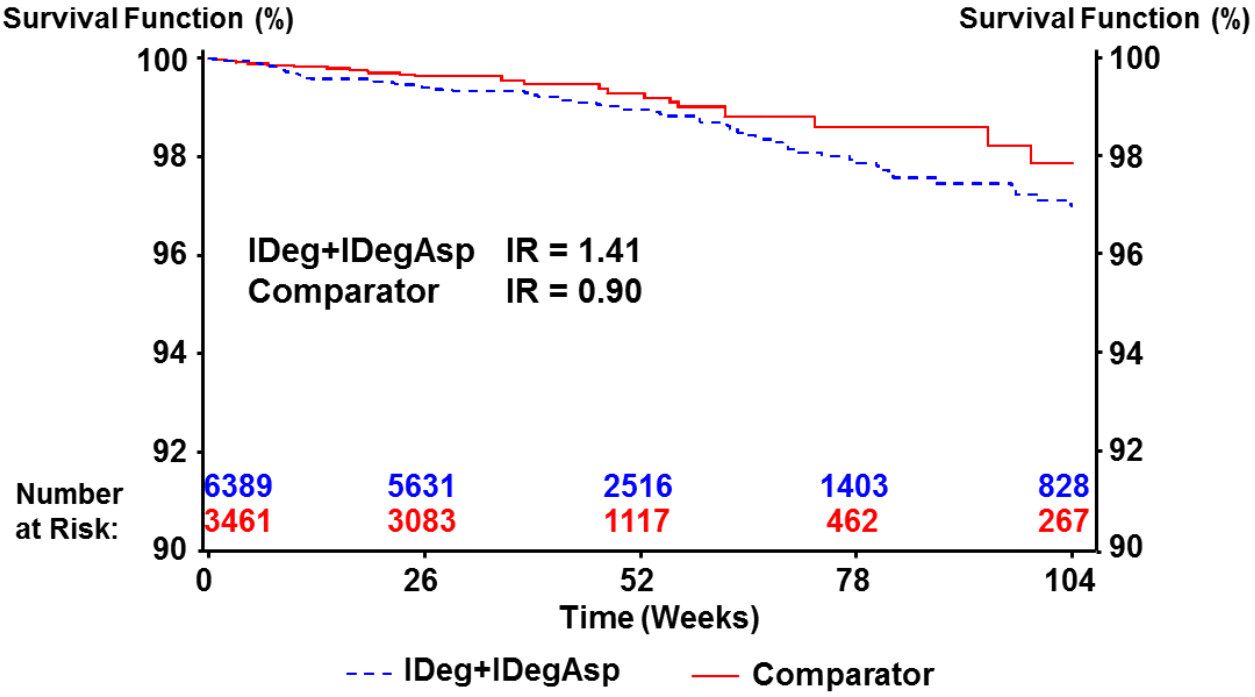
	IDeg+IDegAsp			Comparator		
	N	%	Incidence Rate	N	%	Incidence Rate
Total patients	6389			3461		
Patient years of exposure	5407.8			2562.7		
Total patients with MACE	102	1.60	1.89	39	1.13	1.52
Acute coronary syndrome	63	0.99	1.16	25	0.72	0.98
Unstable angina pectoris	26	0.41	0.48	16	0.46	0.62
Myocardial infarction	37	0.58	0.68	9	0.26	0.35
STEMI	16	0.25	0.30	3	0.09	0.12
NSTEMI	21	0.33	0.39	6	0.17	0.23
Stroke	26	0.41	0.48	7	0.20	0.27
Cardiovascular death	13	0.20	0.24	7	0.20	0.27

N: number of patients with at least 1 event; %: proportion of patients in analysis set with at least 1 event; Incidence rate: number of patients with event divided by patient years of exposure multiplied by 100. Trials included: 3579-3643, 3580, 3582-3667, 3583-3644, 3585-3725, 3586, 3590-3726, 3592, 3593, 3594-3645, 3597, 3668, 3672, 3718, 3724, 3770-main-ext, 3896, 3846, 3923. Table includes both treatment-emergent MACE and non-treatment-emergent MACE up to 30 days after drug discontinuation (7 events [3 NDA, 4 between NDA and May 1, 2012). Full analysis set.

As requested by the FDA, the Cox Regression analysis was repeated using the May 1, 2012 cut-off for all completed phase 3 trials including extensions, including the 7 non-treatment-emergent MACE up to 30 days after drug discontinuation. The estimated hazard ratio for this analysis was 1.290 $[0.881; 1.888]_{95\%CI}$.

At the request of the FDA, an analysis of MACE excluding events of UAP was conducted that included all completed trials as of May 1, 2012 and all MACE reported up to 30 days after drug discontinuation. When excluding UAP from the MACE composite endpoint definition, incidence rates of MACE were 1.41 patients with MACE per 100 PYE for IDeg+IDegAsp, and 0.90 patients with MACE per 100 PYE for comparator (Figure 35). Thus, the incidence rate for IDeg+IDegAsp was approximately the same as in the prespecified NDA analysis, whereas the incidence rate for the comparator group had decreased (Figure 32 and Figure 35).

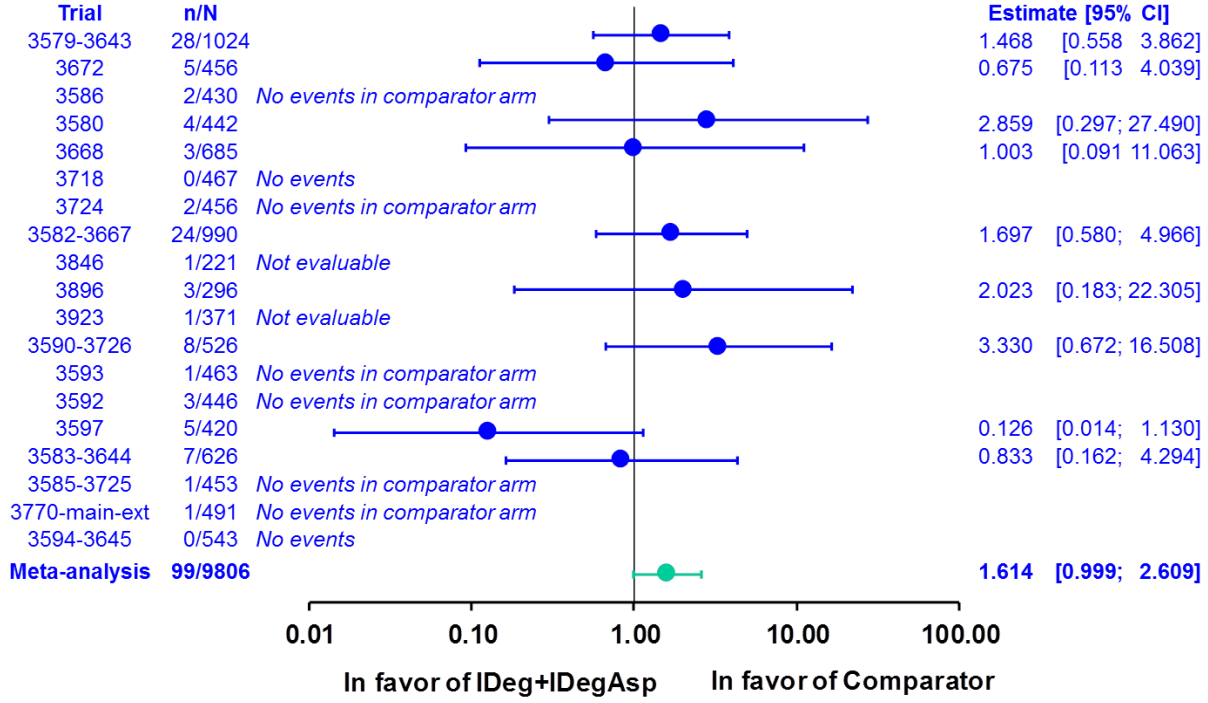
After 52 weeks, the number of patients decreased substantially, and the ratio between IDeg+IDegAsp and comparator increased (see Figure 35). Long-term exposure was obtained from trials with extensions: Trials 3579-3643 (IDeg T2DM BOT) and 3583-3644 (IDeg T1DM BB) provided 2-year exposure (Figure 16).



Incidence rate: number of patients with MACE per 100 PYE. Number at risk: number of patients available with no prior events at the given time-point, IDeg+IDegAsp (first row) and comparator (second row). Includes events reported up to 30 days after drug discontinuation. Full analysis set.

Figure 35 Kaplan-Meier Plot of Time to First MACE within 30 days of Treatment (Excluding UAP) – IDeg+IDegAsp Phase 3 Trials – May 1, 2012

The estimated hazard ratio for IDeg+IDegAsp versus comparators from the May 1, 2012 analysis based on the MACE composite endpoint, excluding events of UAP but including events up to 30 days after drug discontinuation, was 1.614 $[0.999; 2.609]_{95\%CI}$ (Figure 36).



n/N: number of patients with a MACE / number of patients contributing to the analysis; Trials 3846 and 3923 were not evaluable because they compared two IDeg treatment groups. Includes events up to 30 days after drug discontinuation. Full analysis set.

Figure 36 Time to First MACE within 30 Days of Treatment (Excluding UAP) – IDeg+IDegAsp Phase 3 Trials – Cox Regression – Forest Plot – May 1, 2012

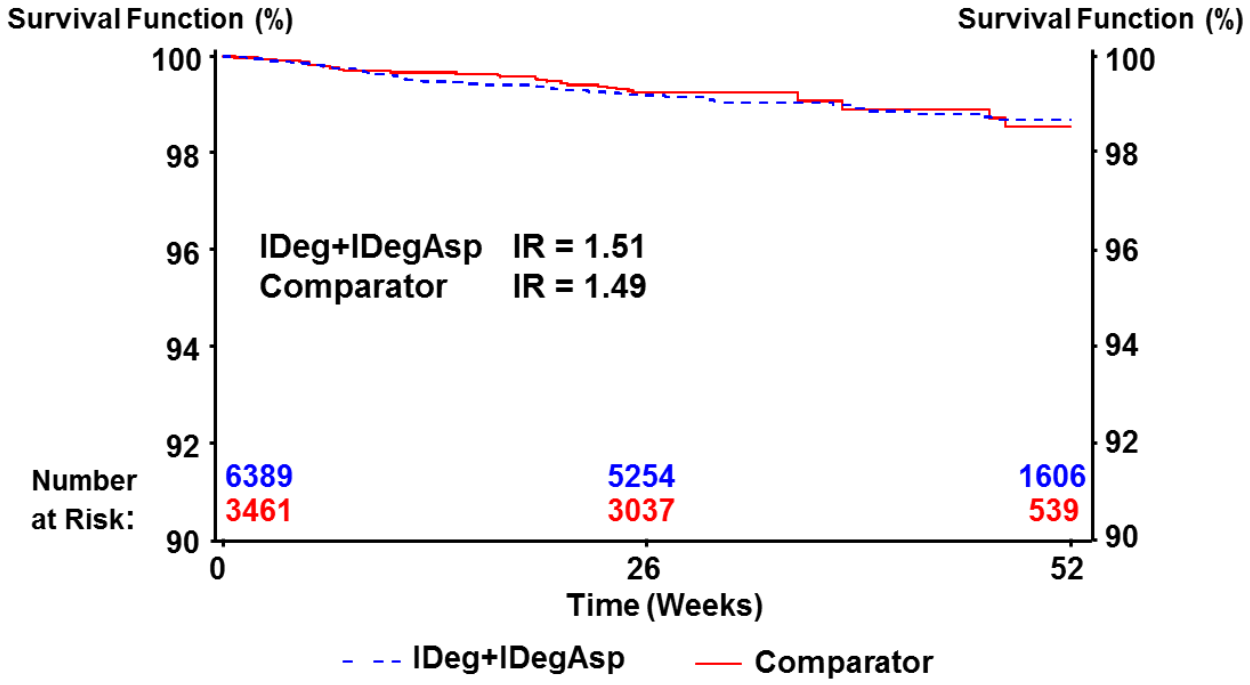
When UAP was excluded, 10 of the 19 trials had no events in one or both treatment arms. To investigate the robustness of the estimate, a sensitivity analysis was made using a stratified (by trial) Mantel-Haenszel approach correcting for treatment arms with zero events (see Section 6.4.3). The result of this analysis was an odds ratio estimate of 1.524 $[0.972; 2.388]_{95\%CI}$.

Analysis of Randomized Trials without Extensions as of May 1, 2012

Data from these extensions represented only a subset (35%) of the original randomized population and provided 2-year cardiovascular outcome information on approximately 10% of the population in the IDeg+IDegAsp programs based on the design of the trials in the development programs. Therefore, the analyses including extension data are not considered as robust as the prespecified NDA analysis.

For this reason, the prespecified analysis (treatment-emergent MACE, prespecified MACE composite endpoint [including UAP]) was repeated using data from randomized controlled phase 3a and 3b trials as of May 1, 2012 and hence without inclusion of all extension trials. Note that the extension to Trial 3594 (Trial 3645), which was part of the primary NDA analysis, was also excluded.

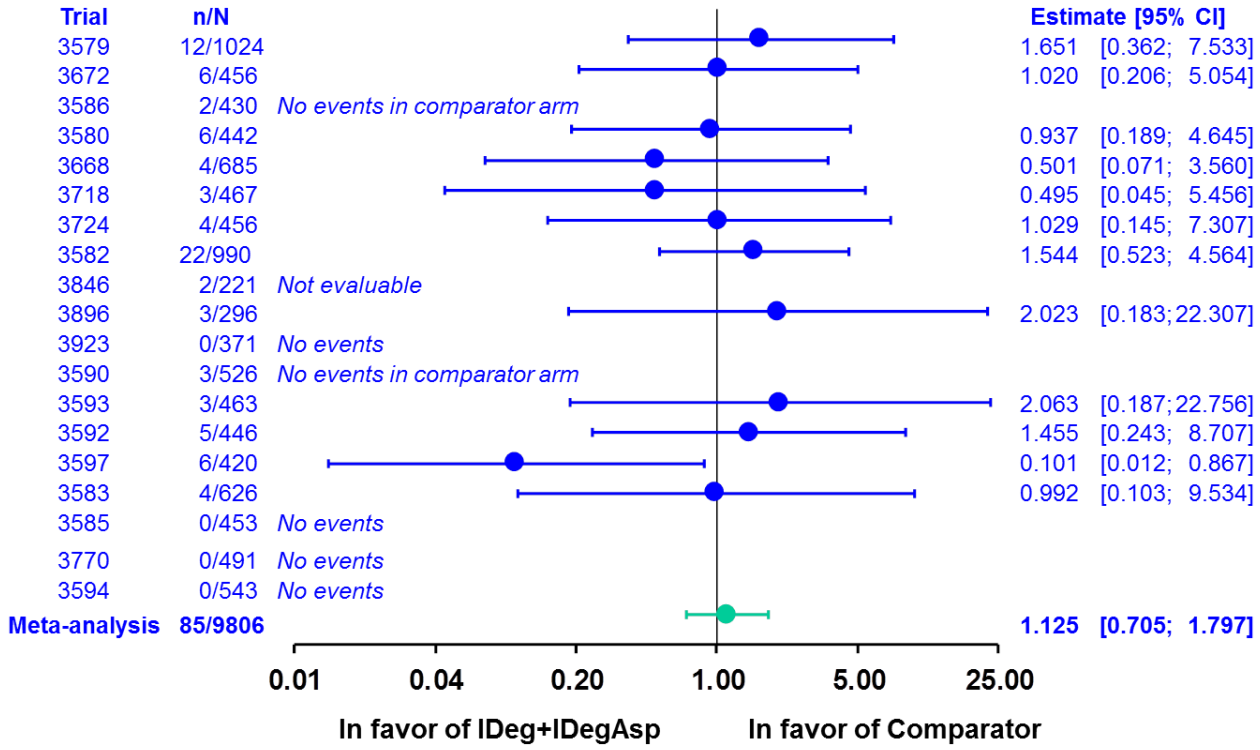
A total of 19 phase 3 trials were included, providing exposure of 9850 patients included in the FAS (6389 with IDeg+IDegAsp and 3461 with comparator). The MACE analysis of all randomized phase 3 trials completed as of May 1, 2012 (Figure 37) demonstrated similar incidence rates for IDeg+IDegAsp and comparator, 1.51 and 1.49 patients per 100 PYE, respectively, as was seen in the original NDA analysis.



Incidence rate: number of patients with MACE per 100 PYE. Number at risk: number of patients available with no prior events at the given time-point, IDeg+IDegAsp (first row) and comparator (second row). Treatment-emergent adverse events. Full analysis set.

Figure 37 Kaplan-Meier Plot of Time to First MACE within 7 Days of Treatment – Randomized IDeg+IDegAsp Phase 3 Trials (Excluding Extensions) – May 1, 2012

The estimated hazard ratio was 1.125 $[0.705; 1.797]_{95\%CI}$, which was consistent with the result of the primary MACE analysis included in the NDA (see Figure 38 and Figure 33). As Trials 3923 and 3846 compared two IDeg treatment groups, these trials do not contribute in the model. A sensitivity analysis not stratified by trial gives an estimated hazard ratio of 1.081 $[0.686; 1.702]_{95\%CI}$.



