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CADTH COMMON DRUG REVIEW

Clinical Review Report

INSULIN DEGLUDEC (TRESIBA)

(Novo Nordisk Canada Inc)

Indication: For once-daily treatment of adults with diabetes mellitus to improve glycemic control

Service Line:	CADTH Common Drug Review
Version:	1.0
Publication Date:	December 2017
Report Length:	170 Pages

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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Abbreviations

A1C	glycated hemoglobin
CDR	CADTH Common Drug Review
CI	confidence interval
EAC	event adjudication committee
FAS	full analysis set
FPG	fasting plasma glucose
HRQoL	health-related quality of life
IDeg	insulin degludec
IDet	insulin detemir
IGlar	insulin glargine
LOCF	last observation carried forward
MACE	major adverse cardiovascular event
NMA	network meta-analysis
NPH	neutral protamine Hagedorn
OAD	oral antidiabetes drug
RCT	randomized controlled trial
MCID	minimal clinically important difference
MID	minimal important difference
SF-36	Short Form (36) Health Survey
SF-36v2	Short Form (36) Health Survey, version 2.0
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TRIM-D	Treatment-Related Impact Measure — Diabetes
TRIM-HYPO	Treatment-Related Impact Measure — Hypoglycemic Events

Drug	Insulin degludec
Indication	For once-daily treatment of adults with diabetes mellitus to improve glycemic control
Reimbursement Request	As per indication
Manufacturer	Novo Nordisk Canada Inc

Executive Summary

Introduction

The therapeutic options for type 1 diabetes mellitus (T1DM) begin and end with recombinant human insulin. Since T1DM is characterized by reduced insulin secretion, the natural therapeutic option for many decades has been the supplementation of insulin. The first major improvement to insulin therapy in T1DM was the introduction of recombinant human insulin in the 1980s, replacing the highly variable and immunogenic animal-derived insulins. The introduction of rapid-acting and short-acting insulin regular and intermediate-acting insulin NPH (neutral protamine Hagedorn) brought the concept of a bolus-basal regimen, which enhanced glycemic control around meals. This addressed the most important remaining issue with insulin therapy, hypoglycemia. Since the advent of insulin regular and insulin NPH, the focus has been on tightening glycemic control and reducing the risk of hypoglycemia. Bolus insulins are now more rapid and shorter acting, while basal insulins (e.g., insulin glargine [IGlar], insulin detemir [IDet]) are of longer duration.

Therapeutic options for type 2 diabetes mellitus (T2DM) begin with diet and lifestyle modifications. When those fail, patients move to a variety of oral antidiabetes drug (OAD) options, which can be summarized as drugs that enhance insulin sensitivity, promote insulin secretion, or reduce blood glucose through other means. Many of the OADs employ a mixture of these strategies and, if not, are combined with other OADs in an effort to include all of these strategies. For example, the first-line drug for T2DM is metformin, which is both an insulin sensitizer and a drug that reduces blood glucose by other means, and this drug is often combined with drugs that promote insulin secretion (the insulin secretagogues). In a subset of patients with T2DM, once pancreatic beta cells begin to fail, supplementation with insulin becomes necessary. These patients may, at least initially, be able to manage with simply a basal regimen of insulin; however, some will need a basal-bolus regimen.

Insulin degludec (IDeg) can be described as an ultra-long-acting insulin.1 The duration of action of current long-acting insulins is typically a maximum of approximately 24 hours, while IDeg has a duration of approximately 42 hours. IDeg received a Notice of Compliance from Health Canada on August 25, 2017 for once-daily treatment of adults with diabetes mellitus to improve glycemic control.

The objective of the current review is to perform a systematic review of the beneficial and harmful effects of IDeg for the treatment of adults with diabetes mellitus to improve glycemic control.

Results and Interpretation

Included Studies

Twenty phase III studies (including extensions) met the inclusion criteria for this systematic review. The largest study, DEVOTE (N = 7,637, randomized 1:1 between IDeg and IGlar), was a noninferiority cardiovascular outcomes study that focused on a population of patients with T2DM and with cardiovascular disease. The DEVOTE study and the two SWITCH studies were double-blind randomized controlled trials (RCTs), while all but one of the remaining RCTs were open label. The SWITCH studies compared IDeg with IGlar in a crossover design in patients with T1DM (SWITCH-1) and T2DM (SWITCH-2). These studies were much smaller than DEVOTE (SWITCH-1, N = 501; SWITCH-2. N = 721). The open-label studies were part of the BEGIN clinical trial program, which focused on four separate subgroups of patients: those with T1DM (Studies 3770 [N = 493], 3585 [N = 456], and 3583 [N = 629], each with an extension), those with T2DM and who were insulin-naive (Studies 3579 [N = 1,030] plus extension, 3580 [N = 458], 3672 [N = 460], 3586 [N = 435], 3587 [N = 833], and 3944 [N = 346]), those with T2DM on a basal insulin (studies 3668 [N = 687] and 3943 [N = 145]), and those with T2DM with a bolus insulin (Study 3582 [N = 1,006] plus extension). Of the BEGIN trials, Study 3943 was 16 weeks, Studies 3583, 3579, and 3582 were 52 weeks, and the remaining were 26 weeks (without extensions). The primary outcome of the DEVOTE trial was a composite of major adverse cardiovascular events (MACE), while the primary outcome of the SWITCH trials was the occurrence of severe or blood glucose–confirmed hypoglycemic events. The primary outcome of all the BEGIN trials was the change from baseline to end of treatment in glycated hemoglobin (A1C), and confirmatory secondary outcomes included change from baseline in fasting plasma glucose, variability in blood glucose, and various measures of hypoglycemic events. Studies that had a basal insulin as comparator (IGlar or IDet) tested noninferiority for the primary outcome and superiority for the confirmatory secondary outcomes.

Key critical appraisal issues included the open-label design of many of the studies, which would be expected to have the greatest potential for bias in subjective outcomes such as the patient-reported outcomes, the Short Form (36) Health Survey (SF-36), and the disease-specific Treatment-Related Impact Measure — Diabetes (TRIM-D) or Treatment-Relegated Impact Measure — Hypoglycemic Events (TRIM-HYPO) instruments. Although most studies assessed health-related quality of life (HRQoL), it was typically not a confirmatory (i.e., higher priority) outcome; DEVOTE, the largest included study, does not appear to have assessed this outcome at all. This is a notable omission given the importance of quality of life to patients. Several studies had withdrawal rates at or above 20%, and although there were generally no obvious differences in the proportion of participants withdrawing between groups, these high withdrawal rates may have compromised the distribution of participants between groups. For example, the SWITCH studies had withdrawals ranging between 18% and 23% across groups.

Efficacy

IDeg was noninferior to IGlar for the primary outcome, a composite of MACE, from the DEVOTE study after a mean of 24 months' treatment (Table 1). Several secondary outcomes related to cardiovascular events, such as myocardial infarction or stroke, as well as overall and cardiovascular mortality, were not statistically significantly different between IDeg and IGlar (Table 1). Severe hypoglycemic events were also assessed as a secondary outcome, and the risk of severe hypoglycemic events was lower with IDeg than with IGlar;

this difference was statistically significant (Table 1). In the SWITCH studies, the primary outcome was severe or blood glucose–confirmed hypoglycemic events, and in both studies IDeg was superior to IGlar for the primary outcome (Table 2). SWITCH employed a crossover design, with each treatment period extending over 32 weeks. There was no difference in the proportion of participants experiencing a MACE in the SWITCH studies, although there were few of these events in both studies. The remaining included trials were the BEGIN trials, which all had a primary outcome of change from baseline in A1C. All studies that compared IDeg with another basal insulin (IGlar, nine studies; IDet, one study) demonstrated noninferiority for IDeg for this primary outcome, while two double-blind studies found superiority of IDeg, one versus sitagliptin, and the other study was placebo-controlled (Table 3). Both of these double-blind studies were in a population with T2DM patients who were insulin-naive. Confirmatory secondary outcomes in the BEGIN studies included change from baseline in fasting plasma glucose, glucose variability, confirmed hypoglycemic events, and confirmed nocturnal hypoglycemic events, and superiority was rarely demonstrated for IDeg versus IGlar or IDet for any of these outcomes. There were no consistent differences in any HRQoL measures, on either the SF-36 or the TRIM-D and TRIM-HYPO scales, between IDeg and comparators.

Harms

Hypoglycemia was often assessed as a confirmatory secondary outcome, and as noted above, in DEVOTE and in the SWITCH studies the risk of severe and severe or blood glucose–confirmed hypoglycemic events was lower with IDeg than with IGlar (Table 1, Table 2). However, in the BEGIN trials, there was no evidence of superiority for IDeg over IGlar or IDet for confirmed hypoglycemic events for any of the included studies, with the exception of Study 3582, in T2DM with a basal-bolus regimen (Table 4). There were no consistent differences in the proportion of participants experiencing an adverse event or serious adverse event or who withdrew due to an adverse event in any of the included studies. Among notable harms, there were no consistent differences between IDeg and IGlar or IDet for injection-site reactions, weight gain, or neoplasms.

Findings from three indirect treatment comparisons (see Appendix 6) suggest that there is no statistically significant difference in the rate of confirmed hypoglycemia between IDeg and IGlar in T1DM. In T2DM, results differed between the indirect treatment comparisons, as a published report found a reduced risk of nocturnal hypoglycemia but an increased risk of symptomatic hypoglycemia with IDeg versus IGlar, both statistically significant. Conversely, in the manufacturer-submitted analysis, there was a reduction in nocturnal hypoglycemia with IDeg versus both IGlar and NPH that was statistically significant; however, the analysis of overall hypoglycemia could not be interpreted because the authors stated that both the fixed-effects and random-effects models showed poor fit with high residual deviance values. Findings from a patient-level meta-analysis (see Appendix 7) suggested that IDeg had a lower rate of hypoglycemia than IGlar, although none of the analyses focused on symptomatic events only.

Potential Place in Therapy[1]

While insulin remains the most effective treatment available to lower blood glucose (and the only treatment for T1DM), the margin between too much and too little insulin is narrow. Patients and their caregivers walk a fine line between hypoglycemia and hyperglycemia to achieve modern targets for good glycemic control. Based on the experience of the clinical expert consulted for this review, patients are frequently frustrated by day-to-day variations in blood glucose that arise after apparently managing their glucose the same way (within-patient variability). Some of these problems arise because of variability in the duration, peak action, and time-action profile of currently available insulins, especially basal insulins. An insulin that has less within-patient variability could theoretically provide a substantial advantage to patients. Greater certainty about the response to insulin, reducing the fear of hypoglycemia, could lead to improved glycemic control and improved quality of life by reducing hypoglycemia and weight gain.

IDeg is a new basal insulin which forms soluble multihexamers on subcutaneous injection, resulting in a depot from which monomers are slowly and continuously absorbed into the circulation. This mechanism leads to the reported ultra-long pharmacokinetic and pharmacodynamic profiles and reduced variability in insulin action compared with IGlar.[2] Trials in a large clinical development program show noninferiority of IDeg to IGlar for the primary outcome of glycemic control for both T1DM and T2DM both in multiple-dose injection therapy and basal plus oral regimens (BEGIN trials) and for cardiovascular outcomes in T2DM.[3] Results for the key secondary outcomes of glucose variability, hypoglycemia, and quality of life are less convincing. While there is a trend to superiority in the reduction of nocturnal hypoglycemic events for people in clinical trials for T1DM, in only one trial does this approach statistical superiority ($P = -0.011$).[4] In T2DM, while again there is a trend to an improved efficacy, there is no consistent statistically significant result. There were no quality-of-life differences. Exclusion criteria for most trials included recent severe or recurrent hypoglycemia, which does not allow evaluation of the role of IDeg in this potential group of patients.

The SWITCH trials included groups of patients said to be at high risk of hypoglycemia (recent severe or non-severe hypoglycemia, hypoglycemia symptom unawareness, moderate chronic renal failure, or long disease duration or long-time insulin use), but the data provided do not include sufficient information to identify which of these very different groups might benefit. Although the results show a significantly lower rate of overall, nocturnal, and severe hypoglycemia versus IGlar in both T1DM and T2DM patients, this finding is specific to the trial definitions of these events and it is not clear how it would translate to clinical practice. Of concern, nocturnal hypoglycemia is defined to a six-hour time period from midnight; results from a longer sleep period from 10 p.m. to 8 a.m. are not given.

One potential advantage is that the BEGIN Flex T1DM and T2DM studies showed that IDeg can be administered at any time of day, with injection timing varied, without compromising glycemic control or safety.[5] This may improve basal insulin adherence by allowing injection-time adjustment according to individual needs; however, there is no evidence to assess this potential advantage.

[1] This information is based on information provided in draft form by the clinical expert consulted by CADTH Common Drug Review for the purpose of this review.

In summary, IDeg appears to achieve similar safety and efficacy outcomes as IGlar in patients with T1DM and T2DM; however, there is no convincing evidence that it is superior in preventing hypoglycemic events. It may be of advantage for those who have difficulty taking basal insulin at a regular time.

Conclusions

Fifteen RCTs plus five extensions met the inclusion criteria for this review. There is evidence from the largest study, the DEVOTE study, in patients with T2DM and a history of cardiovascular disease that IDeg is noninferior to IGlar for the composite of MACEs. There is no evidence of a statistically significant difference in mortality or in cardiovascular events (myocardial infarction, stroke) between IDeg and IGlar in DEVOTE. The other 19 included studies, including the SWITCH studies, were not powered to assess mortality or morbidity; these events tended to be infrequent in these studies. IDeg was consistently noninferior to IGlar for the change from baseline in A1C, whether at 16 weeks, 26 weeks, or 52 weeks, and this was the primary outcome in all the BEGIN trials. Responses for change in fasting plasma glucose and variability in blood glucose did not differ significantly between IDeg and IGlar or IDet in the included trials; however, these outcomes were not the focus of these studies. The results for hypoglycemia differed between studies. In the SWITCH studies, where severe or confirmed hypoglycemic events were a primary outcome and where patients had demonstrated recent issues with hypoglycemia, there was evidence of superiority for IDeg versus IGlar, and this was also the case in DEVOTE, where severe hypoglycemia was a key secondary outcome. However, in the BEGIN trials, there was no consistent evidence of superiority of IDeg over IGlar or IDet for events of confirmed hypoglycemia; and in both published and manufacturer-submitted network meta-analyses, which did not include DEVOTE, SWITCH-1, or SWITCH-2, there was also no evidence of a statistically significant improvement in risk of confirmed hypoglycemia with IDeg compared with other basal insulins. There were no consistent differences in HRQoL, measured by the SF-36, TRIM-D, or TRIM-HYPO, between IDeg and IGlar or other comparators, across the studies; nor were there consistent differences between IDeg and comparators in the proportion of patients experiencing an adverse event, serious adverse event, or withdrawal due to an adverse event. Among notable harms, there were no consistent differences between IDeg and IGlar or IDet in weight gain, neoplasms, or injection-site reactions.

Table 1: Summary of Results — DEVOTE

	DEVOTE	
Primary Composite Cardiovascular Outcome (MACE)	**Degludec N = 3,818**	**Glargine N = 3,819**
N (%) FAS	325 (8.5)	356 (9.3)
HR (95% CI)[a]	0.91 (0.78 to 1.06)	
	Noninferiority met ($P < 0.001$)	
N (%) PP	286 (8.03)	314 (8.83)
HR (95% CI)[a]	0.904 (0.770 to 1.060), $P = 0.214$	
Subgroup: established CVD, n/N (%)	293/3,265 (8.97)	325/3,244 (10.02)
HR (95% CI)[a]	0.887 (0.758 to 1.039)	
Risk factors for CVD, n/N (%)	29/538 (5.39)	30/567 (5.29)
HR (95% CI)[a]	1.034 (0.621 to 1.723)	
P value	$P = 0.5742$	
Expanded Composite Cardiovascular Outcome, n (%)	386 (10.1)	419 (11.0)
HR (95% CI)[a]	0.92 (0.80 to 1.05), $P = 0.22$	
Mortality		
Death from any cause n (%)	202 (5.3)	221 (5.8)
HR (95% CI)[a]	0.91 (0.76 to 1.11), $P = 0.35$	
Non-cardiovascular death n (%)	66 (1.7)	79 (2.1)
HR (95% CI)[a]	0.84 (0.60 to 1.16), $P = 0.28$	
Cardiovascular death n (%)	136 (3.6)	142 (3.7)
HR (95% CI)[a]	0.96 (0.76 to 1.21), $P = 0.71$	
Morbidity		
Non-fatal myocardial infarction n (%)	144 (3.8)	169 (4.4)
HR (95% CI)[a]	0.85 (0.68 to 1.06), $P = 0.15$	
Non-fatal stroke n (%)	71 (1.9)	79 (2.1)
HR (95% CI)[a]	0.90 (0.65 to 1.23), $P = 0.50$	
Unstable angina leading to hospitalization n (%)	71 (1.9)	74 (1.9)
HR (95% CI)[a]	0.95 (0.68 to 1.31), $P = 0.74$	
A1C		
Mean (SD) baseline, %	8.4 (1.6)	8.4 (1.7)
Change from baseline to 24 months, estimated mean	−0.864	−0.872
Treatment difference (95% CI)[b]	0.008 (−0.050 to 0.066), $P = 0.779$	
FPG		
Mean (SD) baseline, mmol/L	9.4 (3.9)	9.6 (3.9)
Change from baseline to 24 months, estimated mean	−2.282	−1.882
Treatment difference (95% CI)[b]	−0.400 (−0.571 to −0.229), $P < 0.001$	
Harms		
Participants with severe hypoglycemia	187 (4.9)	252 (6.6)
Rate ratio (95% CI)[c]	0.60 (0.48 to 0.76), $P < 0.001$	

A1C = glycated hemoglobin; CI = confidence interval; CVD = cardiovascular disease; FAS = full analysis set; FPG = fasting plasma glucose; HR = hazard ratio; MACE = major adverse cardiovascular event; PP = per-protocol; SD = standard deviation.

[a] Model is a Cox regression including treatment as only factor.

[b] Change from baseline to 24 months' visit analyzed using a mixed model for repeated measures within patients using an unstructured residual covariance matrix among visits at 6, 12, and 24 months of study. Interaction between visit and treatment and visit and baseline are included as fixed effects.

[c] Based on negative binomial regression with log-link function and log (duration of observation time) as offset; *P* value refers to two-sided test of rate ratio = 1.0.

Source: CSR for DEVOTE.[6]

Table 2: Summary of Results — SWITCH Studies

	SWITCH-1		SWITCH-2	
	Degludec (N = 418)	**Glargine (N = 422)**	**Degludec (N = 632)**	**Glargine (N = 618)**
Mortality				
Deaths, n (%)	1 (0.2)	2 (0.4)	0	5 (0.8)
Morbidity				
Adjudicated MACEs, n (%)	3 (0.7)	3 (0.7)	12 (1.8)	15 (2.3)
Confirmed MACEs, n (%)	2 (0.4)	3 (0.7)	8 (1.2)	9 (1.4)
A1C				
A1C blood (%), LSM (SE) period 1[a]			7.08 (0.06) N = 326	6.98 (0.06) N = 327
A1C blood (%), LSM (SE) change from baseline, 32 weeks' treatment	−0.76 (0.06)	−0.78 (0.07)	−0.49 (0.06)	−0.58 (0.06)
Treatment difference (95% CI)	0.03 (−0.10 to 0.15)		0.09 (−0.04 to 0.23)	
A1C blood (%), LSM (SE) period 2[a]			7.06 (0.05) N = 310	7.01 (0.05) N = 298
A1C blood (%), LSM (SE) change from baseline	0.09 (0.06)	−0.02 (0.06)	0.06 (0.05)	0.00 (0.05)
Treatment difference (95% CI)	0.11 (−0.00 to 0.23)		0.06 (−0.07 to 0.18)	
FPG				
Mean (SD) change from baseline, FPG (mmol/L), end of first treatment	−1.44 (5.31) N = 248	−1.30 (5.08) N = 252	−1.51 (3.16) N = 355	−1.22 (3.16) N = 358
Mean (SD) change from baseline, FPG (mmol/L), end of second treatment	1.14 (4.91) N = 208	−0.55 (4.78) N = 204	0.43 (3.06) N = 307	0.07 (2.92) N = 311
Harms				
Severe or BG-confirmed symptomatic hypoglycemia during maintenance period				
N (%)	323 (77)	337 (80)	142 (22.5)	195 (31.6)
Event rate/100 PYE	2,200.8	2,462.7	185.60	265.36
LSM, events/100 PYE[b]	1,227.0 N = 501	1,372.3 N = 501	99.10 N = 720	142.17 N = 720
Treatment ratio (95% CI)	0.89 (0.85 to 0.94), *P* < 0.0001 Superiority met		0.70 (0.61 to 0.80) Superiority met	
Severe or BG-confirmed symptomatic nocturnal hypoglycemia	137 (33)	182 (43)	61 (9.7)	91 (14.7)
Event rate	277.1	428.6	55.21	93.63
LSM, events/100 PYE[b]	160.2 N = 501	250.8 N = 501	99.10 N = 720	142.17 N = 720
Treatment ratio (95% CI)	0.64 (0.56 to 0.73), *P* < 0.0001 Superiority met		0.58 (0.46 to 0.74) Superiority met	
Severe hypoglycemia, n (%)	43 (10)	72 (17)	10 (1.6)	15 (2.4)

A1C = glycated hemoglobin; BG = blood glucose; CI = confidence interval; FAS = number of patients in full analysis set; FPG = fasting plasma glucose; LSM = least squares mean; MACE = major adverse cardiovascular event; PYE = patient-years of exposure; SD = standard deviation; SE = standard error.

[a] Treatment period 1: All observed A1C measurements available post-randomization at scheduled measurement times for patients having exposure in maintenance period 1 are analyzed using a mixed model for repeated measurement with treatment, sex, antidiabetes therapy at screening, visit, and dosing time as fixed effects, and age and baseline A1C as covariates. All fixed factors and covariates are nested within visit, and an unstructured covariance matrix is specified. The denominator degrees of freedom is calculated using the Satterthwaite method. Treatment period 2: All observed A1C measurements available post-randomization at scheduled measurement times for patients having any A1C measurements after visit 34 are analyzed using the same model as for treatment period 1.

[b] Patient-years of exposure (1 PYE = 365.25 days): The number of events is analyzed using a Poisson model with logarithm of the exposure time (100 years) as offset. The model includes treatment, period, sequence, and dosing time as fixed effects and patient as a random effect. Severe hypoglycemia: Positively adjudicated by the event adjudication committee according to the American Diabetes Association definition of a severe hypoglycemic episode. Confirmed symptomatic hypoglycemia: Recorded plasma glucose value of < 3.1 mmol/L (56 mg/dL),with symptoms consistent with hypoglycemia.

Table 3: BEGIN Trials, Primary Outcome — Change From Baseline in A1C

Study	Duration	Comparator	Testing	Treatment Difference (95% CI)
T1DM				
3770	26 weeks	IGlar	Noninferior	0.17 (0.04 to 0.30)
3585	26 weeks	IDet	Noninferior	−0.09 (−0.23 to 0.05), *P* < 0.001
3583	52 weeks	IGlar	Noninferior	−0.01 (−0.14 to 0.11), *P* < 0.001
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Noninferior	0.09 (−0.04 to 0.22), *P* < 0.001
3580	26 weeks	Sitagliptin	Superior	−0.43 (−0.61 to −0.24), *P* < 0.001
3672	26 weeks	IGlar	Noninferior	0.04 (−0.11 to 0.19), *P* < 0.001
3586	26 weeks	IGlar	Noninferior	0.11 (−0.03 to 0.24), *P* < 0.001
3587	26 weeks	IGlar	Noninferior	−0.05 (−0.18 to 0.08)
3944	26 weeks	Placebo	Superior	−0.92 (−1.10 to −0.75), *P* < 0.0001
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Noninferior	0.04 (−0.12 to 0.20)
3943	16 weeks	IGlar (crossover)	Noninferior	−0.06 (−0.21 to 0.09), *P* < 0.001
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Noninferior	0.08 (−0.05 to 0.21)

A1C = glycated hemoglobin; CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: Positive values indicate smaller change from baseline for IDeg versus IGlar. *P* value reflects test for noninferiority, superiority.

Table 4: BEGIN Trials, Key Secondary Outcome — Confirmed Hypoglycemic Events

Study	Duration	Comparator	Testing	Treatment Ratio Events/100 PYE (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	1.03 (0.85 to 1.26)
3585	26 weeks	IDet	Superiority not shown	0.98 (0.80 to 1.20), *P* = 0.431
3583	52 weeks	IGlar	Superiority not shown	1.07 (0.89 to 1.28), *P* = 0.758
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Superiority not shown	0.82 (0.64 to 1.04), *P* = 0.053
3580	26 weeks	Sitagliptin	Not in hierarchy	3.81 (2.40 to 6.05)
3672	26 weeks	IGlar	Superiority not shown	0.86 (0.58 to 1.28), *P* = 0.228
3586	26 weeks	IGlar	Superiority not shown	0.82 (0.60 to 1.11), *P* = 0.101
3587	26 weeks	IGlar	Superiority not shown	0.80 (0.59 to 1.10), *P* = 0.084
3944	26 weeks	Placebo	Not in hierarchy	4.67 (2.07 to 10.56)
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	1.03 (0.75 to 1.40)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.59 (0.39 to 0.90)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Superiority	0.82 (0.69 to 0.99), *P* = 0.018

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; PYE = patient-years of exposure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: *P* value reflects test for superiority. Confirmed hypoglycemic episodes consisted of episodes of severe hypoglycemia as well as minor hypoglycemic episodes with a confirmed plasma glucose value of < 3.1 mmol/L. Hypoglycemic episodes were defined as nocturnal if the time of onset was between 00:01 a.m. and 05:59 a.m. inclusive.

Table 5: BEGIN Trials, Key Secondary Outcome— Confirmed Nocturnal Hypoglycemic Events

Study	Duration	Comparator	Testing	Treatment Ratio Events/100 PYE (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	0.60 (0.44 to 0.82)
3585	26 weeks	IDet	Superiority	0.66 (0.49 to 0.88), *P* = 0.002
3583	52 weeks	IGlar	Superiority	0.75 (0.59 to 0.96), *P* = 0.011
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Not in hierarchy	0.64 (0.42 to 0.98)
3580	26 weeks	Sitagliptin	Not in hierarchy	1.93 (0.90 to 4.10)
3672	26 weeks	IGlar	Not in hierarchy	0.64 (0.30 to 1.37)
3586	26 weeks	IGlar	Testing halted	0.62 (0.38 to 1.04), *P* = NT
3587	26 weeks	IGlar	Not in hierarchy	0.77 (0.43 to 1.37)
3944	26 weeks	Placebo	Not in hierarchy	1.75 (0.24 to 12.71)
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	0.77 (0.44 to 1.35)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.66 (0.29 to 1.48)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Not in hierarchy	0.75 (0.58 to 0.99)

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; NT = not tested due to halting of testing due to hierarchy; PYE = patient-years of exposure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: *P* value reflects test for superiority. Nocturnal hypoglycemic episodes: Episodes with time of onset between 00:01 a.m. and 05:59 a.m., inclusive. Hypoglycemic episodes occurring during sleep in the extended time range between 10:01 p.m. and 07:59 a.m. were also analyzed.

Table 6: BEGIN Trials, Key Secondary Outcome — Blood Glucose Variability

Study	Duration	Comparator	Testing	Treatment Ratio CV% (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	0.96 (0.84 to 1.07)
3585	26 weeks	IDet	Testing halted	1.02 (0.91 to 1.12), *P* = NT
3583	52 weeks	IGlar	Testing halted	0.96 (0.86 to 1.05), *P* = NT
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Testing halted	0.99 (0.92 to 1.06)
3580	26 weeks	Sitagliptin	Not in hierarchy	1.39 (1.26 to 1.52)
3672	26 weeks	IGlar	Testing halted	0.92 (0.84 to 1.01), *P* = NT
3586	26 weeks	IGlar	Testing halted	0.89 (0.80 to 0.99), *P* = NT
3587	26 weeks	IGlar	Testing halted	1.10 (1.02 to 1.18), *P* = NT
3944	26 weeks	Placebo	NR	NR
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	0.97 (0.88 to 1.06)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.89 (0.79 to 1.00)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Testing halted	0.94 (0.87 to 1.01), *P* = NT

CI = confidence interval; CV = coefficient of variation; IDet = insulin detemir; IGlar = insulin glargine; NR = not reported; NT = not tested due to halting of testing due to hierarchy; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Table 7: Harms — BEGIN Trials

Study	Duration	Adverse Events, n (%)		Serious Adverse Events, n (%)		Withdrawals Due to Adverse Events, n (%)	
		IDeg	Comparator	IDeg	Comparator	IDeg	Comparator
T1DM							
3770[a]	26 weeks	111 (68) 125 (76)	116 (72)	9 (6) 7 (4)	8 (5)	5 (3) 4 (2)	1 (1)
3770-ext	52 weeks	268 (82)	134 (83)	25 (8)	12 (8)	9 (3)	2 (1)
3585	26 weeks	219 (73)	112 (74)	23 (8)	8 (5)	3 (1)	1 (1)
3725-ext	52 weeks	248 (82)	118 (78)	36 (12)	11 (7)	4 (1)	2 (1)
3583	52 weeks	397 (84)	128 (83)	49 (10)	17 (11)	12 (3)	2 (1)
3644-ext	104 weeks	413 (88)	137 (89)	71 (15)	29 (19)	15 (3)	4 (3)
T2DM, Insulin-Naive							
3579	52 weeks	572 (75)	182 (71)	62 (8)	26 (10)	20 (3)	5 (2)
3643-ext	104 weeks	617 (81)	198 (77)	116 (15)	41 (16)	12 (2)	5 (2)
3580	26 weeks	141 (62)	144 (63)	14 (6)	10 (4)	9 (4)	2 (1)
3672	26 weeks	147 (65)	156 (68)	15 (7)	10 (4)	5 (2)	4 (2)
3586	26 weeks	167 (59)	95 (65)	8 (3)	8 (6)	2 (1)	3 (2)
3587	26 weeks	293 (53)	161 (58)	6 (3)	10 (4)	3 (1)	3 (1)
3944	26 weeks	95 (55)	88 (52)	6 (4)	9 (5)	4 (2)	3 (2)
T2DM, Basal Insulin							
3668[a]	26 weeks	122 (53) 128 (57)	128 (56)	6 (3) 8 (4)	4 (2)	2 (1) 1 (< 1)	2 (1)
3943	16 weeks	45 (32)	50 (35)	4 (3)	4 (3)	0 (0)	1 (1)
T2DM, Basal-Bolus							
3582	52 weeks	610 (81)	199 (79)	112 (15)	40 (16)	31 (4)	9 (4)
3667-ext	104 weeks	630 (84)	208 (83)	139 (19)	53 (21)	35 (5)	9 (4)

ext = extension; IDeg = insulin degludec; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Studies 3770 and 3668 contained two IDeg groups, one a flexible dosing group (IDeg-Flex) and the other a regular IDeg group, and results are reported in this order.

Table 8: BEGIN Trials — Proportion of Patients Experiencing Severe Hypoglycemia

Study	Duration	Degludec n (%)	Comparator n (%)
T1DM			
3770[a]	26 weeks	17 (10.4) 21 (12.7)	16 (9.9)
3770-ext	52 weeks	44 (13.4)	21 (13.0)
3585	26 weeks	32 (10.6)	16 (10.5)
3725-ext	52 weeks	42 (14.0)	18 (11.8)
3583	52 weeks	58 (12.3)	16 (10.4)
3644-ext	104 weeks	72 (15.3)	24 (15.6)
T2DM, Insulin-Naive			
3579	52 weeks	2 (0.3)	5 (1.9)
3643-ext	104 weeks	6 (0.8)	7 (2.7)
3580	26 weeks	1 (0.4)	0
3672	26 weeks	0	0
3586	26 weeks	0	1 (0.7)
3587	26 weeks	2 (0.4)	2 (0.7)
3944	26 weeks	0	0
T2DM, Basal Insulin			
3668[a]	26 weeks	1 (0.4) 2 (0.9)	2 (0.9)
3943	16 weeks	4 (2.9)	1 (0.7)
T2DM, Basal-Bolus			
3582	52 weeks	34 (4.5)	11 (4.4)
3667-ext	104 weeks	39 (5.2)	16 (6.4)

ext = extension; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Studies 3770 and 3668 contained two IDeg groups, one a flexible dosing group (IDeg-Flex) and the other a regular IDeg group, and results are reported in this order.

Introduction

Disease Prevalence and Incidence

Type 1 diabetes mellitus (T1DM) is characterized by the failure of pancreatic beta cells to secrete sufficient insulin to meet the body's metabolic demands. It is believed to be due to an autoimmune attack on pancreatic beta cells, which secrete insulin, leading to their destruction. The initial pathophysiology of type 2 diabetes mellitus (T2DM) differs from that of T1DM as pancreatic beta cells are able to secrete insulin but peripheral cells lack the ability to respond to insulin. Therefore, many of the pharmacologic interventions for T2DM focus on enhancing cell sensitivity to insulin, while others stimulate insulin secretion from beta cells. However, in many cases, as the condition progresses, pancreatic beta cells begin to fail, and patients with T2DM enter a state more closely resembling that of T1DM. At this point, when insulin secretion becomes deficient, patients will often begin a regimen of supplemental insulin. According to Diabetes Canada, there are currently 3.4 million people in Canada living with diabetes mellitus.[7]

Standards of Therapy

The therapeutic options for T1DM begin and end with recombinant human insulin. Since T1DM is characterized by reduced insulin secretion, the natural therapeutic option for many decades has been the supplementation of insulin. The first major improvement to insulin therapy in T1DM was the introduction of recombinant human insulin in the 1980s, replacing the highly variable and immunogenic animal-derived insulins. The introduction of rapid-acting and short-acting insulin regular and intermediate-acting insulin NPH (neutral protamine Hagedorn) brought the concept of a bolus-basal regimen, which enhanced glycemic control around meals. Since the advent of insulin regular and insulin NPH, the focus has been on tightening glycemic control and reducing the risk of hypoglycemia. Bolus insulins are now more rapid and shorter acting, while basal insulins (e.g., insulin glargine [IGlar], insulin detemir [IDet]) are of longer and longer durations.

Therapeutic options for T2DM begin with diet and lifestyle modifications. When those fail, patients move to a variety of oral antidiabetes drug (OAD) options, which can be summarized as drugs that enhance insulin sensitivity, promote insulin secretion, or reduce blood glucose through other means. Many of the OADs employ a mixture of these strategies and, if not, are combined with other OADs in an effort to include all of these strategies. For example, the first-line drug for T2DM is metformin, which is both an insulin sensitizer and a drug that reduces blood glucose by other means; this drug is often combined with drugs that promote insulin secretion (the insulin secretagogues). In a subset of patients with T2DM, once pancreatic beta cells begin to fail, supplementation with insulin becomes necessary. These patients may, at least initially, be able to manage with simply a basal regimen of insulin; however, some will need a basal-bolus regime.

Drug

Insulin degludec (IDeg) can be described as an ultra-long-acting insulin.[1] The duration of action of current long-acting insulins is typically a maximum of approximately 24 hours, while IDeg has a duration of approximately 42 hours. IDeg is currently under review by Health Canada. The anticipated indication is for once-daily subcutaneous administration for the treatment of adults with diabetes mellitus to improve glycemic control.

Table 9: Key Characteristics of Insulin Degludec, Insulin Glargine, and Insulin Detemir

	Insulin Degludec	Insulin Glargine	Insulin Detemir
Mechanism of Action	Exogenous source of supplemental insulin	Exogenous source of supplemental insulin	Exogenous source of supplemental insulin
Indication[a]	For once-daily treatment of adults with diabetes mellitus to improve glycemic control	• For once-daily subcutaneous administration in the treatment of patients more than 17 years of age with T1DM or T2DM who require basal (long-acting) insulin for the control of hyperglycemia • For the treatment of pediatric patients (> 6 years old) with T1DM who require basal (long-acting) insulin for the control of hyperglycemia	• For the treatment of T1DM in adults, adolescents, and children 2 years and above • For the treatment of T2DM in adults when insulin is required for the control of hyperglycemia • For the treatment of T2DM in combination with OADs in adults who are not in adequate metabolic control on OADs alone; for safety reasons, the use of insulin in combination with thiazolidinedione is not indicated • For the treatment of adult patients with T2DM in combination with liraglutide and metformin when liraglutide and metformin do not achieve adequate glycemic control • Also recommended in combination with short- or rapid-acting mealtime insulin
Route of Administration	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Recommended Dose	Initiation of IDeg therapy in insulin-naive patients with T1DM: It is to be used once daily with mealtime insulin and requires subsequent individual dosage adjustments. Initiation of IDeg therapy in patients with T1DM changing from other insulin therapies: It is recommended that the dose of IDeg be reduced by 20% to lower the risk of hypoglycemia. Initiation of IDeg therapy in insulin-naive patients with T2DM: The recommended starting dose	In clinical studies with insulin-naive patients with T2DM, IGlar was started at a dose of 10 units once daily, and subsequently adjusted according to the patient's needs. In clinical studies, when patients were transferred from once-daily NPH human insulin or ultralente human insulin to once-daily IGlar, the initial dose was usually not changed. In studies, when patients were transferred from twice-daily NPH human insulin to glargine once	IDet should be used once daily in combination with: • OADs or • short- or rapid-acting mealtime insulin. When IDet is used as part of a basal-bolus insulin regimen, it can be administered twice daily, depending on the patient's needs. For patients who require twice-daily dosing to optimize blood glucose control, the evening dose can be administered either with the evening meal or at bedtime.

	Insulin Degludec	Insulin Glargine	Insulin Detemir
	is 10 units once daily. Initiation of IDeg therapy in patients with T2DM taking once-daily long or intermediate-acting insulin: Start IDeg at the same unit dose. For patients transferring from twice-daily long-acting or intermediate-acting insulin, it is recommended that the dose of IDeg be reduced by 20% to lower the risk of hypoglycemia. The dosage of IDeg should be individualized and titrated under the supervision of a health care provider in accordance with the metabolic needs of the patient and the glycemic control target and with appropriate glucose monitoring.	daily, the initial dose was usually reduced by approximately 20% (compared with total daily IU of NPH human insulin) and then adjusted based on patient response.	Dosage of IDet is individual and is determined based on the physician's advice in accordance with the needs of the patient.
Serious Side Effects/Safety Issues	Hypoglycemia	Hypoglycemia	Hypoglycemia
Other			

IDeg = insulin degludec; IDet = insulin detemir; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drugs; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Health Canada–approved indication.

Objectives And Methods

Mortality

DEVOTE was the only study where more than 1% of the population died. In this study, there was no statistically significant difference in the proportion of patients who died between the IDeg (5.3% of patients died) and IGlar (5.8%) groups (hazard ratio 0.91 [95% CI, 0.76 to 1.11; *P* = 0.35]). There was no difference between IDeg and IGlar for cardiovascular deaths (3.6% versus 3.7%, respectively) or non-cardiovascular deaths (1.7% versus 2.1%, respectively) (Table 32).

Type 1 Diabetes Mellitus

Across the three studies, there were no deaths in Study 3585 or its extension; there was one death (IDeg, suicide) in Study 3770 but none in the extension; and in Study 3583, there were two deaths in the IDeg group (both myocardial infarction) and one death in the IGlar group (sudden death). In the extension to Study 3583, there were two additional deaths in the IDeg group (sudden death, ventricular tachycardia) and two additional deaths in the IGlar group (gallbladder cancer, ventricular arrhythmia).

Type 2 Diabetes Mellitus

Insulin-Naive

In Study 3579, one death occurred in each of the IDeg and IGlar groups. In the extension, there were an additional three deaths with IDeg and two deaths with IGlar. In Study 3672, there were no deaths with IDeg and one death with IGlar, and there were no deaths in Study 3586. In Study 3580, there was one death in IDeg, and none with sitagliptin.

Insulin-Experienced (Basal)

In Study 3668, there was one death in each of the IDeg and IGlar groups.

Insulin-Experienced (Basal-Bolus)

In Study 3582, there were eight deaths (1.1%) in the IDeg group and two (0.8%) in the IGlar group. Half of the deaths in each group were classed as cardiovascular deaths (four with IDeg and one with IGlar).

Objectives

To perform a systematic review of the beneficial and harmful effects of IDeg for the treatment of adults with diabetes mellitus to improve glycemic control.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 10.

Table 10: Inclusion Criteria for the Systematic Review

Patient Population	Adults with diabetes mellitus *Subgroups:* T1DM versus T2DM T2DM: insulin-naive patients on OADs (and/or GLP-1 agonists) T2DM: insulin-experienced patients on OADs (and/or GLP-1 agonists) T2DM: patients requiring insulin intensification, on a basal-bolus regimen Comorbidities (microvascular and macrovascular disease)
Intervention	Insulin degludec once daily by subcutaneous injection *T1DM* As part of a basal-bolus regimen *T2DM* May be used alone or in combination with a rapid-acting or short-acting insulin and/or an OAD
Comparators	*T1DM* Insulin glargine Insulin detemir Insulin NPH Insulin pump *T2DM* Insulin glargine Insulin detemir Insulin NPH Insulin pump OADs and/or GLP-1 agonists Placebo
Outcomes	**Key efficacy outcomes** • Mortality • Diabetes-related morbidity (macrovascular, microvascular) • Glycemic control (A1C, FPG, glucose variability) • HRQoL **Other outcomes** • Health care resource utilization **Harms outcomes** • Total adverse events • Serious adverse events • Withdrawals due to adverse events • Notable harms: hypoglycemia, cancer, weight gain
Study Design	Published and unpublished RCTs

A1C = glycated hemoglobin; DB = double-blind; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HRQoL = health-related quality of life; NPH = neutral protamine Hagedorn; OAD = oral antidiabetes drug; RCT = randomized controlled trial; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as

the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was insulin degludec (Tresiba).

No methodological filters were applied to limit retrieval by study type. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on June 28, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on October 18, 2017. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Clinical Trials, and Databases (Free). Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Results

Findings From the Literature

A total of 20 studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 11 and described in the Included Studies section. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

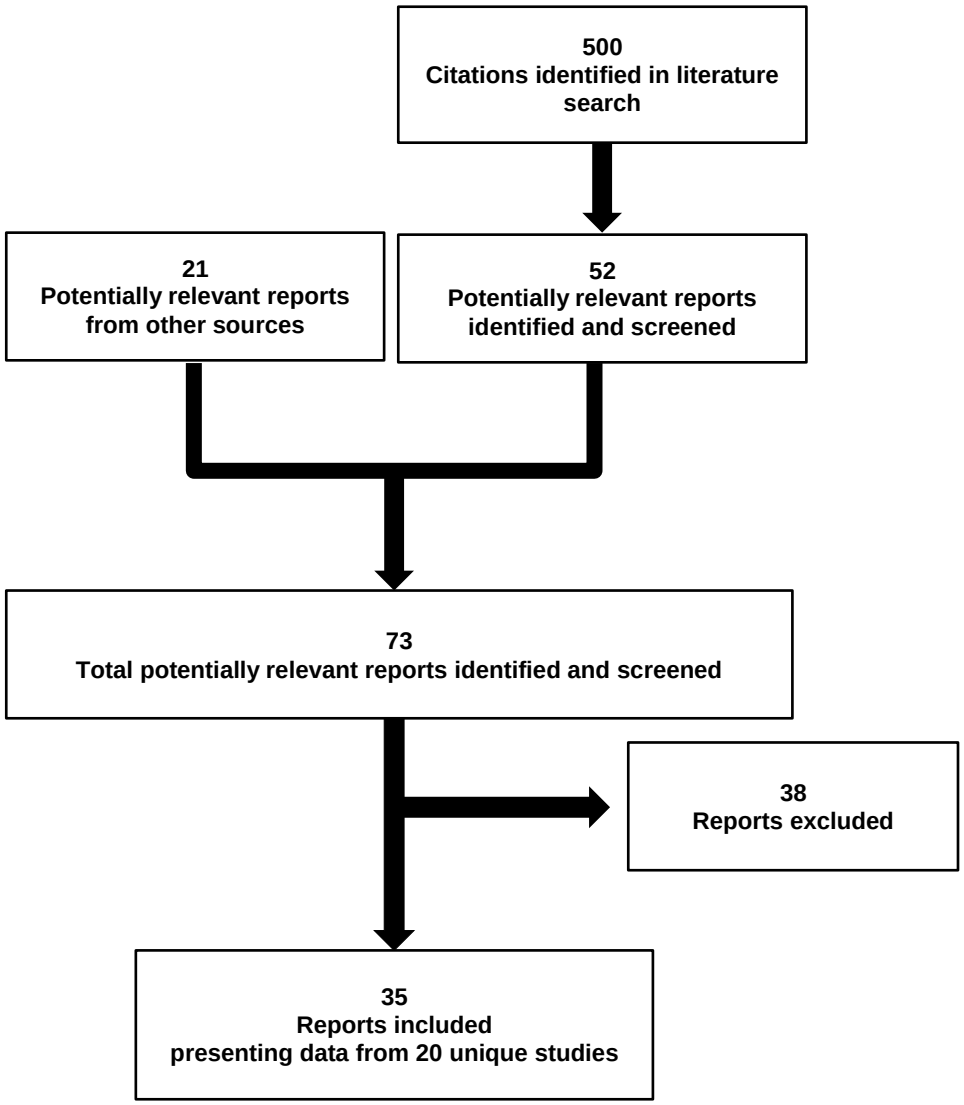


Table 11: Details of Included Studies — DEVOTE, SWITCH-1, and SWITCH-2

		DEVOTE	SWITCH-1 and SWITCH-2
Designs and Populations	**Study Design**	DB RCT	DB RCT (crossover)
	Locations	North America (including Canada), South America, Europe, Asia, India, South Africa	SWITCH-1: US, Poland SWITCH-2: US
	Randomized (N)	7,637	SWITCH-1: 501 SWITCH-2: 721
	Inclusion Criteria	T2DM A1C ≥ 7.0% or A1C < 7.0% and current insulin treatment corresponding to ≥ 20 U/day of basal insulin Current treatment with one or more oral or injectable antidiabetes drugs Age ≥ 50 years at screening and at least one of the following conditions: • prior MI • prior stroke or TIA • prior coronary, carotid, or peripheral arterial revascularization • > 50% stenosis on angiography or other imaging of coronary, carotid, or lower extremity arteries • history of symptomatic coronary heart disease documented by positive exercise stress test or any cardiac imaging, or UAP with ECG changes • asymptomatic cardiac ischemia documented by positive nuclear imaging test or exercise test or dobutamine stress echo • chronic heart failure NYHA class II to class III • chronic kidney disease corresponding to glomerular filtration rate 30 to 59 mL/min/1.73m^2 per CKD-Epi or age ≥ 60 years at screening and at least one of the following risk factors: • microalbuminuria or proteinuria • hypertension and left ventricular hypertrophy by ECG or imaging • left ventricular systolic and diastolic dysfunction by imaging • ankle/brachial index < 0.9	Patients with DM with recent severe or non-severe hypoglycemia, hypoglycemia symptom unawareness, moderate chronic renal failure or long disease duration/long-time insulin use. Thus, the trial populations reflected those at increased risk of experiencing hypoglycemic episodes compared with previously investigated populations. Male or female, age ≥ 18 years at the time of signing informed consent Patients fulfilling at least one of the following: • experienced at least one severe hypoglycemic episode within the last year (according to the ADA definition, April 2013) • moderate chronic renal failure, defined as glomerular filtration rate 30 to 59 mL/min/1.73 m^2 • per CKD-Epi by central laboratory analysis • hypoglycemic symptom unawareness • SWITCH-1: DM > 15 years. SWITCH-2: exposed to insulin for more than 5 years • recent episode of hypoglycemia, defined by symptoms of hypoglycemia and/or episode with low glucose measurement (≤ 3.9 mmol/L) within the last 12 weeks before visit 1 (screening) SWITCH-1: T1DM (diagnosed clinically) ≥ 52 weeks before visit 1 SWITCH-2: T2DM (diagnosed clinically) for ≥ 26 weeks before visit 1 SWITCH-1: Current treatment with a basal-bolus regimen (consisting of NPH insulin q.d. or b.i.d. or insulin detemir q.d. or b.i.d. plus 2 to 4 daily injections of any rapid-acting or fast-acting mealtime insulin) or CSII (with rapid-acting insulin) for ≥ 26 weeks before visit 1 SWITCH-2: Current treatment with any basal insulin (q.d. or b.i.d.) ± any combination of OADs (metformin, DPP-4 inhibitor, alpha-glucosidase inhibitor, TZDs, and SGLT-2 inhibitor) for ≥ 26 weeks before visit 1. For patients on b.i.d. the total daily dose should be < 75 units. SWITCH-1: A1C ≤ 10% by central laboratory

		DEVOTE	SWITCH-1 and SWITCH-2
			analysis SWITCH-2: A1C ≤ 9.5% by central laboratory analysis BMI ≤ 45 kg/m^2
	Exclusion Criteria	An acute coronary or cerebrovascular event in the previous 60 days Planned coronary, carotid, or peripheral artery revascularization Chronic heart failure NYHA class IV Current hemodialysis or peritoneal dialysis or eGFR < 30 mL/min/1.73 m^2 per CKD-Epi End-stage liver disease, defined as the presence of acute or chronic liver disease and recent history of one or more of the following: ascites, encephalopathy, variceal bleeding, bilirubin ≥ 2.0 mg/dL, albumin level > 3.5 g/dL, prothrombin time ≥ 4 seconds prolonged, INR ≥ 1.7, or prior liver transplant Known or suspected hypersensitivity to trial products or related products Female of child-bearing potential who is pregnant or breastfeeding or intends to become pregnant or is not using adequate contraceptive methods	Use of any antidiabetes drug(s) other than those stated in the inclusion criteria within the last 26 weeks before visit 1 Receipt of any IMP within 4 weeks before screening Any chronic disorder or severe disease which, in the opinion of the investigator, might jeopardize the patient's safety or compliance with the protocol Current or past (within the last 5 years) malignant neoplasms (except basal cell and squamous cell carcinoma) Stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty, all within the last 26 weeks before visit 1 Uncontrolled or untreated severe hypertension, defined as systolic blood pressure ≥ 180 mm Hg and/or diastolic blood pressure ≥ 100 mm Hg Impaired liver function, defined as ALAT or ASAT ≥ 2.5 × ULN Severe renal impairment, defined as glomerular filtration rate < 30 mL/min/1.73 m^2 per CKD-Epi
Drugs	**Intervention**	Insulin degludec 100 U/mL administered q.d. in a basal-bolus regimen with insulin aspart as mealtime insulin	Insulin degludec 100 U/mL
	Comparator	Insulin glargine 100 U/mL, administered q.d. in a basal-bolus regimen with insulin aspart as mealtime insulin	Insulin glargine 100 U/mL
Duration	**Phase**		
	Screening	2 weeks	2 weeks
	Double-blind	633 MACEs	64 weeks (32 weeks then cross over)
	Follow-up	30 days	1 week
Outcomes	**Primary End Point**	Time from randomization to first occurrence of an EAC-confirmed 3-component MACE: cardiovascular death, non-fatal MI, or non-fatal stroke	Severe or BG-confirmed symptomatic hypoglycemic episodes during the maintenance period, i.e., after 16 weeks of treatment, in each treatment period (weeks 16 to 32 and weeks 48 to 64)
	Other End Points)	**Confirmatory secondary end points** Number of EAC-confirmed severe hypoglycemic episodes Occurrence of at least one EAC-confirmed severe hypoglycemic episode in a patient (yes/no) **Secondary end points** **Efficacy end points** Change from baseline to last assessment in: • IMP dose • bolus insulin dose	**Secondary outcomes** Number of TE severe or BG-confirmed symptomatic nocturnal hypoglycemic episodes during the maintenance period (weeks 16 to 32 and weeks 48 to 64) Proportion of patients with one or more severe hypoglycemic episodes during the maintenance period (weeks 16 to 32 and weeks 48 to 64). **Supportive secondary end points** Change from baseline in A1C after 32 weeks FPG after 32 weeks

		DEVOTE	SWITCH-1 and SWITCH-2

		• total insulin dose
		• A1C (central laboratory)
		• FPG (central laboratory)
		• other assessments (after baseline):
		  ○ pre-breakfast SMPG
		  ○ 8-point SMPG profiles during one day and across visits
		  ○ mean of 8-point SMPG profile
		
		Safety end points
		Time from randomization to first occurrence of an EAC-confirmed, 4-point MACE (cardiovascular death, non-fatal MI, non-fatal stroke, and UAP requiring hospitalization)
		Time from randomization to first occurrence of each of the following EAC-confirmed events:
		• cardiovascular death
		• non-fatal MI
		• non-fatal stroke
		• UAP requiring hospitalization
		• all-cause death
		• non-cardiovascular death
		• severe hypoglycemic episode
		Time from randomization to first occurrence of heart failure requiring hospitalization
		Number of nocturnal EAC-confirmed severe hypoglycemic episodes
		Number of SAEs
		Number of AEs leading to permanent discontinuation of IMP
		Number of medications errors leading to SAEs
		Number of AEs related to technical complaints
		
		Change from baseline to the last assessment: body weight
			SMPG: 9-point profile
			Patient-reported outcomes: SF-36v2, TRIM-HYPO interview questionnaire
			
			Safety
			Number of TE severe or BG-confirmed symptomatic hypoglycemic episodes
			Number of TE severe or BG-confirmed symptomatic nocturnal hypoglycemic episodes
			Number of TE severe hypoglycemic episodes
			Number of TE hypoglycemic episodes according to ADA classification of hypoglycemic events
			Number of TE adverse events during 32 weeks of treatment
			Change from baseline in clinical evaluations after 32 weeks of treatment
			Change from baseline in laboratory assessments after 32 weeks of treatment
			Change from baseline in body weight after 32 weeks of treatment
			Total daily insulin dose after 32 weeks of treatment

NOTES	**Publications**	Marso 2017[3]	Lane 2017[8] Wysham 2017[9]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; ASAT = aspartate aminotransferase; BG = blood glucose; b.i.d. = twice daily; BMI = body mass index; CKD-Epi = Chronic Kidney Disease Epidemiology Collaboration; CSII = continuous subcutaneous insulin infusion; DB RCT = double-blind randomized controlled trial; DPP-4 = dipeptidyl peptidase-4; DM = diabetes mellitus; EAC = event adjudication committee; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; IMP = investigational medicinal product; INR = international normalized ratio; MACE = major adverse cardiovascular event; MI = myocardial infarction; NPH = neutral protamine Hagedorn; NYHA = New York Heart Association; OAD = oral antidiabetes drug; q.d. = once daily; SAE = serious adverse event; SF-36v2 = Short Form (36) Health Survey, version 2.0; SGLT-2 = sodium glucose transporter-2; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TE = treatment-emergent; TIA = transient ischemic attack; TRIM-HYPO = Treatment-Related Impact Measure — Hypoglycemic Events; TZD = thiazolidinedione; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included: FDA statistical and clinical reviews[10,11] and manufacturer submission.[12]

Source: Clinical Study Reports for DEVOTE,[6] SWITCH-1,[13] and SWITCH-2.[14]

Table 12: Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus Trial Details

Study	Comp	Primary Analysis	Confirmatory Secondary End Points (All Superiority)	Key Inclusion			
				A1C	BMI	Current Treatment	Exclusion
T1DM							
3583	IGlar	NI: A1C	1. Number of confirmed nocturnal hypoglycemia 2. Number of confirmed hypoglycemia 3. Change in FPG 4. Within-patient variability in pre-breakfast PG	≤ 10	≤ 35	Basal-bolus	CVD within 6 months Recurrent severe hypoglycemia[a]
3585	IDet	NI: A1C	1. Number of nocturnal confirmed hypoglycemia 2. Number of confirmed hypoglycemia 3. Change in FPG 4. Within-patient variability in pre-breakfast PG	≤ 10	≤ 35	Basal-bolus	CVD within 6 months Recurrent severe hypoglycemia[a]
3770	IGlar	NI: A1C	No confirmatory secondary end points	≤ 10	≤ 35	Basal-bolus	CVD within 6 months Recurrent severe hypoglycemia[a]
T2DM, Insulin-Naive							
3579	IGlar	NI: A1C	1. Number of confirmed hypoglycemic episodes 2. Change in FPG 3. Within-patient variability in pre-breakfast PG 4. A1C < 7.0% at end of trial w/o confirmed hypoglycemia	7 to 10	≤ 40	MET ± other OAD (SEC, DPP, AGI)	CVD within 6 months Recurrent severe hypoglycemia[a]
3580	Sita	Sup: A1C	1. Change in FPG 2. A1C < 7.0% at end of trial 3. A1C < 7.0% at end of trial w/o confirmed hypoglycemia	7.5 to 11	≤ 40	One or more of: MET, SEC, PIO	CVD within 6 months Recurrent severe hypoglycemia[a]
3586	IGlar	NI: A1C	1. Number of confirmed hypoglycemia 2. Number of nocturnal confirmed hypoglycemia 3. Change in FPG 4. Within-patient variability in pre-breakfast PG	7 to 10	≤ 35	OAD monotherapy or MET + SEC ± AGI or DPP	CVD within 6 months Recurrent severe hypoglycemia[a]
3672	IGlar	NI: A1C	1. Number of confirmed hypoglycemia 2. Change in FPG 3. Within-patient variability in pre-breakfast PG 4. A1C < 7.0% at end of trial w/o confirmed hypoglycemia	7 to 10	≤ 45	MET ± other OAD (SEC, DPP, AGI)	CVD within 6 months Recurrent severe hypoglycemia[a]
3587	IGlar	NI: A1C	1. Number of confirmed hypoglycemia 2. Change in FPG 3. Within-patient variability in pre-breakfast PG 4. A1C < 7.0% at end of trial w/o confirmed	7 to 10	≤ 40	MET ± other OAD (SEC, DPP, AGI)	CVD within 6 months Recurrent severe hypoglycemia[a]

Study	Comp	Primary Analysis	Confirmatory Secondary End Points (All Superiority)	Key Inclusion			
				A1C	BMI	Current Treatment	Exclusion
			hypoglycemia				
3944	Pla	Sup: A1C	No confirmatory secondary end points	7.5 to 10: MET 7 to 9: MET + OAD	≤ 45	MET ± other OAD (SEC, DPP, EXE)	CVD within 6 months Recurrent severe hypoglycemia[a]
T2DM, Basal Insulin							
3943	IGlar	NI: A1C	No confirmatory secondary end points	≥ 7.5	NR	IGlar 65 to 100 U MET ± other OAD	CVD within 6 months Recurrent severe hypoglycemia[a]
3668	IGlar	NI: A1C	No confirmatory secondary end points	7 to 10: OAD 7 to 11: OAD + Ins	≤ 40	OAD, basal ins or both (OAD: MET, SEC, PIO)	CVD within 6 months Recurrent severe hypoglycemia[a]
T2DM, Basal-Bolus							
3582	IGlar	NI: A1C	1. Number of confirmed hypoglycemia 2. Change in FPG 3. Within-patient variability in pre-breakfast PG 4. A1C < 7.0% at end of trial w/o confirmed hypoglycemia	7.5 to 11	≤ 40	Ins (any regimen) ± OAD	CVD within 6 months Recurrent severe hypoglycemia[a]

A1C = glycated hemoglobin; AGI = alpha-glucosidase inhibitor; BMI = body mass index; Comp = comparator; CVD = cardiovascular disease; DPP = dipeptidyl peptidase inhibitor; EXE = exenatide; FPG = fasting plasma glucose; IDet = insulin detemir; IGlar = insulin glargine; ins = insulin; MET = metformin; NI = noninferiority tested for this outcome; NR = not reported; OAD = oral antidiabetes drug; PG = plasma glucose; PIO = pioglitazone; Pla = placebo; SEC = secretagogue; Sita = sitagliptin; Sup = superiority tested for this outcome; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; w/o = without.

