CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Insulin degludec and liraglutide injection (Xultophy)

(Novo Nordisk Canada Inc.)

Indication: An adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control

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Abbreviations

ADA	American Diabetes Association
AE	adverse event
AHA	antihyperglycemic agent
ANCOVA	analysis of covariance
BG	blood glucose
BMI	body mass index
BP	bodily pain
CAS	completer analysis set
CDR	CADTH Common Drug Review
CI	confidence interval
CV	cardiovascular
DBP	diastolic blood pressure
DPP-4	dipeptidyl peptidase-4
DTSQc	Diabetes Treatment Satisfaction Questionnaire change version
DTSQs	Diabetes Treatment Satisfaction Questionnaire status version
FAS	full analysis set
FPG	fasting plasma glucose
GH	general health
GI	gastrointestinal
GLP-1 RA	glucagon-like peptide 1 receptor agonist
HDL	high-density lipoprotein
HRQoL	health-related quality of life
IAsp	insulin aspart
IDeg	insulin degludec
IDegLira	insulin degludec plus liraglutide in a fixed combination
IGlar	insulin glargine
iGlarLixi	insulin glargine and lixisenatide injection
ITC	indirect treatment comparison
ITT	intention-to-treat
LDL	low-density lipoprotein
LOCF	last observation carried forward
LS	least squares
MCID	minimal clinically important difference
MCS	mental component summary

MAR	missing at random
MET	metformin
MH	mental health
MID	minimally important difference
MI	myocardial infarction
MMRM	mixed-effects model for repeated measures
NYHA	New York Heart Association
NI	noninferiority
PCS	physical component summary
PF	physical functioning
PP	per-protocol
PYE	patient-year of exposure
RE	role emotional
RCT	randomized controlled trial
RMA	repeated measurements analysis
RP	role physical
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SF	social functioning
SF-36	Short Form (36) Health Survey
SGLT2	sodium-glucose cotransporter-2
SMPG	self-monitored plasma glucose
SU	sulfonylurea
T1DM	type 1 diabetes mellitus
T2DM	type 2 diabetes mellitus
TRIM-D	treatment-related impact measure for diabetes
TZD	thiazolidinediones
VLDL	very low-density lipoprotein

Drug	Insulin degludec and liraglutide injection (Xultophy)
Indication	An adjunct to lifestyle modifications, for the once-daily treatment of adults with type 2 diabetes mellitus to improve glycemic control in combination with metformin, with or without sulfonylurea, when these combined with basal insulin (< 50 U daily) or liraglutide (≤ 1.8 mg daily) do not provide adequate glycemic control
Reimbursement request	An adjunct to lifestyle modifications to improve glycemic control in adults with type 2 diabetes mellitus when oral glucose-lowering medications combined with basal insulin or basal insulin alone do not provide adequate glycemic control
Dosage form(s)	Solution for subcutaneous injection in a pre-filled pen
Notice of compliance date	April 11, 2018
Manufacturer	Novo Nordisk Canada Inc.

Executive Summary

Introduction

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (BG), also known as hyperglycemia.[1] Prolonged impairment in glycemic control can result in damage to blood vessels, causing dysfunction and organ failure that affects the heart, brain, kidneys, retina, and lower limbs.[1] Type 2 diabetes mellitus (T2DM) accounts for approximately 90% of cases of diabetes mellitus.[2,3] Diabetes has a significant impact on both individuals and societies. In Canada, this is one of the most common chronic diseases. Diabetes Canada estimated that 3.65 million people (9% of the population) were living with diabetes in 2019, and that this number will increase to 4.78 million people (11%) by 2029.[4]

As T2DM progresses, insulin output further declines; therefore, exogenous insulin administration is often required in order to decrease levels of plasma glucose.[5] Although insulin is a benchmark in the treatment of T2DM, its optimization can be limited by side effects, such as hypoglycemia and weight gain.[5] Glucagon-like peptide 1 receptor agonists (GLP-1 RAs), such as liraglutide, stimulate insulin secretion and lower glucagon secretion in a glucose-dependent manner. A delay in gastric emptying is also involved in the mechanism of BG lowering, which can result in weight loss.[6] GLP-1 RAs are also associated with gastrointestinal (GI) side effects, such as nausea, diarrhea, and vomiting.[7]

Xultophy is a titratable fixed-ratio combination of insulin degludec (IDeg) and the GLP-1 RA liraglutide (IDegLira), which is delivered subcutaneously once daily.[8] The Health Canada–approved indication for IDegLira is as an adjunct to lifestyle modifications, for the treatment of adults with T2DM to improve glycemic control in combination with metformin (MET), with or without sulfonylurea (SU), when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control.[8] IDegLira is available in a pre-filled pen format that contains 3 mL equivalent to 300 U of IDeg and 10.8 mg of liraglutide. Each mL contains 100 U of IDeg and 3.6 mg of liraglutide. One U contains 1 U of IDeg and 0.036 mg of liraglutide. The Xultophy pen delivers doses from 1 U to 50 U with each injection.[8]

The objective of this review is to perform a systematic review of the beneficial and harmful effects of IDegLira as an adjunct to lifestyle modifications, for the treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control.

Results and Interpretation

Included Studies

Four phase III randomized controlled trials met the inclusion criteria (DUAL II, DUAL V, DUAL VII, and DUAL III).

- The DUAL II trial (N = 413) was a randomized, double-blind, superiority trial in patients with T2DM inadequately controlled with basal insulin (between 20 U and 40 U per day) and MET, with or without SU or glinides, comparing the efficacy and safety of IDegLira once daily with IDeg once daily, both added on to MET.
- The DUAL V trial (N = 557) was a randomized, open-label, noninferiority (NI) trial that compared the efficacy and safety of IDegLira once daily with insulin glargine (IGlar) once daily, both in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET. NI in the primary end point for IDegLira versus IGlar was concluded, if the 95% confidence interval (CI) for the mean treatment difference in change from baseline in hemoglobin A1C was entirely below 0.30%.
- The DUAL VII trial (N = 506) was a randomized, open-label, NI trial that compared the efficacy and safety of IDegLira once daily with basal-bolus therapy (once-daily IGlar plus prandial insulin aspart [IAsp]), both groups in combination with MET in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET. NI in the primary end point for IDegLira versus basal-bolus was concluded if the upper bound of the two-sided 95% CI for the estimated mean treatment difference in change from baseline in hemoglobin A1C was strictly below 0.3%.
- The DUAL III trial (N = 438) was a randomized, open-label, superiority trial that compared IDegLira versus unchanged GLP-1 RA therapy in controlling glycemia in insulin-naive patients with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to the local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]) and MET ± pioglitazone ± SU.

The primary efficacy outcome in all of the included trials was change from baseline in hemoglobin A1C after 26 weeks of treatment. The secondary efficacy end points included change in body weight, fasting plasma glucose (FPG), systolic blood pressure and diastolic blood pressure, and fasting lipid profile (e.g., total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides). Other secondary efficacy end points in all included trials were responders for hemoglobin A1C (defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%), and health-related quality of life (HRQoL) evaluated using the treatment-related impact measure for diabetes (TRIM-D) in DUAL V, DUAL VII, and DUAL III, the Short Form (36) Health Survey (SF-36) in DUAL V and DUAL VII, and the patient-reported outcomes Diabetes Treatment Satisfaction Questionnaire status version in DUAL III. Safety outcomes were also measured, including mortality, treatment-emergent adverse events (AEs), serious AEs, withdrawal due to AEs, and notable harms, such as confirmed hypoglycemia,

immunogenicity, and pancreatitis. In DUAL II, DUAL V, and DUAL III, confirmed hypoglycemic episodes were defined by Novo Nordisk as either severe (according to the American Diabetes Association [ADA], this is an episode requiring the assistance of another person to actively administer carbohydrate glucagons, or other resuscitative actions) or an episode biochemically confirmed by a plasma glucose value of < 3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycemia. In DUAL VII, the Novo Nordisk definition of "severe or BG-confirmed symptomatic hypoglycemia" referred to an episode that was severe, according to the ADA classification, or BG confirmed by a plasma glucose value < 3.1 mmol/L with symptoms consistent with hypoglycemia.

There were a number of limitations noted for these trials. Firstly, the DUAL V, DUAL VII, and DUAL III trials were open label in their design, which increases potential for bias in the reporting of subjective outcomes, such as the reporting of AEs and HRQoL; in addition, knowing which treatment is being received could result in a change in a patient's desire to remain in a trial as well as a change in their behaviour during the trial (i.e., adherence to diet and exercise, which may have affected hemoglobin A1C results). Secondly, in the DUAL V and DUAL VII trials, although secondary outcomes for the change from baseline in body weight and number of treatment-emergent confirmed hypoglycemic episodes were adjusted for multiple testing, there was no control of multiplicity for the other secondary outcomes analyzed. None of the secondary outcomes in the DUAL II and DUAL III trials were adjusted for multiple testing. Hence, results of the outcomes measures that were not adjusted for multiple testing, such as body weight (in DUAL II and DUAL III), FPG, systolic blood pressure, diastolic blood pressure in all of the included trials, and patient-reported outcomes (in DUAL V, DUAL VII, and DUAL III) should be interpreted with consideration of the potential for inflated type I error. Thirdly, in the DUAL II trial, titration in the IDeg comparator group was limited by a maximum dose of 50 U in order to match the maximum allowable IDeg dose in IDegLira. In a trial designed to demonstrate superiority of IDegLira versus IDeg, there was concern regarding the impact of using a capped insulin dose on the clinical generalizability of the results. In the DUAL III trial, the dose of IDegLira was continuously titrated to achieve a FPG target of 4 mmol/L to 5 mmol/L whereas the GLP-1 RA dose was unchanged from the baseline level for which patients had inadequate glycemic control and with no additional glycemic agents added. However, insulin-naive patients inadequately controlled on liraglutide and in need of treatment intensification would not remain on unchanged liraglutide in clinical practice. The magnitude of treatment difference should be interpreted by considering these limitations due to the inherent inequality between groups in the study design and the difference in hemoglobin A1C effect observed, which may not reflect the effect observed in a health care setting where patients inadequately controlled on liraglutide would receive additional add-on therapy. Hence, there is a concern regarding the clinical generalizability of the results in the DUAL III trial. Finally, all included trials were limited by the 26-week duration (a maximum of 32 weeks, including screening period and follow-up period), which limits the ability to detect changes in more clinically important outcomes, such as cardiovascular (CV)-related outcomes, and mortality.

Efficacy

IDegLira in combination with MET statistically significantly reduced hemoglobin A1C levels after 26 weeks of treatment compared with IDeg (DUAL II trial) or IGlar (DUAL V trial) in combination with MET. The estimated least squares (LS) mean difference was −1.05% (95% CI, −1.25 to −0.84) in DUAL II and −0.59% (95% CI, −0.74 to −0.45) in DUAL V. The clinical expert consulted for this review considered the treatment effects observed as clinically relevant. However, the DUAL II trial had a pre-specified cap on maximum insulin

dose. Therefore, in the DUAL II trial, many of the patients in the IDeg treatment group were not titrated fully during the 26-week trial, and it is questionable whether IDegLira would be a better treatment option than IDeg alone in a setting where basal insulin therapy was optimized without any dosage limitations.

In the DUAL VII trial, IDegLira, in combination with MET, was noninferior to IGlar + IAsp plus MET for the change from baseline in hemoglobin A1C after 26 weeks of treatment, based on a 0.3% NI margin (LS mean difference was −0.02 [95% CI, −0.16 to 0.12]). No statistically significant difference was detected between treatments in the test for superiority.

The DUAL III trial reported that IDegLira in combination with MET ± pioglitazone ± SU statistically significantly reduced hemoglobin A1C levels after 26 weeks of treatment compared with GLP-1 RA in combination with MET ± pioglitazone ± SU. The estimated LS mean difference was −0.94 (95% CI, −1.11 to −0.78; $P < 0.001$), which was statistically significant favouring IDegLira versus GLP-1 RA, indicating that IDegLira is superior to GLP-1 RA therapy. The clinical expert consulted for this review considered the treatment effects observed as clinically relevant. However, given that patients in the GLP-1 RA treatment group were taking the maximum recommended dose of comparator product at trial entry, and the dose was not to be changed during the trial, the lack of improvement in hemoglobin A1C for the GLP-1 RA group was to be expected. In contrast, IDegLira was started at 16 U (16 U of IDeg and 0.6 mg of liraglutide) and titrated to glycemic targets, resulting in a further glucose lowering. Overall, the DUAL III trial was compromised by poor study design but appeared to show the efficacy of IDegLira in achieving target BG levels with continuous dose titration compared with continuation of a treatment regimen consisting of a GLP-1 RA in combination with oral antihyperglycemic agents.

In the DUAL II, DUAL V, and DUAL III trials, more patients in the IDegLira treatment groups achieved target hemoglobin A1C levels (< 7.0% or ≤ 6.5%) than in the IDeg, IGlar, or GLP-1 RA treatment groups. In the DUAL II, DUAL V, and DUAL III trials, the proportion of patients achieving hemoglobin A1C < 7% in the IDegLira treatment group was 60.3%, 71.6%, and 75.3 and was 23.1%, 47.0%, and 35.6% in the IDeg, IGlar, and GLP-1 RA treatment groups, respectively. In these same trials, the proportion of patients achieving hemoglobin A1C ≤ 6.5% in the IDegLira treatment group was 45.2%, 55.4%, and 63.0% and was 13.1%, 30.8%, and 22.6% in the IDeg, IGlar, and GLP-1 RA treatment groups, respectively. In addition, in the DUAL II and DUAL V trials, the proportion of patients reaching the predefined hemoglobin A1C targets (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain or hypoglycemic episodes or both was also higher in the IDegLira treatment groups than in the IDeg or IGlar treatment groups. No differences were detected in the proportion of patients achieving glycemic targets for the IDegLira group versus IGlar + IAsp group in the DUAL VII trial. However, in the DUAL VII trial, treatment with IDegLira, compared with IGlar + IAsp, resulted in higher proportions of patients achieving glycemic targets (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain or treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes, or both. All of these analyses in all of the included trials were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

In the DUAL V and DUAL VII trials, IDegLira showed statistically significant reductions in body weight after 26 weeks of treatment compared with IGlar, and IGlar + IAsp (LS mean

difference of −3.20 kg and −3.57 kg, respectively). In the DUAL II trial, IDegLira also showed reductions in body weight after 26 weeks of treatment compared with IDeg (LS mean difference of −2.51). However, this outcome was not adjusted for multiplicity in DUAL II; hence, any result reported should be interpreted with consideration of the potential for inflated type I error. The clinical expert involved in this CADTH Common Drug Review indicated that while insulin alone is often associated with weight gain, weight loss is to be expected when GLP-1 RA is added to insulin. Although any reduction in weight may be viewed as positive by patients, it is not known whether these changes translate into long-term health benefits. In contrast, in the DUAL III trial, patients treated with IDegLira gained significantly more weight than patients who continued GLP-1 RA therapy. This is to be expected when an insulin-naive population previously treated with GLP-1 RA transfers to insulin containing an antidiabetes product. This outcome was not adjusted for multiplicity in DUAL III; hence, any result reported should be interpreted with consideration of the potential for inflated type I error.

HRQoL measures were included in this systematic review to provide a patient perspective of treatment with IDegLira and because this was considered an important outcome to patients, as reported in the patient input section (see Appendix 1). The HRQoL outcomes measured in the trials were the TRIM-D in DUAL V, DUAL VII, and DUAL III, the SF-36 in DUAL V and DUAL VII, and the Diabetes Treatment Satisfaction Questionnaire status version in DUAL III. While results from these patient-reported outcome questionnaires seemed to favour IDegLira treatment groups, no minimal clinically important differences (MCIDs) were established specific to patients with T2DM, and the clinical significance of the benefit of IDegLira compared with IGlar, IGlar + IAsp, or GLP-1 RA for these assessed outcomes was not clear from the literature. In addition, the difference seen between the IDegLira treatment groups and the IGlar and IGlar + IAsp treatment groups in SF-36 did not exceed the proposed minimally important differences (MID) in the SF-36's user's manual for the questionnaire's physical component summary (PCS) and mental component summary (MCS), or the survey's eight domains. Finally, all three trials were open label. There is a risk of bias with outcomes measured in open-label studies as patients and providers are aware of their assigned intervention. Measurement of subjective outcomes, such as HRQoL, may be at increased risk of bias if patients in the study are aware of their treatment allocation. Analyses of these outcomes were not adjusted for multiplicity and any result reported should be interpreted with consideration of the potential for inflated type I error.

The indirect treatment comparison (ITC) submitted by the manufacturer for patients with T2DM inadequately controlled with basal insulin (in combination with MET ± SU) reported [redacted]. However, due to the considerably high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain, especially for the comparison of [redacted], where there was no supportive evidence from head-to-head trials.

For patients with T2DM inadequately controlled with liraglutide (in combination with MET ± SU), the ITC using the Bucher method showed that [redacted]

[redacted]However, the Bucher ITC provided only limited evidence for the comparative efficacy and safety of IDegLira due to the small number of included studies; in addition, there was lack of evidence for the comparative efficacy and safety versus a number of relevant comparators (e.g., [redacted]).

The sodium-glucose cotransporter-2 inhibitors or dipeptidyl peptidase-4 (DDP-4) inhibitors (in combination with MET) are treatment options for patients with T2DM inadequately controlled with basal insulin. In patients with T2DM inadequately controlled with basal insulin (in combination with MET ± SU), [redacted]

Harms

The overall frequency of AEs was similar between treatment groups within trials. In the DUAL II, DUAL V, and DUAL VII trials, AEs were reported by 57.6% to 59.1% of patients who received IDegLira, and by 61.3%, 50.5%, and 56.9% of patients who received IDeg, IGlar, and IGlar + IAsp, respectively. In the DUAL III trial, AEs were reported by 65.6% of patients treated with IDegLira, and by 63.4% of patients treated with GLP-1 RA. Serious AEs were reported by 1.8% to 4.8% of patients who received IDegLira, and by 5.5%, 3.2%, 4.0%, and 2.1% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively. In all of the included trials, no serious AEs occurred in ≥ 1% of the patients. The rates of AEs leading to withdrawal from the trials were reported by 0.3% to 2.5% of patients who received IDegLira, and by 1.5%, 0.4%, 0%, and 1.4% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively. No deaths were reported during the DUAL II, DUAL VII, and DUAL III trials. In the DUAL V trial, one patient died during the trial; that patient was treated with IGlar and died due to hemorrhagic stroke. The event was considered unlikely to be related to the trial product.

GI AEs were reported more frequently in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups. This was expected from the safety profile of liraglutide. The most frequent GI AEs were nausea, diarrhea, and vomiting. The clinical expert consulted for this review indicated that the rates of nausea with IDegLira were much lower than those reported in the liraglutide clinical trials, and that this could be due to the slower titration of IDegLira (which was consistent with that recommended in the product monograph) compared with the titration of liraglutide alone.

The proportion of patients that experienced severe hypoglycemia as defined by the ADA in each individual study was too low (ranging from 0% to 1.6% across the included trial) to make a judgment on the comparative incidence of severe hypoglycemia. In the DUAL II trial, the proportion of patients with confirmed hypoglycemic episodes was similar between IDegLira and IDeg. In the DUAL V trial, the proportion of patients with confirmed hypoglycemic episodes was lower in the IDegLira group (28.4%) compared with the IGlar group (49.1%). In the DUAL VII trial, the proportion of patients that experienced severe or BG-confirmed hypoglycemic episodes was also lower in the IDegLira group (31.3%) compared with the IGlar + IAsp group (60.9%). In the DUAL III trial, the proportion of patients that experienced confirmed hypoglycemic episodes was higher in the IDegLira group (32%) compared with the GLP-1 RA group (2.8%). It can be explained by the fact

that patients in the IDegLira group were transferred to a treatment regimen containing an insulin component. The clinical expert consulted on this review indicated that any time hypoglycemia is reported, it is due to an insulin component that has been given, and that GLP-1 RAs do not cause hypoglycemia. The use of SU in the DUAL III trial could have also contributed to hypoglycemia episodes in both treatment groups.

The occurrence of other harms of special interest to this review (renal failure, arrhythmia, allergic reaction [immunogenicity], and injection site reactions) was infrequent, and no cases of pancreatitis or antibody formation were reported in the trials.

Potential Place in Therapy[1]

Only about 40% to 50% of patients with T2DM treated with either basal insulin or a GLP-1 RA in combination with or without other non-insulin antihyperglycemic agents achieve hemoglobin A1C targets. Individuals not at target will require additional therapy to improve glycemia. A traditional approach for managing individuals not at target while on basal insulin has been the addition of prandial insulin from one to three times daily, but this therapy increases complexity and number of injections and is associated with weight gain and hypoglycemia. There is an unmet need for patients requiring intensification beyond basal insulin for a simple and convenient therapy that will not increase hypoglycemia and will provide a weight benefit. IDegLira is a fixed-ratio combination of IDeg and the GLP-1 RA liraglutide that provides simple titration regimens, improvement in hemoglobin A1C and postprandial glucose without increasing hypoglycemia, and weight loss benefits. For patients not at target while on a GLP-1 RA with or without other non-insulin agents, the addition of basal insulin can be an effective way to improve fasting glucose and hemoglobin A1C.

For patients on basal insulin who may require a GLP-1 RA, IDegLira offers the convenience of a single injection with only one titration regimen, rather than separate injections of basal insulin and a GLP-1 RA with two different titration regimens. The weight benefit versus insulin alone is also important, given that about 85% of individuals with T2DM are overweight or obese. Furthermore, IDegLira will lead to less nausea than a GLP-1 RA given as a separate agent (due to the different titration recommendations in their respective product monographs) and is associated with a lower insulin dose than insulin therapy alone.

In summary, IDegLira can provide a novel way for clinicians to combine a GLP-1 RA with basal insulin in a convenient single injection for individuals with elevated hemoglobin A1C despite basal insulin therapy with or without other agents. Its use in practice will be consistent with the Diabetes Canada 2018 guidelines[9] that recommend “a GLP-1 receptor agonist be considered as add-on therapy to basal insulin before initiating bolus insulin or intensifying insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared with single or multiple bolus insulin injections.” With IDegLira as an option for adding a GLP-1 RA to basal insulin, clinicians and patients can now decide between adding a daily- or once-weekly administered GLP-1 RA or switching the basal insulin to IDegLira. IDegLira will likely be used in such a scenario only for patients without a history of clinical CV disease, as guidelines recommend agents with proven CV benefit for such patients, which for GLP1-RAs would be liraglutide 1.8 mg daily or semaglutide 1 mg once weekly. As individualization of care is the mainstay of T2DM management, IDegLira now provides another option for adding a GLP-1 RA to basal insulin-treated patients without a history of CV disease. Finally, ADA and the European Association for the Study of Diabetes 2018

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

consensus statement[10] recommend GLP-1 RAs as the first injectable option in T2DM. As that approach becomes more common in clinical practice, IDegLira will be an option for initiating basal insulin for individuals not achieving target on a GLP-1 RA with or without other agents.

Conclusions

Four phase III randomized controlled trials (DUAL II, DUAL V, DUAL VII, and DUAL III) provided evidence on the efficacy and safety of IDegLira in adults with T2DM. In patients who had inadequate glycemic control with basal insulin plus MET, the therapy of titrated IDegLira with MET compared with titrated basal insulin plus MET was found to statistically significantly improve hemoglobin A1C and lower body weight with reduction, or no increase, in hypoglycemia. IDegLira plus MET was also shown to have noninferior glycemic efficacy to a basal-bolus insulin regimen (IGlar + IAsp), with less hypoglycemia. IDegLira demonstrated statistically significant improvement in hemoglobin A1C but with more hypoglycemia and weight increase when switching from a GLP-1 RA to IDegLira while continuing background MET with or without other agents in insulin-naive patients who had inadequate glycemic control with GLP-1 RA. The overall frequency of AEs was similar between treatment groups within trials. GI AEs were reported more frequently in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups, which was expected from the safety profile of liraglutide. The most frequent GI AEs were nausea, diarrhea, and vomiting.