Prespecified MACE composite endpoint (including UAP). n/N: number of patients with a MACE / number of patients contributing to the analysis; Trial 3846 and 3923 was not evaluable because it compared two IDeg treatment groups. Treatment-emergent adverse events. Full analysis set.

Figure 38 Time to First MACE within 7 Days of Treatment – Randomized IDeg+IDegAsp Phase 3 Trials (Excluding Extensions) – Cox Regression – Forest Plot – May 1, 2012

10.3.1.7 MACE Summary

Incidence rates (patients with MACE per 100 PYE) were similar between IDeg+IDegAsp (1.48) and comparator (1.44) in the prespecified primary analysis of MACE presented in the NDA. The corresponding hazard ratio for the prespecified primary analysis of time to first MACE for the NDA was 1.097 [0.681; 1.768]$_{95\%CI}$.

An FDA-requested *post hoc* analysis of all trials completed as of May 1, 2012 including extensions and non-treatment-emergent events reported up to 30 days after drug discontinuation (beyond the 7-day follow-up visit for AE reporting in the clinical trials) had a higher estimated hazard ratio of 1.290 [0.881; 1.888]$_{95\%CI}$. These non-treatment-emergent MACE occurred after patients switched from trial treatment to NPH in most cases and then to another marketed insulin.

An FDA-requested *post hoc* analysis of all trials completed as of May 1, 2012, excluding UAP from the MACE composite endpoint and including non-treatment emergent MACE had the highest estimated hazard ratio: 1.614 $[0.999; 2.609]_{95\%CI}$ in favor of comparator.

These *post hoc* analyses demonstrated the influence of altering the MACE composite endpoint definition and including the data from the long-term safety extensions on the estimated hazard ratio. Of note, data from these extensions represented only 35% of the original randomized population and provided 2-year cardiovascular outcome information on approximately 10% of the population in the IDeg+IDegAsp programs, an expected result given the design of the phase 3 programs. Hence, the analyses including the extension data are not considered as robust as the prespecified NDA analysis.

When all randomized main trials completed as of May 1, 2012 were analyzed (i.e., a total of 7 extensions were excluded), the estimated hazard ratio was 1.125 $[0.705; 1.797]_{95\%CI}$, similar to the original NDA analysis, indicating the effect of the extension data on the analysis.

The analysis excluding extension trials and using the prespecified MACE composite endpoint definition provides the most robust assessment of the May 1, 2012 data.

In conclusion, the prespecifed primary analysis in the NDA did not show an increased risk of MACE for patients treated with IDeg or IDegAsp. However, the hazard ratio increased with an alternative MACE composite endpoint definition that excluded UAP and increased with additional exposure from extensions. Hence, the totality of the data neither confirms nor excludes increased cardiovascular risk. In order to better define the cardiovascular profile, Novo Nordisk will continue to work with the FDA on potential post-approval activities.

10.3.2 Vital Signs

No clinically relevant differences in blood pressure or pulse were observed between IDeg+IDegAsp and comparator either at screening or at end of trial (Table 75).

Table 75 Mean Blood Pressure and Pulse – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg + IDegAsp (N=5635)			Comparator (N=3306)		
	N	Systolic/ diastolic BP (mmHg)	Pulse (beats/ min)	N	Systolic/ diastolic BP (mmHg)	Pulse (beats/ min)
Mean value at baseline	5617	130/78	75	3300	130/78	75
Mean value at Week 26 (LOCF)	5635	129/77	74	3304	129/77	75
Mean value at Week 52 (LOCF) (only 52-week trials)	2353	129/77	74	840	129/77	74

BP: blood pressure; LOCF: last observation carried forward, N: number of patients with BP measurement. LOCF for Week 52 has only been performed for patients attending trials of 52 weeks' duration. Safety analysis set.

10.3.3 ECG and QTc

In the phase 3 IDeg and IDegAsp trials, a 12-lead ECG was performed at screening and at end of trial (26 or 52 weeks). ECG measurements were similar between IDeg+IDegAsp and comparator at baseline and after 26 or 52 weeks of treatment (Table 76).

Table 76 ECG by Treatment Week – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+IDegAsp (N=5635)		Comparator (N=3306)	
	N	%	N	%
Week -1				
N	5635	100.0	3306	100.0
Normal	3943	70.0	2260	68.4
Abnormal, Not Clinically Significant	1609	28.6	999	30.2
Abnormal, Clinically Significant	81	1.4	46	1.4
Unknown	2	0.0	1	0.0
Week 26 (LOCF)				
N	3644	100.0	2644	100.0
Normal	2663	73.1	1874	70.9
Abnormal, Not Clinically Significant	873	24.0	689	26.1
Abnormal, Clinically Significant	51	1.4	37	1.4
Unknown	57	1.6	44	1.7
Week 52 (LOCF)				
N	2353	100.0	842	100.0
Normal	1620	68.8	593	70.4
Abnormal, Not Clinically Significant	662	28.1	232	27.6
Abnormal, Clinically Significant	26	1.1	9	1.1
Unknown	45	1.9	8	1.0

ECG: electrocardiogram; N: number of patients; %: percentage of patients; LOCF: last observation carried forward. LOCF for Week 26 and Week 52 has only been performed for patients attending trials of 26 and 52 weeks of duration, respectively. Safety analysis set.

In agreement with the FDA, a thorough QTc trial was not mandated as part of the IDeg or IDegAsp development programs.

In IDeg T2DM BOT 12m Trial 3579, copies of the 12-lead ECGs recorded prior to baseline and last visit were collected for randomized patients after end of treatment. ECGs were read in a centralized manner regarding QT/QTc by utilizing an external central reading center that was blinded to patient ID, treatment and visit number. There was no statistically significant difference between IDeg and IGlar in change from baseline in either the QTcB interval or the QTcF interval (Table 77).

Table 77 QTc Intervals Change From Baseline – Statistical Analysis – IDeg T2DM BOT 12m Trial 3579 – NDA

	IDeg		IGlar		IDeg - IGlar
	N	LS Mean (SE)	N	LS Mean (SE)	Difference [95% CI]
Full Analysis Set	773		257		
QTcB Interval (msec)	742	415.58 (0.78)	241	417.22 (1.28)	
Change from Baseline	742	0.33 (0.78)	241	1.97 (1.28)	-1.64 [-4.46 ; 1.18]
QTcF Interval (msec)	742	404.17 (0.68)	241	404.76 (1.11)	
Change from Baseline	742	0.87 (0.68)	241	1.45 (1.11)	-0.58 [-3.03 ; 1.87]

N: number of patients contributing to analysis; SE: standard error of the mean. LOCF: last observation carried forward. Missing data is imputed using LOCF. Full analysis set.

10.3.4 Lipids

In the phase 3 trials, levels of HDL cholesterol, LDL cholesterol, total cholesterol and triglycerides were measured at baseline and at end of trial (26 or 52 weeks). As shown in Table 78 mean lipid values appeared similar between IDeg and comparator and between IDegAsp and comparator at baseline, Week 26, and Week 52.

Table 78 Lipids by Treatment Week – IDeg+IDegAsp Phase 3 Trials – NDA

	IDeg+ IDegAsp (N=5635) Mean (SD)			Comparator (N=3306) Mean (SD)		
	Week 0	Week 26 (LOCF)	Week 52 (LOCF)	Week 0	Week 26 (LOCF)	Week 52 (LOCF)
HDL Cholesterol (mg/dL)	50 (16)	51 (15)	51 (15)	49 (15)	51 (15)	53 (17)
LDL Cholesterol (mg/dL)	96 (34)	96 (34)	98 (34)	97 (36)	96 (34)	96 (33)
Triglycerides (mg/dL)	149 (139)	133 (105)	136 (122)	151 (127)	138 (95)	135 (99)
Total Cholesterol (mg/dL)	175 (41)	173 (40)	175 (41)	175 (42)	173 (40)	175 (39)

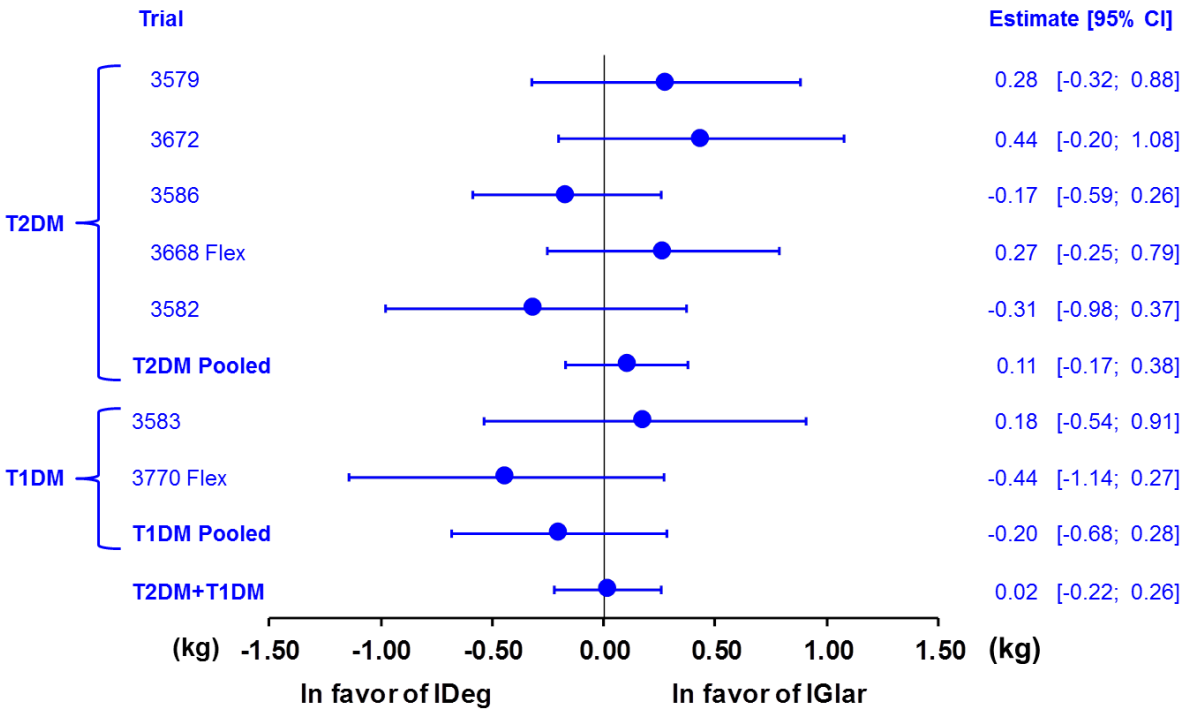
N: number of patients; SD: standard deviation. LOCF: last observation carried forward. Missing data is imputed using LOCF for Week 26 and Week 52. LOCF for Week 52 has only been performed for patients attending trials of 52 weeks of duration. Safety analysis set.

10.4 Other Safety Parameters

10.4.1 Weight

Insulin therapy is generally associated with a moderate increase in body weight due to its anabolic effects and the reduction in caloric loss from glucosuria with treatment. The mean body weight increased in all trials, both with IDeg and IGlar, but decreased with sitagliptin in Trial 3580.

As shown in Figure 39, the increase in body weight was similar with IDeg and IGlar, both in T2DM and T1DM, with no statistically significant treatment differences in any of the trials.



Full analysis set.

Figure 39 Change in Body Weight – IDeg Phase 3 Trials – Forest Plot – IDeg versus IGlar

IDet was the insulin comparator in T1DM Trial 3585. Patients treated with IDet in Trial 3585 gained approximately 1 kg less than patients treated with IDeg. This result is consistent with published data demonstrating that IDet is associated with less weight gain than IGlar.[38,39]

As expected, treatment with the DPP-4 inhibitor sitagliptin resulted in significantly less weight gain compared with IDeg in Trial 3580, with an observed mean reduction of 0.4 kg. However, glycemic control was superior with IDeg treatment compared with sitagliptin treatment.

In the IDegAsp phase 3 trials, body weight increased in all treatment groups, as is expected with initiation or intensification of insulin therapy. The weight increase was smaller for IDegAsp BID compared with BIAsp 30 BID in patients with T2DM, whereas it was greater with IDegAsp OD than IDet in T1DM and greater with IDegAsp OD than IGlar in T2DM. The greater weight gain with IDegAsp compared with IGlar in the once-daily trials was likely due to the bolus component in IDegAsp.

10.4.2 Safety Laboratory Evaluations

Overall, mean laboratory values for hematology, biochemistry and urine remained stable during the trial period, with no clinically relevant difference between IDeg and comparators, or between IDegAsp and comparators. Few patients had changes from normal to high or low values during the

trials with no difference between the treatment groups for any of the parameters. Few individual clinically significant values were reported as adverse events with no difference reported between the two treatment groups.

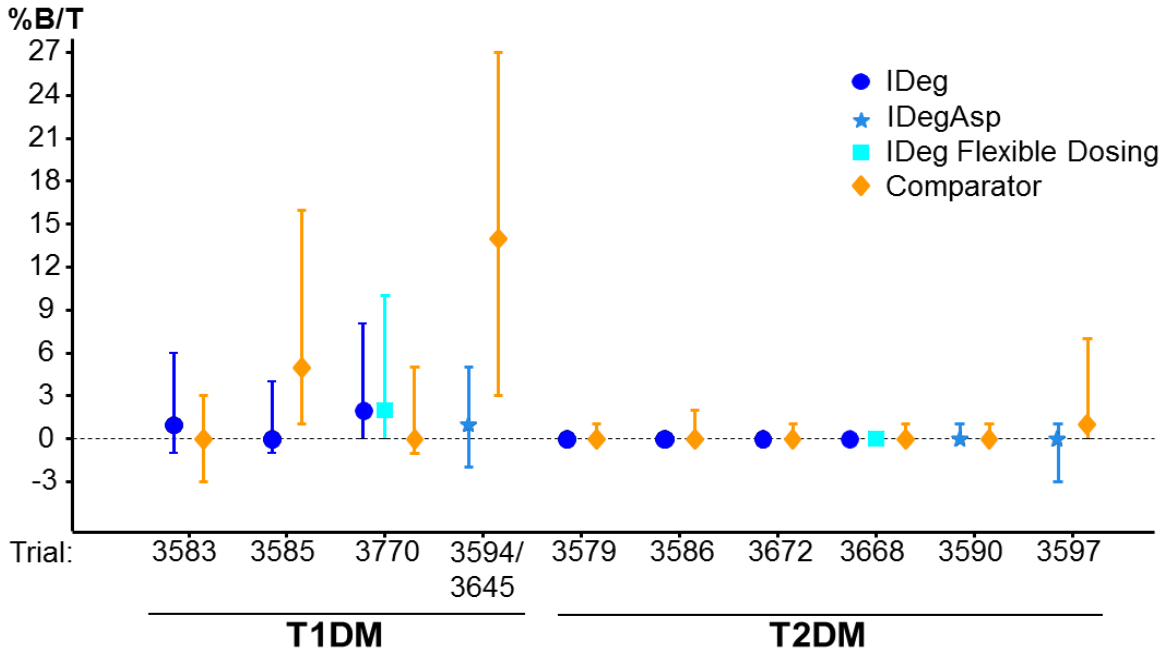
10.4.3 Antibody Formation

Exposure to a new insulin product could trigger antibody development. As part of the assessment of the long-term safety of IDeg or IDegAsp, antibodies specific to IDeg as well as antibodies cross-reacting to human insulin were measured in some phase 3 trials.

Insulin antibodies were measured in 7 IDeg trials: 4 T2DM trials (Trials 3579, 3586, 3668 and 3672) and 3 T1DM trials (Trials 3583, 3585 and 3770). Insulin antibodies were also measured in 3 IDegAsp trials: T2DM Trials 3590 and 3597 and T1DM Trial 3594.

Antibody development against IDeg, IAsp, IDet and IGlar was measured by a validated subtraction radio-immunoassay using radioactively labeled IDeg, Asp, IDet, IGlar or human insulin. The amount of precipitated radioactivity was measured and expressed as percent bound radioactivity (B) of the total amount of radioactivity (T) applied to the sample. The %B/T value is proportional to the amount of anti-insulin antibody present in the sample.

Cross-reacting Antibodies
For all patients, the mean change from baseline to follow-up visit in antibodies cross-reacting with human insulin was low in both the IDeg or IDegAsp and the comparator group, and there was no difference between the treatment groups (Figure 40). The mean level of antibodies cross-reacting with human insulin at baseline and at end of trial (following 27 or 53 weeks of treatment) was similar in the IDeg or IDegAsp and the comparator group.