[a] Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for diabetic ketoacidosis during the previous 6 months.

Included Studies

Description of Studies

Fifteen manufacturer-sponsored randomized controlled trials (RCTs) plus five extensions were included in this systematic review, four of which were double blinded and the remainder open label. The studies featured different populations, T1DM and T2DM. Another four RCTs were excluded because either their small sample size or their short duration suggested they were unlikely to add any additional information beyond what was obtained in the studies summarized in the report.

DEVOTE was a double-blind RCT that compared IDeg with IGlar, both in a basal-bolus regimen, in a population of 7,637 patients with T2DM and cardiovascular disease. The primary outcome was the time to first major adverse cardiovascular event (MACE), testing the noninferiority of IDeg to IGlar, with a margin for noninferiority of 1.3 for the upper limit of the 95% confidence interval (CI) for the hazard ratio. DEVOTE was an event-driven study, targeting 633 MACEs before study completion, and it lasted a mean of 24 months. Confirmatory secondary end points, which all tested the superiority of IDeg to IGlar, included the number of confirmed hypoglycemic episodes and the occurrence of at least one hypoglycemic episode within a participant. The study had a two-week screening period, as well as a 30-day follow-up period at the end of study. DEVOTE is by far the largest of the studies included in this review.

The SWITCH studies, SWITCH-1 (T1DM) and SWITCH-2 (T2DM), employed a crossover design, with patients randomized to start on either IDeg or IGlar and then cross over to the other intervention after 32 weeks of therapy, resulting in a total treatment period of 64 weeks. The primary outcome of the SWITCH studies was the proportion of participants with severe or blood glucose–confirmed symptomatic hypoglycemic episodes during the maintenance period, that is, after 16 weeks of treatment. SWITCH-1 tested the noninferiority of IDeg to IGlar, with noninferiority confirmed if the upper bound of the 95% CI for the rate ratio was ≤ 1.10. SWITCH-2 tested the superiority of IDeg to IGlar. In each study, before testing of the primary outcome could proceed, noninferiority had to be confirmed for the secondary supportive end point of change from baseline in glycated hemoglobin (A1C) after 32 weeks of therapy. The margin for noninferiority was 0.4%, the same margin used in the BEGIN trials, described below. Each of the SWITCH studies had a two-week screening period and a one-week follow-up.

All of the BEGIN trials that compared IDeg with another basal insulin (described in more detail below) were noninferiority trials that tested the noninferiority of IDeg to a comparator for the primary outcome of change from baseline in A1C. Most of the trials had confirmatory secondary outcomes that compared the superiority of IDeg against the comparator. The extension trials, where they occurred, focused on the long-term safety of IDeg; therefore, there were no efficacy outcomes assessed. In the extensions, all patients continued in their originally randomized groups.

Type 1 Diabetes Mellitus

Studies 3583 (BBT1 [basal-bolus TD1M] Long, 52-week treatment period), 3770 (Flex T1, 26 weeks), and 3585 (BBT1, 26 weeks) were all open label, and all had extensions where patients continued on their originally randomized treatments. Study 3585 had IDet as a comparator, while the other two studies compared IDeg with IGlar. In Flex T1, the objective

of the study was to compare a flexible dosing regimen of IDeg with a regular IDeg regimen or to IGlar. The studies had one-week screening and one-week follow-up. The primary outcome of Studies 3770, 3583, and 3585 was the change from baseline to end of treatment in A1C. All of these studies tested the noninferiority of IDeg to a comparator, with a margin for noninferiority of 0.4% for the change from baseline in A1C. All but Study 3770 had confirmatory secondary end points that tested the superiority of IDeg to their respective comparators.

Type 2 Diabetes Mellitus

Insulin-Naive

Five open-label RCTs and one double-blind RCT enrolled patients with T2DM who were insulin-naive. All participants were receiving OADs. The comparator in four of the studies was IGlar, while in Study 3580 (BEGIN Early) the comparator was sitagliptin and in Study 3944, the only double-blind RCT, the comparator was placebo. Study 3672 (BEGIN Low Volume) compared the more concentrated formulation, IDeg 200 U/mL, with IGlar, while the other studies used the standard 100 U/mL concentration. Five studies were 26 weeks in duration, while Study 3579 (BEGIN Once Long) was a 52-week study. All studies except Study 3944 had a one-week screening period and at least a one-week follow-up, while Study 3944 also had a 15-week run-in where participants were initiated on liraglutide, which they would all continue once the double-blind period started. One trial (Study 3579) had an extension while the others did not. The primary outcome in all studies was the change in A1C from baseline to end of study. Studies with IGlar as a comparator tested the noninferiority of IDeg to IGlar for the primary end point, while Studies 3580 and 3944 tested the superiority of IDeg for the primary outcome. Confirmatory secondary outcomes, which all tested the superiority of IDeg to a comparator, included the number of treatment-emergent severe or minor hypoglycemic episodes, change from baseline in fasting plasma glucose (FPG), within-patient variability as measured by coefficient of variation in self-measured FPG, and responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks). The confirmatory secondary outcomes in Study 3580 were change from baseline in FPG, frequency of responders (A1C < 7.0% at end of trial), and frequency of responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment).

Basal Insulin Only (± OADs)

Two open-label RCTs (Studies 3668 and 3943) were included with this population. In Study 3668, all participants received metformin, with or without a dipeptidyl peptidase-4 inhibitor, and IDeg was compared with IGlar over a 26-week treatment course. The trial had a one-week screening period and at least one week of follow-up. The primary outcome was change from baseline in A1C to the study end point at 26 weeks; the study tested the noninferiority of IDeg to IGlar using the same noninferiority margin as the other BEGIN trials, 0.4%. Secondary end points, none of which appeared to be confirmatory, included the number of confirmed hypoglycemic episodes, change from baseline in FPG, within-patient variability in pre-breakfast, self-measured plasma glucose, and responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no confirmed episodes during the last 12 weeks of treatment, including only patients exposed for at least 12 weeks). Study 3943 was a noninferiority, open-label RCT with a crossover design featuring two treatment periods of 16 weeks each where IDeg was compared with IGlar. Participants were all on

metformin plus or minus an additional OAD. The trial had a one-week screening period and a 16-week run-in where participants discontinued their OAD (other than metformin) and were initiated on a regimen of IGlar, as well as a one-week follow-up. The purpose of the run-in was to establish which participants required a "high" dose of IGlar (> 81 units), as this was the population of interest for the study. The primary outcome again tested noninferiority for the change from baseline in A1C. Secondary outcomes were A1C responders, change from baseline in FPG, self-measured plasma glucose, and patient-reported outcomes; however, none of these appeared to be confirmatory.

Basal-Bolus Insulin (± OADs)

One noninferiority open-label RCT (Study 3582) was included with this population. Participants were receiving metformin, plus or minus pioglitazone, and IDeg was compared with IGlar. Participants were on a regimen that combined these basal insulins with insulin aspart. The primary outcome was the change in A1C from baseline to the study end point at 52 weeks. Confirmatory secondary end points included change from baseline in FPG after 52 weeks, frequency of responders (A1C < 7.0% at end of trial), and frequency of responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment).

Populations

Inclusion and Exclusion Criteria

Participants in DEVOTE had T2DM, with an A1C of 7% or more (or below 7% if receiving current insulin therapy of at least 20 units daily). Participants were currently treated with one or more oral or injectable antidiabetes drugs. They had to be at least 50 years old and have evidence of cardiovascular disease or chronic kidney disease (Table 11).

In the trials in T1DM, participants had to have been treated on a basal-bolus regimen for at least 12 months, with an A1C of 10% or less and a BMI of 35 kg/m^2 or less. For a high-level summary of these trials, see Table 12; for detailed summaries, see Table 39 and Table 40.

In the T2DM trials in insulin-naive patients, participants had to have had T2DM for at least six months, an A1C of between 7.0% or 7.5% and 10%, and a maximum BMI of 40 kg/m^2 to 45 kg/m^2. All were receiving OADs for at least three months before randomization in a regimen that typically featured metformin with or without another OAD. See Table 12 for a high-level summary of study designs; for detailed summaries, see Table 41, Table 42, Table 43, Table 44, and Table 45.

Participants in Study 3668 (basal only) had to have had T2DM for at least six months and be on OAD monotherapy, insulin monotherapy, or a combination of the two. The only allowed OADs were metformin, insulin secretagogues, or pioglitazone. Participants on OAD alone had to have an A1C between 7% and 11%. Those on combination basal insulin and OAD or basal insulin monotherapy were to be between 7% and 10%. In the other basal-only study, participants were to have an A1C of at least 7.5% and be on metformin with or without another OAD. For a high-level summary of these two studies, see Table 12; for detailed summaries, see Table 46 and Table 47.

In the basal-bolus study, participants were to have hadT2DM for at least six months and could be on any insulin regimen, with or without OADs, for at least three months before randomization. Their A1C had to be between 7.5% and 11%, and their maximum BMI was

to be 40 kg/m^2. For a high-level summary, see Table 12; for a detailed summary, see Table 48.

Baseline Characteristics

Trials with populations with T1DM tended to feature younger participants (early to mid-40s) versus studies that focused on T2DM (mid-50s to mid-60s), which aligns with the onset and progression of the disease subtypes. Among T2DM studies, the oldest populations were in DEVOTE (65 years of age) and SWITCH-2 (61 years of age) (Table 13, Table 14).

Across all studies, the majority of participants were male, and most were Caucasian, with the exception of Studies 3585 and 3586, where almost all participants were Asian (non-Indian), and Study 3587, where about two-thirds were Asian (non-Indian).

In the T1DM studies, between 14% and 29% of participants had diabetes complications at baseline. In DEVOTE, 86% of participants had established cardiovascular or chronic kidney disease, while in the other T2DM studies, the proportion of participants with diabetes complications varied widely at baseline, from a low of around 10% in Studies 3579 and 3580 to a high of about 40% in Study 3586.

Baseline characteristics were generally balanced between groups within studies. The most common baseline parameter to differ between groups was gender, with the largest difference between groups found in Study 3668, where 59% of participants in the IDeg-Flex (IDeg flexible dosing regimen) group and 48% of participants in the IGlar group were male.

Table 13: Summary of Baseline Characteristics — DEVOTE

Characteristic	DEVOTE	
	Degludec N = 3,818	Glargine N = 3,819
Mean (SD) age, years	64.9 (7.3)	65.0 (7.5)
Male, n (%)	2,396 (63)	2,382 (62)
Race, n (%)		
White	2,903 (76)	2,872 (75)
Black/African American	401 (11)	431 (11)
Asian	391 (10)	385 (10)
American Indian or Alaska native	17 (< 1)	13 (< 1)
Native Hawaiian or other Pacific islander	11 (< 1)	13 (< 1)
Other	94 (3)	104 (3)
Unknown	1 (0)	1 (0)
Mean (SD) BMI, kg/m^2	33.6 (6.8)	33.6 (6.8)
Mean (SD) duration of diabetes, years	16.6 (8.8)	16.2 (8.9)
Mean (SD) A1C, %	8.4 (1.6)	8.4 (1.7)
Mean (SD) FPG, mmol/L	9.4 (3.9)	9.6 (3.9)
Mean (SD) eGFR, mL/min/1.73 m^2	68.1 (21.5)	67.8 (21.6)
Age ≥ 50 years and established cardiovascular or chronic kidney disease, n (%)	3,265 (86)	3,244 (85)
Age ≥ 60 years and risk factors for cardiovascular disease, n (%)	538 (14)	567 (15)
Medication at baseline, n (%)		
Any cardiovascular medication	3,761 (98.5)	3,747 (98.1)
Insulin-naive at baseline	604 (15.8)	624 (16.3)
Most common OADs		
Metformin	2,294 (60.1)	2,270 (59.4)

Characteristic	DEVOTE	
	Degludec N = 3,818	Glargine N = 3,819
Sulfonylurea	1,118 (29.3)	1,111 (29.1)
Dipeptidyl peptidase-4 inhibitors	463 (12.1)	480 (12.6)

A1C = glycated hemoglobin; BMI = body mass index; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; OAD = oral antidiabetes drug; SD = standard deviation.

Source: Clinical Study Report for DEVOTE.[6]

Table 14: Summary of Baseline Characteristics — SWITCH-1 and SWITCH-2

Characteristic	SWITCH-1		SWITCH-2	
	IDeg/IGlar N = 249	IGlar/IDeg N = 252	IDeg/IGlar	IGlar/IDeg
Mean (SD) age, years	45.4 (13.7)	46.4 (14.6)	61.5 (10.7)	61.2 (10.3)
Male, n (%)	126 (50.6)	143 (56.7)	191 (53.1)	191 (53.1)
Race, n (%)				
White	233 (93.6)	229 (90.9)	292 (81.1)	286 (79.4)
Black/African American	13 (5.2)	19 (7.5)	54 (15.0)	52 (14.4)
Asian	1 (0.4)	1 (0.4)	6 (1.7)	16 (4.4)
American Indian or Alaska native	2 (0.8)	0	3 (0.8)	4 (1.1)
Native Hawaiian or other Pacific islander	0	2 (0.8)	1 (0.3)	0 (0.0)
Other	0	1 (0.4)	4 (1.1)	2 (0.6)
Mean (SD) BMI, kg/m^2	27.9 (5.1)	27.0 (4.5)	32.0 (5.6)	32.3 (5.7)
Mean (SD) duration of diabetes, years	23.2 (13.5)	23.6 (13.4)	14.2 (8.3)	13.9 (8.0)
Mean (SD) A1C, %	7.7 (1.0)	7.5 (1.0)	7.6 (1.1)	7.6 (1.1)
Mean (SD) FPG, mmol/L	9.2 (4.3)	9.7 (4.5)	7.7 (3.0)	7.5 (2.9)
eGFR(mL/min/1.73 m^2)	89.9 (21.2)	90.0 (20.9)	78.8 (21.4)	77.7 (21.3)
Diabetes complications, n (%)	43 (17.3)	57 (22.6)	85 (23.6)	87 (24.2)
Diabetes medications, n (%)				
CSII	43 (17.3)	54 (21.4)	-	-
Basal q.d. + 2 to 4 bolus injections	106 (42.6)	118 (46.8)	-	-
Basal b.i.d. + 2 to 4 bolus injections	99 (39.8)	80 (31.7)	-	-
Basal q.d.	-	-	311 (86.4)	295 (81.9)
Basal b.i.d.	-	-	49 (13.6)	65 (18.1)
BG-lowering regimen excluding insulins, n (%)	-	-		
0 active drugs	-	-	69 (19.2)	81 (22.5)
1 active drug	-	-	234 (65.0)	214 (59.4)
≥ 2 active drugs	-	-	57 (15.8)	65 (18.1)

A1C = glycated hemoglobin; b.i.d. = twice daily; BG = blood glucose; BMI = body mass index; CSII = continuous subcutaneous insulin infusion; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; IDeg/IGlar = insulin degludec followed by insulin glargine; IGlar/IDeg = insulin glargine followed by insulin degludec; OAD = oral antidiabetes drug; q.d. = once daily; SD = standard deviation.

Source: Clinical Study Reports for SWITCH-1- and SWTICH-2.[13,14]

Table 15: Summary of Baseline Characteristics — Type 1 Diabetes Mellitus (Studies 3770, 3583, and 3585)

Characteristic	Study 3585						
	Study 3770			Study 3583		Study 3585	
	IDeg-Flex N = 164	Degludec N = 165	Glargine N = 164	Degludec N = 472	Glargine N = 157	Degludec N = 302	Detemir N = 153
Mean (SD) age, years	42.6 (13.4)	44.5 (13.1)	44.1 (12.6)	42.8 (13.7)	43.7 (13.3)	41.1 (14.9)	41.7 (14.4)
Male, n (%)	102 (62)	94 (57)	88 (54)	278 (59)	90 (57)	150 (50)	86 (56)
Race, n (%)							
White	158 (96)	161 (98)	162 (99)	437 (93)	148 (94)	133 (44)	70 (46)
Black/African American	5 (3)	3 (2)	1 (1)	9 (2)	3 (2)	2 (1)	0 (0)
Asian Indian	-	-	-	1 (< 1)	0 (0)	40 (13)	20 (13)
Asian non-Indian	1 (1)	0 (0)	1 (1)	5 (< 1)	3 (2)	125 (41)	62 (41)
American Indian or Alaska native	-	-	-	1 (< 1)	0 (0)	-	-
Native Hawaiian or other Pacific islander	-	-	-	0	1 (1)	-	-
Other	0 (0.0)	1 (1)	0	19 (4)	2 (1)	2 (1)	1 (1)
Mean (SD) BMI, kg/m^2	27.0 (3.8)	26.4 (4.0)	26.8 (4.0)	26.3 (3.7)	26.4 (4.2)	24.0 (3.5)	23.7 (3.4)
Mean (SD) duration of diabetes (years)	17.3 (12.2)	20.0 (12.5)	18.2 (11.9)	19.1 (12.2)	18.2 (11.4)	13.7 (10.6)	14.4 (9.7)
Mean (SD) A1C, %	7.7 (1.0)	7.7 (0.9)	7.7 (0.9)	7.7 (0.9)	7.7 (1.0)	8.0 (1.0)	8.0 (0.9)
Mean (SD) FPG, mmol/L	9.6 (4.1)	10.0 (4.0)	9.7 (4.2)	9.1 (4.0)	9.7 (4.4)	9.9 (4.0)	9.5 (4.0)
All complications, n (% patients with complications)	32 (20)	28 (17)	23 (14)	129 (27)	36 (23)	79 (26)	44 (29)

A1C = glycated hemoglobin; BMI = body mass index; IDeg-Flex = insulin degludec flexible dosing; FPG = fasting plasma glucose; SD = standard deviation.

Source: Clinical Study Reports for Studies 3770,[15] 3583,[4] and 3585.[16]

Table 16: Summary of Baseline Characteristics — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3579, 3580, 3586, and 3672)

Characteristic	Study 3579		Study 3580		Study 3586		Study 3672	
	Degludec N = 773	Glargine N = 257	Degludec N = 225	DPP-4 N = 222	Degludec N = 289	Glargine N = 146	Degludec N = 228	Glargine N = 229
Mean (SD) age, years	59.3 (9.7)	58.7 (9.9)	56.4 (10.2)	54.9 (11.4)	58.8 (9.8)	58.1 (10.1)	57.8 (9.0)	57.3 (9.4)
Male, n (%)	471 (61)	167 (65)	141 (63)	121 (55)	158 (55)	75 (51)	119 (52)	124 (54)
Race, n (%)								
White	680 (88)	231 (90)	135 (60)	139 (63)	0	0	180 (79)	178 (78)
Black/African American	57 (7)	16 (6)	17 (8)	17 (8)	0	0	31 (14)	32 (14)
Asian Indian	8 (1)	3 (1)	56 (25)	53 (24)	5 (2)	4 (3)	5 (2)	3 (1)
Asian non-Indian	10 (1)	0 (0)	1 (< 1)	2 (1)	284 (98)	142 (97)	3 (1)	6 (3)
American Indian or Alaska native	1 (< 1)	1 (< 1)	2 (1)	1 (1)	0	0	1 (< 1)	1 (< 1)
Native Hawaiian or other Pacific islander	1 (< 1)	1 (< 1)	1 (< 1)	0 (0)	0	0	0	1 (< 1)
Other	16 (2)	5 (2)	13 (6)	10 (5)	0	0	7 (3)	4 (2)
Not applicable	-	-	-	-	-	-	16 (7)	19 (8)
Mean (SD) BMI, kg/m^2	30.9 (4.8)	31.6 (4.4)	30.0 (5.1)	30.8 (5.2)	24.6 (3.4)	25.8 (3.7)	32.2 (5.4)	32.7 (5.3)
Mean (SD) duration of diabetes, years	9.4 (6.3)	8.6 (5.7)	7.8 (6.2)	7.7 (5.9)	11.8 (6.5)	11.1 (6.5)	8.4 (6.7)	8.0 (5.6)
Mean (SD) A1C, %	8.2 (0.8)	8.2 (0.8)	8.8 (1.0)	9.0 (1.0)	8.4 (0.8)	8.5 (0.8)	8.3 (1.0)	8.2 (0.9)
Mean (SD) FPG, mmol/L	9.6 (2.6)	9.7 (2.6)	9.4 (2.6)	9.9 (3.1)	8.4 (2.1)	8.6 (1.9)	9.6 (2.9)	9.7 (2.6)
All complications, n (%)	105 (14)	22 (9)	29 (13)	18 (8)	106 (37)	63 (43)	32 (14)	43 (19)
Antidiabetes treatment regimen at screening, n (%)								
OAD combo	-	-	-	-	253 (88)	129 (88)	-	-
OAD monotherapy	-	-	-	-	36 (13)	17 (12)	-	-
Metformin monotherapy	212 (27)	88 (34)	55 (24)	57 (26)	-	-	61 (27)	70 (31)
Metformin ± SU or glinides ± alpha-glucosidase inhibitor	428 (55)	122 (48)	-	-	-	-	128 (56)	125 (55)
Metformin + DPP-4 ± SU or glinides ± alpha-glucosidase inhibitor	133 (17)	47 (18)	-	-	-	-	39 (17)	34 (15)
Pioglitazone ± (SU or glinide) or metformin	-	-	9 (4)	15 (7)	-	-	-	-
SU or glinides ± metformin	-	-	161 (72)	150 (68)	-	-	-	-

A1C = glycated hemoglobin; BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; OAD = oral antidiabetes drug; SD = standard deviation; SU = sulfonylurea.

Source: Clinical Study Reports for Studies 3579,[17] 3580,[18] 3672,[19] and 3586.[20]

Table 17: Summary of Baseline Characteristics — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3587 and 3944)

Characteristic	Study 3587		Study 3944	
	Degludec N = 555	Glargine N = 278	Deg + Lira N = 174	Pla + Lira N = 172
Mean (SD) age, years	55.9 (9.7)	56.6 (9.2)	57.0 (10.0)	57.3 (9.4)
Male, n (%)	299 (54)	132 (48)	98 (56)	104 (61)
Race, n (%)				
White	133 (24)	70 (25)	140 (81)	151 (88)
Black/African American	12 (2)	9 (3)	22 (13)	11 (6)
Asian Indian	9 (2)	1 (< 1)	9 (5)	1 (1)
Asian non-Indian	374 (67)	187 (67)	0 (0)	3 (2)
American Indian or Alaska native	1 (< 1)	0 (0)	1 (1)	0 (0)
Native Hawaiian or other Pacific islander	0	0	0	0
Other	26 (5)	11 (4)	2 (1)	6 (4)
Mean (SD) BMI, kg/m^2	27.4 (4.7)	27.0 (4.6)	32.0 (5.7)	32.4 (5.4)
Mean (SD) duration of diabetes, years	7.55 (5.28)	8.26 (5.45)	9.7 (5.8)	9.3 (5.4)
Mean (SD) A1C, %	8.3 (0.9)	8.3 (0.8)	7.5 (0.6)	7.6 (0.6)
Mean (SD) FPG, mmol/L	9.4 (2.4)	9.4 (2.5)	8.7 (2.1)	9.1 (2.2)
All complications	133 (24)	67 (24)	45 (26)	48 (28)
Antidiabetes treatment regimen at screening, n (%)				
Metformin monotherapy	189 (34)	87 (31)	-	-
Metformin + 1 OAD	314 (57)	159 (57)	-	-
Metformin + > 1 OAD	52 (9)	31 (11)	-	-
Metformin + 1 OAD + insulin therapy	0 (0.0)	1 (< 1)	-	-
Biguanide	-	-	54 (31)	51 (30)
Biguanide + DPP-4 inhibitor	-	-	30 (17)	28 (16)
Biguanide + exenatide	-	-	1 (1)	2 (1)
Biguanide + glinide	-	-	2 (1)	3 (2)
Biguanide + sulfonylurea	-	-	84 (48)	87 (51)
Biguanide + DPP-4 inhibitor + SU	-	-	3 (2)	1 (1)

A1C = glycated hemoglobin; BMI = body mass index; Deg = insulin degludec; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; Lira = liraglutide; OAD = oral antidiabetes drug; Pla = placebo; SD = standard deviation; SU = sulfonylurea.

Source: Clinical Study Reports for Studies 3587[21] and 3944.[22]

Table 18: Summary of Baseline Characteristics — Type 2 Diabetes Mellitus, Basal Insulin (Studies 3668 and 3943)

Characteristic	Study 3668			Study 3943	
	IDeg-Flex N = 229	Degludec N = 228	Glargine N = 230	IDeg/IGlar N = 72	IGlar/IDeg N = 69
Mean (SD) age, years	56.2 (10.3)	56.5 (9.6)	56.7 (8.8)	54.7 (10.2)	55.8 (9.0)
Male, n (%)	135 (59)	124 (54)	111 (48)	42 (58)	48 (67)
Race, n (%)					
White	151 (66)	153 (67)	154 (67)	67 (92)	62 (86)
Black/African American	3 (1)	8 (4)	6 (3)	5 (7)	9 (13)
Asian Indian	49 (21)	46 (20)	50 (22)	1 (1)	1 (1)
Asian non-Indian	21 (9)	20 (9)	20 (9)	0	0
American Indian or Alaska native	0	0	0	0	0
Native Hawaiian or other Pacific islander	0	0	0	0	0
Other	5 (2)	1 (< 1)	0 (0)		
Mean (SD) BMI, kg/m^2	29.3 (4.6)	29.4 (4.9)	30.0 (4.7)	36.9 (6.7)	35.4 (6.6)
Mean (SD) duration of diabetes, years	10.8 (6.9)	10.3 (6.7)	10.8 (6.4)	12.1 (6.7)	12.1 (7.9)
Mean (SD) A1C, %	8.5 (1.0)	8.4 (0.9)	8.4 (0.9)	8.0 (1.1)	8.3 (1.4)
Mean (SD) FPG, mmol/L	9.0 (2.6)	8.8 (2.8)	9.0 (2.8)	7.5 (3.3)	8.5 (4.1)
Participants with diabetic complications, n (%)	46 (20)	59 (26)	64 (28)	28 (38)	24 (33)
Antidiabetes treatment regimen at screening, n (%)					
OAD only	133 (58)	131 (58)	134 (58)		
Basal insulin only	7 (3)	8 (4)	6 (4)		
Basal insulin + at least one OAD	89 (39)	88 (39)	89 (39)		
Metformin monotherapy	-	-	-	53 (73)	55 (76)
Metformin + DPP-4	-	-	-	3 (4)	3 (4)
Metformin ± glinides	-	-	-	1 (1)	-
Metformin ± SU	-	-	-	16 (22)	14 (19)

A1C = glycated hemoglobin; BMI = body mass index; IDeg-Flex = insulin degludec flexible dosing; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; IDeg/IGlar = insulin degludec followed by insulin glargine; IGlar/IDeg = insulin glargine followed by insulin degludec; OAD = oral antidiabetes drug; SD = standard deviation; SU = sulfonylurea.

Source: Clinical Study Reports for Studies 3668[23] and 3943.[24]

Table 19: Summary of Baseline Characteristics — Type 2 Diabetes Mellitus, Basal-Bolus (Study 3582)

Characteristic	3582 (BBT2) FAS	
	Degludec N = 744	Glargine N = 248
Male, n (%)	405 (54.4)	133 (53.6)
Mean (SD) age, years	59.2 (9.1)	58.1 (10.0)
Mean (SD) BMI, kg/m^2	32.3 (4.7)	31.9 (4.5)
Mean (SD) duration of diabetes, years	13.6 (7.4)	13.4 (6.9)
Mean (SD) A1C, %	8.3 (0.8)	8.4 (0.9)
Mean (SD) FPG, mmol/L	9.2 (3.0)	9.2 (3.2)
eGFR, mL/min/1.73 m^2	NR	NR
All complications, n (%)	266 (35.8)	94 (37.9)
Antidiabetes treatment regimen at screening, n (%)		
Basal-bolus therapy ± OADs	362 (48.7)	124 (50.0)
Basal + bolus < b.i.d. ± OADs	19 (2.6)	3 (1.2)
Premix therapy ± OADs	181 (24.3)	61 (24.6)
Basal ± OADs	154 (20.7)	56 (22.6)
Bolus ± OADs	28 (3.8)	4 (1.6)

A1C = glycated hemoglobin; BBT2 = basal-bolus type 2; b.i.d. = twice daily; BMI = body mass index; eGFR = estimated glomerular filtration rate; FAS = full analysis set; FPG = fasting plasma glucose; OAD = oral antidiabetes drug; SD = standard deviation; TD2M = type 2 diabetes mellitus.

Source: Clinical Study Report for Study 3582.[25]

Interventions

The studies generally employed a treat-to-target strategy for insulin dosing. For example, in SWITCH-1, participants' plasma glucose was titrated to a self-measured plasma glucose of 4.0 mmol/L to 5.0 mmol/L. A dose reduction was to be implemented if one or more of the pre-breakfast glucose values was < 4.0 mmol/L. Bolus insulin (insulin aspart) was titrated individually based either on carbohydrate counting or by using a sliding scale based on the lowest of three pre-meal or bedtime glucose values. Participants were typically given an algorithm they used to adjust their insulin regimens throughout the trial.

The majority of studies randomized participants in a 1:1 manner; however, Studies 3585, 3586, and 3587 randomized participants in a 2:1 manner (IDeg to comparator), and Studies 3579, 3583, and 3582 randomized 3:1. Two studies, 3770 and 3668, included an IDeg-Flex regimen in addition to the standard IDeg daily regimen, where participants' injections were to be given in a rotating schedule with eight-hour to 40-hour intervals between doses. These studies randomized participants 1:1:1. If stratification was reported or performed, the most common variable was by region (Studies 3587, 3944, 3586, 3585). Study 3580 stratified by use of pioglitazone at screening, Study 3582 by prior insulin regimen, and Study 3668 by prior treatment (insulin, OAD, or both). The SWITCH studies and DEVOTE did not report whether stratification occurred.

Type 2 Diabetes Mellitus

Inclusion criteria specified adequate minimum doses of OADs to ensure that antidiabetes therapy was optimized before intervention and that inadequacy of glycemic control at baseline was not due to suboptimal dosing of OAD treatment. No washout period was

applied. During the trials, patients continued on the pre-specified OADs at unchanged doses unless dose reduction was required for safety reasons.

Two studies, 3944 and 3943, had extensive run-in periods. In Study 3944, the 15-week run-in was used to initiate participants on liraglutide, which was to become the standard adjunctive therapy, added to IDeg and placebo, during the treatment phase. In Study 3943, the 16-week run-in was used to determine which participants needed a high (> 80 units) dose of IGlar to maintain glycemic control.

Outcomes

The primary outcome of DEVOTE was time from randomization to first occurrence of an event adjudication committee (EAC)–confirmed 3-component MACE: cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Confirmed hypoglycemic episodes consisted of episodes of severe hypoglycemia as well as minor hypoglycemic episodes with a confirmed plasma glucose value of < 3.1 mmol/L. Hypoglycemic episodes were defined as nocturnal if the time of onset was between 00:01 a.m. and 05:59 a.m., inclusive. Severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate or glucagon, or take other resuscitative actions.

Blood samples for A1C were analyzed using a Bio-Rad high performance liquid chromatography method at a central laboratory. A1C samples were collected at multiple visits in the main trial and extensions (where applicable). The assay method used was a National Glycohemoglobin Standardization Program–certified method. Blood samples for FPG were analyzed using a Roche enzymatic method at a central laboratory. FPG samples were collected at multiple visits in the main trials and extensions (where applicable). The patients were to attend these visits in a fasting state.

Within-patient variability as measured by coefficient of variation was to be derived from pre-breakfast plasma glucose values after 26 weeks of treatment. Logarithm-transformed self-measured plasma glucose values were to be analyzed as repeated measures in a linear mixed model with treatment, antidiabetes treatment at screening, sex, and region as fixed factors, age as a covariate, and patient as random factor. The model was to assume independent within-patient and between-patient errors with variances depending on treatment. Within-patient variability as measured by coefficient of variation for a treatment could be calculated from the corresponding residual variance. The CI for the coefficient of variation ratio between treatments was to be calculated using the delta method.

Changes in patients' health-related quality of life (HRQoL) and treatment-related impacts of minor hypoglycemic episodes on patients' daily function and well-being were evaluated using the Short Form (36) Health Survey, version 2.0 (SF-36v2) and Treatment-Related Impact Measure — Hypoglycemic Events (TRIM-HYPO) questionnaires, respectively. Responses for the SF-36v2 were measured on standardized scales from 1998 based on the US general population, with a mean of 50 and standard deviation of 10. Responses for the TRIM-HYPO were standardized to a scale of 0 to 100. In the SF-36v2 questionnaire, higher scores indicate a better HRQoL. In the TRIM-HYPO questionnaire, lower scores indicate better daily function and well-being for the patient.

SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on HRQoL. SF-36 consists of 36 items representing eight dimensions: physical functioning, role physical, bodily pain, general health, vitality,

social functioning, role emotional, and mental health. Item response options are presented on a 3-point to 6-point Likert-like scale. Each item is scored on a 0 to 100 range and item scores are averaged together to create the eight domain scores. SF-36 also provides two component summaries, the physical component summary and the mental component summary, which are created by aggregating the eight domains according to a scoring algorithm. On any of the scales, an increase in score indicates improvement in health status. Based on clinical anchor data, the SF-36 User's Manual proposed the following minimal important differences for general use of the SF-36v2: a change of 2 to 4 points in each domain or 2 to 3 points in each component summary.[26] No minimal clinically important difference (MCID) in patients with T1DM or T2DM was found in the literature.

Treatment-Related Impact Measure — Diabetes (TRIM-D) is a diabetes-specific questionnaire developed to assess the full impact of diabetes treatment on patients' quality of life. This patient-reported outcome measure consists of 28 items encompassed in five domains: treatment burden (six items), daily life (five items), diabetes management (five items), psychological health (eight items), and compliance (four items). Response options are presented on a 5-point Likert-like scale. An increase in score indicates an improvement in health state. Domains can be scored individually or the measure can be scored as a total of these domains.[27,28] No MCID has been determined for the TRIM-D.

TRIM-HYPO is a patient-reported outcome measure developed to measure the impact of non-severe hypoglycemic events on patients' HRQoL arising from the use of insulin to treat both forms of diabetes (T1DM and T2DM). TRIM-HYPO is a self-reported questionnaire comprising 33 Likert-like scale items (scored 1 to 5) in five domains: daily functioning, emotional well-being, diabetes management, work productivity, and sleep disruption. Domains are scored individually. A total score is also calculated, using three of the five domains (daily functioning, emotional well-being, diabetes management), as work productivity and sleep disruption do not apply to all patients. Lower scores on the TRIM-HYPO indicate a better health state. Raw scores are obtained by aggregating scale items into their respective domain scales. A weighted score is then generated, based by the number of non-severe hypoglycemic occurrences in the past 30 days: the higher the number, the greater the impact on the weighted score. This weighting helps account for the difference in HRQoL of patients experiencing few events versus those experiencing many hypoglycemic events. A standard algorithm method transforms the weighted scores into a 0 to 100 score.[29] No MCID has been determined for the TRIM-HYPO.

Statistical Analysis

All included studies carried out power calculations to determine sample size, and all studies randomized sufficient numbers of patients to ensure adequate power for assessing the primary end point.

DEVOTE

The primary end point (time from randomization to first occurrence of an EAC-confirmed, three-component MACE) was presented descriptively in a Kaplan–Meier plot and analyzed using a Cox proportional hazard regression with treatment (IDeg and IGlar) as a factor. The hazard ratio and the corresponding two-sided 95% CI were estimated. Noninferiority of IDeg to IGlar was considered confirmed if the upper limit of the two-sided 95% CI for the hazard ratio was below 1.3 or equivalent if the *P* value for the one-sided test of the null hypothesis, hazard ratio ≥ 1.3, against the alternative hypothesis, hazard ratio < 1.3, was < 2.5%. This is the margin recommended by the FDA for evaluating the cardiovascular safety of new

antihyperglycemic drugs.[30] Results for the full analysis set (FAS) population were also presented as for the per-protocol population.

Any EAC-confirmed MACE occurring after a patient's first EAC-confirmed MACE did not contribute to the analysis (i.e., time to first event only). Where an EAC-confirmed cardiovascular death was linked by the EAC to an earlier myocardial infarction or stroke, the patient contributed to the analysis with time to the cardiovascular death. If a patient did not experience any EAC-confirmed MACE, the time was censored at the patient's individual end-of-trial date.

Patients were allowed to go on and off randomized treatment during the trial (resulting in "on-treatment" and "off-treatment" periods). Sensitivity analyses were made using the same Cox regression model as the primary analysis. but including only EAC-confirmed MACEs occurring during an on-treatment period.

Four sensitivity analyses were performed, covering two types of censoring mechanisms: strict censoring (censor at time of first EAC-confirmed MACE if occurring during an off-treatment period) and censoring where the first EAC-confirmed MACE occurring during an off-treatment period was ignored. These censoring mechanisms were applied to two types of on-treatment definition:

- on-treatment: EAC-confirmed MACEs occurring on randomized treatment
- on-treatment + 30 days: EAC-confirmed MACEs occurring on randomized treatment plus up to 30 days of a subsequent off-treatment period.

Provided that noninferiority for the primary end point was confirmed, the number of EAC-confirmed severe hypoglycemic episodes was analyzed using a negative binomial regression model with log-link function and the logarithm of the observation time as offset. The model included treatment (IDeg versus IGlar) as a fixed factor, and was fitted using the FAS. Superiority was considered confirmed if the upper limit of the two-sided 95% CI for the rate ratio was below 1.0, or equivalent if the *P* value for the one-sided test of the null hypothesis, rate ratio ≥ 1.0, against the alternative hypothesis, rate ratio < 1.0, was less than 2.5%.

Several subgroup analyses were reported for the primary outcome, of which one was relevant to our protocol: cardiovascular risk group (patients with established cardiovascular disease or chronic kidney disease versus patients with risk factors for cardiovascular disease).

Multiplicity

The primary and secondary confirmatory end points were tested in a predefined hierarchical order to control the overall type I error. In this testing sequence, it was necessary to fulfill the test criteria (i.e., to reject the corresponding null hypothesis) in order to go to the next step. If the corresponding null hypothesis was not rejected, the testing was stopped, and no further hypotheses were tested.

- Step 1: Noninferiority of IDeg versus IGlar for the primary end point
- Step 2: Superiority of IDeg versus IGlar for the number of EAC-confirmed severe hypoglycemic episodes
- Step 3: Superiority of IDeg versus IGlar for the occurrence of at least one EAC-confirmed severe hypoglycemic episode in a patient.

Because the statistical tests and results of the interim analysis did not affect the continuation of the trial or the statistical tests and results of the full trial data (as stated in the statistical analysis plan for the interim analysis), there was no need to adjust the alpha level for the statistical tests of the full trial data.

Missing Data

In DEVOTE, a tipping-point analysis was made to address the impact of missing information for patients not completing the trial. Events were added for all patients randomized to IDeg not having an EAC-confirmed MACE in the primary analysis who were non-completers (i.e., 66 patients) and lost to follow-up (i.e., four patients).

As these patients had observation periods of different lengths, the order in which they were added to the analysis could potentially have an impact. Hence, patients were sorted based on the duration of their observation times using the following approaches:

- forward imputation of events, in which events were imputed for patients with the shortest observation period first and the longest observation last
- backward imputation, where events were imputed for patients with the longest observation period first and the shortest observation last
- iImputation using median time to event in reference group for patients with non-informative censoring and observation time less than median time in reference.

Finally, the tipping point was established by adding first EAC-confirmed MACEs to the IDeg group until the tipping point (i.e., upper limit of the one-sided 95% CI for hazard ratio > 1.3) was reached. Each added EAC-confirmed MACE was assumed to have an onset date on the day following the patient's end-of-trial date.

SWITCH (Studies 3995 and 3998)

Analyses of all end points were based on the FAS. Efficacy end points and patient-reported outcomes were summarized using the FAS.

Multiplicity

In both SWITCH studies, before testing the primary end point, the secondary supportive efficacy end point ("Change from baseline in A1C after 32 weeks of treatment") was tested for noninferiority as a prerequisite for testing the primary end point. The analysis was made for each treatment period separately. Analysis was based on a mixed model for repeated measurement; treatment, sex, region, pre-trial insulin treatment regimen, visit, and dosing time were fixed effects, and age and baseline A1C were covariates.

Noninferiority was considered confirmed if the upper bound of the two-sided 95% CI for A1C was equal to or below 0.40% or if the *P* value for the one-sided test of the null hypothesis (treatment difference > 0.40%) against the alternative hypothesis (treatment difference ≤ 0.40%) was less than 2.5% (IDeg once daily + insulin aspart [IAsp] minus IGlar once daily + IAsp).

Upon confirmation of noninferiority for both treatment periods, the primary end point was tested for noninferiority in SWITCH-1 and for superiority in SWITCH-2. The number of treatment-emergent severe or blood glucose–confirmed symptomatic hypoglycemic episodes during the maintenance period was analyzed using a Poisson model with patient as a random effect; treatment, period, sequence, and dosing time as fixed effects; and time exposure to trial drug in each counting period for hypoglycemic episodes as an offset.

Noninferiority was considered confirmed if the 95% CI for the rate ratio (IDeg followed by IGlar) was ≤ 1.10 or if the *P* value for the one-sided test of the null hypothesis (rate ratio > 1.10) against the alternative hypothesis (rate ratio ≤ 1.10) was less than 2.5%, where rate ratio is the estimated rate ratio of IDeg followed by IGlar. If noninferiority was confirmed, the superiority of IDeg followed by IGlar was investigated outside of the test hierarchy. Superiority was considered confirmed if the upper bound of the two-sided 95% CI was < 1.00.

Two confirmatory secondary end points were tested provided that superiority was confirmed for the primary end point. The confirmatory secondary end points are given below together with the direction of the test.

The following safety end points were assessed in the maintenance period (i.e., after 16 weeks of treatment) and in each treatment period (weeks 16 to 32 and weeks 48 to 64):

- number of treatment-emergent severe or blood glucose–confirmed symptomatic nocturnal hypoglycemic episodes
- proportion of patients with one or more severe hypoglycemic episodes.

The number of treatment-emergent severe or blood glucose–confirmed symptomatic nocturnal hypoglycemic episodes during the maintenance period was tested using the same model and sensitivity analyses as for the primary end point. In SWITCH-1, this was a noninferiority analysis, as for the primary outcome, and in SWITCH-2, this was a superiority analysis, as for the primary outcome.

The proportion of patients with one or more severe hypoglycemic episodes in the maintenance period was tested for superiority in both SWITCH studies using McNemar's test, in which the proportion of patients with severe hypoglycemic episodes treated with IDeg was tested against the proportion of patients with severe hypoglycemic episodes treated with IGlar and not treated with IDeg.

Missing Data

Patients who withdrew or dropped out of the trial were explored with the purpose of investigating whether, in particular, the population that dropped out before the first maintenance period was different from the population exposed in the first maintenance period, and whether there were any differences in dropout between the two treatments. This analysis was added to the statistical analysis plan.

In the primary analysis, patients who were not exposed in the second maintenance period contributed to the estimation of the treatment difference. This implies that these patients were assumed to behave like patients who were exposed in both maintenance periods; that is, a "missing completely at random" assumption. To investigate how this assumption influenced the primary results, a sensitivity analysis was added that included only patients who were exposed in both maintenance periods. This analysis follows the randomization principle in that the same patients were analyzed on both treatments. The treatment estimate from this analysis is an unbiased estimate in the subset of patients who were exposed to the maintenance period for both treatments, under the assumption that missing data for patients who drop out in the second maintenance period are missing at random. Since data from patients who were exposed only in the first maintenance period were excluded, the pragmatic effectiveness principle is violated.

BEGIN Trials (Studies 3770 [Plus Extension], 3585 [Plus Extension], 3583 [Plus Extension], 3579, 3580, 3672, 3586, 3587, 3944, 3668, 3943, and 3582 [Plus Extension])

A1C was analyzed centrally using a National Glycohemoglobin Standardization Program–certified method. The primary objective in all the therapeutic confirmatory trials was to confirm the efficacy of IDeg with respect to glycemic control as measured by change in A1C from baseline to end of trial between IDeg and an active comparator. The primary end point was analyzed using an analysis of variance method with treatment, antidiabetes therapy at screening, sex, and region as fixed factors, and age and baseline A1C as covariates. In the three-arm trials, the primary analysis was IDeg-Flex versus the comparator IGlar. It is not clear how multiplicity was adjusted for when the IDeg-Flex group was compared with the IDeg group.

All efficacy analyses, as well as analyses of hypoglycemia and body weight, were based on the FAS and followed the intention-to-treat principle, with patients contributing to the evaluation "as randomized." Unless otherwise specified, missing values (including intermittent missing values) were imputed using the last observation carried forward (LOCF) method as recommended for its transparency in the FDA guidance. Both baseline and post-baseline values were used for LOCF, in line with the intention-to-treat principle. As adherence to the intention-to-treat principle could bias the results toward null (i.e., no difference between treatments), the noninferiority assessments for A1C were also confirmed using a per-protocol analysis set, which included only patients treated for at least 12 weeks with a valid post-baseline A1C assessment. In addition, a post hoc analysis was made including only patients who completed the trial.

With the exception of Studies 3580 and 3944, all trials were noninferiority trials, and efficacy was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment difference for A1C (IDeg versus comparator) was ≤ 0.4%. This limit — which, according to the manufacturer, is in agreement with the FDA guidance on diabetes — has been used in previous submissions for other insulin products (NovoRapid/NovoLog, NovoMix, and Levemir). Study 3580 tested the superiority of IDeg to sitagliptin, and Study 3944 tested the superiority of IDeg to placebo.

There were five extensions among the BEGIN trials. All three studies in T1DM had extensions, as did T2DM Studies 3579 (insulin-naive) and 3582 (basal-bolus). In all cases, the primary objective of the extensions was to assess safety and tolerability; therefore, they focused on outcomes such as hypoglycemia, adverse events, body weight, and insulin dose, which were all considered to be primary end points. The extensions did not have a primary efficacy variable. The data from the core studies and extensions were to be combined and analyzed as one trial using the original baseline values from core trials. This combined data set was to be the basis for derivation, analyses, and presentation of end points. An additional analysis set, the extension trial set, was reported for efficacy analyses.

Data from study site 109 in Study 3582 was excluded from the analysis due to concerns about the quality of the data after an audit.

Multiplicity

The overall type I error rate was controlled using a hierarchical testing procedure. Hence, if noninferiority was confirmed for the primary end point (superiority in Studies 3580 and 3944), the therapeutic confirmatory trials (except for Studies 3668 and 3770) aimed at demonstrating superiority for a number of confirmatory secondary end points, ordered on

the basis of their clinical relevance within the respective treatment regimens and populations investigated. Consequently, superiority could be confirmed only for end points where all previous hypotheses had been confirmed, and the term “superior” is used solely if statistical superiority was confirmed based on hierarchical testing. If superiority was not confirmed, the result was considered to have the same level of evidence as the remaining, non-confirmatory end points.

Missing Data

Type 1 Diabetes Mellitus

Missing values were imputed by LOCF for all end points. To assess the sensitivity of the LOCF method on the conclusion from the analysis of the primary A1C analysis, two sensitivity analyses were performed. The repeated measurement model addressed whether the inclusion of the A1C values at all scheduled visits in the model would provide different results versus the simpler approach in the primary analysis, where only baseline information and the last A1C measurement were included.

All observed A1C measurements available post-randomization at scheduled measurement times were also to be analyzed in a linear mixed model using an unstructured residual covariance matrix (if possible). This approach relies on the assumption that data are missing at random according to the taxonomy defined by Rubin. The results were to be compared against the results of the LOCF method for dealing with missing data. Any marked difference concerning treatment differences between the missing-at-random approach and the LOCF approach was to be commented upon in the clinical trial report

The per-protocol analysis addressed whether the LOCF from patients withdrawing early in the trial (before the A1C measurement had stabilized) or patients randomized in error (not necessarily fulfilling all inclusion and exclusion criteria) influenced the conclusion. The conclusions from these analyses were very similar and resulted in the same conclusion as the primary analysis.

Type 2 Diabetes Mellitus

For studies in T2DM, missing data were accounted for in a similar manner to the studies in T1DM. In Study 3582, an additional sensitivity analysis was performed that addressed the impact of the patients from site 109 who were removed from the FAS.

Analysis Populations

DEVOTE

The following analysis sets were defined in the protocol:

- FAS: All randomized patients. The statistical evaluation of the FAS followed the intention-to-treat principle. Patients were to contribute to the evaluation “as randomized.”
- Per-protocol analysis set: This included all patients who had been continuously on the investigational medicinal product the first three months after randomization, as well as those who had an EAC-confirmed MACE within the first three months and took at least one dose of the investigational medicinal product before the event.

No safety analysis set was defined because safety was analyzed using the FAS. All analyses were based on the FAS population, with the exception of one sensitivity analysis of the primary end point that used the per-protocol population.

SWITCH

The following analysis sets were defined in accordance with the ICH E9 guidance:

- FAS: All randomized patients. In exceptional cases, patients from the FAS could be eliminated. In such cases, the elimination was to be justified and documented. The statistical evaluation of the FAS would follow the intention-to-treat principle and patients would contribute to the evaluation “as randomized.”
- Safety analysis set: All patients receiving at least one dose of the investigational product or its comparator. Patients in the safety set would contribute to the evaluation “as treated.”
- Completer analysis set: All patients who complete both treatment periods. If a patient withdrew during follow-up after the second treatment period, the patient was considered a completer.

Type 1 Diabetes Mellitus (Studies 3585, 3583, and 3770) and Type 2 Diabetes Mellitus (Studies 3579, 3580, 3586, 3672, 3944, 3587, 3668, and 3943)

The following analysis sets were defined in accordance with the ICH-E9 guidance (International Conference on Harmonization, Guideline on Statistical Principles for Clinical Trials, E9):

- FAS: All randomized patients. In exceptional cases, patients from the FAS could be eliminated. In such cases, the elimination was to be justified and documented. The statistical evaluation of the FAS was to follow the intention-to-treat principle, and patients were to contribute to the evaluation “as randomized.”
- Per-protocol analysis set: Patients without any major protocol violations that may have affected the primary end point. Moreover, patients must have been exposed to the investigational product or its comparator for more than 12 weeks and must have had a valid assessment necessary for deriving the primary end point. Patients in the per-protocol set were to contribute to the evaluation “as treated.”
- Safety analysis set: All patients who received at least one dose of the investigational product or its comparator. Patients in the safety set were to contribute to the evaluation “as treated.”

Patient Disposition

The proportion of participants withdrawing varied greatly between studies, with the highest withdrawal rates seen in the SWITCH studies, ranging between 18% and 23% between groups, and the lowest in DEVOTE, around 2% (Table 20). Proportions of withdrawals above 20% were also seen in studies 3579 (22%) and 3580 (24%), although no differences in the proportion of withdrawals were evident between groups (Table 22). The largest difference in proportion of withdrawals was in Study 3944, with the IDeg + liraglutide group having a much lower proportion than the placebo + liraglutide group (8% versus 24%, respectively) (Table 23). In Study 3770, there was a numerically higher proportion of withdrawals in both IDeg groups versus IGlar (16% in each IDeg group versus 7% in IGlar) (Table 21).