The manufacturer-submitted ITC for the patients with T2DM inadequately controlled with basal insulin suggested that [redacted] However, due to the considerably high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain. For patients with T2DM inadequately controlled with liraglutide, the Bucher ITC provided only limited evidence for the comparative efficacy and safety of IDegLira due to the small number of included studies. In addition, there was lack of evidence for the comparative efficacy and safety versus a number of relevant comparators (e.g., [redacted]

Table 1: Summary of Results

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Hemoglobin A1C (%)								
N	199	199	278	279	244	245	292	146
Baseline (week 0) mean (SD)	8.7 (0.7)	8.8 (0.7)	8.4 (0.9)	8.2 (0.9)	8.21 (0.76)	8.24 (0.81)	7.8 (0.6)	7.7 (0.6)
LS mean (SEM) after 26 weeks of treatment	6.88 (0.073)	7.93 (0.073)	6.54 (0.05)	7.14 (0.05)	6.73 (0.05)	6.75 (0.05)	6.44 (0.05)	7.38 (0.07)
LS mean change from baseline (SEM)	−1.92[a] (0.073)	−0.87[a] (0.073)	−1.77[b] (0.05)	−1.17[b] (0.05)	−1.48[c] (0.05)	−1.46[c] (0.05)	−1.32[d] (0.05)	−0.37[d] (0.07)
LS mean difference (95% CI)	−1.05 (−1.25 to −0.84)[a]		−0.59 (−0.74 to −0.45)[b]		−0.02 (−0.16 to 0.12)[c]		−0.94 (−1.11 to −0.78)[d]	
P value	< 0.0001[a]		< 0.001[b]		< 0.0001[c]		< 0.001[d]	
Responder for hemoglobin A1C After 26 Weeks of Treatment								
hemoglobin A1C < 7.0%								
Baseline (week 0), n (%)	0 (0.0)	0 (0.0)	8 (2.9)	15 (5.4)	7 (2.8)	14 (5.5)	11 (3.8)	10 (6.8)
Week 26, n (%)	120 (60.3)	46 (23.1)	199 (71.6)	131 (47.0)	157 (62.3)	162 (63.8)	220 (75.3)	52 (35.6)
Odds ratio (95% CI)	5.44 (3.42 to 8.66)		3.45 (2.36 to 5.05)		0.91 (0.62 to 1.33)		6.84 (4.28 to 10.94)[d]	
P value	< 0.0001		< 0.001		0.6207		< 0.001	
hemoglobin A1C < 6.5%								
Baseline (week 0), n (%)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 26, n (%)	90 (45.2)	26 (13.1)	154 (55.4)	86 (30.8)	118 (46.8)	105 (41.3)	184 (63.0)	33 (22.6)
Odds ratio (95% CI)	5.66 (3.37 to 9.51)		3.29 (2.27 to 4.75)		1.26 (0.88 to 1.82)		7.53 (4.58 to 12.38)	
P value	< 0.0001		< 0.001		0.2116		< 0.001	
FPG (mmol/L)								
N	198	199	275	278	251	254	285	145
Baseline (week 0) mean (SD)	9.7 (2.9)	9.6 (3.1)	8.9 (2.6)	8.9 (2.9)	8.52 (2.65)	8.28 (2.53)	9.0 (2.1)	9.4 (2.3)
LS mean (SEM) after 26 weeks of treatment	6.24 (0.16)	6.97 (0.16)	6.09 (0.12)	6.09 (0.12)	6.14 (0.13)	6.44 (0.13)	6.05 (0.11)	8.69 (0.16)
LS mean change from baseline (SEM)	−3.38 (0.16)	−2.66 (0.16)	−2.80 (0.12)	−2.79 (0.12)	−2.24 (0.13)	−1.93 (0.13)	−3.06 (0.11)	−0.42 (0.16)
LS mean difference (95% CI)	−0.73 (−1.19 to −0.27)		−0.01 (−0.35 to 0.33)		−0.31 (−0.67 to 0.05)		−2.64 (−3.03 to −2.25)	
P value	0.0019		0.963		0.0936		< 0.001	
Body Weight (kg)								
N	199	199	278	279	252	254	292	146
Baseline (week 0) mean (SD)	95.4 (19.4)	93.5 (20.0)	88.3 (17.5)	87.3 (15.8)	87.2 (16.0)	88.2 (17.2)	95.6 (16.6)	95.5 (17.3)
LS mean (SEM) after 26 weeks of treatment	91.86 (0.25)	94.37 (0.25)	86.38 (0.20)	89.58 (0.20)	86.51 (0.22)	90.08 (0.22)	97.52 (0.21)	94.63 (0.30)
LS mean change from baseline (SEM)	−2.59 (0.25)	−0.08 (0.25)	−1.39 (0.20)	1.81 (0.20)	−0.93 (0.22)	2.64 (0.22)	2.00 (0.21)	−0.89 (0.30)

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
LS mean difference (95% CI)	−2.51 (−3.21 to −1.82)		−3.20 (−3.77 to −2.64)		−3.57 (−4.19 to −2.95)		2.89 (2.17 to 3.62)	
P value	< 0.0001		< 0.001		< 0.0001		< 0.001	
SF-36 (Physical Score)								
N	NA	NA	278	277	252	254	NA	NA
Baseline (week 0) mean (SD)	NA	NA	47.4 (9.0)	47.7 (8.4)	47.2 (9.2)	46.7 (8.9)	NA	NA
LS mean (SEM) after 26 weeks of treatment	NA	NA	49.0 (0.4)	47.1 (0.4)	47.85 (0.43)	48.46 (0.43)	NA	NA
LS mean change from baseline (SEM)	NA	NA	1.5 (0.4)	−0.5 (0.4)	0.74 (0.43)	1.35 (0.43)	NA	NA
LS mean difference (95% CI)	NA		1.9 (0.8 to 3.1)		−0.61 (−1.81 to 0.59)		NA	
P value	NA		< 0.001		0.3187		NA	
SF-36 (Mental Score)								
N	NA	NA	278	279	252	254	NA	NA
Baseline (week 0) mean (SD)	NA	NA	46.7 (11.4)	48.1 (9.9)	46.7 (10.7)	47.5 (10.2)	NA	NA
LS mean (SEM) after 26 weeks of treatment	NA	NA	48.7 (0.5)	48.7 (0.5)	49.22 (0.56)	47.39 (0.57)	NA	NA
LS mean change from baseline (SEM)	NA	NA	1.3 (0.5)	1.3 (0.5)	2.11 (0.56)	0.28 (0.57)	NA	NA
LS mean difference (95% CI)	NA		−0.1 (−1.5 to 1.3)		1.83 (0.26 to 3.40)		NA	
P value	NA		0.928		0.0228		NA	
Harms								
Patients with > 0 AEs, N (%)	115 (57.8)	122 (61.3)	160 (57.6)	141 (50.5)	149 (59.1)	144 (56.9)	191 (65.6)	92 (63.4)
Patients with > 0 SAEs, N (%)[e]	7 (3.5)	11 (5.5)	5 (1.8)	9 (3.2)	12 (4.8)	10 (4.0)	9 (3.1)	3 (2.1)
WDAEs, N (%)	1 (0.5)	3 (1.5)	7 (2.5)	1 (0.4)	1 (0.4)	0	1 (0.3)	2 (1.4)
Number of deaths, N (%)	0	0	0	1 (0.4)	0	0	0	0
Notable harms								
Myocardial infarction	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Stroke	0	1 (0.5)	1 (0.4)	0	0	0	2 (0.7)	0
Cardiac arrhythmia	5 (2.5)	4 (2.0)	5 (1.8)	2 (0.7)	6 (2.4)	0	6 (2.1)	2 (1.4)
Pancreatitis	0	0	0	0	0	0	0	0
Renal failure	1 (0.5)	0	0	0	0	1 (0.4)	0	0
Renal failure acute	1 (0.5)		1 (0.4)	0	0	0	0	0
Confirmed hypoglycemia	48 (24.1)	49 (24.6)	79 (28.4)	137 (49.1)	79 (31.3)	154 (60.9)	93 (32.0)	4 (2.8)
Severe hypoglycemia as defined by the American Diabetes Association	1 (0.5)	0	0 (0.0)	1 (0.4)	3 (1.2)	4 (1.6)	1 (0.3)	0

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Allergic reaction (immunogenicity)	0	2 (1.0)	7 (2.5)	7 (2.5)	3 (1.2)	5 (2.0)	8 (2.7)	7 (4.8)
Gastrointestinal AEs	42 (21.1)	23 (11.6)	70 (25.2)	27 (9.7)	59 (23.4)	28 (11.1)	45 (15.5)	22 (15.2)
Injection site reactions	1 (0.5)	5 (2.5)	1 (0.4)	2 (0.7)	0	1 (0.4)	8 (2.7)	1 (0.7)
Antibody formation			0	0	0	0	0	0

AE = adverse event; ANCOVA = analysis of covariance; CI = confidence interval; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LS = least squares; LOCF = last observation carried forward; NA = not applicable; SAE = serious adverse event; SD = standard deviation; SEM = standard error of the mean; SF-36 = Short Form (36) Health Survey; WDAE = withdrawal due to adverse event.

[a] Missing data were imputed using LOCF. Change in hemoglobin A1C from baseline after 26 weeks of treatment was analyzed using an ANCOVA model with treatment, country, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as covariate. *P* value for the difference between IDegLira and IDeg is test for superiority.

[b] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[c] All post-baseline hemoglobin A1C measurements obtained at planned visits before discontinuation from randomized treatment were analyzed via a linear mixed normal model using an unstructured residual covariance matrix for hemoglobin A1C measurements within the same patient. The model included treatment, visit, and region as fixed factors and baseline hemoglobin A1C as a covariate. Interactions between visit and all factors and covariates were also included in the model. *P* value was two-sided test for noninferiority.

[d] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors and baseline hemoglobin A1C value as covariates.

[e] No SAEs occurred in ≥ 1% of patients.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Introduction

Disease Prevalence and Incidence

Diabetes mellitus is a metabolic disease that is characterized by persistent elevations in blood glucose (BG), (hyperglycemia).[1] This persistent elevated BG causes damage to blood vessels on a microvascular level (retinopathy, nephropathy, neuropathy) and macrovascular level (peripheral artery disease, cardiovascular [CV] disease).[1] There are two main subtypes of diabetes mellitus: type 1 diabetes mellitus (T1DM), in which the primary problem is a lack of adequate insulin secretion from pancreatic beta cells, and type 2 diabetes mellitus (T2DM), which occurs when the body does not effectively use the insulin that is produced or when the pancreas does not produce enough insulin.[7] T2DM is more common than T1DM, accounting for approximately 90% of cases of diabetes mellitus.[2,3]

The etiology of diabetes mellitus is associated with genetic factors and environmental triggers that are believed to play a role in the development of disease.[15] The onset of T2DM typically occurs around 40 years of age or older.[16] However, this is changing with an increase in obesity and sedentary behaviours leading to more frequent diagnosis of T2DM in children and younger people.[1] Poor diet and minimal exercise, and associated weight gain, are considered major risk factors for T2DM.[17] Patients with T2DM, who in the initial stages of their disease are able to secrete insulin or may be hyperinsulinemic, may progress to a stage where insulin secretion is reduced, similar to T1DM. As described by the patient input received for this report (see Appendix 1), common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination, and weight change. More serious complications may present for patients with poor glucose control. For example, low glucose may cause confusion, coma, or seizures. High levels of glucose may lead to more long-term issues such as damage to the nerves and blood vessels, which increases the risk of blindness, heart disease, kidney disease, and damage to the extremities. Patients also report that diabetes has a great impact on the patients' emotional, social, and economic status.

Diabetes has a significant impact on both individuals and societies. The prevalence of diabetes is increasing at a dramatic rate around the world. In a report produced by the World Health Organization, there was an estimated 422 million adults living with diabetes globally in 2014, up from 108 million in 1980.[1] Further, this number is projected to increase to 693 million by 2045 if the current trends continue.[15] Diabetes is also a significant problem in Canada, as one of the most common chronic diseases in the country. Diabetes Canada estimated that 3.65 million people (9% of the population) were living with diabetes in 2019, and that this number will increase to 4.78 million people (11%) by 2029.[4] People with diabetes are more likely to be hospitalized and to experience complications requiring care by a specialist. It is estimated that by 2020, the direct and indirect costs of diabetes for the Canadian health care system will increase to $16.9 billion per year.[16]

Standards of Therapy

Treatment regimens and therapeutic targets should be individualized in patients with T2DM. Treatment usually begins with lifestyle modifications, including exercise and diet.[18] When lifestyle interventions are not sufficient to control BG levels, pharmacological treatment becomes necessary.[18] There is a wide variety of classes of antihyperglycemic agents available to treat T2DM, including insulin. Metformin (MET) is widely considered to be the

first-line drug of choice for most patients, with a second or third agent added to MET for patients unable to achieve therapeutic targets.[19]

Several oral antihyperglycemic agents (AHAs) can be used alongside MET, such as sulfonylureas (SUs), meglitinides, thiazolidinediones (TZDs), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DDP-4) inhibitors and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Injectable agents, such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs), and insulin and insulin analogues (rapid-acting, intermediate, or long-acting forms) may also be considered as an add-on to MET with or without other AHAs.[20] However, according to the *Diabetes Canada 2018 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada*, it is recommended that DPP-4 inhibitors, GLP-1 RAs, or SGLT2 inhibitors be considered as first-line add-ons to MET in patients without clinical CV disease as hypoglycemia and weight gain are less of an issue with these agents, provided contraindications, accessibility, and affordability are considered.[7] Key characteristics of these classes of drugs are outlined in Table 2 and Table 3.

Although there are currently numerous therapeutic options and combination therapy strategies available, many patients do not achieve adequate glycemic control on non-insulin therapies alone and require the addition of basal insulin to achieve target hemoglobin A1C levels (i.e., < 7.0%).[18] Despite the use of a basal insulin, some patients will require further treatment to achieve or maintain this glycemic target. The addition of one or more injections of a prandial insulin before mealtime is an option; however, this approach also has disadvantages, including complexity, increased self-BG monitoring, risk of hypoglycemia, and weight gain.[5]

The latest joint position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes suggested that GLP-1 RAs may be a safer addition to basal insulin in comparison with prandial insulin for short-term outcomes, and may be a more appealing option for overweight patients, or those who may find a basal-bolus insulin regimen to be too complex.[21] Although combination products are not specifically mentioned, this sentiment is echoed by the current Diabetes Canada clinical practice guidelines,[7] which recommend that a GLP-1 RA be considered before bolus insulin as add-on therapy in patients on a basal insulin who require antihyperglycemic treatment intensification, if there are no barriers to affordability or access.

Drug

Insulin degludec (IDeg) and liraglutide injection fixed-ratio combination (together known as IDegLira) is a multi-ingredient product that contains a long-acting basal insulin analogue (IDeg) and a GLP-1 RA (liraglutide) in a single pen-injector format.[8] As T2DM progresses, endogenous insulin output further declines; therefore, exogenous insulin, such as insulin analogue, is required in order to decrease levels of plasma glucose.[5] Although insulin is a benchmark in the treatment of T2DM, its optimization can be limited by side effects, such as hypoglycemia and weight gain.[5] GLP-1 RAs, such as liraglutide, stimulate insulin secretion and lower glucagon secretion in a glucose-dependent manner. Thus, when BG is high, insulin secretion is stimulated and glucagon secretion is inhibited. Conversely, when BG is low, liraglutide diminishes insulin secretion and does not impair glucagon secretion. The mechanism of BG lowering also involves a delay in gastric emptying.[6] GLP-1 RAs are also associated with gastrointestinal side effects, such as nausea, diarrhea, and vomiting.[7]

IDegLira contains 100 U/mL IDeg and 3.6 mg/mL liraglutide, which would allow daily doses between 16 U to 50 U of IDeg and 0.58 mg to 1.8 mg of liraglutide to be administered

subcutaneously once daily.[8] Health Canada approved this fixed-ratio combination product (IDegLira) as an adjunct to lifestyle modifications for the treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control.[8]

The recommended starting dosage of IDegLira is 16 U (16 U of IDeg and 0.58 mg of liraglutide) given subcutaneously once daily. After starting with 16 U of IDegLira (16 U of IDeg and 0.58 mg of liraglutide), the dose is titrated upwards or downwards by 2 U every three to four days based on the patient's metabolic needs, BG monitoring results, and glycemic control goal until the desired fasting plasma glucose (FPG) is achieved. The maximum daily dosage of IDegLira is 50 U (50 U of IDeg and 1.8 mg of liraglutide). If patients require an IDegLira daily dosage persistently below 16 U, or more than 50 U, then alternative antihyperglycemic agents should be used.[8]

Soliqua (an insulin glargine [IGlar] and lixisenatide injection, known as iGlarLixi) is the only other basal Insulin and GLP-1 RA combination currently approved in Canada.[22]

Table 2: Key Characteristics of Glucagon-Like Peptide 1 Receptor Agonists, Thiazolidinediones, Dipeptidyl Peptidase-4 Inhibitors, and Insulin

	GLP-1 RAs	DPP-4 Inhibitors	Insulin and Insulin Analogues	Basal Insulin and GLP-1 RA Combination
Mechanism of action	They mimic GLP-1, which: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake.	They increase GLP-1 by inhibiting the DPP-4 enzyme, which inactivates GLP-1 and: • leads to insulin secretion • inhibits glucagon release • delays gastric emptying • reduces food intake.	They substitute for endogenously secreted insulin.	This mechanism of action is associated with that of a GLP-1 RA and insulin in combination.
Indication[a]	**Semaglutide** • Once-weekly treatment of adult patients with T2DM to improve glycemic control, in combination with MET, MET and a SU, MET and basal insulin, or diet and exercise **Liraglutide** • For T2DM in combination with MET or MET and a SU when these drugs, with diet and exercise, do not provide adequate glycemic control • For T2DM in combination with MET and a basal insulin when liraglutide and MET, with diet and exercise, do not provide adequate glycemic control **Exenatide (twice daily)**	**Saxagliptin** • For T2DM in combination with MET or a SU, or insulin (with or without MET) or MET and a SU, when these drugs used alone, with diet and exercise, do not provide adequate glycemic control **Sitagliptin** • For T2DM as monotherapy, or in combination with MET or a SU and MET, or insulin (with or without MET), or pioglitazone, or MET	• For patients with DM who require insulin for control of hyperglycemia	**Xultophy** • An adjunct to lifestyle modifications, for the once-daily treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (< 50 U daily) or liraglutide (≤ 1.8 mg daily) do not provide adequate glycemic control **Soliqua** • An adjunct to diet and exercise to improve glycemic control in adults with T2DM

	GLP-1 RAs	DPP-4 Inhibitors	Insulin and Insulin Analogues	Basal Insulin and GLP-1 RA Combination
	• For T2DM that cannot be adequately controlled by diet and exercise alone; may be used as monotherapy or in combination with MET, a SU, or MET and a SU **Exenatide (extended-released, once weekly)** • For T2DM that cannot be adequately controlled by diet and exercise alone; may be used in combination with MET, a SU, MET and a SU, or basal insulin **Dulaglutide** • For T2DM that cannot be adequately controlled by diet and exercise alone; may be used in combination with MET, MET and a SU, basal insulin with MET, or prandial insulin with MET **Lixisenatide** • For T2DM that cannot be adequately controlled by diet and exercise alone in combination with MET, a SU (alone or with MET), pioglitazone (alone or with MET), or a basal insulin (alone or with MET)	and pioglitazone, when these drugs, with diet and exercise, do not provide adequate glycemic control **Linagliptin** • For T2DM as monotherapy or in combination with MET or a SU, MET and a SU, or MET and empagliflozin, when these drugs, with diet and exercise, do not provide adequate glycemic control		inadequately controlled on basal insulin (< 60 U daily) alone or in combination with MET
Route of administration	Subcutaneous	Oral	Subcutaneous	Subcutaneous
Recommended dose	Varies by drug	Varies by drug	Titrated	Titrated
Serious side effects and safety issues	**Warnings and precautions** • Thyroid cancer • Prolonged PR interval • Hypoglycemia (when combined with SU) • Pancreatitis • GI disorders **Contraindications** • Personal or family history of MTC and in patients with MEN2	**Contraindications** • DKA **Warnings and precautions** • Heart failure • Pancreatitis • Immune suppression	**Serious warnings and precautions** • Hypoglycemia • Immune responses	**Serious warnings and precautions** • Hypoglycemia • Immune response • Pancreatitis • GI disorders **Contraindications** • Pregnancy • Hypersensitivity • Hypoglycemic episodes

DKA = diabetic ketoacidosis; DM = diabetes mellitus; DPP-4 = dipeptidyl peptidase-4; GI = gastrointestinal; GLP-1 = glucagon-like peptide 1; GLP-1 RA = glucagon-like peptide 1 receptor agonist; MEN2 = multiple endocrine neoplasia type 2; MET = metformin; MTC = medullary thyroid carcinoma; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs.[6,8,22-35]

Table 3: Key Characteristics of Sodium-Glucose Cotransporter-2 Inhibitors, Metformin, and Sulfonylureas

	SGLT2 Inhibitors	Biguanides (Metformin)	Sulfonylurea
Mechanism of action	They inhibit the SGLT2 transporter in the kidney, leading to increased glucose excretion.	They reduce gluconeogenesis, increase the conversion of glucose to glycogen, and increase the degradation of glucose.	It promotes insulin secretion by binding to SUR-1, the SU receptor.
Indication[a]	**Canagliflozin** In T2DM: • as monotherapy in patients with T2DM for whom MET is inappropriate • in combination with MET or a SU when diet and exercise plus monotherapy with one of these agents does not provide adequate glycemic control • in combination with MET and either a SU or pioglitazone when diet, exercise, and dual therapy (with MET plus either a SU or pioglitazone) do not provide adequate glycemic control • in combination with MET and sitagliptin when diet, exercise, and dual therapy (with MET and sitagliptin) do not provide adequate glycemic control • in combination therapy with insulin (with or without MET) when diet and exercise, and therapy with insulin (with or without MET), do not provide adequate glycemic control. **Empagliflozin** • As monotherapy for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM • In combination with MET, MET and a SU, pioglitazone (alone or with MET), basal insulin (alone or with MET), or prandial insulin (alone or with MET), when the existing therapy, along with diet and exercise, does not provide adequate glycemic control in adult patients with T2DM **Ertugliflozin** • As monotherapy for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM for whom MET is inappropriate due to contraindications or intolerance	• For T2DM that cannot be controlled by proper dietary management, exercise, and weight reduction or when insulin therapy is not appropriate • For treatment of obese patients with diabetes	• For T2DM in adults, alone or in combination with other antihyperglycemic agents, as an adjunct to exercise and diet

	SGLT2 Inhibitors	Biguanides (Metformin)	Sulfonylurea
	• In combination with MET, or MET and sitagliptin, to improve glycemic control in adult patients with T2DM **Dapagliflozin** • As monotherapy for use as an adjunct to diet and exercise to improve glycemic control in adult patients with T2DM, for whom MET is inappropriate due to contraindications or intolerance • In combination with MET, SU, MET and SU, sitagliptin (alone or with MET), or insulin (alone or with MET), to improve glycemic control in adult patients with T2DM when MET alone or the existing therapy listed previously, along with diet and exercise, do not provide adequate glycemic control		
Route of administration	Oral	Oral	Oral
Recommended dosage	Varies by drug	850 mg to 1,000 mg twice daily	Varies by drug
Serious side effects and safety issues	**Contraindications** • Renally impaired patients (level of renal impairment varies by drug) **Warnings and precautions** • Reduced intravascular volume • Hypoglycemia when combined with antihyperglycemic agents • Increase in LDL-C • Hyperkalemia • Impaired renal function	**Contraindications** • Acute or chronic metabolic acidosis, including diabetic ketoacidosis • Severe renal impairment **Warnings** • Lactic acidosis (rare)	**Contraindications** • Ketoacidosis • Severe liver or renal impairment **Precautions** • Hypoglycemia

LDL-C = low-density lipoprotein cholesterol; MET = metformin; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; SUR-1 = sulfonylurea receptor; T2DM = type 2 diabetes mellitus.

[a] Health Canada indication.

Source: Product monographs.[6,8,22-35]

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of IDeg and liraglutide injection (100 U/mL + 3.6 mg/mL) as an adjunct to lifestyle modifications, for the treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control.

Methods

Studies selected for inclusion in the systematic review included pivotal studies provided in the manufacturer's submission to CADTH Common Drug Review and Health Canada, as well as those meeting the selection criteria presented in Table 4.

Table 4: Inclusion Criteria for the Systematic Review

Patient population	Adults with T2DM who have experienced inadequate glycemic control on therapy with MET ± a SU + (basal insulin or liraglutide) **Subgroups** • Baseline hemoglobin A1C • Renal function (eGFR) • Duration of T2DM • BMI and/or body weight • Background diabetic therapy • History of heart failure • History of CV disease
Intervention	Insulin degludec (100 U/mL) + liraglutide (3.6 mg/mL) injection between 16 U of insulin degludec + 0.58 mg of liraglutide and 50 U of insulin degludec + 1.8 mg of liraglutide daily by subcutaneous injection, in combination with MET ± a SU
Comparators	MET ± a SU in combination with 1 or more of the following: • SGLT2 inhibitors (i.e., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) • GLP-1 RAs (i.e., dulaglutide, liraglutide, lixisenatide, exenatide, semaglutide) • DPP-4 inhibitors (i.e., alogliptin, linagliptin, sitagliptin, saxagliptin) • insulin and insulin analogues (including basal and prandial regimens)

Outcomes	**Efficacy outcomes**
	• Mortality (all-cause, cardiovascular related)
	• Diabetes-related morbidity[a]
	  ○ Macrovascular (e.g., coronary heart disease, cerebrovascular disease, peripheral vascular disease, MI, stroke)
	  ○ Microvascular (e.g., retinopathy, neuropathy, nephropathy)
	• Glycemic control (e.g., hemoglobin A1C, FPG, PPG, glucose excursion)[a]
	• Health-related quality of life (measured by a validated scale)[a]
	• BMI and/or body weight [a]
	• Blood pressure
	• Lipid profile
	• Health care resource utilization (e.g., hospitalization [CV-related, all-cause], glucose test strips)
	
	Harms outcomes
	AEs, SAEs, WDAEs, mortality, notable harms (e.g., hypoglycemia [severe vs. mild or moderate], renal failure, arrhythmia, pancreatitis, immunogenicity, anaphylaxis, angioedema, injection site reactions, gastrointestinal AEs [nausea, vomiting, and diarrhea])

Study design	Published and unpublished RCTs, phase III and phase IV

AE = adverse events; BMI = body mass index; CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; MET = metformin; MI = myocardial infarction; PPG = postprandial glucose; RCT = randomized controlled trial; SAE = serious adverse event; SGLT2 = sodium-glucose cotransporter-2; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; vs. = versus; WDAE = withdrawal due to adverse event.

[a] These outcomes were identified as being of particular importance to patients in the input received by CADTH from patient groups.

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 All (1946–) via Ovid, Embase (1974–) via Ovid, and PubMed. The search strategy consisted of both controlled vocabulary, such as the US National Library of Medicine's Medical Subject Headings, and keywords. The main search concepts were Xultophy (IDegLira — IDeg and liraglutide).

No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. 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 February 28, 2019. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on June 19, 2019. 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 trial registries, databases (free), Internet search, and background. 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.

Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. The reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 5, Table 6, and Table 7; excluded studies (with reasons for exclusion) are presented in Appendix 3.

Results

Findings From the Literature

Four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 5, Table 6, and Table 7. A list of excluded studies is presented in Appendix 3.

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

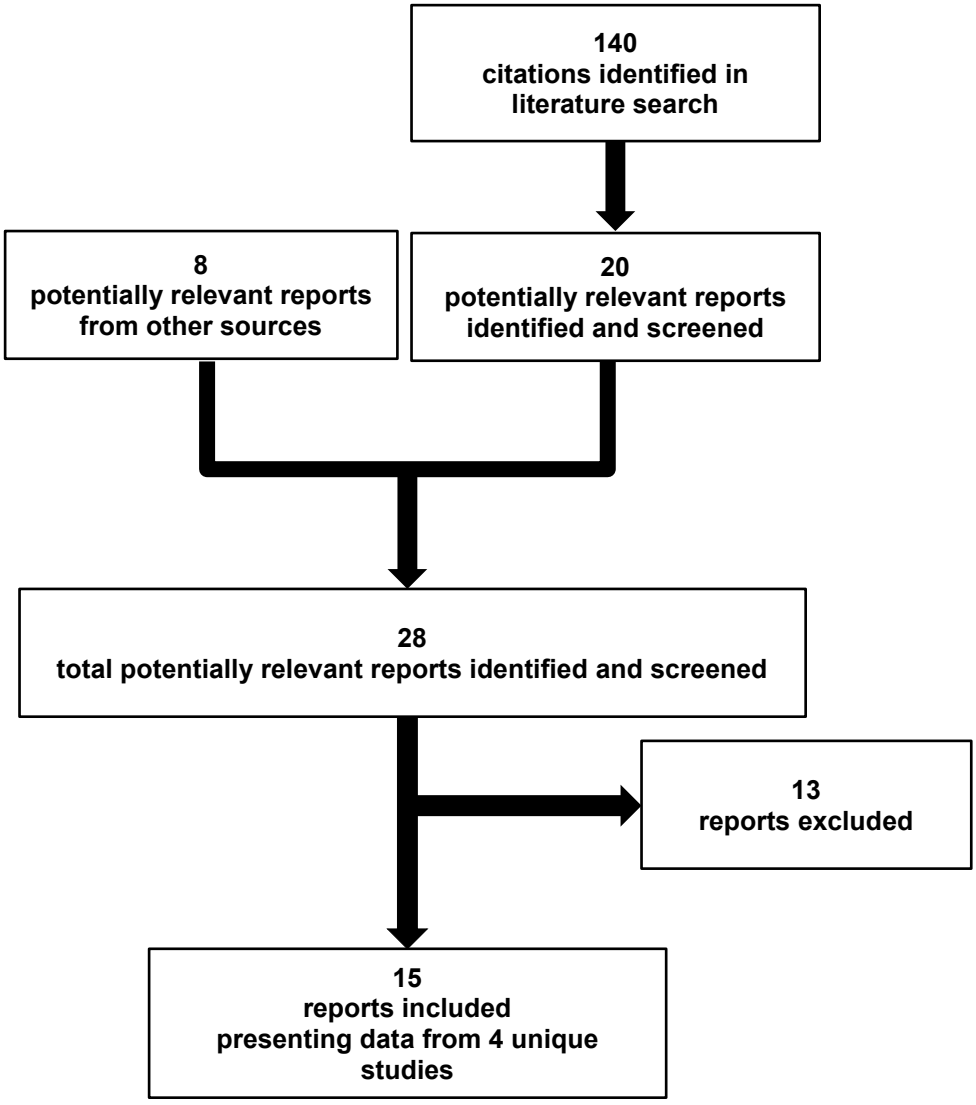


Table 5: Details of DUAL II Study

		DUAL II
Designs and Populations	**Study Design**	Phase III, parallel-group, double-blind RCT
	Locations	Bulgaria, Denmark, Hungary, India, Slovenia, Switzerland, and the US
	Randomized (N)	413

	Inclusion Criteria	• Adults with T2DM
		• Inadequately controlled T2DM defined as hemoglobin A1C level of 7.5% to 10.0% (both inclusive)
		• Patients on stable daily doses for at least 90 days prior to the trial start of basal insulin (total daily basal insulin dose within the range of 20 U to 40 U [individual fluctuations of ± 10% within the 90 days prior to screening were acceptable]) in combination with:
		  ○ MET (≥ 1,500 mg or max. tolerated dose) or
		  ○ MET (≥ 1,500 mg or max. tolerated dose) and SU (≥ half of the max. approved dose according to local label) or
		  ○ MET (≥ 1,500 mg or max. tolerated dose) and glinides (≥ half of the max. approved dose according to local label)
		• BMI ≥ 27 kg/m^2

	Exclusion Criteria	• Treatment with GLP-1 RAs, DPP-4 inhibitors and/or thiazolidinediones within 90 days prior to screening • Use of any drug (except for basal insulin, MET, SU, and glinides) that, in the investigator's opinion, could interfere with glucose level (e.g., systemic corticosteroids) • Females of child-bearing potential who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive methods • Impaired liver function • Impaired renal function defined as serum creatinine ≥ 133 µmol/L for males and ≥ 125 µmol/L for females, or as allowed according to local contraindications for MET • Screening calcitonin ≥ 50 ng/L • Patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 • Cardiac disorder defined as congestive heart failure (NYHA class III or class IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 52 weeks prior to trial start and/or planned coronary, carotid, or peripheral artery revascularization procedures • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg) • Proliferative retinopathy requiring acute treatment or maculopathy (macular edema), according to the investigator's opinion • Patients with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for T2DM), neurological, genitourinary, or hematological system (except for conditions associated with T2DM) that, in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering trial drug • History of chronic pancreatitis or idiopathic acute pancreatitis
Drugs	**Intervention**	IDegLira q.d. starting dose of 16 U (16 U IDeg and 0.6 mg liraglutide) titrated twice weekly (based on the mean of 3 preceding daily fasting SMPG values on 3 consecutive days), which was based on FPG levels. The maximum allowed dose was 50 U (50 U IDeg/1.8 mg liraglutide). Pretrial treatment with basal insulin and SU or glinides (if applicable) was discontinued at visit 2. Throughout the trial, MET treatment was maintained at the stable pre-randomization dose and frequency.
	Comparator(s)	16 U for IDeg q.d. titrated twice weekly according to the predefined titration algorithm, which was based on FPG levels.