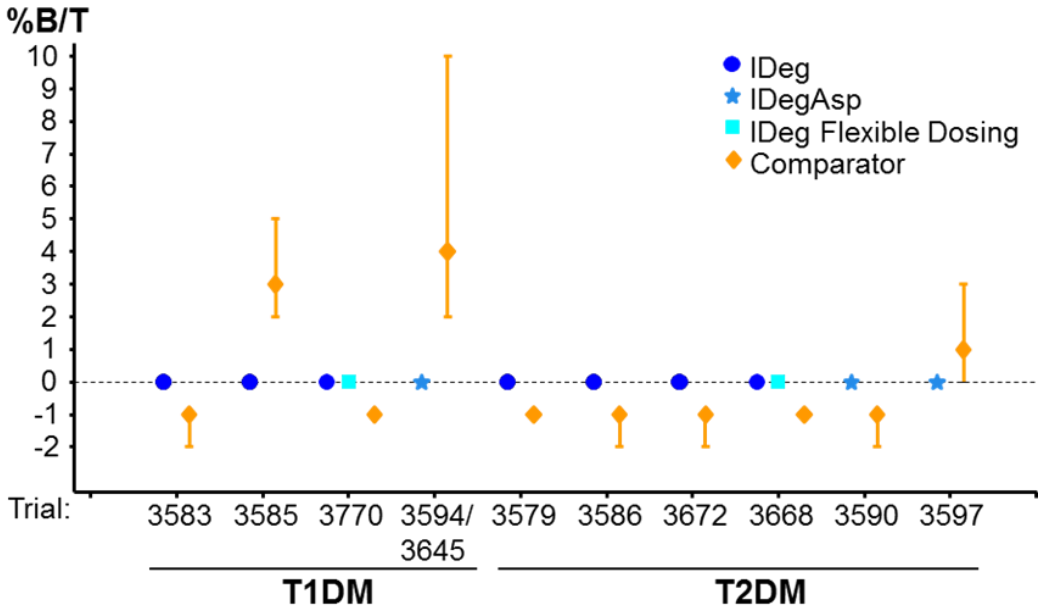


Observed values with 25 and 75 percentiles. %B/T: percent bound over total. Comparators: IGlar (Trials 3583, 3770, 3579, 3586, 3672, 3668 and 3590), IDet (Trials 3585 and 3594) and BIAsp 30 (Trial 3597). Safety analysis set.

Figure 40 Cross-reacting Antibodies at Week 27/53 – Change from Baseline – Phase 3 Trials – IDeg or IDegAsp versus Comparator – NDA

Specific Insulin Analogue Antibodies

For all patients, the mean values of specific insulin analogue antibodies showed no or very little change after 27 and 53 weeks of treatment, and no treatment difference between the IDeg or IDegAsp and the comparator group. The majority of patients in the IDeg or IDegAsp group had no, or little, change in specific IDeg antibodies. In the IDegAsp trials, no change from baseline in IAsp-specific antibodies was seen in any of the treatment groups.



Safety analysis set.

Figure 41 Specific Insulin Analogue Antibodies at Week 27/53 – Phase 3 Trials – IDeg and IDegAsp versus Comparator – Distribution by Trial – NDA

In conclusion, there was no evidence of neutralizing antibodies following treatment with IDeg or IDegAsp. There was no clinically relevant influence of IDeg antibody formation on HbA_{1c}, change in HbA_{1c} at end of trial or total daily dose at the end of the IDeg or IDegAsp trials.

10.5 Clinical Safety Conclusions

Consistent with the *in vitro* and *in vivo* preclinical clinical toxicology profiles of IDeg and IDegAsp, no new or unique adverse events were expected or observed. The adverse event profile of IDeg+IDegAsp was similar to the comparator for the 8941 patients with diabetes included in the clinical development program, including the subsets of both T2DM and T1DM patients. The majority of AEs were mild in severity and the rates of severe AEs were comparable between groups. There were no apparent differences between the IDeg+IDegAsp group and comparators with respect to the patterns of AEs or SAEs leading to withdrawal. Overall, there were no clinically relevant differences between IDeg+IDegAsp and comparators in vital signs, clinical laboratory findings, ECG, after 26 or 52 weeks of treatment.

The frequency of malignant neoplasms with IDeg and IDegAsp was similar to that of comparator. Overall, there were low numbers of malignant neoplasms. No notable differences were seen in allergic reactions or injection-site reactions between IDeg or IDegAsp and comparators.

The phase 3 trials in the IDeg and IDegAsp programs were not specifically designed as cardiovascular outcome trials, but in order to evaluate cardiovascular safety, potential MACE were collected and adjudicated in all phase 3 trials. For the prespecified definition of MACE, incidence rates were similar between IDeg+IDegAsp and comparator for the trials presented in the NDA (1.48 and 1.44 patients with MACE per 100 PYE, respectively). The estimated hazard ratio for the prespecified primary analysis, time to first MACE, was 1.097 $[0.681; 1.768]_{95\%CI}$.

The hazard ratio tended to favor comparator in several additional FDA-requested *post hoc* analyses when altering the prespecified MACE composite endpoint definition and with inclusion of additional exposure from long-term extensions.

There were no clinically relevant differences between IDeg or IDegAsp and comparator in other cardiovascular assessments, namely blood pressure, pulse, lipids, or ECG.

In general, IDeg and IDegAsp were well tolerated and had adverse event profiles similar to that of marketed insulin products. The totality of the cardiovascular data neither confirms nor excludes an increased cardiovascular risk.

11 Dosing Recommendations

Summary

IDeg Dosing Recommendations

- IDeg is recommended to be dosed once daily at any time of the day with the possibility to postpone or advance the injection time (with a minimum of 8 hours between the injection)
- IDeg can be safely initiated at a once-daily dose of 10 U/day in insulin-naïve patients with T2DM.
- Most patients with T1DM can be safely switched from other basal insulin products to IDeg on a unit-to-unit basis. However, patients who transfer from twice-daily basal insulin treatment may need to reduce the starting dose according to individual needs.
- IDeg can be administered alone, in combination with OADs, or in combination with bolus insulin.

IDegAsp Dosing Recommendations

- IDegAsp can be safely initiated at a once-daily dose of 10 U/day in insulin-naïve patients with T2DM.
- IDegAsp can be administered once or twice daily with any main meal(s), providing mealtime coverage through the rapid onset of action of IAsp. If a dose of IDegAsp is missed, the patient should take the next dose with the next main meal of that day.
- Patients switching from once-daily basal or premixed insulin therapy can switch unit-to-unit to once-daily IDegAsp at the same total insulin dose.
- Patients switching from more than once-daily basal or premixed insulin therapy can switch unit-to-unit to twice-daily IDegAsp at the same total insulin dose. Patients switching from basal/bolus or self-mixed insulin therapy to IDegAsp will need to convert their dose based on individual needs.
- IDegAsp can be administered alone or in combination with OADs.

11.1 IDeg Dosing Recommendations

Based on the safety and efficacy outcomes of the phase 3 trials, the recommended dosing of IDeg is once daily, at any time of day.

Data from the five IDeg T2DM trials in insulin-naïve patients (Trials 3579, 3672, 3586, 3580, and 3668) confirmed that IDeg can be safely initiated at a once-daily dose of 10 U/day in insulin-naïve

patients with T2DM as recommended for other basal insulin products. The proportion of patients with confirmed hypoglycemia during the first month of treatment was low and comparable between the treatment arms.

The results of Trials 3668 and 3582 demonstrate that patients with T2DM can safely switch from basal or premixed insulin to IDeg using a unit-to-unit conversion of the basal insulin component. In patients with T1DM, the rates of confirmed hypoglycemia were numerically greater with IDeg than with comparator products during the first month of treatment, while there was no difference between treatments from Month 2–3 and onwards (Figure 30). The higher rate of confirmed hypoglycemia during the first month of treatment in the IDeg group was most pronounced in T1DM patients who transferred from twice-daily basal insulin. Patients using twice-daily basal insulin before the trial decreased their staring basal dose by 20% when assigned to IGlar but transferred on a unit-to-unit basis when assigned to IDeg. As assessed by HbA_{1c} and rates of hypoglycemia in Trials 3583, 3585, and 3770, the majority of patients with T1DM can be safely switched from other basal insulin products to IDeg on a unit-to-unit basis. However, patients who transfer from twice-daily basal insulin treatment may need to reduce the starting dose according to individual needs.

Based on the outcomes of the trials and comparisons of treatment effects in terms of HbA_{1c} and confirmed hypoglycemia by concomitant OAD treatment, IDeg was efficacious and safe when combined with metformin, DPP-4 inhibitors, SUs and the TZD pioglitazone. Moreover, IDeg can be used alone or in combination with a rapid-acting or short-acting insulin.

To ensure patient adherence to recommended therapy, it is generally recommended to administer insulin at approximately the same time every day. The long duration of action and the low day-to-day variation in glucose-lowering effect demonstrated with IDeg at steady state allows patients who forget a dose, or for other reason cannot administer their scheduled dose, a greater flexibility in dosing time, which was confirmed by specifically designed trials. Results from T2DM Trials 3668 and 3580 and T1DM Trial 3770, confirm that patients treated with IDeg can safely administer it once daily at any time of the day with the possibility to postpone or advance the injection time (with a minimum of 8 hours between the injection). Thus, there was no statistically significant difference in the overall rate of confirmed hypoglycemia with IDeg flexible dosing compared to IGlar in the two flexible dosing trials.

11.2 IDegAsp Dosing Recommendations

A 10 U once-daily starting dose of IDegAsp is appropriate for insulin-naïve patients with T2DM as demonstrated by Trial 3590. In newly diagnosed patients with T1DM, IDegAsp should be initiated according to individual needs and dosed once daily in combination with mealtime insulin at the remaining meals. Based on the results from Trial 3594, the recommended starting dose of IDegAsp is 60–70% of the total daily insulin requirement followed by individual dose adjustments.

As demonstrated by the phase 3 trials, it is recommended that IDegAsp be administered once or twice daily with any main meal(s), providing mealtime coverage through IAsp's rapid onset of action in addition to the flat and stable action profile of IDeg. In Trial 3593 (T2DM) and 3594 (T1DM), patients chose the dosing meal that best suited their dietary habits and lifestyle. Furthermore, in Trial 3594, patients were allowed to switch their daily IDegAsp dose to another main meal at their convenience. In both trials, similar results for HbA_{1c} and nocturnal hypoglycemia were shown, regardless of the dosing meal in both trials.

As demonstrated by the IDegAsp phase 3 trials, patients switching from once-daily basal or premixed insulin therapy can be converted unit-to-unit to once daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from more than once-daily basal or premixed insulin therapy can be converted unit-to-unit to twice daily IDegAsp at the same total insulin dose as the patient's previous total daily insulin dose. Patients switching from basal/bolus or self-mixed insulin therapy to IDegAsp will need to convert their dose based on individual needs; typically patients are initiated on the same number of basal units.

IDegAsp can be administered alone or in combination with oral anti-diabetic drugs. In patients with T1DM, IDegAsp must be used in combination with rapid-acting or short-acting insulin at remaining meals.

If a dose of IDegAsp is missed, it is recommended that patient take the next dose with the next main meal of that day, and then resume the usual dosing schedule. Patients should not take an extra dose to make up for a missed dose.

12 Benefit-Risk Profile and Risk Management

Summary

Benefits of IDeg and IDegAsp (Clinical Differentiators)

- Compared with currently marketed basal insulin analogues, IDeg has a longer and more stable action profile that translates into the following benefits for patients with T2DM or T1DM:
  - Less risk of hypoglycemia, particularly at night
  - Patients who forget or miss a scheduled dose can administer IDeg when this is discovered without increasing the risk of hypoglycemia or loss of short-term glycemic control
  - Once-daily dosing for all patients, regardless of dose. (The U200 formulation allows patients with high dose requirements [up to 160 U] to administer their required daily dose of IDeg as one single injection)
- Compared with premixed insulin products, the soluble fixed-ratio combination of IDeg and rapid-acting IAsp (IDegAsp) has the following clinical benefits for patients with T2DM or T1DM:
  - The long duration of action and stable profile of the basal component of IDegAsp supports dosing with one or two main meals with the ability to advance or delay the injection to a different main meal on the same day
  - Less hypoglycemia during the night than either once-daily IGlar or twice-daily analogue premixed insulin
  - The first soluble fixed-ratio combination of basal and bolus insulin that will not require resuspension before administration, thus improving patient convenience and reducing the likelihood of inaccurate dosing due to incomplete suspension of the premixed insulin.

Safety of IDeg and IDegAsp Including Identified and Potential Risks

- No unexpected safety issues were discovered for IDeg or IDegAsp during the comprehensive nonclinical and clinical development regarding safety laboratory evaluations, vital signs, ECG, overall adverse event and serious adverse event profiles, malignant neoplasms, allergic reactions, injection-site reactions, or antibody formation.
- While IDeg and IDegAsp trials were not designed as cardiovascular outcome trials, cardiovascular events suspected to be MACE were adjudicated by an independent committee of experts. The hazard ratio for IDeg+IDegAsp vs. comparator in the prespecified primary analysis of adjudicated MACE was 1.097 $[0.681; 1.768]_{95\%CI}$. However, considering data from the additional *post hoc* analyses that redefine MACE from the prespecified definition and that include extension periods with imbalanced exposure, Novo Nordisk cannot delineate the cardiovascular risk profile. In order to further define the relative cardiovascular profile of IDeg and IDegAsp, Novo Nordisk will continue to work with the FDA on appropriate post-approval activities.
- Based on the totality of the data, IDeg and IDegAsp are associated with a positive benefit-to-risk profile.

The clinical development programs undertaken with IDeg and IDegAsp were the largest ever conducted with an insulin product and consistently substantiated the benefits of IDeg and IDegAsp across a wide range of patients, including those with early onset to more advanced T2DM, as well as patients with T1DM.

12.1 Benefits Associated with IDeg or IDegAsp Treatment

IDeg and IDegAsp Provide Effective Glycemic Control

Both once-daily IDeg and once-or twice-daily IDegAsp effectively improved long-term glycemic control as demonstrated by noninferiority to comparator insulin products in reducing HbA_{1c} in insulin-naïve T2DM, insulin-treated T2DM, and T1DM. Clinically relevant reductions in HbA_{1c} were observed with both IDeg and comparator products, with end-of-trial HbA_{1c} levels at or close to the recommended target level of 7%, using a treat-to-target approach. The improvement in glycemic control was reached with similar doses of basal insulin.

The clinical development programs have demonstrated that IDeg and IDegAsp are efficacious in adults, including elderly patients. Since diabetes also affects the pediatric population, a phase 3b trial has been initiated (and is fully enrolled) to establish the efficacy and safety of IDeg in children and adolescents with T1DM aged between 1 and 18 years (Trial 3561). In this trial, patients are treated with IDeg or IDet, both in combination with IAsp as mealtime insulin.

IDeg and IDegAsp Results in a Low Rate of Hypoglycemia

Hypoglycemia is clinically important because it is the primary limiting factor in achieving glycemic control with insulin. Hypoglycemia, particularly nocturnal hypoglycemia, is the principal point of differentiation between IDeg and IDegAsp, and currently marketed basal insulin or premixed insulin products.

Hypoglycemia in T2DM

The individual trials showed a consistently lower rate of both confirmed and nocturnal confirmed hypoglycemia with basal-only therapy with IDeg compared with IGlar as well as a similar or lower rate of severe hypoglycemic episodes. These results were further substantiated by the meta-analysis, described below, in which the rates of confirmed and nocturnal confirmed hypoglycemia were 17% and 36% lower with IDeg than with IGlar, respectively, both as basal-only therapy.

The lower risk of hypoglycemia is an important advantage for patients and health care providers because it helps overcome the barrier for timely initiation of insulin therapy, which is often delayed due to fear of hypoglycemia. Furthermore, the lower rate of nocturnal hypoglycemia was observed despite consistently larger reductions in FPG with IDeg than with comparator products. This indicates that patients treated with IDeg can strive for more ambitious treatment goals, and heath care providers have the opportunity for providing improved long-term glycemic control in clinical

practice. Finally, the lower rates of hypoglycemia are expected to provide better quality of life for patients, and benefit society by reducing missed work hours and health care expenses.

IDeg was superior to IGlar as part of a basal-bolus regimen with mealtime IAsp, with an 18% lower rate of confirmed hypoglycemia. Still, the effect of basal insulin in a basal-bolus setting is best determined during the night when the influence of meals, physical activity and bolus insulin is minimal. Basal-bolus treatment with IDeg resulted in a 25% lower rate of nocturnal confirmed hypoglycemia than with IGlar. With sustained therapy, a lower rate of especially nocturnal hypoglycemia may prevent hypoglycemic unawareness and thereby reduce the risk of more severe hypoglycemic episodes. The rates of severe hypoglycemia were similar with IDeg and IGlar during 12 months of treatment, with the majority occurring during the day.

In trials testing once-daily IDegAsp in T2DM, the rate of confirmed hypoglycemic episodes was statistically significantly higher for IDegAsp OD relative to IGlar as expected because of the bolus insulin component present in IDegAsp, but not IGlar. In regard to the temporal pattern of the hypoglycemic episodes, the results underscore the importance of administering once-daily IDegAsp with the largest meal of the day, customized to the individual, in order to ensure adequate basal insulin coverage while minimizing the risk of daytime hypoglycemia. However, the rates of nocturnal confirmed hypoglycemia were lower for IDegAsp compared to IGlar, significant in one of the two trials.

In two twice-daily IDegAsp trials in T2DM patients, the rates of confirmed and nocturnal confirmed hypoglycemia were significantly lower for IDegAsp (by 32% and 73%, respectively) compared to BIAsp 30 BID in Trial 3592, and rates were similar in Trial 3597.

Hypoglycemia in T1DM

In T1DM, the rates of confirmed and severe hypoglycemic episodes were generally similar with IDeg and comparator products, apart from a higher rate of confirmed hypoglycemia with IDeg early in the trials (during the titration period). This is believed to result from the fact that a large proportion of patients in the comparator groups remained on their well-known and well-tolerated pretrial insulin. In addition, patients treated on twice-daily basal insulin pretrial reduced their basal insulin dose by 20% in the comparator arm, but were transferred to IDeg on a unit-to-unit basis. The rate of nocturnal confirmed hypoglycemia was consistently lower by 25-40% with IDeg across the individual trials. Hypoglycemia is a very real and inevitable risk in patients with T1DM who depend on insulin as life-sustaining therapy.