Table 20: Patient Disposition — DEVOTE, SWITCH-1, and SWITCH-2

	DEVOTE		SWITCH-1		SWITCH-2	
	Degludec	Glargine	IDeg/IGlar	IGlar/IDeg	IDeg/IGlar	IGlar/IDeg
Screened, N	8,205		634		1,000	
Screen failure	561		133			
Randomized, N (%)	3,818 (100)	3,819 (100)	249 (100)	252 (100)	361 (100)	360 (100)
Randomized and treated, N (%)			249 (100)	251 (99.6)	356 (98.6)	357 (99.2)
Discontinued, N (%)	76 (2.0)	72 (1.9)	49 (19.7)	57 (22.6)	77 (21.3)	63 (17.5)
AE	0	1 (0.0)	11 (4.4)	10 (4.0)	9 (2.5)	11 (3.1)
Lack of efficacy	1 (0.0)	1 (0.0)	0	1 (0.4)	2 (0.6)	2 (0.6)
Lost to follow-up	4 (0.1)	1 (0.0)	6 (2.4)	7 (2.8)	15 (4.2)	5 (1.4)
Protocol violation			7 (2.8)	10 (4.0)	25 (6.9)	20 (5.6)
WD by patient			25 (10.0)	25 (9.9)	26 (7.2)	26 (7.2)
Other	15 (0.4)	19 (0.5)	0 (0.0)	1 (0.4)	2 (0.6)	0 (0.0)
Pregnancy			0 (0.0)	3 (1.2)		
Hypoglycemia	1 (0.0)	1 (0.0)				
Not specified	55 (1.4)	49 (1.3)				
Replaced			23 (9.2)	19 (7.5)	26 (7.2)	22 (6.1)
WD excluding replacement			26 (10.4)	38 (15.1)	51 (14.1)	41 (11.4)
FAS, N (%)	3,818 (100)	3,819 (100)	249 (100)	252 (100)	360 (100)	360 (100)
Per-protocol, N (%)	3,561 (93.3)	3,555 (93.1)	200 (80.3)	195 (77.4)	283 (78.4)	297 (82.5)
Safety, N (%)	-	-	249 (100.0)	251 (99.6)	356 (99)	357 (99)

AE = adverse event; FAS = full analysis set; IDeg/IGlar = insulin degludec followed by insulin glargine; IGlar/IDeg = insulin glargine followed by insulin degludec; WD = withdrawal.

Source: Clinical Study Reports for DEVOTE,[6] SWITCH-1, and SWITCH-2.[13,14]

Table 21: Patient Disposition — Type 1 Diabetes Mellitus (Studies 3770, 3583, and 3585 + Extensions)

	Studies 3770 and 3770-Ext			Studies 3583 and 3644 (Ext)		Studies 3585 and 3725 (Ext)	
	IDeg-Flex	Degludec	Glargine	Degludec	Glargine	Degludec	Detemir
Screened, N	549			722		512	
Screen failure	56			93		56	
Randomized, N (%)	164 (100)	165 (100)	164 (100)	472 (100)	157 (100)	303 (100)	153 (100)
Randomized and treated, N (%)	164 (100)	165 (100)	161 (98.2)	472 (100)	154 (98.1)	301 (99.3)	152 (99.3)
Discontinued, n (%)	26 (15.9)	26 (15.8)	12 (7.3)	68 (14.4)	20 (12.7)	20 (6.6)	15 (9.8)
AE	5 (3.0)	4 (2.4)	1 (0.6)	12 (2.5)	2 (1.3)	3 (1.0)	1 (0.7)
Lack of efficacy	2 (1.2)	1 (0.6)	1 (0.6)	2 (0.4)	0 (0.0)	0 (0.0)	2 (1.3)
Lost to follow-up	-	-	-	-	-	-	-
Protocol violation	6 (3.7)	2 (1.2)	4 (2.4)	11 (2.3)	2 (1.3)	3 (1.0)	4 (2.6)
Other	7 (4.3)	13 (7.9)	4 (2.4)	28 (5.9)	13 (8.3)	8 (2.6)	5 (3.3)
WD criteria	6 (3.7)	6 (3.6)	2 (1.2)	15 (3.2)	3 (1.9)	6 (2.0)	3 (2.0)
Completed main trial, n (%)	138 (84.1)	139 (84.2)	152 (92.7)	404 (85.6)	137 (87.3)	283 (93.4)	138 (90.2)
Completed main trial not screened for extension	38 (11.6)		19 (11.6)	51 (10.8)	18 (11.5)	35 (11.6)	16 (10.5)
Completed main trial screening failure in				2 (0.4)	1 (0.6)	0	0

	Studies 3770 and 3770-Ext			Studies 3583 and 3644 (Ext)		Studies 3585 and 3725 (Ext)	
	IDeg-Flex	Degludec	Glargine	Degludec	Glargine	Degludec	Detemir
extension							
Included in extension, n (%)	239 (72.6)		133 (81.1)	351 (74.4)	118 (75.2)	248 (81.8)	122 (79.7)
Completed extension				330 (69.9)	113 (72.0)	242 (79.9)	115 (75.2)
WD during extension	16 (4.9)		11 (6.7)	21 (4.4)	5 (3.2)	6 (2.0)	7 (4.6)
AE	0 (0.0)		1 (0.6)	3 (0.6)	2 (1.3)	1 (0.3)	1 (0.7)
Ineffective therapy	2 (0.6)		0 (0.0)	1 (0.2)	0	0	0
Non-compliance	5 (1.5)		2 (1.2)	1 (0.2)	2 (1.3)	-	2 (1.3)
WD criteria	2 (0.6)		4 (2.4)	5 (1.1)	0	2 (0.7)	2 (1.3)
Other	7 (2.1)		4 (2.4)	11 (2.3)	1 (0.6)	3 (1.0)	2 (1.3)
FAS, N (%)	164 (100)	165 (100)	164 (100)	472 (100)	157 (100)	302 (99.7)	153 (100)
Per-protocol, N (%)	141 (86.0)	152 (92.1)	156 (95.1)	448 (94.9)	147 (93.6)	291 (96.0)	144 (94.1)
Safety, N (%)	164 (100)	165 (100)	161 (98.2)	472 (100)	154 (98.1)	301 (99.3)	152 (99.3)
Extension trial set (%)	239 (72.6)		133 (81.1)	351 (74.4)	118 (75.2)	248 (81.8)	122 (79.7)

AE = adverse event; IDeg-Flex = insulin degludec flexible dosing; FAS = full analysis set; WD = withdrawal.

Source: Clinical Study Reports for studies 3770 and 3770-ext,[15,31] 3583,[4] 3644,[32] 3585,[16] and 3725.[33]

Table 22: Patient Disposition — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3579, 3643, 3586, 3672, and 3580)

	Studies 3579 and 3643		Study 3586		Study 3672		Study 3580	
	Degludec	Glargine	Degludec	Glargine	Degludec	Glargine	Degludec	DPP-4
Screened, N	1,597		579		697		724	
Screen failure	567		144		237		266	
Randomized, N (%)	773 (100)	257 (100)	289 (100)	146 (100)	230 (100)	230 (100)	229 (100)	229 (100)
Exposed, N (%)	766 (99)	257 (100)	284 (98.3)	146 (100)	228 (99)	228 (99)	226 (98.7)	228 (99.6)
Discontinued, N (%)	166 (21.5)	60 (23.3)	31 (10.7)	10 (6.8)	30 (13.0)	29 (12.6)	55 (24.0)	55 (24.0)
AE	20 (2.6)	5 (1.9)	2 (0.7)	3 (2.1)	5 (2.2)	4 (1.7)	9 (3.9)	2 (0.9)
Lack of efficacy	7 (0.9)	2 (0.8)	1 (0.3)	0 (0.0)	0 (0.0)	2 (0.9)	0 (0.0)	1 (0.4)
Lost to follow-up	-	-	-	-				
Protocol violation	46 (6.0)	18 (7.0)	3 (1.0)	2 (1.4)	5 (2.2)	2 (0.9)	7 (3.1)	12 (5.2)
Other	84 (10.9)	30 (11.7)	12 (4.2)	3 (2.1)	17 (7.4)	12 (5.2)	36 (15.7)	35 (15.3)
WD criteria	9 (1.2)	5 (1.9)	13 (4.5)	2 (1.4)	3 (1.3)	9 (3.9)	3 (1.3)	5 (2.2)
Completed main trial not screened for extension	55 (7.1)	23 (8.9)	-	-	-	-	-	-
Completed main trial screening failure in extension	1 (0.1)	0	-	-	-	-	-	-
Included in extension	551 (71.3)	174 (67.7)	-	-	-	-	-	-
Completed extension	505 (65)	154 (60)	-	-	-	-	-	-
WD during extension	46 (6.0)	20 (7.8)	-	-	-	-	-	-
AE	12 (1.6)	5 (1.9)	-	-	-	-	-	-
Ineffective therapy	3 (0.4)	1 (0.4)	-	-	-	-	-	-
Non-compliance	2 (0.3)	4 (1.6)	-	-	-	-	-	-
WD criteria	6 (0.8)	3 (1.2)	-	-	-	-	-	-

	Studies 3579 and 3643		Study 3586		Study 3672		Study 3580	
	Degludec	Glargine	Degludec	Glargine	Degludec	Glargine	Degludec	DPP-4
Other	23 (3.0)	7 (2.7)	-	-	-	-	-	-
FAS, N (%)	773 (100)	257 (100)	289 (100.0)	146 (100.0)	228 (99.1)	229 (99.6)	225 (98.3)	222 (96.9)
Per-protocol, N (%)	665 (86)	221 (86)	263 (91.0)	142 (97.3)	201 (87.4)	212 (92.2)	182 (79.5)	182 (79.5)
Safety, N (%)	766 (99)	257 (100)	284 (98.3)	146 (100.0)	228 (99.1)	228 (99.1)	226 (98.7)	228 (99.6)
Extension trial set, N (%)	551 (71.3)	174 (67.7)	-	-	-	-	-	-

DPP-4 = dipeptidyl peptidase-4; FAS = full analysis set; WD = withdrawal.

Source: Clinical Study Reports for studies 3579,[17] 3643,[34] 3586,[20] 3672,[19] and 3580.[18]

Table 23: Patient Disposition — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3587 and 3944)

	Study 3587		Study 3944	
	Degludec	Glargine	Deg + Lira	Pla + Lira
Screened, N	1,168		1,504	
Screen failure	335		534	
Entered run-in	-		970	
Ineligible	-		624	
Randomized, N (%)	555 (100)	278 (100)	174 (100)	172 (100)
Exposed, N (%)	553 (99.6)	278 (100)	173 (99.4)	170 (98.8)
Discontinued, N (%)	32 (5.8)	24 (8.6)	14 (8)	41 (24)
AE	3 (1)	3 (1)	5 (3)	3 (2)
Withdrew informed consent	15 (3)	12 (4)		
Lost to follow-up	4 (1)	2 (1)		
Non-compliance	3 (1)	3 (1)	3 (2)	5 (3)
Other	6 (1)	4 (1)	5 (3)	29 (17)
WD criteria	1 (< 1)	0 (0)	1 (1)	4 (2)
FAS, N (%)	555 (100)	278 (100)	174 (100)	172 (100)
Per-protocol, N (%)	538 (96.9)	266 (95.7)	167 (96.0)	153 (89.0)
Safety, N (%)	553 (99.6)	278 (100)	173 (99.4)	170 (98.8)

AE = adverse event; Deg = degludec; FAS = full analysis set; Lira = liraglutide; Pla = placebo; WD = withdrawal.

Source: Clinical Study Reports for Studies 3587[21] and 3944.[22]

Table 24: Patient Disposition — Type 2 Diabetes Mellitus, Basal Insulin (Studies 3668 and 3943)

	Study 3668			Study 3943	
	IDeg-Flex	Degludec	Glargine	IDeg/IGlar	IGlar/IDeg
Screened, N	946			235	
Screen failure	259			90	
Randomized, N (%)	229 (100)	228 (100)	230 (100)	73 (100)	72 (100)
Randomized and treated, N (%)	229 (100)	226 (100)	230 (100)	73 (100)	72 (100)
Discontinued, N (%)	26 (11.4)	24 (10.5)	27 (11.7)	4 (6)	6 (8)
AE	2 (0.9)	1 (0.4)	2 (0.9)	1 (1)	0
Lack of efficacy	2 (0.9)	2 (0.9)	1 (0.4)	-	-
Non-compliance	-	-		1 (1)	2 (3)
WD criteria	5 (2.2)	4 (1.8)	4 (1.7)	0 (0)	1 (1)
Protocol violation	3 (1.3)	3 (1.3)	3 (1.3)	-	-
Other	14 (6.1)	14 (6.1)	17 (7.4)	2 (3)	3 (4)
FAS, N (%)	229 (100)	228 (100)	230 (100)	73 (100)	72 (100)
Per-protocol, N (%)	211 (92.1)	207 (90.8)	210 (91.3)	67 (91.8)	64 (88.9)
Safety, N (%)	229	226	230	73 (100)	72 (100)

AE = adverse event; IDeg-Flex = insulin degludec flexible dosing; FAS = full analysis set; IDeg/IGlar = insulin degludec followed by insulin glargine; IGlar/IDeg = insulin glargine followed by insulin degludec; WD = withdrawal.

Source: Clinical Study Reports for studies 3668[23] and 3943.[24]

Table 25: Patient Disposition — Type 2 Diabetes Mellitus, Basal-Bolus (Studies 3582 and 3667)

	Studies 3582 and 3667	
	Degludec	Glargine
Screened, N	1,440	
Screen failure	434	
Randomized, N (%)	755 (100)	251 (100)
Randomized and treated, N (%)	753 (99.7)	251 (100)
Discontinued after randomization, N (%)	137 (18.1)	40 (15.9)
AE	31 (4.1)	9 (3.6)
Lack of efficacy	3 (0.4)	0 (0.0)
Lost to follow-up		
Protocol violation/nonadherence to protocol	23 (3.0)	12 (4.8)
Met WD criteria	8 (1.1)	2 (0.8)
Other	72 (9.5)	17 (6.8)
Completed main trial, N (%)	618 (81.9)	211 (84.1)
Completed main trial not screened for extension, N (%)	52 (6.9)	20 (8.0)
Completed main trial screening failure in extension, N (%)	0 (0.0)	0 (0.0)
Included in extension, N (%)	566 (75.0)	191 (76.1)
Completed extension, N (%)	539 (71.4)	183 (72.9)
WD during extension	27 (3.6)	8 (3.2)
AE	4 (0.5)	
Ineffective therapy	1 (0.1)	1 (0.4)
Non-compliance	5 (0.7)	
WD criteria	6 (0.8)	2 (0.8)

	Studies 3582 and 3667	
Other	11 (1.5)	5 (2.0)
FAS, N (%)	744 (98.5)	248 (98.8)
PP, N (%)	694 (91.9)	233 (92.8)
Safety, N (%)	753 (99.7)	251 (100)
Extension trial set, N (%)	566 (75.0)	191 (76.1)

AE = adverse event; FAS = full analysis set; PP = per-protocol; WD = withdrawal.

Source: Clinical Study Reports for studies 3582[25] and 3667.[35]

Table 26: Exposure to Study Treatments — Mean

Study	Duration	Glargine Exposure Mean (SD), Years	Comparator Exposure Mean (SD), Years
DEVOTE	NA	1.78 (0.49)	1.76 (0.52)
SWITCH-1	32 weeks	0.57 (0.13)	0.57 (0.14)
SWITCH-2	32 weeks	0.58 (0.12)	0.58 (0.13)
T1DM			
3770[a]	26 weeks	0.44 (0.14) 0.46 (0.11)	0.49 (0.07)
3770-ext	52 weeks	0.82 (0.33)	0.89 (0.24)
3585	26 weeks	0.48 (0.07)	0.47 (0.09)
3725-ext	52 weeks	0.91 (0.24)	0.88 (0.27)
3583	52 weeks	0.92 (0.23)	0.94 (0.20)
3644-ext	104 weeks	1.66 (0.61)	1.70 (0.57)
T2DM, Insulin-Naive			
3579	52 weeks	0.87 (0.28)	0.85 (0.30)
3643-ext	104 weeks	1.58 (0.69)	1.50 (0.72)
3580	26 weeks	0.45 (0.12)	0.43 (0.15)
3672	26 weeks	0.46 (0.11)	0.47 (0.10)
3586	26 weeks	0.47 (0.10)	0.48 (0.07)
3587	26 weeks	0.5 (0.1)	0.5 (0.1)
3944	26 weeks	0.48 (0.09)	0.44 (0.13)
T2DM, Basal Insulin			
3668[a]	26 weeks	0.46 (0.11) 0.46 (0.12)	0.46 (0.12)
3943	16 weeks	0.30 (0.03)	0.30 (0.04)
T2DM, Basal-Bolus			
3582	52 weeks	0.89 (0.26)	0.91 (0.23)
3667-ext	78 weeks	1.3 (0.4)	1.3 (0.4)

ext = extension; IDeg = insulin degludec; NA = not available; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Studies 3770 and 3668 contained two IDeg groups, one a flexible dosing group (IDeg-Flex) and the other a regular IDeg group; results are reported in this order.

Exposure was generally similar between groups among studies, with the largest difference in Study 3944, which is also the study with the largest difference in withdrawal rates between groups.

Table 27: Basal Insulin Dose

Study	Duration	Degludec Mean (SD), U	Comparator Mean (SD), U	Ratio, U	Ratio, U/kg
T1DM					
3770[a]	26 weeks	36 (26) 32 (25)	35 (21)	1.11	1.11
3770-ext	52 weeks	34 (26)	35 (23)	0.97	0.96
3585	26 weeks	25 (16)	29 (20)	0.88	0.87
3725-ext	52 weeks	26 (16)	31 (21)	0.83	0.82
3583	52 weeks	29 (17)	31 (18)	0.93	0.91
3644-ext	104 weeks	31 (19)	33 (20)	0.94	0.93
T2DM, Insulin-Naive					
3579	52 weeks	56 (39)	58 (34)	0.97	0.98
3643-ext					
3580	26 weeks	43 (28)	Sitagliptin	NA	NA
3672	26 weeks	59 (35)	63 (32)	0.95	0.94
3586	26 weeks	19 (13)	24 (17)	0.79	0.80
3587	26 weeks	40 (27)	39 (23)	1.03	0.98
3944	26 weeks	51 (28)	105 (45)	0.48	0.46
T2DM, Basal Insulin					
3668[a]	26 weeks	46 (32) 45 (31)	44 (26)	1.04 1.00	1.06 0.99
3943	16 weeks	157 (67)	152 (64)	1.04	1.04
T2DM, Basal-Bolus					
3582	26 weeks	74 (47)	67 (43)	1.09	1.08

ext = extension; IDeg = insulin degludec; NA = not available; SD = standard deviation; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Studies 3770 and 3668 contained two IDeg groups, one a flexible dosing group (IDeg-Flex) and the other a regular IDeg group; results are reported in this order.

Critical Appraisal

Internal Validity

All studies used an appropriate method of randomization using an interactive voice/Web response system with appropriate allocation concealment. Patient characteristics were generally well balanced in most studies, although in Study 3668 the baseline characteristics were not well balanced with respect to gender. With respect to blinding, only DEVOTE, SWITCH-1, and SWITCH-2, as well as Study 3944, were double blinded, and the insulins were provided in “visually identical” vials. All other studies were open labelled and therefore subject to bias, particularly for subjective outcomes such as HRQoL, which could be influenced by patient knowledge of their assigned treatment. A blinded EAC was employed in DEVOTE, and an interim analysis was prepared and submitted to the FDA.

The BEGIN studies that included an insulin comparator used a noninferiority design for testing the primary outcome (change from baseline to end of treatment in A1C), and all used the same margin for noninferiority of a change in A1C of 0.4%. The manufacturer provided a rationale for the choice of this noninferiority margin, and this rationale appeared to be reasonable. This margin is also suggested by the FDA, which considers an A1C reduction of > 0.3% to be clinically meaningful; therefore, a difference in A1C of 0.3 to 0.4% between treatments could be considered clinically significant.[36] Noninferiority was also tested for the

primary outcome in DEVOTE; again, the rationale of the margin for noninferiority was described and the margin appeared reasonable. The SWITCH studies employed a noninferiority design in a hierarchy in order to determine testing of the primary outcome. In both studies, noninferiority for change from baseline in A1C, a secondary end point, had to be met before the primary end point and subsequent secondary end points in the hierarchy were tested.

A hierarchical testing procedure was employed to account for type I error in all studies that included confirmatory secondary end points, and the hierarchy was adhered to. The studies that did not include confirmatory secondary end points were Studies 3770, 3668, 3943, and 3944.

In the SWITCH-1 study, a per-protocol sensitivity analysis of the primary end point, a test of noninferiority, does not appear to have been conducted, as a per-protocol population was not defined in the study. The use of a per-protocol population is a recommended approach for noninferiority trials; thus, differences between the groups could have been masked, particularly given the high withdrawal rates in these studies.

With the exception of DEVOTE, no studies conducted a true intention-to-treat analysis; however, the small number of participants excluded from the main analysis is unlikely to have biased results.

The proportion of participants withdrawing varied greatly between studies, with the highest withdrawal rates seen in the SWITCH studies, ranging between 18% and 23% between groups. The direction of bias is confounded by the crossover design; however, given the high proportion of withdrawals, it is likely that the results were affected in some way, as the composition of the original randomized population would have been altered significantly throughout the trial. Proportions of withdrawals above 20% were also seen in studies 3579 (22%) and 3580 (24%), although generally no differences in proportion of withdrawals were evident between groups. The largest difference in proportion of withdrawals was in Study 3944, with the IDeg + liraglutide group having a much lower proportion than the placebo + liraglutide group (8% versus 24%, respectively). In Study 3770, there was a numerically higher proportion of withdrawals in both IDeg groups versus IGlar (16% in each, versus 7%). A high proportion of withdrawals may understate important outcomes such as hypoglycemic events, for example; and a higher proportion of withdrawals in one group versus another may bias results in favour of the group with more withdrawals, as they have less exposure to risk of hypoglycemia. Additionally, extensive withdrawals are a concern, given the noninferiority study designs employed across the studies.

The included studies typically accounted for missing data using an LOCF approach. Sensitivity analyses were also performed and appeared to support the results of the primary analysis. The LOCF approach can introduce bias into the results, and the risk of bias would be expected to increase with higher proportions of withdrawals and when there are differential withdrawals between groups within studies; both of these phenomena were seen among the included studies. The fact that the sensitivity analyses supported the conclusions of the LOCF results does allay some concern about the use of this approach for the imputation of missing data; however, a major assumption in the sensitivity analysis is that the data were missing at random, which is rarely the case and could also bias the results. The DEVOTE study, which was an event-driven study, employed a tipping-point analysis to account for missing data due to early withdrawals.

All studies employed a treat-to-target design with respect to dosing; therefore, differences in A1C would not be expected. This approach is recommended by the FDA for assessing differences in safety, tolerability, and clinical utility when insulin dosing and efficacy are maximized. However, these studies have limited utility for evaluating treatment efficacy.

External Validity

There were numerous clinical trials included in this review, with representation across the globe. Across all the included studies, there was a relatively low proportion of Indigenous participants (< 1% across the studies). The consistent majority of participants were Caucasian, with the exception of studies conducted in Asia. The lack of representation of Indigenous populations is a generalizability issue for Canada, given the relatively high proportion of Indigenous peoples diagnosed with diabetes mellitus. The clinical expert also noted that participants had a relatively long duration of disease at baseline, but did not note any other generalizability issues.

The trials largely focused on IGlar as a comparator, with IDet a comparator in only one of the studies. These are the two most commonly used intermediate-acting and long-acting insulins; however, NPH is still a popular option in some patients due to its lower cost. Thus, at least one trial comparing IDeg with NPH may have provided some additional useful insight into the comparative efficacy and harms of IDeg.

DEVOTE had the longest follow-up of all the included studies, with a mean exposure of approximately 24 months, and was powered to assess clinical outcomes in a T2DM population. However, there were no trials that similarly assessed diabetes complications in T1DM. Such trials would likely require a much longer follow-up than those included in this review. Other included trials focused on hypoglycemia as a primary outcome (SWITCH studies); the majority of included studies (BEGIN trials) focused on A1C, a widely used surrogate marker of disease in diabetes mellitus.

Two studies had extensive run-in periods, which can suggest enrichment of the study population. In Study 3943, the run-in period was to establish that the study population was one requiring high-dose insulin (participants were included only if they failed to reach target while on high-dose IGlar); this does seem appropriate, given the study objective. In Study 3944, participants were initiated on liraglutide in the 15-week run-in, which they then continued on in the study. The purpose of the study was to assess the combination of IDeg with liraglutide versus liraglutide alone (i.e., placebo plus liraglutide) in patients on metformin. A large proportion of participants were screened out during the run-in (in most cases due to failure to reach A1C targets); this was consistent with the planned 941 participants in the run-in versus 320 that were to be randomized. The study set a relatively narrow target for A1C (7.0% to 9.0%) for inclusion in the study. The rationale was that, as it was placebo-controlled, this narrow range would reduce the risk of intensified treatment being needed during the 26-week treatment phase.

HRQoL was consistently assessed in the included studies, but not as a confirmatory (i.e., high-priority) secondary outcome and not at all in the largest study, DEVOTE. Thus, HRQoL appears to have been given a lower priority in the included studies than would be expected based on the importance that patients place on this outcome.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below. See Appendix 5: Detailed Outcome Data for detailed efficacy data.

Morbidity

In DEVOTE, the primary composite cardiovascular outcome occurred in fewer IDeg than IGlar participants (8.5% versus 9.3% of participants), for a hazard ratio of 0.91 (95% CI, 0.78 to 1.06) (Table 32). The upper bound of the 95% CI was below 1.3, confirming noninferiority of IDeg relative to IGlar with respect to cardiovascular safety ($P < 0.001$). Other signs of morbidity where there was no difference between IDeg and IGlar were non-fatal myocardial infarction (hazard ratio 0.85; 95% CI, 0.68 to 1.06; $P = 0.15$), non-fatal stroke (hazard ratio 0.90; 95% CI, 0.65 to 1.23; $P = 0.50$), and unstable angina leading to hospitalization (hazard ratio 0.95; 95% CI, 0.68 to 1.31; $P = 0.74$).

Type 1 Diabetes Mellitus

There were few MACEs in any of the three studies in T1DM (Studies 3770, 3583, and 3585) and no clear differences between groups (Table 28).

Type 2 Diabetes Mellitus

There were few MACEs in most of the studies in T2DM and generally no differences between groups. One exception may have been Study 3643, the extension to Study 3579, where after 104 weeks, 3.8% of IDeg and 1.6% of IGlar-treated participants had a MACE (Table 28).

Table 28: BEGIN Trials — Patients With an Adjudicated Major Adverse Cardiovascular Event

Study	Comparator	Duration	Degludec n (%)	Comparator n (%)
T1DM				
3770	IGlar	26 weeks	0/0	0
3770-ext	IGlar	52 weeks	1 (0.3)	2 (1.2)
3585	IDet	26 weeks	0	0
3725-ext	IDet	52 weeks	1 (0.3)	0
3583	IGlar	52 weeks	3 (0.6)	1 (0.6)
3644-ext	IGlar	104 weeks	8 (1.7)	2 (1.3)
T2DM, Insulin-Naive				
3579	IGlar	52 weeks	12 (1.6)	2 (0.8)
3643-ext	IGlar	104 weeks	29 (3.8)	4 (1.6)
3580	Sitagliptin	26 weeks	3 (1.3)	3 (1.3)
3672	IGlar	26 weeks	4 (1.8)	3 (1.3)
3586	IGlar	26 weeks	2 (0.7)	0
3587	IGlar	26 weeks	4 (0.7)	2 (0.7)
3944	Placebo	26 weeks	0	0
T2DM, Basal Insulin				
3668	IGlar	26 weeks	1 (0.4)	2 (0.9)
3943	IGlar (crossover)	16 weeks	0	1 (0.7)
T2DM, Basal-Bolus				
3582	IGlar	52 weeks	18 (2.4)	4 (1.6)

Study	Comparator	Duration	Degludec n (%)	Comparator n (%)
3667-ext	IGlar	104 weeks	29 (3.9)	7 (2.8)

ext = extension; IDet = insulin detemir; IGlar = insulin glargine; MACE = major adverse cardiovascular event; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Health-Related Quality of Life

HRQoL was assessed using the SF-36 and TRIM (both TRIM-D and TRIM-HYPO) instruments.

HRQoL was not assessed in DEVOTE. In SWITCH-1 and SWITCH-2, there was no statistically significant difference between IDeg and IGlar in any of the SF-36 subscales. In SWITCH-2, the manufacturer noted that there was an improvement in TRIM-HYPO for IDeg versus IGlar; however, this outcome was not part of the confirmatory end points and no *P* values were reported (Table 33). There is no MCID for the TRIM-HYPO.

Type 1 Diabetes Mellitus

There were no consistent differences between IDeg and comparators in any of the subscales of the SF-36 or the TRIM-D instruments (Table 49, Table 50, and Table 51).

Type 2 Diabetes Mellitus

There were no consistent differences between IDeg and comparators in any of the subscales of the SF-36 or the TRIM-D instruments (Table 52, Table 53, Table 54, Table 55, Table 56, Table 57, and Table 58).

Glycated Hemoglobin

Type 1 Diabetes Mellitus

Change in A1C from baseline to end of treatment was the primary outcome of Studies 3770, 3583, and 3585. IDeg was noninferior to IGlar (Studies 3770 and 3583) and to IDet (Study 3585) in these studies. In Study 3583, the treatment difference between IDeg and IGlar was −0.01 (95% CI, −0.14 to 0.11), and in Study 3585, after 52 weeks, the treatment difference between IDeg and IDet was −0.09 (95% CI, −0.23 to 0.05). In Study 3770, only the flexible IDeg group was tested versus IGlar, and the treatment difference was 0.17 (95% CI, 0.04 to 0.30), which was judged to be noninferior, as the upper limit of the 95% CI for the estimated treatment difference was > 0 and ≤ 0.4% (Table 29).

Type 2 Diabetes Mellitus

Insulin-Naive

The primary outcome of Studies 3579, 3586, 3587, and 3672 was to test the noninferiority of IDeg to IGlar for the change from baseline to end of study in A1C. In Study 3579, the treatment difference after 52 weeks between IDeg and IGlar was 0.09 (95% CI, −0.04 to 0.22). In Study 3672, after 26 weeks, the treatment difference between IDeg and IGlar was 0.04 (95% CI, −0.11 to 0.19). In Study 3586 after 26 weeks, the treatment difference between IDeg and IGlar was 0.11 (95% CI, −0.03 to 0.24) (Table 29).

The primary outcome of Study 3580 was to test the superiority of IDeg to sitagliptin for the change from baseline to end of treatment (26 weeks) in A1C. IDeg was superior to sitagliptin, with a treatment difference of −0.43 (95% CI, −0.61 to −0.24; $P < 0.001$).

Study 3944 tested the superiority of IDeg + liraglutide to placebo + liraglutide. The combination of IDeg + liraglutide was found to be superior to placebo + liraglutide, with a treatment difference of −0.92 (95% CI, −1.10 to −0.75; *P* < 0.0001) (Table 29).

Insulin-Experienced (Basal Only)

Change from baseline to end of treatment (52 weeks) in A1C was the primary outcome of Study 3668. In Study 3668, after 52 weeks of therapy, IDeg was noninferior to IGlar, with a treatment difference after 52 weeks between IDeg and IGlar of 0.09 (95% CI, −0.04 to 0.22) (Table 29).

Insulin-Experienced (Basal-Bolus)

Change from baseline to end of treatment (26 weeks) in A1C was the primary outcome of Study 3582. In Study 3582, after 26 weeks of therapy, IDeg was noninferior to IGlar, with a treatment difference between IDeg and IGlar of 0.08 (95% CI, −0.05 to 0.21) (Table 29).

Table 29: Primary Outcome — Change From Baseline in Glycated Hemoglobin (BEGIN Trials)

Study	Duration	Comparator	Testing	Treatment Difference (95% CI)
T1DM				
3770	26 weeks	IGlar	Noninferior	0.17 (0.04 to 0.30)
3585	26 weeks	IDet	Noninferior	−0.09 (−0.23 to 0.05), *P* < 0.001
3583	52 weeks	IGlar	Noninferior	−0.01 (−0.14 to 0.11), *P* < 0.001
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Noninferior	0.09 (−0.04 to 0.22), *P* < 0.001
3580	26 weeks	Sitagliptin	Superior	−0.43 (−0.61 to −0.24), *P* < 0.001
3672	26 weeks	IGlar	Noninferior	0.04 (−0.11 to 0.19), *P* < 0.001
3586	26 weeks	IGlar	Noninferior	0.11 (−0.03 to 0.24) , *P* < 0.001
3587	26 weeks	IGlar	Noninferior	−0.05 (−0.18 to 0.08)
3944	26 weeks	Placebo	Superior	−0.92 (−1.10 to −0.75), *P* < 0.0001
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Noninferior	0.04 (−0.12 to 0.20)
3943	16 weeks	IGlar (crossover)	Noninferior	−0.06 (−0.21 to 0.09), *P* < 0.001
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Noninferior	0.08 (−0.05 to 0.21)

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: Positive values indicate smaller change from baseline for IDeg versus IGlar. *P* value reflects test for noninferiority, superiority.

Blood Glucose (Fasting)

Type 1 Diabetes Mellitus

Change in FPG was a confirmatory outcome in Studies 3585 and 3583, and as part of the statistical hierarchy, was not tested. In Study 3770, FPG was not part of a statistical hierarchy and also was not tested (Table 30).

Type 2 Diabetes Mellitus

Insulin-Naive

As part of the statistical hierarchy, the difference in change in FPG between IDeg and comparators was not tested, as testing had been halted by this time. In other studies where FPG was not part of the statistical hierarchy, *P* values were not reported (Table 30).

In Study 3580, IDeg was superior to sitagliptin for change from baseline in FPG, with a treatment difference of −2.17 mmol/L (95% CI, −2.59 to −1.74; $P < 0.001$). IDeg also elicited a statistically significant reduction in FPG versus placebo in Study 3944, with a treatment difference of –2.55 mmol/L (95% CI, −3.07 to −2.02; $P < 0.0001$) (Table 30).

Insulin-Experienced (Basal)

In Studies 3668 and 3943, change from baseline in FPG does not appear to have been part of the statistical hierarchy; therefore, no *P* values were reported (Table 30).

Insulin-Experienced (Basal-Bolus)

In Study 3582, IDeg was not shown to be superior to IGlar for change from baseline in FPG (Table 30).

Table 30: Key Secondary Outcome — Change in Fasting Plasma Glucose (BEGIN Trials)

Study	Duration	Comparator	Testing	Treatment Difference (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	−0.05 (−0.85 to 0.76)
3585	26 weeks	IDet	Halted	−1.66 (−2.37 to −0.95), *P* = NT
3583	52 weeks	IGlar	Halted	−0.33 (−1.03 to 0.36), *P* = NT
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Halted	−0.43 (−0.74 to −0.13), *P* = NT
3580	26 weeks	Sitagliptin	Superiority	−2.17 (−2.59 to −1.74), *P* < 0.001
3672	26 weeks	IGlar	Halted	−0.42 (−0.78 to −0.06), *P* = NT
3586	26 weeks	IGlar	Halted	−0.09 (−0.41 to 0.23), *P* = NT
3587	26 weeks	IGlar	Halted	−0.26 (−0.53 to 0.02), *P* = NT
3944	26 weeks	Placebo	Not in hierarchy	–2.55 (−3.07 to −2.02), *P* < 0.0001
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	−0.42 (−0.82 to −0.02)
3943	16 weeks	IGlar	Not in hierarchy	−0.77 (−1.39 to −0.15)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Superiority not shown	−0.29 (−0.65 to 0.06), *P* = 0.054

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; NT = not tested due to halting of testing due to hierarchy; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Blood Glucose (Variability)

Blood glucose variability was reported in the T1DM trials, and was part of the statistical hierarchy in studies 3585 and 3583; however, testing had been halted by this time, so no *P* value was reported (Table 31).

In the T2DM studies, blood glucose variability was part of the statistical hierarchy, but testing had been halted once this end point was reached, or the outcome was not part of the statistical hierarchy, and no *P* values were reported.

Table 31: Key Secondary Outcome — Blood Glucose Variability (BEGIN Trials)

Study	Duration	Comparator	Testing	Treatment Ratio, CV% (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	0.96 (0.84 to 1.07)
3585	26 weeks	IDet	Testing halted	1.02 (0.91 to 1.12), *P* = NT
3583	52 weeks	IGlar	Testing halted	0.96 (0.86 to 1.05), *P* = NT
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Testing halted	0.99 (0.92 to 1.06)
3580	26 weeks	Sitagliptin	Not in hierarchy	1.39 (1.26 to 1.52)
3672	26 weeks	IGlar	Testing halted	0.92 (0.84 to 1.01), *P* = NT
3586	26 weeks	IGlar	Testing halted	0.89 (0.80 to 0.99), *P* = NT
3587	26 weeks	IGlar	Testing halted	1.10 (1.02 to 1.18), *P* = NT
3944	26 weeks	Placebo	Not reported	NR
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	0.97 (0.88 to 1.06)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.89 (0.79 to 1.00)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Testing halted	0.94 (0.87 to 1.01), *P* = NT

CI = confidence interval; CV = coefficient of variation; IDet = insulin detemir; IGlar = insulin glargine; NT = not tested due to halting of testing due to hierarchy; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Table 32: Key Efficacy Outcomes — DEVOTE

	DEVOTE	
	Degludec N = 3,818	**Glargine N = 3,819**
Primary Composite Cardiovascular Outcome		
N (%)	325 (8.5)	356 (9.3)
HR (95% CI)[a]	0.91 (0.78 to 1.06)	
	Noninferiority met (*P* < 0.001)	
N (%) PP	286 (8.03)	314 (8.83)
HR (95% CI)[a]	0.904 (0.770 to 1.060), *P* = 0.214	
Subgroup: established CVD, n/N (%)	293/3,265 (8.97)	325/3,244 (10.02)
HR (95% CI)	0.887 (0.758 to 1.039)	
Risk factors for CVD	29/538 (5.39)	30/567 (5.29)
HR (95% CI)	1.034 (0.621 to 1.723)	
P value	*P* = 0.5742	
Expanded Composite Cardiovascular Outcome	386 (10.1)	419 (11.0)
HR (95% CI)[a]	0.92 (0.80 to 1.05), *P* = 0.22	
Death From Any Cause		

	DEVOTE	
	Degludec N = 3,818	**Glargine N = 3,819**
Deaths, n (%)	202 (5.3)	221 (5.8)
HR (95% CI)[a]	0.91 (0.76 to 1.11), *P* = 0.35	
Non-cardiovascular death, n (%)	66 (1.7)	79 (2.1)
HR (95% CI)[a]	0.84 (0.60 to 1.16), *P* = 0.28	
Cardiovascular death, n (%)	136 (3.6)	142 (3.7)
HR (95% CI)[a]	0.96 (0.76 to 1.21), *P* = 0.71	
Cardiovascular death excluding undetermined cause of death, n (%)	97 (2.5)	106 (2.8)
HR (95% CI)[a]	0.91 (0.69 to 1.20), *P* = 0.52	
Non-fatal myocardial infarction, n (%)	144 (3.8)	169 (4.4)
HR (95% CI)[a]	0.85 (0.68 to 1.06), *P* = 0.15	
Non-fatal stroke, n (%)	71 (1.9)	79 (2.1)
HR (95% CI)[a]	0.90 (0.65 to 1.23), *P* = 0.50	
Unstable angina leading to hospitalization, n (%)	71 (1.9)	74 (1.9)
HR (95% CI)[a]	0.95 (0.68 to 1.31), *P* = 0.74	
Severe hypoglycemia	187 (4.9)	252 (6.6)
Rate ratio[b] (95% CI)	0.60 (0.48 to 0.76), *P* < 0.001	
Frequency of severe hypoglycemia, n (%)		
≥ 1 event	187 (4.9)	252 (6.6)
Odds ratio (95% CI)[c]	0.73 (0.60 to 0.89), *P* < 0.001	
1 event	141 (3.7)	168 (4.4)
2 events	22 (0.6)	43 (1.1)
≥ 3 events	24 (0.6)	41 (1.1)
No events	3,631 (95.1)	3,567 (93.4)
A1C		
Mean (SD) baseline, %	8.4 (1.6)	8.4 (1.7)
Change from baseline to 24 months, estimated mean	−0.864	−0.872
Treatment difference (95% CI)[d]	0.008 (−0.050 to 0.066), *P* = 0.779	
FPG		
Mean (SD) baseline, mmol/L	9.4 (3.9)	9.6 (3.9)
Change from baseline to 24 months, estimated mean	−2.282	−1.882
Treatment difference (95% CI)[d]	−0.400 (−0.571 to −0.229), *P* < 0.001	

A1C = glycated hemoglobin; CI = confidence interval; CVD = cardiovascular disease; FPG = fasting plasma glucose; HR = hazard ratio; IDeg = insulin degludec; IGlar = insulin glargine; PP = per-protocol; SD = standard deviation; vs. = versus.

[a] Model is a Cox regression including treatment as only factor.

[b] Based on negative binomial regression with log-link function and log (duration of observation time) as offset; *P* value refers to two-sided test of rate ratio = 1.0.

[c] Odds ratio (IDeg vs. IGlar) based on logistic (binomial) regression with log-link function; *P* value refers to two-sided test of odds ratio = 1.0.

[d] Change from baseline to 24 months' visit analyzed using a mixed model for repeated measures within patients using an unstructured residual covariance matrix among visits at six, 12, and 24 months of study. Interactions between visit and treatment and between visit and baseline are included as fixed effects.

Source: CSR for DEVOTE.[6]

Table 33: Key Efficacy Outcomes — SWITCH-1 and SWITCH-2

	SWITCH-1		SWITCH-2	
	Degludec (N = 418)	**Glargine (N = 422)**	**Degludec (N = 632)**	**Glargine (N = 618)**
Mortality				
Deaths, n (%)	1 (0.2)	2 (0.4)	2 (0.3)	5 (0.8)
Morbidity, n (%)				
Adjudicated MACEs	3 (0.7)	3 (0.7)	12 (1.8)	15 (2.3)
Confirmed MACEs	2 (0.4)	3 (0.7)	8 (1.2)	9 (1.4)
HRQoL – SF-36 Scores				
Overall Physical				
Mean (SD) baseline	50.00 (8.62)	49.71 (8.80)	42.70 (10.13)	42.55 (10.17)
Mean (SD) change from baseline to end treatment	0.02 (6.28) N = 449	0.12 (5.86) N = 455	0.04 (7.51) N = 662	0.15 (7.21) N = 653
Physical Functioning				
Mean (SD) baseline	50.78 (9.24)	50.59 (9.55)	42.25 (11.43)	41.95 (11.57)
Mean (SD) change from baseline to end treatment	0.30 (6.99) N = 449	−0.12 (7.27) N = 455	−0.01 (8.98) N = 661	−0.12 (8.83) N = 653
Role Physical				
Mean (SD) baseline	50.54 (9.04)	50.29 (9.02)	43.49 (11.51)	43.71 (11.37)
Mean (SD) change from baseline to end treatment	−0.57 (7.59) N = 449	−0.19 (7.41) N = 455	−0.09 (9.07) N = 661	0.03 (8.76) N = 652
Bodily Pain				
Mean (SD) baseline	51.46 (10.13)	51.35 (10.03)	44.84 (10.82)	44.93 (10.92)
Mean (SD) change from baseline to end treatment	−0.09 (8.85) N = 449	−0.14 (8.32) N = 455	0.27 (9.28) N = 662	0.13 (9.57) N = 653
General Health				
Mean (SD) baseline	46.78 (9.71)	46.65 (9.59)	44.32 (9.56)	44.33 (9.62)
Mean (SD) change from baseline to end treatment	−0.26 (6.52) N = 449	−0.08 (6.13) N = 455	0.99 (8.62) N = 662	0.68 (8.30) N = 653
Overall Mental				
Mean (SD) baseline	50.70 (9.91)	50.87 (9.50)	49.13 (11.42)	49.70 (10.72)
Mean (SD) change from baseline to end treatment	−0.63 (8.58) N = 449	−0.98 (8.53) N = 455	0.25 (9.89) N = 662	−0.43 (9.55) N = 653
Vitality				
Mean (SD) baseline	51.14 (9.83)	51.48 (9.77)	49.45 (10.37)	49.68 (9.91)
Mean (SD) change from baseline to end treatment	−0.10 (7.48) N = 449	−0.94 (7.90) N = 455	0.13 (8.60) N = 662	−0.46 (8.48) N = 653
Social Functioning				
Mean (SD) baseline	51.19 (8.87)	50.58 (8.81)	46.50 (10.72)	47.08 (10.15)
Mean (SD) change from baseline to end treatment	−0.80 (7.43) N = 449	−0.37 (8.42) N = 455	0.07 (9.28) N = 662	−0.54 (9.53) N = 653
Role Emotional				
Mean (SD) baseline	50.27 (9.78)	50.31 (9.46)	44.45 (12.74)	45.02 (12.40)
Mean (SD) change from baseline to end	−0.40 (8.87)	−0.62 (8.23)	0.33 (11.82)	−0.40 (11.07)

	SWITCH-1		SWITCH-2	
	Degludec (N = 418)	**Glargine (N = 422)**	**Degludec (N = 632)**	**Glargine (N = 618)**
treatment	N = 449	N = 455	N = 662	N = 653
Mental Health				
Mean (SD) baseline	50.68 (9.62)	50.98 (9.35)	48.83 (10.88)	48.99 (10.57)
Mean (SD) change from baseline to end treatment	−0.48 (8.30) N = 449	−0.93 (8.46) N = 455	0.14 (9.49) N = 662	−0.01 (8.88) N = 653
TRIM-HYPO Scores				
Daily Function				
Mean (SD) baseline	31.1 (19.8)	31.2 (21.3)	10.3 (16.4)	8.8 (15.2)
Mean (SD) change from baseline to end treatment	1.9 (19.6) N = 432	0.8 (19.3) N = 442	−2.6 (16.6) N = 626	−0.2 (16.7) N = 617
Emotional Well-Being				
Mean (SD) baseline	32.3 (21.4)	31.9 (22.0)	10.2 (16.5)	8.4 (14.5)
Mean (SD) change from baseline to end treatment	2.4 (20.5) N = 432	2.2 (20.5) N = 443	−3.0 (16.4) N = 626	0.1 (17.0) N = 617
Diabetes Management				
Mean (SD) baseline	31.4 (20.2)	30.4 (19.8)	10.5 (16.3)	9.0 (15.2)
Mean (SD) change from baseline to end treatment	1.4 (19.7) N = 432	1.3 (19.6) N = 442	−2.9 (16.4) N = 625	0.0 (17.2) N = 616
Total				
Mean (SD) baseline	31.6 (19.2)	31.3 (19.8)	10.3 (15.9)	8.7 (14.4)
Mean (SD) change from baseline to end treatment	2.0 (18.3) N = 432	1.5 (18.2) N = 443	−2.8 (15.8) N = 626	−0.0 (16.1) N = 617
Sleep Disruption				
Mean (SD) baseline	37.2 (23.7)	33.5 (22.6)	9.8 (18.3)	7.9 (16.7)
Mean (SD) change from baseline to end treatment	−0.6 (20.9) N = 163	1.2 (21.6) N = 170	−2.8 (15.4) N = 351	−0.9 (18.3) N = 345
Work Productivity				
Mean (SD) baseline	21.2 (14.9)	21.0 (14.3)	5.1 (12.1)	4.0 (9.4)
Mean (SD) change from baseline to end treatment	0.5 (15.0) N = 257	0.4 (13.7) N = 247	−2.0 (11.5) N = 349	0.0 (12.7) N = 357
A1C				
A1C blood (%), LSM (SE) period 1[a]			7.08 (0.06) N = 326	6.98 (0.06) N = 327
A1C blood (%), LSM (SE) change from baseline, 32 weeks treatment	−0.76 (0.06)	−0.78 (0.07)	−0.49 (0.06)	−0.58 (0.06)
LSM difference (95% CI)	0.03 (−0.10 to 0.15) Noninferior		0.09 (−0.04 to 0.23) Noninferior	
A1C blood (%), LSM (SE) Period 2[a]			7.06 (0.05) N = 310	7.01 (0.05) N = 298
A1C blood (%), LSM (SE) change from baseline, 32 weeks' treatment	0.09 (0.06)	−0.02 (0.06)	0.06 (0.05)	0.00 (0.05)
LSM difference (95% CI)	0.11 (−0.00 to 0.23) Noninferior		0.06 (−0.07 to 0.18) Noninferior	

	SWITCH-1		SWITCH-2	
	Degludec (N = 418)	Glargine (N = 422)	Degludec (N = 632)	Glargine (N = 618)
FPG	IDeg/IGlar	IGlar/IDeg	IDeg/IGlar	IGlar/IDeg
Change in FPG (mmol/L), end of first treatment	−1.44 (5.31) N = 248	−1.30 (5.08) N = 252	−1.51 (3.16) N = 355	−1.22 (3.16) N = 358
Change in FPG (mmol/L), end of second treatment	1.14 (4.91) N = 208	−0.55 (4.78) N = 204	0.43 (3.06) N = 307	0.07 (2.92) N = 311

A1C = glycated hemoglobin; CI = confidence interval; FPG = fasting plasma glucose; HRQoL = health-related quality of life; IDeg/IGlar = insulin degludec followed by insulin glargine; IGlar/IDeg = insulin glargine followed by insulin degludec; LSM = least squares mean; MACE = major adverse cardiovascular event; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TRIM-HYPO = Treatment-Related Impact Measure — Hypoglycemic Events.

[a] Treatment period 1: All observed A1C measurements available post-randomization at scheduled measurement times for patients having exposure in maintenance period 1 are analyzed using a mixed model for repeated measures with treatment, sex, antidiabetes therapy at screening, visit, and dosing time as fixed effects, and age and baseline A1C as covariates. All fixed factors and covariates are nested within visit and an unstructured covariance matrix is specified. The denominator degrees of freedom are calculated using the Satterthwaite method. Treatment period 2: All observed A1C measurements available post-randomization at scheduled measurement times for patients having any A1C measurements after visit 34 are analyzed using the same model as for treatment period 1.

Harms

Only those harms identified in the review protocol (see the Objectives and Methods section) are reported here. See Appendix 5 for detailed harms data.

Table 34: Harms — BEGIN Trials

Study	Duration	Adverse Events, n (%)		Serious Adverse Events, n (%)		Withdrawal Due to Adverse Events, n (%)	
		IDeg	Comparator	IDeg	Comparator	IDeg	Comparator
T1DM							
3770[a]	26 weeks	111 (68) 125 (76)	116 (72)	9 (6) 7 (4)	8 (5)	5 (3) 4 (2)	1 (1)
3770-ext	52 weeks	268 (82)	134 (83)	25 (8)	12 (8)	9 (3)	2 (1)
3585	26 weeks	219 (73)	112 (74)	23 (8)	8 (5)	3 (1)	1 (1)
3725-ext	52 weeks	248 (82)	118 (78)	36 (12)	11 (7)	4 (1)	2 (1)
3583	52 weeks	397 (84)	128 (83)	49 (10)	17 (11)	12 (3)	2 (1)
3644-ext	104 weeks	413 (88)	137 (89)	71 (15)	29 (19)	15 (3)	4 (3)
T2DM, Insulin-Naive							
3579	52 weeks	572 (75)	182 (71)	62 (8)	26 (10)	20 (3)	5 (2)
3643-ext	104 weeks	617 (81)	198 (77)	116 (15)	41 (16)	12 (2)	5 (2)
3580	26 weeks	141 (62)	144 (63)	14 (6)	10 (4)	9 (4)	2 (1)
3672	26 weeks	147 (65)	156 (68)	15 (7)	10 (4)	5 (2)	4 (2)
3586	26 weeks	167 (59)	95 (65)	8 (3)	8 (6)	2 (1)	3 (2)
3587	26 weeks	293 (53)	161 (58)	6 (3)	10 (4)	3 (1)	3 (1)
3944	26 weeks	95 (55)	88 (52)	6 (4)	9 (5)	4 (2)	3 (2)
T2DM, Basal Insulin							
3668[a]	26 weeks	122 (53) 128 (57)	128 (56)	6 (3) 8 (4)	4 (2)	2 (1) 1 (< 1)	2 (1)
3943	16 weeks	45 (32)	50 (35)	4 (3)	4 (3)	0 (0)	1 (1)
T2DM, Basal-Bolus							
3582	52 weeks	610 (81)	199 (79)	112 (15)	40 (16)	31 (4)	9 (4)
3667-ext	104 weeks	630 (84)	208 (83)	139 (19)	53 (21)	35 (5)	9 (4)

ext = extension; IDeg = insulin degludec; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Studies 3770 and 3668 contained two IDeg groups: one a flexible dosing group (IDeg-Flex) and the other a regular IDeg group; results are reported in this order.

Adverse Events

There were no clear differences in the overall proportion of participants with an adverse event in DEVOTE or in the SWITCH studies. The most common adverse event was nasopharyngitis (Table 37).

In the BEGIN trials, in Study 3770, there was a numerically lower proportion of IDeg (68%) participants who were on a flexible dosing regimen who experienced an adverse event versus those on a regular IDeg (76%) regimen or on IGlar (72%) (Table 59). In Study 3586, 59% of IDeg-treated and 65% of IGlar participants experienced an adverse event (Table 64). Otherwise, there were no clear differences in the proportion of IDeg versus IGlar participants experiencing an adverse event in Study 3583 (or extension) or Study 3579 or extension (Study 3643), or between IDeg and IDet in Study 3585, while in the extension (Study 3725), 82% of IDeg and 78% of IDet participants had experienced an adverse event by 104 weeks There was no clear difference in the proportion of participants with an adverse event with IDeg compared with sitagliptin in Study 3580.

Serious Adverse Events

There were no clear differences between IDeg and IGlar in the proportion of participants experiencing a serious adverse event in DEVOTE or in the SWITCH studies (Table 37).

In the BEGIN trials, there was no clear difference in the proportion of participants with a serious adverse event between IDeg and IGlar (Table 34). In Study 3725, the extension to Study 3585, 12% of IDeg versus 7% of IDet participants had a serious adverse event. There was no clear difference in proportion of participants with a serious adverse event with IDeg compared with sitagliptin in Study 3580 or with IDeg + liraglutide versus placebo + liraglutide in Study 3944.

Withdrawals Due to Adverse Events

There were no clear differences in the proportion of participants who withdrew due to an adverse event in DEVOTE or in the SWITCH studies (Table 37). In the BEGIN trials, there were numerically more IDeg participants who withdrew due to an adverse event compared with sitagliptin (4% versus 1%) (Table 34).

Notable Harms

DEVOTE

In DEVOTE, the number of EAC-confirmed severe hypoglycemic episodes and the occurrence of at least one EAC-confirmed severe hypoglycemic episode within a patient were confirmatory secondary end points. The risk of a severe hypoglycemic event was lower in the IDeg treatment group compared with the IGlar treatment group, and this difference was statistically significant, with a rate ratio of 0.73 (95% CI, 0.60 to 0.89; $P < 0.001$) (Table 37).

SWITCH-1 and SWITCH-2

Severe or blood glucose–confirmed hypoglycemic episodes during the maintenance period (16 weeks into treatment) was the primary outcome of both SWITCH trials. In both trials, there was a statistically significant reduction in these episodes for IDeg versus IGlar, with a

treatment ratio of 0.89 (95% CI, 0.85 to 0.94; *P* < 0.0001) in SWITCH-1 and 0.70 (95% CI, 0.61 to 0.80) in SWITCH-2 (Table 37).

BEGIN trials

Confirmed hypoglycemic events, both overall and nocturnal events, were consistently reported across the BEGIN trials as confirmatory secondary end points. In two of three studies where it was tested in T1DM and in all four comparisons versus IGlar in T2DM, insulin-naive patients, IDeg was not shown to be superior to IGlar (five studies) or IDet (one study) (Table 35). The only study that reported a statistically significant decrease in the risk of hypoglycemia with IDeg versus comparator (IGlar) was Study 3582, with a treatment ratio of 0.82 (95% CI, 0.69 to 0.99; *P* = 0.018) (Table 35). Data were collected for this outcome in other studies but not as a confirmatory end point, and no *P* values were reported.