		DUAL II
		Pretrial treatment with basal insulin and SU or glinides (if applicable) was discontinued at visit 2. Throughout the trial, MET treatment was maintained at the stable pre-randomization dose and frequency.
Duration	**Phase**	
	Screening period	2 weeks
	Double blind	26 weeks
	Open label	NA
	Follow-up	1 week
Outcomes	**Primary End Point**	Change in hemoglobin A1C from baseline after 26 weeks of treatment

	Other End Points	• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without weight gain
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without hypoglycemic episodes
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without hypoglycemic episodes and weight gain
		• Change from baseline after 26 weeks of treatment in:
		  ○ body weight
		  ○ FPG
		  ○ systolic blood pressure and diastolic blood pressure
		  ○ lipid parameters
		• Safety

Notes	**Publications**	Buse et al.[36]

BMI = body mass index; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; max. = maximum; MET = metformin; NA = not applicable; NYHA = New York Heart Association; q.d. = once daily; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; SU = sulfonylurea; T2DM = type 2 diabetes mellitus.

Note: Four additional reports were included — a CADTH Common Drug Review submission,[37] a Health Canada reviewer's report,[38] and the FDA medical and statistical reviews.[39,40]

Source: Buse et al.,[36] Vilsboll et al.,[41] Vilsboll et al.,[42] Clinical Study Report of DUAL II.[11]

Table 6: Details of DUAL V and DUAL VII Studies

		DUAL V	DUAL VII
Designs and Populations	**Study Design**	Phase III, parallel-group, open-label RCT	Phase III, parallel-group, open-label RCT
	Locations	Argentina, Australia, Greece, Hungary, Mexico, Russia, Slovakia, South Africa, Spain, and the US	Argentina, Czech Republic, France, Greece, Hungary, Israel, Mexico, Russia, Slovakia, Spain, Turkey, and the US
	Randomized (N)	557	506
	Inclusion Criteria	• Adults with T2DM • Inadequately controlled T2DM defined as hemoglobin A1C level of 7.0% to 10.0% (both inclusive) • Current treatment with IGlar for at least 90 days prior to screening • Stable daily dose of IGlar between 20 U and 50 U (both inclusive) for at least 56 days prior to screening. Total daily dose should be within the range of 20 U to 50 U, both inclusive, on the day of screening, but individual fluctuations of ± 10% within the 56 days prior to screening were acceptable. • Stable daily dose of MET (≥ 1,500 mg or max. tolerated dose) for at least 90 days prior to screening • BMI ≤ 40 kg/m^2	• Adults with T2DM (diagnosed clinically) ≥ 6 months prior to screening • Inadequately controlled T2DM defined as hemoglobin A1C level of 7.0% to 10.0% (both inclusive) • Current treatment with IGlar for at least 90 days prior to screening • Stable daily dose of IGlar between 20 U and 50 U (both inclusive) for at least 56 days prior to screening. Individual fluctuations of ± 10% within the 56 days prior to screening are acceptable; however, on the day of screening, total daily dose should be within the range of 20 U to 50 U, both inclusive • Stable daily dose of MET (≥ 1,500 mg or max. tolerated dose) for at least 90 days prior to screening • BMI ≤ 40 kg/m^2
	Exclusion Criteria	• Any use of oral AHAs (except for MET) within 90 days prior to visit 1 (screening) • Current use of any drug (except MET and IGlar) or anticipated change in concomitant medication that, in the investigator's opinion, could interfere with the glucose metabolism (e.g., systemic corticosteroids) • Previous and/or current treatment with any insulin regimen other than basal insulin, e.g., prandial or pre-mixed insulin (short-term treatment due to intercurrent illness, including gestational diabetes, is allowed at the discretion of the investigator) • Previous and/or current treatment with GLP-1 RAs (e.g., exenatide, liraglutide) • Suffer from a life-threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer) • History of chronic pancreatitis or idiopathic acute pancreatitis • Impaired renal function defined as serum creatinine ≥ 133 µmol/L for males and ≥ 125 µmol/L for females, or as allowed, according to local contraindications for MET • Cardiac disorder defined as congestive heart failure (NYHA class III or class IV), diagnosis of unstable angina pectoris, cerebral stroke,	• Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening • History of pancreatitis (acute or chronic) • Renal impairment eGFR < 60 mL/minute/1.73 m^2 as per CKD-EPI • Patients presently classified as being in NYHA class IV • Within the past 180 days, any of the following: MI, stroke, or hospitalization for unstable angina and/or TIA • Currently planned coronary, carotid, or peripheral artery revascularization • Inadequately treated blood pressure (systolic ≥ 160 mm Hg or diastolic ≥ 100 mm Hg) • Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps, and in-situ carcinomas)

		DUAL V	DUAL VII
		and/or MI within the last 26 weeks prior to trial start and/or planned coronary, carotid, or peripheral artery revascularization procedures • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg) • Patients with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for T2DM), neurological, genitourinary, or hematological system (except for conditions associated with T2DM) that, in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering the trial drug	
		• Females of child-bearing potential who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive methods • Impaired liver function • Screening calcitonin ≥ 50 ng/L • Patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 • Proliferative retinopathy requiring acute treatment or maculopathy (macular edema) according to the investigator's opinion	
DRUGS	**Intervention**	IDegLira q.d. starting dose of 16 U (16 U IDeg and 0.6 mg liraglutide) titrated twice weekly (based on the mean of 3 preceding daily fasting SMPG values on 3 consecutive days), which was based on FPG levels. The maximum allowed dose was 50 U (50 U IDeg/1.8 mg liraglutide). All patients continued pretrial doses of MET.	IDegLira q.d. with a starting dose of 16 U (16 U IDeg and 0.6 mg liraglutide), and titrated twice weekly according to a predefined titration algorithm with a maximum daily dose of 50 U (50 U IDeg/1.8 mg liraglutide). In combination with MET in pretrial doses
	Comparator(s)	IGlar was given at a starting dose equal to the pretrial daily dose of IGlar (dose-to-dose switch) and was titrated according to a predefined titration algorithm with no maximum dose. All patients continued pretrial doses of MET.	IGlar q.d. (with a starting dose equal to the pretrial daily dose and titrated twice weekly in accordance with a predefined titration algorithm) plus prandial IAsp (with a starting dose of 4 U and titrated twice weekly in a treat-to-target fashion in accordance with a predefined titration algorithm). There was no maximum dose specified for IGlar or IAsp. In combination with MET in pretrial doses
DURATION	**Phase**		
	Screening period	2 weeks	2 weeks
	Double blind	NA	NA
	Open label	26 weeks	26 weeks
	Follow-up	1 week	4 weeks
OUTCOMES	**Primary End Point**	Change from baseline in hemoglobin A1C after 26 weeks of treatment (noninferiority of IDegLira vs. IGlar was considered as confirmed, if the 95% CI for the mean	Change from baseline in hemoglobin A1C after 26 weeks of treatment (noninferiority of IDegLira vs. IGlar plus prandial IAsp was considered as

		DUAL V	DUAL VII
		treatment difference was entirely < 0.30 %)	confirmed, if the 95% CI for the mean treatment difference was entirely < 0.30%)

	Other End Points	• Number of treatment-emergent confirmed hypoglycemic episodes during 26 weeks of treatment
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without weight gain
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without hypoglycemic episodes
		• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26 without hypoglycemic episodes and weight gain
		• Change from baseline after 26 weeks of treatment in:
		  ○ body weight
		  ○ FPG
		  ○ systolic blood pressure and diastolic blood pressure
		  ○ lipid parameters
		  ○ TRIM-D
		  ○ SF-36v2
		• Safety	

NOTES	**Publications**	Lingvay et al.[43]	Billings et al.[44]

AHA = antihyperglycemic agent; BMI = body mass index; CI = confidence interval; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; eGFR = estimated glomerular filtration rate; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; MET = metformin; MI = myocardial infarction; NA = not applicable; NYHA = New York Heart Association; q.d. = once daily; RCT = randomized controlled trial; SF-36v2 = Short Form (36) Health Survey version 2; SMPG = self-monitored plasma glucose; T2DM = type 2 diabetes mellitus; TIA = transient ischemic attack; TRIM-D = treatment-related impact measure for diabetes; vs. = versus.

Note: Four additional reports were included — CADTH Common Drug Review submission,[37] Health Canada reviewer's report,[38] and the FDA medical and statistical reviews.[39,40]

Source: Lingvay et al.,[43] Billings et al.,[44] Vilsboll et al.,[42] Lingvay et al.,[45] and clinical study reports of DUAL V and DUAL VII.[13,14]

Table 7: Details of DUAL III Study

		DUAL III
DESIGNS AND POPULATIONS	**Study Design**	Phase III, parallel-group, open-label RCT
	Locations	Australia, France, Hungary, Slovakia, and the US
	Randomized (N)	438
	Inclusion Criteria	• Adults with T2DM • Inadequately controlled T2DM defined as hemoglobin A1C level of 7.0% to 9.0% (both inclusive) • Treatment with daily GLP-1 RA at max. dose according to local label (i.e., 1.8 mg q.d. liraglutide or 10 mcg b.i.d. exenatide) or documented max. tolerated dose (i.e., 1.2 mg q.d. liraglutide or 5 mcg b.i.d. exenatide) in combination with a stable daily dose of MET (≥ 1,500 mg or documented max. tolerated dose) ± stable daily dose of pioglitazone (≥ 30 mg) ± stable daily dose of SU (≥ half of the max. approved dose according to local label) ≥ 90 days prior to screening visit • BMI ≤ 40 kg/m^2
	Exclusion Criteria	• Any use of oral AHAs (except for MET, pioglitazone, and SU) ≤ 90 days prior to screening visit (visit 1) • Use of any drug (except MET, pioglitazone, SU, and GLP-1 RA) that, in the investigator's opinion, could interfere with the blood glucose level (e.g., systemic corticosteroids) • Treatment with any insulin regimen (short-term treatment due to intercurrent illness, including gestational diabetes, is allowed at the discretion of the investigator)

		DUAL III
		• Suffer from a life-threatening disease, including malignant neoplasms and medical history of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer) • Females of child-bearing potential who are pregnant, breastfeeding, or intend to become pregnant or are not using adequate contraceptive methods • Impaired liver function • Impaired renal function defined as serum creatinine ≥ 133 µmol/L for males and ≥ 125 µmol/L for females, or as allowed according to local contraindications for MET • Screening calcitonin ≥ 50 ng/L • Patients with personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 • Cardiac disorder defined as congestive heart failure (NYHA class III or class IV), diagnosis of unstable angina pectoris, cerebral stroke and/or myocardial infarction within the last 52 weeks prior to trial start and/or planned coronary, carotid, or peripheral artery revascularization procedures • Severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg) • Proliferative retinopathy requiring acute treatment or maculopathy (macular edema) according to the investigator's opinion • Patients with a clinically significant, active (during the past 12 months) disease of the gastrointestinal, pulmonary, endocrinological (except for T2DM), neurological, genitourinary, or hematological system (except for conditions associated with T2DM) that, in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering the trial drug • History of chronic pancreatitis or idiopathic acute pancreatitis
Drugs	**Intervention**	IDegLira q.d. starting dose of 16 U (16 U IDeg and 0.6 mg liraglutide) titrated twice weekly (based on the mean of 3 preceding daily fasting SMPG values on 3 consecutive days) that was based on FPG levels. The maximum allowed dose was 50 U (50 U IDeg/1.8 mg liraglutide). Patients were to continue MET, pioglitazone, and SU in stable pretrial doses (unless there was a safety concern).
	Comparator(s)	Patients randomized to continue their pretrial GLP-1 RA treatment were instructed to keep the dose and treatment schedule unchanged throughout the trial period. Patients were to continue MET, pioglitazone, and SU in stable pretrial doses (unless there was a safety concern).
Duration	**Phase**	
	Screening period	2 weeks
	Double blind	NA
	Open label	26 weeks
	Follow-up	1 week
Outcomes	**Primary End Point**	Change in hemoglobin A1C from baseline after 26 weeks of treatment

	Other End Points	• Percentage of patients reaching hemoglobin A1C ≤ 6.5% and hemoglobin A1C < 7.0% at week 26
		• Change from baseline after 26 weeks of treatment in:
		  ○ body weight
		  ○ FPG
		  ○ systolic blood pressure and diastolic blood pressure
		  ○ lipid parameters
		  ○ TRIM-D
		  ○ DTSQs
		• Safety

		DUAL III
Notes	**Publications**	Lingjawi et al.[46]

AHA = antihyperglycemic agent; b.i.d. = twice daily; BMI = body mass index; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; max. = maximum; MET = metformin; NA =a not applicable; NYHA = New York Heart Association; q.d. = once daily; RCT = randomized controlled trial; SMPG = self-monitored plasma glucose; SU = sulfonylurea; T2DM = type 2 diabetes mellitus; TRIM-D = treatment-related impact measure for diabetes.

Note: Four additional reports were included — CADTH Common Drug Review submission,[37] Health Canada reviewer's report,[38] and the FDA medical and statistical reviews.[39,40]

Source: Lingjawi et al.,[46] Clinical Study Report of DUAL III.[12]

Included Studies

Description of Studies

Four phase III randomized controlled trials (RCTs) met the inclusion criteria (DUAL II, DUAL V, DUAL VII, and DUAL III).

The DUAL II trial (N = 413) was a randomized, double-blind, treat-to-target trial in patients with T2DM inadequately controlled with basal insulin (between 20 U and 40 U daily) and MET, with or without SU or glinides, comparing the efficacy and safety of IDegLira once daily with IDeg once daily, both added on to MET. Eligible patients were randomized in a 1:1 ratio to receive either once daily IDegLira or once daily IDeg, both in combination with MET. Pretrial treatment with basal insulin and SU or glinides (if applicable) was to be discontinued at visit 2 (week 0). Throughout the trial, MET treatment was maintained at the stable, pre-randomization dose and frequency, with dose adjustments for safety reasons allowed. The starting doses were 16 U for IDegLira and 16 U for IDeg, and were titrated twice weekly according to the predefined titration algorithm, which was based on FPG levels.

The DUAL V trial (N = 557) was a randomized, open-label, treat-to-target trial in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET. The DUAL V trial was a noninferiority (NI) trial that compared the efficacy and safety of IDegLira once daily with IGlar once daily, both in combination with MET. The NI of IDegLira versus IGlar was assessed on glycemic control using a NI margin of 0.30%. Eligible patients were randomized in a 1:1 ratio to receive either IDegLira or IGlar, both administered once daily subcutaneously. IGlar was given at a starting dose equal to the pretrial daily dose of IGlar (dose-to-dose switch) and was titrated according to a predefined titration algorithm with no maximum dose. All patients continued pretrial doses of MET.

The DUAL VII trial (N = 506) was a randomized, open-label, treat-to-target trial in patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET. The DUAL VII trial was a NI trial that compared the efficacy and safety of IDegLira once daily with basal-bolus therapy (once-daily IGlar plus prandial insulin aspart [IAsp]), both groups in combination with MET. The NI of IDegLira versus IGlar plus prandial IAsp was assessed on glycemic control, and the NI margin used was 0.30%. Eligible patients were randomized in a 1:1 ratio to receive either IDegLira or IGlar plus prandial IAsp. Patients received once-daily IDegLira or once-daily IGlar plus prandial IAsp before each main meal, both groups in combination with MET in pretrial

doses. The starting dose of IGlar was equal to the pretrial daily dose. Patients discontinued the pretrial IGlar treatment and started Novo Nordisk-provided IGlar that was titrated according to a predefined titration algorithm. IAsp was added to the IGlar therapy with a starting dose of 4 U and was titrated in a treat-to-target fashion in accordance with a predefined titration algorithm. There was no maximum dose specified for IGlar or IAsp.

The DUAL III trial (N = 438) was a randomized, open-label, treat-to-target trial in insulin-naive patients with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to the local label of GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]) and MET ± pioglitazone ± SU. The DUAL III trial was a superiority trial that compared IDegLira versus unchanged GLP-1 RA therapy in controlling glycemia. Eligible patients were randomized in a 2:1 ratio to receive either IDegLira once daily or to continue their unchanged pretrial GLP-1 RA medication in stable pretrial doses. Both treatment groups continued pretrial doses of MET ± pioglitazone ± SU.

In all the trials, the starting dose of IDegLira was 16 U (16 U IDeg/0.6 mg liraglutide) and was titrated according to a predefined titration algorithm with a maximum dose of 50 U (50 U IDeg/1.8 mg liraglutide).

In all the trials, randomization was conducted using an interactive voice Web response system. In DUAL II, the randomization was stratified by current background treatment (basal insulin and MET, or basal insulin and MET with SU or glinides). There was no stratification for randomization in DUAL V and DUAL VII. In DUAL III, the randomization was stratified according to the prior type of GLP-1 RA (i.e., Victoza or Byetta).

All the trials had a two-week screening period. Patients on stable doses of background therapies who met the inclusion criteria were randomly assigned to treatment with IDegLira or the comparators. The treatment duration was 26 weeks. In DUAL II, DUAL V, and DUAL III, patients had a one-week follow-up period after the last dose of the study drug, while DUAL VII patients had a four-week follow-up period after the last dose. In all of the included trials, patients attended the follow-up visit for safety-related assessments.

Populations

Inclusion and Exclusion Criteria

Patients enrolled in the trials were adults (≥ 18 years of age) with T2DM. The required hemoglobin A1C levels at baseline ranged from 7.5% to 10% in the DUAL II trial, 7% to 10% in the DUAL V and DUAL VII trials, and 7% to 9% in the DUAL III trial. The body mass index (BMI) of the enrolled patients had to be ≤ 40 kg/m^2 in the DUAL V, DUAL VII, and DUAL III trials, and ≥ 27 kg/m^2 in the DUAL II trial.

Patients enrolled in the DUAL II trial had to be on stable daily doses for at least 90 days prior to screening of basal insulin (e.g., IGlar, insulin detemir, neutral protamine Hagedorn insulin) in combination with MET (≥ 1,500 mg or maximum tolerated dose), MET (≥ 1,500 mg or maximum tolerated dose) and SU (≥ half of the maximum approved dose according to the local label), or MET (≥ 1,500 mg or maximum tolerated dose) and glinides (≥ half of the maximum approved dose according to the local label).

Patients enrolled in the DUAL V and DUAL VII trials had to be on stable daily doses of IGlar between 20 U and 50 U (both inclusive) for at least 56 days prior to screening, with current treatment with IGlar for at least 90 days prior to screening, and stable daily doses of MET (≥ 1,500 mg or maximum tolerated dose) for at least 90 days prior to screening.

Patients enrolled in DUAL III had to be on treatment with daily GLP-1 RA at maximum dose according to the local label (i.e., 1.8 mg once daily Victoza or 10 mcg twice daily Byetta) or documented maximum tolerated dose (i.e., 1.2 mg once daily Victoza or 5 mcg twice daily Byetta) in combination with a stable daily dose of MET (≥ 1,500 mg or documented maximum tolerated dose) ± stable daily dose of pioglitazone (≥ 30 mg) ± stable daily dose of SU (≥ half of the maximum approved dose according to the local label) ≥ 90 days prior to screening visit (visit 1).

Exclusion criteria were similar across trials in excluding patients with a history of acute or chronic pancreatitis, impaired liver function, screening calcitonin ≥ 50 ng/L, patients with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2, and proliferative retinopathy requiring acute treatment or maculopathy (macular edema), according to the investigator's opinion.

In addition, the DUAL II trial excluded patients who used any drug (except for basal insulin, MET, SU, and glinides) that, in the investigator's opinion, could interfere with their glucose level (e.g., systemic corticosteroids) or received treatment with GLP-1 RAs (e.g., exenatide, liraglutide), DPP-4 inhibitors, and/or TZDs within 90 days prior to screening.

The DUAL V trial also excluded patients with any use of oral AHAs (except for MET) within 90 days prior to visit 1 (screening), current use of any drug (except MET and IGlar) or anticipated change in concomitant medication that, in the investigator's opinion, could interfere with the glucose metabolism (e.g., systemic corticosteroids), or previous and/or current treatment with any insulin regimen other than basal insulin, e.g., prandial or pre-mixed insulin (short-term treatment due to intercurrent illness, including gestational diabetes, was allowed at the discretion of the investigator), or previous and/or current treatment with GLP-1 RAs (e.g., exenatide, liraglutide).

The DUAL VII trial also excluded patients receiving treatment with any medication for the indication of diabetes or obesity other than that stated in the inclusion criteria in a period of 90 days before screening, or anticipated initiation or change in concomitant medications in excess of 14 days known to affect weight or glucose metabolism (e.g., sibutramine, orlistat, thyroid hormones, corticosteroids).

The DUAL III trial also excluded patients with any use of oral AHAs (except for MET, pioglitazone, and SU) ≤ 90 days prior to screening visit (visit 1), use of any drug (except MET, pioglitazone, SU, and GLP-1 RA) that, in the investigator's opinion, could interfere with the BG level (e.g., systemic corticosteroids), treatment with any insulin regimen (short-term treatment due to intercurrent illness, including gestational diabetes, was allowed at the discretion of the investigator).

The DUAL II, DUAL V, and DUAL III trials also excluded patients with impaired renal function defined as serum creatinine ≥ 133 µmol/L for males and ≥ 125 µmol/L for females, or as allowed according to local contraindications for MET, patients with severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg), and patients with a clinically significant, active (during the past 12 months) disease of the gastrointestinal (GI), pulmonary, endocrinological (except for T2DM), neurological, genitourinary, or hematological system (except for conditions associated with T2DM) that, in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering the trial drug. The DUAL II and DUAL III trials also excluded patients with CV disorder, defined as congestive heart failure (New York Heart Association [NYHA] class III or class IV), diagnosis of

unstable angina pectoris, cerebral stroke, and/or myocardial infarction (MI) within the last 52 weeks prior to trial start and/or planned coronary, carotid, or peripheral artery revascularization procedures. DUAL V also excluded patients with CV disorders defined as congestive heart failure (NYHA class III or class IV), diagnosis of unstable angina pectoris, cerebral stroke, and/or MI within the past 26 weeks prior to visit 1 and/or planned coronary, carotid, or peripheral artery revascularization procedures. DUAL VII also excluded patients presently classified as being in NYHA class IV; patients within the past 180 days having MI, stroke, or hospitalization for unstable angina and/or transient ischemic attack; patients with currently planned coronary, carotid, or peripheral artery revascularization; patients with inadequately treated blood pressure defined as Class II hypertension or higher (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg); and patients with renal impairment estimated glomerular filtration rate < 60 mL/minute/1.73 m^2 as per the Chronic Kidney Disease Epidemiology Collaboration.

Baseline Characteristics

The proportion of patients who were male ranged from 43.7% to 56.3% per treatment group and the mean age per treatment group was 56.8 to 59.1 years (see Table 8 and Table 9). The patients enrolled were predominantly white (76% to 95%) with a mean BMI per group ranging from 31.7 kg/m^2 to 33.8 kg/m^2, and average body weight ranging from 87.2 kg to 95.6 kg. The baseline hemoglobin A1C in the DUAL II, DUAL V, and DUAL VIII trials ranged from 8.2% to 8.8%, while in DUAL III, it ranged from 7.7% to 7.8%. The mean duration of diabetes in all trials ranged from 10.3 years to 13.3 years. Baseline characteristics were generally similar between groups within trials, although some differences in the FPG (9.0 mmol/L in the IDegLira group and 9.4 mmol/L in the GLP-1 RA group) and the occurrence of nephropathy and macroangiopathy in the DUAL III trial were noted.

In the DUAL II trial, the proportion of patients receiving oral AHA treatment was equally distributed between patients receiving MET (48.5%) and patients receiving MET + SU (49.5%). Only a minor proportion of patients received MET + glinides (1.5%) or MET with SU or glinides (0.5%). Basal doses at screening were equally distributed between treatments groups, with a mean daily dose that ranged from 28.1 U to 32.5 U for the IDegLira group and from 28.1 U to 31.3 U for the IDeg group.

In the DUAL V trial, the mean daily dose of IGlar at screening was similar for the IDegLira group (31 U) and the IGlar group (32 U). The daily dose of MET ranged from 500 mg to 3,000 mg and the mean daily dose of MET was 2,014 mg in the IDegLira group and 2,031 mg in the IGlar group. In the DUAL VII trial, the mean dose was 34 U in the IDegLira group and 33 U in the IGlar + IAsp group. The daily dose of MET ranged from 500 mg to 3,400 mg and the mean daily dose of MET was 2,049 mg in the IDegLira group and 2,091 mg in the IGlar + IAsp group.

In DUAL III, patients were stratified with respect to their prior type of GLP-1 RA (79.5% liraglutide and 20.5% exenatide in each treatment group). The mean daily dose of liraglutide at screening was 1.7 mg in both treatment groups and the mean daily dose of exenatide at screening was 18.5 mcg in both treatment groups. The required minimum dosage of liraglutide (1.2 mg/day) and exenatide (10 mcg/day) was met for all patients. The proportion of patients receiving MET was 74.2%, MET + SU was 21.2%, MET + pioglitazone was 2.5%, and MET + SU + pioglitazone was 2.1%. These proportions were equally distributed between treatment groups. Accordingly, 25.7% of all patients were treated with SU in combination with MET with or without pioglitazone.