When once-daily IDegAsp was used along with bolus IAsp at remaining meals, a significantly lower rate of nocturnal confirmed hypoglycemia was achieved relative to IDet + bolus IAsp. Importantly, the rate of nocturnal hypoglycemia was also statistically significantly lower with IDegAsp compared with IDet, which should help ensure compliance with titration targets in everyday clinical practice.

Hypoglycemia Meta-analysis with IDeg Therapy

The benefits of IDeg in relation to hypoglycemia were further substantiated by the prespecified meta-analysis comparing IDeg to IGlar. IDeg was superior to IGlar in terms of a 9% lower rate of confirmed hypoglycemia and a 26% lower rate of nocturnal confirmed hypoglycemia in the pooled population of patients with T1DM and T2DM. The rate of severe hypoglycemia was similar with IDeg and IGlar in the pooled population of patients with T1DM and T2DM.

The meta-analysis demonstrated that elderly patients >65 years of age had an 18% lower rate of confirmed and a 35% lower rate of nocturnal confirmed hypoglycemia with IDeg compared to IGlar. This is particularly important as elderly people are generally more vulnerable to the effects of hypoglycemia than younger patients due to defective counter-regulatory responses and more frequent use of concomitant medication (such as beta-blocking agents), which may mask the symptoms of hypoglycemia. Furthermore, elderly patients more often live alone, making intervention in cases of hypoglycemia challenging.

In both T2DM and T1DM, the lower rate of hypoglycemia with IDeg was most pronounced during the maintenance phase after glycemic control and dosing stabilized. Rates of nocturnal hypoglycemia during the maintenance phase were 38% (T2DM) and 25% (T1DM) lower for IDeg than IGlar. This period is considered of greatest importance when evaluating a lifelong treatment such as insulin therapy.

The lower rate of nocturnal hypoglycemia was a robust and consistent finding across the individual trials regardless of insulin regimen (basal-only or basal-only therapy), time of dosing (OD evening or flexible intervals), or patient population (T1DM, T2DM, insulin naïve, insulin-treated and geriatric patients).

A higher rate of confirmed hypoglycemia was observed in patients with T1DM in the first month of treatment with IDeg. This was particularly evident in patients who transferred to IDeg from a twice-daily basal insulin regimen and in patients with relatively good glycemic control. In order to avoid an undue risk of hypoglycemia, it is recommended that patients with T1DM switching from twice-daily basal insulin or with an HbA_{1c} <8% at time of transfer reduce their starting dose of IDeg and/or adjust the bolus insulin dose. In the phase 2 trials, a reduction of 20% of the total daily basal insulin dose was used for patients transferred from a BID regimen and this appeared to be safe, as it gave rise to a very low rate of hypoglycemia. Another phase 3b trial will investigate the use of self-titration with a simple titration algorithm (Trial 3846) with the goal of providing patients and health care providers with recommendations regarding the optimal titration of IDeg once initiated. In addition, a phase 1 trial (Trial 3999) is planned to investigate the effect of IDeg during exercise in patients with T1DM in a controlled setting.

IDeg Offers Flexibility in Dosing

Results from the two IDeg flexible dosing trials that investigated the extremes of once-daily dosing, support the administration of IDeg in a flexible manner to accommodate individual patient needs without loss of glycemic control. IDeg flexible dosing was also associated with a similar or lower rate of confirmed hypoglycemia and nocturnal confirmed hypoglycemia compared with IGlar in these two trials.

While it is recommended to inject IDeg at approximately the same time every day, the stable action profile of IDeg combined with the low day-to-day variation in glucose-lowering effect at steady state, allows patients to advance or delay the daily administration of IDeg when needed, with no impact on short-term glycemic control and minimal risk of hypoglycemia. Thus, if an injection is forgotten, delayed or omitted, the patient can inject IDeg upon discovery and thereafter resume the usual dosing schedule while ensuring a minimum of 8 hours between injections. This may also be relevant for patients traveling across time zones, patients with shift work, and patients who rely on health care providers to administer their insulin during home visits.

IDeg U200 Benefits Patients with High Dose Requirements

Obesity is a growing problem in the US and worldwide, and it is anticipated that more patients will require high doses of insulin to cover their daily basal insulin requirements. IDeg U200 will specifically benefit the 20−30% of patients in the US who require more than 80 U of basal insulin per injection. These patients will be able to inject up to 160 U in one injection rather than administrating the dose as two consecutive injections as is required for other basal insulin products. A phase 3b trial (Trial 3943) is planned to further investigate the potential benefits of IDeg U200 compared with IGlar in patients with T2DM with high daily basal insulin requirements. IDeg U200 will only be available in a prefilled pen injector device to avoid potential mix-ups between U200 and U100 cartridges for use with durable pens.

12.2 Safety of IDeg and IDegAsp Including Identified and Potential Risks

Novo Nordisk has conducted an extensive clinical development program for IDeg and IDegAsp in both T2DM and T1DM, with data from 16 therapeutic confirmatory phase 3 clinical trials (with 1 extension) in more than 8900 patients available at the time of the NDA, and from 19 trials and 7 extensions in more than 9800 patients available as of May 1, 2012. However, it is important to note that the program was designed to evaluate the efficacy and safety profile of IDeg or IDegAsp versus comparator agents in terms of glycemic control and general safety parameters; the program was not specifically designed as a cardiovascular outcome program.

IDeg retains all of the biological properties of naturally occurring human insulin and has a similar mode of action upon binding to the insulin receptor. The adverse event profiles of IDeg and IDegAsp were similar in type, frequency, and severity to that observed with IGlar, IDet, and

BIAsp 30, and was comparable to the profile reported with sitagliptin in Trial 3580. The rate of death was low and similar with IDeg, IDegAsp, and comparator products, as was the pattern of adverse events and serious adverse events leading to withdrawal, which were dispersed across the entire treatment period.

The adverse events of interest with IDeg and IDegAsp are those also observed with other insulin products and include hypoglycemia, injection-site disorders and those observed with diabetes in general such as neoplasms. There were no clinically relevant differences in the rates of these adverse events between IDeg+IDegAsp and comparator products, but, considering their clinical importance, Novo Nordisk will continue to collect detailed safety information for these during the phase 3b program.

Diabetes has been shown to be associated with an increased risk of cancer, the mechanism behind which has yet to be determined. The rate of malignant neoplasms was low in both treatment groups and the majority of the malignant neoplasms in the IDeg+IDegAsp group were reported within 3 months after start of trial treatment, making a causal relationship unlikely.

One of the major concerns in patients with diabetes is the increased risk of cardiovascular disease. Insulin treatment *per se* has not been shown to be associated with an increased cardiovascular risk. The overall estimated hazard ratio for MACE based on the prespecified analysis of the pooled population from the original NDA dataset was 1.097 $[0.681; 1.768]_{95\%CI}$, with no consistent pattern across individual trials. The difference in the hazard ratio estimates between the NDA and *post hoc* analyses were based on altering the MACE definition and on extended exposure data driven by a small number of events from a few extension trials with imbalanced exposure. Considering the importance of cardiovascular disease, Novo Nordisk continues to adjudicate MACE from all ongoing and planned trials in the clinical phase 3b program. Furthermore, in order to further define the relative cardiovascular profile of IDeg and IDegAsp, Novo Nordisk will continue to work with the FDA on appropriate post-approval activities.

12.3 Risk Management and Post-approval Activities

Routine pharmacovigilance activities are currently planned to further characterize the risks in populations for which important information is missing. This includes patients with severe renal impairment or hepatic impairment, as well as children and adolescents.

Results from the IDeg and IDegAsp development programs indicate that IDeg and IDegAsp do not contribute to the development or worsening of diabetic comorbidities such as diabetic retinopathy, diabetic neuropathy, and neoplasms. The cardiovascular safety evaluation neither confirms nor excludes increased cardiovascular risk, and therefore, Novo Nordisk will continue to work with the FDA on potential post-approval activities designed to better define the cardiovascular profile.

12.4 Conclusions for the Benefit-Risk Evaluation

Based on the clinical data presented above, Novo Nordisk concludes that IDeg and IDegAsp constitute a valuable treatment option for patients with T2DM and T1DM. IDeg and IDegAsp are associated with a favorable benefit-to-risk profile, and provide considerable advantages over current basal or premixed insulin products. IDeg and IDegAsp are well tolerated with adverse event profiles similar to that of other marketed basal insulin products, and no unacceptable risks have been identified. Due to its distinct pharmacological profile, IDeg has been shown to be efficacious in terms of lowering HbA_{1c} and FPG with a lower risk of overall and nocturnal hypoglycemia compared with current basal insulin products due to its distinct pharmacological profile. This allows patients who miss a dose, or for other reasons cannot inject their dose at the scheduled time, to administer IDeg when this is discovered without compromising efficacy and safety.

Based on the totality of the data, IDeg and IDegAsp are associated with a positive benefit-to-risk profile. Novo Nordisk believes that the proposed labeling and post-approval activities presented above will be adequate.

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Novo Nordisk

Insulin Degludec and Insulin Degludec/Aspart Treatment to Improve Glycemic Control in Patients with Diabetes Mellitus

NDAs 203314 and 203313

Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

November 8, 2012

Appendix 1

Advisory Committee Briefing Materials: Available for Public Release

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Table 1 IDeg Relative Affinity Ratios for IGF-1 receptor/Insulin receptor Binding

Species	Receptor type	Albumin (%)	Endpoint	Affinity (relative to HI)	Affinity ratio IGF-IR/IR
Human	Solubilized IR-A & IR-B	0	IR binding	13 and 15%	<1
	Solubilized IGF-1R	0	IGF-1R binding	2%	
Human	Membrane IR-A & IR-B	0.1	IR binding	4.2 and 3.2%	<1
	Membrane IGF-1R	0.1	IGF-1R binding	0.4%	
Rat	Membrane IR-A & IR-B	0.1	IR binding	2.3 and 3.0%	<1
	Membrane IGF-1R	0.1	IGF-1R binding	1.2%	
Dog	Liver membrane IR	0.1	IR binding	7%	<1
	Membrane IGF-1R	0.1	IGF-1R binding	0.7%	

IR: Insulin receptor; IGF-R: IGF-1 receptor; HI: human insulin.

Table 2 Comparison of Mitogenic to Metabolic Potency Ratio

Assay	Albumin (%)	Endpoint	Potency relative to HI (%)	Range (%)
Metabolic potency				
Rat hepatocytes	0	Glycogen accumulation	21	4 – 21
Rat hepatocytes	0.1	Glycogen accumulation	10	
Rat hepatocytes	0.1	PEPCK mRNA expression	13.4	
Rat muscle cells	0.1	Glycogen synthesis	3.9	
Human muscle cells	0.1	Glycogen synthesis	4.4	
L6-hIR	0.1	Glycogen synthesis	11.5	
MCF-7	0	Glycogen synthesis	7.7	
Mitogenic potency				
COLO-205	0	DNA synthesis	5.4	5 – 10
HMEC	0	DNA synthesis	6.6	
L6-hIR	0	DNA synthesis	9.6	
MCF-7	0	DNA synthesis	8.5	

L6-hIR = L6 myoblasts over-expressing the human insulin receptor; MCF-7 = human mammary; HI: human insulin; mRNA: messenger ribonucleic acid;.adenocarcinoma cells; PEPCK: phosphoenolpyruvate carboxykinase; COLO-205: human colon adenocarcinoma cells; HMEC: primary human mammary epithelial cells.

Table 3 Incidence Table of Mammary Hyperplasia, Benign and Malignant Tumors in Female Sprague Dawley Rats after 52 Weeks of Treatment

Treatment	**Vehicle**		**IDeg**		**Human Insulin[b]**
Dose (nmol/kg/day)	**0**	**20**	**40**	**60**	**40**
Number of animals	**40**	**40**	**40**	**50**	**50**
Hyperplasia	1	1	3	0	4
Benign tumors					
Fibroadenoma	1	3	0	0	4
Malignant tumors					
Adenocarcinoma	4	2	0	0	3
Fibrosarcoma	0	1	0	0	0
Malignant mixed	0	1	0	0	0
Mammary gland: Number of tumor-bearing animals[a]	5	7	0	0	7
Incidence (%)	**13%**	**18%**	**0%**	**0%**	**14%**

a: Combined benign and malignant tumors
b: Administered as NPH insulin.

Table 4 Pair-wise Comparison of Pharmacokinetic Endpoints for IDeg at Steady State between Black/African American, Hispanic/Latino and White Patients with T2DM

Race/ethnic Group	**$AUC_{IDeg,\tau,SS}$ (pmol·h/L) Mean ratio [95% CI]**	**$C_{max,IDeg,SS}$ (pmol/L) Mean ratio [95% CI]**
Black/African American vs. Hispanic/Latino	1.13 [0.95; 1.34]	1.06 [0.89; 1.27]
Black/African American vs. White	1.10 [0.91; 1.31]	1.07 [0.89; 1.28]
Hispanic/Latino vs. White	0.97 [0.82; 1.16]	1.00 [0.84; 1.20]

Trial 3762: 0.6 U/kg. Statistical analyses were based on 18 Black/African American patients, 22 Hispanic/Latino patients and 19 White patients.
CI: confidence interval.

Table 5 Observed Change in HbA_{1c} from Baseline to End of Trial by Age Group, Ethnicity, Race, and Renal Function − IDeg T2DM Trials

	IDeg		Comparator	
Factor	**No. Patients**	**Δ HbA_{1c}**	**No. Patients**	**Δ HbA_{1c}**
Age group				
18 to 65 years	1863	-1.20	852	-1.31
>65 to 75 years	557	-1.05	225	-1.18
<75 years	71	-0.92	33	-1.11
Ethnicity				
Hispanic/Latino	284	-1.18	121	-1.31
Non-Hispanic/Latino	2183	-1.16	976	-1.28
Race				
White	1783	-1.16	766	-1.25
Black/African American	166	-1.08	81	-1.18
Asian Indian	131	-1.13	67	-1.55
Asian non-Indian	370	-1.21	174	-1.33
Renal function				
Normal renal function	2071	-1.18	946	-1.29
Mild renal impairment	392	-1.05	149	-1.20
Moderate renal impairment	26	-1.05	13	-0.88

Full analysis set.

Table 6 Observed Change in HbA_{1c} from Baseline to End of Trial by Age Group, Ethnicity, Race, and Renal Function − IDeg T1DM Trials

	IDeg		Comparator	
Factor	**No. Patients**	**Δ HbA_{1c}**	**No. Patients**	**Δ HbA_{1c}**
Age group				
18 to 65 years	1026	-0.49	444	-0.54
>65 to 75 years	68	-0.48	25	-0.68
>75 years	9	-0.30	5	-0.22
Ethnicity				
Hispanic	46	-0.53	23	-0.60
Non-Hispanic	1057	-0.49	451	-0.54
Race				
White	889	-0.39	380	-0.46
Black	19	-0.58	4	-0.35
Asian Indian	41	-1.13	20	-0.75
Asian non-Indian	131	-0.94	66	-0.95
Renal function				
Normal renal function	967	-0.48	415	-0.51
Mild renal impairment	117	-0.58	50	-0.73
Moderate renal impairment	14	-0.77	4	-0.55

Full analysis set.

Table 7 Observed Change in HbA_{1c} from Baseline to End of Trial by Age Group, Ethnicity, Race, and Renal Function − IDegAsp T2DM Trials

	IDegAsp		Comparator	
Factor	**No. Patients**	**Δ HbA_{1c}**	**No. Patients**	**Δ HbA_{1c}**
Age group				
18 to 65 years	744	-1.37	630	-1.41
>65 to 75 years	224	-1.24	202	-1.26
>75 years	32	-1.22	28	-1.01
Ethnicity				
Hispanic	63	-1.76	74	-1.68
Non-Hispanic	906	-1.31	764	-1.33
Race				
White	437	-1.32	441	-1.38
Black	43	-1.51	29	-1.29
Asian Indian	170	-1.24	161	-1.22
Asian non-Indian	345	-1.37	224	-1.45
Renal function				
Normal renal function	766	-1.36	659	-1.40
Mild renal impairment	213	-1.27	186	-1.24
Moderate renal impairment	21	-1.12	13	-1.39

Full analysis set. Trials included: 3593, 3590, 3592 and 3597 . Normal Renal Function: Estimated Creatinine Clearance > 80; Mild Renal Impairment: 50 <= Estimated Creatinine Clearance <= 80; Moderate Renal Impairment: 30 <= Estimated Creatinine Clearance < 50. End of Trial: a patient's last trial visit excluding the follow-up. Missing values are imputed by LOCF.