Table 35: Key Secondary Outcome — Confirmed Hypoglycemic Events (BEGIN Trials)

Study	Duration	Comparator	Testing	Treatment Ratio, Events/100 PYE (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	1.03 (0.85 to 1.26)
3585	26 weeks	IDet	Superiority not shown	0.98 (0.80 to 1.20), *P* = 0.431
3583	52 weeks	IGlar	Superiority not shown	1.07 (0.89 to 1.28), *P* = 0.758
T2DM, Insulin-Naive				
3579	52 weeks	IGlar	Superiority not shown	0.82 (0.64 to 1.04), *P* = 0.053
3580	26 weeks	Sitagliptin	Not in hierarchy	3.81 (2.40 to 6.05)
3672	26 weeks	IGlar	Superiority not shown	0.86 (0.58 to 1.28), *P* = 0.228
3586	26 weeks	IGlar	Superiority not shown	0.82 (0.60 to 1.11), *P* = 0.101
3587	26 weeks	IGlar	Superiority not shown	0.80 (0.59 to 1.10), *P* = 0.084
3944	26 weeks	Placebo	Not in hierarchy	4.67 (2.07 to 10.56)
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	1.03 (0.75 to 1.40)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.59 (0.39 to 0.90)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Superiority	0.82 (0.69 to 0.99), *P* = 0.018

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; PYE = patient-years of exposure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: *P* value reflects test for superiority.

Confirmed hypoglycemic episodes consisted of episodes of severe hypoglycemia as well as minor hypoglycemic episodes with a confirmed plasma glucose value of < 3.1 mmol/L. Hypoglycemic episodes were defined as nocturnal if the time of onset was between 00:01 a.m. and 05:59 a.m., inclusive. Hypoglycemic episodes occurring during sleep in the extended time range from 10:01 p.m. to 07:59 a.m. were also analyzed.

Table 36: Key Secondary Outcome — Confirmed Nocturnal Hypoglycemic Events (BEGIN Trials)

Study	Duration	Comparator	Testing	Treatment Ratio, Events/100 PYE (95% CI)
T1DM				
3770	26 weeks	IGlar	Not in hierarchy	0.60 (0.44 to 0.82)
3585	26 weeks	IDet	Superiority	0.66 (0.49 to 0.88), *P* = 0.002
3583	52 weeks	IGlar	Superiority	0.75 (0.59 to 0.96), *P* = 0.011
T2DM, Insulin-naive				
3579	52 weeks	IGlar	Not in hierarchy	0.64 (0.42 to 0.98)
3580	26 weeks	Sitagliptin	Not in hierarchy	1.93 (0.90 to 4.10)
3672	26 weeks	IGlar	Not in hierarchy	0.64 (0.30 to 1.37)
3586	26 weeks	IGlar	Testing halted	0.62 (0.38 to 1.04), *P* = NT
3587	26 weeks	IGlar	Not in hierarchy	0.77 (0.43 to 1.37)
3944	26 weeks	Placebo	Not in hierarchy	1.75 (0.24 to 12.71)
T2DM, Basal Insulin				
3668	26 weeks	IGlar	Not in hierarchy	0.77 (0.44 to 1.35)
3943	16 weeks	IGlar (crossover)	Not in hierarchy	0.66 (0.29 to 1.48)
T2DM, Basal-Bolus				
3582	52 weeks	IGlar	Not in hierarchy	0.75 (0.58 to 0.99)

CI = confidence interval; IDet = insulin detemir; IGlar = insulin glargine; NT = not tested due to halting of testing due to hierarchy; PYE = patient-years of exposure; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Note: *P* value reflects test for superiority.

Table 37: Harms — DEVOTE, SWITCH-1, and SWITCH-2

	DEVOTE		SWITCH-1		SWITCH-2	
	Degludec N = 3,818	**Glargine N = 3,819**	**Degludec N = 454**	**Glargine N = 460**	**Degludec N = 671**	**Glargine N = 665**
AEs						
Patients with > 0 AEs, N (%)	1,488 (39.0)	1,529 (40.0)	294 (64.8)	310 (67.4)	384 (57.2)	406 (61.1)
Most common AEs (≥ 5% in any group)						
Nasopharyngitis	NA	NA	68 (15.0)	61 (13.3)	50 (7.5)	41 (6.2)
Upper respiratory tract infection	NA	NA	29 (6.4)	39 (8.5)	44 (6.6)	37 (5.6)
Hypoglycemia	NA	NA	17 (3.7)	33 (7.2)	2 (0.3)	9 (1.4)
Most common severe AEs						
Hypoglycemia	NA	NA	15 (3.3)	27 (5.9)	2 (0.3)	7 (1.1)
Hypoglycemic unconsciousness	NA	NA	15 (3.3)	18 (3.9)	0	1 (0.2)
Hypoglycemic seizure	NA	NA	3 (0.7)	4 (0.9)	NA	NA
SAEs						
Patients with > 0 SAEs, N (%)	1,473 (38.6)	1,517 (39.7)	58 (12.8)	70 (15.2)	64 (9.5)	65 (9.8)
Most common SAE (≥ 1% in any group)						
Excluding severe hypoglycemia	1,451 (38.0)	1,489 (39.0)				
Hypoglycemia	64 (1.7)	49 (1.3)	17 (3.7)	33 (7.2)	2 (0.3)	9 (1.4)
Hypoglycemic unconsciousness			18 (4.0)	19 (4.1)	0	1 (0.2)
Hypoglycemic seizure			3 (0.7)	5 (1.1)	NA	NA
Cardiac arrhythmia	135 (3.5)	146 (3.8)	NA	NA	NA	NA
Acute myocardial infarction	98 (2.6)	115 (3.0)	NA	NA	NA	NA
Cardiac failure congestive	134 (3.5)	143 (3.7)	NA	NA	NA	NA
WDAEs						

	DEVOTE		SWITCH-1		SWITCH-2	
	Degludec N = 3,818	**Glargine N = 3,819**	**Degludec N = 454**	**Glargine N = 460**	**Degludec N = 671**	**Glargine N = 665**
WDAEs, N (%)	200 (5.2)	222 (5.8)	9 (2.0)	7 (1.5)	6 (0.9)	10 (1.5)
Mortality						
Number of deaths, N (%)	202 (5.3)	221 (5.8)	1 (0.2)	2 (0.4)	2 (0.3)	5 (0.8)
Most common reasons						
Cardiovascular death	97 (2.5)	106 (2.8)	NA	NA	NA	NA
Notable Harms						
Neoplasms by SOC/preferred term	121 (3.2)	115 (3.0)	10 (2.2)	11 (2.4)	18 (2.7)	20 (3.0)
Most common reasons						
Malignant	93 (2.4)	99 (2.6)	NA	NA	NA	NA
Benign	26 (0.7)	19 (0.5)	NA	NA	NA	NA
Unclassifiable	2 (0.1)	0	NA	NA	NA	NA
Severe or BG-confirmed symptomatic hypoglycemia						
N (%)	NA	NA	323 (77)	337 (80)	142 (22.5)	195 (31.6)
Event rate	NA	NA	2,200.8	2,462.7	185.60	265.36
LSM, events/100 PYE	NA	NA	1,227.0 N = 418	1,372.3 N = 422	99.10 N = 632	142.17 N = 618
Treatment ratio (95% CI)[a]	NA	NA	0.89 (0.85 to 0.94), $P < 0.0001$		0.70 (0.61 to 0.80)	
Severe or BG-confirmed symptomatic nocturnal hypoglycemia	NA	NA	137 (33)	182 (43)	61 (9.7)	91 (14.7)
Event rate	NA	NA	277.1	428.6	55.21	93.63
LSM, events/100 PYE	NA	NA	160.2 N = 418	250.8 N = 422	32.78 N = 632	56.35 N = 618
Treatment ratio (95% CI)[a]	NA	NA	0.64 (0.56 to 0.73), $P < 0.0001$		0.58 (0.46 to 0.74)	
Severe hypoglycemia	187 (4.9)	252 (6.6)	43 (10)	72 (17)	10 (1.6)	15 (2.4)
Odds ratio (95% CI)[b]	0.73 (0.60 to 0.89), $P < 0.001$		NR		NR	
Event rate			69.1	92.2	5.26	9.10
No events	3,631 (95.1)	3,567 (93.4)	311 (77)	NA	576 (97)	NA
Events on IGlar but not IDeg	NA	NA	50 (12)	NA	11 (2)	NA
Events on IDeg but not IGlar	NA	NA	23 (6)	NA	7 (1)	NA
Events on both	NA	NA	19 (5)	NA	3 (1)	NA
McNemar's test	NA	NA	0.0016	NA	0.3458	NA
Injection-site reactions	2	1	9 (2.0)	6 (1.3)	5 (0.7)	6 (0.9)
Weight gain, end treatment mean (SD)	2.1 (7.1)	1.8 (7.2)	0.0	0.7	0.9	0.5

AE = adverse event; BG = blood glucose; CI = confidence interval; IDeg = insulin degludec; IGlar = insulin glargine; LSM = least squares mean; NA = not available; NR = not reported; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; SOC = system organ class; WDAE = withdrawal due to adverse event; vs. = versus.

Note: All safety analyses used the safety analysis set with the exception of DEVOTE, which used the full analysis set population.

[a] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

[b] Odds ratio (IDeg vs. IGlar) based on logistic (binomial) regression with log-link function; *P* value refers to two-sided test of odds ratio = 1.0.

Source: Clinical Study Reports for DEVOTE,[6] SWITCH-1, and SWITCH-2.[13,14]

Discussion

Summary of Available Evidence

Twenty phase III studies (including five extension studies) met the inclusion criteria for this systematic review. By far the largest study, DEVOTE (N = 7,637, randomized 1:1 between IDeg and IGlar), was a cardiovascular outcomes study that focused on a population of patients with T2DM and with cardiovascular disease. This and the SWITCH studies were double-blind RCTs, while the remaining RCTs that compared IDeg against another basal insulin were open label. The SWITCH studies also compared IDeg with IGlar in a crossover design in patients with T1DM (SWITCH-1) and T2DM (SWITCH-2). These studies were much smaller than DEVOTE (SWITCH-1, N = 501; SWITCH-2, N = 720). The open-label studies were part of the BEGIN clinical trial program, which focused on four separate subgroups of patients: those with T1DM (Studies 3770, 3585, and 3583, each with an extension), those with T2DM and insulin-naive (Studies 3579 [plus extension], 3580, 3672, 3586, 3587, and 3944), those with T2DM on a basal insulin (Studies 3668 and 3943), and those with T2DM with a bolus insulin (Study 3582 [plus extension]). Of the BEGIN trials, Study 3943 was 16 weeks, Studies 3583 and 3579 were 52 weeks, and the remaining studies were 26 weeks (without extensions).

The primary outcome of the DEVOTE trial tested the noninferiority of IDeg versus IGlar for a composite of MACEs, while the primary outcome of the SWITCH trials was the occurrence of severe or blood glucose–confirmed hypoglycemic events. SWITCH-1 was a noninferiority study and SWITCH-2 was a superiority study. Other key secondary outcomes across all trials were various measures of hypoglycemic events, change in FPG, and glucose variability. The primary outcome of all the BEGIN trials was the change from baseline to end of treatment in A1C. All studies with another basal insulin as a comparator were noninferiority designs, and the other two studies tested the superiority of IDeg to sitagliptin and to placebo. Key critical appraisal issues included the open-label design in many of the studies, which would be expected to have the greatest potential for bias in subjective outcomes such as the patient-reported outcomes, the SF-36, and the disease-specific TRIM-D instrument. Several studies had withdrawal rates at or above 20%, and although there were generally no obvious differences in the proportion of participants withdrawing between groups, these high withdrawal rates may have compromised the distribution of patients between groups.

Interpretation of Results

Efficacy

The only included trial that was designed to assess the impact of IDeg on cardiovascular outcomes was DEVOTE, and in this study, IDeg was noninferior to IGlar for a composite of MACEs in a population with T2DM and cardiovascular disease. In the SWITCH and BEGIN trials, these types of cardiovascular events were infrequent; therefore, there was no clear evidence of any difference between groups across these trials. Macrovascular disease, as opposed to microvascular, is more common in T2DM than in T1DM, while complications related to microvascular disease, such as renal failure, retinopathy, and neuropathy, are more associated with T1DM. Given that IDeg is an insulin, T1DM will be the condition where it would be expected to have the greatest impact, although since T2DM is far more common

than T1DM, IDeg may also be commonly used in T2DM. There was no evidence of an impact of IDeg on development of microvascular disease, and this was not a focus of any of the included trials; therefore, the impact of IDeg on morbidity in T1DM is essentially unknown.

Although there was no evidence that IDeg or its comparators reduced the risk of microvascular complications of T1DM, there was consistent evidence that IDeg was noninferior to other basal insulins (IGlar and IDet) with respect to reducing A1C. A1C is a well-established surrogate for clinical complications of diabetes mellitus; therefore, the consistent effects of IDeg versus its basal insulin comparators in reducing A1C does enhance confidence in its clinical effects despite the lack of clinical outcomes data in T1DM. Given that A1C is an established marker of control over the disease, patient input suggests that A1C is of importance to patients. Variability in blood glucose is an additional marker of glycemic control, and there were no consistent differences noted in extent of blood glucose variability between IDeg and other basal insulins, although many trials were not designed to test superiority for this outcome. The pharmacokinetic data would suggest that IDeg is longer acting than comparators; however, there is not enough consistent evidence to suggest that this longer action translates into a meaningful clinical benefit for the patient. Due to the longer action, the clinical expert notes that an advantage of IDeg may be that it can be administered at any time of day, which may be meaningful to patients as it increases flexibility in dosing.

Quality of life was typically not assessed as a confirmatory outcome in the included studies, and significant differences between IDeg and comparators were seen infrequently and not very consistently across the included trials; therefore, one cannot conclude that IDeg improves HRQoL compared with other basal insulins or other comparators. Quality of life is an important issue to patients with diabetes mellitus; however, the lack of improvement in quality of life is perhaps not surprising given that the frequency of administration and adverse effects did not differ consistently between IDeg and its basal insulin comparators.

Harms

Hypoglycemia is a key safety issue associated with the use of insulins, particularly in T1DM, where the risk of hypoglycemia is high. The longer duration of action of IDeg may have the potential to reduce the risk of hypoglycemia by reducing the risk of variability in plasma glucose; however, the hypoglycemia results were mixed among the included trials. In DEVOTE, there was a statistically significant reduction in the risk of severe hypoglycemia events, although the effect size between groups was small (4.9% of IDeg participants experienced a severe hypoglycemia event versus 6.6% of IGlar participants). In the SWITCH studies, where occurrence of severe or blood glucose–confirmed hypoglycemia events was a primary outcome, there was a reduced risk of events occurring with IDeg versus IGlar in each of the trials, and these differences were again statistically significant; this was also the case for nocturnal hypoglycemia events. This was the case both in a population with T1DM (SWITCH-1) and T2DM (SWITCH-2), both studies featuring participants with a previous history of issues with hypoglycemic events (a severe hypoglycemic event in the past year, hypoglycemic symptom “unawareness,” and a recent hypoglycemic event within 12 weeks of randomization). Even with the statistically significant difference in event rate between groups, the difference between groups in proportion of participants experiencing a hypoglycemic event was relatively small, particularly in SWITCH-1 (77% with IDeg and 80% with IGlar). Conversely, in the BEGIN trials, there was no consistent evidence of an improvement in risk of confirmed hypoglycemic events with

IDeg versus other insulins in either T1DM or T2DM. Populations in BEGIN trials were not to have had recurrent episodes of severe hypoglycemia before enrolment. The SWITCH trials were the only studies that were designed to focus on hypoglycemic events; however, there were a large number of hypoglycemic events in the BEGIN trials as well, particularly in the trials in T1DM.

Findings from three indirect treatment comparisons (see Appendix 6) suggest that there is no statistically significant difference in rate of confirmed hypoglycemia between IDeg and IGlar in T1DM. In T2DM, results differed between the indirect treatment comparison, as a published report found a reduced risk of nocturnal hypoglycemia but an increased risk of symptomatic hypoglycemia with IDeg versus IGlar, both statistically significant. Conversely, in the manufacturer-submitted analysis, there was a reduction in nocturnal hypoglycemia with IDeg versus both IGlar and NPH which was statistically significant; however, the analysis of overall hypoglycemia could not be interpreted because the authors stated that both the fixed-effects and random-effects models showed poor fit with high residual deviance values. Findings from a patient-level meta-analysis (see Appendix 7) suggested that IDeg had a lower rate of hypoglycemia than IGlar, although none of the analyses focused on symptomatic events only. In agreement with the findings of the CADTH Common Drug Review clinical review, the network meta-analysis also found no statistically significant differences between groups for change from baseline in A1C.

Potential Place in Therapy[2]

While insulin remains the most effective treatment available to lower blood glucose (and the only treatment for T1DM), the margin between too much and too little insulin is narrow. Patients and their caregivers walk a fine line between hypoglycemia and hyperglycemia to achieve modern targets for good glycemic control. Based on the experience of the clinical expert consulted for this review, patients are frequently frustrated by day-to-day variations in blood glucose that arise after apparently managing their glucose the same way (within-patient variability). Some of these problems arise because of variability in the duration, peak action, and time-action profile of currently available insulins, especially basal insulins. An insulin that has less within-patient variability could theoretically provide a substantial advantage to patients. Greater certainty about the response to insulin by reducing the fear of hypoglycemia could lead to improved glycemic control and improved quality of life by reducing hypoglycemia and weight gain.

IDeg is a new basal insulin that forms soluble multihexamers on subcutaneous injection, resulting in a depot from which monomers are slowly and continuously absorbed into the circulation. This mechanism leads to the reported ultra-long pharmacokinetic and pharmacodynamic profiles and reduced variability in insulin action compared with IGlar.[2] Trials in a large clinical development program show noninferiority of IDeg to IGlar for the primary outcome of glycemic control for both T1DM and T2DM both in multiple-dose injection therapy and basal plus oral regimens (BEGIN trials) and for cardiovascular outcomes in T2DM.[3] Results for the key secondary outcomes of glucose variability, hypoglycemia, and quality of life are less convincing. While there is a trend to superiority in the reduction of nocturnal hypoglycemic events for people in clinical trials for T1DM, in only one trial does this approach statistical superiority ($P = -0.011$).[4] In T2DM, while again there is a trend to an improved efficacy, there is no consistent statistically significant result. There were no quality-of-life differences. Exclusion criteria for most trials included recent severe or

2 This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

recurrent hypoglycemia, which does not allow evaluation of the role of IDeg in this potential group of patients.

The SWITCH trials included groups of patients said to be at high risk of hypoglycemia (recent severe or non-severe hypoglycemia, hypoglycemia symptom unawareness, moderate chronic renal failure, or long disease duration or long-time insulin use) but the data provided do not include sufficient information to identify which of these very different groups might benefit. Although the results show a significantly lower rate of overall, nocturnal, and severe hypoglycemia versus IGlar in both T1DM and T2DM patients, this finding is specific to the trial definitions of these events, and it is not clear how it would translate to clinical practice. Of concern, nocturnal hypoglycemia is defined to a six-hour time period from midnight, and results from a longer sleep period (10 p.m. to 8 a.m.) are not given.

One potential advantage is that the BEGIN Flex T1DM and T2DM studies showed that IDeg can be administered at any time of day, with injection timing varied, without compromising glycemic control or safety.[5] This may improve basal insulin adherence by allowing injection-time adjustment according to individual needs; however, there is no evidence to assess this potential advantage.

In summary, IDeg appears to achieve similar safety and efficacy outcomes as IGlar in patients with T1DM and T2DM; however, there is no convincing evidence that it is superior in preventing hypoglycemic events. It may be of advantage for those who find difficulty taking basal insulin at a regular time.

Conclusions

Fifteen RCTs plus five extension studies met the inclusion criteria for this review. There is evidence from the largest study, the DEVOTE study, in patients with T2DM and a history of cardiovascular disease, that IDeg is noninferior to IGlar for the composite of MACEs. There was no evidence of a statistically significant difference in mortality or in cardiovascular events (myocardial infarction, stroke) between IDeg and IGlar in DEVOTE. The other 19 included studies, including the SWITCH studies, were not powered to assess mortality or morbidity, and these events tended to be infrequent in these studies. IDeg was consistently noninferior to IGlar for the change from baseline in A1C, whether at 16 weeks, 26 weeks, or 52 weeks, and this was the primary outcome in all the BEGIN trials. Responses for change in FPG and variability in blood glucose did not differ significantly between IDeg and IGlar or IDet in the included trials; however, these outcomes were not the focus of these studies. The results for hypoglycemia differed between studies. In the SWITCH studies, where severe or confirmed hypoglycemic events was a primary outcome and where patients had demonstrated recent issues with hypoglycemia, there was evidence of superiority for IDeg versus IGlar, and this was also the case in DEVOTE, where severe hypoglycemia was a key secondary outcome. However, in the BEGIN trials, there was no consistent evidence of superiority of IDeg over IGlar or IDet for events of confirmed hypoglycemia, and in both the published and manufacturer-submitted network meta-analysis, which did not include DEVOTE, SWITCH-1, or SWITCH-2, there was also no evidence of a statistically significant improvement in risk of confirmed hypoglycemia with IDeg compared with other basal insulins. There were no consistent differences in HRQoL, measured by the SF-36 or either TRIM (TRIM-D or TRIM-HYPO) instrument, between IDeg and IGlar or other comparators across the studies. Across the studies, there were no consistent differences between IDeg and comparators in the proportion of patients experiencing an adverse event, serious

adverse event, or withdrawals due to an adverse event. Among notable harms, there were no consistent differences between IDeg and IGlar or IDet in weight gain, neoplasms, or injection-site reactions.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Groups Supplying Input

Three patient groups provided feedback. Type 1 Together brings together Canadians living with type 1 diabetes mellitus (T1DM) to make living with diabetes easier through connections, sharing, and advocacy. Type 1 Together reports no conflicts of interest with regard to the completion of this submission and received no funding from industry. Patient Commando aims to improve health care practice by connecting patients and their experiences to health care professionals. This group provides a diverse collection of patient stories describing lived illness experiences, delivers accredited continuing medical education in narrative competency, and facilitates meaningful conversations and unique collaborations between patients and health care professionals. The executive director of Patient Commando has received honorariums for speaking and delivering educational programs to AbbVie, Sanofi, Novo Nordisk, Astellas, and Actavis. Diabetes Canada helps people with diabetes live healthily while supporting research for a cure. It is supported by a network of volunteers, employees, health care professionals, researchers, and partners who provide education and services, advocate on behalf of people with diabetes, support research, and translate this research into practical applications. Diabetes Canada receives financial support from a number of foundations and corporate sponsors, including the manufacturer of Tresiba (Novo Nordisk Canada Inc.). The development of Diabetes Canada's submission was supported by a consultant, Jane Tsai.

2. Condition-Related Information

Type 1 Together collected data through an online survey (115 responses), interviews with members, and diabetes forum posts. Patient Commando obtained the information for its patient input from a variety of sources, including its website story collection, community responses to its Experience Exchange program, personal interviews and group discussions, and conversation threads on social media platforms. Diabetes Canada collected information through two patient input surveys conducted in October 2016 and June 2017, solicited through social media and e-blasts. The first survey collected information on the impact of diabetes from 790 Canadians with type 2 diabetes mellitus (T2DM) and 57 caregivers of patients with this disease. The second survey collected information on patients' experiences with available drug therapies and the therapy currently under review (329 Canadian respondents: 52 patients with T1DM; 185 patients with T2DM; 38 caregivers).

T1DM occurs when the body does not produce insulin or produces very little insulin, while T2DM occurs when the pancreas does not produce enough insulin or when the body does not effectively use the insulin that it does produce. While these are different diseases, the immediate goal of diabetes management is to keep glucose levels within the target range while minimizing symptoms and avoiding side effects (especially hypoglycemia). Glycemic excursions can result in acute crises and serious long-term complications. Long-term complications of diabetes include blindness, hearing impairment, erectile dysfunction, cardiovascular disease, nephropathy or kidney failure, nerve damage, and amputation, among numerous others. The consequences of hypoglycemia are often immediate and sudden, including anger, anxiety, sweating, weakness, shakiness, dizziness, headaches, blurred vision, drowsiness, confusion, cognitive impairment, seizures, unconsciousness, brain damage, and death, including "dead-in-bed" syndrome. The emotional experience of

Canadians with T1DM is dominated by feelings of anger, helplessness, fear, and depression.

T2DM requires considerable self-management and education, including healthy eating, regular physical activity, healthy body weight, adherence to prescribed treatment regimens, monitoring blood glucose, and stress management. People with T1DM report that fear of hypoglycemia can be "debilitating." Diabetes management is a "constant struggle," and the majority suffer emotionally from frustration, fatigue, worry, and a sense of powerlessness. For the majority of respondents, in all surveys, diabetes has negatively affected all aspects of their lives and has limited activities, opportunities, and careers. Some respondents felt that diabetes "dictates" their lives, that they are "held captive by diabetes." Some have lost their driving privileges, employment, independence, and spontaneity in daily life. Many respondents indicated that they are experiencing combinations of the short-term symptoms (fatigue, weight gain, and high blood pressure, among others) and long-term complications listed above. There was also an emphasis on the psychological and emotional impact of diabetes on the lives of respondents, family members, and caregivers as a result of adjustments to diet and lifestyle; daily medication and treatment management; strain on relationships with family; stress and anxiety about hypoglycemia, disease symptoms and complications; and financial burden. For individuals who have to manage diabetes and care for other members of the family, it is particularly difficult. Many caregivers must sacrifice their own well-being to adequately monitor and assist their loved ones: For example, one respondent said, "My husband has lost his eyesight; can no longer help out around the house." Finally, the financial burden of diabetes is experienced by many. Another remarked, "My doctor asked me, 'What plan are you on?' It occurred to me afterwards what a difference that question makes to the treatment chosen or available to a patient." Each patient is unique and experiences individual challenges. While concerns about the symptoms and complications of diabetes prevail for many, some expressed strong anxiety relating to the financial burdens of their disease.

3. Current Therapy-Related Information

The data in this section were provided by the survey conducted by Type 1 Together and the survey from Diabetes Canada of T1DM and T2DM patients and caregivers. Summaries, statements, and respondents' quotes were assembled from the narratives provided in all three submissions (Diabetes Canada, Patient Commando, and Type 1 Together). Current therapies include a variety of insulins and prescribed medications; routes of delivery include oral, injection, pen, and pump.

Type 1 Together reported that existing treatments for T1DM do not control glycemia well, and the fear of hypoglycemia, particularly nocturnal hypoglycemia, is substantial for many patients. There is an unmet need related to managing blood glucose levels, to the complications of diabetes (73% of Canadian diabetics had complications), and to the burdens associated with controlling the disease, including emotional burdens. These were reported to have negative impacts on physical health in 71% of respondents, as well as on finances (51%), leisure activities (54%), and emotional well-being (66%). Insulin management is an immense burden. More than one in three patients wake up at least twice a night, every night, due to T1DM, and nearly half are affected by delays in insulin delivery greater than 15 minutes. People with T1DM need, but typically do not have, tools, technologies, and skills that make T1DM safer, easier to manage, and less psychologically distressing to live with.

Currently available treatments and delivery systems for diabetes have led to an improvement in blood glucose levels for the majority of respondents based on a survey by Diabetes Canada. These medications have helped reduce other symptoms, including hypoglycemia (46%), weight issues (33%), gastrointestinal issues (24%), thirst or dehydration (27%), infections (24% to 26%), and fractures or organ damage (19%). With a variety of insulin formulations ranging from rapid-acting to long-acting, some patients have managed to find a balance and maintain better control alongside their other medications, meal choices, physical activities, and lifestyles. Patients' experiences vary, but shared themes that emerge include problems with treatment and regimen adherence, the lack of predictability of treatment effects from one day to the next, side effects, issues with managing the disease symptoms, and serious long-term complications. The fear and anxiety of experiencing hypoglycemia are highlighted from both the patients' and caregivers' perspectives. One patient commented, "I struggle between maintaining tight control and having lows. It's easier to keep blood sugars somewhat elevated and not worry so much about lows.... You can't function when you're low."

The Patient Commando submission emphasized the importance of treating the whole person, and not looking at the patient from the isolated viewpoint of a single therapy. The choice of treatment should be based on the individual patient's needs, the health care provider's preferences and training, and support from both professional and family caregivers, among other factors. Type 1 Together emphasized the need for predictable and safer drugs and technologies that will permit a lifetime of emotionally and behaviourally sustainable disease management while attenuating the high levels of emotional distress that interfere with diabetes outcomes.

4. Expectations About the Drug Being Reviewed

It was expressed that an insulin consistently providing steady blood glucose levels over a longer, more predictable time frame would be of value. Other expectations include the following:

- improvement or consistency in blood glucose control, without weight gain
- prevention of side effects, especially hypoglycemia, nocturnal hypoglycemia, and severe hypoglycemia
- reductions in the many symptoms and long-term complications of both T1DM and T2DM
- improvement in treatment adherence made possible by reduced frequency of injections, fewer conflicts between an individual's schedule and the treatment regimen, fewer injections to forget, fewer medications to remember, and fewer side effects
- improvement in the predictability of an individual's daily response to insulin
- reduction in dependence on insulin and other medications
- reduction in the demands and requirements of disease management (more independence from strict treatment regimens, lifestyle requirements, and meal plans; reduced emotional burden)
- affordability (lower cost or coverage through public drug plans).

The Diabetes Canada survey received 15 responses from Canadian patients taking insulin degludec made available through manufacturer supply or clinical trial. One patient did not have a positive experience with Tresiba and another returned to a different long-acting insulin after taking Tresiba for nine months. The remainder of Canadian respondents shared similar experiences, such as "comfortable to manage because there is no peak time" and

“easy to use and titrate and have had a reduction in hypoglycemia” (quotes from T1DM patients). Those with T2DM also reported fewer hypoglycemia events and more stable insulin action. Comparable experiences are described in Patient Commando’s and Type 1 Together’s submissions of patient experiences in countries where Tresiba is available and from forum posts, such as: “No more random hypos and the release is super steady and predictable,” and “I have seen several posts from people who are not pleased with their results from Tresiba. But I have not seen anyone have significant issues with it either.”

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	June 28, 2017
Alerts:	Bi-weekly search updates until Oct 18, 2017
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
fs	Floating subheading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
#	Truncation symbol for one character
?	Truncation symbol for one or no characters only
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kw	Keyword
.kf	Author supplied keyword
.pt	Publication type
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; E-pub ahead of print, MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(degludec* or Tresiba* or nn1250 or nn 1250 or Tregludec*).ti,ab,kf,ot,hw,rn,nm.
2	(844439-96-9 or 54Q18076QB).rn,nm.
3	1 or 2
4	3 use ppez
5	*insulin degludec/
6	(degludec* or Tresiba* or nn1250 or nn 1250 or Tregludec*).ti,ab,kw.
7	5 or 6
8	7 use oemezd
9	8 not conference abstract.pt.
10	4 or 9
11	remove duplicates from 10

OTHER DATABASES		
PubMed	Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	Search current to June 19-23, 2017
Keywords:	degludec OR Tresiba OR nn1250 OR nn 1250 OR Tregludec OR diabetes mellitus
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for evidence-based searching" (https://www.cadth.ca/resources/finding-evidence/grey-matters-practical-search-tool-evidence-based-medicine) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Clinical Trials
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (Free)
- Internet Search

Appendix 3: Excluded Studies

Reference	Reason for Exclusion
IWASAKI et al. Diabetology International 2017;8(2):228-36	Non-RCT
KADOWAKI et al. Diabetology International 2017;8(1):87-94 FULCHER et al. Diabetes Technol Ther 2016;18()(pp S49-S50), 2016. S49-S50 HARRIS et al. Diabetes Obes Metab 2017;19(6):858-65 ONISHI et al. J 2017;diabetes investig.. 8(2):210-7 KADOWAKI et al. J 2016;diabetes investig.. 7(5):711-7 FRANEK et al. Diabet Med 2016;33(4):497-505 KANEKO et al. Diabetes Res Clin Pract 2015;107(1):139-47 FULCHER et al. Diabetes Care 2014;37(8):2084-90 MATHIEU et al. Diabetes Obes Metab 2014;16(7):636-44 NISKANEN et al. Eur 2012;J. ENDOCRINOL.. 167(2):287-94	Comparator not of interest
KAHL. Diabetologe 2016;12(3):201-2 GOUGH et al. Diabetes Technol Ther 2014;16(Suppl 1):S37-S38 RODBARD et al. Diabetes Obes Metab 2014;16(9):869-72	Review
YAMADA et al. Diabetology International 2014;5(1):74-7 KOMURO et al. J Diabetes Sci Technol 2015;9(3):632-8 KOEHLER et al. Diabetologia 2014;57(1):40-9 IGA et al. Diabetes Ther 2017;	Short duration
LINJAWI et al. Diabetes Ther 2017;8(1):101-14 KUMAR et al. Diabet Med 2017;34(2):180-8 HIRSCH et al. Diabet Med 2017;34(2):167-73 RODBARD et al. Diabet Med 2017;34(2):189-96 KUMAR et al. PLoS ONE 2016;11(10):e0163350, 2016 LINGVAY et al. JAMA 2016;315(9):898-907 GOUGH et al. Diabetes Obes Metab 2015;17(10):965-73 GOUGH et al. Lancet Diabetes Endocrinol 2014;2(11):885-93 BUSE et al. Diabetes Care 2014;37(11):2926-33 ONISHI et al. Diabetes Obes Metab 2013;15(9):826-32 HIRSCH et al. Diabetes Care 2012;35(11):2174-81 HEISE et al. Diabetes Care 2011;34(3):669-74 HOME et al. Diabet Med 2012;29(6):716-20	Intervention not of interest (fixed dose combo)
IWAMOTO et al. J 2013;diabetes investig.. 4(1):62-8 BIRKELAND et al. Diabetes Care 2011;34(3):661-5	Phase II study
ZINMAN et al. Lancet Diabetes Endocrinol 2013;1(2):123-31	Regimen not of interest (three times weekly)

RCT = randomized controlled trial.

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Short Form (36) Health Survey (SF-36)
- Treatment-Related Impact Measure — Diabetes (TRIM-D)
- Treatment-Related Impact Measure — Hypoglycemic Events (TRIM-HYPO)

Findings

A focused literature search was conducted to identify the psychometric properties and minimal clinically important difference of each of the stated outcome measures. Table 38 summarizes the findings.

Table 38: Validity and Minimal Clinically Important Difference of Outcome Measures

Instrument	Type	Evidence of Validity	MCID	References
SF-36v2	Generic tool to measure multidimensional health concepts and to capture a full range of health states	Yes	MID benchmarks are 1-point changes in SF-36v2 scores in diabetes General (non–disease-specific) MID: 2 points in PCS; 3 points in MCS; 2 to 4 points for individual dimensions	Bjorner 2013[37] SF-36v2 User's manual[26]
TRIM-D	Disease-specific tool designed to evaluate the impact of treatment in both T1DM and T2DM	Yes	No MCID	Brod 2009[28] Brod 2011[27]
TRIM-HYPO	Disease-specific tool designed to evaluate the impact of treatment-related non-severe hypoglycemia in both T1DM and T2DM	Yes	No MCID	Brod 2015[29]

MCS = mental component summary; MCID = minimal clinically important difference; MID = minimal important difference; PCS = physical component summary; SF-36v2 = Short Form 36 Health Survey, version 2.0; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; TRIM-HYPO = Treatment-Related Impact Measure — Hypoglycemic Events.

Short Form (36) Health Survey

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on health-related quality of life (HRQoL). The SF-36 consists of 36 items representing eight dimensions: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Item response options are presented on a 3-point to 6-point Likert-like scale. Each item is scored on a 0 to 100 range, and item scores are averaged together to create the eight domain scores. The SF-36 also provides two component summaries, the physical component summary and the mental component summary, which are created by aggregating the eight domains according to a scoring algorithm. Therefore, the physical and mental component summaries and eight dimensions are each measured on a scale of 0 to 100, which are t-scores (mean of 50 and standard deviation of 10) that have been standardized

to the US general population.[26] Thus, a score of 50 on any scale would be at the average or norm of the general US population and a score 10 points lower (i.e., 40) would be one standard deviation below the norm.[26] On any of the scales, an increase in score indicates improvement in health status. In general use of the SF-36 version 2.0 (SF-36v2), the *User's Manual* proposed the following minimal important differences (MIDs): a change of 2 points on the physical component summary and 3 points on the mental component summary. The manual also proposes the following minimal mean group differences, in terms of t-score points, for SF-36v2 individual dimension scores: physical functioning, 3; role physical, 3; bodily pain, 3; general health, 2; vitality, 2; social functioning, 3; role emotional, 4; and mental health, 3. It should be noted that these MID values were determined as appropriate for groups with mean t-score ranges of 30 to 40; for higher t-score ranges, values may be higher.[26] MID values do not represent patient-derived scores. The MIDs for the SF-36v2 are based on clinical and other non–patient-reported anchors.[26]

Two versions of the SF-36 exist: the original and version 2.0 (SF-36v2 was made available in 1996).[26] The SF-36v2 contains minor changes to the original survey, including changes to instructions (reduced ambiguity), questions and answers (better layout), item-level response choices (increased), and cultural and language comparability (increased), and the elimination of a response option from the items in the mental health and vitality dimensions.[26]

One study has investigated benchmarks for MIDs for 1-point lower SF-36 scores in populations with diabetes.[37] SF-36 surveys of three general US patient populations were analyzed to derive statistical models using non–patient-reported anchors of two-year mortality, seven-year mortality, ability to work, hospitalization within six months from baseline, and loss of ability to work within six months from baseline. The authors accounted for certain variables, including age, number of comorbidities, education, marital status, and score levels as well as interactions and nonlinear effects in their analyses. The three surveys produced different outcome risks associated with 1-point changes in SF-36 dimension and component scores. The models were then applied to the diabetes subpopulations within each patient population to estimate the relative risk associated with each outcome and a 1-point hypothetical decrease in SF-36 scores. Different risks were associated with each population and each outcome. For example, using the Medicare Health Outcome Survey, 1-point lower dimension and component scores were associated with increased risks of two-year mortality ranging from 1.8% to 6.4%, while the Medical Outcomes Survey data generated increased risks of seven-year mortality ranging from 2.0% to 9.0%. One-point lower scores using Medical Outcomes Survey data were associated with a six-month increased risk of hospitalization ranging from not statistically significant to 3.7% and an increased risk of losing the ability to work within six months of baseline ranging from 2.8% to 6.9%.[37] While MID benchmarks can be helpful in interpreting SF-36 scores in the absence of minimal clinically important differences (MCIDs), the magnitude of the increased risk, while statistically significant, can be difficult to interpret from a clinical and patient perspective. Furthermore, the 1-point score decrease associated with a small risk of hospitalization within a six-month time frame is difficult to interpret as clinically meaningful. Finally, the study failed to adjust for potentially important confounding variables relating to diabetes, including disease type (type 1 diabetes mellitus [T1DM] versus type 2 diabetes mellitus [T2DM]), disease duration, treatment type, glycemic control, lifestyle factors (such as smoking), and socioeconomic factors (such as income level).[37] As such, the validity of these 1-point score difference benchmarks remains unclear.

Validation of the Short Form (36) Health Survey in Type 1 and Type 2 Diabetes

Validation of the SF-36 has been performed in a number of studies in T1DM and T2DM combined populations[38-41] and in T2DM general populations in Germany (N = 144),[42] the United Kingdom (N = 131),[43] Pima Indian adults (N = 54),[44] older Chinese adults (N = 182),[45] and US veterans (N = 331; 98% male).[46] All validation studies were performed in male and female adults; none assessed the SF-36 in T1DM patients exclusively. Validation tests in these populations are described in the sections below.

Reliability

Cronbach's alpha correlation coefficients measure internal consistency and reliability, conveying how well an item relates to its hypothesized dimension. Alpha coefficients varied according to study and population with some ranges reporting internal reliability ≥ 0.7 to 0.94 for all dimensions,[41,43] while others found some dimensions to have lower reliability: social functioning,[38,44] role emotional, role physical, vitality,[42] and general health.[39,42,45] Internal reliability discrepancies (dimensions with alpha lower than 0.7) may relate to the specific characteristics, health states, and socioeconomic or cultural traits of the population used to validate the instrument. No dimensions were found to have alpha coefficients ≥ 0.95, though some exceeded 0.9 (higher alpha coefficients may suggest redundancy).

One US study of the adult population (18 to 60 years of age; 64% T1DM, 31% T2DM) measured test-retest reliability by comparing baseline to six-month surveys. All correlations were positive, but ranges of coefficients were reported for the different dimensions: 0.902 for physical function; > 0.6 to 0.9 for social function, role physical, role emotional, mental health, vitality, and general health perception; and 0.433 for pain. As a reference point of the measure of maintenance of health state, a diabetes-specific health status questionnaire served as a reference point for each patient at both time points, with a correlation coefficient of 0.827.[40] Test-retest reliability was also measured in a German population of T2DM (approximately 70 patients, approximately 50% taking insulin, approximately 50% male) within one to three days of the original test. Measures of internal consistency at both time points were captured, but no correlations were calculated. Internal consistency ranged from 0.67 to 0.96 at baseline and from 0.61 to 0.89 at retest. Upon retest, some dimensions were more affected than others, including role emotional and role physical (both lower) and general health (higher).[42]

Responsiveness has been assessed in a single study of 331 US veterans (98% male, mean age of 63.5 years, 91% T2DM). The observational, prospective study of 25 diabetic complications, sampled at two time points over a mean interval of 3.1 years, was powered to detect a minimum difference of 5 points across all dimensions of the SF-36 and used Cohen's effect size to evaluate responsiveness (effect size ranges were defined as "trivial" [< 0.20], "small" [≥ 0.20 to < 0.50], "moderate" [≥ 0.50 to < 0.80], or "large" [≥ 0.80]).[46] Six of the SF-36 dimensions (general health, physical functioning, social functioning, role physical, bodily pain, and vitality) were found to be responsive when patients who developed two or more complications were compared with those who were stable or improved (effect size 0.31 to 0.66); an increase of more than one complication was associated with a loss of 4.1 points to 23.6 points on these six scales. Statistically significant changes in SF-36 dimension scores were related to any renal complication in five of these six dimensions (general health, physical functioning, social functioning. role physical, vitality) or to any neuropathy complication in four of them (general health, physical functioning, role physical, vitality).[46]

Validity

Two cross-sectional studies conducted in Taiwan[38] and mainland China[45] primarily studying T2DM patients (mean ages 63[38] and 69[45]) evaluated the internal validity of the SF-36 by factor analysis (eigenvalues ≥ 1.0 and factor loadings ≥ 0.4 were significant). In one study, all dimensions loaded onto their hypothesized component summary (physical or mental).[38] In the other study, factor analysis revealed appropriate loading except for general health on the mental component summary and role physical on both the mental component summary and the physical component summary. Item-dimension correlations ranged from 0.27 to 0.81 across all dimensions and summary scores; only the physical functioning dimension had a scaling of success rates < 100% (physical functioning, 99%).[45] In a large observational cohort study of chronic disease in the United States (T1DM and T2DM subgroup, N = 624), item-dimension correlations ranged from 0.62 to 0.76 in all but the general health (0.38 to 0.71) and physical functioning (0.52 to 0.82).[41] Scaling success rates from 280 tests, based on item correlation with hypothesized dimension exceeding that of all others by more than two standard errors, were 100% in all but general health (90%) and physical functioning (99%).[41] General health was found to correlate with both the physical component summary and the mental component summary during SF-36 development.[26]

Inter-dimension correlations of the SF-36 in a T1DM and T2DM patient population ranged from 0.179 (mental health correlation with physical functioning) to 0.637 (role physical with pain),[40] suggesting that different dimensions are measuring somewhat different constructs.

One challenge when validating a pre-established, generic HRQoL instrument for use in a specific disease population is in the identification of appropriate measures against which to test the instrument (construct validity) when no gold standard is available (criterion validity). A number of studies have assessed the association between glycated hemoglobin (A1C), a known surrogate marker in both forms of diabetes, and SF-36 dimensions, or have performed known-group comparisons based on A1C level stratification. These studies have established that there is no clear relationship between dimensions of the SF-36 and A1C levels, reporting unexpected, poor, or negligible correlations[44,47] or an inability of the SF-36 to discriminate between known groups based on A1C levels.[38,40] An initial study comparing physician assessment of patient health to the patient-reported SF-36 dimension scores reported unsatisfactory correlations (0.39 to 0.64).[40] Construct validity testing was based on exploratory and a priori hypotheses. The SF-36 showed evidence of measuring effects of diabetic complications,[43] treatment type, and changes following diabetes interventions,[42,44] but it was also influenced by non-diabetic comorbidity[43,44] and other non–diabetes-specific factors, such as age:[43,44]

- Age: Physical functioning, role physical, social functioning, and mental health deteriorated in older age groups (Spearman rank correlation coefficients, −0.52 to −0.40; $P < 0.005$)[44]; physical functioning and role physical were impaired in older age groups ($P < 0.05$),[43] but role emotional was impaired in younger age groups ($P < 0.01$).[43]
- Sex: No statistically significant differences were found.43,44 Women had lower scores on multiple dimensions ($P < 0.05$).[42]
- Education level: No correlation was found.[44]
- Socioeconomic status and income: No statistically significant differences were found.[43,44]
- Diabetes-related laboratory markers: No correlation was found.[44]

- Diabetic complications: These were associated with lower dimension scores for social functioning, role emotional, vitality (P < 0.01), and role physical (P < 0.05)[43]; all dimensions of the SF-36 were lower with more than one late complication (P < 0.01).[42]
- Non-diabetic comorbidities: These showed lower scores in physical functioning and role physical (both with P = 0.001), vitality and general health (P < 0.01), and mental health (P < 0.05).[43]
- Comorbidities: These showed lower scores in physical functioning, role physical, role emotional, mental health, and social functioning (Spearman rank correlation coefficients, −0.42 to −0.32; P < 0.02).[44]
- Diabetic treatment: Insulin was associated with lower scores than non-insulin treatment in physical functioning, role physical, social functioning, and general health (Spearman rank correlation coefficients, 0.31 to 0.40; P < 0.03),[44] and in vitality and mental health (P < 0.01).[42]
- Response to diabetes intervention (treatment, education, or both) showed statistically significant score changes for the following dimensions: Role physical, general health, vitality, and social functioning (P < 0.05 or less).[42]

Validity of the SF-36 dimensions was also evaluated using diabetes-specific HRQoL measures. The Audit of Diabetes Dependent Quality of Life is a validated tool for measuring the impact of diabetes on general quality of life across 13 domains. SF-36 correlated better with this tool in patients without any other disease or comorbidity than in those with comorbidities (Spearman's rank coefficients, 0.30 to 0.44) across five domains: social functioning, role physical, mental health, vitality, and general health (*P* < 0.05).[43] Another study compared validation of the SF-36 with Diabetes-39, a five-dimension measure consisting of 39 items that probe diabetes-related HRQoL.[38] The SF-36 performed better than Diabetes-39 on some dimensions and in the physical component summary for cardiovascular disease and cerebrovascular complications (Cohen's effect sizes highest in the physical dimensions) and for the diabetic all-complication summary known-group comparison: effect sizes of SF-36 were 0.38 compared with the Diabetes-39 summary score of 0.15. The Diabetes-39 had discriminative power over the SF-36 (based on C-statistic) in two-hour post-prandial glucose (0.7 versus 0.63; *P* < 0.05); the SF-36 generally performed better than the Diabetes-39 for complication-known groups. SF-36 dimensions performed better at a statistically significant level than Diabetes-39 subscales for cardiovascular disease and the all-complication–known groups;[38] in the German T2DM population, SF-36 showed statistically significant multidimensional changes after diabetes intervention when the Diabetes-39 did not.[42] Based on a priori hypotheses, known-groups comparisons of self-reported high blood pressure, heart problems, and measured depression levels showed significantly higher SF-36 dimension scores for patients without high blood pressure, heart problems, or moderate to high depressive levels (no effect sizes presented).[45]

Critical Appraisal

The SF-36 requires further and more comprehensive validation across the combined population of T1DM and T2DM patients, across different ethnic and cultural populations, and in T1DM patient groups. As SF-36 was developed as a generic instrument, it has been suggested that the tool be evaluated and possibly revalidated whenever a new study is undertaken in any diabetes population, as some items and dimensions of the SF-36 did not respond optimally during validation in various groups.[38,45] Furthermore, in the CADTH Common Drug Review (CDR) search of the literature, few studies were identified that attempted to validate the test-retest reliability,[40,42] responsiveness,[46] or MCID of the SF-36 in the general diabetes population, in separate T1DM and T2DM populations, and in more

specific diabetes subgroups. The SF-36 has shown evidence of measuring the effects of diabetic complications,[42,43] but it is also influenced by non-diabetic comorbidity[43,44] and other non–diabetes-specific factors, such as age.[43,44] It does not demonstrate evidence of association with surrogate markers of disease severity,[38,40,44,47] but does respond to treatment type and changes following diabetes interventions.[42,44] The SF-36 and diabetes-specific instruments likely provide some degree of overlap, but also address different features of a patient's overall HRQoL.[38,45] Taken together, the evidence suggests that the SF-36 is not likely an appropriate stand-alone tool for the evaluation of all facets of HRQoL in patients with diabetes, but can provide useful insight when used in combination with the appropriate, complementary diabetes-specific treatment evaluation and HRQoL instruments. Comprehensive validation of the SF-36 in T1DM and T2DM is incomplete, and no MCID specifically in diabetes has been established.

Treatment-Related Impact Measure — Diabetes

TRIM-D was developed in English by The Brod Group and by Novo Nordisk as a questionnaire appropriate for both T1DM and T2DM diabetes patients. This patient-reported outcome measure was developed to address gaps in reporting of treatment impact in both forms of diabetes. TRIM-D is a 28-item, self-reported questionnaire encompassing five domains: treatment burden (six items), daily life (five items), diabetes management (five items), psychological health (eight items), and compliance (four items). Response options are presented on a 5-point Likert-like scale. An increase in score indicates an improvement in health state. Domains can be scored individually or the measure can be scored as a total of these domains.[28] No MCID was been determined for TRIM-D.

Validation of the Treatment-Related Impact Measure — Diabetes in Type 1 and Type 2 Diabetes Mellitus

Content validity was addressed during instrument development. Item development was initially extracted from the literature and T1DM and T2DM patient and expert input, and then compiled[28,48] and assembled into an early version of the survey measuring the multifaceted impact of diabetes. Five individual telephone interviews of pre-filled early surveys were conducted; findings were reviewed and decisions made about changes to measures. These blocks of five interviews continued until a consensus was met by an entire block. The initial validation study recruited 507 diabetes patients ranging from 18 to 80 years (mean 51.4 years) to respond to Web-based questionnaires (initial TRIM-D and a battery of other patient-reported measures). The group was stratified across income, age, ethnicity, and diabetes medications: 53% female, 84% white, 6% African American, 74% T2DM.[28] Analysis of ceiling effect (> 50%), inter-item correlations (> 0.7), and conceptual framework led to the refined 28-item TRIM-D.

Reliability

Evaluation of internal consistency produced Cronbach's alpha correlation coefficients of 0.94 (for the total score) and ranged from 0.86 to 0.91 (for the subscale scores);[28] follow-up internal reliability alphas exceeded 0.7 and fell within 0.1 of those found in the development study.[27] Test-retest analysis was performed using data from a subset of 56 patients who completed the questionnaire within the permitted time gap of two weeks ± one day, with coefficients for total score measured at 0.85, and those for the subscales ranging from 0.71 to 0.83[28] (coefficients ≥ 0.7 are considered acceptable, ≥ 0.8 are good, and ≥ 0.9 are excellent).

Validity

Validation of the TRIM-D total questionnaire and domains was performed using a battery of Web-based survey outcomes measures (validated and not validated in diabetes). Convergent validity was reported based on a priori hypotheses using a two-tailed Pearson's correlation coefficient (r), significance < 0.05, with r > 0.40 considered evidence of moderate to strong associations. The following significant correlations were found between TRIM-D (total or subdomain) and the indicated outcome measure:[28]

- r = 0.63: Global satisfaction scale of the Treatment Satisfaction Questionnaire for Medication
- r = 0.45: Diabetes Medication Satisfaction Measure, burden subscale
- r = −0.67: Activity Impairment Assessment total score
- r = 0.66 and 0.60: Diabetes Medication Satisfaction, efficacy, and the Treatment Satisfaction Questionnaire for Medication, effectiveness scales, respectively
- r = −0.75: TRIM-D, psychological health, with the Problem Areas in Diabetes
- r = −0.69: TRIM-D, compliance, with the Medication Compliance Scale.

A number of known-groups validity a priori hypotheses were tested for the TRIM-D total score and subscales by one-way analysis of variance (groups as fixed factors; ANOVA F-value (F); significance *P* values < 0.05).[28]

- The total TRIM-D distinguished between willingness of respondents to change diabetes treatment (F = 83.7; P < 0.001) and between those compliant versus not compliant with their treatment (F = 136.6; P < 0.001).
- The TRIM-D burden domain distinguished between the types of treatment (oral, pump, and syringe, F = 27.7; P < 0.001), but not between number of daily injections.
- The TRIM-D daily life domain distinguished (P < 0.001) between levels of satisfaction (measured by the Quality of Life Enjoyment and Satisfaction Questionnaire, F = 47.5) and work days lost due to diabetes (F = 43.1).
- The TRIM-D diabetes management domain distinguished between A1C levels (F = 16.6; P < 0.001), the number of medical visits (F = 4.8; P < 0.01), the changing of diabetes treatment plans (none, 1 to 2 times, or > 3, F = 8.5; P < 0.001), and diabetes control (F = 115.8; P < 0.001).
- The psychological health subscale distinguished between depression severity (F = 152.9; P < 0.001) and level of social support (F = 92.6; P < 0.001).
- The TRIM-D compliance domain distinguished between the type of treatment (oral versus other, F = 14.3; P < 0.001).

Responsiveness

Internal and external responsiveness of the TRIM-D were assessed in a 2-by-12-week, crossover, randomized controlled trial (RCT) using two different pre-filled insulin pens, with participation of 242 patients aged 18 years or older with T1DM or T2DM.[27] Internal responsiveness measurements found statistically significant score changes ranging from 18.6 (effect size = 0.84, TRIM-D treatment burden) to 3.1 (effect size = 0.17, TRIM-D psychological health).[27] External responsiveness using the Insulin Treatment Satisfaction Questionnaire change found a strong association with the TRIM-D total score (r = 0.72; *P* < 0.001). The Insulin Treatment Satisfaction Questionnaire summary score showed the following correlations with TRIM-D domain items: treatment burden items (r ranging

between 0.32 and 0.53), daily life items (r = 0.37 to 0.45), diabetes management items (r = 0.22 to 0.38), psychological health items (r = 0.35 to 0.51), and compliance domain items (r = 0.14 to 0.25). Five of 28 items within the domains were not responsive. Responsiveness of each domain may vary according to study design, and this should be taken into account when defining, a priori, the TRIM-D domains that will be expected to respond to change within a study.[27]

Preliminary, exploratory estimates of MIDs in this study[27] were based on self-reported anchor items, without longitudinal data. The statistical analysis plan defined the MID threshold criterion to be half the standard deviation of the TRIM-D domain score differences (Δ) corresponding with minimal important anchor response intervals of "slightly" and "somewhat." Based on this criterion, each of the TRIM-D domains met the MID threshold except for the compliance domain, for which no overall anchor item had been established:[28]

- Treatment burden, Δ = 10.6; ½ SD = 9.5
- Daily life, Δ = 16.0; ½ SD = 9.2
- Diabetes management, Δ = 12.0; ½ SD = 8.2
- Psychological, Δ = 17.8; ½ SD = 8.7
- TRIM-D total score, Δ = 17.6; ½ SD = 7.8.[27]

Critical Appraisal

The TRIM-D demonstrated good internal consistency (with Cronbach's alphas > 0.7 and < 0.95) and acceptable test-retest reliability (with coefficients > 0.7). Good construct validity of the five domains and the total score of the TRIM-D were supported by a priori hypotheses (demonstrating moderate to strong associations) and known-groups methods. Most items of the TRIM-D were responsive in an RCT setting of T1DM and T2DM patients, but five did not respond as expected. Further validation of the TRIM-D should also be considered (1) in different subpopulations of T1DM and T2DM, (2) in different countries or languages and cultural settings, (3) using non–Web-based methods, and (4) using non–patient-reported outcomes and clinical factors to assess validity. At present, no MCID has been determined for the TRIM-D.