Table 8: Summary of Baseline Characteristics in DUAL II, DUAL V, and DUAL VII Trials

Baseline Characteristics	DUAL II		DUAL V		DUAL VII	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
Sex, n (%)						
Female	87 (43.7)	93 (46.7)	135 (48.6)	142 (50.9)	142 (56.3)	137 (53.9)
Male	112 (56.3)	106 (53.3)	143 (51.4)	137 (49.1)	110 (43.7)	117 (46.1)
Age (Years)						
Mean (SD)	56.8 (8.9)	57.5 (10.5)	58.4 (9.8)	59.1 (9.3)	58.6 (9.0)	58.0 (8.6)
Median (range)	56.2 (31.4 to 76.9)	58.2 (29.5 to 85.8)	59.6 (29.2 to 81.7)	59.6 (27.6 to 80.4)	59 (31 to 78)	58 (36 to 86)
Body Weight (kg)						
Mean (SD)	95.4 (19.4)	93.5 (20.0)	88.3 (17.5)	87.3 (15.8)	87.2 (16.0)	88.2 (17.2)
Median (range)	93.5 (57.5 to 171.5)	90.3 (58.9 to 191.9)	88 (46.9 to 140.2)	86 (49.9 to 133.3)	86 (47.5 to 144.2)	87.1 (45.4 to 146.6)
BMI (kg/m^2)						
Mean (SD)	33.6 (5.7)	33.8 (5.6)	31.7 (4.4)	31.7 (4.5)	31.7 (4.4)	31.7 (4.5)
Median (range)	32.3 (26.5 to 56.5)	32.8 (25.8 to 54.7)	31.8 (21.7 to 40.0)	31.6 (18.9 to 40.6)	31.6 (20.9 to 40)	31.5 (18.9 to 40)
Duration of Diabetes (Years)						
Mean (SD)	10.30 (6.01)	10.91 (7.04)	11.64 (7.44)	11.33 (6.59)	13.2 (7.0)	13.3 (6.8)
Median (range)	8.7 (0.79 to 30.42)	9.5 (0.76 to 40.42)	10.4 (0.29 to 47.60)	10.3 (0.43 to 44.64)	12 (1.0 to 31.7)	12.8 (0.9 to 36.1)
Hemoglobin A1C (%)						
Mean (SD)	8.7 (0.7)	8.8 (0.7)	8.4 (0.9)	8.2 (0.9)	8.21 (0.76)	8.24 (0.81)
Median (range)	8.6 (7.2 to 12.3)	8.9 (7.3 to 10.9)	8.3 (6.4 to 11.6)	8.2 (5.9 to 10.8)	8.1 (6.6 to 10.30)	8.3 (6.7 to 10.30)
FPG (mmol/L)						
N	198	199	275	278	251	254
Mean (SD)	9.7 (2.9)	9.6 (3.1)	8.9 (2.6)	8.9 (2.9)	8.52 (2.65)	8.28 (2.53)
Median (range)	9.5 (3.0 to 19.1)	9.3 (4.2 to 29.9)	8.4 (3.6 to 20.4)	8.6 (3.2 to 18.7)	8.2 (2.7 to 19.00)	8 (3.7 to 16.40)
Race, n (%)						
White	157 (78.9)	151 (75.9)	262 (94.2)	265 (95.0)	236 (93.7)	235 (92.5)
Black or African-American	9 (4.5)	10 (5.0)	6 (2.2)	5 (1.8)	8 (3.2)	6 (2.4)
Asian Indian	31 (15.6)	34 (17.1)	9 (3.2)	9 (3.2)	1 (0.4)	3 (1.2)
Asian non-Indian	2 (1.0)	2 (1.0)				
Native Hawaiian or other Pacific Islander	(0.0)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	(0.0)	1 (0.5)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Missing	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.8)	9 (3.5)
Diabetes Complications at Screening, n (%)						

Baseline Characteristics	DUAL II		DUAL V		DUAL VII	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
Diabetic nephropathy, yes	9 (4.5)	12 (6.0)	32 (11.5)	24 (8.6)	37 (14.7)	29 (11.4)
Diabetic neuropathy, yes	89 (44.7)	85 (42.7)	86 (30.9)	74 (26.5)	86 (34.1)	79 (31.1)
Diabetic retinopathy, yes	31 (15.6)	33 (16.6)	79 (28.4)	56 (20.1)	74 (29.4)	75 (29.5)
Macroangiopathy, yes	15 (7.5)	11 (5.5)	36 (12.9)	37 (13.3)	34 (13.5)	32 (12.6)
Oral Antidiabetes Treatment at Screening, n (%)						
MET	95 (47.7)	98 (49.2)	278 (100)	279 (100)	252 (100)	254 (100)
MET + glinides	4 (2.0)	2 (1.0)	NA	NA	NA	NA
MET + SU	99 (49.7)	98 (49.2)	NA	NA	NA	NA
MET with SU or glinides	1 (0.5)	1 (0.5)	NA	NA	NA	NA
Daily Oral Antidiabetes Treatment Dose (mg) at Screening						
MET						
Mean (SD)	NR	NR	2,014 (426)	2,031 (421)	2,048.81 (456.01)	2,091.14 (458.29)
Median (range)	NR	NR	2,000 (500 to 3,000)	2,000 (750 to 3,000)	2,000 (500 to 3,400)	2,000 (750 to 3,000)
Basal Insulin Dose (U) at Screening						
Insulin detemir						
N	32	35	NA	NA	NA	NA
Mean (SD)	32.5 (7.2)	31.3 (7.2)	NA	NA	NA	NA
Median (range)	34.0 (20 to 40)	30 (20 to 42)	NA	NA	NA	NA
IGlar						
N	85	89	278 (100)	278 (99.6)	252 (100)	254 (100)
Mean (SD)	28.6 (8.1)	29.2 (7.7)	31 (10)	32 (10)	33.83 (10.71)	32.98 (10.36)
Median (range)	30 (5 to 44)	30 (20 to 43)	28 (20 to 50)	30 (20 to 50)	32 (20 to 50)	30 (20 to 50)
Other basal insulin						
N	79	73	NA	NA	NA	NA
Mean (SD)	28.1 (7.2)	28.1 (7.8)	NA	NA	NA	NA
Median (range)	28 (20 to 44)	28 (20 to 40)	NA	NA	NA	NA

BMI = body mass index; FPG = fasting plasma glucose; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; MET = metformin; NA = not applicable; NR = not reported; SD = standard deviation; SU = sulfonylurea.

Source: Clinical study reports of DUAL II, DUAL V, and DUAL VII.[11,13,14]

Table 9: Summary of Baseline Characteristics in DUAL III Trial

Baseline Characteristics	DUAL III	
	IDegLira (N = 292)	GLP-1 RA (N = 146)
Sex, n (%)		
Female	139 (47.6)	75 (51.4)
Male	153 (52.4)	71 (48.6)
Age (Years)		
Mean (SD)	58.3 (9.9)	58.4 (8.8)

Baseline Characteristics	DUAL III	
	IDegLira (N = 292)	GLP-1 RA (N = 146)
Median (range)	59.8 (22.0 to 7.9)	58.8 (37.8 to 78.3)
Body Weight (kg)		
Mean (SD)	95.6 (16.6)	95.5 (17.3)
Median (range)	95.5 (57.0 to 141.1)	93.9 (57.0 to 146.1)
BMI (kg/m^2)		
Mean (SD)	32.9 (4.4)	33.0 (4.1)
Median (range)	32.8 (21.6 to 40.6)	33.6 (22.8 to 40.7)
Duration of Diabetes (Years)		
Mean (SD)	10.36 (5.79)	10.39 (5.81)
Median (range)	9.6 (NR to 31.34)	9.2 (NR to 31.89)
Hemoglobin A1C (%)		
Mean (SD)	7.8 (0.6)	7.7 (0.6)
Median (range)	7.7 (6.7 to 9.2)	7.6 (6.6 to 9.7)
FPG (mmol/L)		
N	285	145
Mean (SD)	9.0 (2.1)	9.4 (2.3)
Median (range)	8.7 (2.8 to 15.9)	8.8 (4.8 to 18.5)
Race, n (%)		
White	269 (92.1)	131 (89.7)
Black or African-American	15 (5.1)	12 (8.2)
Asian	6 (2.1)	2 (1.4)
American Indian or Alaska Native	1 (0.3)	0 (0.0)
Other	1 (0.3)	1 (0.7)
Diabetes Complications at Screening, n (%)		
Diabetic nephropathy, yes	27 (9.2)	6 (4.1)
Diabetic neuropathy, yes	74 (25.3)	33 (22.6)
Diabetic retinopathy, yes	29 (9.9)	14 (9.6)
Macroangiopathy, yes	26 (8.9)	6 (4.1)
Oral Antidiabetes Treatment at Screening, n (%)		
MET	217 (74.3)	108 (74.0)
MET + SU	61 (20.9)	32 (21.9)
MET + TZD	7 (2.4)	4 (2.7)
MET + SU + TZD	7 (2.4)	2 (1.4)
Daily Oral Antidiabetes Treatment Dose (mg) at Screening		
MET		
Mean (SD)	1,973.6 (468.6)	1,944.5 (476.3)
Median (range)	2,000 (500 to 4,000)	2,000 (500 to 3,000)
Daily GLP-1 RA Treatment Dose at Screening		
Exenatide (mcg)		
N (%)	60 (20.5)	30 (20.5)
Mean (SD)	18.4 (3.9)	18.7 (3.5)
Median (range)	20.0 (NR to 20.0)	20.0 (10.0 to 20.0)
Liraglutide (mg)		
N (%)	232 (79.5)	116 (79.5)

Baseline Characteristics	DUAL III	
	IDegLira (N = 292)	GLP-1 RA (N = 146)
Mean (SD)	1.7 (0.2)	1.7 (0.2)
Median (range)	1.8 (NR to 1.8)	1.8 (1.2 to 1.8)

BMI = body mass index; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; MET = metformin; NR = not reported; SD = standard deviation; SU = sulfonylurea; TZD = thiazolidinediones.

Source: Clinical Study Report of DUAL III.[12]

Interventions

The DUAL II trial was a double-blind trial (i.e., the treatment was blinded for the investigator and the patient). In order to maintain blinding, IDegLira and IDeg were visually identical. The DUAL V, DUAL VII, and DUAL III trials were open label, and both patients and investigators were aware of the actual treatment.

In all the trials, IDegLira was supplied in a 3 mL pre-filled pen injector with a fixed IDeg/liraglutide ratio of 100 U/3.6 mg per mL solution. IDegLira was to be injected subcutaneously in the thigh, upper arm (deltoid region), or abdomen once daily, approximately at the same time every day. The chosen injection area was to remain unchanged throughout the trial, but rotation within the area was recommended. The IDegLira dosing unit was defined as a dose step, where one IDegLira dose step consists of 1 U IDeg and 0.036 mg liraglutide. Treatment with IDegLira was initiated at 16 U containing 16 U IDeg and 0.6 mg liraglutide. Adjustment of the IDegLira dose was to be performed twice weekly based on the mean of three preceding daily fasting self-monitored plasma glucose (SMPG) values on three consecutive days. Adjustments occurred in 2 U, aiming at a fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L (see Table 10). The maximum allowed dose was 50 U (50 U IDeg/1.8 mg liraglutide).

In the DUAL II trial, for patients randomized to receive IDeg, IDeg was available at concentrations of 100 U/mL and was supplied in a 3 mL pre-filled pen injector. IDeg was injected subcutaneously in the thigh, upper arm (deltoid region), or abdomen once daily, preferably at the same time every day. The injection area chosen was to remain unchanged throughout the trial, but rotation within the area was recommended. IDeg treatment was initiated with 16 U and titrated twice weekly to the fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L based on the mean fasting SMPG from three proceeding measurements, as described for IDegLira in the preceding paragraph (see Table 10). The maximum allowed dose was 50 U. For both treatment groups, MET was the background medication for all patients and was therefore treated as a non-investigational medicinal product. It was not supplied by Novo Nordisk. MET was to be purchased or otherwise delivered to patients in accordance with local requirements. The MET dose was to be maintained at the stable, pre-randomized dose and frequency level.

In DUAL V, for patients randomized to receive IGlar, IGlar 100 U/mL solution was supplied in a 3 mL pre-filled pen injector. IGlar was to be injected subcutaneously once daily according to the approved label and using the pretrial dosing time and injection site throughout the trial. Patients randomized for treatment with IGlar discontinued on the pretrial, stable IGlar treatment prior to initiating Novo Nordisk-provided IGlar treatment with a starting dose of IGlar equal to the pretrial daily dose (dose-to-dose switch). No predefined maximum dose was specified for IGlar treatment. Adjustment of the dose of IGlar was to be performed twice weekly based on the mean of three preceding daily fasting SMPG values

on three consecutive days. Adjustments were to occur in increments or decrements of 2 U, aiming at a fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L (Table 10). For both treatment groups, MET was considered a non-investigational medicinal product. All patients were to continue with MET at the stable pretrial dose level unless there was a safety concern.

In DUAL VII, for patients randomized to receive IGlar + IAsp, IGlar was supplied in a 3 mL pre-filled pen injector at 100 U/mL solution. IAsp was also supplied in a 3 mL pre-filled pen injector at 100 U/mL solution. Patients received IGlar once daily. IGlar was added to current MET therapy with a starting dose equal to the pretrial daily dose. Patients discontinued the pretrial IGlar treatment and started Novo Nordisk-provided IGlar that was titrated according to a predefined titration algorithm. IAsp was added to the IGlar therapy with a starting dose of 4 U as a preprandial bolus insulin treatment and was titrated in a treat-to-target fashion in accordance with a predefined titration algorithm. There was no maximum dose specified for IGlar or IAsp. Dose adjustment for IGlar was similar to that of IDegLira (see Table 10). The dose of IAsp was titrated twice weekly on Mondays and Thursdays. Adjustment was based on preprandial and bedtime SMPGs obtained on the three previous days in accordance with fasting SMPG, as described in Table 10. For both treatment groups, MET was considered a non-investigational medicinal product. All patients were to continue with MET at the stable pretrial dose level unless there was a safety concern.

In the DUAL III trial, patients randomized to continue their pretrial GLP-1 RA treatment were instructed to keep the dose and treatment schedule unchanged throughout the trial period. For all patients in both treatment groups, MET, pioglitazone, and SU were considered non-investigational medicinal products. Patients were to continue with these oral AHAs in stable pretrial doses unless there was a safety concern.

In all trials, patients received training on the pre-filled pen injectors used.

The following medications and treatments were not allowed in the DUAL II trial:

- the use of any drug (except for basal insulin and MET) that, in the investigator's opinion, could interfere with the glucose level
- the use of SU or glinides from visit 2 to the end of the trial
- the use of GLP-1 RAs, DPP-4 inhibitors, and/or TZDs within 90 days prior to visit 1
- the use of any investigational product within 30 days prior to visit 1
- the initiation of any systemic treatment with products that, in the investigator's opinion, could interfere with glucose or lipid metabolism.

The following medications and treatments were not allowed in the DUAL V trial:

- any investigational medicinal product received within 30 days prior to visit 1 (screening)
- any use of oral AHAs (except for MET) within 90 days prior to visit 1 (screening)
- the initiation of any systemic treatment with products that, in the investigator's opinion, could interfere with glucose metabolism (e.g., systemic corticosteroids)
- the use of any insulin regimen other than basal insulin, e.g., prandial or pre-mixed insulin
- the use of GLP-1 RAs.

The following medications and treatments were not allowed in the DUAL VII trial:

- any investigational medicinal product received within 30 days before screening
- the initiation or significant change in concomitant medications for more than 14 days that, in the investigator's opinion, could affect weight or glucose metabolism.

The following medications and treatments were not allowed in the DUAL III trial:

- any investigational medicinal product received within 30 days prior to screening visit (visit 1)
- any use of oral AHAs (except for MET, pioglitazone, and SU) for 90 days or less prior to screening visit (visit 1)
- treatment with any insulin regimen (short-term treatment due to intercurrent illness, including gestational diabetes, is allowed at the discretion of the investigator).
- the initiation of any systemic treatment with products that, in the investigator's opinion, could interfere with glucose metabolism (e.g., systemic corticosteroids, beta-blockers and monoamine oxidase inhibitors).

The patient was to be called for an unscheduled visit as soon as possible if the fasting SMPG values taken on three consecutive days — or if any of the FPG samples analyzed exceeded the limit of:

- 15.0 mmol/L from baseline to week 6
- 13.3 mmol/L from week 7 to week 12
- 11.1 mmol/L from week 13 to week 26.

The patient should be called for an unscheduled visit as soon as possible. A confirmatory FPG was to be obtained and analyzed. If this FPG exceeded the limits described previously, and no treatable intercurrent cause for the hyperglycemia was identified, the patient was withdrawn from the trial in DUAL II, DUAL V, and DUAL III, and the patient had the trial product discontinued in DUAL VII.

Table 10: Adjustment (Titration)

Mean Fasting Plasma Glucose	Dose Adjustment			Adjustment of IAsp	
mmol/L	Dose Steps for IDegLira	Dose Steps for IDeg	Dose Steps for IGlar	Dose Adjustment	Rules for Dose Adjustments
< 4.0	− 2 U	− 2 U	− 2 U	− 1 U	≥ 1 SMPGs below target
4.0 to 5.0	0	0	0	NA	
> 5.0	+ 2 U	+ 2 U	+ 2 U	NA	
4.0 to 6.0	NA	NA	NA	0	0 to 1 SMPG above target No SMPGs below target
> 6.0	NA	NA	NA	+ 1 U	≥ 2 SMPGs above target No SMPGs below target

IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; NA= not applicable; SMPG = self-monitored plasma glucose.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Outcomes

Mortality (All-Cause, Cardiovascular Related)

This outcome was assessed in all included trials, and the cases of death required to be confirmed by an external independent event adjudication committee.

Diabetes-Related Morbidity

This outcome was not measured in any of the included trials.

Glycemic Control

The primary end point in all trials was change from baseline in hemoglobin A1C after 26 weeks of treatment. Change from baseline after 26 weeks of treatment in FPG was a secondary efficacy end point in all included trials. Both of these values derived from blood samples that were drawn at screening and at multiple time points over 26 weeks, including week 0, week 4, week 8, week 12, week 16, week 20, and week 26. Other secondary efficacy end points in all included trials were responders for hemoglobin A1C (defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%). In addition, responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain (defined as change from baseline in body weight below or equal to zero) or hypoglycemic episodes (defined as confirmed episodes during the last 12 weeks of treatment) or both were performed as a secondary efficacy end point in DUAL II and DUAL V, and responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain (defined as change from baseline in body weight below or equal to zero) or treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes (defined as treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during the last 12 weeks of treatment) or both were performed as a secondary efficacy end point in DUAL VII.

Health-Related Quality of Life

Patients' health-related quality of life (HRQoL) was evaluated using the treatment-related impact measure for diabetes (TRIM-D), the Short Form (36) Health Survey (SF-36), or the Diabetes Treatment Satisfaction Questionnaire status version (DTSQs).

TRIM-D is a diabetes-specific instrument designed to measure the treatment-related impact of diabetes medications on patients.[47,48] TRIM-D was developed in English by The Brod Group and by Novo Nordisk as a questionnaire appropriate for both patients with T1DM and patients with T2DM.[48] This patient-reported outcome measure was developed to address gaps in the 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 five-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.[48] The highest possible summed score within a subdomain ranges from 20 points (compliance subdomain) to 40 points (psychological health subdomain) and the highest possible total score is 140 points. All domain scores and the total score are transformed to a zero to 100 scale. 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 patients with T1DM and patients with T2DM, but five individual items from the psychological health domain (depressed, worried that the medication is not helping to slow down or prevent complications from my diabetes, worried about my blood sugar control, unhealthy, and angry) did not respond as expected. No minimal clinically important difference (MCID) has been determined for the TRIM-D. TRIM-D was measured in DUAL V, DUAL VII, and DUAL III.

The SF-36 is a generic health assessment questionnaire that has been used in clinical trials to study the impact of chronic disease on 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 three- to six-point, Likert-like scale. All items are scored so that a high

score defines a more favourable health state. In addition, each item is scored on a zero to 100 range so that the lowest and highest possible scores are zero and 100, respectively. Scores represent the percentage of total possible score achieved. Item scores are averaged together to create the eight domain scores. The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS). These are created by aggregating the eight domains according to a scoring algorithm, with scores ranging from zero to 100. Higher scores indicate better health status. The domain and summary scores (PCS and MCS) are standardized t scores to the US population with a mean equal to 50 and standard deviation equal to 10. The SF-36 has shown evidence of measuring effects of diabetic complications,[49,50] but it is also influenced by non-diabetic comorbidity[50,51] and other non-diabetes–specific factors such as age.[50,51] It does not demonstrate evidence of association with surrogate markers of disease severity,[51-54] but does respond to treatment type and changes following diabetes interventions.[49,51] The SF-36 and diabetes-specific instruments likely provide some degree of overlap, but also address different features of a patient's overall HRQoL.[52,55] 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 diabetic patients, but it can provide useful insight when used in combination with the appropriate, complementary diabetes-specific treatment evaluation and HRQoL instruments. In general use of version 2 of the SF-36, the questionnaire's user's manual[56] proposed the following minimally important differences (MID): a change of two points on the PCS and three points on the MCS. The manual also proposed the following minimal mean group differences, in terms of t score points, for SF-36 version 2 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.[56] Comprehensive validation of the SF-36 in T1DM and T2DM is incomplete, and no MCID specifically in diabetes has been established. SF-36 version 2 was measured in DUAL V and DUAL VII.

The Diabetes Treatment Satisfaction Questionnaire was used to assess patient satisfaction with treatment (six items) and perception of change in hyperglycemia and hypoglycemia (two items).[57] This questionnaire has two versions that have eight items each: the original status version (DTSQs) and the Diabetes Treatment Satisfaction Questionnaire change version. Six of the eight items measure treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, and likelihood of continuing on or recommending current treatment). The item scores range from "very satisfied" (= a score of six) to "very unsatisfied" (= a score of zero), and the sum of these items is taken to generate a DTSQs score, ranging from zero to 36. Higher DTSQs scores indicate greater satisfaction with treatment. For the two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia, the items are scored on seven-point response scales ranging from "most of the time" (= a score of six) to "none of the time" (= a score of zero). Lower DTSQs scores indicate more ideal BG levels in this case. The psychometric properties of different language versions of the DTSQs were assessed in a study of T1DM and T2DM patients treated with insulin or poorly controlled on SUs who then started on insulin treatment. The DTSQs was shown to be consistently reliable in all languages studied and significantly sensitive to change in T1DM patients at week 8, week 20, week 24, and at the last available visit.[58] However, it has also been observed that because patients tend to report satisfaction with current treatment in the absence of experience with alternatives for comparison, the DTSQs often exhibits a ceiling

effect.[57] A MCID for the DTSQs in patients with T2DM was not identified. Change in DTSQs from baseline to end of study was measured in DUAL III.

Body Mass Index and/or Body Weight

Change from baseline in body weight after 26 weeks of treatment was a secondary efficacy end point in all included trials.

Blood Pressure

Change from baseline after 26 weeks of treatment in systolic blood pressure (SBP) and diastolic blood pressure (DBP) were secondary efficacy end points in all included trials. In all included trials, DBP and SBP were assessed while the patient was in a sitting position. Measurements were performed after five minutes of rest.

Lipid Profile

Change from baseline after 26 weeks of treatment in fasting lipid profile (e.g., total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and triglycerides) was a secondary efficacy end point in all included trials.

Health Care Resource Utilization

This outcome was not measured in any of the included trials.

Safety

An adverse event (AE) was defined as any untoward medical occurrence in a patient who has been administered a product, and which does not necessarily have a causal relationship with this treatment. It can be any unfavourable and unintended sign, symptom, or disease temporally associated with the use of a product, whether or not considered related to the product. A treatment-emergent AE was defined as an event that had an onset date on or after the first day of exposure to randomized treatment and no later than seven days after the last day of treatment.

A serious adverse event (SAE) was defined as an event that resulted in death, was life threatening, resulted in hospitalization or prolongation of existing hospitalization, was persistent or a significant disability, was a congenital anomaly or birth defect, or other important medical event.

In addition, AEs leading to treatment discontinuation was measured in the included trials. Safety areas of special interest, such as GI disorders, CV events, severe hypoglycemia, pancreatitis, or injection site reaction were explored.

Hypoglycemic episodes were classified according to the Novo Nordisk classification of confirmed hypoglycemia and the ADA classification of hypoglycemia. According to the ADA classification, severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagon, or take other resuscitative actions. Plasma glucose concentrations may not be available during an event, but neurological recovery following the return of plasma glucose to normal was considered sufficient evidence that the event was induced by a low plasma glucose concentration.[59]

In DUAL II, DUAL V, and DUAL III, confirmed hypoglycemic episodes were defined by Novo Nordisk as either severe (i.e., an episode requiring the assistance of another person to

actively administer carbohydrate, glucagon, or other resuscitative actions) or an episode biochemically confirmed by a plasma glucose value < 3.1 mmol/L, with or without symptoms consistent with hypoglycemia. In DUAL VII, the Novo Nordisk definition of severe or BG-confirmed symptomatic hypoglycemia referred to an episode that was severe, according to the ADA classification, or BG confirmed by a plasma glucose value < 3.1 mmol/L with symptoms consistent with hypoglycemia. The number of treatment-emergent confirmed hypoglycemic episodes during 26 weeks of treatment was a secondary end point in DUAL V and DUAL III, and the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment was a secondary end point in DUAL VII. Treatment-emergent hypoglycemic episodes were defined as hypoglycemic episodes that occurred on or after the first day of exposure to randomized treatment and no later than seven days after the last day of treatment.

Statistical Analysis

No interim analyses were planned or performed for any of the included trials.

In all trials, analyses of all efficacy end points and patient-reported outcome end points were based on a full analysis set (FAS).

DUAL II

In DUAL II, an analysis of covariance (ANCOVA) model with treatment, previous antidiabetes treatment, and country as fixed factors and baseline hemoglobin A1C value as a covariate was used for the analysis of the primary efficacy outcome. Superiority was tested as two-sided hypotheses at a 5% level of significance. No adjustments for multiplicity were performed. Details on the statistical testing procedure and power estimates are listed in Table 12.

Missing values were imputed using the last observation carried forward (LOCF) approach (see Table 11). This approach was also used to impute missing values in a completer analysis set (CAS).

The primary analysis of change in hemoglobin A1C from baseline after 26 weeks of treatment was repeated on CAS as a sensitivity analysis. Another sensitivity analysis was performed using FAS only, which used a repeated measurements analysis (RMA) of hemoglobin A1C from baseline to week 26 that was performed to evaluate the sensitivity of using LOCF. All hemoglobin A1C values available post baseline at scheduled measurement times were analyzed in a linear mixed normal model using an unstructured residual covariance matrix for hemoglobin A1C measurements within the same patient. The model included treatment, previous antidiabetes treatment, visit, and country as fixed factors and baseline hemoglobin A1C value as a covariate. Furthermore, the model included interaction terms between treatment and visit, between previous antidiabetes treatment and visit, between country and visit, and between baseline hemoglobin A1C and visit.

Analyses of the two “responder for hemoglobin A1C” and “responders for hemoglobin A1C without hypoglycemic episodes” end points were based on a logistic regression model with treatment, region, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as a covariate. The analyses of the two “responders for hemoglobin A1C without weight gain” and “responders for hemoglobin A1C without hypoglycemic episodes and weight gain” end points were based on a logistic regression model with treatment, region, and previous antidiabetes treatment as fixed factors, and baseline body weight and hemoglobin A1C value as covariates. Change from baseline in body weight,

FPG, SBP, and DBP after 26 weeks of treatment were analyzed using an ANCOVA model with treatment, country, and previous antidiabetes treatment as fixed factors, and baseline body weight, FPG, SBP, and DBP, respectively, as covariates. Lipid parameters after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, country, and previous antidiabetes treatment as fixed factors. In these statistical analyses, the end point and the baseline covariate were log-transformed.

DUAL V

In DUAL V, the primary end point — change from baseline in hemoglobin A1C after 26 weeks of treatment — was analyzed using an ANCOVA model with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. NI of IDegLira versus IGlar was concluded, if the 95% confidence interval (CI) for the mean treatment difference was entirely below 0.30%.