Table 8 Observed Change in HbA_{1c} from Baseline to End of Trial by Age Group, Ethnicity, Race, and Renal Function − IDegAsp T1DM Trial 3594

	IDegAsp OD		IDet	
Factor	**No. Patients**	**Δ HbA_{1c}**	**No. Patients**	**Δ HbA_{1c}**
Age group				
18 to 65 years	355	-0.74	168	-0.67
>65 to 75 years	7	-0.37	12	-0.63
>75 years	4	-0.15	2	-1.90
Ethnicity				
Hispanic	10	-0.93	7	-0.04
Non-Hispanic	339	-0.75	167	-0.71
Race				
White	333	-0.77	162	-0.68
Black	10	-0.45	6	-0.38
Asian Indian	1	-1.20	3	-0.83
Asian non-Indian	3	0.57	1	-1.50
Renal function				
Normal renal function	346	-0.75	161	-0.68
Mild renal impairment	19	-0.44	21	-0.70
Moderate renal impairment	1	0.10	-	-

Full analysis set. Normal Renal Function: Estimated Creatinine Clearance > 80; Mild Renal Impairment: 50 <= Estimated Creatinine Clearance <= 80; Moderate Renal Impairment: 30 <= Estimated Creatinine Clearance < 50. End of Trial: a patient's last trial visit excluding the follow-up. Missing values are imputed by LOCF.

Table 9 Confirmed Hypoglycemic Episode Rate by Age Group, Ethnicity, Race, and Renal Function − IDeg T2DM Trials

	IDeg		Comparator	
Factor	**No. Patients**	**Event Rate per 100 PYE**	**No. Patients**	**Event Rate per 100 PYE**
Age group				
18 to 65 years	1011	520.2	430	555.1
>65 to 75 years	335	636.0	136	649.0
>75 years	42	468.5	20	1027.7
Ethnicity				
Hispanic	168	530.0	74	579.3
Non-Hispanic	1205	550.4	506	588.1
Race				
White	1006	566.8	402	628.1
Black	98	740.8	43	676.1
Asian Indian	77	526.9	36	588.3
Asian non-Indian	186	316.0	95	364.5
Renal function				
Normal renal function	1136	526.6	487	581.5
Mild renal impairment	238	664.1	89	660.5
Moderate renal impairment	13	419.8	10	426.6

Safety analysis set.

Table 10 Confirmed Hypoglycemic Episode Rate by Age Group, Ethnicity, Race, and Renal Function − IDeg T1DM Trials

	IDeg		Comparator	
Factor	No. Patients	Event Rate per 100 PYE	No. Patients	Event Rate per 100 PYE
Age group				
18 to 65 yrs	976	5164.4	415	5200.4
>65 to 75 yrs	66	5703.7	22	5596.0
>75 yrs	7	5164.9	5	4133.5
Ethnicity				
Hispanic	44	4740.2	23	5932.6
Non-Hispanic	1005	5217.3	419	5167.2
Race				
White	844	5210.6	352	5131.4
Black	17	4239.0	4	5508.9
Asian Indian	36	3409.1	18	4224.4
Asian non-Indian	129	5883.6	64	5636.8
Renal function				
Normal renal function	920	5107.6	389	5251.7
Mild renal impairment	112	6305.3	46	5228.8
Moderate renal impairment	13	3212.3	4	3160.4

Safety analysis set.

Table 11 Confirmed Hypoglycemic Episode Rate by Age Group, Ethnicity, Race, and Renal Function − Statistical Analysis – IDegAsp T2DM Trials

	IDeg		Comparator	
Factor	**No. Patients**	**Event Rate per 100 PYE**	**No. Patients**	**Event Rate per 100 PYE**
Age group				
18 to 65 yrs	434	658.8	328	604.8
>65 to 75 yrs	148	839.4	121	817.8
>75 yrs	24	663.8	19	606.2
Ethnicity				
Hispanic	35	609.2	30	173.3
Non-Hispanic	557	714.5	431	712.5
Race				
White	257	652.6	228	590.2
Black	20	409.8	15	342.7
Asian Indian	80	434.4	80	702.0
Asian non-Indian	244	887.1	144	788.1
Renal function				
Normal renal function	441	642.6	334	572.0
Mild renal impairment	147	866.8	125	930.3
Moderate renal impairment	18	1109.2	9	872.5

Safety analysis set.

Table 12 Patients Who Died in Completed Phase 3 IDeg and IDegAsp Trials – May 1, 2012

Trial ID	Trial Product	Age (yrs) /Sex	Type of Diabetes	Preferred Term
IDeg+IDegAsp				
NDA				
3770	IDeg	46/F	T1DM	Completed suicide, Hypoglycemic coma
3583	IDeg	67/M	T1DM	Myocardial infarction*
3583	IDeg	60/M	T1DM	Myocardial infarction*
3668	IDeg	72/F	Insulin-treated T2DM	Anemia Myelo-dysplastic syndrome
3582	IDeg	65/M	Insulin-treated T2DM	Arteriosclerosis*, Hypertensive heart disease
3582	IDeg	58/M	Insulin-treated T2DM	Myocardial infarction*
3582	IDeg	69/M	Insulin-treated T2DM	Hemorrhage intracranial*
3582	IDeg	63/M	Insulin-treated T2DM	Cardio-respiratory arrest*
3582	IDeg	69/M	Insulin-treated T2DM	Hematemesis
3582	IDeg	67/F	Insulin-treated T2DM	Cardiac arrest*
3582	IDeg	53/M	Insulin-treated T2DM	Myocardial infarction†
3582	IDeg	57/M	Insulin-treated T2DM	Road traffic accident
3580	IDeg	49/M	Insulin-naïve T2DM	Myocardial infarction*
3586	IDeg	69/M	Insulin-naïve T2DM	Drowning
3592	IDegAsp	41/M	Insulin-treated T2DM	Interstitial lung disease
3597	IDegAsp	85/F	Insulin-treated T2DM	Interstitial lung disease
3590	IDegAsp	62/M	Insulin-naïve T2DM	Hepatic cancer metastatic
3590	IDegAsp	60/M	Insulin-naïve T2DM	Death*
NDA to May 1, 2012				
3579-3643	IDeg	71/M	Insulin-naïve T2DM	Small cell lung cancer
3579-3643	IDeg	68/F	Insulin-naïve T2DM	Large intestine perforation, Pseudomembranous colitis, Multi Organ Failure
3579-3643	IDeg	76/M	Insulin-naïve T2DM	Death*
3579-3643	IDeg	47/M	Insulin-naïve T2DM	Rectal cancer
3582-3667	IDeg	58/M	Insulin-treated T2DM	Brain stem haemorrhage*
3582-3667	IDeg	55/M	Insulin-treated T2DM	Death*
3582-3667	IDeg	66/M	Insulin-tretaed T2DM	Bronchial carcinoma, Metastasis to central nervous system
3583-3644	IDeg	37/M	T1DM	Sudden death*
3583-3644	IDeg	69/M	T1DM	Ventricular tachycardia*
3846	IDeg	72/M	Insulin naïve T2DM	Metastasis to liver
3590-3726	IDegAsp	55/M	Insulin naïve T2DM	Myocardial infarction*
3590-3726	IDegAsp	68/M	Insulin naïve T2DM	Cellulitis

Patients Who Died in Completed Phase 3 IDeg and IDegAsp Trials – May 1, 2012 (continued)

Trial ID	Trial Product	Age (yrs) /Sex	Type of Diabetes	Preferred Term
Comparator				
NDA				
3583	IGlar	26/F	T1DM	Sudden death*
3582	IGlar	61/M	Insulin-treated T2DM	Metastatic neoplasm
3582	IGlar	49/M	Insulin-treated T2DM	Myocardial infarction*
3668	IGlar	63/M	Insulin-treated T2DM	Death*
3579	IGlar	73/M	Insulin-naïve T2DM	Urosepsis
3672	IGlar	64/M	Insulin-naïve T2DM	Myocardial ischemia*
3672	IGlar	55/M	Insulin-naïve T2DM	Pneumonia, Acute myocardial infarction*
3592	BIAsp 30	71/M	Insulin-treated T2DM	Head injury
NDA to May 1, 2012				
3579-3643	IGlar	45/M	Insulin-naïve T2DM	Road traffic accident
3579-3643	IGlar	56/M	Insulin-naïve T2DM	Myocardial infarction*
3583-3644	IGlar	51/F	T1DM	Gall bladder cancer metastatic
3583-3644	IGlar	75/F	T1DM	Ventricular arrhythmia*
3590-3726	IGlar	58/F	Insulin-naïve T2DM	Ischaemic stroke*, Brain oedema

* Fatal events in these patients were also categorized as Major Adverse Cardiovascular Events (MACE)
† Event was not adjudicated as MACE because the patient died from hemodynamic collapse following prostatectomy.

Three fatal events were considered non-treatment-emergent and not included in the above table:

Trial ID: 3579-3643, Sudden cardiac death (IDeg); 3579-3643, Cardiac arrest (IGlar); 3579-3643, Cardio-respiratory arrest (IGlar). Another death occurred in a therapeutic exploratory trial: Trial ID: 1792; cardiac failure (BIAsp 30).

Table 13 Malignant Neoplasms by Preferred Term – IDeg + IDegAsp Phase 3 Trials – All Patients – NDA

	IDeg + IDegAsp				Comparator			
	N	(%)	E	R	N	(%)	E	R
Safety Analysis Set	5635				3306			
Total Exposure (yrs)	3578.4				1878.0			
All Adverse Events	30	(0.5)	31	0.9	15	(0.5)	15	0.8
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	30	(0.5)	31	0.9	14	(0.4)	14	0.7
Basal cell carcinoma	5	(0.1)	5	0.1				
Breast cancer	2	(0.0)	2	0.1	3	(0.1)	3	0.2
Colon cancer	5	(0.1)	5	0.1				
Thyroid cancer	1	(0.0)	1	0.0	3	(0.1)	3	0.2
Squamous cell carcinoma	3	(0.1)	3	0.1				
Bladder cancer					2	(0.1)	2	0.1
Squamous cell carcinoma of skin	1	(0.0)	1	0.0	1	(0.0)	1	0.1
Adenocarcinoma	1	(0.0)	1	0.0				
Bladder adenocarcinoma stage unspecified	1	(0.0)	1	0.0				
Bone neoplasm malignant	1	(0.0)	1	0.0				
Carcinoid tumor of the stomach	1	(0.0)	1	0.0				
Colon cancer stage III					1	(0.0)	1	0.1
Endometrial cancer					1	(0.0)	1	0.1
Large intestine carcinoma	1	(0.0)	1	0.0				
Laryngeal cancer	1	(0.0)	1	0.0				
Lung neoplasm	1	(0.0)	1	0.0				
Lung neoplasm malignant	1	(0.0)	1	0.0				
Malignant melanoma	1	(0.0)	1	0.0				
Metastases to liver	1	(0.0)	1	0.0				
Metastatic gastric cancer					1	(0.0)	1	0.1
Metastatic neoplasm					1	(0.0)	1	0.1
Pancreatic carcinoma					1	(0.0)	1	0.1
Penis carcinoma	1	(0.0)	1	0.0				
Prostate cancer stage I	1	(0.0)	1	0.0				
Renal cancer	1	(0.0)	1	0.0				
Uterine cancer	1	(0.0)	1	0.0				
Surgical and medical procedures					1	(0.0)	1	0.1
Skin neoplasm excision					1	(0.0)	1	0.1

All Malignant Neoplasms occurring post randomization are considered, including non-treatment emergent events . There was one non-treatment emergent malignant neoplasm: basal cell carcinoma that occurred 47 days after last dose of IDeg; this event is included in the table.
N: Number of Patients with adverse events; %: Proportion of patients in analysis set having adverse events; E: Number of adverse events; R: Number of events divided by Patient years of exposure multiplied by 100; Total Exposure (yrs): Total Exposure in years for Safety Analysis Set.
All Malignant Neoplasms are considered including non-treatment-emergent.

Table 14 Patient Disposition for Individual Trials Completed as of May 1, 2012

Trial	Description	Randomized		Completed Main		Entered Ext		Completed Ext	
		IDeg/ IDegAsp N	Comparator N	IDeg/ IDegAsp N (%)	Comparator N (%)	IDeg/ IDegAsp N (%)	Comparator N (%)	IDeg/ IDegAsp N (%)	Comparator N (%)
3579-3643	T2DM BOT 12m-12m IDeg vs. IGlar	773	257	607 (78.5)	197 (76.7)	551 (71.3)	174 (67.7)	505 (65.3)	154 (59.9)
3672	T2DM BOT 6m IDeg U200 vs. IGlar	230	230	200 (87.0)	201 (87.4)				
3586	T2DM BOT Asia 6m IDeg vs. IGlar	289	146	258 (89.3)	136 (93.2)				
3580	T2DM BOT 6m IDeg vs. Sita	229	229	174 (76)	174 (76)				
3668	T2DM BOT 6m IDeg vs. IDeg flex dosing vs. IGlar	228(IDeg) 229 (Flex)	230	204 (89.5) 203 (88.6)	203 (88.3)				
3724	T2DM BOT 6m IDeg U200 3TW vs. IGlar	230	230	192 (83.5)	206 (89.6)				
3718	T2DM BOT 6m IDeg U200 3TW vs. IGlar	233	234	208 (89.3)	209 (89.3)				
3590-3726	T2DM 6m-6m IDegAsp OD vs. IGlar	266	264	219 (82.3)	232 (87.9)	192 (72.2)	221 (83.7)	179 (67.3)	209 (79.2)
3582-3667	T2DM BB 12m-6m IDeg vs. IGlar	755	251	618 (81.9)	211 (84.1)	566 (75.0)	191 (76.1)	539 (71.4)	183 (72.9)
3593	T2DM 6m IDegAsp OD vs. IGlar	232	233	196 (84.5)	205 (88)				
3592	T2DM 6 m IDegAsp BID vs. BIAsp30 BID	224	223	197 (87.9)	188 (84.3)				
3597	T2DM Asia IDegAsp BID vs BIAsp 30 BID	282	142	245 (86.9)	126 (88.7)				
3583-3644	T1DM BB 12 mo-12 mo IDeg OD vs. IGlar OD	472	157	404 (85.6)	137 (87.3)	351 (74.4)	118 (75.2)	330 (69.9)	113 (72.0)
3585-3725	T1DM BB 6m-6m IDeg OD vs. IDet	303	153	283 (93.4)	138 (90.2)	248 (81.8)	122 (79.7)	242 (79.9)	115 (75.2)
3770-3770	T1DM 6m-6 m IDeg vs. IDeg Flex vs. IGlar	165 IDeg) 164 (Flex)	164	139 (84.2) 138 (84.1)	152 (92.7)	239 (72.6)	133 (81.1)	223 (67.8)	122 (74.4)
3594-3645	T1DM BB 6m-6m IDegAsp OD vs. IDet	366	182	320 (87.4)	156 (85.7)	254 (69.4)	122 (67.0)	233 (63.7)	113 (62.1)
3846	T2DM Titration 6m, Phase 3b IDeg simple vs. IDeg step wise	111	111	99 (89.2)	98 (88.3)				
3923	T2DM 6m, Phase 3b IDeg U200 vs. IDeg U100	186	187	184 (98.9)	187 (100.0)				
3896	T2DM Japan 6m, IDegAsp vs. IGlar	147	149	137 (93.2)	137 (91.9)				

N; number of patients; %: proportion of randomized patients; Ext: extension trial; BOT: basal-only therapy; IDeg: insulin degludec; IGlar: insulin glargine: Sita: sitagliptin; IDegAsp: insulin degludec/insulin aspart; BB: basal-bolus; IDet: insulin detemir; OD: once daily; BID: twice daily; 6m: 6-month trial; 12m: 12-month trial. Flex: IDeg flexible dosing.

Novo Nordisk

Insulin Degludec and Insulin Degludec/Insulin Aspart Treatment to Improve Glycemic Control in Patients with Diabetes Mellitus

NDAs 203314 and 203313

Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

November 8, 2012

Appendix 2

Advisory Committee Briefing Materials: Available for Public Release

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1 Overview of Key IDeg and IDegAsp Clinical Pharmacology Trials

Appendix Table 1

Trial	Trial Objectives	Treatment
IDeg - T2DM		
1987	PK/PD (dose-response) at steady state (MD)	IDeg: 0.4, 0.6, 0.8 U/kg; IDeg U200: 0.6 U/kg
3762	PK/PD at steady state in different races, ethnicities (MD)	IDeg & IDet: 0.6 U/kg
IDeg - T1DM		
1991	Within-patient variability at steady state (MD)	IDeg & IGlar: 0.4 U/kg
1993	PK/PD (dose-response) at steady state (MD)	IDeg & IGlar: 0.4, 0.6, 0.8 U/kg
1994	PK/PD at steady state in elderly & younger adults (MD)	IDeg & IGlar: 0.4 U/kg
1995	PK & safety profile in children, adolescents & adults (SD)	IDeg & IGlar: 0.4 U/kg
1996	PK/PD at steady state in Japanese patients (MD)	IDeg & IDet: 0.4 U/kg
3538	Hypoglycemic response (MD)	IDeg and IGlar: individual doses
3678	PK/PD of IDeg U100 vs. IDeg U200 at steady state (MD)	IDeg U100 & IDeg U200: 0.4 U/kg
IDeg - Healthy Volunteers		
1988	BE between two IDeg products with different drug substance manufacturing strains (SD)	IDeg: 0.4 U/kg
1989	PK & safety in subjects with/without hepatic impairment (SD)	IDeg: 0.4 U/kg
1990	PK & safety in subjects with/without renal impairment (SD)	IDeg: 0.4 U/kg
1992	PK/PD after s.c. administration at three different injection regions, and i.m. and i.v. administration (SD)	IDeg: 0.4 U/kg s.c. & i.m., 0.04 U/kg i.v.
3769	BE between IDeg drug product before & after optimization of drug substance manufacturing process (SD)	IDeg: 0.4 U/kg
IDegAsp - T2DM		
1978	PK/PD (dose-response) (SD)	IDegAsp & BIAsp 30: 0.4, 0.6, 0.8 U/kg
IDegAsp - T1DM		
1959	PK/PD of IAsp and IDeg when co-formulated in IDegAsp (SD)	IDegAsp: 0.92 U/kg (0.28 U/kg IAsp + 0.64 U/kg IDeg); IDeg: 0.64 U/kg + IAsp: 0.28 U/kg; BIAsp 30: 0.64 U/kg
1981	PK/PD in elderly & younger adults (SD)	IDegAsp & BIAsp 30: 0.5 U/kg
1982	PK & safety profile in children, adolescents and adults (SD)	IDegAsp: 0.5 U/kg
1983	PK/PD in Japanese patients (SD)	IDegAsp & BIAsp 30: 0.5 U/kg
3539	PK/PD (dose-response) (SD)	IDegAsp & BIAsp 30: 0.4, 0.6, 0.8 U/kg
3857	PK/PD of IDegAsp vs. IDeg and IAsp (product distinctiveness) (SD)	IDegAsp, IDeg, IAsp: 0.5 U/kg
1979	PK/PD of IDegAsp at steady state (MD). Phase 3b*.	IDegAsp: 0.6 U/kg
IDegAsp – Healthy Volunteers		
1980	BE between two IDegAsp products with different drug substance manufacturing strains (SD)	IDegAsp: 0.5 U/kg

i.m.: intramuscularly; i.v.: intravenously; PD: pharmacodynamics; PK: pharmacokinetics; s.c.: subcutaneously. SD: single dose; MD: multiple dose; BE: bioequivalence; BIAsp 30: biphasic insulin aspart 30.
*Trial completed after submission of the NDA.