Treatment-Related Impact Measure — Hypoglycemic Events

The Treatment-Related Impact Measure — Hypoglycemic Events (TRIM-HYPO), a patient-reported outcome measure, was developed in English by The Brod Group in collaboration with Novo Nordisk A/S and Health Research Associates, Inc. The TRIM-HYPO was developed to measure the impact of non-severe hypoglycemic events on patients' HRQoL arising from the use of insulin to treat both forms of diabetes (T1DM and T2DM). TRIM-HYPO is a self-reported questionnaire, comprising 33 Likert-like scale items (scored 1 to 5) in five domains: daily functioning, emotional well-being, diabetes management, work productivity, and sleep disruption.[29]

Domains are scored individually. A total score is also calculated using three of the five domains (daily functioning, emotional well-being, and diabetes management), as work productivity and sleep disruption do not apply to all patients. Lower scores on the TRIM-HYPO indicate a better health state. Raw scores are obtained by aggregating scale items into their respective domain scales. A weighted score is then generated based by the number of non-severe hypoglycemic occurrences in the past 30 days: the higher the number, the greater the impact on the weighted score. This weighting helps account for the

difference in HRQoL of patients experiencing few versus those experiencing many hypoglycemic events. A standard algorithm method transforms the weighted scores into a 0 to 100 score. No MCID has been determined for the TRIM-HYPO.[29]

Validation of the Treatment-Related Impact Measure — Hypoglycemic Events in Type 1 and Type 2 Diabetes Mellitus

Content validity was addressed during instrument development. Item development was initially generated from literature review, expert opinion, and focus groups (T1DM and T2DM patients requiring insulin). Responses were coded, grouped into domains, and assembled into an early version of the survey. Blocks of three individual telephone interviews of pre-filled early surveys were conducted to assess the instructions, readability, and relevance of items. Findings were reviewed and decisions made about changes to measures. These blocks of interviews continued until a consensus was met by an entire block. Edits made to the survey based on these interviews were reviewed by a final block before the validation began. The non-interventional validation study recruited 407 diabetes patients in the United States ranging from 18 years to 89 years (mean 50.2 years) to respond to Web-based questionnaires (including the initial five-domain, 46-item TRIM-HYPO along with a battery of other patient-reported measures relevant to hypoglycemia and HRQoL). Group characteristics included 48% female, 77.9% white, 10.3% African American, and 67.3% T2DM.[29]

Removal of items due to floor and ceiling effects (> 50% responses at extremes) and inter-item Pearson's correlations (> 0.7) led to the refined 33-item TRIM-HYPO. Principle component analysis supported the retention of all five domains. Item-to-scale correlations (or item-total correlations, which describe how well individual items behave relative to the scale average) ranged from 0.492 to 0.662. Item Response Theory was applied during the questionnaire refinement process. Rasch item reliability ranged from 0.95 to 0.98 (> 0.9 was considered an acceptable threshold), and item separation coefficients ranged from 4.20 to 7.37 (a threshold > 2.0 was considered appropriate). Fit analyses found that there were many responses above and below the items' coverage and that gaps between items existed.[29]

Reliability

Evaluation of internal consistency produced Cronbach's alpha coefficients of 0.86 to 0.95 (minimum threshold for consistency was 0.7). Test-retest analysis was performed using data from a subset of 42 patients who completed the questionnaire within the permitted time gap of three weeks, with coefficients for total score measured at 0.84 and those for the subscales ranging from 0.75 to 0.98.[29]

Validity

Convergent validity was reported based on a priori hypotheses using a two-tailed Pearson's correlation coefficient (significance $P < 0.05$, with coefficients > 0.40 considered evidence of moderate to strong associations). All hypotheses tested showed significant correlations ($P < 0.01$) between the total (or subscale) scores and the related measures tested. Anchors included the following:

- Activity Impairment Assessment total score
- Psychological General Well-being Index global score
- Insulin Treatment Satisfaction Questionnaire, HYPO control domain score
- Medical Outcomes Survey — Sleep, problems index I and II

- Work Productivity and Activity Impairment, per cent overall work impairment due to problem
- Sheehan Disability Scale

Known-group validity testing confirmed all but one known-group hypothesis ($P < 0.001$ or $P < 0.0001$) and the expected discrimination between the known relationships.[29] These known groups were based on the following:

- Self-reported hypoglycemia management
- Quality of Life Enjoyment and Satisfaction Questionnaire — Short Form, total score
- Self-reported recovery time after hypoglycemic event
- UCLA Loneliness Scale, total score
- Self-reported level of emotional well-being
- Treatment Satisfaction Questionnaire for Medication (ver. 2), side effect subscale score
- Self-report on extra blood glucose monitoring after a hypoglycemic event
- Fatigue Symptom Inventory, severity of fatigue domain score
- Self-reported number of nocturnal hypoglycemic events within last 30 days
- Self-reported recovery time after nocturnal hypoglycemic event
- Self-reported degree of hypoglycemia interference with work.

Critical Appraisal

The TRIM-HYPO was specifically developed for use by patients with diabetes as a means of comprehensively assessing the impact of non-severe hypoglycemia, an important side effect of insulin therapy. A preliminary study confirmed aspects of the measure's validity (content validity, construct validity, and reliability).[29] Further steps may be required to fully develop the TRIM-HYPO for use in the diabetes population, as item analysis identified deficiencies in item coverage and gaps between some items. Further validation should also be considered (1) in different subpopulations of T1DM and T2DM, (2) in different countries or languages and cultural settings, (3) using non–Web-based methods, (4) using non–patient-reported outcomes and clinical factors to assess validity, and (5) to assess MCID and responsiveness using longitudinal data and the selection of anchors appropriate to the study and the long-term outcomes in diabetes. To date, no MCID is available for this measure.

Summary

The SF-36 was developed as a generic HRQoL measure and has shown good validity and reliability in diabetes populations; however, the performance of each dimension, and of the summary component scores, varies between populations and according to study design. No MCID has been established in diabetes populations. The SF-36 should be used in combination with other instruments when studying the HRQoL of patients with diabetes. The TRIM-D is a patient-reported outcome measure that was developed to address gaps in the reporting of treatment impact in both forms of diabetes. The TRIM-D demonstrated good internal consistency and acceptable test-retest reliability. Most items of the TRIM-D were responsive in an RCT setting of T1DM and T2DM patients, but five did not respond as expected. No MCID has been determined for the TRIM-D. The TRIM-HYPO was developed to comprehensively assess the impact of non-severe hypoglycemia in patients with diabetes, and only one study was found to assess the validity of the measure. No MCID is currently available.

Appendix 5: Detailed Outcome Data

Table 39: Type 1 Diabetes Mellitus — Studies 3770 and 3583

		Study 3770, BEGIN, Flex T1	Study 3583
Designs and Populations	**Study Design**	OL RCT	OL RCT
	Locations	US, Europe	US, South Africa, Europe
	Randomized (N)	493	629
	Inclusion Criteria	Males or females ≥ 18 years of age T1DM (diagnosed clinically and treated on basal-bolus regimen) for ≥ 12 months, the last 3 months with injection-based therapies Current treatment with any basal insulin (e.g., IGlar, IDet, NPH insulin) using 1 or 2 daily injections and no fewer than three injections with bolus insulin (e.g., IAsp, insulin lispro, insulin glulisine, human insulin) as mealtime bolus insulin therapy A1C ≤ 10.0% by central laboratory analysis BMI ≤ 35.0 kg/m^2 Ability to self-manage insulin therapy as assessed by confirmation (verbal confirmation at screening visit) of a changed bolus insulin dose within the 2 months before screening	Males or females ≥ 18 years of age T1DM (diagnosed clinically) ≥ 12 months Current treatment with any basal-bolus insulin regimen for at least 12 months before visit 1 A1C ≤ 10.0% by central laboratory analysis BMI ≤ 35.0 kg/m^2
	Exclusion Criteria	Use within last 3 months before visit 1 of any antidiabetes glucose-lowering drug other than insulin Initiation or significant change of any systemic treatment which, in the investigator's opinion, could interfere with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN Impaired renal function, defined as serum creatinine ≥ 180 µmol/L Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal	Use within the last 3 months before visit 1 of any antidiabetes glucose-lowering drug other than insulin Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT > 2.5 × ULN Impaired renal function, defined as serum creatinine ≥ 180 µmol Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during the last 12 months) or hypoglycemic unawareness or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)

		Study 3770, BEGIN, Flex T1	Study 3583
		cell skin cancer or squamous cell skin cancer)	
Drugs	**Intervention**	IDeg-Flex IDeg administered q.d. in a flexible dosing regimen in a rotating schedule with approximately 8-hour, 24-hour, or 40-hour intervals between doses IDeg q.d. combined with 3 or more injections of IAsp	IDeg q.d. injected s.c. IAsp was to be injected just before each main meal (breakfast, lunch, and dinner) and was to be titrated individually based on the pre-meal PG values
	Comparators	IGlar q.d. combined with 3 or more injections of IAsp	IGlar q.d. injected s.c. IAsp was to be injected just before each main meal (breakfast, lunch and dinner) and was to be titrated individually based on the pre-meal PG values NPH insulin b.i.d.
Duration	**Phase**	**3**	**3**
	Screen	1 week	1 week
	Double-blind	26 weeks	52 weeks
	Follow-up	1 week	1 week
Outcomes	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks	Change from baseline in A1C (%) after 52 weeks
	Other End Points	**Supportive secondary end points** Responder is a dichotomous end point defined based on whether a patient met the ADA A1C target (A1C < 7%). Change in FPG from baseline **SMPG** 9-point profile • mean • fluctuation • prandial PG increment • changes in nocturnal SMPG measurements 4-point profile obtained throughout the trial for dose adjustment • mean PG before meal • responder for PG titration target • time from randomization (measured in weeks) to achieve titration target • within-patient variability as measured by CV% **Safety** AEs including injection-site disorders Number of hypoglycemic episodes classified both according to Novo Nordisk A/S and ADA definitions Body weight	Number of nocturnal severe or minor hypoglycemic episodes Number of severe or minor hypoglycemic episodes Change from baseline in FPG after 52 weeks of treatment (analyzed at central laboratory) Within-patient variability in pre-breakfast PG after 52 weeks of treatment **Supportive secondary end points** A1C responder end points SMPG 9-point profile SMPG values used for dosing Continuous glucose monitoring Mean variation and nighttime characteristics of IGlar profile Meal characteristics Near hypoglycemic and hyperglycemic episodes **Safety** AEs Number of hypoglycemic episodes classified according to both ADA and the additional definition for minor episodes Body weight

		Study 3770, BEGIN, Flex T1	Study 3583
Notes	**Publications**	Mathieu 2013[5]	Bode 2013[49]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; IAsp = insulin aspart; IDeg = insulin degludec; IDeg-Flex = insulin degludec flexible dosing; IDet = insulin detemir; IGlar = insulin glargine; MI = myocardial infarction; NPH = neutral protamine Hagedorn; NYHA = New York Heart Association; OL RCT = open-label randomized controlled trial; q.d. = once daily; PG = plasma glucose; s.c. = subcutaneous; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSRs for Studies 3770[15] and 3583.[4]

Table 40: Type 1 Diabetes Mellitus — Study 3585

		Study 3585
Designs and Populations	**Study Design**	OL RCT
	Locations	Europe, Japan, South America, India
	Randomized (N)	456
	Inclusion Criteria	Males or females ≥ 18 years of age (≥ 20 years for Japan) T1DM ≥ 12 months Current treatment with any basal-bolus insulin regimen for ≥ 12 months before visit 1 A1C ≤ 10.0% by central laboratory analysis BMI ≤ 35.0 kg/m^2
	Exclusion Criteria	Use within the last 3 months before visit 1 of any antidiabetes glucose-lowering drug other than insulin Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN Impaired renal function, defined as serum creatinine ≥ 180 µmol/L (one retest within a week from receipt of the result permitted, last sample being conclusive) Recurrent severe hypoglycemia (> 1 severe hypoglycemic episode during the last 12 months) or hypoglycemic unawareness or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal or squamous cell skin cancer)
Drugs	**Intervention**	IDeg q.d. injected s.c. in the evening IAsp as bolus insulin, injected s.c. in the abdomen as mealtime insulin
	Comparators	IDet q.d. injected s.c. in the evening IAsp as bolus insulin, injected s.c. in the abdomen as mealtime insulin
Duration	**Phase**	**3**
	Screening	1 week

		Study 3585
	Double-blind	26 weeks
	Follow-up	1 week
Outcomes	**Primary End Point**	A1C (after 26 weeks of treatment)
	Other End Points	Nocturnal severe and minor hypoglycemic episodes Severe or minor hypoglycemic episodes Change from baseline in FPG after 26 weeks Variability in pre-breakfast SMPG after 26 weeks A1C responder end points SMPG **Safety** AEs Number of hypoglycemic episodes (ADA) Body weight
Notes	**Publications**	Davies 2016[50]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; IAsp = insulin aspart; IDeg = insulin degludec; IDet = insulin detemir; MI = myocardial infarction; NYHA = New York Heart Association; OL RCT = open-label randomized controlled trial; q.d. = once daily; s.c. = subcutaneous; SMPG = self-measured plasma glucose; T1DM = type 1 diabetes mellitus; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3585.[16]

Table 41: Type 2 Diabetes Mellitus, Insulin-Naive — Studies 3586 and 3579

		Study 3586	Study 3579
Designs and Populations	**Study Design**	OL RCT	OL RCT
	Locations	Asia	Canada, US, Europe
	Randomized (N)	435	1,030
	Inclusion Criteria	Male or female ≥ 18 years old (≥ 20 years for Japan) T2DM (diagnosed clinically) ≥ 6 months Insulin-naive patients (allowed were previous short-term insulin treatment up to 14 days, or treatment during hospitalization or during gestational diabetes for periods longer than 14 days) Current treatment with monotherapy or combination of an insulin secretagogue and metformin, with or without addition of alpha-glucosidase inhibitors or a DPP-4 inhibitor with unchanged dosing for at least 3 months before visit 1 with	Male or female ≥ 18 years of age T2DM (diagnosed clinically) for ≥ 6 months Insulin-naive patients (allowed were previous short-term insulin treatment up to 14 days, or treatment during hospitalization or during gestational diabetes for periods longer than 14 days) Current treatment with metformin monotherapy or metformin in any combination with an insulin secretagogue (SU or glinide), DPP-4 inhibitor, or alpha-glucosidase inhibitors (acarbose) with unchanged dosing for at least 3 months before visit 1 with the minimum doses stated: • Metformin: alone or in combination (including fixed combination) 1,500 mg daily, or maximum tolerated dose (at least 1,000 mg daily) • Insulin secretagogue (SU or glinide): minimum half of the daily maximal dose or according to local labelling • DPP-4 inhibitor: minimum 100 mg daily or according to local labelling • Alpha-glucosidase inhibitors (acarbose): minimum half of the daily

		Study 3586	Study 3579
		the minimum doses stated: • Insulin secretagogue (SU or glinide): minimum half of the daily maximal dose according to local labelling • Metformin: alone or in combination (including fixed combination), maximum tolerated dose • Alpha-glucosidase inhibitors: minimum half of the daily maximal dose or maximum tolerated dose • DPP-4 inhibitor: according to local labelling A1C 7.0% to 10.0% (both inclusive) by central laboratory analysis BMI ≤ 35.0 kg/m^2	maximal dose or maximum tolerated dose A1C 7.0% to 10.0% (both inclusive) by central laboratory analysis BMI ≤ 40.0 kg/m^2
	Exclusion Criteria	Use within the last 3 months before visit 1 of TZD, exenatide, or liraglutide Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN (one retest analyzed at the central laboratory within a week from receipt of the result permitted, with the result of the last sample being conclusive) Impaired renal function, defined as serum creatinine ≥ 125 µmol/L for males and ≥ 110 µmol/L for females (one retest within a week from receipt of the	Use within the last 3 months before visit 1 of TZDs, exenatide, or liraglutide Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Metformin contraindications or restrictions according to approved labelling Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN (one retest analyzed at the central laboratory within a week from receipt of the result permitted, with the result of the last sample being conclusive) Impaired renal function, defined as serum creatinine ≥ 125 µmol/L for males and ≥ 110 µmol/L for females or according to local label for metformin Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, or the intention of becoming pregnant or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)

		Study 3586	Study 3579
		result permitted, with the result of the last sample being conclusive) Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, or the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)	
DRUGS	**Intervention**	IDeg q.d. injected s.c. in the evening Continue treatment with OAD(s) at the stable, pre-randomization dose regimen, except for DPP-4 inhibitors, which were to be discontinued	IDeg q.d. added to metformin ± DPP-4 inhibitor treatment (according to local labelling) as used before randomization
	Comparator	IGlar q.d. injected s.c. In combination with OAD(s)	IGlar q.d. added to metformin ± DPP-4 inhibitor treatment (according to local labelling) as used before randomization
DURATION	**Phase**	**3**	**3**
	Screen	1 week	1 week
	Double-blind	26 weeks	52 weeks
	Follow-up	1 week	1 week (minimum)
OUTCOMES	**Primary End Point**	A1C (after 26 weeks of treatment)	A1C (after 52 weeks of treatment)
	Other End Points	**Confirmatory secondary end points** Number of treatment-emergent severe or minor hypoglycemic episodes Change from baseline in FPG after 26 weeks Within-patient variability as measured by CV% in self-measured FPG after 26 weeks Responder without	**Confirmatory secondary end points** Number of treatment-emergent confirmed hypoglycemic episodes Change from baseline in FPG after 52 weeks of treatment Within-patient variability as measured by CV% in self-measured FPG after 52 weeks of treatment Responder without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks) **Supportive secondary end points**

		Study 3586	Study 3579
		hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks) **Supportive secondary efficacy end points** A1C responder end points SMPG **Other** DiabMedSat DPM SF-36v2 TRIM-D Hypoglycemic Episode Interview Questionnaire **Safety** AEs Number of hypoglycemic episodes according to the ADA definition and the additional definition for minor episodes Body weight Insulin dose	A1C responder end points SMPG Continuous glucose monitoring Meal characteristics Low or high interstitial glucose **Safety** AEs Number of hypoglycemic episodes Body weight Insulin dose Hypoglycemic episodes
NOTES	**Publications**	Onishi 2013;[51] Davies 2014[52]	Rodbard 2013[53]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; CV = coefficient of variation; DiabMedSat DPM = Diabetes Medication Satisfaction Questionnaire — Productivity Measure; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; IDeg = insulin degludec; IGlar = insulin glargine; MI = myocardial infarction; NYHA = New York Heart Association; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; s.c. = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; TZD = thiazolidinedione; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSRs for Studies 3579[17] and 3586.[20]

Table 42: Type 2 Diabetes Mellitus, Insulin-Naive — Study 3672

		Study 3672
Designs and Populations	**Study Design**	OL RCT
	Locations	Canada, US, Europe, South Africa
	Randomized (N)	460
	Inclusion Criteria	Male or female ≥ 18 years of age T2DM (diagnosed clinically) for > 6 months Insulin-naive (allowed previous short-term insulin treatment up to 14 days, or treatment during hospitalization or during gestational diabetes for periods longer than 14 days) Current treatment: metformin monotherapy or metformin in any combination with insulin secretagogues, DPP-4 inhibitor, alpha-glucosidase inhibitor with unchanged dosing for at least 3 months before visit 1 with the minimum doses stated: • Metformin: alone or in combination (including fixed combination) 1,500 mg daily or maximum tolerated dose (at least 1,000 mg daily) • Insulin secretagogue: minimum half of the daily maximal dose according to local labelling • DPP-4 inhibitor: minimum half of the daily maximal dose according to local labelling • Alpha-glucosidase inhibitor: minimum half of the daily maximal dose or maximum tolerated dose A1C 7.0% to 10.0% (both inclusive) by central laboratory analysis BMI ≤ 45.0 kg/m^2
	Exclusion Criteria	Use within the last 3 months before visit 1 of TZDs, exenatide, or liraglutide Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP ≥ 180 mm Hg or BP ≥ 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN (one retest analyzed at the central laboratory within a week of receipt of the result permitted, with the result of the last sample being conclusive) Impaired renal function, defined as serum creatinine > 125 µmol/L for males and > 110 µmol/L for females or according to local label for metformin Recurrent severe hypoglycemia (> 1 severe hypoglycemic episode during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)
Drugs	**Intervention**	IDeg q.d. 200 U/mL s.c., administered with the main evening meal in combination with metformin ± DPP-4 inhibitor treatment as used before randomization
	Comparators	IGlar q.d. administered at the same time each day in combination with metformin ± DPP-4 inhibitor treatment as used before randomization
Duration	**Phase**	**3**
	Screen	1 week
	Double-blind	26 weeks
	Follow-up	1 week (minimum)

		Study 3672
Outcomes	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks
	Other End Points	Number of confirmed hypoglycemic episodes Change from baseline in FPG Within-patient variability in pre-breakfast SMPG Responder without hypoglycemic episodes (A1C < 7.0% at end of trial and no confirmed episodes during the last 12 weeks of treatment including only patients exposed for at least 12 weeks) **Supportive secondary efficacy end points** A1C responder end points SMPG **Other** DiabMedSat DPM TRIM SF-36v2 Hypoglycemic Episode Interview Questionnaire **Safety and tolerability (throughout trial)** AEs Number of hypoglycemic episodes according to the ADA definition and the additional definition for minor episodes Body weight
Notes	**Publications**	Gough 2013[54]

A1C = glycated hemoglobin; ADA = American Diabetes Association; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; DiabMedSat DPM = Diabetes Medication Satisfaction Questionnaire — Productivity Measure; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; IDeg = insulin degludec; IGlar = insulin glargine; MI = myocardial infarction; NYHA = New York Heart Association; OL RCT = open-label randomized controlled trial; q.d. = once daily; s.c. = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; TRIM = Treatment-Related Impact Measure; TZD = thiazolidinedione; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3672.[19]

Table 43: Type 2 Diabetes Mellitus, Insulin-Naive — Study 3580

		Study 3580: BEGIN Early
Designs and Populations	**Study Design**	OL RCT
	Locations	Argentina, Canada, India, Mexico, South Africa, Turkey, US
	Randomized (N)	458
	Inclusion Criteria	Males or females ≥ 18 years of age T2DM (diagnosed clinically) for ≥ 6 months Insulin-naive (except for short treatment duration ≤ 14 days or during gestational diabetes) DPP-4 inhibitor-naive Ongoing treatment with 1 or 2 of the following OADs: metformin, insulin secretagogue (SU or glinides) or pioglitazone, unchanged dose ≥ 3 months BMI ≤ 40.0 kg/m^2 A1C 7.5% to 11.0% (7.5% to 10.0% for Argentina) by central laboratory analysis
	Exclusion Criteria	Use within the last 3 months before visit 1 of exenatide, liraglutide, rosiglitazone, or acarbose Anticipated change in concomitant medication known to interfere significantly with glucose

		Study 3580: BEGIN Early
		metabolism, such as systemic corticosteroids, beta-blockers, or monoamine oxidase inhibitors Contraindications or restrictions against using the antidiabetes medication allowed in the trial Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension: systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg (systolic BP ≥ 150 mm Hg or diastolic BP ≥ 90 mm Hg for Argentina) Impaired liver function, defined as ALAT ≥ 2.5 × ULN (one retest analyzed at the central laboratory within a week of receipt of the result permitted, with the result of the last sample being conclusive) Impaired renal function, defined as serum creatinine ≥ 125 µmol/L for males and ≥ 110 µmol/L for females or according to local label for metformin use (one retest within a week of receipt of the result permitted, with the result of the last sample being conclusive) Recurrent severe hypoglycemia (> 1 severe hypoglycemic episode during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer)
DRUGS	**Intervention**	IDeg q.d. injected s.c., added on to any combination of 1 to 2 OADs (metformin, SU, glinides, or pioglitazone)
	Comparator	Sitagliptin q.d., oral, added on to any combination of 1 to 2 OADs (metformin, SU, glinides, or pioglitazone)
DURATION	**Phase**	**3**
	Screening	1 week
	Treatment period	26 weeks
	Follow-up	1 to 2 weeks
OUTCOMES	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks of treatment
	Other End Points	**Confirmatory secondary end points** Change from baseline in FPG after 26 weeks of treatment (analyzed at central laboratory) Frequency of responders (A1C < 7.0% at end of trial) Frequency of responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment) **Supportive secondary end points** A1C responder end points FPG SMPG (9-point profile) Patient-reported outcomes: SF-36v2, TRIM-D, Hypoglycemic Episode Interview Questionnaire **Safety end points** AEs Number of hypoglycemic episodes classified according to the ADA definition and the additional definition for minor episodes **Safety and tolerability (throughout trial)** Body weight Insulin dose and time point of administration

		Study 3580: BEGIN Early
Notes	**Publications**	Philis-Tsimikas 2013[55]

A1C = glycated hemoglobin; ADA = American Diabetes Association; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; IDeg = insulin degludec; MI = myocardial infarction; NYHA = New York Heart Association; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; s.c. = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3580.[18]

Table 44: Type 2 Diabetes Mellitus, Insulin-Naive — Study 3587

		Study 3587
Designs and Populations	**Study Design**	OL RCT
	Locations	Brazil, Canada, China, South Africa, Ukraine, US
	Randomized (N)	833
	Inclusion Criteria	≥18 years of age T2DM diagnosed clinically for ≥ 6 months A1C between 7.0 and 10.0 % (both inclusive) BMI ≤ 40 kg/m^2 Insulin-naive, and treated with stable doses of OADs (metformin monotherapy or in combination with an insulin secretagogue, DPP-4 inhibitor, or alpha-glucosidase inhibitors) for ≥ 3 months before randomization
	Exclusion Criteria	Treatment with TZD or GLP-1 receptor agonists within 3 months before screening, cardiovascular disease within 6 months before screening, uncontrolled severe hypertension, impaired hepatic or renal function, current or medical history of cancer, recurrent severe hypoglycemia, proliferative retinopathy or maculopathy, or use of non-herbal Chinese medicine with unknown content
Drugs	**Intervention**	IDeg 100 U/mL q.d. for 26 weeks
	Comparators	IGlar 100 U/mL q.d. for 26 weeks
Duration	**Phase**	**3**
	Screen	1 week
	Double-blind	26 weeks
	Follow-up	1 week minimum
Outcomes	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks
	Other End Points	Responders in A1C (patients achieving A1C < 7 and ≤ 6.5 %) Responders in A1C without confirmed hypoglycemic episodes during the last 12 weeks of treatment Change in central laboratory–measured FPG SMPG (9-point profile) Within-patient variability (CV%) in pre-breakfast SMPG HRQoL assessed by SF-36v2 and TRIM-D
Notes	**Publications**	Pan 2016[56]

A1C = glycated hemoglobin; BMI = body mass index; CV = coefficient of variation; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HRQoL = health-related quality of life; IDeg = insulin degludec; IGlar = insulin glargine; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; TZD = thiothiazolidinedione.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3587.[21]

Table 45: Type 2 Diabetes Mellitus, Insulin-Naive — Study 3944

		Study 3944
Designs and Populations	**Study Design**	DB RCT
	Locations	Canada, US, Europe, Israel, United Arab Emirates, South Africa
	Randomized (N)	346
	Inclusion Criteria	≥ 18 years T2DM not previously treated with insulin BMI ≤ 45 kg/m^2 Patients had to be receiving ongoing therapy with metformin ± an SU, glinide, DPP-4 inhibitor, or exenatide (twice daily only), and had to have an A1C level of 7.5% to 10.0% inclusive (patients on metformin monotherapy) or 7.0% to 9.0% inclusive (patients on metformin combination therapy).
	Exclusion Criteria	Calcitonin level ≥ 50 ng/L History of chronic pancreatitis or idiopathic acute pancreatitis Current or past malignant neoplasm (except basal cell and squamous cell carcinoma)
Drugs	**Intervention**	IDeg 10U q.d. s.c. in addition to liraglutide and metformin
	Comparators	Placebo once daily subcutaneously in addition to liraglutide and metformin
Duration	**Phase**	**3**
	Run-in	1-week screening, 15-week run-in (liraglutide)
	Treatment period	26 weeks
	Follow-up	1 week minimum
Outcomes	**Primary End Point**	Change from baseline in A1C after 26 weeks
	Other End Points	Change in FPG Percentage of responders achieving A1C < 7.0% Change from baseline in the following: • mean pre-breakfast SMPG measurements used for titration of IDeg + placebo dose • 8-point SMPG profile • mean of the 8-point profile Changes from baseline in body weight and HRQoL, and dose of IDeg + placebo
Notes	**Publications**	Aroda 2016[57]

A1C = glycated hemoglobin; BMI = body mass index; DB RCT = double-blind randomized controlled trial; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; HRQoL = health-related quality of life; IDeg = insulin degludec; q.d. = once daily; s.c. = subcutaneous; SMPG = self-measured plasma glucose; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3944.[22]

Table 46: Type 2 Diabetes Mellitus, Basal Insulin Only ± Oral Antidiabetes Drug — Study 3668

		Study 3668 Flex
Designs and Populations	**Study Design**	OL RCT
	Locations	Europe, Mexico, S America, Asia, India, South Africa
	Randomized (N)	687
	Inclusion Criteria	Male or female ≥ 18 years of age T2DM (diagnosed clinically) for ≥ 6 months Current treatment: OAD(s) alone, basal insulin alone, or a combination of OAD(s) and basal insulin; allowed OADs (alone or in combination with basal insulin) were metformin, insulin secretagogues, or pioglitazone with unchanged dosing for at least 3 months before visit 1 with the minimum doses stated: • Metformin: alone or in combination (including fixed combination) 1,500 mg daily, or maximum tolerated dose (at least 1,000 mg daily) • Insulin secretagogue (SU or glinide): minimum half the daily maximal dose according to local labelling • Pioglitazone: minimum half the daily maximal dose according to local labelling or maximum tolerated dose A1C: OAD-only users with A1C 7.0% to 11.0 % (both inclusive); basal insulin ± OADs users with A1C 7.0% to 10.0% (both inclusive) by central laboratory analysis BMI ≤ 40.0 kg/m^2
	Exclusion Criteria	Use within the last 3 months before visit 1 of GLP-1 agonists, rosiglitazone, DPP-4 inhibitors, alpha-glucosidase inhibitors Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension (systolic BP > 180 mm Hg or diastolic BP > 100 mm Hg) Impaired liver function, defined as ALAT ≥ 2.5 × ULN (one retest analyzed at the central laboratory within a week of receipt of the result permitted, with the result of the last sample being conclusive) Impaired renal function, defined as serum creatinine of ≥ 125 µmol/L for males and ≥ 110 µmol/L for females or according to local label for metformin use Recurrent severe hypoglycemia (> 1 severe hypoglycemic event during last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer and squamous cell skin cancer)
Drugs	**Intervention**	IDeg-Flex ± OADs: IDeg injected q.d. in a fixed-flexible injection scheme IDeg q.d. ± OADs: IDeg injected q.d. with evening meal
	Comparator	IGlar q.d. ± OADs: IGlar injected q.d. according to local labelling
Duration	**Phase**	**3**
	Screen	1 week
	Double-blind	26 weeks
	Follow-up	1 week (minimum)

		Study 3668 Flex
Outcomes	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks
	Other End Points	A1C responder end points FPG SMPG 9-point profile (SMPG) SMPG values used for dosing **Safety** AEs Number of hypoglycemic episodes (ADA) Body weight
Notes	**Publications**	Meneghini 2013[58]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; BMI = body mass index; BP = blood pressure; DKA = diabetic ketoacidosis; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; IDeg = insulin degludec; IGlar = insulin glargine; MI = myocardial infarction; NYHA = New York Heart Association; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; ULN = upper limit of normal; UAP = unstable angina pectoris.
Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).
Source: CSR for Study 3668.[23]

Table 47: Type 2 Diabetes Mellitus, Basal Insulin Only ± Oral Antidiabetes Drug — Study 3943

		Study 3943
Designs and Populations	**Study Design**	OL RCT (crossover)
	Locations	US
	Randomized (N)	145
	Inclusion Criteria	≥ 18 years of age T2DM (diagnosed clinically) for ≥ 24 weeks before visit 1 Current treatment with once-daily IGlar in vials with a daily dose ≥ 65 U and ≤ 100 U Current treatment with a stable dose of metformin ± one additional OAD for ≥ 12 weeks before visit 1 A1C ≥ 7.5%
	Exclusion Criteria	Treatment with insulin other than IGlar in vials within 24 weeks before visit 1 Treatment with TZDs within the last 12 weeks before visit 1 Treatment with GLP-1 receptor agonists within the last 12 weeks before visit 1 Stroke, heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty, all within the last 24 weeks before visit 1 Uncontrolled or untreated severe hypertension, defined as systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg Proliferative retinopathy or maculopathy requiring treatment; verification by fundoscopy or fundus photography performed within 12 weeks before visit 1 Impaired liver function Impaired renal function Cancer (except basal cell skin cancer and squamous cell cancer) Female of child-bearing potential who is pregnant (as determined by central laboratory beta-hCG) or breastfeeding, intends to become pregnant, or is not using adequate contraceptive methods Recurrent severe hypoglycemia (more than one severe hypoglycemic event during last 12 months)

		Study 3943
		or hypoglycemic unawareness as judged by the investigator
Drugs	**Intervention**	IDeg 200 U/mL q.d., treat-to-target
	Comparator	IGlar 100 U/mL q.d., treat-to-target
Duration	**Phase**	**3**
	Screen/Run-in	1-week screening; 16-week run-in (all participants on IGlar, discontinuing OAD)
	Double-blind	32 weeks (crossover: 16 weeks in each treatment period)
	Follow-up	1 week
Outcomes	**Primary End Point**	Change from baseline in A1C
	Other End Points	A1C responder Change from baseline in FPG SMPG Patient-reported outcomes (SF-36, TRIM-D) **Safety** AEs Hypoglycemia Number of treatment-emergent hypoglycemic episodes according to both the ADA definition and the Novo Nordisk definition for minor hypoglycemic episodes Number of treatment-emergent nocturnal (00:01 a.m. to 05:59 a.m.) severe or minor hypoglycemic episodes Changes from baseline in body weight at the end of each 16-week treatment period Insulin dose at the end of each 16-week treatment period Withdrawal rate and reason for withdrawal (if available)
Notes	**Publications**	Warren 2017[59]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; IDeg = insulin degludec; IGlar = insulin glargine; MI = myocardial infarction; NYHA = New York Heart Association; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; TZD = thiazolidinedione; UAP = unstable angina pectoris.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3943.[24]

Table 48: Type 2 Diabetes Mellitus, Basal-Bolus ± Oral Antidiabetes Drug — Study 3582

		Study 3582 (BBT2)
Designs and Populations	**Study Design**	OL RCT
	Locations	Bulgaria, Germany, Hong Kong, Ireland, Italy, Romania, Russia, Slovakia, South Africa, Spain, Turkey, US
	Randomized (N)	1,006
	Inclusion Criteria	Males or females ≥ 18 years of age T2DM (diagnosed clinically) for ≥ 6 months Current treatment with any insulin regimen — premix, self-mix, basal only, basal-bolus (one or more boluses), bolus-only, or pump — for at least 3 months ± OAD(s) before visit 1 BMI ≤ 40.0 kg/m^2 A1C 7.5% to 11.0% by central laboratory analysis

		Study 3582 (BBT2)
	Exclusion Criteria	Use within the last 3 months before visit 1 of GLP-1 receptor agonist (exenatide, liraglutide) or rosiglitazone Anticipated change in concomitant medication known to interfere significantly with glucose metabolism Contraindications or restrictions against using the antidiabetes medication allowed in the trial For pioglitazone users: clinically significant peripheral edema or contraindications or restrictions against pioglitazone use Cardiovascular disease within the last 6 months before visit 1, defined as stroke, decompensated heart failure NYHA class III or IV, MI, UAP, or coronary arterial bypass graft or angioplasty Uncontrolled treated or untreated severe hypertension: systolic BP ≥ 180 mm Hg or diastolic BP ≥ 100 mm Hg (systolic BP ≥ 150 mm Hg or diastolic BP ≥ 90 mm Hg for Argentina) Impaired liver function, defined as ALAT ≥ 2.5 × ULN Impaired renal function, defined as serum creatinine ≥ 125 µmol/L for males and ≥ 110 µmol/L for females or according to local label for metformin use Recurrent severe hypoglycemia (> 1 severe hypoglycemic episode during the last 12 months) or hypoglycemic unawareness as judged by the investigator or hospitalization for DKA during the previous 6 months Proliferative retinopathy or maculopathy requiring treatment according to the investigator Pregnancy, breastfeeding, the intention of becoming pregnant, or not using adequate contraceptive measures according to local requirements Cancer or medical history of cancer (except basal cell skin cancer or squamous cell skin cancer).
DRUGS	**Intervention**	IDeg q.d. injected s.c. and IAsp injected s.c. at mealtime, and current regimen of any combination of metformin and pioglitazone (if applicable); all other OADs discontinued
	Comparators	IGlar q.d. injected s.c. and IAsp injected s.c. at mealtime, and current regimen of any combination of metformin and pioglitazone (if applicable); all other OADs discontinued
DURATION	**Phase**	**3**
	Screening	1 week
	Treatment	52 weeks
	Follow-up	1 to 2 weeks
OUTCOMES	**Primary End Point**	Change from baseline in A1C (%) after 26 weeks
	Other End Points	**Confirmatory secondary end points** Number of severe or minor hypoglycemic episodes Change from baseline in FPG after 52 weeks Within-patient variability in pre-breakfast SMPG after 52 weeks Responders without hypoglycemic episodes (A1C < 7.0% at end of trial and no severe or minor hypoglycemic episodes during the last 12 weeks of treatment, including only patients exposed for at least 12 weeks) **Supportive Secondary End points** A1C responder end points SMPG (9-point profile) Patient-reported outcomes: DiabMedSat DPM, SF-36v2, TRIM-D, Hypoglycemic Episode Interview Questionnaire **Safety end points** AEs Number of hypoglycemic episodes classified according to the ADA definition and the additional definition for minor episodes

		Study 3582 (BBT2)
		Safety and tolerability (throughout trial) Body weight Insulin dose
NOTES	**Publications**	Garber 2012[60]; Hollander 2015[61]

A1C = glycated hemoglobin; ADA = American Diabetes Association; AE = adverse event; ALAT = alanine aminotransferase; BBT2 = basal-bolus type 2; BMI = body mass index; BP = blood pressure; DKA = diabetic ketoacidosis; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; IAsp = insulin aspart; IGlar = insulin glargine; MI = myocardial infarction; NYHA = New York Heart Association; OAD = oral antidiabetes drug; OL RCT = open-label randomized controlled trial; q.d. = once daily; s.c. = subcutaneous; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; T2DM = type 2 diabetes mellitus; TRIM-D = Treatment-Related Impact Measure — Diabetes; UAP = unstable angina pectoris; ULN = upper limit of normal.

Note: Three additional reports were included (FDA statistical and clinical reviews[10,11] and manufacturer submission[12]).

Source: CSR for Study 3582.[25]

Clinical Efficacy

Table 49: Key Efficacy Outcomes — Type 1 Diabetes Mellitus (Study 3770 + Extension)

	Study 3770			Study 3770-Ext	
	IDeg-Flex N = 164	**Degludec N = 165**	**Glargine N = 164**	**IDeg-Flex**	**Glargine**
A1C					
Mean (SD) baseline, %	7.7 (1.0)	7.7 (0.9)	7.7 (0.9)		
LSM (SE) change from baseline to 26 weeks, 52 weeks, FAS	−0.40 (0.05)	−0.41 (0.05)	−0.57 (0.05)	−0.13 (0.04) N = 329	−0.20 (0.05) N = 164
LS MD IDeg q.d. FF vs Glar q.d. (95% CI)[a]	0.17 (0.04 to 0.30)			0.07 (−0.05 to 0.19)	
LSM (SE) change from baseline to 26 weeks, PP	−0.43 (0.05)	−0.41 (0.05)	−0.59 (0.05)	NR	NR
Treatment contrast IDeg q.d. FF vs IGlar q.d. (95% CI)[a]	0.15 (0.01 to 0.29)				
LSM (SE) change from baseline to 26 weeks, 52 weeks, XTS				−0.09 (0.04)	−0.17 (0.06)
Treatment contrast (95% CI)				0.08 (−0.06 to 0.22)	
A1C < 7.0% (ADA)					
n (%), week 26 (LOCF)	61 (37.2)	61 (37.0)	67 (40.9)	91 (27.7)	42 (25.6)
Treatment odds ratio IDeg q.d. FF vs IGlar q.d. (95% CI)[b]	0.69 (0.40 to 1.21)			0.94 (0.55 to 1.59)	
A1C < 7.0% w/o Severe Hypo					
n (%), week 26 (LOCF)	54 (37.8)	56 (36.6)	60 (38.5)	85 (28.7)	37 (23.7)
Treatment odds ratio IDeg q.d. FF vs IGlar q.d. (95% CI)[b]	0.76 (0.43 to 1.33)			1.06 (0.62 to 1.84)	
A1C < 7.0% w/o Confirmed Hypo					
n (%), week 26 (LOCF)	4 (2.8)	8 (5.2)	5 (3.2)	10 (3.4)	3 (1.9)
Treatment odds ratio IDeg q.d. FF vs Glar q.d. (95% CI)[b]	0.72 (0.18 to 2.84)			1.50 (0.39 to 5.70)	
FPG					
Mean (SD) baseline, mmol/L	9.6 (4.1)	10.0 (4.0)	9.7 (4.2)	9.8 (4.0)	9.7 (4.2)
LSM (SE) change from baseline to 26 weeks, 52 weeks	−1.37 (0.30)	−2.32 (0.30)	−1.33 (0.30)	−1.71 (0.23)	−0.64 (0.32)

	Study 3770			Study 3770-Ext	
	IDeg-Flex N = 164	**Degludec N = 165**	**Glargine N = 164**	**IDeg-Flex**	**Glargine**
Treatment contrast IDeg q.d. FF vs IGlar q.d. (95% CI)	−0.05 (−0.85 to 0.76)			−1.07 (−1.82 to −0.32)	
Within-Patient Variation in SMPG for Dose Adjustment					
Pre-breakfast within-patient CV (%) after 26 weeks, 52 weeks	40.11	42.20	41.97	39.80	43.62
Treatment ratio IDeg q.d. FF vs IGlar q.d. (95% CI)	0.96 (0.84 to 1.07)			0.91 (0.82 to 1.01)	
Morbidity					
Adjudicated Cardiovascular Events, n (%)	2 (1.2)	1 (0.6)	0	4 (1.2)	3 (1.9)
MACE	0	0	0	1 (0.3)	2 (1.2)
Deaths					
Patients, n	0	1	0		
TRIM-D	NR				
HRQoL (SF-36)	NR				

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; IDeg-Flex = insulin degludec flexible dosing; Ext = extension; FAS = full analysis set; FF = fixed-flexible; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDeg = insulin degludec; IGlar = insulin glargine; LOCF = last observation carried forward; LSM = least squares mean; LS MD = least squares mean difference; MACE = major adverse cardiovascular event; NR = not reported; PP = per-protocol; q.d. = once daily; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without; XTS = extension trial set.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

Source: CSRs for Studies 3770 and 3770-ext.[15,31]

Table 50: Key Efficacy Outcomes — Type 1 Diabetes Mellitus (Study 3585 + Extension Study 3725)

	Study 3585		Study 3725 (Ext)	
	Degludec N = 303	**Detemir N = 152**	**Degludec**	**Detemir**
A1C				
Mean (SD) baseline, %	8.4 (0.8)	8.5 (0.8)		
LSM (SE) change from baseline to 26 weeks, 52 weeks, FAS	−0.71 (0.06)	−0.61 (0.07)	−0.48 (0.06)	−0.47 (0.08)
Treatment contrast[a,b] (95% CI)	−0.09 (−0.23 to 0.05) Noninferiority confirmed ($P < 0.001$)		−0.01 (−0.17 to 0.14)	
LSM (SE) change from baseline to 26 weeks, 52 weeks, PP	−0.71 (0.06)	−0.62 (0.07)	−0.48 (0.07)	−0.47 (0.08)
Treatment contrast (95% CI)[a]	−0.08 (−0.23 to 0.06)		−0.01 (−0.17 to 0.16)	
LSM (SE) change from baseline to 26 weeks, 52 weeks, XTS			−0.51 (0.07)	−0.54 (0.09)
Treatment contrast (95% CI)[a]			0.03 (−0.15 to 0.20)	
A1C < 7.0% (ADA)				
n (%), weeks 26, 53 (LOCF), FAS	124 (41.1)	57 (37.3)	95 (31.5)	49 (32.0)
Treatment odds ratio (95% CI)[c]	1.27 (0.77 to 2.09)		1.01 (0.61 to 1.65)	

	Study 3585		Study 3725 (Ext)	
	Degludec N = 303	**Detemir N = 152**	**Degludec**	**Detemir**
A1C ≤ 6.5% (IDF)				
n (%), weeks 26, 53 (LOCF), FAS	73 (24.2)	33 (21.6)	48 (15.9)	19 (12.4)
Treatment odds ratio (95% CI)[c]	1.15 (0.68 to 1.96)		1.43 (0.75 to 2.74)	
A1C < 7.0% w/o Severe Hypo				
n (%), weeks 26, 53 (LOCF), FAS	116 (39.7)	53 (36.6)	89 (30.5)	45 (31.0)
Treatment odds ratio (95% CI)[c]	1.26 (0.76 to 2.09)		1.03 (0.62 to 1.71)	
A1C ≤ 6.5% w/o Severe Hypo				
n (%), weeks 26, 53 (LOCF), FAS	69 (23.6)	30 (20.7)	45 (15.4)	18 (12.4)
Treatment odds ratio (95% CI)[c]	1.22 (0.70 to 2.12)		1.40 (0.72 to 2.72)	
A1C < 7.0% w/o Confirmed Hypo				
n (%), weeks 26, 53 (LOCF), FAS	18 (6.2)	10 (6.9)	19 (6.5)	17 (11.7)
Treatment odds ratio (95% CI)[c]	0.82 (0.32 to 2.08)		0.46 (0.19 to 1.09)	
A1C ≤ 6.5% w/o Confirmed Hypo				
n (%), weeks 26, 53 (LOCF), FAS	15 (5.1)	8 (5.5)	10 (3.4)	10 (6.9)
Treatment odds ratio (95% CI)[c]	0.83 (0.30 to 2.28)		0.46 (0.17 to 1.25)	
FPG				
Mean (SD) baseline, mmol/L	8.4 (2.1)	8.6 (1.9)		
LSM (SE) change from baseline to 26 weeks, 52 weeks, FAS	−2.40 (0.28)	−0.75 (0.35)	−2.51 (0.28)	−1.40 (0.35)
Treatment contrast (95% CI)	−1.66 (−2.37 to −0.95), *P* = NR		−1.11 (−1.83 to −0.40)	
Within-patient variability in pre-breakfast PG after 26 weeks, 52 weeks				
Within-patient variation (CV%)	36.1%	35.5%	37.41	33.49
Treatment ratio (95% CI)	1.02 (0.91 to 1.12), *P* = NT		1.12 (1.00 to 1.23)	
Morbidity				
Adjudicated cardiovascular events				
MACE	0	0	1 (0.3)	0
Deaths				
Patients, n	0	0	0	0
TRIM-D Scores				
Treatment Burden				
Mean (SD) baseline	55.0 (23.9)	56.1 (23.4)	NR	NR
LSM (SE) change	5.8 (1.3)	4.1 (1.7)		
Treatment contrast (95% CI)[a]	1.7 (−1.7 to 5.1)			
Daily Life				
Mean (SD) baseline	76.1 (18.3)	78.4 (16.7)	NR	NR
LSM (SE) change	0.2 (1.0)	−0.6 (1.3)	NR	NR
Treatment contrast (95% CI)[a]	0.8 (−1.8 to 3.4)		NR	NR
Diabetes Management				
Mean (SD) baseline	53.7 (20.8)	53.5 (21.8)	NR	NR
LSM (SE) change	2.2 (1.4)	−0.4 (1.7)	NR	NR
Treatment contrast (95% CI)[a]	2.5 (−0.9 to 6.0)		NR	NR
Compliance				
Mean (SD) baseline	74.9 (16.8)	77.4 (15.2)	NR	NR
LSM (SE) change	5.1 (1.1)	4.6 (1.4)	NR	NR
Treatment contrast (95% CI)[a]	0.5 (−2.3 to 3.3)		NR	NR

	Study 3585		Study 3725 (Ext)	
	Degludec N = 303	Detemir N = 152	Degludec	Detemir
Psychological Health				
Mean (SD) baseline	77.9 (17.4)	77.5 (18.6)	NR	NR
LSM (SE) change	0.8 (1.0)	−1.1 (1.2)	NR	NR
Treatment contrast (95% CI)[a]	1.9 (−0.6 to 4.5)			
TRIM-D Total				
Mean (SD) baseline	67.9 (14.4)	68.8 (14.3)	NR	NR
LSM (SE) change	2.7 (0.8)	0.9 (0.9)	NR	NR
Treatment contrast (95% CI)[a]	1.7 (−0.2 to 3.6)		NR	NR
HRQoL (SF-36) Scores				
Physical Score				
Mean (SD) baseline	52.2 (7.1)	52.2 (6.3)	NR	NR
LSM (SE) change	−1.0 (0.4)	−0.4 (0.5)	NR	NR
Treatment contrast (95% CI)[a]	−0.6 (−1.6 to 0.4)		NR	NR
Physical Functioning				
Mean (SD) baseline	52.4 (7.9)	52.9 (7.3)	NR	NR
LSM (SE) change	−0.8 (0.4)	−0.5 (0.5)	NR	NR
Treatment contrast (95% CI)[a]	−0.3 (−1.4 to 0.8)		NR	NR
Role Physical				
Mean (SD) baseline	52.2 (7.2)	52.5 (6.7)	NR	NR
LSM (SE) change	−1.7 (0.5)	−0.9 (0.6)	NR	NR
Treatment contrast (95% CI)[a]	−0.8 (−2.0 to 0.4)		NR	NR
Bodily Pain				
Mean (SD) baseline	54.5 (9.5)	54.5 (9.3)	NR	NR
LSM (SE) change	−1.7 (0.6)	−0.9 (0.8)	NR	NR
Treatment contrast (95% CI)[a]	−0.8 (−2.3 to 0.8)		NR	NR
General Health				
Mean (SD) baseline	45.7 (8.9)	46.5 (9.0)	NR	NR
LSM (SE) change	0.2 (0.5)	0.1 (0.6)	NR	NR
Treatment contrast (95% CI)[a]	0.1 (−1.2 to 1.3)		NR	NR
Mental Score				
Mean (SD) baseline	50.3 (8.7)	51.8 (8.1)	NR	NR
LSM (SE) change	−0.9 (0.6)	−0.5 (0.8)	NR	NR
Treatment contrast (95% CI)[a]	−0.4 (−2.0 to 1.1)		NR	NR
Vitality				
Mean (SD) baseline	54.0 (9.3)	56.0 (8.2)	NR	NR
LSM (SE) change	−0.6 (0.6)	−0.7 (0.7)	NR	NR
Treatment contrast (95% CI)[a]	0.0 (−1.5 to 1.5)		NR	NR
Social Functioning				
Mean (SD) baseline	51.7 (7.8)	52.0 (7.7)	NR	NR
LSM (SE) change	−2.3 (0.6)	−0.7 (0.7)	NR	NR
Treatment contrast (95% CI)[a]	−1.5 (−3.0 to −0.1)		NR	NR
Role Emotional				
Mean (SD) baseline	50.0 (8.4)	50.9 (8.4)	NR	NR
LSM (SE) change	−1.3 (0.6)	−0.8 (0.7)	NR	NR
Treatment contrast (95% CI)[a]	−0.5 (−1.9 to 1.0)		NR	NR

	Study 3585		Study 3725 (Ext)	
	Degludec N = 303	Detemir N = 152	Degludec	Detemir
Mental Health				
Mean (SD) baseline	50.1 (9.0)	51.8 (8.3)	NR	NR
LSM (SE) change	−0.3 (0.6)	−0.3 (0.8)	NR	NR
Treatment contrast (95% CI)[a]	−0.0 (−1.6 to 1.6)		NR	NR

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; Ext = extension; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDF = International Diabetes Federation; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; PG = plasma glucose; NR = not reported; NT = not tested due to halting of testing due to hierarchy; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without; XTS = extension trial set.