If NI was concluded, then the primary end point (change in hemoglobin A1C) was also tested for superiority. Likewise, change in body weight and number of treatment-emergent confirmed hypoglycemic episodes after 26 weeks of treatment were also tested for superiority as secondary end points.

The family-wise type I error rate for all three end points tested for superiority (the primary end point and two secondary end points [change in body weight and number of treatment-emergent confirmed hypoglycemic episodes after 26 weeks of treatment]) were controlled using the Holm–Bonferroni method. The superiority tests were based on the FAS, and the family-wise type I error rate was controlled using the Holm–Bonferroni method at a 2.5% significance level. No adjustments for multiplicity were performed for the remaining secondary outcomes. Details on the statistical testing procedure and power estimates are listed in Table 12.

The Holm–Bonferroni method implies that a two-sided *P* value should be calculated for each of the three comparisons for the end points tested for superiority, and then ordered from the smallest to the largest. Testing would proceed until an insignificant result shows as detailed in the following three steps:

1. If the smallest of the *P* values is below the adjusted significance level of 0.05/3 (*P* value < 0.0167) and the associated estimated mean treatment difference (ratio) is strictly below zero (one), superiority would be considered confirmed and the testing could proceed. Otherwise, the testing should stop with no additional claims of superiority.
2. If the testing is allowed to proceed and the second smallest *P* value is below the adjusted significance level of 0.05/2 (*P* value < 0.025) and the associated estimated mean treatment difference (ratio) is strictly below zero (one), superiority would be considered confirmed and the testing could proceed. Otherwise, the testing should stop with no additional claims of superiority.
3. If the testing is allowed to proceed and the largest *P* value is below the adjusted significance level of 0.05/1 (*P* value < 0.05) and the associated estimated mean treatment difference (ratio) is strictly below zero (one), superiority would be considered confirmed.

Missing values were imputed using the LOCF approach (see Table 11). This approach was also used to impute missing values in the CAS.

The primary end point analysis was repeated using the per-protocol (PP) analysis set and the CAS. In addition, an RMA of hemoglobin A1C from baseline to week 26 was performed

on the FAS to evaluate the sensitivity of using LOCF. In the RMA, all hemoglobin A1C values available post baseline at scheduled measurement times were analyzed in a linear mixed normal model using an unstructured residual covariance matrix for hemoglobin A1C measurements within the same patient. The model included treatment, visit, and region as fixed factors and baseline hemoglobin A1C value as a covariate. Furthermore, the model included interaction terms between treatment and visit, between region and visit, and between baseline hemoglobin A1C and visit.

No adjustment for multiplicity of testing was conducted for any secondary end points beyond the three superiority end points mentioned previously.

An ANCOVA model was applied for the secondary end points (change from baseline in body weight, FPG, SBP, DBP, and the questionnaires SF-36 version 2 and TRIM-D [total score and subdomains]). The model included treatment and region as fixed factors and the corresponding baseline value as a covariate. The number of treatment-emergent confirmed hypoglycemic episodes during 26 weeks of treatment was analyzed using a negative binomial regression model with a loglink function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset. The model included treatment and region as fixed factors.

Analysis of each of the two hemoglobin A1C responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) was based on a logistic regression model with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. Similarly, analysis of each of the two hemoglobin A1C responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) without either weight gain (defined as change from baseline below or equal to zero) or hypoglycemic episodes (defined as confirmed episodes during the last 12 weeks of treatment) or both was performed. These analyses were based on a logistic regression model with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate for responders without hypoglycemic episodes or baseline hemoglobin A1C value and body weight as covariates for responders without weight gain ± additional hypoglycemic episodes.

Lipid parameters after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors; in these statistical analyses, the end point and the baseline covariate were log-transformed.

DUAL VII

In DUAL VII, the primary end point — change from baseline in hemoglobin A1C after 26 weeks of treatment — was analyzed with a mixed-effects model for repeated measures (MMRM). The model had an unstructured covariance matrix and included treatment, visit, and region as fixed factors and the corresponding baseline value as a covariate. Interactions between visit and all factors and the covariate were also included in the model. The model assumed that data were missing at random (MAR). This model will be referred to as the standard MMRM model. In the analysis, all post-baseline hemoglobin A1C measurements obtained at planned visits before discontinuation from randomized treatment were included.

NI in the primary end point for IDegLira versus basal-bolus was concluded if the upper bound of the two-sided 95% CI for the estimated mean treatment difference in change from baseline in hemoglobin A1C (IDegLira minus basal-bolus) was strictly below 0.3%. Conclusion of NI was based on the FAS. In addition to the NI margin of 0.3%, the upper bound of the CI for the estimated mean treatment difference of IDegLira versus basal-bolus

was also compared with a 0.00% margin. This test was not part of the hierarchical testing procedure (see Table 11).

To investigate the robustness of the result from the MMRM with respect to the assumption of MAR, several different sensitivity analyses were performed. The primary analysis was repeated on the PP analysis set and on the CAS, and based on all data recorded after randomization, including data from patients who discontinued randomized treatment as sensitivity analysis. Sensitivity analysis was also performed on the FAS via an ANCOVA model with missing data imputed using the LOCF method. The model included treatment and region as fixed factors and the corresponding baseline hemoglobin A1C as a covariate (see Table 11).

The tests for superiority of the secondary end points (number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment and change from baseline in body weight after 26 weeks of treatment) were carried out only if NI of IDegLira versus basal-bolus with regards to the primary end point was confirmed. In order to control the overall type I error on a 5% level with regards to the secondary end points, a hierarchical testing procedure was used. If superiority with respect to the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment was confirmed, the second end point was tested for superiority. No adjustments for multiplicity were performed for the remaining secondary outcomes. Details on the statistical testing procedure and power estimates are listed in Table 12.

A negative binomial model with a loglink function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset was used to analyze the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment. The model further included treatment and region as fixed factors. Superiority with respect to number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment was considered confirmed if the upper bound of the two-sided 95% CI for the estimated treatment rate ratio (IDegLira versus basal-bolus) was strictly below one or, equivalently, if the *P* value for the one-sided test of the rate ratio was less than 0.025. Two sensitivity analyses for the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes were conducted. In the first sensitivity analysis, for withdrawn or prematurely discontinued patients, the number of events in the missing period (time of premature discontinuation to planned treatment-emergent period [maximum of 27 weeks and longest treatment-emergent exposure time observed in the trial]) were imputed using a multiple imputation technique, and assuming that all patients had an event rate in the period before and after premature discontinuation corresponding to the event rate in the basal-bolus group. In the second analysis, IDegLira patients were assumed to have the event rate of the IDegLira group prior to withdrawal or premature discontinuation and the event rate of the basal-bolus group after withdrawal or premature discontinuation. The method followed the multiple imputation mentioned previously, but in the second step pre-discontinuation rates were the respective group rates while the post-discontinuation rate was the rate of the basal-bolus group.

Change from baseline in body weight after 26 weeks of treatment was analyzed using a MMRM with an unstructured covariance matrix. Superiority for change from baseline in body weight was considered confirmed if the upper bound of the two-sided 95% CI for the estimated mean treatment difference (IDegLira versus basal-bolus) was below or equal to

zero or, equivalently, if the *P* value for the one-sided test of the treatment difference was less than 0.025.

Analysis of each of the two responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5 %) was based on a logistic regression model with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. Any missing response data at week 26 were imputed from the MMRM analysis of the primary end point change from baseline in hemoglobin A1C after 26 weeks of treatment.

The responder for hemoglobin A1C without weight gain after 26 weeks of treatment was defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5% at the end of treatment and change from baseline in body weight below or equal to zero. Analysis of each of the two responder end points was based on a logistic regression model with treatment and region as fixed factors and baseline hemoglobin A1C and baseline body weight as covariates. Any missing response data at week 26 were imputed from the MMRM analysis of the primary end point change from baseline in hemoglobin A1C after 26 weeks of treatment or the secondary end point change in body weight at 26 weeks.

Responder for hemoglobin A1C without treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes after 26 weeks of treatment was defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5% at the end of treatment and without treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during the last 12 weeks of treatment. Analysis of each of the two responder end points was similar to that described earlier for the two responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5 %).

The responder for hemoglobin A1C without treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes and weight gain after 26 weeks of treatment was defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5% at the end of treatment, without treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during the last 12 weeks of each treatment period, and change from baseline in body weight below or equal to zero. Analysis of each of the two responder end points was similar to that described earlier for the responder for hemoglobin A1C without weight gain after 26 weeks of treatment.

The secondary end points change from baseline in body weight, FPG, SBP, DBP, and the questionnaires SF-36 version 2 and TRIM-D (total score and subdomains) after 26 weeks of treatment were analyzed using the standard MMRM model.

Lipid parameters after 26 weeks of treatment were analyzed separately using the standard MMRM model. In these statistical analyses, the end point and corresponding baseline covariate were log-transformed.

DUAL III

In the DUAL III trial, the primary end point was analyzed using an ANCOVA model with treatment, pretrial GLP-1 RA (Victoza or Byetta), and region as fixed factors and baseline hemoglobin A1C value as a covariate.

Superiority of IDegLira over continued GLP-1 RA therapy was concluded when the 95% CI for the treatment differences for change in hemoglobin A1C lay entirely below 0%, implying that the two-sided *P* value calculated by the ANCOVA model for testing the hypothesis of no difference between treatments was less than 5%. No adjustments for multiplicity were

performed. Details on the statistical testing procedure and power estimates are listed in Table 12.

Missing values were imputed using the LOCF approach (see Table 11). This approach was also used to impute missing values in the CAS and PP analysis set.

An analysis using a MMRM of hemoglobin A1C from baseline to week 26 was further performed to evaluate the sensitivity of using LOCF. In this analysis, all post-baseline hemoglobin A1C measurements were the dependent variables, and visit, treatment, pretrial GLP-1 RA (Victoza or Byetta), and region were included as fixed factors and baseline hemoglobin A1C as a covariate. Furthermore, interaction terms of visit by treatment, visit by pretrial GLP-1 RA, visit by region, and visit by baseline hemoglobin A1C were included, and an unstructured covariance matrix for hemoglobin A1C measurements within the same patient was employed. Analyses of the primary end point were also repeated on the CAS and PP analysis set as sensitivity analyses.

Analysis of each of the two responders for hemoglobin A1C after 26 weeks of treatment end points were based on a logistic regression model with treatment, pretrial GLP-1 RA (Victoza or Byetta), and region as fixed factors and baseline hemoglobin A1C value as a covariate. Change from baseline after 26 weeks in body weight, FPG, SBP, DBP, and the questionnaires TRIM-D and DTSQs (total score and subdomains) were analyzed using an ANCOVA model with treatment, pretrial GLP-1 RA (Victoza or Byetta), and region as fixed factors and using baseline for the respective variables as covariates. Lipid parameters after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza or Byetta), and region as fixed factors. In these statistical analyses, the end point and baseline covariate were log-transformed.

Subgroup Analyses

No subgroup analyses were planned for any of the trials.

Lingvay et al.[45] conducted post hoc subgroup analyses for the DUAL V trial, in which patients were grouped according to baseline hemoglobin A1C (≤ 7.5%, > 7.5% to ≤ 8.5%, and > 8.5%), and BMI (< 30 kg/m^2, ≥ 30 kg/m^2 to < 35 kg/m^2, and ≥ 35 kg/m^2). The following end points were analyzed for each category at the end of the trial: change in hemoglobin A1C, change in body weight, patients reaching hemoglobin A1C < 7%, and patients reaching composite end points (hemoglobin A1C < 7% without hypoglycemia [in the last 12 weeks], and hemoglobin A1C < 7% without hypoglycemia [in the last 12 weeks] and without weight gain). Within each baseline category, the change from baseline in hemoglobin A1C and body weight were analyzed using an ANCOVA model with treatment and region as fixed factors and the corresponding baseline value as a covariate. The responder (reaching hemoglobin A1C targets) and composite end points were analyzed using a logistic regression model with a logit link function. The model included treatment and region as fixed factors and baseline hemoglobin A1C value and weight, when weight was included in the composite, as covariates. For all end points, missing data were imputed using LOCF. In addition, the treatment contrasts were compared between subgroups by interaction analyses, testing the null hypothesis of equal treatment effect across the different subgroups when comparing IDegLira with IGlar U100.

Vilsboll et al.[42] conducted post hoc subgroup analyses for the DUAL II, DUAL V, and DUAL VII trials, in which patients were grouped according to duration of diabetes (< 10 years, ≥ 10 years). End points from the original trials included in this analysis were changes from baseline to week 26 in hemoglobin A1C, body weight, SBP, DBP, and lipid profile.

Change in body weight, SBP, DBP, and log-transformed lipid end points were analyzed using ANCOVA in DUAL II and DUAL V, including treatment, pretrial diabetes treatment (DUAL II only), region, subgroup, and interaction between treatment and subgroup as fixed factors, and baseline response (log-transformed for lipid end points) as a covariate. Missing data were imputed using LOCF. In DUAL VII, body weight, SBP, DBP, and log-transformed lipid end points were analyzed using a MMRM with an unstructured covariance matrix, including subgroup, visit, treatment, region, and interaction between treatment and subgroup as fixed factors and baseline response (log-transformed for lipid end points) as a covariate. Interactions between visit and all factors and covariates were also included.

In the DUAL III trial, subgroup analyses were conducted on the subset of patients who had been on liraglutide. These analyses were post hoc subgroup analyses and were exploratory in nature. They were unplanned and performed after data were collected.

Table 11: Summary of Statistical Testing Methods

Study	Outcome	Statistical Model	Imputation of Missing Data	Sensitivity Analyses
DUAL II	Change in hemoglobin A1C from baseline after 26 weeks of treatment	The primary statistical analysis was based on the FAS. An ANCOVA model was used with treatment, previous antidiabetes treatment, and country as fixed factors and baseline hemoglobin A1C value as a covariate.	LOCF	• Using CAS • RMA using FAS
DUAL V	Change in hemoglobin A1C from baseline after 26 weeks of treatment	The primary statistical analysis was based on the FAS. An ANCOVA model was used with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. The NI analysis set was based on FAS and supplemented by an analysis with the PP analysis.	LOCF	• PP analysis • Using CAS • RMA using FAS
DUAL VII	Change in hemoglobin A1C from baseline after 26 weeks of treatment	The primary statistical analysis was based on the FAS. An MMRM model was used with treatment, visit, and region as fixed factors and the corresponding baseline value as a covariate. Interactions between visit and all factors and the covariate were also included in the model. The model assumed that data were MAR. The NI analysis set was based on the FAS and supplemented by an analysis with the PP analysis.	MMRM imputation	• PP analysis • Using CAS • ANCOVA model with missing data imputed using LOCF
DUAL III	Change in hemoglobin A1C from baseline after 26 weeks of treatment	The primary statistical analysis was based on the FAS. An ANCOVA model was used with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide]), and region as fixed factors and baseline hemoglobin A1C value as covariate.	LOCF	• PP analysis • Using CAS • MMRM imputation

ANCOVA = analysis of covariance; CAS = completer analysis set; FAS = full analysis set; GLP-1 RA = glucagon-like peptide 1 receptor agonist; LOCF = last observation carried forward; MAR = missing at random; MMRM = mixed-effects model for repeated measures; NI = noninferiority; PP = per-protocol; RMA = repeated measurements analysis.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 12: Adjustment for Multiplicity and Power Estimates

Study	Adjustment for Multiplicity	Statistical Power
DUAL II	There were no end points that were adjusted for multiplicity.	The sample size was calculated using a 2-sided t-test of size 5%. The mean difference in the primary end point between IDegLira and IDeg was assumed to be 0.4%, with a SD of 1.2%. From these assumptions, it was estimated that a sample size of 191 patients per treatment group was needed in order to obtain a power of 90% of meeting the primary end point.
DUAL V	Change from baseline after 26 weeks of treatment in the following outcomes were adjusted for multiplicity: • noninferiority in change in hemoglobin A1C • superiority in change in hemoglobin A1C • superiority in change in body weight • superiority in number of treatment-emergent confirmed hypoglycemic. Noninferiority of IDegLira vs. IGlar was concluded if the 95% CI for the mean treatment difference was entirely below 0.30%. If noninferiority was confirmed, then the primary end point (change in hemoglobin A1C) was also tested for superiority. Likewise, change in body weight and number of treatment-emergent confirmed hypoglycemic episodes after 26 weeks of treatment were also tested for superiority as secondary end points. The superiority tests were based on the FAS, and the family-wise type I error rate was controlled using the Holm–Bonferroni method at a 2.5% significance level.	The sample size was calculated using a t-statistic under the assumptions of a 1-sided test at a 2.5% level of significance, a mean treatment difference of 0%, a SD of 1%, and a noninferiority margin of 0.30%. It was also assumed that 15% of the randomized patients was excluded from the PP analysis set. Noninferiority was investigated for both the FAS and PP analysis set. From these assumptions and based on a 1:1 randomization, the sample size was set to 277 patients per treatment group; in total, 554 patients. This ensured a power of at least 90% for confirming the primary outcome in the PP analysis set.
DUAL VII	Change from baseline after 26 weeks of treatment in the following outcomes were tested in the following order: 1. noninferiority on change in hemoglobin A1C 2. superiority on number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes 3. superiority on change in body weight. Noninferiority of IDegLira vs. basal-bolus was concluded if the 95% CI for the mean treatment difference was entirely below 0.30%. Superiority with respect to number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment was claimed if the upper bound of the 2-sided 95% CI for the estimated treatment rate ratio (IDegLira vs. basal-bolus) was strictly < 1 or, equivalently, if the *P* value for the 1-sided test of the rate ratio was < 2.5%. Superiority for change in body weight was claimed if the upper limit of the 2-sided 95% CI for the estimated mean difference was ≤ 0 kg, or equivalently if the *P*	Sample size was calculated using a t-statistic under the assumptions of a 1-sided test of size 2.5%, a mean treatment difference of 0.0%, a SD of 1.0%, and a noninferiority margin of 0.30%. It was also assumed that 15% of the randomized patients would be excluded from the PP analysis set. Noninferiority was investigated for both the FAS and the PP analysis set. From these assumptions and based on a 1:1 randomization, the sample size was set to 250 patients per treatment group; in total, 500 patients were to be randomized. This ensured a power of at least 85% for confirming the primary outcome in the PP analysis set.

Study	Adjustment for Multiplicity	Statistical Power
	value for the 1-sided test of the treatment difference was < 2.5%.	
DUAL III	No end points were adjusted for multiplicity.	The sample size was calculated using a 2-sided t-test of 5%. The mean difference in the primary end point between IDegLira and continued GLP-1 RA therapy was assumed to be 0.4% with a SD of 1.2%. From these assumptions, the sample size was set to a total of 429 patients, which is 286 in the IDegLira treatment group and 143 in the unchanged GLP-1 RA group, in order to obtain a power of 90% of meeting the primary end point.

BG = blood glucose; CI = confidence interval; FAS = full analysis set; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; PP = per-protocol; SD = standard deviation; vs. = versus.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Analysis Populations

Full Analysis Set

For all included trials, the efficacy analyses were conducted based on a FAS, which was defined as all randomized patients. In exceptional cases, patients could be excluded from the FAS. In such cases, the exclusions were justified and documented. The statistical evaluation of the FAS followed the intention-to-treat (ITT) principle and patients contributed to the evaluation "as randomized" in all trials except the DUAL II trial, where the FAS was a modified ITT.

Per-Protocol Analysis Set

The PP analysis set was defined as all patients in the FAS who fulfilled the following criteria:

- had not violated any inclusion criteria
- had not fulfilled any exclusion criteria
- had a non-missing hemoglobin A1C at screening or randomization
- had at least one non-missing hemoglobin A1C after 12 weeks of exposure
- had at least 12 weeks of exposure.

Patients in the PP analysis set contributed to the evaluation "as treated."

The DUAL II trial did not have PP analysis set.

Safety Analysis Set

In all included trials, the safety analysis set was defined as all patients receiving at least one dose of the investigational product or comparator. Patients in the safety set contributed to the evaluation "as treated."

Completer Analysis Set

In all included trials, the CAS was defined as all randomized patients who completed the trial. Patients in the CAS contributed to the evaluation "as randomized."

Patient Disposition

Patient disposition is summarized in Table 13. The randomized sample size per trial ranged from 413 patients (DUAL II trial) to 557 patients (DUAL V trial).

In DUAL II, a total of 831 patients were screened. Of these, 418 patients were screening failures and 90.2% of them failed to meet the inclusion criterion of hemoglobin A1C (hemoglobin A1C of 7.5% to 10.0%, both inclusive). A total of 413 patients entered the trial and all these patients were exposed to randomized trial treatment. A total of 16.2% of the patients withdrew during the trial. The withdrawal rate was 15.5% in the IDegLira treatment group and 17.0% in the IDeg treatment group. A total of 6.7% of the patients withdrew due to fulfillment of withdrawal criteria (13 patients in IDegLira [6.3%] and 15 patients in IDeg [7.3%]). Of the patients withdrawing due to fulfilling withdrawal criteria, more patients in the IDeg treatment group (five out of 15) withdrew due to continuous high SMPG compared with the IDegLira treatment group (one out of 13). In total, 30 patients withdrew with their primary reason being “other;” 15 of these patients withdrew due to closure of site. The remaining 15 patients were randomized in error (did not meet certain inclusion or exclusion criteria). Overall, 83.8% of patients completed the 26-week trial period (the completion rates for IDegLira and IDeg were 84.5% and 83.0%, respectively).

In DUAL V, a total of 767 patients were screened. Of these, 210 patients were screening failures, of which the majority (71.9%) failed to meet the inclusion criterion of hemoglobin A1C (hemoglobin A1C of 7.0% to 10.0%, both inclusive). In total, 557 patients were randomized in the trial and all 557 randomized patients were exposed to trial treatment. A total of 7.5% of the patients withdrew during the trial, with a higher proportion of withdrawn patients in the IDegLira group (10.1%) compared with the IGlar group (5.0%). A higher number of patients in the IDegLira group (nine patients [3.2%]) withdrew due to AEs compared with the IGlar group (one patient [0.4%]). Withdrawals due to randomization in contravention of the inclusion and/or exclusion criteria (one of the withdrawal criterion in DUAL V) was higher in the IDegLira group (eight patients [2.9%]) compared with the IGlar group (four patients [1.4%]). Overall, 92.5% of the patients completed the 26-week trial period — 89.9% of the patients in the IDegLira group and 95.0% of the patients in the IGlar group

In the DUAL VII trial, a total of 672 patients were screened. Of these, 166 patients were screening failures, of which the majority (54.2%) failed to meet the inclusion criterion of hemoglobin A1C (hemoglobin A1C of 7.0% to 10.0%, both inclusive). In total, 506 patients were randomized in the trial and 505 randomized patients were exposed to trial treatments. One patient who was randomized to the IGlar + IAsp group withdrew consent before exposure to trial product due to personal reasons. A lower proportion of patients withdrew from the IDegLira group (0.8%) compared with the IGlar + IAsp group (2.0%). One patient in the IDegLira group withdrew due to an AE, while there were no withdrawals due to AEs in the IGlar + IAsp group. A lower number of patients in the IDegLira group (one patient) withdrew at will (withdrawal by patient) compared with the IGlar + IAsp group (four patients). A total of five patients (two patients in the IDegLira group and three patients in the IGlar + IAsp group) were discontinued due to violation of the inclusion and/or exclusion criteria. Overall, 98.6% of the patients completed the 26-week trial period — 99.2% in the IDegLira group and 98.0% in the IGlar + IAsp group. In total, 93.1% completed week 26 without permanent discontinuation of trial product.

In the DUAL III trial, a total of 704 patients were screened. Of these, 266 patients failed screening. The majority of screening failures (74.1%) was due to inclusion criteria of hemoglobin A1C (hemoglobin A1C of 7.0% to 9.0%, both inclusive). A total of 438 patients were randomized in the trial, but two of these patients withdrew before being exposed to trial product. A total of 10.3% of the patients withdrew during the trial, with a lower proportion of withdrawn patients in the IDegLira group (5.5%) compared with the GLP-1 RA group (19.9%). In the IDegLira group, one patient (0.3%) withdrew due to an AE compared with two patients (1.4%) in the GLP-1 RA group. Withdrawal due to continuous high SMPG was more pronounced in the GLP-1 RA group (11 patients) compared with the IDegLira group (two patients). Overall, 89.7% of the patients completed the 26-week trial period — 94.5% of the patients in the IDegLira group and 80.1% of the patients in the GLP-1 RA group.

Table 13: Patient Disposition

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira	IDeg	IDegLira	IGlar	IDegLira	IGlar + IAsp	IDegLira	GLP-1 RA
Screened, N	831		767		672		704	
Screening Failures, N (%)	418 (50.3)		210 (27.4)		166 (24.7)		266 (37.8)	
Randomized, N	207	206	278	279	252	254	292	146
Randomized and Treated, N (%)	207 (100.0)	206 (100.0)	278 (100.0)	279 (100.0)	252 (100.0)	253 (99.6)	291 (99.7)	145 (99.3)
Permanent Discontinuation of Treatment or Withdrawn From Trial	NR	NR	NR	NR	14 (5.6)	21 (8.3)	NR	NR
Withdrawn at or After Randomization, N (%)	32 (15.5)	35 (17.0)	28 (10.1)	14 (5.0)	2 (0.8)	5 (2.0)	16 (5.5)	29 (19.9)
Adverse event	1 (0.5)	3 (1.5)	9 (3.2)	1 (0.4)	1 (0.4)	0	1 (0.3)	2 (1.4)
Ineffective therapy	1 (0.5)	2 (1.0)	0	0	0	0	0	0
Non-compliance with protocol	0	2 (1.0)	2 (0.7)	1 (0.4)	0	0	9 (3.1)	3 (2.1)
Withdrawal criteria	13 (6.3)	15 (7.3)	16 (5.8)	11 (3.9)	1 (0.4)	4 (1.6)	2 (0.7)	14 (9.6)
Other	17 (8.2)	13 (6.3)	1 (0.4)	1 (0.4)	0	1 (0.4)	4 (1.4)	10 (6.8)
Permanent discontinuation of treatment	NR	NR	NR	NR	12 (4.8)	19 (7.5)	NR	NR
Adverse event	NR	NR	NR	NR	6 (2.4)	1 (0.4)	NR	NR
Other	NR	NR	NR	NR	2 (0.8)	12 (4.7)	NR	NR
Protocol violation	NR	NR	NR	NR	2 (0.8)	6 (2.4)	NR	NR
Rescue criteria	NR	NR	NR	NR	2 (0.8)	0	NR	NR
Pregnancy	NR	NR	NR	NR	0	0	NR	NR
Completed (CAS), N (%)	175 (84.5)	171 (83.0)	250 (89.9)	265 (95.0)	250 (99.2)	249 (98.0)	276 (94.5)	117 (80.1)
Completed Week 26 Visit Without Permanent Discontinuation of Trial Product	NR	NR	NR	NR	238 (94.4)	233 (91.7)	NR	NR
Full Analysis Set, N (%)	199 (96.1)	199 (96.6)	278 (100.0)	279 (100.0)	252 (100.0)	254 (100.0)	292 (100.0)	146 (100.0)
PP, N (%)	NR	NR	257 (92.4)	270 (96.8)	239 (94.8)	238 (93.7)	279 (95.5)	135 (92.5)

	DUAL II		DUAL V		DUAL VII		DUAL III	
Safety, N (%)	199 (96.1)	199 (96.6)	278 (100.0)	279 (100.0)	252 (100.0)	253 (99.6)	291 (99.7)	145 (99.3)

CAS = completer analysis set; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; NR = not reported; PP = per-protocol.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Exposure to Study Treatments

In the DUAL II trial, 199 patients were exposed to IDegLira and 199 patients were exposed to IDeg. The total exposure (in patient-years) was approximately 90 years for both IDegLira and IDeg (see Table 14). The majority of patients in both treatment groups (IDegLira [89.4%] and IDeg [85.4%]) were exposed to trial product for 25 weeks to 28 weeks. The median dose after 26 weeks of treatment for patients treated with IDegLira was 50 U (dose range 12 U to 50 U) and 50 U with IDeg (dose range 10 U to 51 U). The mean dose of insulin after 26 weeks of treatment was 45 U for both IDegLira and IDeg. The majority of patients in both treatment groups (IDegLira [65.3%] and IDeg [67.3%]) reached the maximum allowed daily dose of 50 U during the trial for IDegLira and IDeg, respectively.