2 Overview of Insulin Degludec Phase 3 Trials

Appendix Table 2

Trial ID	Insulin Initiation, Intensification or Optimization	Trial Length	IDeg Regimen	Comparator	IDeg Formulation
Basal-only therapy in T2DM					
3579	Initiation	12 months	Once-daily IDeg + OAD(s)	Once-daily IGlar + OAD(s)	100 U/mL
3672	Initiation	6 months	Once-daily IDeg + metformin ± DPP-4	Once-daily IGlar + metformin ± DPP-4	200 U/mL
3586	Initiation	6 months	Once-daily IDeg + OAD(s)	Once-daily IGlar + OAD(s)	100 U/mL
3580	Initiation	6 months	Once-daily IDeg + 1-2 OAD(s)	Once-daily Sitagliptin + 1-2 OAD(s)	100 U/mL
3668	Initiation/ Intensification/ Optimization	6 months	Once-daily IDeg (flexible dosing) ± OAD(s)	Once-daily IDeg (fixed dosing) ± OAD(s) Once-daily IGlar ± OAD(s)	100 U/mL
3724	Initiation	6 months	Three-times-weekly IDeg + metformin ± DPP-4I	Once-daily IGlar + metformin ± DPP-4I	200 U/mL
3718	Initiation	6 months	Three-times-weekly IDeg + metformin ± DPP-4I	Once-daily IGlar + metformin ± DPP-4I	200 U/mL
Basal-bolus therapy in T2DM					
3582	Intensification/ Optimization	12 months	Once-daily IDeg + mealtime IAsp ± metformin ± pioglitazone	Once-daily IGlar + mealtime IAsp ± metformin ± pioglitazone	100 U/mL
Basal-bolus therapy in T1DM					
3583	Optimization	12 months	Once-daily IDeg + mealtime IAsp	Once-daily IGlar + mealtime IAsp	100 U/mL
3585	Optimization	6 months	Once-daily IDeg + mealtime IAsp	Once-daily IDet* + mealtime IAsp	100 U/mL
3770	Optimization	6 months	Once-daily IDeg (flexible dosing) + mealtime IAsp	Once-daily IDeg (fixed dosing) + mealtime IAsp Once-daily IGlar + mealtime IAsp	100 U/mL

All therapeutic confirmatory IDeg phase 3 a trials are shown.

*Investigators had the option of initiating a second dose of IDet if glycemic control was inadequate after 8 weeks of once-daily treatment.
OAD: oral antidiabetic drug; DPP-4I: dipeptidyl peptidase-4 inhibitor.

3 Overview of Insulin Degludec/Aspart Phase 3 Trials

Appendix Table 3

Trial ID	Insulin Initiation, Intensification or Optimization	Trial Length	IDegAsp Regimen	Comparator	IDegAsp Formulation
Once-daily Therapy in T2DM					
3590	Initiation	6 months	Once-daily IDegAsp + metformin	Once-daily IGlar + metformin	100 U/mL
3593	Intensification/ Optimization	6 months	Once-daily IDegAsp + metformin ± DPP-4I ± pioglitazone	Once-daily IGlar + metformin ± DPP-4I ± pioglitazone	100 U/mL
Twice-daily Therapy in T2DM					
3592	Intensification/ Optimization	6 months	Twice-daily IDegAsp ± metformin ± DPP-4I ± pioglitazone	Twice-daily BIAsp 30 ± metformin ± DPP-4I ± pioglitazone	100 U/mL
3597	Intensification/ Optimization	6 months	Twice-daily IDegAsp ± metformin	Twice-daily BIAsp 30 ± metformin	100 U/mL
Basal-bolus therapy in T1DM					
3594	Intensification/ Optimization	6 months	Once-daily IDegAsp + IAsp at remaining meals	Once-daily IDet* + mealtime IAsp	100 U/mL

All therapeutic confirmatory IDegAsp phase 3 a trials are shown.

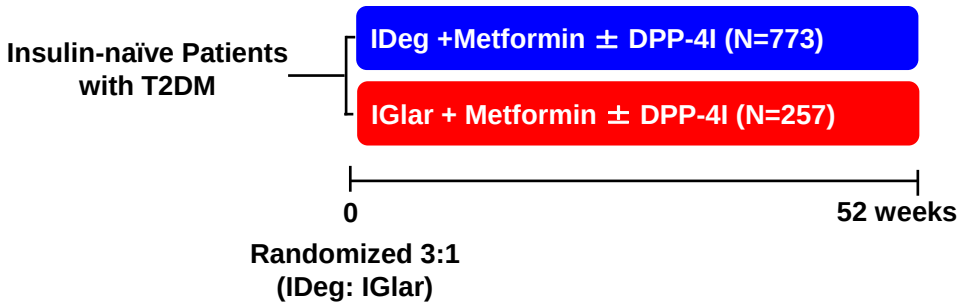
*Investigators had the option of initiating a second dose of IDet if glycemic control was inadequate after 8 weeks of once-daily treatment.
DPP-4I: dipeptidyl peptidase-4 inhibitor.

4 Detailed Descriptions of Once-Daily Insulin Degludec Phase 3 Trials

4.1 Basal-only Therapy in T2DM

4.1.1 Trial 3579 (T2DM BOT 12m)

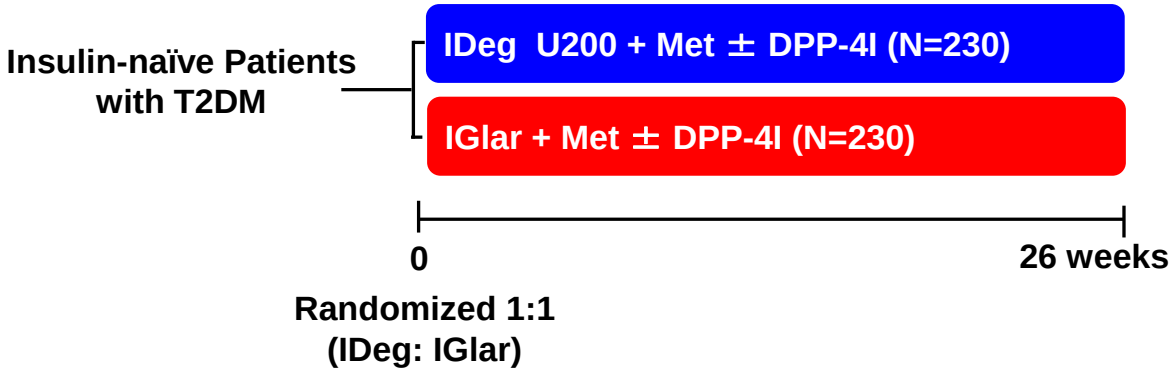
- **Trial Description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar both injected once daily in combination with OADs in patients with T2DM
- **Trial duration**: 12 months
- **Population**:
  - Insulin-naïve patients with T2DM
  - Current treatment: OAD(s)
  - Qualify for intensified treatment
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule:**
  - IDeg: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDeg to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment



DPP-4I: dipeptidyl peptidase-4 inhibitor; N: Number of randomized patients;

4.1.2 Trial 3672 (T2DM BOT U200 6m)

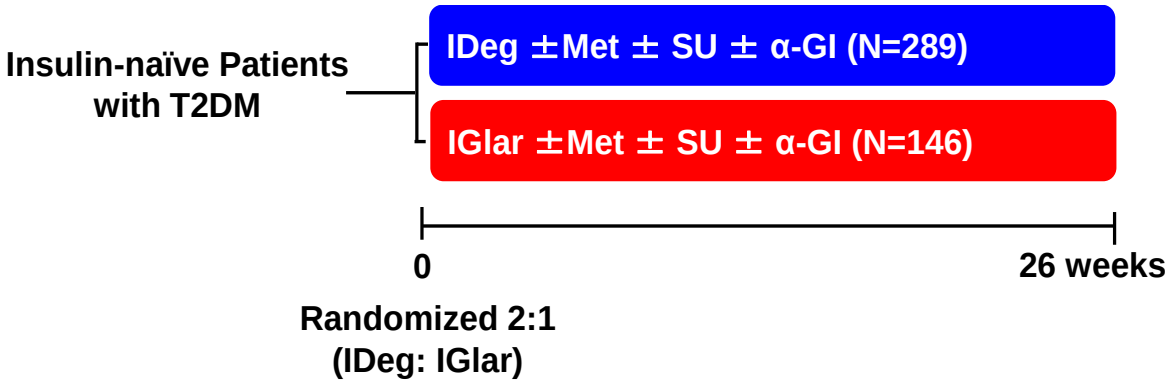
- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg U200 and IGlar both injected once daily in combination with OADs in patients with T2DM
- **Trial duration**: 6 months
- **Population**:
  - Insulin-naïve patients with T2DM
  - Current treatment: OAD(s)
  - Qualify for intensified treatment
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤45 kg/m^2
- **Dosing schedule:**
  - IDeg U200: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint:** change from baseline HbA_{1c} (noninferiority of IDeg to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment



Met: Metformin; DPP-4I: dipeptidyl peptidase-4 inhibitor; N: Number of randomized patients.

4.1.3 Trial 3586 (T2DM BOT 6m Asia)

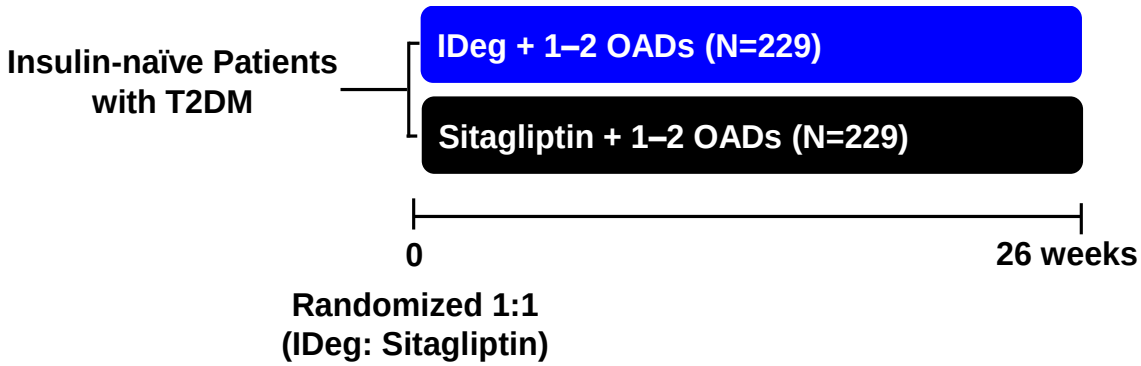
- **Trial description:** Pan-Asian, randomized, controlled, open-label, multicenter, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar both injected once daily in combination with OADs in patients with T2DM
- **Trial duration:** 6 months
- **Population:**
  - Insulin-naïve Asian patients with T2DM
  - Current treatment: OAD(s)
  - Qualify for intensified treatment
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤35 kg/m^2
- **Dosing schedule:**
  - IDeg: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint:** change from baseline in HbA_{1c} (noninferiority of IDeg to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)
  - HbA_{1c} <7.0% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment



Met: Metformin; SU: sulfonylurea; α-GI: alpha-glucosidase inhibitor; N: Number of randomized patients.

4.1.4 Trial 3580 (T2DM BOT 6m vs. Sitagliptin)

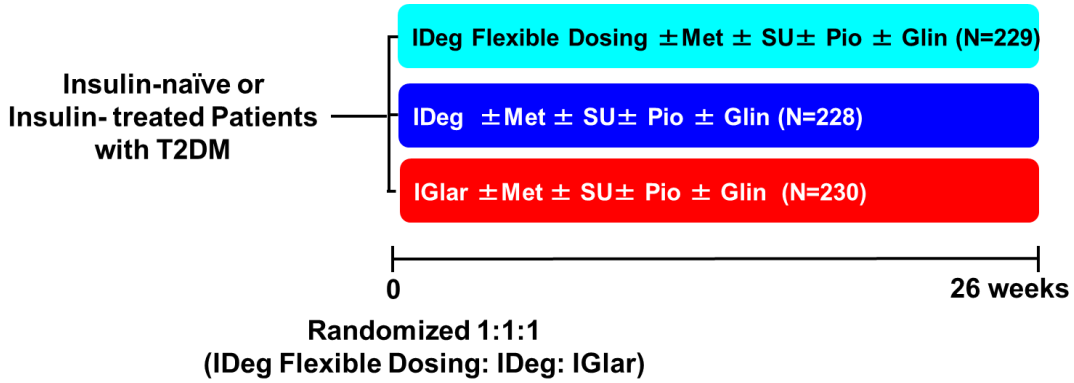
- **Trial description:** Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and sitagliptin both administered once daily in combination with OADs in patients with T2DM
- **Trial duration:** 6 months
- **Population:**
  - Insulin-naïve patients with T2DM
  - Current treatment: 1–2 OAD(s)
  - Qualify for intensified treatment
  - HbA_{1c} 7.5% to 11.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule:**
  - IDeg: once-daily flexible dosing (i.e., when preferred by the patient in the period from morning awakening until bedtime. Variation of injection time from day to day was allowed while maintaining a minimum of 8 hours and a maximum of 40 hours between injections).
  - Sitagliptin: once daily at the same time each day (per product labeling)
- **Primary endpoint:** change from baseline in HbA_{1c} (superiority of IDeg to sitagliptin was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to sitagliptin was tested):
  - Change from baseline in FPG
  - HbA_{1c} <7% at end of trial
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment



OADs: oral antidiabetic drugs. N: Number of randomized patients.

4.1.5 Trial 3668 (T2DM BOT FLEX 6m)

- **Trial description:** Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg in a flexible dosing regimen with IGlar both injected once daily with or without OAD treatment in patients with T2DM
- **Trial duration:** 6 months
- **Population:**
  - Patients with T2DM ≥6 months
  - Current treatment: basal insulin alone, OAD(s) alone, or OAD(s) in combination with basal insulin
  - HbA_{1c} 7.0% to 11.0%, inclusive (OAD[s] only) or 7.0% to 10.0%, inclusive (basal insulin + OAD[s] only)
  - BMI ≤40 kg/m^2
- **Dosing schedule:**
  - IDeg Flexible Dosing: once daily in a flexible dosing regimen (alternating 8- to 40-hour intervals between doses and a 24-hour interval between Saturdays and Sundays)
  - IGlar: once daily at the same time each day (per product labeling)
  - IDeg: once daily in the evening
- **Primary endpoint:** change from baseline in HbA_{1c} (noninferiority of IDeg in a flexible dosing regimen to IGlar was tested)
  - Comparison of IDeg in a flexible regimen to IDeg in a fixed regimen with regard to change from baseline in HbA_{1c} was a secondary objective
- **Key secondary endpoints**:
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - HbA_{1c} <7.0%
  - HbA_{1c} <7.0% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment

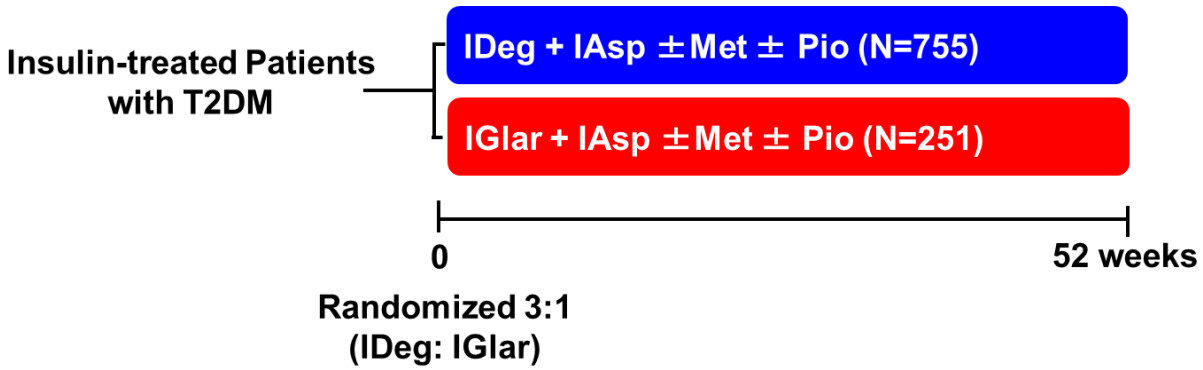


Met: metformin; SU: sulfonylurea; Pio: pioglitazone; Glin: glinides; N: Number of randomized patients.