[a] The response and change from baseline in the response after treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

[c] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

Source: CSRs for Studies 3585[16] and 3725.[33]

Table 51: Key Efficacy Outcomes — Type 1 Diabetes Mellitus (Study 3583 + Extension Study 3644)

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	Glargine N = 157	Degludec	Glargine
A1C				
Mean (SD) baseline, %	7.7 (1.0)	7.7 (1.0)		
LSM (SE) change from baseline to 52 weeks, 104 weeks, FAS	−0.36 (0.05)	−0.34 (0.07)	−0.30 (0.05)	−0.26 (0.07)
Treatment contrast[a,b] (95% CI)	−0.01 (−0.14 to 0.11) Noninferiority confirmed (*P* < 0.001)		−0.04 (−0.17 to 0.09)	
LSM (SE) change from baseline to 52 weeks, PP	−0.37 (0.05)	−0.36 (0.07)		
Treatment contrast[a] (95% CI)	−0.01 (−0.14 to 0.12)			
LSM (SE) change from baseline to 104 weeks, XTS			−0.34 (0.06)	−0.24 (0.08)
Treatment contrast (95% CI)			−0.10 (−0.26 to 0.05)	
A1C < 7.0% (ADA)				
n (%), weeks 52, 104 (LOCF)	188 (39.8)	67 (42.7)	162 (34.3)	49 (31.2)
Treatment odds ratio[c] (95% CI)	0.82 (0.51 to 1.33)		1.31 (0.79 to 2.16)	
A1C < 7.0% w/o Severe Hypo				
n (%), weeks 52, 104 (LOCF)	174 (38.4)	63 (42.3)	146 (32.2)	45 (30.2)
Treatment odds ratio[c] (95% CI)	0.75 (0.46 to 1.22)		1.16 (0.69 to 1.93)	
A1C < 7.0% w/o Confirmed Hypo				
n (%), weeks 52, 104 (LOCF)	33 (7.3)	8 (5.4)	30 (6.6)	8 (5.4)
Treatment odds ratio[c] (95% CI)	1.40 (0.61 to 3.20)		1.27 (0.55 to 2.94)	
FPG				
Mean (SD) baseline, mmol/L	9.1 (4.0)	9.7 (4.4)		
LSM (SE) change from baseline to 52 weeks, 104 weeks	−1.53 (0.29)	−1.20 (0.38)	−1.43 (0.28)	−1.14 (0.38)
Treatment contrast[b] (95% CI)	−0.33 (−1.03 to 0.36), *P* = NT		−0.29 (−0.97 to 0.40)	
Within-patient variability in pre-breakfast PG				
Within-patient CV (%) after 52 weeks	38.20	39.86	37.2	39.3

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	**Glargine N = 157**	**Degludec**	**Glargine**
Treatment ratio[d] (95% CI)	0.96 (0.86 to 1.05), *P* = NT		0.95 (0.85 to 1.04)	
Morbidity				
Adjudicated cardiovascular events, n (%)	5 (1.1)	1 (0.6)	11 (2.3)	3 (1.9)
MACE n (%)	3 (0.6)	1 (0.6)	8 (1.7)	2 (1.3)
Mortality				
Deaths, n (%)	2 (0.4)	1 (0.6)	4 (0.8)	2 (1.3)
Cardiovascular deaths, n (%)	2 (0.4)	1 (0.6)		
TRIM-D scores				
Treatment Burden				
Mean (SD) baseline	59.2 (21.2)	57.0 (22.2)	NR	NR
LSM (SE) change	7.0 (1.2)	6.4 (1.6)	NR	NR
Treatment contrast[a] (95% CI)	0.6 (−2.4 to 3.7)		NR	NR
Daily Life			NR	NR
Mean (SD) baseline	76.6 (18.2)	75.6 (16.5)	NR	NR
LSM (SE) change	3.8 (1.0)	3.6 (1.3)	NR	NR
Treatment contrast[a] (95% CI)	0.3 (−2.1 to 2.7)		NR	NR
Diabetes Management			NR	NR
Mean (SD) baseline	54.8 (20.4)	53.7 (20.3)	NR	NR
LSM (SE) change	5.1 (1.3)	1.5 (1.7)	NR	NR
Treatment contrast[a] (95% CI)	3.6 (0.5 to 6.6)		NR	NR
Compliance			NR	NR
Mean (SD) baseline	76.0 (18.0)	77.2 (16.5)	NR	NR
LSM (SE) change	3.6 (0.9)	2.7 (1.2)	NR	NR
Treatment contrast[a] (95% CI)	0.8 (−1.5 to 3.1)		NR	NR
Psychological Health			NR	NR
Mean (SD) baseline	81.4 (16.6)	80.9 (16.3)	NR	NR
LSM (SE) change	2.4 (0.9)	2.8 (1.2)	NR	NR
Treatment contrast[a] (95% CI)	−0.4 (−2.6 to 1.8)		NR	NR
TRIM-D Total			NR	NR
Mean (SD) baseline	70.2 (14.8)	69.4 (13.8)	NR	NR
LSM (SE) change	4.2 (0.8)	3.4 (1.0)	NR	NR
Treatment contrast[a] (95% CI)	0.7 (−1.2 to 2.6)		NR	NR
HRQoL (SF-36) Scores				
Physical Score				
Mean (SD) baseline	52.5 (7.3)	51.8 (7.1)		
LSM (SE) change	−0.1 (0.4)	−0.8 (0.5)	−0.1 (0.4)	−0.5 (0.5)
Treatment contrast[a] (95% CI)	0.7 (−0.2 to 1.7)		0.4 (−0.6 to 1.3)	
LSM (SE) change, XTS			0.1 (0.4)	−0.3 (0.6)
Treatment contrast[a] (95% CI)			0.5 (−0.6 to 1.5)	
Physical Functioning				
Mean (SD) baseline	52.7 (7.9)	52.5 (6.7)		
LSM (SE) change	−0.3 (0.4)	−0.7 (0.5)	−0.3 (5.6)	−0.8 (6.2)
Treatment contrast[a] (95% CI)	0.4 (−0.5 to 1.4)		0.4 (−0.6 to 1.4)	
LSM (SE) change, XTS			−0.2 (0.4)	−0.5 (0.6)
Treatment contrast[a] (95% CI)			0.3 (−0.8 to 1.4)	

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	Glargine N = 157	Degludec	Glargine
Role Physical				
Mean (SD) baseline	52.1 (7.2)	51.1 (8.0)		
LSM (SE) change	−0.2 (0.4)	−0.9 (0.6)	−0.2 (0.5)	−0.6 (0.6)
Treatment contrast[a] (95% CI)	0.7 (−0.4 to 1.8)		0.4 (−0.7 to 1.5)	
LSM (SE) change, XTS			0.0 (0.5)	−0.5 (0.7)
Treatment contrast[a] (95% CI)			0.6 (−0.7 to 1.9)	
Bodily Pain				
Mean (SD) baseline	54.0 (9.3)	53.4 (8.8)		
LSM (SE) change	−0.2 (0.6)	−0.6 (0.8)	−0.2 (0.6)	−0.3 (0.8)
Treatment contrast[a] (95% CI)	0.4 (−1.0 to 1.8)		0.1 (−1.3 to 1.5)	
LSM (SE) change, XTS			0.0 (0.7)	−0.4 (0.9)
Treatment contrast[a] (95% CI)			0.4 (−1.2 to 2.0)	
General Health				
Mean (SD) baseline	48.3 (9.8)	47.0 (9.9)		
LSM (SE) change	0.7 (0.5)	0.1 (0.6)	0.5 (0.4)	0.5 (0.6)
Treatment contrast[a] (95% CI)	0.6 (−0.5 to 1.7)		0.1 (−1.0 to 1.2)	
LSM (SE) change, XTS			0.9 (0.5)	0.7 (0.7)
Treatment contrast[a] (95% CI)			0.2 (−1.1 to 1.5)	
Mental Score				
Mean (SD) baseline	50.4 (9.1)	49.8 (9.9)		
LSM (SE) change	−0.3 (0.5)	−0.3 (0.7)	−0.4 (0.6)	−0.5 (0.8)
Treatment contrast[a] (95% CI)	0.0 (−1.3 to 1.3)		0.1 (−1.4 to 1.5)	
LSM (SE) change, XTS			−0.2 (0.6)	−0.2 (0.9)
Treatment contrast[a] (95% CI)			0.0 (−1.6 to 1.6)	
Vitality				
Mean (SD) baseline	52.9 (9.5)	52.9 (9.6)		
LSM (SE) change	−0.5 (0.5)	−1.4 (0.7)	−0.4 (0.5)	−1.0 (0.7)
Treatment contrast[a] (95% CI)	0.9 (−0.3 to 2.1)		0.7 (−0.6 to 2.0)	
LSM (SE) change, XTS			−0.1 (0.6)	0.0 (0.8)
Treatment contrast[a] (95% CI)			−0.1 (−1.6 to 1.4)	
Social Functioning				
Mean (SD) baseline	51.1 (8.6)	50.5 (8.6)		
LSM (SE) change	−0.7 (0.5)	−1.0 (0.7)	−0.8 (0.5)	−1.4 (0.7)
Treatment contrast[a] (95% CI)	0.3 (−0.9 to 1.6)		0.5 (−0.8 to 1.9)	
LSM (SE) change, XTS			−0.6 (0.6)	−1.5 (0.8)
Treatment contrast[a] (95% CI)			0.9 (−0.5 to 2.4)	
Role emotional				
Mean (SD) baseline	50.3 (8.3)	49.2 (10.2)		
LSM (SE) change	0.2 (0.5)	0.5 (0.7)	−0.1 (8.1)	0.4 (8.6)
Treatment contrast[a] (95% CI)	−0.2 (−1.5 to 1.1)		−0.0 (−1.4 to 1.3)	
LSM (SE) change, XTS			0.3 (0.6)	−0.0 (0.8)
Treatment contrast[a] (95% CI)			0.4 (−1.1 to 1.8)	
Mental Health				
Mean (SD) baseline	51.1 (8.7)	50.8 (8.6)		
LSM (SE) change	−0.6 (0.5)	−0.8 (0.7)	−0.6 (8.4)	−0.2 (7.2)

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	Glargine N = 157	Degludec	Glargine
Treatment contrast[a] (95% CI)	0.2 (−1.1 to 1.4)		−0.2 (−1.6 to 1.1)	
LSM (SE) change, XTS			−0.6 (0.6)	−0.1 (0.8)
Treatment contrast[a] (95% CI)			−0.5 (−2.0 to 1.1)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; Ext = extension; FAS = full analysis set; FPG = fasting plasma glucose; Hypo = hypoglycemia; HRQoL = health-related quality of life; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NR = not reported; PG = plasma glucose; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without; XTS = extension trial set.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

[c] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

[d] Mean self-measured plasma glucose profile is defined as the area under the profile divided by measurement time. The response after treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and mean profile at baseline as covariates.

Source: CSRs for Studies 3583[4] and 3644.[32]

Table 52: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3579 + Extension Study 3643)

	Study 3579		Study 3643 (Ext)	
	Degludec N = 773	Glargine N = 257	Degludec	Glargine
A1C				
Mean (SD) baseline, %	8.2 (0.8)	8.2 (0.8)	NR	NR
LSM (SE) change from baseline to 52,104 weeks, FAS	−1.06 (0.04)	−1.15 (0.06)	−0.96 (0.04)	−1.08 (0.06)
Treatment contrast (95% CI)[a,b]	0.09 (−0.04 to 0.22) Noninferiority confirmed (*P* < 0.001)		0.12 (−0.01 to 0.25)	
LSM (SE) change from baseline to 52 weeks, PP	−1.14 (0.04)	−1.27 (0.06)		
Treatment contrast (95% CI)[a]	0.13 (−0.01 to 0.26)			
LSM (SE) change from baseline to 104 weeks, XTS			−1.11 (0.04)	−1.18 (0.07)
Treatment contrast (95% CI)[a]			0.07 (−0.07 to 0.22)	
A1C Responders				
A1C < 7.0% (ADA)				
n (%), weeks 52,105 (LOCF)	400 (51.7)	139 (54.1)	365 (47.2)	136 (52.9)
Treatment odds ratio (95% CI)[c]	0.88 (0.65 to 1.19)		0.77 (0.58 to 1.04)	
A1C ≤ 6.5% (IDF)				
n (%), weeks 52,105 (LOCF)	238 (30.8)	90 (35.0)	211 (27.3)	77 (30.0)
Treatment odds ratio (95% CI)[c]	0.80 (0.58 to 1.10)		0.88 (0.64 to 1.22)	
A1C < 7.0% w/o Severe Hypo				
n (%), weeks 52,105 (LOCF)	390 (55.5)	136 (58.6)	354 (50.4)	133 (57.3)
Treatment odds ratio (95% CI)[c]	0.85 (0.62 to 1.17)		0.73 (0.54 to 1.01)	
A1C ≤ 6.5% w/o Severe Hypo				
n (%), weeks 52,105 (LOCF)	234 (33.3)	88 (37.9)	206 (29.3)	75 (32.3)
Treatment odds ratio (95% CI)[c]	0.79 (0.57 to 1.10)		0.87 (0.62 to 1.22)	
A1C < 7.0% w/o Confirmed Hypo				
n (%), weeks 52,105 (LOCF)	296 (42.1)	106 (45.7)	263 (37.4)	105 (45.3)
Treatment odds ratio (95% CI)[c]	0.86 (0.63 to 1.17), *P* = NT		0.72 (0.53 to 0.98)	
A1C ≤ 6.5% w/o Confirmed Hypo				

	Study 3579		Study 3643 (Ext)	
	Degludec N = 773	**Glargine N = 257**	**Degludec**	**Glargine**
n (%), weeks 52,105 (LOCF)	177 (25.2)	67 (28.9)	152 (21.6)	54 (23.3)
Treatment odds ratio (95% CI)[c]	0.82 (0.58 to 1.17)		0.93 (0.65 to 1.35)	
FPG				
Mean (SD) baseline, mmol/L	9.6 (2.6)	9.7 (2.6)		
LSM (SE) change from baseline to 52 weeks, 104 weeks	−3.77 (0.09)	−3.34 (0.14)	−3.63 (0.09)	−3.25 (0.15)
Treatment contrast (95% CI)	−0.43 (−0.74 to −0.13), *P* = NT		−0.38 (−0.70 to −0.06)	
Within-patient variability in pre-breakfast PG				
Within-patient CV (%) 52, 104 weeks	16.57	16.74	15.95	16.09
Treatment contrast (95% CI)	0.99 (0.92 to 1.06)		0.99 (0.92 to 1.06)	
Morbidity				
Adjudicated cardiovascular events, n (%)	32 (4.2)	8 (3.1)	67 (8.7)	12 (4.7)
MACE, n (%)	12 (1.6)	2 (0.8)	29 (3.8)	4 (1.6)
Deaths				
Patients, n	1	1	4	3
TRIM-D Scores, Week 52				
Treatment Burden				
Mean (SD) baseline	63.6 (20.5)	63.2 (20.5)	NR	NR
LSM (SE) change	3.2 (0.7)	2.5 (1.2)	NR	NR
Treatment contrast (95% CI)[a]	0.7 (−1.9 to 3.4)		NR	NR
Daily Life			NR	NR
Mean (SD) baseline	77.5 (19.3)	76.8 (21.1)	NR	NR
LSM (SE) change	1.7 (0.6)	1.9 (1.1)	NR	NR
Treatment contrast (95% CI)[a]	−0.2 (−2.5 to 2.2)		NR	NR
Diabetes Management			NR	NR
Mean (SD) baseline	46.9 (22.2)	47.5 (21.4)	NR	NR
LSM (SE) change	13.6 (0.8)	12.7 (1.2)	NR	NR
Treatment contrast (95% CI)[a]	0.9 (−1.8 to 3.6)		NR	NR
Compliance			NR	NR
Mean (SD) baseline	77.5 (17.3)	77.4 (18.5)	NR	NR
LSM (SE) change	5.8 (0.6)	6.4 (0.9)	NR	NR
Treatment contrast (95% CI)[a]	−0.5 (−2.6 to 1.5)		NR	NR
Psychological Health				
Mean (SD) baseline	77.3 (18.4)	77.9 (18.9)	NR	NR
LSM (SE) change	6.2 (0.6)	6.5 (0.9)	NR	NR
Treatment contrast (95% CI)[a]	−0.4 (−2.4 to 1.6)		NR	NR
TRIM-D Total			NR	NR
Mean (SD) baseline	69.0 (13.8)	69.1 (14.2)	NR	NR
LSM (SE) change	6.0 (0.5)	5.9 (0.8)	NR	NR
Treatment contrast (95% CI)[a]	0.1 (−1.6 to 1.7)		NR	NR
HRQoL (SF-36) Scores				
Physical Score				
Mean (SD) baseline	46.1 (9.3)	45.8 (9.3)		
LSM (SE) change	0.5 (0.3)	−0.5 (0.4)	0.2 (0.3)	−0.9 (0.5)
Treatment contrast (95% CI)[a]	1.0 (0.1 to 2.0)		1.1 (0.1 to 2.1)	
Physical Functioning				

	Study 3579		Study 3643 (Ext)	
	Degludec N = 773	Glargine N = 257	Degludec	Glargine
Mean (SD) baseline	45.6 (10.4)	45.4 (10.1)		
LSM (SE) change	0.5 (0.3)	−0.9 (0.5)	−0.1 (0.3)	−1.2 (0.5)
Treatment contrast (95% CI)[a]	1.4 (0.3 to 2.4)		1.1 (0.0 to 2.3)	
Role Physical				
Mean (SD) baseline	45.7 (10.6)	45.5 (10.4)		
LSM (SE) change	0.3 (0.3)	0.2 (0.5)	0.1 (0.3)	−0.1 (0.5)
Treatment contrast (95% CI)[a]	0.1 (−1.0 to 1.2)		0.2 (−1.0 to 1.3)	
Bodily Pain				
Mean (SD) baseline	48.8 (11.4)	48.4 (11.5)		
LSM (SE) change	0.3 (0.4)	−0.8 (0.6)	−0.0 (0.4)	−1.6 (0.6)
Treatment contrast (95% CI)[a]	1.1 (−0.3 to 2.5)		1.5 (0.2 to 2.9)	
General Health				
Mean (SD) baseline	44.5 (9.7)	44.9 (9.3)		
LSM (SE) change	1.1 (0.3)	0.6 (0.5)	1.1 (0.3)	0.7 (0.5)
Treatment contrast (95% CI)[a]	0.5 (−0.5 to 1.5)		0.3 (−0.7 to 1.4)	
Mental Score				
Mean (SD) baseline	48.4 (11.3)	48.9 (11.4)		
LSM (SE) change	0.5 (0.3)	0.9 (0.5)	0.4 (0.3)	0.7 (0.5)
Treatment contrast (95% CI)[a]	−0.4 (−1.6 to 0.7)		−0.3 (−1.5 to 0.9)	
Vitality				
Mean (SD) baseline	49.6 (10.7)	49.7 (10.4)		
LSM (SE) change	0.8 (0.3)	0.4 (0.5)	0.7 (0.3)	0.1 (0.5)
Treatment contrast (95% CI)[a]	0.4 (−0.8 to 1.5)		0.5 (−0.6 to 1.7)	
Social Functioning				
Mean (SD) baseline	48.1 (10.2)	48.2 (11.0)		
LSM (SE) change	0.3 (0.3)	0.2 (0.5)	−0.1 (0.3)	−0.1 (0.6)
Treatment contrast (95% CI)[a]	0.1 (−1.1 to 1.3)		−0.0 (−1.2 to 1.2)	
Role Emotional				
Mean (SD) baseline	45.4 (11.8)	45.8 (11.9)		
LSM (SE) change	0.4 (0.4)	0.8 (0.6)	0.1 (0.4)	0.3 (0.6)
Treatment contrast (95% CI)[a]	−0.5 (−1.8 to 0.9)		−0.2 (−1.6 to 1.2)	
Mental Health				
Mean (SD) baseline	48.5 (11.2)	48.7 (11.5)		
LSM (SE) change	0.4 (0.3)	0.5 (0.5)	0.2 (0.3)	0.1 (0.5)
Treatment contrast (95% CI)[a]	−0.1 (−1.3 to 1.1)		0.1 (−1.1 to 1.3)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; Ext = extension; FAS = full analysis set; FPG = fasting plasma glucose; Hypo = hypoglycemia; HRQoL = health-related quality of life; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NR = not reported; PG = plasma glucose; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without; XTS = extension trial set.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

[c] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

Source: CSRs for Studies 3579[17] and 3643.[34]

Table 53: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3580)

	Study 3580 (BEGIN Early)	
	Degludec (N = 225)	**DPP-4 Inhibitor (N = 222)**
A1C Levels, FAS		
Mean (SD) baseline, %	8.8 (1.0)	9.0 (1.0)
A1C blood (%), week 26, LSM (SE)	7.35 (0.10)	7.77 (0.10)
A1C blood (%), LSM (SE) change from baseline to week 26 (LOCF)	−1.52 (0.10)	−1.09 (0.10)
LS MD IDeg versus comparator (95% CI)[a,b]	−0.43 (−0.61 to −0.24) *P* value < 0.001	
A1C Levels, PP		
A1C blood (%), week 26, LSM (SE)	7.24 (0.11)	7.67 (0.10)
A1C blood (%), LSM (SE) change from baseline to week 26 (LOCF)	−1.67 (0.11)	−1.24 (0.10)
LS MD IDeg versus comparator (95% CI)[a]	−0.44 (−0.63 to −0.24)	
Fasting Plasma Glucose at End of Treatment Period[a]		
FPG (mmol/L), LSM (SE)	6.26 (0.24)	8.43 (0.23)
FPG (mmol/L), change from baseline to week 26 (LOCF), LSM (SE)	−3.41 (0.24)	−1.24 (0.23)
LS MD IDeg versus comparator (95% CI)[a,b]	−2.17 (−2.59 to −1.74) *P* value < 0.001	
A1C Responders		
A1C responders < 7.0% (ADA), week 26 (LOCF), LSM, odds	0.38	0.23
A1C responders < 7.0% (ADA), week 26, treatment odds ratio, IDeg versus comparator[b,c]	1.60 (1.04 to 2.47) *P* value = 0.017	
A1C responders ≤ 6.5% (IDF), week 26 (LOCF), LSM, odds	0.16	0.08
A1C responders ≤ 6.5% (IDF), week 26, treatment odds ratio, IDeg versus comparator[c]	1.98 (1.17 to 3.33)	
A1C Responders Without Confirmed Hypoglycemia[a]		
A1C responders < 7.0% (ADA), week 26 (LOCF), LSM, odds	0.23	0.25
A1C responders < 7.0% (ADA), week 26, treatment odds ratio, IDeg versus comparator[b,c]	0.92 (0.55 to 1.53) *P* value = 0.372	
A1C responders ≤ 6.5% (IDF), week 26 (LOCF), LSM, odds	0.11	0.09
A1C responders ≤ 6.5% (IDF), week 26, treatment odds ratio, IDeg versus comparator[c]	1.19 (0.62 to 2.28)	
A1C Responders Without Severe Hypoglycemia		
A1C responders < 7.0% (ADA), week 26 (LOCF), LSM, odds	0.40	0.27
A1C responders < 7.0% (ADA), week 26, treatment odds ratio, IDeg versus comparator[c]	1.51 (0.94 to 2.43)	
A1C responders ≤ 6.5% (IDF), week 26 (LOCF), LSM, odds	0.18	0.10
A1C responders ≤ 6.5% (IDF), week 26, treatment odds ratio, IDeg versus comparator[c]	1.83 (1.06 to 3.18)	
Mean of 9-Point SMPG Profile[d]	n = 203	n = 202
SMPG (mmol/L), LSM (SE) week 26	7.37 (0.21)	8.68 (0.21)
LS MD IDeg versus comparator (95% CI)	−1.31 (−1.69 to −0.94)	
Within-Patient Variation in SMPG[e]	n = 225	n = 222
Within-patient CV (%), week 26 (LOCF)	17.10	12.28
Treatment (CV) ratio, IDeg versus comparator (95% CI)	1.39 (1.26 to 1.52)	
HRQoL, SF-36v2 Scores		
Physical Score		
Mean (SD) baseline	45.6 (8.8) (n = 222)	46.2 (7.6) (n = 222)
LSM change (SE) from baseline to week 26 (LOCF)	1.0 (0.7)	1.8 (0.7)
LS MD IDeg versus comparator (95% CI)[a]	−0.8 (−2.0 to 0.4)	
Physical Functioning		
Mean (SD) baseline	43.6 (10.5) (n = 218)	44.1 (10.9) (n = 222)
LSM change (SE) from baseline to week 26 (LOCF)	0.4 (0.8)	1.4 (0.8)

	Study 3580 (BEGIN Early)	
	Degludec (N = 225)	**DPP-4 Inhibitor (N = 222)**
LS MD IDeg versus comparator (95% CI)[a]	−0.9 (−2.4 to 0.5)	
Role Physical		
Mean (SD) baseline	43.3 (10.3) (n = 218)	46.1 (9.5) (n = 220)
LSM change (SE) from baseline to week 26 (LOCF)	1.3 (0.8) (n = 218)	2.1 (0.8) (n = 220)
LS MD IDeg versus comparator (95% CI)[a]	−0.8 (−2.3 to 0.6)	
Bodily Pain		
Mean (SD) baseline	46.9 (10.7) (n = 220)	47.4 (10.4) (n = 221)
LSM change (SE) from baseline to week 26 (LOCF)	2.6 (0.9) (n = 220)	3.0 (0.9) (n = 221)
LS MD IDeg versus comparator (95% CI)[a]	−0.4 (−2.0 to 1.3)	
General Health		
Mean (SD) baseline	44.0 (9.8) (n = 218)	44.9 (9.0) (n = 219)
LSM change (SE) from baseline to week 26 (LOCF)	2.1 (0.7) (n = 218)	1.9 (0.7) (n = 219)
LS MD IDeg versus comparator (95% CI)[a]	0.2 (−1.1 to 1.4)	
Overall Mental		
Mean (SD) baseline	44.3 (11.6) (n = 222)	46.3 (11.6) (n = 222)
LSM change (SE) from baseline to week 26 (LOCF)	2.7 (0.8) (n = 222)	2.4 (0.8) (n = 222)
LS MD IDeg versus comparator (95% CI)[a]	0.3 (−1.1 to 1.8)	
Vitality		
Mean (SD) baseline	49.1 (9.7) (n = 217)	49.5 (10.8) (n = 220)
LSM change (SE) from baseline to week 26 (LOCF)	2.4 (0.8) (n = 217)	2.7 (0.8) (n = 220)
LS MD IDeg versus comparator (95% CI)[b]	−0.3 (−1.8 to 1.1)	
Social Functioning		
Mean (SD) baseline	44.5 (10.4) (n = 221)	46.2 (10.7) (n = 220)
LSM change (SE) from baseline to week 26 (LOCF)	2.3 (0.9) (n = 221)	2.9 (0.8) (n = 220)
LS MD IDeg versus comparator (95% CI)[a]	−0.6 (−2.2 to 0.9)	
Role Emotional		
Mean (SD) baseline	40.1 (13.1) (n = 219)	43.1 (12.2) (n = 219)
LSM change (SE) from baseline to week 26 (LOCF)	2.4 (0.9) (n = 219)	2.6 (0.9) (n = 219)
LS MD IDeg versus comparator (95% CI)[a]	−0.2 (−1.8 to 1.5)	
Mental Health		
Mean (SD) baseline	44.9 (10.9) (n = 218)	46.2 (11.2) (n = 219)
LSM change (SE) from baseline to week 26 (LOCF)	1.9 (0.9) (n = 218)	1.7 (0.8) (n = 219)
LS MD IDeg versus comparator (95% CI)[a]	0.2 (−1.3 to 1.8)	
TRIM-D Scores		

	Study 3580 (BEGIN Early)	
	Degludec (N = 225)	**DPP-4 Inhibitor (N = 222)**
Treatment Burden		
Mean (SD) baseline	56.3 (23.6) (n = 216)	58.7 (20.2) (n = 219)
LSM change (SE) from baseline to week 26 (LOCF)	7.2 (1.9)	11.4 (1.9)
LS MD IDeg versus comparator (95% CI)[a]	−4.2 (−7.7 to −0.7)	
Daily Life		
Mean (SD) baseline	73.9 (19.4) (n = 215)	76.8 (17.7) (n = 216)
LSM change (SE) from baseline to week 26 (LOCF)	2.4 (1.6)	5.0 (1.6)
LS MD IDeg versus comparator (95% CI)[a]	−2.6 (−5.6 to 0.3)	
Diabetes Management		
Mean (SD) baseline	46.7 (21.8) (n = 215)	45.9 (20.4) (n = 216)
LSM change (SE) from baseline to week 26 (LOCF)	15.0 (2.1)	14.7 (2.1)
LS MD IDeg versus comparator (95% CI)[a]	0.4 (−3.3 to 4.1)	
Compliance		
Mean (SD) baseline	73.4 (19.0) (n = 213)	75.4 (18.1) (n = 215)
LSM change (SE) from baseline to week 26 (LOCF)	5.6 (1.5)	5.7 (1.5)
LS MD IDeg versus comparator (95% CI)[a]	−0.1 (−2.9 to 2.7)	
Psychological Health		
Mean (SD) baseline	73.8 (18.6) (n = 216)	73.7 (18.7) (n = 217)
LSM change (SE) from baseline to week 26 (LOCF)	8.2 (1.4)	6.7 (1.4)
LS MD IDeg versus comparator (95% CI)[a]	1.5 (−1.1 to 4.1)	
Total		
Mean (SD) baseline	65.2 (14.8) (n = 216)	66.3 (13.6) (n = 218)
LSM change (SE) from baseline to week 26 (LOCF)	7.6 (1.2)	8.3 (1.2)
LS MD IDeg versus comparator (95% CI)[a]	−0.7 (−2.9 to 1.4)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; DPP-4 = dipeptidyl peptidase-4; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; IDeg = insulin degludec; IDF = International Diabetes Federation; LOCF = last observation carried forward; LSM = least squares mean; LS MD = least squares mean difference; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

[c] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

[d] Mean SMPG profile is defined as the area under the profile divided by measurement time. The response after treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and mean profile at baseline as covariates.

[e] Log-transformed pre-breakfast SMPG values after treatment period are analyzed as repeated measures in a mixed linear model with treatment, antidiabetes treatment at screening, region, and sex as fixed effects, age as covariate, and patient as random effect. The model assumes independent within-patient and between-patient variances, with variances depending on treatment.

Source: CSR for Study 3580.[18]

Table 54: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3672)

	Study 3672	
	Degludec N = 230	**Glargine N = 230**
A1C		
Mean (SD) baseline, %	8.3 (1.0)	8.2 (0.9)
LSM (SE) change from baseline to 26 weeks, FAS	−1.18 (0.09)	−1.22 (0.08)
Treatment contrast (95% CI)[a,b]	0.04 (−0.11 to 0.19), *P* < 0.001	
LSM (SE) change from baseline to 26 weeks, PP	−1.28 (0.09)	−1.32 (0.08)
Treatment contrast (95% CI)[a]	0.04 (−0.11 to 0.19)	
A1C Responders		
A1C < 7.0% (ADA)		
n (%), week 26 (LOCF)	119 (52.2)	128 (55.9)
Treatment odds ratio (95% CI)[a,c]	0.85 (0.56 to 1.30)	
A1C ≤ 6.5% (IDF)		
n (%), week 26 (LOCF)	86 (37.7)	98 (42.8)
Treatment odds ratio (95% CI)[a,c]	0.80 (0.52 to 1.22)	
A1C < 7.0% w/o Severe Hypo		
n (%), week 26 (LOCF)	117 (55.7)	126 (58.6)
Treatment odds ratio (95% CI)[a,c]	0.88 (0.57 to 1.38)	
A1C ≤ 6.5% w/o Severe Hypo		
n (%), week 26 (LOCF)	85 (40.5)	98 (45.6)
Treatment odds ratio (95% CI)[a,c]	0.79 (0.51 to 1.23)	
A1C < 7.0% w/o Confirmed Hypo		
n (%), week 26 (LOCF)	95 (45.2)	96 (44.7)
Treatment odds ratio (95% CI)[a,c]	1.05 (0.69 to 1.61), *P* = NT	
A1C ≤ 6.5% w/o Confirmed Hypo		
n (%), week 26 (LOCF)	67 (31.9)	75 (34.9)
Treatment odds ratio (95% CI)[a,c]	0.88 (0.56 to 1.38)	
FPG		
Mean (SD) baseline, mmol/L	9.6 (2.9)	9.7 (2.6)
LSM (SE) change from baseline to 26 weeks	−3.94 (0.20)	−3.52 (0.20)
Treatment contrast (95% CI)	−0.42 (−0.78 to −0.06), *P* = NT	
Within-Patient Variability in Pre-Breakfast PG		
Within-patient CV (%) after 26 weeks	16.66	18.02
Treatment ratio (95% CI)	0.92 (0.84; 1.01), *P* = NT	
Morbidity		
Adjudicated Cardiovascular Events, n (%)	8 (3.5)	5 (2.2)
MACE, n (%)	4 (1.8)	3 (1.3)
Deaths		
Patients, n (%)	0	1 (0.4)
TRIM-D Scores		
Treatment Burden		
Mean (SD) baseline	64.1 (21.5)	64.4 (21.1)
LSM (SE) change	2.7 (2.1)	2.1 (2.0)
Treatment contrast (95% CI)[a]	0.6 (−3.1 to 4.3)	
Daily Life		
Mean (SD) baseline	76.9 (19.7)	77.0 (19.0)

	Study 3672	
	Degludec N = 230	**Glargine N = 230**
LSM (SE) change	2.2 (1.5)	0.6 (1.5)
Treatment contrast (95% CI)[a]	1.6 (−1.1 to 4.2)	
Diabetes Management		
Mean (SD) baseline	46.2 (20.7)	45.9 (21.3)
LSM (SE) change	15.0 (2.0)	16.6 (1.9)
Treatment contrast (95% CI)[a]	−1.6 (−5.1 to 1.9)	
Compliance		
Mean (SD) baseline	76.1 (17.7)	77.8 (18.3)
LSM (SE) change	4.2 (1.4)	6.0 (1.4)
Treatment contrast (95% CI)[a]	−1.8 (−4.3 to 0.7)	
Psychological Health		
Mean (SD) baseline	75.9 (17.8)	76.8 (16.9)
LSM (SE) change	5.4 (1.5)	5.2 (1.4)
Treatment contrast (95% CI)[a]	0.3 (−2.4 to 2.9)	
TRIM-D Total		
Mean (SD) baseline	68.4 (13.7)	68.9 (13.3)
LSM (SE) change	5.7 (1.2)	5.8 (1.2)
Treatment contrast (95% CI)[a]	−0.1 (−2.2 to 2.0)	
HRQoL, SF-36 Scores		
Physical Score		
Mean (SD) baseline	45.8 (9.1)	45.1 (9.0)
LSM (SE) change	1.7 (0.7)	1.3 (0.6)
Treatment contrast (95% CI)[a]	0.4 (−0.8 to 1.5)	
Physical Functioning		
Mean (SD) baseline	46.4 (9.8)	44.3 (10.6)
LSM (SE) change	1.4 (0.8)	1.5 (0.8)
Treatment contrast (95% CI)[a]	−0.1 (−1.5 to 1.3)	
Role Physical		
Mean (SD) baseline	46.2 (10.6)	45.9 (10.0)
LSM (SE) change	1.1 (0.7)	0.7 (0.7)
Treatment contrast (95% CI)[a]	0.4 (−1.0 to 1.7)	
Bodily Pain		
Mean (SD) baseline	46.7 (11.0)	47.9 (11.0)
LSM (SE) change	2.0 (0.9)	0.4 (0.9)
Treatment contrast (95% CI)[a]	1.6 (0.1 to 3.2)	
General Health		
Mean (SD) baseline	44.3 (9.2)	43.4 (9.7)
LSM (SE) change	2.6 (0.7)	1.8 (0.7)
Treatment contrast (95% CI)[a]	0.8 (−0.5 to 2.0)	
Mental Score		
Mean (SD) baseline	48.4 (10.9)	48.6 (10.2)
LSM (SE) change	1.8 (0.9)	0.4 (0.8)
Treatment contrast (95% CI)[a]	1.4 (−0.1 to 2.9)	
Vitality		
Mean (SD) baseline	49.4 (10.2)	49.5 (10.0)

	Study 3672	
	Degludec N = 230	**Glargine N = 230**
LSM (SE) change	1.9 (0.8)	0.4 (0.8)
Treatment contrast (95% CI)[a]	1.5 (0.1 to 3.0)	
Social Functioning		
Mean (SD) baseline	47.6 (10.1)	47.4 (10.4)
LSM (SE) change	2.2 (0.8)	0.9 (0.8)
Treatment contrast (95% CI)[a]	1.3 (−0.1 to 2.7)	
Role Emotional		
Mean (SD) baseline	45.8 (11.7)	46.4 (10.8)
LSM (SE) change	1.0 (0.9)	0.1 (0.9)
Treatment contrast (95% CI)[a]	0.9 (−0.7 to 2.6)	
Mental Health		
Mean (SD) baseline	48.4 (10.7)	47.6 (10.7)
LSM (SE) change	1.9 (0.9)	0.9 (0.9)
Treatment contrast (95% CI)[a]	1.0 (−0.5 to 2.6)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDF = International Diabetes Federation; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NT = not tested; PG = plasma glucose; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without.

[a] The response and change from baseline in the response after treatment periods are analyzed using an ANOVA method with treatment, region, sex. and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

[c] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

Source: CSR for Study 3672.[19]

Table 55: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3586)

	Study 3586	
	Degludec N = 289	**Glargine N = 146**
A1C		
Mean (SD) baseline, %	8.4 (0.8)	8.5 (0.8)
LSM (SE) change from baseline to 26 weeks, FAS	−1.42 (0.06)	−1.52 (0.07)
Treatment contrast (95% CI)[a,b]	0.11 (−0.03 to 0.24), *P* < 0.001	
Mean (SD) baseline, %		
LSM (SE) change from baseline to 26 weeks, PP	−1.48 (0.05)	−1.55 (0.07)
Treatment contrast (95% CI)[a]	0.07 (−0.06 to 0.20)	
A1C < 7.0% (ADA)		
n (%), week 26 (LOCF)	118 (40.8)	71 (48.6)
Treatment odds ratio (95% CI)[a]	0.70 (0.45 to 1.07)	
A1C ≤ 6.5% (IDF)		
n (%), week 26 (LOCF)	52 (18.0)	36 (24.7)
Treatment odds ratio (95% CI)[a]	0.64 (0.39 to 1.06)	
A1C < 7.0% w/o Severe Hypo		
n (%), week 26 (LOCF)	52 (18.0)	36 (24.7)
Treatment odds ratio (95% CI)[a]	0.64 (0.39 to 1.06)	
A1C < 7.0% w/o Confirmed Hypo		

	Study 3586	
	Degludec N = 289	**Glargine N = 146**
n (%), week 26 (LOCF)	78 (29.1)	45 (31.5)
Treatment odds ratio (95% CI)[a]	0.89 (0.56 to 1.42), *P* = NT	
A1C ≤ 6.5% w/o Severe Hypo		
n (%), week 26 (LOCF)	52 (19.4)	36 (25.2)
Treatment odds ratio (95% CI)[a]	0.69 (0.42 to 1.14)	
A1C ≤ 6.5% w/o Confirmed Hypo		
n (%), week 26 (LOCF)	31 (11.6)	26 (18.2)
Treatment odds ratio (95% CI)[a]	0.57 (0.31 to 1.02)	
FPG		
Mean (SD) baseline, mmol/L	8.4 (2.1)	8.6 (1.9)
LSM (SE) change, baseline to 26 weeks	−3.03 (0.13)	−2.94 (0.16)
Treatment contrast	−0.09 (−0.41 to 0.23), *P* = NT	
Within-Patient Variability (CV%) in Pre-Breakfast SMPG		
Within-patient CV (%) 26 weeks	16.30	18.21
Treatment contrast	0.89 (0.80; 0.99), *P* = NT	
Adjudicated Cardiovascular Events		
MACE, n (%)	2 (0.7)	0
Deaths		
Patients, n	0	0
TRIM-D Scores		
Treatment Burden		
Mean (SD) baseline	51.7 (22.2)	52.3 (24.9)
LSM (SE) change	0.2 (1.6)	−0.9 (2.0)
Treatment contrast (95% CI)[a]	1.1 (−3.0 to 5.1)	
Daily Life		
Mean (SD) baseline	79.9 (17.9)	82.2 (15.7)
LSM (SE) change	−1.4 (1.3)	−1.6 (1.6)
Treatment contrast (95% CI)[a]	0.2 (−2.9 to 3.3)	
Diabetes Management		
Mean (SD) baseline	46.3 (23.5)	45.8 (23.2)
LSM (SE) change	8.4 (1.5)	6.7 (1.9)
Treatment contrast (95% CI)[a]	1.7 (−2.0 to 5.4)	
Compliance		
Mean (SD) baseline	75.7 (17.7)	76.4 (17.1)
LSM (SE) change	5.6 (1.2)	5.8 (1.5)
Treatment contrast (95% CI)[a]	−0.2 (−3.2 to 2.7)	
Psychological Health		
Mean (SD) baseline	75.7 (18.8)	78.9 (16.0)
LSM (SE) change	2.0 (1.2)	3.2 (1.4)
Treatment contrast (95% CI)[a]	−1.2 (−4.0 to 1.7)	
TRIM-D Total		
Mean (SD) baseline	66.2 (14.0)	67.5 (13.7)
LSM (SE) change	2.4 (0.9)	2.2 (1.1)
Treatment contrast (95% CI)[a]	0.2 (−2.1 to 2.5)	
HRQoL, SF-36 Scores		
Physical Score		
Mean (SD) baseline	49.3 (6.7)	48.4 (7.1)
LSM (SE) change	0.7 (0.4)	0.5 (0.6)

	Study 3586	
	Degludec N = 289	**Glargine N = 146**
Treatment contrast (95% CI)[a]	0.3 (−0.8 to 1.4)	
Physical Functioning		
Mean (SD) baseline	49.3 (7.4)	48.1 (8.6)
LSM (SE) change	0.0 (0.6)	0.1 (0.8)
Treatment contrast (95% CI)[a]	−0.0 (−1.6 to 1.5)	
Role Physical		
Mean (SD) baseline	48.6 (9.2)	49.7 (8.9)
LSM (SE) change	0.6 (0.6)	0.8 (0.8)
Treatment contrast (95% CI)[a]	−0.1 (−1.7 to 1.5)	
Bodily Pain		
Mean (SD) baseline	52.4 (9.5)	52.2 (9.5)
LSM (SE) change	0.6 (0.6)	0.3 (0.8)
Treatment contrast (95% CI)[a]	0.3 (−1.2 to 1.9)	
General Health		
Mean (SD) baseline	42.5 (9.6)	42.2 (8.9)
LSM (SE) change	2.4 (0.5)	1.6 (0.6)
Treatment contrast (95% CI)[a]	0.8 (−0.4 to 2.1)	
Mental Score		
Mean (SD) baseline	47.8 (9.2)	50.0 (8.8)
LSM (SE) change	1.4 (0.6)	0.7 (0.7)
Treatment contrast (95% CI)[a]	0.7 (−0.8 to 2.2)	
Vitality		
Mean (SD) baseline	51.4 (10.1)	53.0 (9.6)
LSM (SE) change	1.4 (0.6)	0.7 (0.8)
Treatment contrast (95% CI)[a]	0.6 (−0.9 to 2.2)	
Social Functioning		
Mean (SD) baseline	49.4 (8.3)	50.0 (8.6)
LSM (SE) change	1.2 (0.6)	0.0 (0.7)
Treatment contrast (95% CI)[a]	1.2 (−0.3 to 2.7)	
Role Emotional		
Mean (SD) baseline	46.2 (10.7)	47.6 (11.4)
LSM (SE) change	1.7 (0.7)	1.4 (0.9)
Treatment contrast (95% CI)[a]	0.3 (−1.5 to 2.1)	
Mental Health		
Mean (SD) baseline	48.2 (10.1)	49.9 (8.8)
LSM (SE) change	0.5 (0.7)	0.5 (0.9)
Treatment contrast (95% CI)[a]	−0.1 (−1.7 to 1.6)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDF = International Diabetes Federation; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NT = not tested; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

Source: CSR for Study 3586.[20]

Table 56: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3587 and 3944)

	Study 3587		Study 3944	
	IDeg N = 555	**IGlar N = 278**	**IDeg + Lira N = 174**	**Pla + Lira N = 172**
A1C				
Mean (SD) baseline, %	8.3 (0.9)	8.3 (0.8)	7.5 (0.6)	7.6 (0.6)
LSM (SE) change from baseline to 26 weeks, FAS	−1.29 (0.05)	−1.24 (0.06)	−0.99 (0.08)	−0.07 (0.08)
Treatment contrast (95% CI)[a,b]	−0.05 (−0.18 to 0.08) Noninferiority confirmed (P < 0.001)		−0.92 (−1.10 to −0.75) Superiority confirmed (P < 0.0001)	
LSM (SE) change from baseline to 26 weeks, PP	−1.33 (0.05)	−1.29 (0.06)		
Treatment contrast (95% CI)[a]	−0.05 (−0.17 to 0.08)			
A1C < 7.0% (ADA)				
Patients, week 26 n (%)	301 (54.2)	143 (51.4)	135 (77.6)	61 (35.5)
Treatment odds ratio (95% CI)	1.14 (0.84 to 1.54)		7.79 (4.57 to 13.27)	
A1C ≤ 6.5% (IDF)				
Patients, week 26 n (%)	198 (35.7)	87 (31.3)	NR	NR
Treatment odds ratio (95% CI)	1.23 (0.89 to 1.70)			NR
A1C < 7.0% w/o Severe Hypo			NR	NR
Patients, week 26 n (%)	298 (55.4)	143 (53.2)	NR	NR
Treatment odds ratio (95% CI)	1.12 (0.82 to 1.52)			
A1C ≤ 6.5% w/o Severe Hypo				
Patients, week 26 n (%)	196 (36.4)	87 (32.3)	NR	NR
Treatment odds ratio (95% CI)	1.21 (0.88 to 1.68)			NR
A1C < 7.0% w/o Confirmed Hypo			NR	NR
Patients, week 26 n (%)	252 (46.8)	114 (42.4)	NR	NR
Treatment odds ratio (95% CI)	1.24 (0.91 to 1.69), P = NT			NR
A1C ≤ 6.5% w/o Confirmed Hypo			NR	NR
Patients, week 26 n (%)	171 (31.8)	71 (26.4)	NR	NR
Treatment odds ratio (95% CI)	1.33 (0.94 to 1.87)			NR
FPG				
Mean (SD) baseline, mmol/L	9.4 (2.4)	9.4 (2.5)		
Mean (SD) change from baseline to 26 weeks (LOCF)	−3.35 (2.91)	−3.14 (2.71)	−2.60 (2.91)	−0.28 (2.44)
Change from baseline, LSM (SE), LOCF	−3.24 (0.11)	−2.98 (0.14)	−2.73 (0.23)	−0.19 (0.24)
Treatment contrast (95% CI)	−0.26 (−0.53 to 0.02), P = NT		−2.55 (−3.07 to −2.02), P < 0.0001	
Pre-Breakfast SMPG Values				
Within-patient variability, CV%	14.2	12.9		
Treatment contrast (95% CI)	1.10 (1.02 to 1.18), P = NT		−2.34 (−2.67 to −2.01), P < 0.0001	
Morbidity				
Adjudicated cardiovascular events, n (%)	6 (1.1)	4 (1.4)		
MACE, n (%)	4 (0.7)	2 (0.7)	0	0
Mortality				
Deaths, n	0	1	0	0
TRIM-D Scores				
Treatment Burden				
Mean (SD) baseline	52.3 (18.3)	52.4 (20.0)	NR	NR
LSM (SE) change	11.7 (1.0)	10.3 (1.3)	NR	NR
Treatment contrast (95% CI)[a]	1.4 (−1.1 to 3.9)			NR

	Study 3587		Study 3944	
	IDeg N = 555	IGlar N = 278	IDeg + Lira N = 174	Pla + Lira N = 172
Daily Life			NR	NR
Mean (SD) baseline	75.9 (17.6)	76.8 (16.5)	NR	NR
LSM (SE) change	4.6 (0.9)	4.1 (1.2)	NR	NR
Treatment contrast (95% CI)[a]	0.5 (−1.8 to 2.8)			NR
Diabetes Management			NR	NR
Mean (SD) baseline	46.2 (18.9)	45.9 (18.2)	NR	NR
LSM (SE) change	15.0 (1.0)	15.2 (1.3)	NR	NR
Treatment contrast (95% CI)[a]	−0.2 (−2.7 to 2.3)			NR
Compliance			NR	NR
Mean (SD) baseline	70.2 (19.6)	69.3 (18.4)	NR	NR
LSM (SE) change	8.0 (0.9)	7.8 (1.2)	NR	NR
Treatment contrast (95% CI)[a]	0.2 (−2.1 to 2.6)			NR
Psychological Health			NR	NR
Mean (SD) baseline	73.0 (18.8)	74.1 (18.4)	NR	NR
LSM (SE) change	8.0 (0.9)	6.8 (1.1)	NR	NR
Treatment contrast (95% CI)[a]	1.2 (−1.0 to 3.3)			NR
TRIM-D Total			NR	NR
Mean (SD) baseline	63.9 (13.5)	64.3 (12.9)	NR	NR
LSM (SE) change	9.3 (0.7)	8.6 (0.9)	NR	NR
Treatment contrast (95% CI)[a]	0.7 (−1.0 to 2.4)			NR
HRQoL, SF-36 Scores				
Physical Score				
Mean (SD) baseline	48.6 (7.5)	48.4 (7.5)	47.2 (9.6)	47.7 (8.4)
LSM (SE) change	0.4 (0.4)	0.4 (0.4)	0.1 (0.6)	−0.3 (0.6)
Treatment contrast (95% CI)[a]	−0.0 (−0.9 to 0.9)		0.4 (−0.9 to 1.7)	
Physical Functioning				
Mean (SD) baseline	49.6 (8.0)	49.0 (8.8)	46.8 (9.8)	47.3 (9.1)
LSM (SE) change	−0.2 (0.4)	−0.0 (0.5)	−0.1 (0.7)	−0.9 (0.8)
Treatment contrast (95% CI)[a]	−0.2 (−1.1 to 0.8)		0.8 (−0.8 to 2.5)	
Role Physical				
Mean (SD) baseline	47.6 (9.4)	47.3 (9.4)	46.6 (10.6)	47.0 (9.8)
LSM (SE) change	0.6 (0.4)	0.9 (0.6)	0.7 (0.8)	−0.6 (0.8)
Treatment contrast (95% CI)[a]	−0.2 (−1.4 to 0.9)		1.3 (−0.4 to 3.0)	
Bodily Pain				
Mean (SD) baseline	51.1 (10.2)	50.7 (10.5)	49.9 (11.2)	49.8 (11.0)
LSM (SE) change	0.6 (0.5)	−0.4 (0.7)	0.4 (0.8)	0.4 (0.8)
Treatment contrast (95% CI)[a]	1.0 (−0.3 to 2.4)		−0.1 (−1.8 to 1.7)	
General Health				
Mean (SD) baseline	41.5 (9.9)	42.5 (9.9)	45.9 (9.1)	45.5 (8.3)
LSM (SE) change	1.9 (0.5)	2.4 (0.6)	1.6 (0.5)	0.9 (0.6)
Treatment contrast (95% CI)[a]	−0.6 (−1.7 to 0.6)		0.7 (−0.5 to 1.9)	
Mental Score				
Mean (SD) baseline	47.4 (10.3)	47.8 (9.8)	49.8 (10.6)	48.6 (9.5)
LSM (SE) change	1.5 (0.5)	1.4 (0.6)	1.4 (0.7)	−0.2 (0.8)
Treatment contrast (95% CI)[a]	0.1 (−1.1 to 1.3)		1.6 (−0.1 to 3.3)	

	Study 3587		Study 3944	
	IDeg N = 555	IGlar N = 278	IDeg + Lira N = 174	Pla + Lira N = 172
Vitality				
Mean (SD) baseline	52.2 (9.6)	52.3 (10.0)	51.9 (9.3)	51.4 (9.7)
LSM (SE) change	1.0 (0.5)	0.9 (0.6)	0.4 (0.7)	−0.6 (0.7)
Treatment contrast (95% CI)[a]	0.1 (−1.1 to 1.3)		1.0 (−0.5 to 2.6)	
Social Functioning				
Mean (SD) baseline	47.9 (9.9)	48.4 (9.6)	48.8 (9.4)	48.2 (9.0)
LSM (SE) change	1.2 (0.4)	1.0 (0.6)	0.2 (0.8)	−0.8 (0.8)
Treatment contrast (95% CI)[a]	0.2 (−0.9 to 1.3)		1.0 (−0.8 to 2.8)	
Role Emotional				
Mean (SD) baseline	44.9 (11.0)	45.1 (10.6)	46.6 (11.8)	46.2 (10.8)
LSM (SE) change	1.8 (0.5)	1.6 (0.7)	0.8 (0.9)	−1.0 (0.9)
Treatment contrast (95% CI)[a]	0.2 (−1.1 to 1.6)		1.7 (−0.2 to 3.7)	
Mental Health				
Mean (SD) baseline	48.5 (10.4)	48.3 (10.0)	49.7 (10.8)	48.7 (9.8)
LSM (SE) change	0.5 (0.5)	0.5 (0.6)	2.1 (0.7)	0.7 (0.8)
Treatment contrast (95% CI)[a]	−0.0 (−1.3 to 1.2)		1.5 (−0.2 to 3.1)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDeg = insulin degludec; IDF = International Diabetes Federation; IGlar = insulin glargine; Lira = liraglutide; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NR = not reported; NT = not tested; Pla = placebo; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[b] *P* values are from the one-sided two-group t-test for superiority evaluated at the 2.5% level.

Source: CSR for Studies 3587[21] and 3944.[22]

Table 57: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Basal Insulin (Studies 3668 and 3943)

	Study 3668			Study 3943	
	IDeg-Flex N = 229	IDeg N = 228	IGlar N = 230	IDeg N = 140	IGlar N = 142
A1C					
Mean (SD) baseline, %	8.5 (1.0)	8.4 (0.9)	8.4 (0.9)	8.0 (1.1)	8.3 (1.4)
LSM (SE) change from baseline to 26 weeks (for Study 3668), 16 weeks (for Study 3943)	−1.17 (0.08)	−1.03 (0.08)	−1.21 (0.08)	−0.12 (0.09)	−0.06 (0.09)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d. FAS	0.04 (−0.12 to 0.20) Noninferiority confirmed (*P* < 0.001)			−0.06 (−0.21 to 0.09) Noninferiority confirmed (*P* < 0.001)	
LSM (SE) change from baseline to 26 weeks, 16 weeks (PP)	−1.25 (0.08)	−1.14 (0.08)	−1.31 (0.08)	−0.13 (0.09)	−0.08 (0.09)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.06 (−0.09 to 0.22)			−0.05 (−0.20 to 0.11)	
A1C Responders					
A1C < 7.0% (ADA)					
Patients, n (%), week 26	89 (38.9)	93 (40.8)	101 (43.9)	27 (19.6)	19 (13.8)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.82 (0.54 to 1.23)				

	Study 3668			Study 3943	
	IDeg-Flex N = 229	IDeg N = 228	IGlar N = 230	IDeg N = 140	IGlar N = 142
A1C ≤ 6.5% (IDF)					
Patients, n (%), week 26	55 (24.0)	52 (22.8)	59 (25.7)	13 (9.4)	13 (9.4)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.92 (0.58 to 1.46)				
A1C < 7.0% w/o Severe Hypo					
Patients, n (%), week 26	86 (40.8)	93 (44.3)	99 (46.9)	26 (18.8)	19 (13.8)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.82 (0.53 to 1.25)				
A1C < 7.0% w/o Confirmed Hypo					
Patients, n (%), week 26	56 (26.5)	63 (30.0)	68 (32.2)	25 (18.1)	14 (10.1)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.80 (0.51 to 1.26)				
A1C ≤ 6.5% w/o Severe Hypo					
Patients, n (%), week 26	55 (26.1)	52 (24.8)	59 (28.0)	13 (9.4)	13 (9.4)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.95 (0.59 to 1.52)				
A1C ≤ 6.5% w/o Confirmed Hypo					
Patients, n (%), week 26	36 (17.1)	37 (17.6)	44 (20.9)	12 (8.7)	10 (7.2)
Treatment odds ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.79 (0.48 to 1.33)				
FPG					
Mean (SD) baseline, mmol/L	9.0 (2.6)	8.8 (2.8)	9.0 (2.8)	8.1 (3.8)	7.9 (3.7)
LSM (SE) change from baseline to 26 weeks	−3.05 (0.20)	−3.01 (0.19)	−2.64 (0.20)	−0.82 (0.38)	−0.05 (0.38)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−0.42 (−0.82 to −0.02)			−0.77 (−1.39 to −0.15)	
Mean 9-Point Profile, SMPG (mmol/L)					
Fluctuation (mmol/L), LSM (SE) after 26 weeks	1.18	1.26	1.23	20.20	22.65
Treatment ratio (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.97 (0.88 to 1.06)			0.89 (0.79 to 1.00)	
Adjudicated Cardiovascular Events, n (%)	2 (0.9)	2 (0.9)	4 (1.7)		
MACE, n (%)	1 (0.4)	1 (0.4)	2 (0.9)	0	1 (0.7)
Cardiovascular Deaths					
Patients, n (%)	0	0	1 (0.4)	0	0
TRIM-D Scores					
Treatment Burden					
Mean (SD) baseline	60.8 (19.9)	56.6 (21.3)	59.0 (21.5)	NR	NR
LSM (SE) change at 26 weeks	7.6 (1.9)	6.5 (1.8)	6.1 (1.8)	NR	NR
Treatment contrast (95% CI)[a] Study IDeg q.d. FF vs IGlar q.d.	1.5 (−2.2 to 5.1)				
Daily Life				NR	NR
Mean (SD) baseline	75.4 (18.5)	72.9 (19.4)	74.3 (18.8)	NR	NR
LSM (SE) change at 26 weeks	1.6 (1.6)	2.8 (1.5)	1.9 (1.5)	NR	NR
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−0.3 (−3.4 to 2.8)				
Diabetes Management				NR	NR
Mean (SD) baseline	49.1 (22.0)	48.5 (20.9)	48.7 (21.4)	NR	NR

	Study 3668			Study 3943	
	IDeg-Flex N = 229	**IDeg N = 228**	**IGlar N = 230**	**IDeg N = 140**	**IGlar N = 142**
LSM (SE) change at 26 weeks	13.0 (1.8)	11.7 (1.7)	12.7 (1.8)	NR	NR
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.3 (−3.2 to 3.9)				
Compliance				NR	NR
Mean (SD) baseline	74.3 (17.9)	74.7 (18.5)	74.8 (18.4)	NR	NR
LSM (SE) change at 26 weeks	6.0 (1.4)	8.8 (1.4)	8.0 (1.4)	NR	NR
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−2.1 (−4.8 to 0.7)				
Psychological Health				NR	NR
Mean (SD) baseline	73.1 (19.5)	72.6 (19.0)	75.3 (19.3)	NR	NR
LSM (SE) change at 26 weeks	6.9 (1.4)	7.3 (1.3)	6.2 (1.4)	NR	NR
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.6 (−2.1 to 3.4)				
TRIM-D Total					
Mean (SD) baseline	66.7 (15.1)	65.4 (13.7)	66.9 (14.6)	NR	NR
LSM (SE) change at 26 weeks	7.0 (1.2)	7.3 (1.1)	6.7 (1.1)	NR	NR
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.3 (−2.0 to 2.6)				
HRQoL, SF-36 Scores					
Physical Score					
Mean (SD) baseline	47.8 (8.0)	46.4 (8.1)	46.2 (7.8)	43.8 (10.8)	43.9 (10.7)
LSM (SE) change at 26 weeks	0.3 (0.6)	0.4 (0.6)	1.0 (0.6)	−0.73 (0.66)	−0.52 (0.66)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−0.7 (−1.9 to 0.5)			−0.20 (−1.44 to 1.03)	
Physical Functioning					
Mean (SD) baseline	45.8 (10.2)	45.9 (9.4)	45.7 (9.8)	42.5 (12.3)	42.7 (12.1)
LSM (SE) change at 26 weeks	0.4 (0.7)	0.4 (0.7)	−0.6 (0.7)	0.06 (0.80)	0.54 (0.80)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	1.1 (−0.4 to 2.5)			−0.49 (−1.95 to 0.97)	
Role Physical					
Mean (SD) baseline	46.3 (9.9)	45.3 (9.5)	44.6 (10.2)	45.7 (11.9)	45.7 (11.8)
LSM (SE) change at 26 weeks	−0.2 (0.7)	0.3 (0.7)	−0.1 (0.7)	−1.23 (0.85)	−1.18 (0.85)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−0.1 (−1.5 to 1.3)			−0.05 (−1.63 to 1.52)	
Bodily Pain					
Mean (SD) baseline	50.5 (10.5)	48.3 (10.5)	47.9 (11.3)	45.2 (11.1)	45.2 (11.1)
LSM (SE) change at 26 weeks	0.1 (0.9)	0.0 (0.8)	1.7 (0.9)	−0.08 (0.78)	−0.13 (0.78)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−1.6 (−3.3 to 0.1)			0.06 (−1.54 to 1.65)	
General Health					
Mean (SD) baseline	43.5 (9.5)	42.9 (8.8)	42.9 (8.2)	43.6 (10.1)	43.4 (10.0)
LSM (SE) change at 26, 16 weeks	1.8 (0.7)	1.7 (0.7)	2.9 (0.7)	−0.16 (0.66)	−0.64 (0.66)
Treatment contrast (95% CI)[a]	−1.1 (−2.4 to 0.2)			0.49 (−0.75 to 1.72)	

	Study 3668			Study 3943	
	IDeg-Flex N = 229	IDeg N = 228	IGlar N = 230	IDeg N = 140	IGlar N = 142
Study 3668: IDeg q.d. FF vs IGlar q.d.					
Mental Score					
Mean (SD) baseline	46.1 (11.8)	46.7 (10.8)	46.0 (11.8)	47.5 (11.9)	47.4 (11.9)
LSM (SE) change at 26, 16 weeks	0.9 (0.8)	1.2 (0.8)	0.4 (0.8)	0.77 (0.84)	0.37 (0.84)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.5 (−1.1 to 2.1)			0.40 (−1.19 to 1.98)	
Vitality					
Mean (SD) baseline	51.2 (10.6)	50.1 (10.2)	50.5 (10.5)	48.3 (10.6)	48.3 (10.3)
LSM (SE) change at 26, 16 weeks	0.6 (0.8)	1.0 (0.7)	0.5 (0.7)	0.06 (0.76)	0.15 (0.77)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.1 (−1.3 to 1.6)			−0.09 (−1.57 to 1.38)	
Social Functioning					
Mean (SD) baseline	47.2 (9.6)	46.6 (10.2)	45.6 (10.4)	45.5 (11.5)	45.4 (11.4)
LSM (SE) change at 26, 16 weeks	1.0 (0.8)	2.0 (0.7)	1.6 (0.7)	0.06 (0.87)	−0.38 (0.87)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	−0.6 (−2.1 to 0.9)			0.44 (−1.23 to 2.11)	
Role Emotional					
Mean (SD) baseline	42.6 (12.5)	43.8 (11.9)	42.9 (11.7)	43.8 (13.6)	44.0 (13.5)
LSM (SE) change at 26,16 weeks	0.6 (0.9)	0.6 (0.9)	−0.1 (0.9)	0.77 (1.02)	0.78 (1.02)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.7 (−1.1 to 2.5)			−0.02 (−1.86 to 1.83)	
Mental Health					
Mean (SD) baseline	46.4 (12.1)	46.7 (10.3)	46.1 (12.5)	47.8 (11.6)	47.5 (11.6)
LSM (SE) change at 26,16 weeks	0.7 (0.8)	0.9 (0.8)	0.1 (0.8)	0.53 (0.83)	0.07 (0.83)
Treatment contrast (95% CI)[a] Study 3668: IDeg q.d. FF vs IGlar q.d.	0.6 (−1.0 to 2.2)			0.45 (−1.04 to 1.95)	

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; CI = confidence interval; CV = coefficient of variation; IDeg-Flex = insulin degludec flexible dosing; FAS = full analysis set; FF = fixed-flexible; FPG = fasting plasma glucose; HRQoL = health-related quality of life; Hypo = hypoglycemia; IDeg = insulin degludec; IDF = International Diabetes Federation; IGlar = insulin glargine; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; NR = not reported; PP = per-protocol; q.d. = once daily; SD = standard deviation; SE = standard error; SF-36 = Short Form (36) Health Survey; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; w/o = without.