In the DUAL V trial, 278 patients were exposed to IDegLira and 279 patients were exposed to IGlar, with the total exposure (in patient-years) being 129.6 years in the IDegLira group and 135.1 years in the IGlar group (see Table 14). The majority of patients in both treatment groups (87.8% in the IDegLira group and 95.3% in the IGlar group) were exposed to trial product for 25 weeks to 28 weeks. At the end of the trial, the mean (median [range]) daily insulin dose was 41 U (46 U [16 U to 50 U]) and 66 U (60 U [17 U to 153 U]) for patients treated with IDegLira and IGlar, respectively.

In the DUAL VII trial, 252 patients were exposed to IDegLira and 253 patients were exposed to IGlar + IAsp. The total patient-years of exposure were 120.4 years in the IDegLira group and 119.3 years in the IGlar + IAsp group (see Table 14). The majority of patients in both treatment groups (92.9% in the IDegLira group and 89.4% in the IGlar + IAsp group) were exposed to trial product for 26 weeks to 27 weeks. At the end of the trial, the mean (median [range]) daily total insulin dose was 40.39 U (44 U [8.75 U to 50.00 U]) for patients treated with IDegLira and 84.11 U (74 U [18.00 U to 263.33 U]) for those treated with IGlar + IAsp.

In the DUAL III trial, 291 patients were exposed to IDegLira and 145 patients were exposed to GLP-1 RA, both added to MET ± pioglitazone ± SU. The total exposure (in patient-years) was 140.9 years in the IDegLira group and 65.9 years in the GLP-1 RA group (see Table 14). The majority of patients in both treatment groups (94.8% in the IDegLira group and 80.7% in the GLP-1 RA group) were exposed to trial product for 25 weeks to 28 weeks. The proportion of patients with an exposure of 25 weeks to 28 weeks in the GLP-1 RA group compared with the IDegLira group was lower; this was caused by a higher withdrawal rate throughout the trial period in the GLP-1 RA group. Approximately 50% of the patients in the IDegLira group received the maximum daily dose of 50 U at the end of the trial. The maximum dose was exceeded in eight patients; these deviations were documented as protocol deviations. At the end of the trial, the mean (median [range]) daily insulin dose was 43 U (50 U [8 U to 50 U]) for patients treated with IDegLira.

Table 14: Exposure (Safety Analysis Set)

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
N	199	199	278	279	252	253	291	145
Total Exposure (Years)	91.93	90.00	129.6	135.1	120.4	119.3	140.9	65.9
Exposure (Years)								
N	199	199	278	279	252	253	291	145
Mean (SD)	0.46 (0.11)	0.45 (0.13)	0.5 (0.1)	0.5 (0.1)	0.48 (0.09)	0.47 (0.10)	0.5 (0.1)	0.5 (0.1)
Median	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Min., max.	0.02, 0.51	0.01, 0.54	0.0, 0.6	0.0, 0.5	0.01, 0.54	0.00, 0.53	0.0, 0.6	0.0, 0.6

GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; max. = maximum; min. = minimum; SD = standard deviation.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Critical Appraisal

Internal Validity

All four included studies used accepted methods to conceal allocation and randomize patients to treatments, and the patients' characteristics appeared to be balanced at baseline between groups within trials, with no major differences observed between treatment groups.

DUAL II was a double-blind trial; however, it is possible that patients and investigators could have reviewed and discussed changes in the hemoglobin A1C levels, body weight, and AEs — particularly some specific drug effects that are known to be associated with the administration of GLP-1 RAs, such as GI AEs. This may have allowed certain patients and/or investigators to surmise the assigned treatment, and subsequently may have had an impact on patient-reported outcomes (e.g., HRQoL) or AEs. In addition, knowing which treatment the patient was receiving could have resulted in a change in a patient's behaviour during the trial (i.e., diet and exercise, which may have affected hemoglobin A1C results). For trials with open-label design (DUAL V, DUAL VII, and DUAL III), patients were aware of the treatment allocation; therefore, the evaluation of patient-reported outcomes or AEs may also have been affected by an unblinded treatment regimen because reporting bias could have been introduced. Furthermore, knowing which treatment the patient was receiving could have resulted in a change in a patient's behaviour during the trial (i.e., diet and exercise, which may have affected hemoglobin A1C results). In addition, open-label design introduces potential investigator bias. Also, patients in the open-labelled trials DUAL III and DUAL V who were randomized to the comparator group were to continue their pretrial medication, which may have predisposed them to reporting bias (i.e., either over-reporting or under-reporting AEs). Finally, patients' willingness to continue therapy may have been influenced by knowledge of the treatment received, which might have contributed to the high and differential withdrawal rate in the DUAL III trial, where almost 20% of patients in the GLP-1 RA treatment group withdrew from the study in comparison with 5.5% in the IDegLira treatment group.

Except for the DUAL V and DUAL VII trials, which included the change from baseline in body weight and number of treatment-emergent confirmed hypoglycemic episodes in their fixed statistical testing procedure, there was no control from multiplicity among other secondary outcomes analyzed and all secondary outcomes in DUAL II and DUAL III. Hence, the results of these end points should be interpreted with consideration of the potential for inflated type I error.

The proportion of missing data was 12.1% in DUAL II, 7.4% in DUAL V, 2.6% in DUAL VII, and 10.3% in DUAL III. The proportion of missing data was differential between IDegLira and the controls in DUAL V and DUAL III. Patients who discontinued protocol treatment were not asked to come back for the 26-week assessment. The LOCF method was used to impute missing data in the DUAL II, DUAL V, and DUAL III trials; however, in a chronic progressive disease like diabetes where patients continue to lose glycemic control over time, the LOCF method can introduce bias as it assumes patients remain stable for all subsequent time points, which is rarely the case in the real world. In addition, the FDA no longer recommends LOCF as the approach for dealing with missing data. It recommends a study collect all efficacy measurements regardless of treatment adherence and analyses that use all efficacy measurements regardless of treatment adherence.[39] Sensitivity analyses were conducted to assess the validity of using LOCF with RMA in DUAL II and DUAL V, and MMRM in DUAL III. The results of all sensitivity analyses were similar in magnitude, direction, and statistical significance and in support of the primary analyses in these trials. Although these analyses showed results similar to those of the primary data analysis, these analyses cannot fully account for the impact of missing data, especially in DUAL V and DUAL III. Moreover, all approaches to missing data assumed data were MAR, which is unlikely to be true in these trials and may have biased the results. In response to the missing data, the FDA did additional analysis for some of the included trials where a pattern mixture model was used to better mimic an ITT scenario and a tipping point analysis was used to determine how impactful the missing data were on the efficacy results observed. The FDA concluded that the overall primary analyses remained robust with these additional approaches.[39]

The DUAL V and DUAL VII trials were NI studies. Although neither trial provided justification for the 0.3% NI margin, this threshold was consistent with the 2008 FDA draft guidance for diabetes mellitus, which accepted a non-margin of 0.3% or 0.4% hemoglobin A1C percentage units.[60] In both trials, the primary statistical model for change in hemoglobin A1C (primary outcome) was tested using data from the FAS and PP populations; they were consistent in their findings.

The Novo Nordisk definition of confirmed hypoglycemia is uncertain since it does not inherently require symptoms to be part of the definition, thereby decreasing its specificity. Other factors that may have affected the detection of hypoglycemic results include incorrect storage of reagents (i.e., test strips, which are sensitive to temperature and humidity) and use of control solution. Because of the multitude of potential sources of error, the FDA clinical review report[40] focused on the ADA's definition of severe hypoglycemia and documented symptomatic hypoglycemia, since these definitions have established clinical relevance.

In the DUAL II trial, titration in the IDeg comparator group was limited by a maximum dose of 50 U. In clinical practice, there is no maximum approved dose for IDeg, when administered alone, and hence the liraglutide component of IDegLira defined the upper dose limit in the fixed-ratio product (50 U IDeg/1.8 mg liraglutide). The majority of patients in

the IDeg treatment group (67.3%) reached the maximum allowed dose of 50 U during the trial for IDeg. It is likely that patients in the IDeg group would have titrated to doses higher than 50 U if allowed by design. The fact that they could not titrate higher biased the assessment of efficacy in favour of IDegLira, and the difference in hemoglobin A1C effect observed may not reflect the effect that would be observed in health care settings where patients inadequately controlled on basal insulin would receive additional add-on therapy. In addition, treatment with IDeg at randomization was initiated with 16 U IDeg when the mean basal insulin dose at baseline was 29 U. Pretrial randomized patients were already uncontrolled on basal insulin. Initiating therapy with the decreased dose of basal insulin for the IDeg group in addition to discontinuing their non-MET oral AHAs therapy biased efficacy results in favour of the IDegLira group.

The Health Canada indication for IDegLira is to be used as an adjunct to lifestyle modifications, for the once-daily treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control. In the DUAL III trial, the GLP-1 RA that patients were taking at baseline (and continued on if not randomized to IDegLira) was liraglutide for 79.5% of patients and exenatide for 20.5% of patients. The Health Canada reviewer report indicated that results in patients previously on exenatide were similar to those of the subset of patients who had been on liraglutide. Subgroup analyses were conducted on the subset of patients who had been on liraglutide; the results of these subgroup analyses are presented in Table 27. While the results from the subset of patients who had been on liraglutide were in line with those of the overall patient population in the DUAL III trial, it is worth noting that these analyses were post hoc subgroup analyses and were exploratory in nature — they were unplanned and performed after data were collected. In addition, multiplicity and potential inflated type I error are concerns within this subgroup. As a result, these analyses should be interpreted with these considerations in mind.

In the DUAL III trial, patients in the GLP-1 RA treatment group were taking the maximum recommended (or tolerated) dose of comparator product at trial entry, and the dose was not to be changed during the trial. Therefore, the lack of decline in hemoglobin A1C for the GLP-1 RA group was to be expected. The clinical expert indicated that the reduction in hemoglobin A1C reported in the GLP-1 RA treatment group was likely a diabetes-trial placebo effect, where patients pay more attention to their T2DM and monitor more often when they enrol in a trial; a 0.3% to 0.4% change is to be expected. In contrast, IDegLira was started at 16 U and titrated to glycemic targets resulting in a further glucose lowering. The magnitude of treatment difference should be interpreted with this consideration. The difference in the hemoglobin A1C effect observed may not reflect the effect that would be observed in health care settings where patients inadequately controlled on liraglutide would receive additional add-on therapy.

In the DUAL III trial, patient withdrawal in the GLP-1 RA group may have been influenced by the fact that enrolled patients did not have glycemic control and were continued on their baseline GLP-1 RA dose for the duration of the trial. This resulted in higher withdrawal rates due to SMPG criteria, where withdrawal due to continuous high SMPG was more pronounced in the GLP-1 RA group (11 patients [7.5%]) compared with the IDegLira group (two patients [0.6%]).

In the DUAL III trial, data about the doses of GLP-1 RA used in the GLP-1 RA treatment group were not collected. Not having collected these data during the trial is a source of bias, since it assumes that the dose remained unchanged in this group.

In the DUAL VII trial, data were missing for HRQoL outcomes among patients at the end point (4.7% in the IDegLira group and 6.2% in the IGlar + IAsp group), and there was no apparent framework in place to account for these missing values in the protocol. Missing data in these outcomes and the exclusion of these patients could be due to non-response bias and could underestimate the variability in the results, which can potentially overestimate HRQoL results.

While the analyses in the DUAL VII trial indicate that it was based in the FAS population, which followed the ITT principle, the number of patients included in each analysis after 26 weeks of treatment was lower than the FAS population, as a number of randomized patients were not included in the analyses. Also, in DUAL II, the FAS population did not include all randomized patients. Hence, in both trials, the FAS analysis set was effectively a modified ITT population, and the term “ITT” is therefore potentially misleading.

Subgroup analyses conducted on these patients were not defined in the individual study protocols. Instead, these were post hoc subgroup analyses and were exploratory in nature — they were unplanned and performed after data were collected. In addition, multiplicity and potential inflated type I error are concerns within the subgroups. As a result, the interpretation of subgroup analyses should be interpreted with these considerations in mind. Moreover, DUAL V and DUAL VII are NI trials. It is unclear how specific subgroup effects should have been interpreted with respect to the NI margins that were defined for the overall population, or whether subgroup-specific margins should have been employed.

External Validity

Although the patients enrolled in the trials appear to be similar, in general, to patients with T2DM in Canada who are inadequately controlled on MET, with or without SU, in combination with basal insulin or liraglutide, the trials excluded patients with advanced comorbid conditions. Also, patients with BMI > 40 kg/m^2 were excluded from the DUAL V, DUAL VII, and DUAL III trials, which may limit interpretations of the efficacy findings to patients with less insulin resistance, and results may not be representative of patients with more severe obesity.

DUAL II, DUAL V, and DUAL III excluded patients with advanced cardiac disease (i.e., NYHA class III or class IV, unstable angina, stroke, or MI) within the preceding 26 weeks (DUAL II and DUAL V) or 52 weeks (DUAL III), and DUAL VII excluded patients who, at the time, were classified as NYHA class IV, or MI or having had stroke or been hospitalized for unstable angina and/or an transient ischemic attack that occurred within the past 180 days. These exclusions make the overall CV risk in the population in these trials lower than that of typical diabetic patients in Canada.

In DUAL II, DUAL V, DUAL VII, and DUAL III, 418 patients (50.3%), 210 patients (27.4%), 166 patients (24.7%), and 266 patients (37.8%) of the screened patients were recorded as screening failures, respectively. The main reason they failed to meet the inclusion criteria was that their hemoglobin A1C was not in the pre-specified range for inclusion (7.5% to 10.0% in DUAL II, 7.0% to 10.0% in DUAL V and DUAL VII, and 7.0% to 9.0% in DUAL III). Stringent inclusion and exclusion criteria can potentially lead to the inclusion of a select group of patients that may not be representative of the T2DM population in Canada who are

inadequately controlled on MET, with or without SU, in combination with basal insulin (less than 50 U daily) or liraglutide (less than or equal to 1.8 mg daily). This can potentially limit the generalizability of the trial results.

Patients in all of the included studies were overwhelmingly Caucasian, which is not entirely representative of the T2DM population in Canada, since Canada is home to a significant population of immigrants at a higher risk of T2DM. Also, only one patient of Aboriginal descent was included in the trials. As of 2011, South Asians, Chinese, and blacks accounted for 61.3% of the total visible minority population, and Aboriginal people accounted for 4.3% of the Canadian population.[2] Furthermore, no Canadian sites were included in any of the studies. As a result, the generalizability of these trial results to the Canadian T2DM population is potentially limited.

It is unknown if superiority of IDegLira exists over IDeg at doses beyond 50 U, since doses in the IDeg group were also capped at 50 U in order to match the dose limitation of the IDeg component in the IDegLira group in the DUAL II trial. Therefore, it is unknown whether IDegLira would be a better treatment option than IDeg alone in a setting where basal insulin therapy was optimized without any dose limitations.

In the DUAL II, DUAL V, and DUAL VII trials, a treatment algorithm was to be titrated twice weekly according to the predefined titration algorithm, which was based on FPG levels. Adjustments for IDeg and IGlar treatments occurred in 2 U every three to four days, aiming at a fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L. According to the clinical expert involved in this study, this titration was considered to be conservative for increasing IDeg and IGlar and may not be appropriate for a T2DM population that is not yet at target and requires aggressive treatment.

All included trials were designed to have a treatment period of 26 weeks which, according to the clinical expert, is the minimum duration that could be used to evaluate changes in glycemic control. These trials were not designed to address morbidity and mortality outcomes that are important to patients or to assess longer-term maintenance of glycemic control and durability of the interventions. T2DM is a chronic condition with risks of multiple serious complications that take years to develop. Therefore, it is unlikely that a trial of this nature — like the trials included here — can be designed to assess these key outcomes. hemoglobin A1C is widely used as a surrogate marker for glycemic control; however, the exact nature of improvement required in hemoglobin A1C to achieve clinical benefit has not been fully elucidated. Furthermore, it is unclear whether the duration of the treatment period in the included trials allowed for sufficient time to adequately assess HRQoL outcomes and whether weight changes observed throughout the period of the trials would have a meaningful impact on patients over time.

In general, diet and exercise are part of the standard care of patients with T2DM. In all included trials, it was unknown whether diet and exercise was background therapy and, if so, to what extent these factors were optimized. Thus, trial findings may not reflect the effectiveness to be achieved in a real-world setting.

The included trials provide direct evidence for comparisons between IDegLira and IDeg, IGlar, IGlar plus prandial IAsp, and GLP-1 RAs. There is a lack of direct evidence on comparisons between IDegLira and other currently available active treatment, such as iGlarLixi, DPP-4 inhibitors, and SGLT2 inhibitors.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported as follows (see Table 4). See Appendix 4 for detailed efficacy data.

Mortality (All-Cause, Cardiovascular Related)

While data on mortality was collected for all of the included studies, none of the trials was designed to compare between treatment groups for this outcome.

Diabetes-Related Morbidity

While data on diabetes-related morbidity was collected for all of the included studies, none of the trials was designed to compare between treatment groups for this outcome.

Glycemic Control

The change from baseline in hemoglobin A1C after 26 weeks of treatment was the primary efficacy outcome in all of the included trials.

DUAL II

The DUAL II trial enrolled patients with T2DM inadequately controlled on basal insulin and MET, with or without SU or glinides, and who were randomized to IDegLira or a starting dose of 16 U for IDeg. In DUAL II, the mean hemoglobin A1C at baseline was 8.7% in the IDegLira treatment group and 8.8% in the IDeg treatment group, and was reduced by 1.9% to 6.9% (least squares [LS] mean estimate) on IDegLira and by 0.89% to 8.0% (LS mean estimate) on IDeg after 26 weeks of treatment (see Table 15). The estimated LS mean difference for the change from baseline was −1.05% (95% CI, −1.25 to −0.84; $P < 0.0001$). This was statistically significant favouring IDegLira versus IDeg, indicating that IDegLira is superior to IDeg.

The sensitivity analyses results of the change in hemoglobin A1C from baseline after 26 weeks of treatment were consistent with the results of the primary analysis (see Table 18).

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 2).

DUAL V

The DUAL V trial enrolled patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET, and randomized patients to IDegLira or to continue their pretrial medication (IGlar). In DUAL V, the mean hemoglobin A1C at baseline was 8.4% in the IDegLira group and 8.2% in the IGlar group. After 26 weeks of treatment, the LS mean hemoglobin A1C had decreased by 1.81% to 6.6% in the IDegLira group and by 1.13% to 7.1% in the IGlar group (see Table 15). The estimated LS mean difference for the change from baseline in hemoglobin A1C for IDegLira versus IGlar was −0.59% (95% CI, −0.74 to −0.45). Given that the 95% CI for the mean treatment difference for the change from baseline was entirely below 0.30% (NI margin 0.3%), treatment with IDegLira was concluded to be noninferior to treatment with IGlar.

The robustness of the primary analysis was confirmed by three sensitivity analyses: the repeated measurement model (LS mean treatment difference for the change from baseline was −0.66% [95% CI, −0.80 to −0.52]), the completer analysis (LS mean treatment

difference for the change from baseline was −0.65% [95% CI, −0.79 to −0.51]), and the PP analysis (LS mean treatment difference for the change from baseline was −0.65% [95% CI, −0.79 to −0.51]). All agreed with the primary analysis conducted on LOCF (see Table 18).

The change in hemoglobin A1C from baseline to week 26 was tested for superiority using an ANCOVA model with an adjusted significance level. The estimated LS mean treatment difference for the change from baseline in hemoglobin A1C for IDegLira versus IGlar was −0.59% (95% CI, −0.74 to −0.45; $P < 0.001$), confirming superiority of IDegLira compared with IGlar regarding effect on hemoglobin A1C.

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 3). In other post hoc subgroup analyses according to baseline hemoglobin A1C (≤ 7.5%, > 7.5% to ≤ 8.5%, and > 8.5%) and BMI (< 30 kg/m^2, ≥ 30 kg/m^2 to < 35 kg/m^2, and ≥ 35 kg/m^2), the interaction analysis indicated no difference in effect of IDegLira versus IGlar across baseline hemoglobin A1C categories (see Figure 4) and across BMI categories (see Figure 5).

DUAL VII

The DUAL VII trial enrolled patients with T2DM inadequately controlled on IGlar at a daily dose between 20 U and 50 U (both inclusive) in combination with MET, and randomized patients to IDegLira or a starting dose of IGlar equal to the pretrial daily dose plus prandial IAsp. In DUAL VII, the mean hemoglobin A1C at baseline was 8.21% in the IDegLira group and 8.24% in the IGlar + IAsp group. After 26 weeks of treatment, LS mean hemoglobin A1C had decreased by 1.48% to 6.73% in the IDegLira group and by 1.46% to 6.75% in the IGlar + IAsp group (see Table 15). The estimated LS mean difference for the change from baseline in hemoglobin A1C for IDegLira versus IGlar + IAsp was −0.02 (95% CI, −0.16 to 0.12). Given that the 95% CI for the mean treatment difference was entirely below 0.30% (NI margin 0.3%), treatment with IDegLira was concluded to be noninferior to treatment with IGlar + IAsp.

The NI outcome of the primary analysis, which applied MMRM to the FAS, was in agreement with the results of each of the six sensitivity analyses that were performed. MMRM applied to the PP analysis, the CAS, and the FAS (including retrieved data at week 26 from patients who prematurely discontinued treatment), while ANCOVA applied to the FAS with LOCF imputed values, the FAS with conditional multiple imputation, and the FAS with unconditional multiple imputation. These sensitivity analyses produced estimated LS mean treatment differences of −0.04 to 0.00%. The 95% CI for the LS mean treatment difference for the change from baseline was entirely below 0.30% for all of the sensitivity analyses conducted (see Table 18).

The upper bound of the 95% CI for the estimated LS mean treatment difference for the change from baseline of IDegLira versus IGlar + IAsp was also compared with a 0.00% margin. However, in none in the analyses was the 95% CI for the LS mean treatment difference entirely below 0.00%, indicating that IDegLira is noninferior but not superior to IGlar + IAsp. This test was not part of the hierarchical testing procedure.

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 6).

DUAL III

The DUAL III trial enrolled insulin-naive patients with T2DM inadequately controlled on a maximum tolerated dose or maximum dose according to the local label of GLP-1 RA and MET ± pioglitazone ± SU, and randomized patients to IDegLira or to continue their unchanged pretrial GLP-1 RA medication in stable pretrial doses. In DUAL III, the mean hemoglobin A1C at baseline was 7.8% in the IDegLira group and 7.7% in the GLP-1 RA group. After 26 weeks of treatment, mean hemoglobin A1C had decreased by 1.32% to 6.4% in the IDegLira group and by 0.37% to 7.4% in the GLP-1 RA group (see Table 15). The estimated LS mean difference for the change from baseline was −0.94 (95% CI, −1.11 to −0.78). This was statistically significant favouring IDegLira versus GLP-1 RA ($P < 0.001$), indicating that IDegLira is superior to unchanged GLP-1 RA therapy.

The robustness of the primary analysis for the change from baseline in hemoglobin A1C was confirmed by three sensitivity analyses: the repeated measurement model (LS mean treatment difference was −0.93% [95% CI, −1.09 to −0.76], $P < 0.001$), the completer analysis (LS mean treatment difference was −0.85% [95% CI, −1.02 to −0.68], $P < 0.001$) and the PP analysis (LS mean treatment difference was −0.98% [95% CI, −1.15 to −0.81], $P < 0.001$). All showed high similarity to the primary analysis conducted on LOCF (see Table 18).

Subgroup analyses were conducted on the subset of patients who had been on liraglutide; results of these subgroup analyses are presented in Table 27. While the results from the subset of patients who had been on liraglutide were in line with the overall patient population in the DUAL III trial, it is worth noting that these analyses were post hoc subgroup analyses and were exploratory in nature — they were unplanned and performed after data were collected.

Table 15: Hemoglobin A1C After 26 Weeks of Treatment

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Hemoglobin A1C (%)								
Baseline (Week 0)								
N	199	199	278	279	244	245	292	146
Mean (SD)	8.7 (0.7)	8.8 (0.7)	8.4 (0.9)	8.2 (0.9)	8.21 (0.76)	8.24 (0.81)	7.8 (0.6)	7.7 (0.6)
After 26 Weeks of Treatment								
N	199	199	278	279	244	245	292	146
LS mean (SEM)	6.88 (0.073)	7.93 (0.073)	6.54 (0.05)	7.14 (0.05)	6.73 (0.05)	6.75 (0.05)	6.44 (0.05)	7.38 (0.07)
Change From Baseline After 26 Weeks of Treatment								
N	199	199	278	279	244	245	292	146
LS mean (SEM)	−1.92 (0.073)	−0.87 (0.073)	−1.77 (0.05)	−1.17 (0.05)	−1.48 (0.05)	−1.46 (0.05)	−1.32 (0.05)	−0.37 (0.07)
LS mean difference after 26 weeks of treatment (95% CI)	−1.05 (−1.25 to −0.84)		−0.59 (−0.74 to −0.45)		−0.02 (−0.16 to 0.12)		−0.94 (−1.11 to −0.78)	

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
P value	< 0.0001		< 0.001		< 0.0001		< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. Change in hemoglobin A1C from baseline after 26 weeks of treatment was analyzed using an ANCOVA model with treatment, country, and previous antidiabetes treatment as fixed factors and baseline A1C value as a covariate. *P* value for IDegLira minus IDeg is test for superiority.

[b] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[c] All post-baseline A1C measurements obtained at planned visits before discontinuation from randomized treatment were analyzed via a linear mixed normal model using an unstructured residual covariance matrix for A1C measurements within the same patient. The model included treatment, visit, and region as fixed factors and baseline A1C as a covariate. Interactions between visit and all factors and covariates were also included in the model. *P* value is two-sided test for noninferiority.

[d] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]) and region as fixed factors and baseline A1C value as a covariate.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Responders for hemoglobin A1C

Responders for hemoglobin A1C (defined as hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) were secondary end points in all of the included trials. In addition, these responder end points (A1C < 7.0% or A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain, or hypoglycemic episodes, or both were performed as secondary efficacy end points in DUAL II and DUAL V. As well, these responder end points (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain or treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes or both were performed as secondary efficacy end points in DUAL VII. All of these outcomes were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

DUAL II

After 26 weeks of treatment, the proportion of patients achieving hemoglobin A1C < 7% was 60.3% in the IDegLira treatment group and 23.1% in the IDeg treatment group, and the proportion of patients achieving hemoglobin A1C ≤ 6.5% was 45.2% in the IDegLira treatment group and 13.1% in the IDeg treatment group (see Table 19). The estimated odds of achieving the targets of hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% after 26 weeks of treatment were higher for patients in the IDegLira treatment group compared with patients in the IDeg treatment group (estimated odds ratios: 5.44 [95% CI, 3.42 to 8.66] and 5.66 [95% CI, 3.37 to 9.51], respectively). The *P* value for each of these analyses was < 0.0001 (see Table 19).