4.2 Basal-bolus Therapy in T2DM

4.2.1 Trial 3582 (T2DM BB 12m)

- **Trial description:** Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar both injected once daily in a basal-bolus regimen with mealtime IAsp ± metformin ± pioglitazone in patients with T2DM
- **Trial duration**: 12 months
- **Population**:
  - T2DM patients ≥6 months
  - Current treatment: any insulin regimen ≥3 months ± OAD(s)
  - Qualify for intensified treatment
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule**:
  - IDeg: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDeg to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment

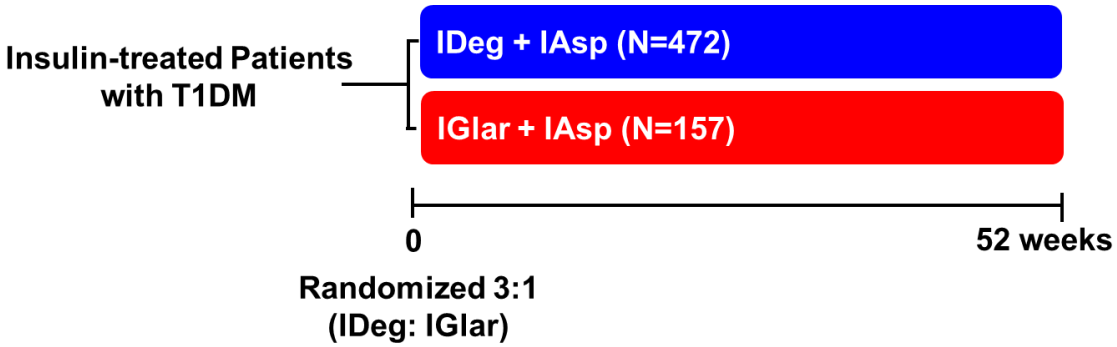


Met: Metformin; Pio: pioglitazone; N: Number of randomized patients.

4.3 Basal-bolus Therapy in T1DM

4.3.1 Trial 3583 (T1DM BB 12m)

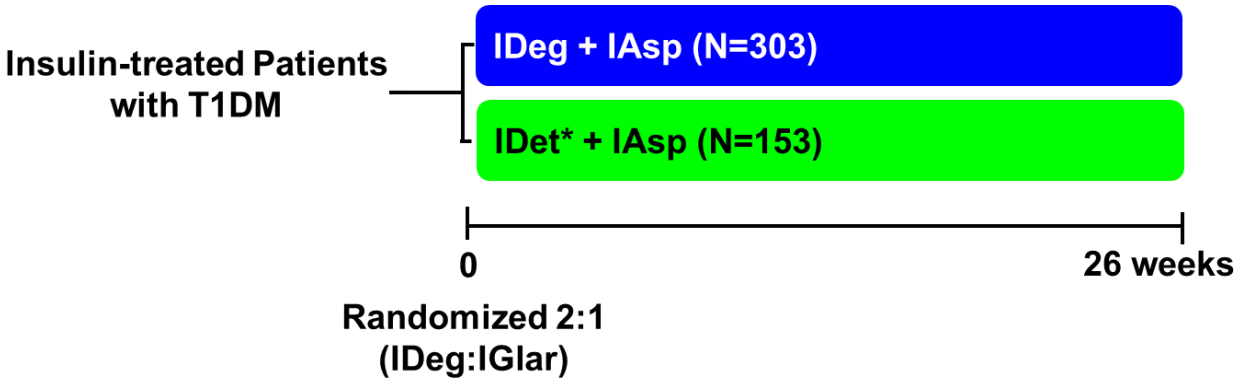
- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IGlar both injected once daily in a basal-bolus regimen with mealtime IAsp in patients with T1DM
- **Trial duration**: 12 months
- **Population**:
  - T1DM patients ≥12 months
  - Current treatment: any basal-bolus insulin regimen ≥12 months
  - HbA_{1c} ≤10.0%
  - BMI ≤35 kg/m^2
- **Dosing schedule:**
  - IDeg: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDeg to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of nocturnal confirmed hypoglycemic episodes
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)



N: Number of randomized patients.

4.3.2 Trial 3585 (T1DM BB 6m)

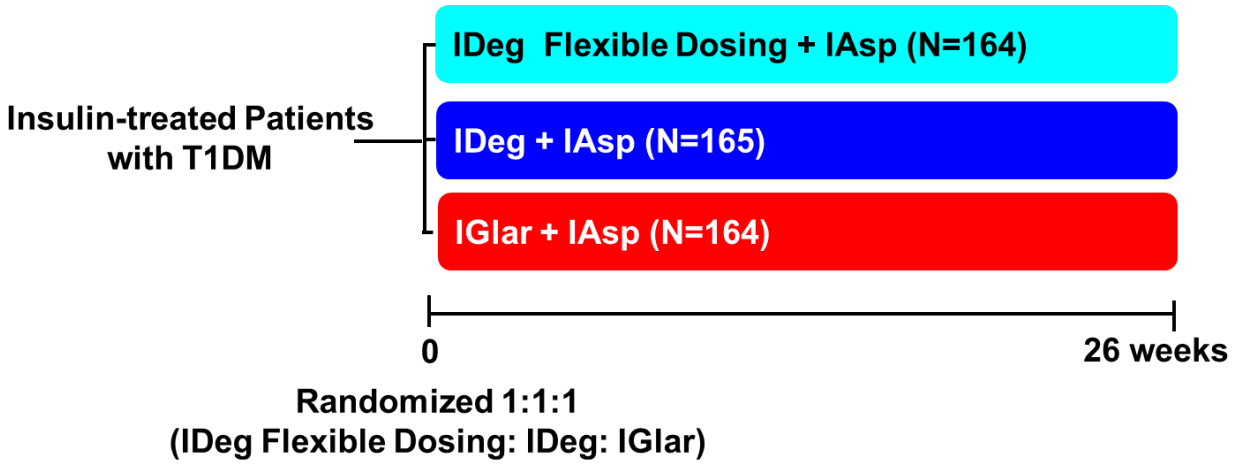
- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg and IDet both injected once daily in a basal-bolus regimen with mealtime IAsp in patients with T1DM
- **Trial duration**: 6 months
- **Population**:
  - T1DM patients ≥12 months
  - Current treatment: any basal-bolus insulin regimen ≥12 months
  - HbA_{1c} ≤10.0%
  - BMI ≤35 kg/m^2
- **Dosing schedule**:
  - IDeg: once daily in the evening
  - IDet: once daily in the evening at randomization. (Investigators had the option of initiating a second dose of IDet if glycemic control was inadequate after 8 weeks of once-daily treatment.)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDeg to IDet was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDeg to IGlar was tested):
  - Number of nocturnal confirmed hypoglycemic episodes
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - Within-patient variability in prebreakfast self-measured plasma glucose (end of trial)



*A second IDet dose could be added after 8 weeks in case of inadequate glycemic control.
N: Number of randomized patients.

4.3.3 Trial 3770 (T1DM BB FLEX 6m)

- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDeg in a flexible dosing regimen with IGlar both injected once daily in a basal-bolus regimen with mealtime IAsp in patients with T1DM
- **Trial duration**: 6 months
- **Population**:
  - T1DM patients ≥12 months
  - Current treatment: any basal-bolus insulin regimen
  - HbA_{1c} ≤10.0%
  - BMI ≤35 kg/m^2
- **Dosing schedule**:
  - IDeg Flex: once daily in a flexible dosing regimen (alternating 8- to 40-hour intervals between doses and a 24-hour interval between Saturdays and Sundays)
  - IGlar: once daily at the same time each day (per product labeling)
  - IDeg: once daily in the evening
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDeg in a flexible regimen to IGlar was tested)
  - Comparison of IDeg in a flexible regimen to IDeg in a fixed regimen with regard to change from baseline in HbA_{1c} was a secondary objective
- **Key secondary endpoints**:
  - Number of confirmed hypoglycemic episodes
  - Change from baseline in FPG
  - HbA_{1c} <7.0%
  - HbA_{1c} <7.0% at end of trial without confirmed hypoglycemic episodes during the last 12 weeks of treatment



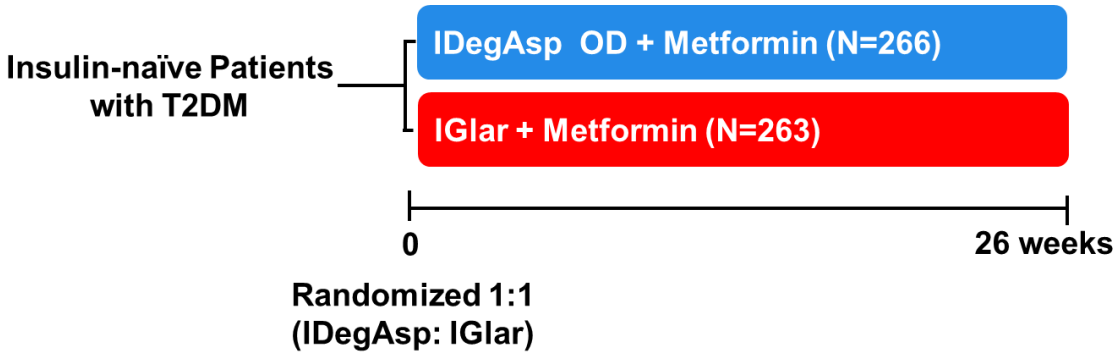
N: Number of randomized patients.

5 Detailed Descriptions of Insulin Degludec/Aspart Phase 3 Trials

5.1 Once-daily Therapy in T2DM

5.1.1 Trial 3590 (T2DM OD 6m)

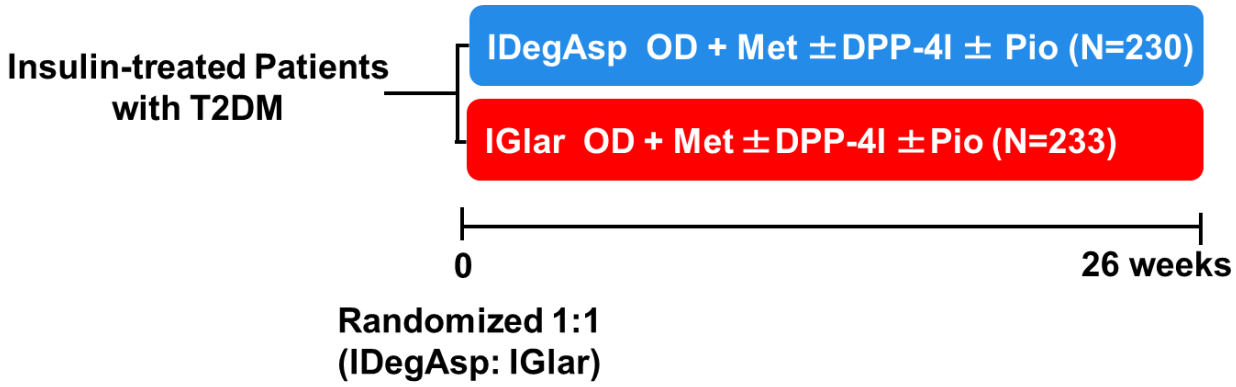
- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDegAsp and IGlar both injected once daily in combination with metformin in insulin-naïve patients with T2DM
- **Trial duration**: 6 months
- **Population**:
  - Insulin-naïve patients with T2DM for ≥6 months
  - Current treatment: metformin + at least one other OAD ≥3 months
  - HbA_{1c} 7.5% to 11.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule**:
  - IDegAsp: once daily in the morning
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDegAsp to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDegAsp to IGlar was tested):
  - Self-measured plasma glucose increment at breakfast
  - Fluctuation in nocturnal IG
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during last 12 weeks of treatment
  - Number of nocturnal confirmed hypoglycemic episodes
  - Change from baseline in body weight



N: Number of randomized patients; OD: once daily; IG: interstitial glucose.

5.1.2 Trial 3593 (T2DM OD 6m)

- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDegAsp and IGlar both injected once daily in combination with OAD(s) in patients with T2DM
- **Trial duration**: 6 months
- **Population**:
  - Patients with T2DM for ≥6 months
  - Current treatment: basal insulin regimen for ≥3 months
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule**:
  - IDegAsp: once daily in the evening
  - IGlar: once daily at the same time each day (per product labeling)
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDegAsp to IGlar was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDegAsp to IGlar was tested):
  - Self-measured plasma glucose increment at dinner
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during last 12 weeks of treatment
  - Fluctuation in nocturnal IG
  - Number of nocturnal confirmed hypoglycemic episodes
  - Body weight

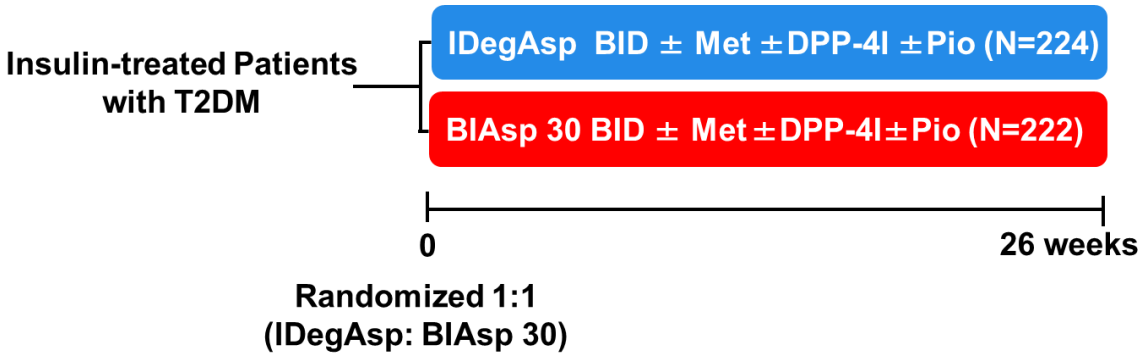


Met: Metformin; DPP-4I: dipeptidyl peptidase-4 inhibitor; Pio: pioglitazone; N: Number of randomized patients; OD: once daily.

5.2 Twice-daily Therapy in T2DM

5.2.1 3592 (T2DM BID 6m)

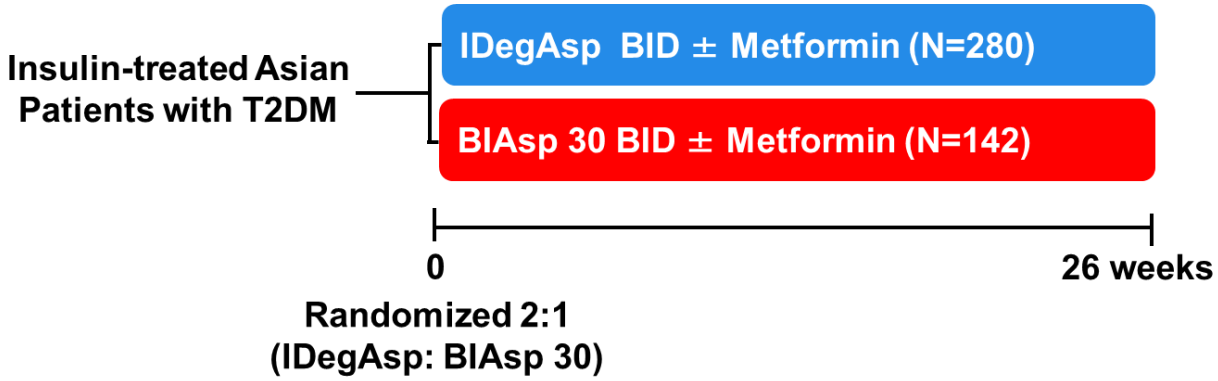
- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDegAsp and BIAsp 30 both injected twice daily ± metformin ± DPP-4I ± pioglitazone in patients with T2DM
- **Trial duration**: 6 months
- **Population**:
  - T2DM for ≥6 months
  - Current treatment: premix human or analogue insulin or self-mix insulin regimen ± OAD(s) for ≥3 months
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤40 kg/m^2
- **Dosing schedule**:
  - IDegAsp: twice daily in the morning and evening
  - BIAsp 30: twice daily in the morning and evening
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDegAsp to BIAsp was tested)
- **Confirmatory secondary endpoints** (In order of priority, the superiority of IDegAsp to BIAsp was tested):
  - Change from baseline in FPG
  - Number of confirmed hypoglycemic episodes
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during last 12 weeks of treatment
  - Change from baseline in body weight
  - Number of nocturnal confirmed hypoglycemic episodes



Met: Metformin; DPP-4I: dipeptidyl peptidase-4 inhibitor; Pio: pioglitazone; N: Number of randomized patients; BID: twice daily.