[a] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates,

[b] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

Source: CSRs for Studies 3668[23] and 3943.[24]

Table 58: Key Efficacy Outcomes — Type 2 Diabetes Mellitus, Basal-Bolus (Study 3582 + Extension Study 3667)

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	IDeg (N = 744)	**IGlar (N = 248)**	**IDeg**	**IGlar**
A1C Levels, FAS[a]				
Mean (SD) baseline, %				
A1C blood (%), LSM (SE) change from baseline, end of treatment[a] (LOCF)	−1.10 (0.06)	−1.18 (0.08)	−1.03 (0.07)	−1.19 (0.09)
LS MD IDeg versus comparator (95% CI)[b,c]	0.08 (−0.05 to 0.21) Noninferiority confirmed ($P < 0.001$)		0.16 (0.02 to 0.30)	
A1C Levels, PP[a]				
A1C blood (%), LSM (SE) change from baseline, end of treatment[a] (LOCF)	−1.18 (0.06)	−1.22 (0.08)	−1.09 (0.07)	−1.23 (0.09)
LS MD IDeg versus comparator (95% CI)[b]	0.05 (−0.08 to 0.18)		0.14 (−0.01 to 0.28)	
A1C Levels, XTS[a]				
A1C blood (%), LSM (SE) change from baseline, end of treatment[a] (LOCF)	−1.18 (0.06)	−1.22 (0.08)	−1.09 (0.07)	−1.23 (0.09)
LS MD IDeg versus comparator (95% CI)[b]	0.05 (−0.08 to 0.18)		0.14 (−0.01 to 0.30)	
FPG at End of Treatment Period[a]				
Mean (SD) baseline, mmol/L	9.2 (3.0)	9.2 (3.2)	9.2 (3.0)	9.2 (3.2)
FPG (mmol/L), change from baseline, end of treatment[a], LSM (SE), LOCF	−2.25 (0.17)	−1.96 (0.22)	−2.30 (0.18)	−2.17 (0.22)
LS MD IDeg versus comparator (95% CI)[b,c]	−0.29 (−0.65 to 0.06) $P = 0.054$		−0.13 (−0.50 to 0.24)	
A1C Responders[a,d]				
A1C responders < 7.0% (ADA) at end of trial (LOCF)	368 (49.5)	124 (50.0)	291 (39.1)	109 (44.0)
A1C responders < 7.0% (ADA) at end of trial, treatment odds ratio IDeg versus comparator[e]	0.88 (0.65 to 1.21)		0.73 (0.536 to 1.00)	
A1C responders ≤ 6.5% (IDF) at end of trial (LOCF)	229 (30.8)	82 (33.1)	174 (23.4)	70 (28.2)
A1C responders ≤ 6.5% (IDF) at end of trial, treatment odds ratio IDeg versus comparator[e]	0.83 (0.60 to 1.15)		0.71 (0.506; 0.998)	
A1C Responders Without Confirmed Hypoglycemia[a,d,f]				
A1C responders < 7.0% (ADA) at end of trial (LOCF)	171 (24.4)	55 (23.2)	145 (20.7)	49 (20.7)
A1C responders < 7.0% (ADA) at end of trial, treatment odds ratio IDeg versus comparator[c,e]	1.02 (0.72 to 1.47) *P* value NT		0.96 (0.66 to 1.40)	
A1C responders ≤ 6.5% (IDF) at end of trial (LOCF)	107 (15.3)	34 (14.3)	84 (12.0)	29 (12.2)
A1C responders ≤ 6.5% (IDF) at end of trial, treatment odds ratio IDeg versus comparator[e]	1.03 (0.67 to 1.59)		0.94 (0.59 to 1.48)	
A1C Responders Without Severe Hypoglycemia[a,d,f]				
A1C responders < 7.0% (ADA) at end of trial (LOCF)	360 (51.4)	123 (51.9)	282 (40.3)	107 (45.1)
A1C responders < 7.0% (ADA) at end of trial, treatment odds ratio IDeg versus comparator[e]	0.90 (0.65 to 1.24)		0.75 (0.55 to 1.03)	
A1C responders ≤ 6.5% (IDF) at end of trial (LOCF)	226 (32.3)	81 (34.2)	170 (24.3)	69 (29.1)
A1C responders ≤ 6.5% (IDF) at end of trial, treatment odds ratio IDeg versus comparator[e]	0.86 (0.61 to 1.20)		0.73 (0.52 to 1.03)	

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	IDeg (N = 744)	**IGlar (N = 248)**	**IDeg**	**IGlar**
Mean of 9-point SMPG[a,g]	n = 707	n = 235	n = 707	n = 234
SMPG (mmol/L), LSM (SE) at end of trial (LOCF)	7.04 (0.12)	6.59 (0.15)	6.97 (0.12)	6.53 (0.15)
LS MD IDeg versus comparator (95% CI)	0.44 (0.20 to 0.69)		0.45 (0.20 to 0.70)	
Within-Patient Variability in Pre-Breakfast PG[a,h]	n = 742	n = 247	n = 742	n = 247
Within-patient CV (%), LOCF	21.41	22.88	20.39	21.94
Treatment ratio IDeg versus comparator (95% CI)[c]	0.94 (0.87 to 1.01) *P* value NT		0.93 (0.86 to 1.00)	
HRQoL, SF-36v2[a] **Scores**			NR	NR
Physical Score			NR	NR
Mean (SD), baseline	44.9 (9.4) (n = 740)	44.7 (8.9) (n = 248)	NR	NR
LSM (SE) change (LOCF)	−0.9 (0.5)	−1.3 (0.6)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.4 (−0.7 to 1.4)			
Physical Functioning			NR	NR
Mean (SD), baseline	44.8 (10.5) (n = 734)	45.3 (10.0) (n = 245)	NR	NR
LSM (SE) change (LOCF)	−1.1 (0.6)	−1.0 (0.7)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	−0.1 (−1.3 to 1.1)			
Role Physical			NR	NR
Mean (SD), baseline	45.3 (10.3) (n = 732)	45.9 (10.1) (n = 244)	NR	NR
LSM (SE) change (LOCF)	−1.6 (0.6)	−1.9 (0.7)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.3 (−0.9 to 1.5)			
Bodily Pain			NR	NR
Mean (SD), baseline	46.9 (11.0) (n = 735)	46.6 (10.9) (n = 247)	NR	NR
LSM (SE) change (LOCF)	−0.7 (0.6)	−2.2 (0.8)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	1.4 (0.1 to 2.7)			
General Health			NR	NR
Mean (SD), baseline	42.6 (9.6) (n = 736)	41.7 (10.1) (n = 243)	NR	NR
LSM (SE) change (LOCF)	0.6 (0.5)	0.1 (0.6)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.5 (−0.6 to 1.5)			
Overall Mental			NR	NR
Mean (SD), baseline	47.8 (11.2) (n = 740)	48.3 (10.8) (n = 248)	NR	NR
LSM (SE) change (LOCF)	0.3 (0.6)	−0.5 (0.7)	NR	NR
Treatment contrast	0.8 (−0.5 to 2.0)			

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	IDeg (N = 744)	**IGlar (N = 248)**	**IDeg**	**IGlar**
IDeg versus comparator (95% CI)[b]				
Vitality			NR	NR
Mean (SD), baseline	49.1 (10.6) (n = 726)	49.0 (9.9) (n = 244)	NR	NR
LSM (SE) change (LOCF)	−0.5 (0.6)	−0.7 (0.7)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.2 (−1.0 to 1.4)			
Social Functioning			NR	NR
Mean (SD), baseline	47.3 (10.3) (n = 737)	47.2 (10.3) (n = 248)	NR	NR
LSM (SE) change (LOCF)	0.4 (0.6)	−0.8 (0.8)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	1.2 (−0.1 to 2.5)			
Role Emotional			NR	NR
Mean (SD), baseline	44.5 (12.0) (n = 731)	45.7 (11.3) (n = 244)	NR	NR
LSM (SE) change (LOCF)	−1.1 (0.7)	−1.7 (0.8)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.6 (−0.8 to 2.0)			
Mental Health			NR	NR
Mean (SD), baseline	47.8 (11.1) (n = 726)	48.1 (11.0) (n = 244)	NR	NR
LSM (SE) change (LOCF)	0.1 (0.6)	−0.5 (0.7)	NR	NR
Treatment contrast IDeg versus comparator (95% CI)[b]	0.6 (−0.6 to 1.7)			
TRIM-D[a] Scores				
Treatment Burden			NR	NR
Mean (SD) baseline	54.5 (21.2) (n = 730)	55.0 (22.5) (n = 245)	NR	NR
LSM change (SE) from baseline (LOCF)	7.4 (1.4)	6.9 (1.7)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	0.5 (−2.3 to 3.3)			
Daily Life			NR	NR
Mean (SD) baseline	71.0 (18.5) (n = 728)	70.9 (18.5) (n = 245)	NR	NR
LSM change (SE) from baseline (LOCF)	2.0 (1.2)	1.3 (1.5)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	0.7 (−1.8 to 3.2)			
Diabetes Management			NR	NR
Mean (SD) baseline	44.9 (20.7) (n = 725)	44.7 (21.4) (n = 245)	NR	NR
LSM change (SE) from baseline (LOCF)	9.8 (1.4)	10.6 (1.7)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	−0.7 (−3.5 to 2.0)			
Compliance			NR	NR
Mean (SD) baseline	76.4 (16.9)	74.9 (18.8)	NR	NR

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	IDeg (N = 744)	**IGlar (N = 248)**	**IDeg**	**IGlar**
	(n = 728)	(n = 246)		
LSM change (SE) from baseline (LOCF)	1.2 (1.0)	1.8 (1.3)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	−0.6 (−2.7 to 1.5)			
Psychological Health			NR	NR
Mean (SD) baseline	74.9 (18.0) (n = 729)	72.8 (19.1) (n = 243)	NR	NR
LSM change (SE) from baseline (LOCF)	3.4 (1.1)	3.1 (1.3)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	0.4 (−1.8 to 2.6)			
Total			NR	NR
Mean (SD) baseline	64.7 (14.0) (n = 735)	63.8 (14.6) (n = 246)	NR	NR
LSM change (SE) from baseline (LOCF)	4.4 (0.9)	4.4 (1.1)	NR	NR
LS MD IDeg versus comparator (95% CI)[b]	0.0 (−1.8 to 1.8)			

A1C = glycated hemoglobin; ADA = American Diabetes Association; ANOVA = analysis of variance; BBT2 = basal-bolus type 2; CI = confidence interval; CV = coefficient of variation; FAS = full analysis set; FPG = fasting plasma glucose; HRQoL = health-related quality of life; IDeg = insulin degludec; IDF = International Diabetes Federation; IGlar = insulin glargine; LOCF = last observation carried forward; LSM = least squares mean; LS MD = least squares mean difference; NR = not reported; NT = not tested; PG = plasma glucose; PP = per-protocol; SD = standard deviation; SE = standard error; SF-36v2 = Short Form (36) Health Survey, version 2.0; SMPG = self-measured plasma glucose; TRIM-D = Treatment-Related Impact Measure — Diabetes; XTS = extension set.

[a] End of treatment period for Study 3582 was 52 weeks; for Study 3667, it was 78 weeks.

[b] The response and change from baseline in the response after treatment period are analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

[c] *P* values are from the one-sided two-group t-test for noninferiority and superiority, respectively, evaluated at the 2.5% level.

[d] Responders met A1C targets according to ADA or IDF classification.

[e] The binary end point is analyzed in a logistic regression model using a logit link. The model includes treatment, sex, region, and antidiabetes treatment at screening as fixed effects, and age and A1C as covariates.

[f] Without hypoglycemia refers to no treatment-emergent hypoglycemia events in the last 12 weeks of treatment or seven days of follow-up, and patient must be exposed to treatment for at least 12 weeks. Confirmed hypoglycemia is an episode wherein a patient is unable to self-treat, or with recorded plasma glucose < 3.1 mmol/L. Severe hypoglycemia is defined according to ADA classification.

[g] Mean SMPG is defined as the area under the profile divided by measurement time. The response after treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and mean profile at baseline as covariates.

[h] Log-transformed pre-breakfast SMPG values after treatment period are analyzed as repeated measures in a mixed linear model with treatment, antidiabetes treatment at screening, region, and sex as fixed effects, age as covariate, and patient as random effect. The model assumes independent within-patient and between-patient variances with variances depending on treatment.

Source: CSRs for Studies 3582[25] and 3667.[35]

Harms

Table 59: Harms — Type 1 Diabetes Mellitus (Study 3770 + Extension)

	Study 3770			Study 3770-Ext	
	IDeg-Flex N = 164	IDeg N = 165	IGlar N = 164	IDeg-Flex	IGlar
AEs					
Patients with > 0 AEs, N (%)	111 (67.7)	125 (75.8)	116 (72.0)	268 (81.5)	134 (83.2)
Most common AEs (≥ 5% of patients)					
Nasopharyngitis	31 (18.9)	43 (26.1)	29 (18.0)	99 (30.1)	48 (29.8)
Sinusitis	5 (3.0)	10 (6.1)	7 (4.3)	23 (7.0)	13 (8.1)
Upper respiratory tract infection	6 (3.7)	9 (5.5)	13 (8.1)	28 (8.5)	21 (13.0)
Gastroenteritis	4 (2.4)	9 (5.5)	5 (3.1)	19 (5.8)	6 (3.7)
Gastroenteritis viral				9 (2.7)	10 (6.2)
Headache	10 (6.1)	16 (9.7)	18 (11.2)	33 (10.0)	24 (14.9)
Diarrhea	4 (2.4)	1 (0.6)	9 (5.6)	9 (2.7)	12 (7.5)
Nausea	9 (5.5)	7 (4.2)	8 (5.0)	18 (5.5)	8 (5.0)
Vomiting	4 (2.4)	9 (5.5)	5 (3.1)	18 (5.5)	11 (6.8)
Cough	7 (4.3)	4 (2.4)	10 (6.2)	17 (5.2)	11 (6.8)
Oropharyngeal pain	7 (4.3)	11 (6.7)	11 (6.8)	28 (8.5)	14 (8.7)
Hypoglycemia	11 (6.7)	18 (10.9)	10 (6.2)	32 (9.7)	15 (9.3)
SAEs					
Patients with > 0 SAEs, N (%)	9 (5.5)	7 (4.2)	8 (5.0)	25 (7.6)	12 (7.5)
Most common SAE (≥ 1% in any group)					
Hypoglycemia	3 (1.8)	3 (1.8)	2 (1.2)	8 (2.4)	4 (2.5)
Hypoglycemic unconsciousness	3 (1.8)	1 (0.6)	3 (1.9)	5 (1.5)	4 (2.5)
WDAEs					
WDAEs, N (%)	5	4	1	9	2
Number of deaths, N (%)	1				
Most common reasons	Suicide				
Notable Harms					
Neoplasms, SOC/preferred term	1 (0.6)	0	0	5 (1.5)	3 (1.9)
Hypoglycemia, confirmed	154 (93.9)	164 (99.4)	156 (96.9)	319 (97.0)	157 (97.5)
Events	5,988	6,724	6,263	18,297	9,119
Events/100 PYE	8,238	8,825	7,973	6,811	6,341
LSM, events/100 PYE	7,954.68	8,629.14	7,709.88	NR	NR
Treatment ratio IDeg q.d. FF vs IGlar q.d. (95% CI)	1.03 (0.85 to 1.26)			1.09 (0.91 to1.29)	
ADA definition, participants, n (%)	159 (97.0)	165 (100.0)	157 (97.5)	324 (98.5)	158 (98.1)
Severe	17 (10.4)	21 (12.7)	16 (9.9)	44 (13.4)	21 (13.0)
Nocturnal hypoglycemia, confirmed	111 (67.7)	121 (73.3)	117 (72.7)	256 (77.8)	126 (78.3)
Events	453	732	782	1,720	1,219
Events/100 PYE	623	961	996	640	848
LSM, events/100 PYE	598.70	950.26	990.67	631.28	866.89
Treatment ratio IDeg q.d. FF vs IGlar q.d. (95% CI)	0.60 (0.44 to 0.82)			0.73 (0.54 to 0.98)	
ADA definition, participants, n (%)	123 (75.0)	134 (81.2)	128 (79.5)	271 (82.4)	133 (82.6)
Severe	5 (3.0)	5 (3.0)	5 (3.1)	14 (4.3)	6 (3.7)

	Study 3770			Study 3770-Ext	
	IDeg-Flex N = 164	IDeg N = 165	IGlar N = 164	IDeg-Flex	IGlar
Injection-site reactions	8 (4.9)	3 (1.8)	4 (2.5)	12 (3.6)	4 (2.5)
Weight gain (kg), change from baseline at 26 or 53 weeks, mean (SD)	1.2 (3.5)	0.8 (2.5)	1.6 (3.7)	1.3 (3.6)	1.9 (4.5)
Weight change, treatment contrast IDeg q.d. FF vs IGlar q.d. (95% CI)	−0.44 (−1.14 to 0.27)			−0.51 (−1.24 to 0.22)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; Ext = extension; FF = fixed-flexible; IDeg = insulin degludec; IDeg-Flex = insulin degludec flexible dosing; IGlar = insulin glargine; LSM = least squares mean; PYE = patient-years of exposure; q.d. = once daily; SAE = serious adverse event; SD = standard deviation; SE = standard error; SOC = system organ class; vs = versus; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

Source: CSRs for Studies 3770 and 3770-ext.[15,31]

Table 60: Harms — Type 1 Diabetes Mellitus (Study 3583 + Extension Study 3644)

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	Glargine N = 154	Degludec	Glargine
AEs				
Patients with > 0 AEs, N (%)	397 (84.1)	128 (83.1)	413 (87.5)	137 (89.0)
Most common AEs (≥ 5% in any group)				
Nasopharyngitis	130 (27.5)	41 (26.6)	160 (33.9)	51 (33.1)
Sinusitis	37 (7.8)	13 (8.4)	58 (12.3)	23 (14.9)
Upper respiratory tract infection	94 (19.9)	23 (14.9)	123 (26.1)	31 (20.1)
Gastroenteritis	29 (6.1)	4 (2.6)	44 (9.3)	10 (6.5)
Gastroenteritis viral	NA	NA	25 (5.3)	6 (3.9)
Headache	68 (14.4)	21 (13.6)	84 (17.8)	22 (14.3)
Diarrhea	25 (5.3)	7 (4.5)	39 (8.3)	9 (5.8)
Nausea	26 (5.5)	10 (6.5)	40 (8.5)	14 (9.1)
Vomiting	16 (3.4)	8 (5.2)	26 (5.5)	11 (7.1)
Cough	23 (4.9)	11 (7.1)	33 (7.0)	17 (11.0)
Oropharyngeal pain	25 (5.3)	13 (8.4)	34 (7.2)	14 (9.1)
Bronchitis	18 (3.8)	8 (5.2)	38 (8.1)	11 (7.1)
Influenza	33 (7.0)	15 (9.7)	44 (9.3)	17 (11.0)
Urinary tract infection	25 (5.3)	8 (5.2)	35 (7.4)	12 (7.8)
Hypoglycemia	51 (10.8)	12 (7.8)	66 (14.0)	19 (12.3)
Nasal congestion	NA	NA	17 (3.6)	11 (7.1)
Sinus congestion	NA	NA	22 (4.7)	9 (5.8)
Back pain	NA	NA	33 (7.0)	9 (5.8)
Seasonal allergy	NA	NA	10 (2.1)	10 (6.5)
SAEs				
Patients with > 0 SAEs, N (%)	49 (10.4)	17 (11.0)	71 (15.0)	29 (18.8)
Most common SAE (≥ 1% in any group)				
Hypoglycemia	19 (4.0)	5 (3.2)	27 (5.7)	7 (4.5)
DKA	NA	NA	2 (0.4)	3 (1.9)
Hypoglycemic unconsciousness	12 (2.5)	2 (1.3)	15 (3.2)	4 (2.6)
Hypoglycemic seizure	NA	NA	3 (0.6)	2 (1.3)
WDAEs				
WDAEs, N (%)	12	2	15 (3.2)	4 (2.6)

	Study 3583		Study 3644 (Ext)	
	Degludec N = 472	**Glargine N = 154**	**Degludec**	**Glargine**
Most common reasons				
Hypoglycemia-related	4	0		
Deaths				
Number of deaths, N (%)	2	1	4	3
Most common reasons	MI	Sudden death	Sudden death Ventricular tachycardia	Gallbladder cancer Ventricular arrhythmia
Notable Harms				
Neoplasms, SOC/preferred term	7 (1.5)	4 (2.6)	19 (4.0)	6 (3.9)
Hypoglycemia, confirmed[a]	451 (95.6)	147 (95.5)	454 (96.2)	147 (95.5)
Events	18,389	5,796	29,312	9,798
Events/100 PYE	4,254	4,018	3,750	3,743
LSM, events/100 PYE	4,460.12	4,177.82	4,077.23	3,979.95
Treatment ratio[b] (95% CI)	1.07 (0.89 to 1.28), *P* = 0.758		1.02 (0.85 to 1.24)	
ADA definition, participants, n (%)	464 (98.3)	153 (99.4)	466 (98.7)	153 (99.4)
Severe	58 (12.3)	16 (10.4)	72 (15.3)	24 (15.6)
Nocturnal hypoglycemia, confirmed	341 (72.2)	114 (74.0)	366 (77.5)	122 (79.2)
Events	1,905	845	3,049	1,392
Events/100 PYE	441	586	390	532
LSM, events/100 PYE	413.66	548.20	381.42	508.49
Treatment ratio[b] (95% CI)	0.75 (0.59 to 0.96), *P* = 0.011		0.75 (0.59 to 0.95)	
ADA definition, participants, n (%)	385 (81.6)	128 (83.1)	404 (85.6)	133 (86.4)
Severe	18 (3.8)	3 (1.9)	25 (5.3)	6 (3.9)
Injection-site reactions	2.8%	5.2%	3.0%	5.8%
Mean (SD) change in weight, kg	1.8 (4.0)	1.6 (4.3)	2.1 (4.8)	2.0 (4.6)
LSM change	2.14 (0.30)	1.95 (0.40)	2.36 (0.35)	2.24 (0.47)
Treatment contrast (95% CI)	0.18 (−0.54 to 0.91)		0.12 (−0.73 to 0.98)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; DKA = diabetic ketoacidosis; LSM = least squares mean; MI = myocardial infarction; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SOC = system organ class; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSRs for Studies 3583[4] and 3644.[32]

Table 61: Harms — Type 1 Diabetes Mellitus (Study 3585 + Extension Study 3725)

	Study 3585		Study 3725 (Ext)	
	Degludec N = 302	**Detemir N = 153**	**Degludec N = 301**	**Detemir N = 152**
AEs				
Patients with > 0 AEs, N (%)	219 (72.8)	112 (73.7)	248 (82.4)	118 (77.6)
Most common AEs (≥ 5% in any group)				
Nasopharyngitis	59 (19.6)	34 (22.4)	94 (31.2)	49 (32.2)
Upper respiratory tract infection	22 (7.3)	11 (7.2)	34 (11.3)	17 (11.2)
Gastroenteritis	NA	NA	22 (7.3)	10 (6.6)
Headache	36 (12.0)	10 (6.6)	42 (14.0)	12 (7.9)

	Study 3585		Study 3725 (Ext)	
	Degludec N = 302	**Detemir N = 153**	**Degludec N = 301**	**Detemir N = 152**
Diarrhea	NA	NA	20 (6.6)	9 (5.9)
Cough	13 (4.3)	8 (5.3)	21 (7.0)	8 (5.3)
Influenza	NA	NA	14 (4.7)	9 (5.9)
Hypoglycemia	19 (6.3)	15 (9.9)	23 (7.6)	16 (10.5)
Hypoglycemic unconsciousness	NA	NA	18 (6.0)	6 (3.9)
Pyrexia	NA	NA	16 (5.3)	9 (5.9)
Back pain	NA	NA	22 (7.3)	5 (3.3)
Diabetic retinopathy	NA	NA	20 (6.6)	7 (4.6)
SAEs				
Patients with > 0 SAEs, N (%)	23 (7.6)	8 (5.3)	36 (12.0)	11 (7.2)
Most common SAE (≥ 1% in any group)				
Hypoglycemia	7 (2.3)	5 (3.3)	12 (4.0)	5 (3.3)
Hypoglycemic unconsciousness	4 (1.3)	3 (2.0)	9 (3.0)	5 (3.3)
Hypoglycemic coma	3 (1.0)	0	4 (1.3)	1 (0.7)
WDAEs				
WDAEs, N (%)	3	1	4	2
Most common reasons				
Hypoglycemia	1	1	1	1
Number of deaths, N (%)	0	0	0	0
Notable Harms				
Neoplasms, SOC/preferred term	6 (2.0)	0	7 (2.3)	0
Hypoglycemia, confirmed[a]	280 (93.0)	139 (91.4)	285 (94.7)	141 (92.8)
Events	6,673	3,295	10,326	5,269
Events/100 PYE	4,583	4,569	3,778	3,926
LSM, events/100 PYE	4,571.38	4,652.97	3,874.11	4,060.32
Treatment ratio[b] (95% CI)	0.98 (0.80 to 1.20)		0.95 (0.78 to 1.17)	
ADA definition, participants, n (%)	295 (98.0)	150 (98.7)	297 (98.7)	150 (98.7)
Severe	32 (10.6)	16 (10.5)	42 (14.0)	18 (11.8)
Nocturnal hypoglycemia, confirmed	176 (58.5)	89 (58.6)	205 (68.1)	98 (64.5)
Events	603	428	924	646
Events/100 PYE	414	593	338	481
LSM, events/100 PYE	390.72	591.59	333.00	497.06
Treatment ratio[b] (95% CI)	0.66 (0.49 to 0.88)		0.67 (0.51 to 0.88)	
ADA definition, participants, n (%)	219 (72.8)	106 (69.7)	236 (78.4)	114 (75.0)
Severe	12 (4.0)	5 (3.3)	16 (5.3)	6 (3.9)
Injection-site reactions	12 events	3 events	14 events	4 events
Weight gain, mean change (kg) baseline to weeks 26, 53 (LOCF)	1.5 (2.7)	0.4 (2.4)	1.9 (3.3)	0.8 (2.8)
LSM change (SE)	1.50 (0.20)	0.42 (0.24)	1.99 (0.24)	0.92 (0.29)
Treatment contrast (95% CI)	1.08 (0.58 to 1.57)		1.07 (0.47 to 1.67)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; LOCF = last observation carried forward; LSM = least squares mean; NA = not available; PYE = patient-years of exposure; SAE = serious adverse event; SE = standard error; SOC = system organ class; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSRs for Studies 3585[16] and 3725.[33]

Table 62: Harms — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3579 + Extension Study 3643)

	Study 3579		Study 3643 (Ext)	
	Degludec N = 773	**Glargine N = 257**	**Degludec**	**Glargine**
AEs				
Patients with > 0 AEs, N (%)	572 (74.7)	182 (70.8)	617 (80.5)	198 (77.0)
Most common AEs (≥ 5% in any group)				
Nasopharyngitis	145 (18.9)	48 (18.7)	183 (23.9)	65 (25.3)
Sinusitis	NA	NA		
Upper respiratory tract infection	54 (7.0)	12 (4.7)	78 (10.2)	19 (7.4)
Gastroenteritis	25 (3.3)	13 (5.1)	35 (4.6)	16 (6.2)
Headache	93 (12.1)	25 (9.7)	106 (13.8)	30 (11.7)
Diarrhea	66 (8.6)	26 (10.1)	83 (10.8)	28 (10.9)
Nausea	NA	NA	41 (5.4)	11 (4.3)
Vomiting	27 (3.5)	13 (5.1)	34 (4.4)	17 (6.6)
Cough	50 (6.5)	11 (4.3)	61 (8.0)	14 (5.4)
Bronchitis	48 (6.3)	12 (4.7)	70 (9.1)	20 (7.8)
Influenza	NA	NA	45 (5.9)	13 (5.1)
Urinary tract infection	NA	NA	46 (6.0)	14 (5.4)
Back pain	52 (6.8)	17 (6.6)	76 (9.9)	23 (8.9)
Arthralgia	NA	NA	45 (5.9)	12 (4.7)
Musculoskeletal pain	NA	NA	30 (3.9)	13 (5.1)
Osteoarthritis	NA	NA	23 (3.0)	13 (5.1)
Pain in extremity	NA	NA	44 (5.7)	11 (4.3)
Dizziness	NA	NA	31 (4.0)	14 (5.4)
Hypertension	NA	NA	54 (7.0)	13 (5.1)
Edema peripheral	NA	NA	46 (6.0)	11 (4.3)
SAEs				
Patients with > 0 SAEs, N (%)	62 (8.1)	26 (10.1)	116 (15.1)	41 (16.0)
Most common SAE (≥ 1% in any group)				
Coronary artery disease	NA	NA	10 (1.3)	0
WDAEs				
WDAEs, N (%)	20 (2.6)	5 (1.9)	12 (1.6)	5 (1.9)
Number of deaths, N (%)	1	1	4	3
Notable Harms				
Neoplasms, SOC/preferred term	25 (3.3)	8 (3.1)	46 (6.0)	14 (5.4)
Neoplasms, events	28	8	57	14
Reported as SAE	7	2	19	4
Hypoglycemia, confirmed[a]	356 (46.5)	119 (46.3)	444 (58.0)	141 (54.9)
Events	1014	403	2081	789
Events/100 PYE	152	185	172	205
LSM, events/100 PYE	140.97	171.91	157.65	187.70
Treatment ratio[b] (95% CI)	0.82 (0.64 to 1.04)		0.84 (0.68 to 1.04)	
ADA definition, participants, n (%)	643 (83.9)	200 (77.8)	667 (87.1)	211 (82.1)
Severe	2 (0.3)	5 (1.9)	6 (0.8)	7 (2.7)
Nocturnal hypoglycemia, confirmed	106 (13.8)	39 (15.2)	158 (20.6)	61 (23.7)
Events	169	84	325	176

	Study 3579		Study 3643 (Ext)	
	Degludec N = 773	Glargine N = 257	Degludec	Glargine
Events/100 PYE	25	39	27	46
LSM, events/100 PYE	24.02	37.62	23.98	42.40
Treatment ratio[b] (95% CI)	0.64 (0.42 to 0.98)		0.57 (0.40 to 0.81)	
ADA definition, participants, n (%)	283 (36.9)	94 (36.6)	337 (44.0)	120 (46.7)
Severe	1 (0.1)	0 (0.0)	1 (0.1)	2 (0.8)
Injection-site reactions	5.6%	6.2%	6.1%	6.6%
Weight gain				
Mean (SD) weight change from baseline, kg (LOCF)	2.4 (4.3)	2.1 (4.1)	2.7 (5.2)	2.4 (4.7)
LSM change (SE)	2.57 (0.17)	2.29 (0.27)	2.96 (0.20)	2.59 (0.33)
Treatment contrast (95% CI)	0.28 (−0.32 to 0.88)		0.37 (−0.35 to 1.10)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; LOCF = last observation carried forward; LSM = least squares mean; NA = not available; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; SOC = system organ class; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSRs for Studies 3579[17] and 3643.[34]

Table 63: Harms — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3672)

	Study 3672	
	Degludec N = 228	Glargine N = 228
AEs		
Patients with > 0 AEs, N (%)	147 (64.5)	156 (68.4)
Most common AEs (≥ 5% in any group)		
Nasopharyngitis	17 (7.5)	12 (5.3)
Upper respiratory tract infection	7 (3.1)	15 (6.6)
Headache	20 (8.8)	24 (10.5)
Diarrhea	17 (7.5)	19 (8.3)
Patients with hypoglycemia episodes (ADA)	160 (70.2)	171 (75.0)
Severe	0 (0)	0 (0)
Confirmed hypoglycemia[a]	65 (28.5)	70 (30.7)
SAEs		
Patients with > 0 SAEs, N (%)	15 (6.6)	10 (4.4)
Most common SAE (≥ 1% in any group)		
Chest pain	4 (1.8)	0
WDAEs		
WDAEs, N (%)	5	4
Most common reasons	None in > 1 patient	
Number of deaths, N (%)	0	2
Notable Harms		
Neoplasms by SOC/preferred term	6 (2.6)	5 (2.2)
Confirmed TE hypoglycemia episodes, N (%)	65 (28.5)	70 (30.7)
Events	129	152

	Study 3672	
	Degludec N = 228	**Glargine N = 228**
Events/100 PYE	122	142
LSM, events/100 PYE	107.54	125.00
Treatment ratio[b] (95% CI)	0.86 (0.58 to 1.28)	
ADA definition, participants, n (%)	160 (70.2)	171 (75.0)
Severe	0	0
Nocturnal confirmed symptomatic hypoglycemia, N (%)	14 (6.1)	20 (8.8)
Events	19	30
Events/100 PYE	18	28
LSM, events/100 PYE	10.93	17.13
Treatment ratio, IDeg versus comparator (95% CI)	0.64 (0.30 to 1.37)	
ADA definition, participants, n (%)	61 (26.8)	67 (29.4)
Severe	0	0
Injection-site reactions	6.1%	6.1%
Mean (SD) weight change from baseline, kg	1.9 (3.5)	1.5 (3.5)
LSM change	2.30 (0.36)	1.86 (0.35)
Treatment contrast (95% CI)	0.44 (−0.20 to 1.08)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; IDeg = insulin degludec; LSM = least squares mean; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SOC = system organ class; TE = treatment-emergent; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSR for Study 3672.[19]

Table 64: Harms — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3586)

	Study 3586	
	Degludec N = 284	**Glargine N = 146**
AEs		
Patients with > 0 AEs, N (%)	167 (58.8)	95 (65.1)
Most common AEs (≥ 5% in any group)		
Nasopharyngitis	26 (9.2)	20 (13.7)
Upper respiratory tract infection	22 (7.7)	16 (11.0)
Diabetic retinopathy	15 (5.3)	6 (4.1)
SAEs		
Patients with > 0 SAEs, N (%)	8 (2.8)	8 (5.5)
Most common SAE (≥ 1% in any group)	NA	NA
WDAEs		
WDAEs, N (%)	2	3
None in > 1 participant		
Reason		Hypoglycemia
Mortality		
Number of deaths, N (%)	1	0
Most common reasons	Drowning	
Notable Harms		
Externally classified neoplasms	6 (2.1)	3 (2.1)

	Study 3586	
	Degludec N = 284	**Glargine N = 146**
Hypoglycemia, confirmed[a]	142 (50.0)	78 (53.4)
Events	397	260
Events/100 PYE	298	370
LSM, events/100 PYE	244.22	299.31
Treatment ratio[b] (95% CI)	0.82 (0.60 to 1.11), *P* = 0.101	
ADA definition, participants, n (%)	258 (90.8)	130 (89.0)
Severe	0	1 (0.7)
Nocturnal hypoglycemia, confirmed	58 (20.4)	35 (24.0)
Events	104	87
Events/100 PYE	78	124
LSM, events/100 PYE	51.83	83.05
Treatment ratio (95% CI)	0.62 (0.38 to 1.04), *P* = NT	
ADA definition, participants, n (%)	150 (52.8)	80 (54.8)
Severe	0	0
Injection-site reactions	1.8%	2.1%
Mean (SD) **weight change** from baseline, kg	1.3 (2.2)	1.4 (2.2)
LSM (SE) change	1.54 (0.17)	1.71 (0.21)
Treatment contrast (95% CI)	−0.17 (−0.59 to 0.26)	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; LSM = least squares mean; NA = not available; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSR for Study 3586.[20]

Table 65: Harms — Type 2 Diabetes Mellitus, Insulin-Naive (Study 3580)

	Study 3580	
AEs	**Degludec (N = 226)**	**DPP-4 Inhibitor (N = 228)**
Patients with > 0 AEs, N (%)	141 (62.4)	144 (63.2)
Possibly or probably related to study treatment[a]	26 (11.5)	35 (15.4)
Most common AEs,[b] N (%)		
Diarrhea	13 (5.8)	19 (8.3)
Headache	24 (10.6)	15 (6.6)
Nasopharyngitis	13 (5.8)	18 (7.9)
Nausea	8 (3.5)	14 (6.1)
Patients with hypoglycemia episodes[c]	169 (74.8)	72 (31.6)
Severe	1 (0.4)	0
Documented symptomatic	96 (42.5)	32 (14.0)
Asymptomatic hypoglycemia	137 (60.6)	50 (21.9)
Probable symptomatic hypoglycemia	10 (4.4)	7 (3.1)
Relative	21 (9.3)	9 (3.9)
Unclassifiable	14 (6.2)	2 (0.9)
Confirmed hypoglycemia[d]	96 (42.5)	29 (12.7)

	Study 3580	
AEs	**Degludec (N = 226)**	**DPP-4 Inhibitor (N = 228)**
SAEs		
Patients with > 0 SAEs, N (%)	14 (6.2)	10 (4.4)
Possibly or probably related to study treatment[a]	0 (0)	0 (0)
Mortality		
Number of deaths, N (%)	1 (0.4)	0
Cardiovascular death	1 (0.4)	0
WDAEs		
WDAEs, N (%)	9 (4.0)	2 (0.9)
Death	1 (0.4)	0
Symptoms possibly or probably related to treatment[a]	4 (1.8)	0
Cardiovascular Events		
Non-MACE	1 (0.4)	2 (0.9)
MACE	3 (1.3)	3 (1.3)
Acute coronary syndrome	1 (0.4)	2 (0.9)
Stroke	1 (0.4)	1 (0.4)
Cardiovascular death	1 (0.4)	0
Notable Harms		
Externally classified neoplasms, N (%)	3 (1.3)	2 (0.9)
Most common reasons		
Serious adverse events		1 (bladder cancer)
Confirmed TE hypoglycemia episodes, N (%)[e]	96 (42.5)	29 (12.7)
Events (safety set)	311	123
Events/100 PYE	307	126
LSM, events/100 PYE, FAS	166.38 (n = 211)	43.68 (n = 211)
Treatment ratio IDeg versus comparator (95% CI)[f]	3.81 (2.40 to 6.05)	
Nocturnal[g] confirmed symptomatic hypoglycemia	29 (12.8)	13 (5.7)
Events (safety set)	53	29
Events/100 PYE	52	30
LSM, events/100 PYE (FAS)	0.01	0.01
Treatment ratio IDeg versus comparator (95% CI)[f]	1.93 (0.90 to 4.10)	
Injection-site reactions	4.4%	NA
Mean (SD) weight, change from baseline, kg (LOCF), safety set	2.4 (4.7)	−0.3 (3.9)
LSM (SE) change from baseline (LOCF), FAS	2.71 (0.44)	−0.05 (0.43)
Treatment contrast: IDeg versus comparator (95% CI)[h]	2.75 (1.97 to 3.54)	

ADA = American Diabetes Association; AE = adverse event; ANOVA = analysis of variance; CI = confidence interval; DPP-4 = dipeptidyl peptidase-4; FAS = full analysis set; IDeg = insulin degludec; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; SOC = system organ class; TE = treatment-emergent; WDAE = withdrawal due to adverse event.

[a] As per investigator and Novo Nordisk A/S.

[b] AE frequency ≥ 5%.

[c] As classified by the ADA.

[d] Patient was unable to self-treat or recorded a plasma glucose level < 3.1 mmol/L.

[e] Confirmed hypoglycemia is an episode wherein a patient is unable to self-treat, or with recorded plasma glucose < 3.1 mmol/L. Severe hypoglycemia is defined according to ADA classification.

[f] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

[g] Nocturnal is the period between 00:01 a.m. and 05:59 a.m., inclusive.

[h] Change from baseline in the response at end of treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

Source: CSR for Study 3580.[18]

Table 66: Harms — Type 2 Diabetes Mellitus, Insulin-Naive (Studies 3587 and 3944)

	Study 3587		Study 3944	
	Degludec N = 553	**Glargine N = 278**	**IDeg + Lira N = 173**	**Pla + Lira N = 170**
AEs				
Patients with > 0 AEs, N (%)	293 (53.0)	161 (57.9)	95 (54.9)	88 (51.8)
Most common AEs (≥ 5% in any group)				
Nasopharyngitis	41 (7.4)	27 (9.7)	14 (8.1)	11 (6.5)
Upper respiratory tract infection	60 (10.8)	32 (11.5)		
Diarrhea	NA	NA	10 (5.8)	13 (7.6)
Lipase increased	NA	NA	10 (5.8)	13 (7.6)
SAEs				
Patients with > 0 SAEs, N (%)	6 (2.9)	10 (3.6)	6 (3.5)	9 (5.3)
Most common SAE (≥ 1% in any group)	NA	NA	NA	NA
WDAEs				
WDAEs, N (%)	3 (0.5)	3 (1.1)	5 (2.9)	3 (1.7)
None in > 1 participant				
Mortality				
Number of deaths, N (%)	0	1	0	0
Most common reasons		Cardiac fail, peritonitis, gastric cancer		
Notable Harms				
Neoplasms by SOC/preferred term, n (%)	5 (0.9)	4 (1.4)	2 (1.2)	2 (1.2)
Hypoglycemia, confirmed[a]	128 (23.1)	79 (28.4)	30 (17)	8 (4.7)
Events	228	130	47	9
Events/100 PYE	85	97	57	12
LSM, events/100 PYE	73.7	91.7	49.41	10.58
Treatment ratio[b] (95% CI)	0.80 (0.59 to 1.10), *P* = 0.084		4.67 (2.07 to 10.56)	
ADA definition, participants, n (%)	440 (79.6)	233 (83.8)	101 (58.4)	27 (15.9)
Severe	2 (0.4)	2 (0.7)	0	0
Nocturnal hypoglycemia, confirmed	40 (7.2)	25 (9.0)	3 (1.7)	2 (1.2)
Events	58	32	4	2
Events/100 PYE	22	24	5	3
LSM, events/100 PYE	17.2	22.3	0.00	0.00
Treatment ratio[b] (95% CI)	0.77 (0.43 to 1.37)		1.75 (0.24 to 12.71)	
ADA definition, participants, n (%)	160 (28.9)	98 (35.3)	19 (11.0)	6 (3.5)
Severe	1 (0.2)	0	0	0
Injection-site reactions	9 (1.6)	2 (0.7)	37 events/100 PYE	3 events/100 PYE
Mean (SD) **weight change** from baseline, kg	2.2 (3.1)	1.8 (3.1)	2.0 (3.2)	−1.3 (2.8)
LSM (SE) change	2.55 (0.18)	2.20 (0.22)	NR	NR
Treatment contrast	0.34 (−0.09 to 0.78)		NR	

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; LSM = least squares mean; NA = not available; NR = not reported; Pla = placebo; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; SOC = system organ class; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSRs for Studies 3587[21] and 3944.[22]

Table 67: Harms — Type 2 Diabetes Mellitus, Basal Insulin (Studies 3668 and 3943)

	Study 3668			Study 3943	
	IDeg-Flex N = 229	IDeg N = 228	IGlar N = 230	IDeg N = 140	IGlar N = 142
AEs					
Patients with > 0 AEs, N (%)	122 (53.0)	128 (56.6)	128 (55.9)	45 (32.1)	50 (35.2)
Most common AEs (≥ 5% in any group)					
Nasopharyngitis	23 (10.0)	20 (8.8)	18 (7.9)	2 (1.4)	9 (6.3)
Upper respiratory tract infection	20 (8.7)	11 (4.9)	20 (8.7)	NA	NA
Dizziness	3 (1.3)	3 (1.3)	12 (5.2)	NA	NA
Headache	16 (7.0)	16 (7.1)	9 (3.9)	NA	NA
Diarrhea	10 (4.3)	14 (6.2)	10 (4.4)	NA	NA
Back pain	12 (5.2)	9 (4.0)	6 (2.6)	NA	NA
SAEs					
Patients with > 0 SAEs, N (%)	6 (2.6)	8 (3.5)	4 (1.7)	4 (2.9)	4 (2.8)
Most common SAE (≥ 1% in any group)					
WDAEs					
WDAEs, N (%)	2	1	2		1
Mortality					
Number of deaths, N (%)	0	1	1	0	0
Most common reasons		Anemia, myelodysplastic syndrome	Unknown		
Notable Harms					
Neoplasms by SOC/preferred term	3 (1.3)	4 (1.8)	1 (0.4)	1 (0.7)	1 (0.7)
Hypoglycemia, confirmed[a]	117 (50.9)	99 (43.8)	113 (49.3)	37 (26.4)	52 (36.6)
Events	388	378	368	82	123
Events/PYE	364	363	348	192	288
LSM, events/100 PYE	372.94	340.18	363.75	71.320	120.118
Treatment ratio[b] (95% CI)	1.03 (0.75 to 1.40)			0.59 (0.39 to 0.90)	
ADA definition, participants, n (%)	204 (88.7)	184 (81.4)	195 (85.2)	88 (62.9)	99 (69.7)
Severe	1 (0.4)	2 (0.9)	2 (0.9)	4 (2.9)	1 (0.7)
Nocturnal hypoglycemia, confirmed	31 (13.5)	24 (10.6)	49 (21.4)	13 (9.3)	16 (11.3)
Events	67	58	79	16	27
Events/PYE	63	56	75	38	63
LSM, events/100 PYE	31.67	26.77	41.01	20.27	30.94
Treatment ratio IDeg q.d. FF vs IGlar q.d. (95% CI)	0.77 (0.44 to 1.35)			0.66 (0.29 to 1.48)	
ADA definition, participants, n (%)	90 (39.1)	76 (33.6)	104 (45.4)	23 (16.4)	33 (23.2)
Severe	1 (0.4)	0 (0.0)	1 (0.4)	1 (0.7)	0
Injection-site reactions	1.3%	3.5%	1.7%		
Weight gain, kg, weeks 26,16 (LOCF)	1.5 (3.0)	1.6 (2.8)	1.3 (2.8)	0.4 (3.7)	1.0 (3.5)
LSM (SE) change from baseline (LOCF)	1.86 (0.27)	1.86 (0.25)	1.59 (0.26)	0.42 (0.31)	1.04 (0.31)
Treatment contrast	0.27 (−0.25 to 0.79)			−0.62 (−1.25 to 0.01)	

	Study 3668			Study 3943	
	IDeg-Flex N = 229	IDeg N = 228	IGlar N = 230	IDeg N = 140	IGlar N = 142
IDeg q.d. FF vs IGlar q.d. (95% CI)					

ADA = American Diabetes Association; AE = adverse event; CI = confidence interval; FF = fixed-flexible; IDeg = insulin degludec; IDeg-Flex = insulin degludec flexible dosing; IGlar = insulin glargine; LSM = least squares mean; PYE = patient-years of exposure; q.d. = once daily; SAE = serious adverse event; SE = standard error; SOC = system organ class; vs = versus; WDAE = withdrawal due to adverse event.

Note: All safety analyses used the safety analysis set.

[a] Confirmed hypoglycemia: patient unable to treat himself or herself or has a recorded plasma glucose < 3.1 mmol/L.

[b] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age as covariate.

Source: CSRs for Studies 3668[23] and 3943.[24]

Table 68: Harms — Type 2 Diabetes Mellitus, Basal-Bolus Insulin (Studies 3582 + Extension Study 3667)

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	Degludec (N = 753)	Glargine (N = 251)	Degludec (N = 753)	Glargine (N = 251)
AEs				
Patients with > 0 AEs, N (%)	610 (81.0)	199 (79.3)	630 (83.7)	208 (82.9)
Possibly or probably related to study treatment[a]	127 (16.9)	35 (13.9)	156 (20.7)	47 (18.7)
Most common AEs,[b] N (%)				
Arthralgia	32 (4.2)	20 (8.0)	43 (5.7)	26 (10.4)
Back pain	41 (5.4)	18 (7.2)	56 (7.4)	21 (8.4)
Bronchitis	30 (4.0)	12 (4.8)	50 (6.6)	13 (5.2)
Cough	44 (5.8)	16 (6.4)	61 (8.1)	21 (8.4)
Diarrhea	46 (6.1)	20 (8.0)	59 (7.8)	26 (10.4)
Headache	65 (8.6)	18 (7.2)	71 (9.4)	20 (8.0)
Hypertension	41 (5.4)	13 (5.2)	52 (6.9)	15 (6.0)
Influenza	42 (5.6)	15 (6.0)	58 (7.7)	20 (8.0)
Nasopharyngitis	107 (14.2)	35 (13.9)	124 (16.5)	37 (14.7)
Nausea	29 (3.9)	12 (4.8)	39 (5.2)	15 (6.0)
Peripheral edema	45 (6.0)	14 (5.6)	55 (7.3)	17 (6.8)
Pain in extremity	41 (5.4)	18 (7.2)	47 (6.2)	19 (7.6)
Sinusitis	37 (4.9)	12 (4.8)	45 (6.0)	18 (7.2)
Upper respiratory tract infection	107 (14.2)	32 (12.7)	123 (16.3)	42 (16.7)
Vomiting	23 (3.1)	9 (3.6)	28 (3.7)	14 (5.6)
Wrong drug administered	56 (7.4)	8 (3.2)	60 (8.0)	9 (3.6)
Patients with hypoglycemia episodes (ADA)[c]	711 (94.4)	238 (94.8)	712 (94.6)	240 (95.6)
Severe	34 (4.5)	11 (4.4)	39 (5.2)	16 (6.4)
Documented symptomatic	637 (84.6)	215 (85.7)	649 (86.2)	218 (86.9)
Asymptomatic hypoglycemia	592 (78.6)	193 (76.9)	607 (80.6)	203 (80.9)
Probable symptomatic hypoglycemia	89 (11.8)	31 (12.4)	105 (13.9)	33 (13.1)
Relative	120 (15.9)	41 (16.3)	127 (16.9)	46 (18.3)
Unclassifiable	130 (17.3)	41 (16.3)	133 (17.7)	43 (17.1)
Confirmed hypoglycemia[d]	609 (80.9)	206 (82.1)	617 (81.9)	208 (82.9)
SAEs				
Patients with > 0 SAEs, N (%)	112 (14.9)	40 (15.9)	139 (18.5)	53 (21.1)
Possibly or probably related to study treatment[a]	15 (2.0)	3 (1.2)	19 (2.5)	3 (1.2)
WDAEs				

	Study 3582 (BBT2)		Study 3667 (BBT2-Ext)	
	Degludec (N = 753)	**Glargine (N = 251)**	**Degludec (N = 753)**	**Glargine (N = 251)**
WDAEs, N (%)	31 (4.1)	9 (3.6)	35 (4.6)	9 (3.6)
Death	8 (1.1)	2 (0.8)	11 (1.5)	2 (0.8)
Mortality				
Number of deaths, N (%)	8 (1.1)	2 (0.8)	11 (1.5)	2 (0.8)
Most common reasons			Myocardial infarction	
Cardiovascular death	4 (0.5)	1 (0.4)	5 (0.7)	1 (0.4)
Cardiovascular Events				
Non-MACE	20 (2.7)	8 (3.2)	30 (4.0)	12 (4.8)
MACE	18 (2.4)	4 (1.6)	29 (3.9)	7 (2.8)
Acute coronary syndrome	11 (1.5)	3 (1.2)	17 (2.3)	6 (2.4)
Stroke	3 (0.4)	0 (0)	7 (0.9)	0 (0.0)
Cardiovascular death	4 (0.5)	1 (0.4)	5 (0.7)	1 (0.4)
Notable Harms				
Externally classified neoplasms, N (%)	25 (3.3)	7 (2.8)	28 (3.7)	10 (4.0)
Most common reasons				
SAEs	6	3	9	3
Confirmed TE hypoglycemia episodes, N (%)[e]	609 (80.9)	206 (82.1)	617 (81.9)	208 (82.9)
Events (safety set)	7,437	3,120	9,847	4,098
Events/100 PYE	1,109	1,363	1,039	1,271
LSM, events/100 PYE, FAS	728.90	886.07	670.78	790.44
Treatment ratio, IDeg versus comparator (95% CI)[f,g]	0.82 (0.69 to 0.99), *P* = 0.018		0.85 (0.70 to 1.02)	
Nocturnal[h] confirmed symptomatic hypoglycemia, N (%)	298 (39.6)	119 (47.4)	316 (42.0)	132 (52.6)
Events (safety set)	930	422	1266	567
Events/100 PYE	139	184	134	176
LSM, events/100 PYE, FAS	112.72	149.32	104.83	138.12
Treatment ratio IDeg versus comparator (95% CI)[f]	0.75 (0.58 to 0.99)		0.76 (0.58 to 1.00)	
Injection-site reactions	3.6%	2.8%	4.2%	3.2%
Mean (SD) weight, change from baseline, kg (LOCF), safety set	3.6 (4.9)	4.0 (4.6)	4.0 (5.2)	4.4 (4.8)
LSM (SE) change from baseline (LOCF), FAS	3.23 (0.33)	3.54 (0.41)	3.84 (0.36)	4.18 (0.44)
Treatment contrast, IDeg versus comparator (95% CI)[i]	−0.31 (−0.98 to 0.37)		−0.34 (−1.05 to 0.38)	

AE = adverse event; ADA = American Diabetes Association; ANOVA = analysis of variance; BBT2 = basal-bolus type 2; CI = confidence interval; Ext = extension; FAS = full analysis set; IDeg = insulin degludec; LOCF = last observation carried forward; LSM = least squares mean; MACE = major adverse cardiovascular event; PYE = patient-years of exposure; SAE = serious adverse event; SD = standard deviation; SE = standard error; TE = treatment-emergent; WDAE = withdrawal due to adverse event.