In the IDegLira treatment group, 48.7% of patients achieved the hemoglobin A1C target of < 7% after 26 weeks of treatment without confirmed hypoglycemic episodes, and the proportion was 36.2% for the hemoglobin A1C target ≤ 6.5% without confirmed hypoglycemia. These proportions were higher than those reported in the IDeg treatment group (15.6% and 7.0%) for hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5%, respectively. The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without confirmed hypoglycemia) after 26 weeks of treatment were higher for patients in the IDegLira treatment group compared with patients in the IDeg treatment

group (estimated odds ratio: 5.57 [95% CI, 3.36 to 9.21] and 7.79 [95% CI, 4.11 to 14.76], respectively) (see Table 19).

In the IDegLira treatment group, 50.8% of patients achieved the hemoglobin A1C target of < 7% after 26 weeks of treatment without weight gain. The proportion was 38.2% for the hemoglobin A1C target ≤ 6.5% without weight gain. These proportions were higher than the corresponding proportions reported in the IDeg treatment group (12.1% and 8.0%). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IDeg treatment group (estimated odds ratios: 7.65 [95% CI, 4.50 to 13.02] and 7.32 [95% CI, 3.98 to 13.46], respectively) (see Table 19).

In the IDegLira treatment group, 40.2% of patients achieved the hemoglobin A1C target of < 7% without hypoglycemic episodes and weight gain. The proportion was 29.6% for the hemoglobin A1C target ≤ 6.5% without hypoglycemia and weight gain. These proportions were higher than the corresponding proportions observed with IDeg (8.5% and 4.5%). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IDeg treatment group (estimated odds ratios: 7.44 [95% CI, 4.08 to 13.57] and 8.85 [95% CI, 4.15 to 18.89], respectively) (see Table 19).

As mentioned previously, all of these analyses for responders for hemoglobin A1C were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

DUAL V

After 26 weeks of treatment, the proportion of patients achieving hemoglobin A1C < 7% was 71.6% in the IDegLira treatment group and 47.0% in the IGlar treatment group, and the proportion of patients achieving hemoglobin A1C ≤ 6.5% was 55.4% in the IDegLira treatment group and 30.8% in the IGlar treatment group (see Table 19). The estimated odds of achieving the targets of hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% after 26 weeks of treatment were higher for patients in the IDegLira treatment group compared with patients in the IGlar treatment group (estimated odds ratios: 3.45 [95% CI, 2.36 to 5.05] and 3.29 [95% CI, 2.27 to 4.75], respectively). The *P* value for each of these analyses was < 0.001 (see Table 19).

In the IDegLira treatment group, 54.3% of patients achieved the hemoglobin A1C target of < 7% after 26 weeks of treatment without confirmed hypoglycemic episodes, and the proportion was 41.4% for the hemoglobin A1C target ≤ 6.5% without confirmed hypoglycemia. These proportions were higher than those reported in the IGlar treatment group (29.4% and 19.0%) for hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5%, respectively. The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without confirmed hypoglycemia) after 26 weeks of treatment were higher for patients in the IDegLira treatment group compared with patients in the IGlar treatment group (estimated odds ratios: 3.24 [95% CI, 2.24 to 4.70] and 3.39 [95% CI, 2.27 to 5.05], respectively) (see Table 19).

In the IDegLira treatment group, 50.0% of patients achieved the hemoglobin A1C target of < 7% after 26 weeks of treatment without weight gain. The proportion was 41.7% for the hemoglobin A1C target ≤ 6.5% without weight gain. These proportions were higher than the corresponding proportions reported in the IGlar treatment group (19.7% and 12.5%). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without

weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IGlar treatment group (estimated odds ratios: 5.18 [95% CI, 3.43 to 7.83] and 6.14 [95% CI, 3.90 to 9.68], respectively) (see Table 19).

In the IDegLira treatment group, 38.8% of patients achieved the hemoglobin A1C target of < 7% without hypoglycemic episodes and weight gain. The proportion was 31.7% for the hemoglobin A1C target ≤ 6.5% without hypoglycemia and weight gain. These proportions were higher than the corresponding proportions observed with IGlar (12.2% and 7.5%). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IGlar treatment group (estimated odds ratios: 5.53 [95% CI, 3.49 to 8.77] and 6.76 [95% CI, 3.96 to 11.55], respectively) (see Table 19).

As mentioned previously, all of these analyses for responders for hemoglobin A1C were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Post hoc subgroup analyses for patients reaching hemoglobin A1C < 7% and composite end points (hemoglobin A1C < 7% without hypoglycemia [in the last 12 weeks] and hemoglobin A1C < 7% without hypoglycemia [in the last 12 weeks] and without weight gain) were conducted according to baseline hemoglobin A1C (≤ 7.5%, > 7.5% to ≤ 8.5%, and > 8.5%) and BMI (< 30 kg/m^2, ≥ 30 kg/m^2 to < 35 kg/m^2, and ≥ 35 kg/m^2). The interaction analysis indicated no difference in effect of IDegLira versus IGlar across baseline hemoglobin A1C categories (see Figure 7) and across BMI categories (see Figure 8).

DUAL VII

Consistent with the outcome of the primary analysis, similar proportions of patients in the IDegLira group and the IGlar + IAsp group achieved the hemoglobin A1C targets (< 7.0% and ≤ 6.5%). After 26 weeks of treatment, the proportion of patients achieving hemoglobin A1C < 7% was 62.3% in the IDegLira treatment group and 63.8% the IGlar + IAsp treatment group, and the proportion of patients achieving hemoglobin A1C ≤ 6.5% was 46.8% in the IDegLira treatment group and 41.3% in the IGlar + IAsp treatment group (see Table 19). The estimated odds ratios of achieving the targets of hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% after 26 weeks of treatment were 0.91 (95% CI, 0.62 to 1.33; *P* = 0.6207), and 1.26 (95% CI, 0.88 to 1.82; *P* = 0.2116), respectively, indicating no statistically significant difference between treatment groups (see Table 19).

In contrast to the similarity between groups with respect to responders for hemoglobin A1C alone, the proportions of patients reaching each hemoglobin A1C target without any severe or BG-confirmed symptomatic hypoglycemic episode during the last 12 weeks of treatment were higher in the IDegLira treatment group (54.4% and 41.7% for hemoglobin A1C < 7% and hemoglobin A1C ≤ 6.5%, respectively), compared with the IGlar + IAsp treatment group (31.9% and 23.2% for hemoglobin A1C < 7% and hemoglobin A1C ≤ 6.5%, respectively) (see Table 19). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IGlar + IAsp treatment group (estimated odds ratios: 2.58 [95% CI, 1.78 to 3.74] and 2.59 [95% CI, 1.73 to 3.87], respectively) (see Table 19).

Similarly, the proportions of patients reaching each hemoglobin A1C target without weight gain from baseline to 26 weeks were higher in the IDegLira treatment group (40.9% and 30.2% for hemoglobin A1C < 7% and hemoglobin A1C ≤ 6.5%, respectively), compared with the IGlar + IAsp treatment group (15.0% and 10.2% for hemoglobin A1C < 7% and

hemoglobin A1C ≤ 6.5%, respectively) (see Table 19). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% without weight gain) were higher for patients in the IDegLira treatment group compared with patients in the IGlar + IAsp treatment group (estimated odds ratios: 4.46 [95% CI, 2.89 to 6.89] and 4.15 [95% CI, 2.52 to 6.84], respectively) (see Table 19).

The proportions of patients reaching each hemoglobin A1C target with neither weight gain nor any severe or BG-confirmed symptomatic hypoglycemic episode were also higher in the IDegLira treatment group (36.1% and 27.0% for hemoglobin A1C < 7% and hemoglobin A1C ≤ 6.5%, respectively), compared with the IGlar + IAsp treatment group (6.3% and 4.7% for hemoglobin A1C < 7% and hemoglobin A1C ≤ 6.5%, respectively) (see Table 19). The odds of achieving these targets (hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% with neither weight gain nor severe or BG-confirmed symptomatic hypoglycemic episode) were higher for patients in the IDegLira treatment group compared with patients in the IGlar + IAsp treatment group (estimated odds ratios: 10.39 [95% CI, 5.76 to 18.75] and 9.23 [95% CI, 4.68 to 18.20], respectively) (see Table 19).

As mentioned previously, all of these analyses for responders for hemoglobin A1C were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

DUAL III

After 26 weeks of treatment, the proportion of patients achieving hemoglobin A1C < 7% was 75.3% in the IDegLira treatment group and 35.6% in the GLP-1 RA treatment group, and the proportion of patients achieving hemoglobin A1C ≤ 6.5% was 63.0% in the IDegLira treatment group and 22.6% in the GLP-1 RA treatment group (see Table 19). The estimated odds ratios of achieving the targets of hemoglobin A1C < 7% or hemoglobin A1C ≤ 6.5% after 26 weeks of treatment were higher for patients in the IDegLira treatment group compared with patients in the GLP-1 RA treatment group (estimated odds ratios: 6.84 [95% CI, 4.28 to 10.94] and 7.53 [95% CI, 4.58 to 12.38], respectively). The *P* value for each of these analyses was < 0.001 (see Table 19). As mentioned previously, all of these analyses for responders for hemoglobin A1C were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Fasting Plasma Glucose

The change from baseline after 26 weeks of treatment in FPG was a secondary efficacy end point in all included trials. In the DUAL II and DUAL III trials, the difference between treatments after 26 weeks of treatment favoured IDegLira versus IDeg and GLP-1 RA (LS mean treatment difference for the change from baseline: −0.73 mmol/L [95% CI, −1.19 to −0.27] and −2.64 mmol/L [95% CI, −3.03 to −2.25], respectively), whereas in the DUAL V and DUAL VII trials, no statistically significant difference was found between IDegLira and IGlar and between IDegLira and IGlar + IAsp (LS mean treatment difference for the change from baseline: −0.01 mmol/L [95% CI, −0.35 to 0.33] and −0.31 mmol/L [95% CI, −0.67 to 0.05], respectively) (see Table 20). The change from baseline after 26 weeks of treatment in FPG was not adjusted for multiplicity in all of the trials, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Health-Related Quality of Life Outcomes

HRQoL was not evaluated in DUAL II. Patients' HRQoL was evaluated using the TRIM-D in DUAL V, DUAL VII, and DUAL III, the SF-36 in DUAL V and DUAL VII, and the DTSQs in DUAL III. Patient-reported HRQoL data were not adjusted for multiplicity in all of the trials, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Treatment-Related Impact Measure for Diabetes

DUAL V

In both treatment groups, all subdomain scores and the total score increased throughout the trial; however, the increase was higher in the IDegLira group compared with the IGlar group. After 26 weeks of treatment, the total score was higher for patients in the IDegLira group compared with the IGlar group with an estimated LS mean for the change from baseline treatment difference of 2.8 points (95% CI, 0.9 to 4.7). This higher total score for IDegLira compared with IGlar was mainly driven by higher scores after 26 weeks of treatment for two subdomains (treatment burden and diabetes management) (see Table 21).

DUAL VII

After 26 weeks of treatment, all subdomain scores and the total score increased from baseline in the IDegLira group, and the total score and all subdomain scores except one (daily life subdomain) increased in the IGlar + IAsp group. After 26 weeks of treatment, the total score was higher for patients in the IDegLira group compared with patients in the IGlar + IAsp group; the estimated LS mean difference for the change from baseline was 6.50 (95% CI, 4.44 to 8.57). Similarly, all subdomains were higher for patients in the IDegLira group compared with patients in the IGlar + IAsp group after 26 weeks of treatment (see Table 21).

DUAL III

All subdomain scores and the total score increased after 26 weeks of treatment in both treatment groups. After 26 weeks of treatment, the total score was higher for patients in the IDegLira group compared with patients in the GLP-1 RA group; the estimated LS mean difference for the change from baseline was 5.0 points (95% CI, 2.9 to 7.2). Similarly, all subdomains were higher for patients in the IDegLira group compared with patients in the GLP-1 RA group after 26 weeks of treatment (see Table 21).

Short Form (36) Health Survey Version 2

DUAL V

The score for all domains within the PCS score increased after 26 weeks of treatment for IDegLira indicating improved physical health, whereas the score for all except one (general health) of the physical domains decreased for IGlar. After 26 weeks of treatment, the PCS score, physical functioning, bodily pain, and general health were higher for patients in the IDegLira group compared with patients in the IGlar group (Table 22); however, the between-group differences for the PCS score and its domains were ≤ 2, indicating that the improvements may not be considered clinically important.

All mental health domains (except role emotional in the IGlar group) increased marginally for both treatment groups after 26 weeks of treatment; however, no statistically significant difference between the IDegLira and IGlar groups was reported for the MCS score and its domains (see Table 22).

DUAL VII

After 26 weeks of treatment, all scores increased from baseline in the IDegLira and the IGlar + IAsp treatment groups. After 26 weeks of treatment, the mental health domain and the MCS score were higher for patients in the IDegLira group compared with patients in the IGlar + IAsp treatment group (see Table 22); however, the between-group differences for the mental health domain and the MCS score were ≤ 3, indicating that the improvements may not be considered clinically important. No statistically significant difference between the IDegLira and IGlar + IAsp groups was reported for the PCS score and all other domains (seeTable 22).

Diabetes Treatment Satisfaction Questionnaire, Status Version

DUAL III

After 26 weeks of treatment, the treatment satisfaction scale total was higher for patients in the IDegLira group compared with patients in the GLP-1 RA group; the estimated LS mean treatment difference for the change from baseline was 2.0 (95% CI, 1.1 to 2.8), indicating more patient satisfaction associated with the IDegLira treatment. Patients scored “hypoglycemia” higher in the IDegLira group compared with patients in the GLP-1 RA group; the estimated LS mean treatment difference for the change from baseline was 0.4 (95% CI, 0.1 to 0.6). Meanwhile, patients scored “hyperglycemia” lower in the IDegLira group compared with patients in the GLP-1 RA group; the estimated LS mean treatment difference for the change from baseline was −1.0 (95% CI, −1.4 to −0.7) (see Table 23).

Body Weight

Change from baseline in body weight after 26 weeks of treatment was a secondary efficacy end point in all included trials. This outcome was adjusted for multiple testing in the DUAL V and DUAL VII trials, but was not adjusted for multiplicity in the DUAL II and DUAL III trials; hence, any result reported for DUAL II and DUAL III should be interpreted with consideration of the potential for inflated type I error.

DUAL II

Body weight at baseline was 95.4 kg for IDegLira and 93.5 kg for IDeg. On IDegLira, body weight decreased, whereas it remained relatively stable throughout the trial on IDeg. After 26 weeks of treatment, LS mean body weight was 91.86 kg and 94.37 kg corresponding to a change in body weight from baseline to week 26 of −2.59 kg and −0.08 kg, for IDegLira and IDeg, respectively. The estimated LS mean treatment difference for the change from baseline between IDegLira and IDeg was −2.51 kg (95% CI, −3.21 to −1.82), demonstrating a greater reduction in body weight on IDegLira compared with IDeg (see Table 24).

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 2).

DUAL V

At baseline, the observed mean body weight was 88.3 kg in the IDegLira group and 87.3 kg in the IGlar group. After 26 weeks of treatment, the LS mean body weight was 86.38 kg and 89.58 kg, corresponding to a change in body weight from baseline to week 26 of −1.39 kg and +1.81 kg in the IDegLira and IGlar groups, respectively. The change in body weight from baseline to week 26 was analyzed using an ANCOVA model with an adjusted significance level. The estimated LS mean treatment difference for the change from baseline in body weight between IDegLira and IGlar was −3.20 kg (95% CI, −3.77 to −2.64), $P < 0.001$ (see Table 24). This indicated superiority of IDegLira compared with IGlar with regard to reduction in body weight.

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 3). Other post hoc subgroup analyses according to baseline hemoglobin A1C (≤ 7.5%, > 7.5% to ≤ 8.5%, and > 8.5%) indicated that, for all baseline hemoglobin A1C categories, IDegLira was associated with weight loss and IGlar with weight gain (see Figure 9). The interaction analysis indicated an increasing weight difference with higher baseline hemoglobin A1C. In the post hoc subgroup analyses according to baseline BMI (< 30 kg/m^2, ≥ 30 kg/m^2 to < 35 kg/m^2, and ≥ 35 kg/m^2), the interaction analysis indicated no difference in effect of IDegLira versus IGlar (see Figure 10).

DUAL VII

At baseline, the observed mean body weight was 87.2 kg in the IDegLira group and 88.2 kg in the IGlar + IAsp group. After 26 weeks of treatment, the LS mean body weight was 86.51 kg and 90.08 kg, corresponding to a change in body weight from baseline to week 26 of −0.93 kg and +2.64 kg in the IDegLira and IGlar + IAsp groups, respectively. The estimated LS mean treatment difference for change from baseline in body weight after 26 weeks of treatment with IDegLira versus IGlar + IAsp was −3.57 kg (95% CI, −4.19 to −2.95), $P < 0.0001$ (see Table 24). This demonstrates the superiority of IDegLira versus IGlar + IAsp.

Post hoc subgroup analyses by duration of diabetes (< 10 years, ≥ 10 years) showed no difference in treatment effect between the diabetes duration subgroups (see Figure 6).

DUAL III

Body weight at baseline was 95.6 kg in the IDegLira group and 95.5 kg in the GLP-1 RA group. This changed to 97.5 kg and 94.6 kg after 26 weeks of treatment with IDegLira and GLP-1 RA, respectively. This corresponded to a LS mean change of 2.0 kg for patients in the IDegLira group and −0.89 kg for patients in the GLP-1 RA group. The estimated LS mean treatment difference for the change from baseline between the IDegLira and GLP-1 RA groups was 2.89 kg (95% CI, 2.17 to 3.62), demonstrating a greater increase in body weight on IDegLira compared with GLP-1 RA (see Table 24).

Subgroup analyses were conducted on the subset of patients who had been on liraglutide; the results of these subgroup analyses are presented in Table 27. While the results from the subset of patients who had been on liraglutide were in line with the overall patient population in the DUAL III trial, it is worth noting that these analyses were post hoc subgroup analyses and were exploratory in nature — they were unplanned and performed after data were collected.

Blood Pressure

Change from baseline after 26 weeks of treatment in SBP and DBP were secondary efficacy end points in all included trials.

At baseline, the mean SBP ranged from 130.2 mm Hg to 133.0 mm Hg across all treatment groups in the four trials. Across the included trials, the LS mean SBP decreased 0.08 mm Hg to 5.41 mm Hg after 26 weeks of treatment. In the DUAL II, DUAL V, and DUAL VII trials, the difference between treatments in SBP after 26 weeks of treatment favoured IDegLira versus IDeg, IGlar, and IGlar + IAsp. The LS mean treatment difference for the change from baseline was as follows: −3.71 mm Hg (95% CI, −6.13 to −1.29), −3.57 mm Hg (95% CI, −5.54 to −1.59), and −3.70 mm Hg (95% CI, −5.68 to −1.72), respectively. In the DUAL III trial, however, no statistically significant difference was found between IDegLira and GLP-1 RA. The LS mean treatment difference was −0.75 mm Hg (95% CI, −3.10 to 1.59) (see Table 25).

At baseline, the mean DBP ranged from 76.75 mm Hg to 79.4 mm Hg across all treatment groups in the four trials. After 26 weeks of treatment, the LS mean DBP decreased in all treatment groups except in the GLP-1 RA treatment group in the DUAL III trial, where it increased by 0.14 mm Hg. Across the included trials, the reduction in DBP ranged from 0.13 mm Hg to 1.38 mm Hg after 26 weeks of treatment — except in the GLP-1 RA treatment group in the DUAL III trial, where it increased by 0.14 mm Hg. There was no statistically significant difference in DBP between treatment groups in the four trials (see Table 25).

The change from baseline after 26 weeks of treatment in SBP and DBP were not adjusted for multiplicity in all of the trials, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Post hoc subgroup analyses for the change from baseline in SBP after 26 weeks by duration of diabetes (< 10 years, ≥ 10 years) was conducted in DUAL II, DUAL V, and DUAL VII. These analyses showed no difference in treatment effect between the diabetes duration subgroups (see Figure 2, Figure 3, and Figure 6).

Post hoc subgroup analyses for the change from baseline in DBP after 26 weeks by duration of diabetes (< 10 years, ≥ 10 years) was conducted in DUAL II, DUAL V, and DUAL VII. These analyses showed no difference in treatment effect between the diabetes duration subgroups (see Figure 2, Figure 3, and Figure 6).

Fasting Lipid Profile

Change from baseline after 26 weeks of treatment in fasting lipid profile (e.g., total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein (VLDL) cholesterol, and triglycerides) was a secondary efficacy end point in all included trials. With the exception of HDL cholesterol, lower levels of these lipids are considered favourable.

Overall, the changes from baseline to week 26 in fasting lipid levels were small across all treatment groups in the four trials. After 26 weeks of treatment, total cholesterol and LDL cholesterol were reduced to lower levels with IDegLira than with IDeg and IGlar, favouring IDegLira in the DUAL II and DUAL V trials, respectively. Total cholesterol was reduced to lower levels with IDegLira than with IGlar + IAsp (favouring IDegLira), and HDL cholesterol was increased to higher levels with IGlar + IAsp than with IDegLira (favouring IGlar + IAsp)

in the DUAL VII trial. Total cholesterol, VLDL cholesterol, and triglycerides were lower with IDegLira than with GLP-1 RA (favouring IDegLira) after 26 weeks of treatment in the DUAL III trial (see Table 26). The change from baseline after 26 weeks of treatment in fasting lipid profile was not adjusted for multiplicity in all of the trials, and any result reported should be interpreted with consideration of the potential for inflated type I error.

Post hoc subgroup analyses for the change from baseline in total cholesterol, HDL cholesterol, LDL cholesterol, VLDL cholesterol, and triglycerides after 26 weeks by duration of diabetes (< 10 years, ≥ 10 years) was conducted in DUAL II, DUAL V, and DUAL VII. These analyses showed no difference in treatment effect between the diabetes duration subgroups (see Figure 11, Figure 12, Figure 13, Figure 14, Figure 15, and Figure 16).

Other Efficacy Outcomes

Efficacy outcomes such as changes in health care resource utilization and hospitalization were not reported in any of the trials.

Harms

Only those harms identified in the review protocol are reported as follows (see section 2.2.1, Protocol). See Table 16, Table 30, and Table 31 for detailed harms data.

Adverse Events

The overall frequency of AEs was similar between treatment groups within trials. In the DUAL II, DUAL V, and DUAL VII trials, AEs were reported by 57.6% to 59.1% of patients who received IDegLira, and by 61.3%, 50.5%, and 56.9% of patients who received IDeg, IGlar, and IGlar + IAsp, respectively. In the DUAL III trial, AEs were reported by 65.6% of patients treated with IDegLira, and by 63.4% of patients treated with GLP-1 RA. This small difference in frequency of AEs in the IDegLira treatment group between those reported in the DUAL III trial and the rest of the trials could be because all patients in DUAL III were concomitantly treated with MET ± pioglitazone ± SU, while in the other trials, patients were concomitantly treated with MET only.

In the DUAL II trial, the most frequently reported AEs in the IDegLira group were GI disorders (diarrhea and nausea) and headache, occurring in 6.0% to 6.5% of the patients. In the IDeg group, nasopharyngitis was the most reported AE, occurring in 6.0% of the patients. In the DUAL V trial, the most frequently reported AEs in the IDegLira group were GI disorders (nausea, diarrhea, and vomiting, occurring in 9.4%, 7.2%, and 5.0% of the patients, respectively); in the IGlar group, the most frequently reported AE was headache (occurring in 5.0% of the patients). In the DUAL VII trial, the most frequently reported AEs were nausea, diarrhea, influenza, and upper respiratory tract infection among patients treated with IDegLira, occurring in 11.1%, 6.3%, 7.1%, and 6.0% of the patients, respectively, and nasopharyngitis, upper respiratory tract infection, headache, and diabetic retinopathy among those treated with IGlar + IAsp, occurring in 11.9%, 6.7%, 7.1%, and 5.5% of the patients, respectively (Table 16).

In the DUAL III trial, the most frequently reported AEs were nasopharyngitis (8.9% of patients in the IDegLira group and 13.1% of patients in the GLP-1 RA group), upper respiratory tract infection (6.2% of patients in the IDegLira group and 5.5% of patients in the GLP-1 RA group), lipase increased (10.0% of patients in the IDegLira group and 4.8% of patients in the GLP-1 RA group), headache (9.3% of patients in the IDegLira group and

6.2% of patients in the GLP-1 RA group), and diarrhea (4.5% of patients in the IDegLira group and 5.5% of patients in the GLP-1 RA group) (see Table 16).

Serious Adverse Events

SAEs were reported by 1.8% to 4.8% of patients who received IDegLira, and by 5.5%, 3.2%, 4.0%, and 2.1% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively (see Table 16). In all of the included trials, no SAEs occurred in ≥ 1% of the patients. Details of the SAEs that occurred are presented in Table 30.

In the DUAL II trial, 22 SAEs were reported by 18 patients during the trial. All SAEs were reported by single patients only, except for acute MI and pneumonia, which were both reported by two patients, one in each treatment group.

In the DUAL V trial, 14 SAEs were reported: five events in five patients (1.8%) in the IDegLira group and nine events in nine patients (3.2%) in the IGlar group, including one event with a fatal outcome.

In the DUAL VII trial, 24 SAEs were reported in this trial, with 13 events in 12 patients (4.5%) in the IDegLira group and 11 events in 10 patients (4.0%) in the IGlar + IAsp group.

In the DUAL III trial, 15 SAEs were reported in 12 patients during the trial. Two patients in the IDegLira group reported two and three SAEs, respectively. The remaining 10 patients reported one SAE each.

Withdrawals Due to Adverse Events

The rates of AEs leading to withdrawal from the trials were reported by 0.3% to 2.5% of patients who received IDegLira, and by 1.5%, 0.4%, 0%, and 1.4% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively (see Table 16). Details of the AEs leading to treatment discontinuation that occurred are presented in Table 30.

In the DUAL II trial, four (1.0%) of 398 patients withdrew or were withdrawn from the trial due to AEs: one patient in the IDegLira group and three patients in the IDeg group. The only AE leading to withdrawal in the IDegLira group was major depression, as noted in Table 30.

In the DUAL V trial, eight patients (1.4%) had 12 AEs leading to withdrawal: seven patients (2.5%) in the IDegLira group and one patient (0.4%) in the IGlar group. The primary reason for withdrawal in the IDegLira group was GI AEs (this occurred in four patients [1.4%]). The only AE leading to withdrawal in the IGlar group was hemorrhagic stroke with a fatal outcome, as noted in Table 30.

In the DUAL VII trial, seven patients (1.3%) had 11 AEs leading to permanent discontinuation of treatment. Six (2.4%) of these patients were in the IDegLira group and one patient (0.4%) was in the IGlar + IAsp group. The AEs leading to permanent discontinuation of treatment in the IDegLira group were GI and cardiac disorders (five patients [1.98%] had GI AEs and one patient [0.4%] had both GI AEs and palpitations), while the patient in the IGlar + IAsp group experienced worsening of a psychiatric disorder, as noted in Table 30.

In the DUAL III trial, three patients (0.7%) had AEs leading to withdrawal: one patient (0.3%) in the IDegLira group with drug hypersensitivity and two patients (1.4%) in the GLP-1 RA group with abdominal discomfort and foot fracture, as noted in Table 30.

Mortality

No deaths were reported during the DUAL II, DUAL VII, and DUAL III trials.

In the DUAL V trial, one patient died during the trial; that patient was treated with IGlar and died due to hemorrhagic stroke. The event was considered unlikely to be related to the trial product.

Notable Harms

Notable harms are detailed in Table 31.

The proportion of patients who experienced confirmed hypoglycemic episodes in the IDegLira group ranged from 24.1% to 32.0% across the trials, and confirmed hypoglycemic episodes was experienced by 24.6%, 49.1%, 60.9%, and 2.8% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively (see Table 16). The proportion of patients that experienced severe hypoglycemia as defined by ADA in each individual study ranged from 0% to 1.6% across the treatment groups in the included trials.