5.2.2 3597 (T2DM BID 6m ASIA)

- **Trial description**: Pan-Asian, randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDegAsp and BIAsp 30 both injected twice daily ± metformin in patients with T2DM
- **Trial duration**: 6 months
- **Population**:
  - Asian patients with T2DM for ≥6 months
  - Current treatment: basal, premixed, or self-mixed insulin regimen ± metformin for ≥ 3 months
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤35 kg/m^2
- **Dosing schedule**:
  - IDegAsp: twice daily in the morning and evening
  - BIAsp 30: twice daily in the morning and evening
- **Primary endpoint:** change from baseline in HbA_{1c} (noninferiority of IDegAsp to BIAsp 30 was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDegAsp to BIAsp 30 was tested):
  - Change from baseline in FPG
  - Number of confirmed hypoglycemic episodes
  - HbA_{1c} <7% at end of trial without confirmed hypoglycemic episodes during last 12 weeks of treatment
  - Change from baseline in body weight
  - Number of nocturnal confirmed hypoglycemic episodes

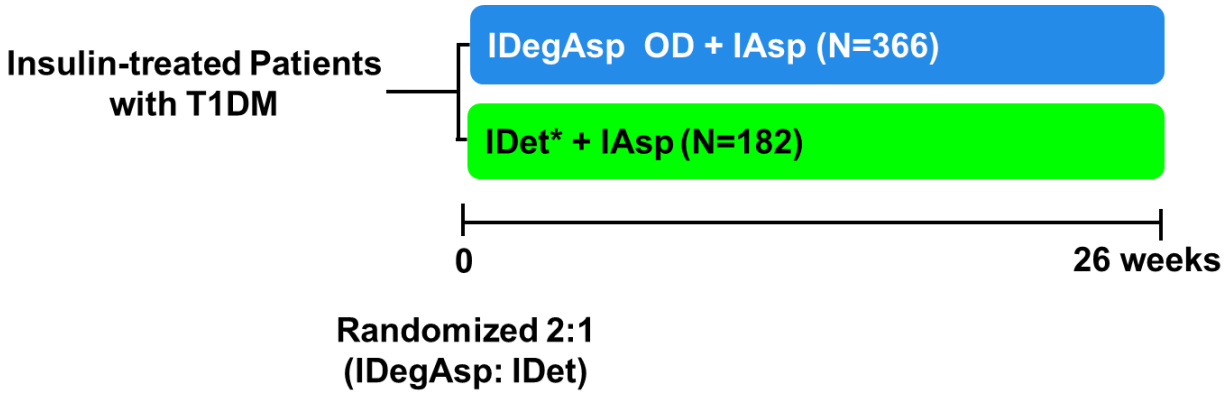


N: Number of randomized patients; BID: twice daily.

5.3 Basal-bolus Therapy in T1DM

5.3.1 3594 (T1DM OD 6m)

- **Trial description**: Randomized, controlled, open-label, multicenter, multinational, treat-to-target trial comparing the efficacy and safety of IDegAsp once daily + IAsp for the remaining meals and basal-bolus treatment with IDet + mealtime IAsp in patients with T1DM
- **Trial duration**: 6 months
- **Population**:
  - Patients with T1DM for ≥12 months
  - Current treatment: basal/bolus, premix, or self-mixed insulin regimen
  - HbA_{1c} 7.0% to 10.0%, inclusive
  - BMI ≤35 kg/m^2
- **Dosing schedule**:
  - IDegAsp: once daily flexible
  - IDet: once daily in the evening
- **Primary endpoint**: change from baseline in HbA_{1c} (noninferiority of IDegAsp to IDet was tested)
- **Confirmatory secondary endpoints** (In order of priority, superiority of IDegAsp to IDet was tested):
  - Change from baseline in FPG
  - HbA_{1c} <7% at end of trial without severe hypoglycemic episodes during last 12 weeks of treatment
  - Number of nocturnal confirmed hypoglycemic episodes



*A second IDet dose could be added after 8 weeks in case of inadequate glycemic control.
OD: once daily; N: total number of patients.

Novo Nordisk

Insulin Degludec and Insulin Degludec/Insulin Aspart Treatment to Improve Glycemic Control in Patients with Diabetes Mellitus

NDA 203314

Briefing Document

Endocrinologic and Metabolic Drug Advisory Committee

November 8, 2012

Appendix 3

Advisory Committee Briefing Materials: Available for Public Release

Table of Contents

Page

1 Definitions and Classifications

1.1 Acute Coronary Syndrome

ACS conditions range from unstable angina pectoris (UAP) to non-ST elevation MI (NSTEMI—subendocardial or nontransmural) and ST elevation MI (STEMI—transmural).

1.1.1 Myocardial Infarction

MI is diagnosed based on any of the following criteria, which is based on the redefinitions suggested by the ESC (European Society of Cardiology)/ACCF (American College of Cardiology Foundation)/AHA (American Heart Association)/WHF (World Heart Federation) task force[1]:

1.1.1.1 MI Criteria

Criteria for STEMI: New ST segment elevation of > 1 millimeter (mm) or millivolt (mV) is present in 2 or more contiguous leads on the 12-lead ECG.

Criteria for NSTEMI: ST segment elevation of > 1mm or mV is absent in 2 or more contiguous leads on the 12-lead ECG.

Below, is a description of the criteria defining Acute Myocardial Infarction.

The term "MI" should be used when there is evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia. Under these conditions, any one of the following criteria meets the diagnosis for MI:

Detection of rise and/or fall of cardiac biomarkers (preferably troponin) with at least 1 value above the 99th percentile of the upper reference limit (URL) together with evidence of myocardial ischemia with at least 1 of the following:

- Symptoms of ischemia
- ECG changes indicative of new ischemia (new ST-T changes or new left bundle branch block [LBBB])
- Development of pathological Q waves in the ECG
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality

[1] Thygesen K, et al. Universal definition of myocardial infarction. J Am Coll Cardiol. 2007 Nov 27; 50(22):2173-95

Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and/or evidence of fresh thrombus by coronary angiography and/or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood. Note: It is important that the Cardiovascular Event Evaluation Group (CEEG) identify resuscitated cardiac arrest (non-fatal) events. Such events will be considered possible ACS events, not Cardiovascular Death events, as resuscitated sudden death may be adjudicated as a category of non-fatal MI.

For percutaneous coronary interventions (PCI) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 3 × 99th percentile URL have been designated as defining PCI-related MI. A subtype related to a documented stent thrombosis is recognized.

For coronary artery bypass grafting (CABG) in patients with normal baseline troponin values, elevations of cardiac biomarkers above the 99th percentile URL are indicative of peri-procedural myocardial necrosis. By convention, increases of biomarkers greater than 5 × 99th percentile URL plus either new pathological Q waves or new LBBB, or angiographically documented new graft or native coronary artery occlusion, or imaging evidence of new loss of viable myocardium have been designated as defining CABG-related MI.

Pathological findings of an acute MI.

The following criteria apply to defining Prior MI. Any one of the following criteria meets the diagnosis for prior MI:

Development of new pathological Q waves with or without symptoms.

Imaging evidence of a region of loss of viable myocardium that is thinned and fails to contract, in the absence of a non-ischemic cause.

Pathological findings of a healed or healing MI.

When the 99th percentile URL is not available, for operational purposes, the local site's URL for measures of troponin I or T, CKMB or CK will be used.

1.1.1.2 MI Classifications

For CEC adjudication the following classifications of MI will be identified.

Type 1: Spontaneous MI related to ischemia due to a primary coronary event such as plaque fissuring or rupturing.

Type 2: MI secondary to ischemia due to imbalance between oxygen demand and supplies, e.g., coronary spasm.

Type 3: Sudden cardiac death with symptoms of myocardial ischemia, accompanied by new ST elevation or LBBB, or verified coronary thrombus by angiography, but death occurring before blood samples could be obtained.

Type 4: MI associated with PCI. (4a—peri-PCI; 4b—stent thrombosis)

Type 5: MI associated with CABG.

In addition to classification, the CEC Adjudicators will identify the category of URL increase that correlates with the possible event. The Adjudicator will indicate if troponin was not available and will have the option to identify other biomarkers.

1.1.2 Unstable Angina Pectoris

UAP is defined as cardiac ischemic events that do not fulfil the criteria of acute MI (NSTEMI or STEMI). If neither of these conditions is present by the criteria above in the MI sections of this document, then UAP may be present. The symptoms in UAP are often of shorter duration and/or are relapsing and represent a significant worsening of the patient's baseline symptoms to an extent as being the primary cause of unplanned hospitalization. For UAP to be present, NSTEMI and STEMI cannot be present.

Severe recurrent ischemia (UAP) is defined as ischemic discomfort or equivalent meeting the following criteria in the absence of MI criteria:

1. Lasting at least 10 minutes at rest, or repeated episodes at rest lasting ≥ 5 minutes, or an accelerating pattern of ischemic discomfort (episodes that are more frequent, severe, longer in duration, and precipitated by minimal exertion), considered to be myocardial ischemia upon final diagnosis.

AND

2. At least one of the following additional criteria for coronary artery disease and/or ischemia:

    a. New and/or dynamic ST-depression > 0.05 mV, ST-elevation > 0.1 mV, or symmetric T wave inversion > 0.2 mV on a resting ECG

b. Definite evidence of ischemia on stress echocardiography, myocardial scintigraphy (eg, an area of clear reversible ischemia), or ECG-only stress test (eg, significant dynamic ST shift, horizontal or down sloping)

c. Angiographic evidence of epicardial coronary artery stenosis of > 70% diameter reduction and/or evidence for intraluminal arterial thrombus.

During adjudication, it should then be noted if the event required:

1. Hospitalization (including an overnight stay on an inpatient unit) within 48 hours of the most recent symptoms.

2. Coronary revascularization during an unscheduled visit to a healthcare facility or during an unplanned (or prolonged) hospitalization for the symptoms.

1.2 Stroke

Stroke is classified when an event is determined to not be due to a readily identifiable cause, such as a tumour or seizure. Stroke is defined as a focal neurological deficit caused by an ischemic or hemorrhagic central nervous system event with residual symptoms at least 24 hours after onset, or leading to death. Stroke is documented by imaging (e.g., CT or MRI scan). Evidence obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can also be supportive to the diagnosis.

Neurological deficits lasting less than 24 hours will not be considered stroke and will be considered transient ischemic attacks, and will be identified as such in the eCRF, unless medical interventions or objective clinical findings such as the following are reported:

a. A pharmacologic (ie, thrombolytic drug administration) or non-pharmacologic (ie, neuro-interventional procedure such as intracranial angioplasty) intervention was performed—this should be considered and adjudicated as stroke, or

b. Available brain imaging clearly documents a new haemorrhage or infarct—this should be considered and adjudicated as stroke, or

c. The neurological deficit results in death—this should be considered and adjudicated as stroke.

For situations "*b*" and "*c*" above, the following comment must be made in the eCRF: "Symptoms lasted for less than 24 hours."

Micro-haemorrhages are defined as rounded < 5 to 10 mm foci of susceptibility artifact on gradient-echo (T2*) MRI sequences. These appear hypo-intense without signal characteristics of acute or sub

acute haemorrhage and are distinct from other causes of signal loss on gradient echo (T2*) MRI sequences (e.g., vascular flow voids, leptomeningeal hemosidarosis, or non-hemorrhagic sub cortical mineralization). (NB: When found in the setting of acute or sub acute stroke symptoms, hemosiderin alone [micro-haemorrhages] without MR signal changes consistent with acute or sub acute stroke should be considered incidental and not the cause of the stroke symptoms.) While data pertaining to the occurrence of micro-haemorrhages will be collected as exploratory data, the occurrence of micro-haemorrhage will not be included in the primary endpoint.

1.2.1 Classifications of Stroke

Hemorrhagic stroke is defined as a stroke with documentation of cerebral haemorrhage on imaging (e.g., CT or MRI scan), i.e., intraparenchymal, intraparenchymal with penetration into the ventricles, intraventricular, or subarachnoidal haemorrhage. Subdural and epidural bleedings are not included. Evidence of hemorrhagic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis.

Ischemic stroke is defined as a stroke that results from a thrombus or embolus impairing central nervous system perfusion (not due to haemorrhage) and is documented by imaging. Evidence of ischemic stroke obtained from autopsy can also confirm the diagnosis. Findings on lumbar puncture can be supportive to the diagnosis.

Ischemic infarction with hemorrhagic conversion is defined as an infarction with blood felt to represent hemorrhagic conversion and not a primary haemorrhage. This will be further divided into symptomatic and asymptomatic hemorrhagic conversion.

A stroke with unknown etiology will be classified as ischemic if the type of stroke could not be determined by imaging or other means.

1.3 Mortality from CV Causes

CV mortality includes death from CV disease, cerebro-vascular disease, and any other vascular abnormality, as well as deaths for which there was no clearly documented non-vascular cause.

CV mortality includes sudden cardiac death, death due to acute MI, death due to heart failure, death due to stroke, and death due to other cardiovascular causes, as follows:

Sudden Cardiac Death: refers to death that occurs unexpectedly in a previously stable patient and includes the following deaths:

a. Witnessed and instantaneous without new or worsening symptoms

b. Witnessed within 60 minutes of the onset of new or worsening cardiac symptoms

c. Witnessed and attributed to an identified arrhythmia (e.g., captured on an ECG recording or witnessed on a monitor by either a medic or paramedic)

d. Subjects unsuccessfully resuscitated from cardiac arrest or successfully resuscitated from cardiac arrest but who die within 24 hours without identification of a non-cardiac etiology

e. Un-witnessed death or other causes of death (information regarding the patient's clinical status within the week preceding death should be provided)

Death due to Acute MI: death occurring up to 14 days after a documented acute MI (verified either by the diagnostic criteria outlined for acute MI or by autopsy findings showing recent MI or recent coronary thrombus) and where there is no conclusive evidence of another cause of death. If death occurs before biochemical confirmation of myocardial necrosis can be obtained, adjudication should be based on clinical presentation and ECG evidence. Death due to a MI that occurs as a direct consequence of a cardiovascular investigation/procedure/operation will be classified as death due to other cardiovascular cause.

Death due to Heart Failure or Cardiogenic Shock: refers to death occurring in the context of clinically worsening symptoms and/or signs of heart failure without evidence of another cause of death. New or worsening signs and/or symptoms of congestive heart failure (CHF) include any of the following:

a. New or increasing symptoms and/or signs of heart failure requiring the initiation of, or an increase in, treatment directed at heart failure or occurring in a patient already receiving maximal therapy for heart failure

b. Heart failure symptoms or signs requiring continuous intravenous therapy or oxygen administration

c. Confinement to bed predominantly due to heart failure symptoms

d. Pulmonary oedema sufficient to cause tachypnea and distress not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure

e. Cardiogenic shock not occurring in the context of an acute MI or as the consequence of an arrhythmia occurring in the absence of worsening heart failure. Cardiogenic shock is defined as systolic blood pressure (SBP) < 90 mm Hg for greater than 1 hour, not responsive to fluid resuscitation and/or heart rate correction, and felt to be secondary to cardiac dysfunction and associated with at least one of the following signs of hypo-perfusion:

    - Cool, clammy skin or

- Oliguria (urine output < 30 mL/hour) or
- Altered sensorium or
- Cardiac index < 2.2 L/min/m^2

Cardiogenic shock can also be defined as SBP ≥ 90 mm Hg as a result of positive inotropic or vasopressor agents alone and/or with mechanical support in less than 1 hour. The outcome of cardiogenic shock will be based on CEC assessment and must occur after randomization. Episodes of cardiogenic shock occurring before and continuing after randomization will not be part of the study endpoint. This category will include sudden death occurring during an admission for worsening heart failure.

Death due to Stroke: (intracranial haemorrhage or non-hemorrhagic stroke): refers to death occurring up to 30 days after a suspected stroke based on clinical signs and symptoms as well as neuroimaging and/or autopsy, and where there is no conclusive evidence of another cause of death. The FDA Stroke Team Definition of Death due to Stroke can also refer to death occurring up to 30 days after a stroke that is either due to the stroke or caused by a complication of the stroke.

Death due to Other Cardiovascular Causes: death must be due to a fully documented cardiovascular cause not included in the above categories (e.g., dysrhythmia, pulmonary embolism, or cardiovascular intervention).

1.3.1 Classification of Death Events

Causes of death events will be initially identified as either "Known" or "Unknown." If classified as Unknown, no further adjudication of the event will be performed. If Known is selected, the Adjudicator will then be prompted to rate the likelihood that the death can be classified as a CV death event, by making one of the following selections for CV-Related Death: 1) Documented, 2) Probable, 3) Possible, or 4) Unlikely. If one of the first 3 choices is selected, the death event will be classified as CV-related. If "Unlikely" is selected or if cause of death is not suspected to be CV related, the Adjudicator will rate the likelihood that the death event was a non-CV death event by making one of the following selections for Non-CV-Related Death: 1) Documented, 2) Probable, 3) Possible, or 4) Unlikely.

The definitions of classifications are as follows:

Documented – There is documented evidence for classification
Probable – There is good reason and sufficient documentation
Possible – Conceivable and cannot be dismissed
Unlikely – The event is most likely related to an alternative cause other than a cardiovascular cause (e.g., medical history relevant for cancer).