[a] As per investigator and Novo Nordisk A/S.

[b] AE frequency ≥ 5%.

[c] As classified by the ADA.

[d] Patient was unable to self-treat or recorded a plasma glucose level < 3.1 mmol/L.

[e] Confirmed hypoglycemia is an episode wherein a patient is unable to self-treat, or has a recorded plasma glucose < 3.1 mmol/L. Severe hypoglycemia is defined according to ADA classification.

[f] The number of events is analyzed using a negative binomial regression model using a log link and the logarithm of the exposure time (100 years) as offset. The model includes treatment, region, sex,and antidiabetes treatment at screening as fixed effects, and age as covariate.

[g] *P* value is from the one-sided test for superiority evaluated at the 2.5% level.

[h] Nocturnal is the period between 00:01 a.m. and 05:59 a.m., inclusive.

[i] Change from baseline in the response at end of treatment period is analyzed using an ANOVA method with treatment, region, sex, and antidiabetes treatment at screening as fixed effects, and age and baseline response as covariates.

Source: CSRs for Studies 3582[25] and 3667.[35]

Appendix 6: Summary of Indirect Comparisons

Objective

The objective of this appendix is to summarize and critically appraise the indirect treatment comparisons for insulin degludec (IDeg) in adults with type 1 or type 2 diabetes mellitus (T1DM or T2DM). Head-to-head studies were available comparing IDeg to insulin glargine (IGlar) and insulin detemir (IDet), but not to other basal insulins. Thus, a review of indirect comparisons was warranted.

In addition to the systematic search (see Appendix 2), a literature search was conducted by CADTH (MEDLINE, EMBASE, up to July 7, 2017) to identify potentially relevant indirect comparisons that included IDeg. Two published network meta-analyses (NMAs) were identified.[62,63] The manufacturer also provided an NMA as part of the CADTH Common Drug Review (CDR) submission.[12]

Description of Indirect Comparisons Identified

The manufacturer-submitted NMA included patients with T1DM and T2DM, whereas the report by Freemantle et al.[63] included T2DM patients and the report by Dawoud et al.[62] included T1DM patients (Table 69). The manufacturer's NMA was limited to three treatments (IDeg, IGlar, and neutral protamine Hagedorn [NPH] insulin) and focused on hypoglycemia events as the primary outcome. The other two NMAs included all the basal insulins of interest to this CDR review and examined efficacy outcomes (e.g., glycated hemoglobin [A1C], body weight) as well as hypoglycemia.

Freemantle et al. and Dawoud et al. conducted systematic review to identify studies for inclusion in the NMA. The manufacturer-submitted NMA was based on data from two other meta-analyses: an analysis conducted by Novo Nordisk and published as a poster in 2012[64] that compared IDeg and IGlar, and a meta-analysis conducted by CADTH published in 2008 that compared IGlar and NPH. The NMA authors conducted an update to the CADTH meta-analysis and searched for any randomized controlled trials (RCTs) comparing IGlar with insulin NPH that had been published since the CADTH review. This update identified six relevant trials, of which three were included in the NMA (two pediatric were excluded, along with one other study that reported data as dichotomous events only).

All three indirect comparisons conducted Bayesian NMAs with Markov Chain Monte Carlo simulations. A summary of the indirect comparison methods has been included in Table 69. Freemantle and Dawoud analyzed continuous outcomes using a generalized linear model with normal likelihood and identity link function; hypoglycemia rates were analyzed using a Poisson process and a log-link function. The manufacturer-submitted NMA analyzed hypoglycemia rate ratio data from individual treatment comparisons on a log scale using a logistic regression model and a normal likelihood.

Separate analyses were conducted in patients with T2DM based on the patients' treatment history (e.g., basal insulin, basal + bolus insulin, or insulin-naive). Freemantle et al. and Dawoud et al. conducted several sensitivity analyses or used meta-regression to explore potential sources of heterogeneity or model assumptions. Dawoud et al. analyzed both fixed-effects and random-effects models and selected the random-effects model based on model fit. Freemantle et al. ran random-effects models (no justification provided or exploration of model fit). The authors of the manufacturer-submitted NMA stated that a

fixed-effects model was selected due to the limited number of studies available. However, there were issues with model fit, and in at least two cases, a random-effects model was reported to have a better fit. The authors did not report residual deviance or deviance information criterion values to allow the reader to compare models.

Table 69: Network Meta-Analysis Study Characteristics

	Manufacturer-Submitted[12]	Freemantle et al., 2016[63]	Dawoud et al., 2017[62]
SR Criteria			
Population	Adults with T1DM or T2DM	Adults with T2DM treated with basal insulin (with or without bolus insulin) Studies must include patients from at least one of the following countries: US, France, Germany, UK, Spain, or Italy	Adults with T1DM
Interventions	• IDeg • IGlar • Insulin NPH (Doses not specified)	• IGlar (100 u/mL or 300 U/mL) • IDeg • IGlar • IDet • Insulin NPH • Premixed insulin (Doses not specified)	• IDeg (q.d.) • IGlar (q.d.) • IDet (q.d. or b.i.d.) • Insulin NPH (q.d., b.i.d., or q.i.d.) Insulin at UK licensed doses
Outcomes	• Severe hypoglycemia • Nocturnal hypoglycemia • Overall hypoglycemia (No definitions for these events were provided)	• Change from baseline in A1C (%) • Change from baseline in body weight (kg) • Documented symptomatic hypoglycemia events per PY (defined as symptoms of hypoglycemia were accompanied by measured plasma glucose level below a threshold; no limit placed on plasma glucose thresholds used in trials) • Nocturnal hypoglycemia events per PY (confirmed or symptomatic event occurring overnight)	• Change from baseline in A1C (%) • Severe or major hypoglycemia events per PY (defined as event requiring assistance or a third party)
Study Design	RCTs > 48 hours in duration	English-language, published RCTs > 20 weeks in duration	English-language, published RCTs > 4 weeks in duration
Exclusions	Pediatric studies	None listed	Premixed insulin, studies in children or pregnant women, crossover studies, studies reporting data for mixed populations (T1DM and T2DM), studies comparing different dosages of the same insulin or those using different short-acting insulins across treatment groups, abstracts, letters, or review articles
SR Methods	• Data from several sources: meta-analysis comparing IDeg and glargine conducted by Novo Nordisk and published as a poster in 2012; meta-analysis comparing	• Literature search (1980 to date not specified) of multiple databases for English-language RCTs • Conference abstracts from	• Literature search (up to August 2014) of multiple databases for published English-language RCTs • Reference lists of included studies searched for RCTs

	Manufacturer-Submitted[12]	Freemantle et al., 2016[63]	Dawoud et al., 2017[62]
	IGlar and NPH conducted by CADTH in 2008; and an update to the CADTH meta-analysis conducted by Abacus International in 2012 • Other than the PICO elements, no details provided on the methods to conduct the update to the CADTH report • No details provided on the meta-analysis of IDeg/IGlar • No quality assessment of individual trials	specific diabetes congresses also searched (2011 to 2013) • Abstracts and posters accepted if they were the terminal source document; clinical study reports for IGlar 300 U/mL trials included • Study selection and data extraction by two independent researchers • Individual studies assessed for methods of randomization, allocation concealment, blinding, and losses to follow-up	• Study selection and appraisal by one researcher • Study quality assessed using the Cochrane risk of bias tool • Data extraction verified by a second reviewer • Hypoglycemia rate calculated if necessary based on the number of events divided by the mean follow-up duration multiplied by the sample size • Studies reporting zero events in both groups excluded from the NMA
Analysis			
NMA Methods	• Bayesian NMA using WinBUGS software • NMA for continuous data was run using a fixed effect model (due to small number of trials). • Rate ratio and 95% CI data for each treatment comparison from RCTs were converted to natural log and standard error calculated. A normal likelihood on the log rate ratio was used to calculate rate ratios based on a logistic regression model with MCMC simulation. • Non-informative priors • No adjustment for sparse data or rare events was reported to be necessary in the NMA • Goodness of fit was tested with residual deviance and DIC. • Burn-in of 20,000 iterations with 50,000 iterations was used to estimate posterior distribution. • Separate analyses were planned for different subpopulations: T1DM, T2DM receiving basal insulin; T2DM receiving basal plus bolus insulin; all T2DM patients. • No evaluation of consistency was possible, as there were no closed loops • No methods to assess model convergence were described. • The author stated that it was not possible to conduct meta-regression or subgroup analyses due to the small number of studies. Some sensitivity analyses	• Direct meta-analysis was conducted using an inverse variance-weighted method. • Bayesian NMA with MCMC using OpenBUGS (random-effects model) was conducted based on NICE guidance. • Continuous outcomes were modelled assuming a normal likelihood and an identity link. • Event rate data were modelled using a Poisson mixed likelihood and log link. • Non-informative priors • Base-case analysis included patients on BOT. • Sensitivity analysis included all patients (BOT and basal/bolus insulin); patients on BOT excluding premixed insulin; insulin-naive patients; studies with week 24 to week 28 results; excluding IDeg three-times-a-week dosing. • Meta-regression was conducted adjusting for baseline study A1C, diabetes duration, and basal-bolus population. • Analyses using a broader definition of hypoglycemia were also conducted (no details provided). • No information describing how convergence, goodness of fit, or inconsistency were assessed; no information on number of burn-in iterations.	• Direct meta-analyses were conducted using Review Manager (random-effects model). • Bayesian NMA was conducted using WinBUGS. • NMA was conducted as per NICE Decision Support Unit recommendations. • For the change from baseline in A1C (%) a generalized linear model with normal likelihood and identity link function was used. Parameters were estimated using MCMC simulation. • Insulin NPH b.i.d. was used as the baseline treatment effect (standard of care in UK) with a mean change in A1C of −0.32% (95% CI, −0.49 to −0.15%) based on a single-arm meta-analysis of seven studies. • For the severe hypoglycemia event rate, a Poisson process with a constant event rate was assumed, and a log-link function used to model the event rate. Baseline event rate of 0.35 events per PY (95% CrI 0.11, 0.95) based on single-arm Bayesian meta-analysis in the NPH b.i.d. trials. • Non-informative priors (mean 0 SD 100, normal distribution for difference in A1C, not specified for hypoglycemia). • 100,000 burn-in and 100,000 simulations for parameter estimates. • Convergence assessed by

	Manufacturer-Submitted[12]	Freemantle et al., 2016[63]	Dawoud et al., 2017[62]
	were run excluding some trials (with poor model fit) but it was unclear if these analyses were pre-planned or if the methods used to select trials for exclusion were appropriate.		examining the history, kernel density plots, and Brooks–-Gelman–Rubin plots. • Goodness of fit was tested using residual deviance. • Random-effects and fixed-effects models were run and DIC used to select model. • Inconsistency assessed using Bucher test (A1C) and chi-square test for inconsistency (hypoglycemia). • Sensitivity analyses were run excluding open-label studies, those with inadequate allocation concealment, using half-normal prior distribution for between-study heterogeneity instead of vague priors, and testing the impact of treatment effect estimate from the largest study on the pooled treatment effect.
Included Studies	20 RCTs	86 studies were identified for data extraction (41 included in NMA)[a]	29 RCTs included in SR (28 included in NMA)
Funding	Novo Nordisk	Sanofi	NICE

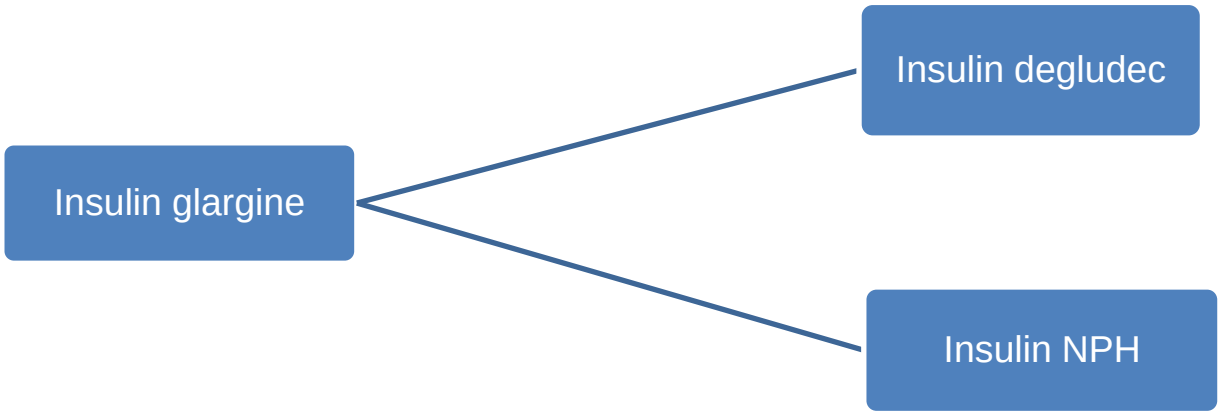
A1C = glycated hemoglobin; b.i.d. = twice daily; BOT = basal insulin–supported oral therapy; CI = confidence interval; CrI = credible interval; DIC = deviance information criterion; IDeg = insulin degludec; IGlar = insulin glargine; IDet = insulin detemir; MCMC = Markov Chain Monte Carlo; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NPH = neutral protamine Hagedorn; PICO = patient/problem/population, intervention, comparison/control/comparator, outcome; PY = patient-year; q.d. = once daily; q.i.d. = four times daily; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] No details were provided regarding the reason for exclusion for the 45 studies, except a statement that the studies had to have at least two treatment groups with a relevant insulin in the network.

Summary of the Manufacturer-Submitted Network Meta-Analysis

A total of 20 RCTs were included in the manufacturer-submitted NMA, including seven RCTs comparing IDeg with IGlar (T1DM: studies 3583 and 3770 [total N = 958]; T2DM: Studies 3579, 3672, 3586, 3582, and 3668 [total N = 3,389]). For the comparison between IGlar and NPH, 13 RCTs were included (T1DM: seven RCTs, N = 1,739; T2DM: six RCTs, N = 2,813). The trials were 12 weeks to five years in duration; except for one single-blind study, all were open label. No evaluation of potential sources of bias in the included trials was reported. The mean age per treatment group of patients enrolled ranged from 31.3 to 44.5 years for those with T1DM and from 50.3 to 59.3 years for those with T2DM. The mean baseline glycated hemoglobin (A1C) was 7.7% per treatment group among patients with T1DM, and ranged from 8.2% to 8.5% among patients with T2DM in the trials comparing IDeg with IGlar. The duration of diabetes ranged from 18.2 to 20.0 years in the T1DM trials and from 8.0 to 13.6 years in the T2DM trials for IDeg versus IGlar. No information on the mean A1C or duration of diabetes was provided for trials comparing IGlar with NPH. In total, 637 patients with T1DM and 2,275 with T2DM who were treated with IDeg were included in the NMA. The network diagram is presented in Figure 2.

Figure 2: Network Diagram for Manufacturer-Submitted Network Meta-Analysis



NPH = neutral protamine Hagedorn.

The outcomes analyzed included severe hypoglycemia, nocturnal hypoglycemia, and overall hypoglycemia. No definitions for these events were provided. A Bayesian NMA was conducted using the log rate ratio data from each trial (details provided in Table 69). Data from the flexible dosing groups in sStudies 3770 and 3668 were excluded from the NMA. Four different populations were proposed for analysis: T1DM (nine RCTs), T2DM receiving basal insulin (eight RCTs), T2DM receiving basal + bolus insulin (unable to assess due to insufficient data), and all T2DM patients (basal or basal + bolus insulin, 11 RCTs).

The results of the manufacturer-submitted NMA are included in Table 70. Among patients with T1DM, no statistically significant differences were detected between IDeg, IGlar, and NPH on the rate of severe hypoglycemia or overall hypoglycemia based on a fixed-effects model. The rate of nocturnal hypoglycemia was lower for IDeg versus NPH based on the fixed-effects model; however, the model fit was better with the random-effects model, which showed no statistically significant differences. No significant differences were detected in the rate of nocturnal hypoglycemia for IDeg versus IGlar based on the fixed-effects or random-effects models.

In the analyses in patients with T2DM who received basal insulin, the authors stated that both the fixed-effects and random-effects models for overall hypoglycemia rates showed poor model fit with high residual deviance values. The model fit was better for the random-effects model than the fixed-effects model in the analysis of severe hypoglycemia. The random-effects model found no statistically significant differences between treatments, whereas the fixed-effects model suggested a lower rate of severe hypoglycemia for IDeg than for IGlar or NPH. The rates of nocturnal hypoglycemia events were lower for IDeg versus IGlar or NPH based on the fixed-effects model, which also showed some evidence of poor model fit. Residual deviance and deviance information criterion values were not reported for any NMA.

The NMA that included all T2DM patients (who received basal insulin or basal + bolus insulin) found no statistically significant differences between IDeg and IGlar on the incidence of severe hypoglycemia; however, the rates of nocturnal and overall hypoglycemia events were lower with IDeg. The indirect data suggested that the rates of severe, nocturnal, or any hypoglycemia events were lower for IDeg than for NPH. No information on model fit was provided.

Table 70: Results from Manufacturer-Submitted Network Meta-Analysis — T1DM and T2DM

	Severe Hypoglycemia Median Rate Ratio (95% CrI)[a]	Nocturnal Hypoglycemia Median Rate Ratio (95% CrI)[a]	Overall Hypoglycemia Median Rate Ratio (95% CrI)[a]
T1DM			
IDeg versus IGlar	1.12 (0.68 to 1.85)[b]	Fixed: 0.83 (0.69 to 1.00) Random: 0.85 (0.29 to 2.55)[c]	1.10 (0.97 to 1.26)[b]
IDeg versus insulin NPH	1.09 (0.64 to 1.87)[b]	Fixed: 0.57 (0.47 to 0.69) Random: 0.57 (0.15 to 2.19)[c]	1.11 (0.97 to 1.27)[b]
IGlar versus insulin NPH	0.98 (0.82 to 1.17)[b]	Fixed: 0.69 (0.65 to 0.72) Random: 0.62 (0.31 to 1.46)[c]	1.00 (0.98 to 1.03)[b]
T2DM, Basal			
IDeg versus IGlar	Fixed: 0.14 (0.03 to 0.68) Random: 0.14 (0.01 to 2.89)[c]	0.63 (0.47 to 0.85)[b]	0.83 (0.70 to 0.99)[d]
IDeg versus insulin NPH	Fixed: 0.07 (0.01 to 0.37) Random: 0.07 (0.00 to 2.16)[c]	0.31 (0.23 to 0.41)[b]	0.68 (0.57 to 0.82)[d]
IGlar versus insulin NPH	Fixed: 0.53 (0.33 to 0.84) Random: 0.50 (0.10 to 2.50)[c]	0.48 (0.45 to 0.52)[b]	0.83 (0.79 to 0.87)[d]
T2DM, All Patients			
IDeg versus IGlar	0.84 (0.46 to 1.51)[e]	0.69 (0.58 to 0.83)[e]	0.83 (0.74 to 0.93)[e]
IDeg versus insulin NPH	0.49 (0.24 to 0.97)[e]	0.33 (0.27 to 0.41)[e]	0.69 (0.61 to 0.78)[e]
IGlar versus insulin NPH	0.58 (0.40 to 0.84)[e]	0.48 (0.45 to 0.52)[e]	0.83 (0.79 to 0.87)[e]

CrI = credible interval; DIC = deviance information criterion; IDeg = insulin degludec; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

[a] Fixed-effects model unless otherwise specified.

[b] Some evidence of poor model fit. Sensitivity analyses excluding specific trials with poor fit were run and showed results similar to the base case. No residual deviance values were reported, and no random-effects models were analyzed.

[c] The model fit was better for the random-effects model than the fixed-effects model (no DIC values were reported).

[d] Model fit for fixed-effects and random-effects models were poor with high residual deviance values.

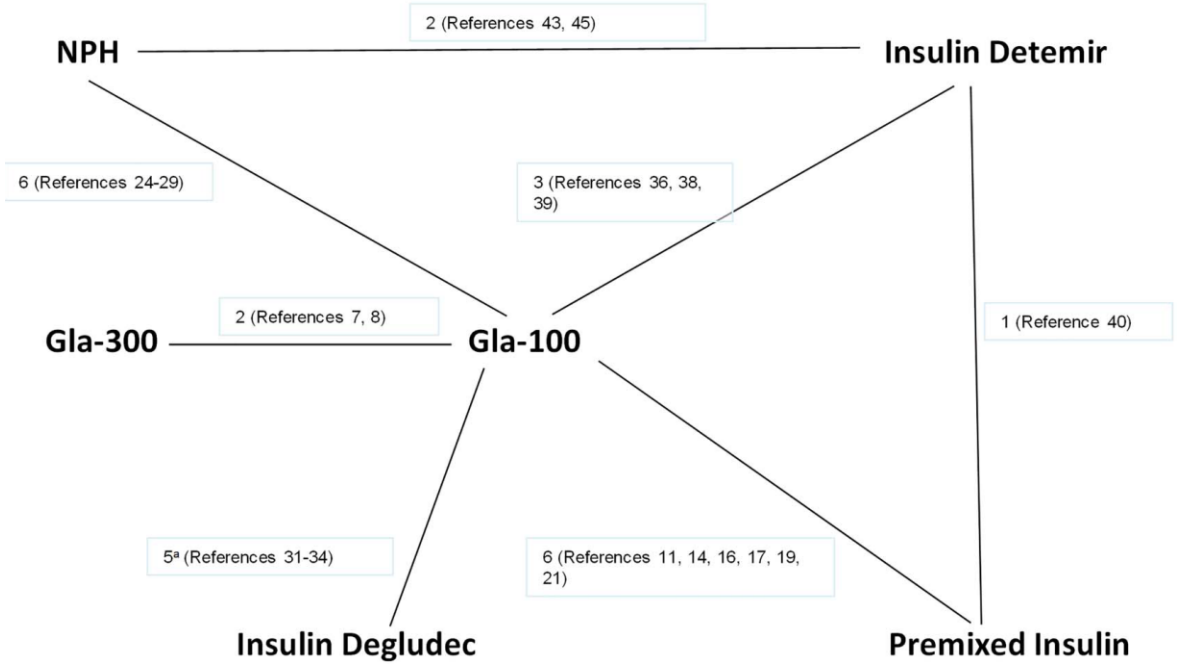
[e] No information provided on model fit.

Source: CADTH Common Drug Review submission for Tresiba.[12]

Summary of the Network Meta-Analysis by Freemantle Et Al.

The NMA by Freemantle et al.[63] included 41 RCTs. Twelve of the studies (29%) had unclear allocation concealment and 40 (98%) were open label, with losses to follow-up ranging from 1.6% to 28.5%. Basal insulin–supported oral therapy was used in 25 (61%) trials (N = 15,746); patients in these studies had a mean age per study ranging from 52.4 to 61.7 years, duration of diabetes ranging from 8.2 to 13.8 years, and A1C ranging from 7.8% to 9.8%. Five of the included RCTs compared IDeg once daily (Studies 3582, 3672, 3668, and 3579)[54,58,60,65] or three times per week (Study 3724)[66] with IGlar (100 U/mL). The network diagram for A1C is presented in Figure 3.

Figure 3: Network Diagram for Glycated Hemoglobin From Freemantle



Gla-100 = insulin glargine 100 U/mL; Gla-300 = insulin glargine 300 U/mL.

Source: Reproduced from BMJ Open, Safety and efficacy of insulin glargine 300 u/mL compared with other basal insulin therapies in patients with type 2 diabetes mellitus: a network meta-analysis, Freemantle N, et al., vol. 6, e009421, copyright 2016 with permission from BMJ Publishing Group Ltd.[63]

IDeg was associated with a statistically significant increase in A1C and body weight compared with IGlar 100 U/mL in the direct meta-analyses (Table 71). However, the clinical importance of the differences is unclear given the magnitude of the differences observed (mean difference in A1C: 0.13%; weight: 0.21 kg). No statistically significant differences in glycemic control or body weight were detected between IDeg and IGlar (100 U/mL or 300 U/mL) in the NMA.

Based on the direct meta-analysis, IDeg was associated with a statistically significantly lower rate of nocturnal hypoglycemia but a higher rate of symptomatic hypoglycemia compared with IGlar (100 U/mL). However, based on the NMA, the differences between treatments were not significant. The point estimates were similar in the direct meta-analysis and the NMA, but the direct meta-analysis had tighter confidence intervals.

The authors stated that results were generally similar across the numerous sensitivity analyses that were conducted. Data for all T2DM patients and insulin-naive patients are presented in Table 71, as well as the analyses that excluded the IDeg three-times-a-week dosing study. No results were reported comparing IDeg with NPH, IDet, or premixed insulin.

Table 71: Results From Network Meta-Analysis by Freemantle 2016 (T2DM)

	Change From Baseline in A1C (%)	Change From Baseline in Body Weight (kg)	Risk of Nocturnal Hypoglycemia	Risk of Symptomatic Hypoglycemia
Meta-Analysis	**MD (95% CI)**	**MD (95% CI)**	**RR (95% CI)**	**RR (95% CI)**
IDeg versus IGlar (100 U/mL)	0.13 (0.06 to 0.20)	0.21 (0.03 to 0.38)	0.79 (0.67 to 0.93)	1.35 (1.27 to 1.44)
NMA in Patients on BOT	**MD (95% CrI)[a]**	**MD (95% CrI)[a]**	**RR (95% CrI)[a]**	**RR (95% CrI)[a]**
IDeg versus IGlar (100 U/mL)	0.14 (−0.03 to 0.30)	0.18 (−0.35 to 0.70)	0.88 (0.57 to 1.38)	1.30 (0.75 to 2.24)
IGlar (300 U/mL) versus IDeg	−0.12 (−0.42 to 0.20)	−0.63 (−1.63 to 0.35)	0.66 (0.28 to 1.50)	0.55 (0.23 to 1.34)
Sensitivity Analyses				
All T2DM patients				
IGlar (300 U/mL) versus IDeg	−0.12 (−0.42 to 0.18)	−0.35 (−1.58 to 0.88)	0.75 (0.41 to 1.34)	0.64 (0.36 to 1.16)
Insulin-naive				
IGlar (300 U/mL) versus IDeg	−0.12 (−0.62 to 0.37)	−0.46 (−1.71 to 0.80)	0.61 (0.10 to 3.48)	0.61 (0.17 to 2.25)
Excluding IDeg three times per week dosing				
IGlar (300 U/mL) versus IDeg	−0.01 (−0.32 to 0.31)	−0.79 (−1.90 to 0.33)	0.83 (0.42 to 1.46)	NR

A1C = glycated hemoglobin; BOT = basal insulin–supported oral therapy; CI = confidence interval; CrI = credible interval; IDeg = insulin degludec; IGlar = insulin glargine; MD = mean difference; NMA = network meta-analysis; NR = not reported; RR = rate ratio; T2DM = type 2 diabetes mellitus.

[a] Random-effects model.

Source: Freemantle 2016.[63]

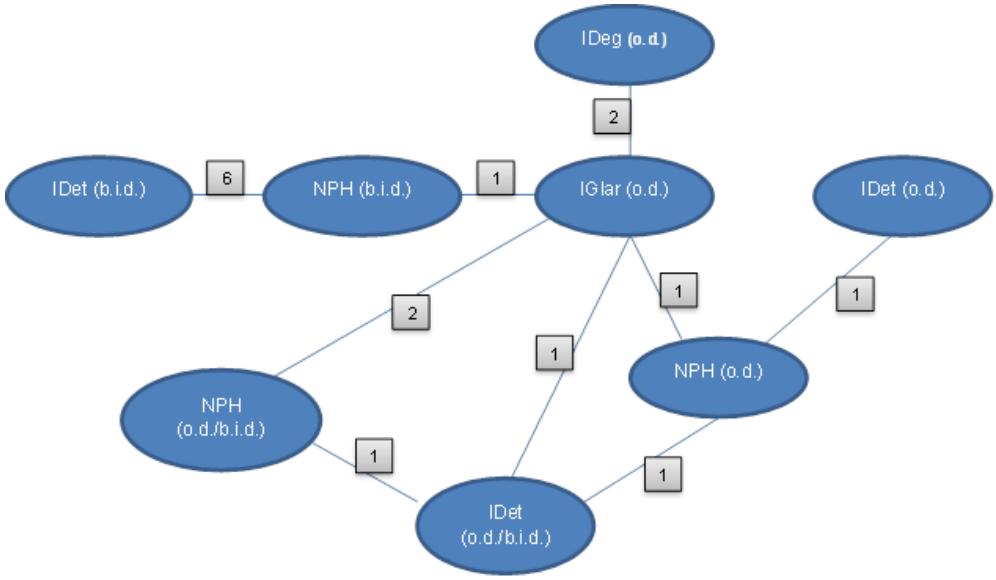
Summary of the NMA by Dawoud et al.

The NMA by Dawoud et al. included 29 RCTs in patients with T1DM. Of these, one was excluded from the NMA, as it did not report A1C and there were no hypoglycemia events in any treatment group. All trials were considered to have moderate or high risk of bias, mainly due to allocation concealment or lack of blinding. The trials ranged from four weeks to 52 weeks in duration and had a sample size ranging from 51 to 629 patients. No other details regarding the study or patient characteristics were reported.

Three of the included RCTs compared IDeg with IGlar (Studies 1835, 3583, and 3770).[5,67,68]

Data from 25 RCTs were included in the NMA for the change from baseline in A1C (%). The included studies were rated as low to high risk of bias. Three studies were excluded because they did not report A1C. The analysis of severe hypoglycemia included 16 RCTs that had serious or very serious risk of bias (Figure 4). Twelve RCTs were excluded because they did not report severe hypoglycemia, or did not report it as a rate, or had zero events in all treatment groups.

Figure 4: Network Diagram for Severe Hypoglycemia From Dawoud



b.i.d = twice daily; IDeg = insulin degludec; IDet = insulin detemir; IGlar = insulin glargine; NPH = neutral protamine Hagedorn; o.d. = once daily.

Source: Reprinted from Value in Health, Published online: June 20, 2017, Dawoud, Dalia et al., Basal Insulin Regimens for Adults with type 1 diabetes Mellitus: A Systematic Review and Network Meta-Analysis, Copyright (2017), with permission from Elsevier.[62]

The direct meta-analysis of three RCTs showed no statistically significant difference between IDeg and IGlar in the change from baseline in A1C (mean difference 0.07; 95% confidence interval [CI] −0.02 to 0.17) (Table 72). For the NMA, the random-effects model had a better fit with a lower deviance information criterion than the fixed-effects model. Based on the random-effects model, no statistically significant differences were detected between IDeg and NPH (once or twice daily), IGlar (daily), or IDet (once daily or twice daily), but A1C was statistically significantly lower for IDeg versus NPH administered four times daily (mean difference −0.34%; 95% credible interval, −0.59% to −0.11%). No statistically significant difference was detected between IDeg and either NPH or IDet administered in a mixed population that received either once-daily or twice-daily basal insulin (data not summarized in this report).

No statistically significant difference was detected between IDeg and IGlar on the rate of severe hypoglycemia based on a direct meta-analysis of two RCTs (rate ratio 1.03; 95% CI, 0.63 to 1.67), or between IDeg and IGlar, IDet, or NPH based on the NMA (Table 72). There was substantial uncertainty in some of the NMA estimates given the wide credible intervals reported; however, the direct and indirect estimates were consistent for IDeg versus IGlar.

Table 72: Results From Network Meta-Analysis by Dawoud 2017 (T1DM)

	Change From Baseline in A1C (%)	Severe Hypoglycemia
Meta-Analysis	**MD (95% CI)[a]**	**RR (95% CI)[a]**
IGlar (q.d.) versus IDeg	0.07 (−0.02 to 0.17)	1.03 (0.63 to 1.67)
NMA	**MD (95% CrI)[a]**	**Median HR (95% CrI)[a]**
Insulin NPH (q.d.) versus:		
IDeg (q.d.)	0.07 (−0.25 to 0.38)	1.09 (0.27 to 4.93)
IDeg (q.d.) versus:		
IGlar (q.d.)	0.07 (−0.08 to 0.22)	1.04 (0.39 to 2.72)
IDet (q.d.)	0.04 (−0.19 to 0.28)	0.82 (0.11 to 5.68)
IDet (b.i.d.)	−0.13 (−0.12 to 0.39)	1.11 (0.02 to 69.82)
Insulin NPH (b.i.d.)	−0.03 (−0.31 to 0.26)	1.07 (0.02 to 63.67)
Insulin NPH (q.i.d.)	−0.24 (−0.59 to −0.11)	NR

A1C = glycated hemoglobin; b.i.d. = twice daily; CI = confidence interval; CrI = credible interval; HR = hazard ratio; IDeg = insulin degludec; IDet = insulin detemir; IGlar = insulin glargine MD = mean difference; NMA = network meta-analysis; NPH = neutral protamine Hagedorn; NR = not reported; q.d. = once daily; q.i.d. = four times daily; RR = rate ratio; T1DM = type 1 diabetes mellitus.

[a] Random-effects model.

Source: Dawoud 2017.[62]

Appraisal of NMAs

Key limitations of the three analyses have been summarized in Table 73. The quality of the included studies was an issue of concern in all three reports. The evidence was based largely on open-label trials; thus, subjective outcomes, such as hypoglycemia, may be prone to bias. The scope of the manufacturer's NMA was limited to three basal insulins and excluded IDet. In addition, there was no systematic search for relevant trials, so it is unclear if all potentially relevant studies were included. In Dawoud et al.'s and the manufacturer-submitted reports, the data describing the study and patient characteristics were limited; thus, it was not possible for the reader to assess if the included studies were sufficiently similar to pool. There was no information on insulin dosing or glycemic targets in any of the reports. Limited information was available in all three reports on concurrent diabetes medications. Use of sulfonylureas, which have an increased risk of hypoglycemia, was more common in the trials for NPH versus IGlar than for those comparing IDeg and IGlar in the manufacturer's NMA. The clinical importance of these differences in unclear.

The methods used to conduct the Bayesian NMA by Dawoud et al. were clearly and completely reported and appear to meet accepted standards. Several sensitivity analyses were run to test the robustness of the findings. The network was sparse, particularly for severe hypoglycemia; therefore, there is uncertainty in the estimates.

Freemantle et al. also conducted a Bayesian NMA, but only a random-effects model was run, with no justification for selecting this model and no exploration of other models or testing model assumptions (e.g., impact of informative versus non-informative priors). No information was provided on how convergence, goodness of fit, or inconsistency were assessed. Complete results from all treatment comparisons were not reported; thus, many comparisons of interest in this review were not available.

In the manufacturer-submitted NMA, the log rate ratio of hypoglycemia events was analyzed as a continuous outcome. This is in contrast to the other two NMAs that used a Poisson model with follow-up time as an offset. In the manufacturer's NMA, the trial duration was 26 to 52 weeks for studies comparing IDeg with IGlar, whereas the duration of trials comparing

NPH with IGlar ranged from 12 weeks to five years. The authors stated that a fixed-effects model was chosen because of the limited number of trials that informed the network; thus, there were too few studies with which to estimate between-study heterogeneity. Although model fit was tested, the deviance information criterion or residual deviance values were not reported. The authors stated that there were issues with model fit, and based on residual deviance values calculated for individual trials, some studies with poor fit were excluded in a sensitivity analysis. It is unclear if these sensitivity analyses were pre-planned, as they were not described in the methods section; furthermore, purposeful exclusion of studies based on deviance values calculated for individual studies is unconventional, and exclusion of these studies may increase the risk of bias in the results. For some analyses, a random-effects model was run, and in two cases, the model fit was better with the random-effects estimates. Ideally, both fixed-effects and random-effects models would have been run, and informative and non-informative priors used for the between-study variance parameter in the random-effects model. Given the issues with model fit in the analysis of nocturnal hypoglycemia in patients with T1DM and severe hypoglycemia in those with T2DM on basal insulin, the results of the random-effects model should be preferred over those of the fixed-effects model. The authors stated that model fit was poor for both the fixed-effects and random-effects models for overall hypoglycemia in patients with T2DM on basal insulin; thus, the results of this analysis should be interpreted with caution.

Another limitation of the manufacturer's report is that no direct meta-analyses were conducted. Because the network had no closed loops, it was not possible to test for inconsistency with the usual methods. Thus, having access to both a traditional meta-analysis and NMA estimates would be desirable. This is especially true given the concerns with model fit in the NMA. Had the meta-analysis results been similar to the NMA findings, it would have increased confidence in the NMA's findings. The lack of sensitivity analyses beyond model fit is a further limitation. There was limited exploration of the effects of heterogeneity on study results.

Table 73: Key Limitations

	Manufacturer[12]	Freemantle et al., 2016[63]	Dawoud et al., 2017[62]
SR	• No information was provided on the methods used to identify relevant studies that informed two of the previously published meta-analyses, and limited data were provided for the update conducted by the NMA authors. It is unclear if each meta-analysis used the same criteria to select trials. • No search for recently published trials comparing IDeg with IGlar. At least one potentially relevant study has been published since (Study 3587 in insulin-naive patients with T2DM). • No evaluation of potential sources of bias in the individual trials. The NMA authors report that many of the trials included in the 2008 CADTH report were considered poor quality. Except for one single-blind study, all the included studies were open label and, therefore, at high risk of bias.	• English-language studies only. • 45 studies that were selected for data extraction were excluded from the NMA. No reasons for exclusion were provided.	• Single reviewer selected and appraised RCTs • English-language published studies only

	Manufacturer[12]	Freemantle et al., 2016[63]	Dawoud et al., 2017[62]
NMA	• The scope of the NMA was limited by excluding IDet. • Only hypoglycemia outcomes were assessed; glycemic control was not. • No definitions of hypoglycemia events were provided; thus, it is unclear if all trials measured events the same way. • Incomplete patient and study characteristics data were reported for individual trials; therefore, it was not possible for the reader to assess if the transitivity assumption was met. The authors reported that it was not possible to conduct any subgroup or meta-regression analyses due to limited number of trials. • There was no consideration of study quality in the NMA. • A fixed-effects model was selected due to the limited number of trials included in the analysis. Several of the analyses reportedly had poor model fit; however, no details were provided and residual deviance values were not reported. Alternate models were not run in all cases; thus, data to justify the selection of the fixed-effects model were missing. In at least two instances, the random-effects model had a better fit. • Sensitivity analyses were run excluding some trials that were said to have poor model fit based on residual deviance values that were calculated for individual trials. • Rate data were analyzed as a continuous outcome using logistic regression model based on the log rate ratio data from treatment comparisons (rather than rate information from individual treatment groups within a trial). No direct meta-analysis was conducted.	• Appear to have conducted the NMA using accepted methods • Random-effects model selected with no justification provided and no exploration of alternate models • No information describing how convergence, goodness of fit, or inconsistency were assessed • No mention if over-dispersion was accounted for in the Poisson model • Reporting of results was incomplete as the focus of the NMA was the efficacy of IGlar (300 U/mL) versus other treatments	• Methods used to conduct NMA appear to be robust, with clear and complete reporting. • Treatment duration varied substantially (4 weeks to 52 weeks). • There were few details regarding the characteristics of patients enrolled in the RCTs or insulin doses received; thus, it was not possible to evaluate if the transitivity assumption was met. However, the authors did measure between-study heterogeneity and conducted sensitivity analyses to test for some sources of heterogeneity. • Sparse network, particularly for severe hypoglycemia, thus, there was considerable. uncertainty in the estimates. • No mention if over-dispersion was accounted for in the Poisson model. • Many of the trials included had a high risk of bias (particularly an issue for hypoglycemia analysis).

IDeg = insulin degludec; IDet = insulin detemir; IGlar = insulin glargine; NMA = network meta-analysis; RCT = randomized controlled trial; SR = systematic review; T2DM = type 2 diabetes mellitus.

Discussion

Type 1 Diabetes Mellitus

Both the manufacturer-submitted NMA and Dawoud et al.'s NMA found no statistically significant differences between IDeg and IGlar on the rate of severe hypoglycemia events in patients with T1DM, which was consistent with the direct evidence. Similarly, no statistically significant differences were found when comparing IDeg with NPH insulin in both analyses, or for IDeg versus IDet in Dawoud et al.'s report. The 95% credible intervals for severe hypoglycemia were wide in Dawoud's analysis, showing uncertainty in the results, and the authors stated that the trials had a high risk of bias.

The rates of nocturnal hypoglycemia and overall hypoglycemia also showed no statistically significant difference between IDeg and IGlar or NPH in the manufacturer's submission. Given the issues with model fit described above, the random-effects model is preferred over the fixed-effects model for nocturnal hypoglycemia.

No statistically or clinically important differences in A1C were detected for IDeg versus insulin NPH, IGlar, or IDet.

Type 2 Diabetes Mellitus

Due to the focus on IGlar 300 U/mL in Freemantle's report and differences in outcomes assessed in the manufacturer's NMA, it is difficult to compare the findings. The direct meta-analysis found a statistically significantly lower risk of nocturnal hypoglycemia (rate ratio 0.79; 95% CI, 0.67 to 0.9) but a statistically higher risk of symptomatic hypoglycemia (rate ratio 1.35; 95% CI, 1.27 to 1.44) for IDeg versus IGlar 100 U/mL in Freemantle et al. 2016.[63] The point estimates from the NMA were similar for these outcomes, but the credible intervals were wider and non-significant. There were no clinically important differences in A1C and weight found between IDeg and IGlar, although the direct meta-analysis was statistically significant. All studies included in the NMA were of relatively low quality; thus, the results are at high risk of bias.

Among patients with T2DM on basal insulin, the manufacturer's NMA showed a statistically significantly lower rate of nocturnal hypoglycemia for IDeg versus IGlar and NPH; however, no statistically significant difference was found for the rate of severe hypoglycemia based on the random-effects model, which had better fit. Similar findings were reported for the analysis that included all T2DM patients. Data from the analysis of overall hypoglycemia could not be interpreted because the authors stated that both the fixed-effects and random-effects models showed poor fit with high residual deviance values. It appears that the model selection has an important impact on the findings, with fixed-effects models suggesting statistically significant differences, while random-effects models have wider credible intervals (as expected) and non-significant differences. Since the manufacturer's NMA did not consistently run both models and did not report deviance information criterion and residual deviance values, it is difficult to interpret its findings.

Conclusion

Three indirect treatment comparisons were identified that compared IDeg with other basal insulins in patients with T1DM or T2DM. All three conducted Bayesian NMAs and analyzed hypoglycemia rates; two reports analyzed A1C; and one analyzed body weight. The manufacturer's NMA[12] and the NMA by Freemantle et al[63] were limited in scope and did not include or report data for all basal insulins of interest to this review.

In patients with T1DM, the direct evidence for IDeg versus IGlar showed no statistically significant differences in the rate of severe hypoglycemia or change from baseline in A1C. The indirect evidence also suggested no statistically or clinically important differences between IDeg and IGlar, IDet, or NPH on the rate of hypoglycemia or change in A1C.

In patients with T2DM receiving basal insulin therapy, the direct meta-analysis found a statistically significantly lower risk of nocturnal hypoglycemia, but a statistically higher risk of symptomatic hypoglycemia for IDeg versus IGlar 100 U/mL in Freemantle et al. 2016.[63] The point estimates from the NMA were similar for these outcomes, but the credible intervals

were wider and non-significant. No clinically important differences in A1C and weight were found between IDeg and IGlar, although the direct meta-analysis was statistically significant.

Among patients with T2DM on basal insulin, the NMA suggested that the rate of nocturnal hypoglycemia was statistically significantly lower for IDeg versus IGlar and NPH in the manufacturer's NMA. No statistically significant difference was found for the rate of severe hypoglycemia based on the random-effects model, which had better fit. Similar findings were reported for the analysis that included all patients with T2DM. Data from the analysis of overall hypoglycemia could not be interpreted because the authors stated that both the fixed-effects and random-effects models showed poor fit, with high residual deviance values.

All analyses were limited by the quality of the included studies. Also, the analyses were missing more recently completed head-to-head studies comparing IDeg with IGlar (e.g., SWITCH trials).The manufacturer's NMA did not justify the model or analysis methods selected and indicated that there were issues with model fit. It appears that the model selection has an important impact on the findings. Given these issues, an exploration of alternate models and model assumptions was warranted, as was a comparison with the results of direct meta-analysis.

Appendix 7: Summary of Meta-Analyses

Objective

The objective of this appendix is to summarize and critically appraise the meta-analyses of randomized controlled trials (RCTs) comparing insulin degludec (IDeg) with insulin glargine (IGlar) that were used to inform the pharmacoeconomic analysis. Information on this meta-analysis was included in Appendices 1, 2, and 3 of the manufacturer's pharmacoeconomic submission.[12]

Summary of Meta-Analyses

Three separate patient-level meta-analyses were reported: two examining hypoglycemia events and one analyzing total daily dose of insulin for IDeg versus IGlar. The analyses of hypoglycemia events (meta-analyses 1 and 2) used the same statistical approach. Five end points were analyzed in meta-analysis 1 and three end points were analyzed in meta-analysis 2 (Table 74), with different definitions of hypoglycemia, during day or night, or based on either the total treatment period (titration and maintenance phase) or just the maintenance period. In meta-analysis 1, there is overlap between different types of hypoglycemia events, whereas in meta-analysis 2, an event could be counted in only one category. The authors report that the meta-analyses were pre-planned, and the FDA provided input on the statistical plan.

A total of six RCTs were included in the meta-analyses. The data were pooled separately based on the patient populations: type 1 diabetes mellitus (T1DM) (Studies 3583 and 3770), insulin-naive type 2 diabetes mellitus (T2DM) on basal oral therapy (Studies 3579, 3672, and 3586), and T2DM receiving basal + bolus therapy (Study 3582).

Studies 3585 and 3580 were excluded because they did not include an IGlar treatment group, and Study 3668 was excluded because it enrolled a mixed treatment population that included insulin-naive patients and patients on basal insulin. Data from the IDeg flexible dosing group (IDeg-Flex) was also excluded from Study 3770.

Table 74: Outcomes and Time Points or Treatment Periods in Meta-Analyses 1 and 2

Outcome	Definition	Period
Meta-Analysis 1		
Overall confirmed hypoglycemia	Plasma glucose confirmed to be < 3.1 mmol/L, with or without symptoms consistent with hypoglycemia	• Total treatment period • Maintenance period
Nocturnal confirmed hypoglycemia	Confirmed hypoglycemic episodes with an onset between 00:01 a.m. and 05:59 a.m., inclusive	• Total treatment period • Maintenance period
Severe hypoglycemia	Episodes that required assistance from another person	• Maintenance period
Meta-Analysis 2		
Non-severe confirmed hypoglycemia[a]	Plasma glucose confirmed to be < 3.1 mmol/L, with or without symptoms consistent with hypoglycemia that occurred	• Daytime (06:00 a.m. and 24:00 p.m. or with an unknown time) • Nocturnal (00:01 a.m. to 05:59 a.m.)
Severe hypoglycemia[a]	Episodes that required assistance from another person	• Total treatment period

[a] Analyses were based on the total treatment period.

The number of hypoglycemia episodes per patient was analyzed using a negative binomial regression model with log-link function. The logarithm of the time interval (i.e., extent of exposure plus seven days) was used as an offset. Differences in reporting patterns between patients were accounted for in the over-dispersion parameter included in the negative binomial model. The model included the following covariates: trial, treatment, antidiabetes treatment at screening, sex, and region as fixed factors, and age as a continuous covariate. Two alternative models were planned if the primary analysis did not converge. First, covariates were removed from the model one at a time; if that was unsuccessful, a Poisson model was estimated.

The final model was a negative binomial model, except for severe hypoglycemia, where a Poisson model was used. The results of meta-analysis 1 and meta-analysis 2 are summarized in Table 75 and Table 76 respectively.

Table 75: Results of Meta-Analysis 1

	T1DM (Basal + Bolus Insulin) Rate Ratio (95% CI)	T2DM (Insulin-Naive: Basal + OAD) Rate Ratio (95% CI)	T2DM (Basal + Bolus) Rate Ratio (95% (CI)
Overall Confirmed Hypoglycemia			
Total treatment period	1.10 (0.96 to 1.26)	0.83 (0.70 to 0.98)	0.82 (0.69 to 0.99)
Maintenance period	1.02 (0.88 to 1.19)	0.72 (0.58 to 0.88)	0.82 (0.67 to 1.01)
Nocturnal Hypoglycemia			
Total treatment period	0.83 (0.69 to 1.00)	0.64 (0.48 to 0.86)	0.76 (0.58 to 0.99)
Maintenance period	0.75 (0.60 to 0.94)	0.51 (0.36 to 0.72)	0.72 (0.51 to 1.00)
Severe Hypoglycemia			
Maintenance period	1.12 (0.68 to 1.86)	0.14 (0.03 to 0.70)	0.14 (0.60 to 2.17)

CI = confidence interval; OAD = oral antidiabetes drug; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Source: CADTH Common Drug Review submission for Tresiba.[12]

Table 76: Results of Meta-Analysis 2

	T1DM (Basal + Bolus Insulin) Rate Ratio (95% CI)	T2DM (Insulin-Naive: Basal + OAD) Rate Ratio (95% CI)	T2DM (Basal + Bolus) Rate Ratio (95% (CI)
Daytime Non-Severe Confirmed Hypoglycemia			
Total treatment period	1.14 (0.99 to 1.31)	0.89 (0.75 to 1.07)	0.83 (0.69 to 1.00)
Nocturnal Non-Severe Hypoglycemia			
Total treatment period	0.82 (0.69 to 1.00)	0.64 (0.48 to 0.86)	0.75 (0.57 to 0.98)
Severe Hypoglycemia			
Total treatment period	1.12 (0.68 to 1.86)	0.14 (0.03 to 0.70)	1.14 (0.60 to 2.17)

CI = confidence interval; OAD = oral antidiabetes drug; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Source: CADTH Common Drug Review submission for Tresiba.[12]

The third meta-analysis analyzed the total daily insulin dose (U/kg), with separate analyses for total daily basal dose and total daily bolus dose for T1DM and T2DM patients on basal + bolus insulin. The total daily insulin dose (U/kg) was defined as the dose in units reported as actually taken by the patient at the end of the trial divided by the weight of the patient at baseline. The log of the dose was analyzed using an analysis of covariance model with trial, treatment, antidiabetes treatment at screening, sex, and region as fixed factors, and age at baseline as a continuous covariate. Missing data were imputed using last observation carried forward.

These analyses included two RCTs for patients with T1DM, one RCT for patients with T2DM on basal + bolus insulin, and three RCTs for patients with T2DM receiving basal insulin + oral antidiabetes drugs. The results of this analysis are summarized in Table 77, showing the dose ratio of IDeg versus IGlar.

Table 77: Results of Meta-Analysis of Insulin Dose

	T1DM (Basal + Bolus Insulin) Dose Ratio (95% CI)	T2DM (Basal + OAD) Dose Ratio (95% CI)	T2DM (Basal + Bolus) Dose Ratio (95% CI)
Total daily insulin dose	0.88 (0.85 to 0.92)	0.90 (0.85 to 0.95)	1.03 (0.97 to 1.10)
Total basal insulin dose	0.87 (0.83 to 0.92)	0.90 (0.85 to 0.95)	1.08 (1.01 to 1.15)
Total bolus insulin dose	0.88 (0.82 to 0.94)	NA	0.97 (0.89 to 1.06)

CI = confidence interval; NA = not applicable; OAD = oral antidiabetes drug; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.

Source: CADTH Common Drug Review submission for Tresiba.[12]

Discussion

The meta-analysis included a select number of trials, and the criteria used to choose these studies were not stated. The manufacturer commented that all phase IIIa trials available at the time of publication were included in the meta-analysis. The meta-analysis does not include Study 3587 (insulin-naive patients with T2DM) or the crossover SWITCH studies, which the manufacturer states were not available at the time. No updated meta-analyses with these new data were published. It is unclear what impact, if any, the exclusion of these studies may have had on the results. All trials were open label; thus, subjective outcomes, such as hypoglycemia, may be prone to bias.

The analyses were conducted using accepted statistical methods, although the analyses did not account for within-trial clustering and correlation, which is likely to lead to a less conservative estimate. The authors state that no tests for heterogeneity between trials were made because the design and scope of the included studies were similar. No data were provided on study or patient characteristics. Had estimates of heterogeneity been conducted, they would have provided evidence to confirm that the rate ratios and insulin dose ratios were indeed similar between trials, and that no substantial between-study heterogeneity was present.

As the data were pooled for specific diabetes populations and hypoglycemia outcomes, it is difficult to compare these results (based on patient-level data) with the direct meta-analyses (analyzed based on trial-level data) that were reported in the review of indirect treatment comparisons. Dawoud et al.[62] reported a severe hypoglycemia rate ratio of 1.03 (95% confidence interval [CI], 0.63 to 1.67) for IGlar versus IDeg in patients with T1DM. The meta-analysis by Freemantle et al.[63] reported a rate ratio of 0.79 (95% CI, 0.67 to 0.93) for

IDeg versus IGlar for nocturnal hypoglycemia events in patients with T2DM on basal insulin–supported oral therapy. These results are similar to the data reported above. In Freemantle et al.,[63] the risk of symptomatic hypoglycemia was higher for IDeg versus IGlar (rate ratio 1.35; 95% CI, 1.27 to 1.44). In comparison, the patient-level meta-analysis generally suggested that IDeg had a lower rate of hypoglycemia than IGlar, although none of the analyses focused on symptomatic events only.

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