The number of treatment-emergent confirmed hypoglycemic episodes during 26 weeks of treatment was a secondary end point in DUAL V and DUAL III, and the number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes during 26 weeks of treatment was a secondary end point in DUAL VII. This outcome was adjusted for multiple testing in the DUAL V and DUAL VII trials, but was not adjusted for multiplicity in the DUAL III trial; hence, any result reported for DUAL III should be interpreted with consideration of the potential for inflated type I error. In the DUAL V trial, patients in the IDegLira treatment group experienced 289 confirmed hypoglycemic episodes in total (a rate of 2.23 episodes per patient-year of exposure [PYE]) versus patients in the IGlar treatment group who experienced 683 confirmed hypoglycemic episodes in total (a rate of 5.05 episodes per PYE). The estimated treatment ratio of IDegLira versus IGlar was 0.43 (95% CI, 0.30 to 0.61; $P < 0.001$), with a statistically significantly lower rate of confirmed hypoglycemic episodes in the IDegLira group compared with the IGlar group (see Table 28). In the DUAL VII trial, patients in the IDegLira treatment group experienced 129 severe or BG-confirmed symptomatic hypoglycemic episodes in total (a rate of 1.07 episodes per PYE) versus patients in the IGlar + IAsp treatment group who experienced 975 severe or BG-confirmed symptomatic hypoglycemic episodes in total (a rate of 8.17 episodes per PYE). The estimated treatment ratio was 0.11 (95% CI, 0.08 to 0.17; $P < 0.0001$), demonstrating the superiority of IDegLira versus IGlar + IAsp (see Table 29). In the DUAL III trial, patients in the IDegLira treatment group experienced 397 confirmed hypoglycemic episodes in total (a rate of 2.81 episodes per PYE) versus patients in the GLP-1 RA treatment group who experienced eight confirmed hypoglycemic episodes in total (a rate of 0.12 episodes per PYE). The estimated treatment ratio of IDegLira versus GLP-1 RA was 25.36 (95% CI, 10.63 to 60.51; $P < 0.001$), demonstrating a higher rate of confirmed hypoglycemic episodes with IDegLira compared with GLP-1 RA (see Table 28).

The frequency of GI disorders was higher in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups, and it was similar to that reported in the GLP-1 RA treatment group (see Table 16 and Table 31).

The occurrence of other harms of special interest to this review (renal failure, arrhythmia, allergic reaction [immunogenicity], and injection site reactions) was infrequent, and no cases of pancreatitis or antibody formation were reported in the trials (see Table 16 and Table 31).

Table 16: Harms

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
AEs								
Patients with ≥ 1 AEs, N (%)	115 (57.8)	122 (61.3)	160 (57.6)	141 (50.5)	149 (59.1)	144 (56.9)	191 (65.6)	92 (63.4)
Most common AEs[a]								
Diarrhea	13 (6.5)	7 (3.5)	20 (7.2)	7 (2.5)	16 (6.3)	10 (4.0)	13 (4.5)	8 (5.5)
Nausea	13 (6.5)	7 (3.5)	26 (9.4)	3 (1.1)	28 (11.1)	4 (1.6)	9 (3.1)	6 (4.1)
Lipase increased	12 (6.0)	7 (3.5)	9 (3.2)	4 (1.4)	6 (2.4)	3 (1.2)	29 (10.0)	7 (4.8)
Nasopharyngitis	5 (2.5)	12 (6.0)	10 (3.6)	10 (3.6)	12 (4.8)	30 (11.9)	26 (8.9)	19 (13.1)
Headache	12 (6.0)	4 (2.0)	11 (4.0)	14 (5.0)	14 (5.6)	18 (7.1)	27 (9.3)	9 (6.2)
Vomiting	7 (3.5)	0	14 (5.0)	5 (1.8)	9 (3.6)	6 (2.4)	4 (1.4)	4 (2.8)
Upper respiratory tract infection	7 (3.5)	5 (2.5)	6 (2.2)	6 (2.2)	15 (6.0)	17 (6.7)	18 (6.2)	8 (5.5)
Influenza	3 (1.5)	2 (1.0)	7 (2.5)	10 (3.6)	18 (7.1)	12 (4.7)	12 (4.1)	2 (1.4)
Diabetic retinopathy	2 (1.0)	2 (1.0)	1 (0.4)	7 (2.5)	9 (3.6)	14 (5.5)	3 (1.0)	3 (0.7)
SAEs								
Patients with ≥ 1 SAEs, N (%)[b]	7 (3.5)	11 (5.5)	5 (1.8)	9 (3.2)	12 (4.8)	10 (4.0)	9 (3.1)	3 (2.1)
WDAEs								
WDAEs, N (%)	1 (0.5)	3 (1.5)	7 (2.5)	1 (0.4)	1 (0.4)	0	1 (0.3)	2 (1.4)
Deaths								
Number of deaths, N (%)	0	0	0	1 (0.4)	0	0	0	0
Hemorrhagic stroke	0	0	0	1 (0.4)	0	0	0	0
Notable Harms								
Myocardial infarction	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Stroke	0	1 (0.5)	1 (0.4)	0	0	0	2 (0.7)	0
Cardiac arrhythmia	5 (2.5)	4 (2.0)	5 (1.8)	2 (0.7)	6 (2.4)	0	6 (2.1)	2 (1.4)
Pancreatitis	0	0	0	0	0	0	0	0
Renal failure	1 (0.5)	0	0	0	0	1 (0.4)	0	0
Renal failure acute	1 (0.5)	NR	1 (0.4)	0	0	0	0	0
Confirmed hypoglycemia	48 (24.1)	49 (24.6)	79 (28.4)	137 (49.1)	79 (31.3)	154 (60.9)	93 (32.0)	4 (2.8)
Severe hypoglycemia as defined by the American Diabetes Association	1 (0.5)	0	0 (0.0)	1 (0.4)	3 (1.2)	4 (1.6)	1 (0.3)	0
Allergic reaction (immunogenicity)	0	2 (1.0)	7 (2.5)	7 (2.5)	3 (1.2)	5 (2.0)	8 (2.7)	7 (4.8)
Gastrointestinal AEs	42 (21.1)	23 (11.6)	70 (25.2)	27 (9.7)	59 (23.4)	28 (11.1)	45 (15.5)	22 (15.2)
Injection site reactions	1 (0.5)	5 (2.5)	1 (0.4)	2 (0.7)	0	1 (0.4)	8 (2.7)	1 (0.7)
Antibody formation	NR	NR	0	0	0	0	0	0

AE = adverse event; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; NR= nor reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] Frequency ≥ 5%.

[b] No SAEs occurred in more than 1% of patients.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Discussion

Summary of Available Evidence

Four phase III RCTs (DUAL II, DUAL V, DUAL VII, and DUAL III) provided evidence on the efficacy and safety of IDegLira in adults with T2DM and inadequate glycemic control that is controlled with various background antihyperglycemic agents, such as basal insulin in combination with MET, with or without SU or glinides (DUAL II), IGlar in combination with MET (DUAL V and DUAL VII), and GLP-1 RA (liraglutide or exenatide injection) in combination with MET± pioglitazone ± SU. These trials examined short-term (26 weeks) surrogate outcomes, including hemoglobin A1C, body weight, and blood pressure. In all trials, the starting dose of IDegLira was 16 U (16 U IDeg/0.6 mg liraglutide) and was titrated according to a predefined titration algorithm with a maximum dose of 50 U (50 U IDeg/1.8 mg liraglutide) in combination with MET (DUAL II, DUAL V, and DUAL VII) or in combination with MET, with or without SU and with or without pioglitazone (DUAL III). Change from baseline in level of hemoglobin A1C was the primary outcome in all of the included trials. In all trials, secondary outcomes included the change from baseline in body weight, FPG, SBP, DBP, and fasting lipids after 26 weeks of treatment. The change from baseline after 26 weeks of treatment in HRQoL was evaluated using the TRIM-D in DUAL V, DUAL VII, and DUAL III, the SF-36 in DUAL V and DUAL VII, and the DTSQs in DUAL III.

In addition to the main trials reviewed, two clinical trials (DUAL VIII and the extension phase of DUAL I) were reviewed and critically appraised, and safety results are reported in Appendix 6. In addition, the manufacturer provided an indirect treatment comparison (ITC) that compared IDegLira with [redacted] with T2DM and inadequate glycemic control on basal insulin and MET, [redacted] with T2DM and inadequate glycemic control on liraglutide and MET (± SU). These are summarized and critically appraised in Appendix 7. Also reported in Appendix 8 was a summary and critical appraisal for the manufacturer-submitted pooled analysis that compared IDegLira with basal-bolus or GLP-1 RA added to basal insulin or up-titration of basal insulin-only therapy in the treatment of patients with T2DM uncontrolled on basal insulin (with or without MET or other oral AHAs).

Interpretation of Results

Efficacy

The Health Canada–approved indication for IDegLira details two populations that are eligible to use this product for T2DM. These are as follows:

- Population 1: For the once-daily treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with basal insulin (less than 50 U daily) do not provide adequate glycemic control
- Population 2: For the once-daily treatment of adults with T2DM to improve glycemic control in combination with MET, with or without SU, when these combined with liraglutide (less than or equal to 1.8 mg daily) do not provide adequate glycemic control

The DUAL II, DUAL V, and DUAL VII trials provide the efficacy and safety data for population 1, while the DUAL III trial provides the efficacy and safety data for population 2.

The manufacturer is requesting that IDegLira be reimbursed as an adjunct to lifestyle modifications to improve glycemic control in adults with T2DM when oral glucose-lowering medications combined with basal insulin, or basal insulin alone, do not provide adequate glycemic control. The manufacturer clarified that the requested reimbursement criteria that focuses on "or basal insulin alone do not provide adequate glycemic control" include patients with T2DM who are taking basal insulin without oral glucose-lowering medications other than MET.

IDegLira in combination with MET statistically significantly reduced hemoglobin A1C levels after 26 weeks of treatment compared with IDeg (DUAL II trial) or IGlar (DUAL V trial) in combination with MET in patients inadequately controlled on basal insulin and MET, with or without SU or glinides (DUAL II), or patients inadequately controlled on IGlar in combination with MET (DUAL V). The estimated LS mean difference for the change from baseline was −1.05% (95% CI, −1.25 to −0.84) in DUAL II and −0.59% (95% CI, −0.74 to −0.45) in DUAL V. The clinical expert consulted for this review considered the treatment effects observed as clinically relevant. However, the DUAL II trial had a pre-specified cap on maximum insulin dose. Therefore, many of the patients in the IDeg treatment group were not titrated fully during the 26-week trial but might have if the trial had been longer or if the dose had been changed more frequently. Clinical practice does not put a cap on insulin dose. In addition, pretrial randomized patients were already uncontrolled on basal insulin. Initiating therapy with the decreased dose of basal insulin for the IDeg group in addition to discontinuing their non-MET oral AHAs therapy biased efficacy results in favour of the IDegLira treatment group. Hence, the claim of superiority of IDegLira when compared with IDeg in the DUAL II trial is unsubstantiated. It is also uncertain if the efficacy results would have been different if the insulin comparator had been titrated fully, as would be the case in clinical practice. In contrast, in the DUAL V trial, patients in the IGlar group did not have to reduce their basal insulin dose and there was no cap on maximum insulin dose; while IDegLira was superior to IGlar, the magnitude for the treatment difference in hemoglobin A1C levels was not as large as that reported in the DUAL II trial for IDegLira versus capped basal insulin.

IDegLira, in combination with MET, was noninferior to IGlar + IAsp plus MET for the change from baseline in hemoglobin A1C after 26 weeks of treatment based on a 0.3% NI margin (DUAL VII). No statistically significant difference was detected between treatments in the test for superiority (LS mean difference was −0.02 [95% CI, −0.16 to 0.12]).

The DUAL III trial reported that IDegLira in combination with MET ± pioglitazone ± SU statistically significantly reduced hemoglobin A1C levels after 26 weeks of treatment compared with GLP-1 RA in combination with MET ± pioglitazone ± SU in patients inadequately controlled on a maximum tolerated dose or maximum dose, according to the local label of GLP-1 RA and MET ± pioglitazone ± SU. The estimated LS mean difference was −0.94 (95% CI, −1.11 to −0.78), which was statistically significant favouring IDegLira versus GLP-1 RA ($P < 0.001$). This indicated that IDegLira is superior to GLP-1 RA therapy. The clinical expert consulted for this review considered the treatment effects observed as clinically relevant. However, given that patients in the GLP-1 RA treatment group were taking the maximum recommended dose of comparator product at trial entry, and the dose was not to be changed during the trial, the lack of decline in hemoglobin A1C for the GLP-1 RA group was to be expected. The clinical expert indicated that the reduction reported in hemoglobin A1C in the GLP-1 RA treatment group is likely a diabetes-trial placebo effect,

where patients pay more attention to their T2DM and monitor more often than when they enrol in a trial, so a 0.3% to 0.4% change is to be expected. In contrast, IDegLira was started at 16 U and titrated to glycemic targets, resulting in a further glucose lowering. Overall, the DUAL III trial was compromised by poor study design but appeared to show efficacy of IDegLira in achieving target BG levels with continuous dose titration compared with continuation of a treatment regimen consisting of a GLP-1 RA in combination with oral AHAs.

In the DUAL II, DUAL V, and DUAL III trials, more patients in the IDegLira treatment groups achieved target hemoglobin A1C levels (< 7.0% or ≤ 6.5%) than in the IDeg, IGlar, or GLP-1 RA treatment groups. In addition, in the DUAL II and DUAL V trials, the proportion of patients reaching the predefined hemoglobin A1C targets (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain or hypoglycemic episodes or both was also higher in the IDegLira treatment groups than in the IDeg or IGlar treatment groups. No differences were detected in the proportion of patients achieving glycemic targets for the IDegLira group versus the IGlar + IAsp group in the DUAL VII trial. In addition, in the DUAL VII trial, treatment with IDegLira, compared with IGlar + IAsp, resulted in higher proportions of patients achieving glycemic targets (hemoglobin A1C < 7.0% or hemoglobin A1C ≤ 6.5%) after 26 weeks of treatment without either weight gain or treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes or both. However, all of these analyses in all the included trials were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error.

The change from baseline after 26 weeks of treatment in FPG was a secondary efficacy end point in all included trials. In the DUAL II and DUAL III trials, the difference between treatments after 26 weeks of treatment favoured IDegLira versus IDeg and GLP-1 RA (LS mean treatment difference for the change from baseline: −0.73 mmol/L [95% CI, −1.19 to −0.27] and −2.64 mmol/L [95% CI, −3.03 to −2.25] , respectively), whereas in the DUAL V and DUAL VII trials, no statistically significant difference was found between IDegLira and IGlar or between IDegLira and IGlar + IAsp (LS mean treatment difference for the change from baseline: −0.01 mmol/L [95% CI, −0.35 to 0.33] and −0.31 mmol/L [95% CI, −0.67 to 0.05], respectively). However, the change from baseline after 26 weeks of treatment in FPG was not adjusted for multiplicity in all of the trials, and any result reported should be interpreted with consideration of the potential for inflated type I error. The clinical expert consulted for this review indicated that results reported in the DUAL V and DUAL VII trials are typical in these treat-to-target trials.

HRQoL measures were included in this systematic review to provide a patient perspective of treatment with IDegLira and because this was considered an important outcome to patients, as reported in the patient input section (see Appendix 1). The HRQoL outcomes measurement tools used in the trials were the TRIM-D in DUAL V, DUAL VII, and DUAL III, the SF-36 in DUAL V and DUAL VII, and the DTSQs in DUAL III. Analyses of these outcomes were not adjusted for multiplicity, and any result reported should be interpreted with consideration of the potential for inflated type I error. While results from these patient-reported outcome questionnaires seemed to favour IDegLira treatment groups, no MCIDs were established specific to patients with T2DM, and the clinical significance of the benefit of IDegLira compared with IGlar, IGlar + IAsp, or GLP-1 RA for these assessed outcomes was not clear from the literature. In addition, the difference seen between the IDegLira, IGlar, and IGlar + IAsp treatment groups in SF-36 did not exceed the proposed MIDs in the user's manual for PCS, MCS, and all SF-36 domains. Finally, these three trials — DUAL V,

DUAL VII, and DUAL III — were open label. There is a risk of bias with outcomes measured in open-label studies as patients and providers are aware of their assigned intervention. The measurement of subjective outcomes, such as HRQoL, may be at increased risk of bias if patients in the study are aware of their treatment allocation.

Body weight was identified as an important outcome to patients in the patient input summary. In DUAL V and DUAL VII, IDegLira showed statistically significant reductions in body weight after 26 weeks of treatment compared with IGlar, and IGlar + IAsp (the LS mean difference was −3.20 kg and −3.57 kg, respectively). In the DUAL II trial, IDegLira also showed reductions in body weight after 26 weeks of treatment compared with IDeg (the LS mean difference was −2.51 kg). However, this outcome was not adjusted for multiplicity in the DUAL II trial; hence, any result reported should be interpreted with consideration of the potential for inflated type I error. The clinical expert involved in this CDR indicated that while insulin alone is often associated with weight gain, weight loss is to be expected when GLP-1 RA is added to insulin. Although any reduction in weight may be viewed as positive by patients, it is not known whether these changes translate into long-term health benefits. Furthermore, it is not clear whether this difference would have a meaningful impact on patients over a sustained length of time due to the fact that these trials were held over a short duration of 26 weeks. The magnitude of weight gain may also be confounded by the fact that all patients were on insulin at baseline.

In contrast, in the DUAL III trial, patients treated with IDegLira gained significantly more weight than patients who continued GLP-1 RA therapy. This is to be expected when an insulin-naive population previously treated with GLP-1 RA transfers to an insulin containing antidiabetes product. This outcome was not adjusted for multiplicity in the DUAL III trial; hence, any result reported should be interpreted with consideration of the potential for inflated type I error.

The differences in blood pressure and fasting lipid profile were small, and according to the clinical expert involved in this CDR, these differences are too small to be considered clinically important.

There is insufficient information from the included trials to determine which patients are likely to require more than 50 U of IDegLira, and thus would not benefit from this medication. This information may be absent due to lack of enrolment of patients with significant insulin resistance (i.e., patients who are severely obese) and the fact that going beyond 50 U was not an option given the study protocols. Also, it is unknown if patients on doses above 50 U of basal insulin who transitioned to IDegLira would derive glycemic benefit.

The ITC submitted by the manufacturer for the patients with T2DM inadequately controlled with basal insulin (in combination with MET ± SU) reported [redacted] However, there was a considerably high level of heterogeneity across the included studies in terms of patient characteristics, intervention and comparators, outcome measures, and study design, which were potential effect modifiers and were not adjusted in the ITC (e.g., by meta-regression or sensitivity analysis). Therefore, it was uncertain whether the assumption of transitivity in the

ITC analysis was justified. The findings of the ITC could be potentially biased, although the direction of bias is unclear. [redacted] Taken together, due to the considerably high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain, especially for the comparison of [redacted]

For the patients with T2DM inadequately controlled with liraglutide (in combination with MET ± SU), [redacted] However, the Bucher ITC provided only limited evidence for the comparative efficacy and safety of IDegLira due to the small number of included studies; in addition, there was lack of evidence for the comparative efficacy and safety versus a number of relevant comparators (e.g., [redacted]).

The SGLT2 inhibitors or DPP-4 inhibitors (in combination with MET) are treatment options for patients with T2DM inadequately controlled with basal insulin. In patients with T2DM inadequately controlled with basal insulin (in combination with MET ± SU), [redacted]

The pooled analyses submitted by the manufacturer that compared IDegLira with basal-bolus, or GLP-1 RA added to basal insulin or up-titration of basal insulin-only therapy in the treatment of patients with T2DM uncontrolled on basal insulin (with or without in combination with MET or other oral AHAs), showed a greater reduction in hemoglobin A1C with IDegLira compared with basal-bolus, GLP1-RA in combination with basal insulin, and basal insulin up-titration regimens. It also indicated a greater reduction in body weight with IDegLira compared with basal-bolus and a basal insulin up-titration regimen. A greater reduction in total cholesterol, LDL, and overall confirmed hypoglycemia were also observed with IDegLira compared with a basal insulin up-titration regimen. However, due to considerable methodological limitations, the findings of the pooled analysis should be interpreted with caution. No credible conclusions can be drawn based on the pooled analysis.

Harms

The overall frequency of AEs was similar between treatment groups within trials. In the DUAL II, DUAL V, and DUAL VII trials, AEs were reported by 57.6% to 59.1% of patients who received IDegLira, and by 61.3%, 50.5%, and 56.9% of patients who received IDeg, IGlar, and IGlar + IAsp, respectively. In the DUAL III trial, AEs were reported by 65.6% of patients treated with IDegLira, and by 63.4% of patients treated with GLP-1 RA. This small difference in frequency of AEs in the IDegLira treatment group between those reported in the DUAL III trial and the rest of the trials could be because all patients in DUAL III were concomitantly treated with MET ± pioglitazone ± SU while, in the other trials, patients were concomitantly treated with MET only. SAEs were reported by 1.8% to 4.8% of patients who received IDegLira, and by 5.5%, 3.2%, 4.0%, and 2.1% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively. In all of the included trials, no SAEs

occurred in ≥ 1% of the patients. The rates of AEs leading to withdrawal from the trials were reported by 0.3% to 2.5% of patients who received IDegLira, and by 1.5%, 0.4%, 0%, and 1.4% of patients who received IDeg, IGlar, IGlar + IAsp, and GLP-1 RA, respectively. No deaths were reported during the DUAL II, DUAL V, and DUAL III trials. In the DUAL V trial, one patient died during the trial; that patient was treated with IGlar and died due to hemorrhagic stroke. The event was considered unlikely to be related to the trial product.

GI AEs were reported more frequently in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups, which was expected from the safety profile of liraglutide. The most frequent GI AEs were nausea, diarrhea, and vomiting. The clinical expert consulted for this review indicated that the rates of nausea with IDegLira were much lower than those reported in the liraglutide clinical trials; that could be due to the slower titration of IDegLira (which was consistent with that recommended in the product monograph) compared with the titration of liraglutide alone.

The proportion of patients that experienced severe hypoglycemia as defined by ADA in each individual study was too low (ranging from 0% to 1.6% across the included trials) to make a judgment on the comparative incidence of severe hypoglycemia. In the DUAL II trial, the proportion of patients with confirmed hypoglycemic episodes was similar between IDegLira and IDeg. Only one severe hypoglycemic episode was reported in the DUAL II trial (with IDegLira). In the DUAL V trial, the proportion of patients with confirmed hypoglycemic episodes was lower in the IDegLira group (28.4%) compared with the IGlar group (49.1%). Only one severe hypoglycemic episode was reported in the DUAL V trial (in the IGlar group). In the DUAL VII trial, the proportion of patients that experienced severe or BG-confirmed hypoglycemic episodes was also lower in the IDegLira group (31.3%) compared with the IGlar + IAsp group (60.9%). Three patients (1.2%) in the IDegLira group and four patients (1.6%) in the IGlar + IAsp group experienced severe hypoglycemic episodes in the DUAL VII trial.

In the DUAL III trial, the proportion of patients that experienced confirmed hypoglycemic episodes was higher in the IDegLira (32%) group compared with the GLP-1 RA group (2.8%). This can be explained by the fact that patients in the IDegLira group were transferred to a treatment regimen containing an insulin component. The clinical expert consulted on this review indicated that any time hypoglycemia is reported, it is due to an insulin component, given that GLP-1 RAs do not cause hypoglycemia. In addition, a minor fraction of patients in both groups was treated with SU. Treatment with SU per se is associated with increased risk of hypoglycemia.

The occurrence of other harms of special interest to this review (renal failure, arrhythmia, allergic reaction [immunogenicity], and injection site reactions) was infrequent, and no cases of pancreatitis or antibody formation were reported in the trials.

Two open-label studies comparing IDegLira to either IDeg and Lira individually (DUAL I) or to IGlar (DUAL VIII) were included in this review as a supplemental issue to record safety data not afforded by the shorter trials that met the inclusion criteria for this review. The DUAL I and DUAL VIII trials did not meet the inclusion and exclusion criteria for this review due to inappropriate background therapy. DUAL I was a 52-week study, which included a 26-week extension, while DUAL VIII was a 104-week duration study. Overall, no new safety signals emerged from these longer-term studies. The most commonly reported AEs were GI (diarrhea and nausea). The proportions of patients experiencing hypoglycemia were similar across IDegLira and insulin treatment groups within trials. No SAEs were reported in

proportions ≥ 1%, and no safety signal for renal failure, pancreatitis, CV outcomes, injection site reactions, or immunogenicity emerged from these studies.

Other Considerations

There is insufficient information from the included studies to determine which patients are likely to require more than 50 U of IDegLira, and thus would not benefit from this product. This data may not be available due to lack of enrolment of patients with significant insulin resistance (i.e., patients who are severely obese). Also, it is unknown if patients on doses above 50 U of basal insulin who transitioned to IDegLira would derive glycemic benefit. On the other hand, IDegLira is not indicated for patients who are using more than 50 U of basal insulin.

The clinical expert consulted on this review indicated that while liraglutide 1.8 mg in the LEADER trial[61] (which assessed the long-term effects of liraglutide on CV outcomes in patients with T2DM who were at high risk for CV disease) was beneficial to CV disease, it is unknown if lower doses of liraglutide would provide the same CV benefit. In addition, all of the included trials excluded those who have had a CV event or CV disease; hence, there is no evidence showing whether IDegLira would be beneficial in such patients.

Potential Place in Therapy[2]

Only about 40% to 50% of patients with T2DM treated with either basal insulin or a GLP-1 RA in combination with or without other non-insulin antihyperglycemic agents achieve hemoglobin A1C targets. Individuals not at target will require additional therapy to improve glycemia. A traditional approach for managing individuals not at target while on basal insulin has been the addition of prandial insulin, from one to three times daily, but this therapy increases complexity and number of injections and is associated with weight gain and hypoglycemia. There is an unmet need for patients requiring intensification beyond basal insulin for a simple and convenient therapy that will not increase hypoglycemia and provide a weight benefit. IDegLira is a fixed-ratio combination of IDeg and the GLP-1 RA liraglutide, which provides simple titration regimens, improvement in hemoglobin A1C and postprandial glucose without increasing hypoglycemia, and weight loss benefits. For patients not at target while on a GLP-1 RA with or without other non-insulin agents, the addition of basal insulin can be an effective way to improve fasting glucose and hemoglobin A1C.

For patients on basal insulin who may require a GLP-1 RA, IDegLira offers the convenience of a single injection with only one titration regimen, rather than separate injections of basal insulin and a GLP-1 RA with two different titration regimens. The weight benefit versus insulin alone is also important, given that about 85% of individuals with T2DM are overweight or obese. Furthermore, IDegLira will lead to less nausea than a GLP-1 RA given as a separate agent (due to the different titration recommendations in their respective product monographs) and is associated with a lower insulin dose than insulin therapy alone.

In summary, IDegLira can provide a novel way for clinicians to combine a GLP-1 RA with basal insulin in a convenient single injection for individuals with elevated hemoglobin A1C despite basal insulin therapy with or without other agents. Its use in practice will be consistent with Diabetes Canada 2018 guidelines[9] that recommend “a GLP-1 RA be considered as add-on therapy to basal insulin before initiating bolus insulin or intensifying

[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.

insulin to improve glycemic control with weight loss and a lower hypoglycemia risk compared with single or multiple bolus insulin injections." With IDegLira as an option for adding a GLP-1 RA to basal insulin, clinicians and patients can now decide between adding a daily- or once-weekly administered GLP-1 RA or switching the basal insulin to IDegLira. IDegLira will likely be used in such a scenario only for patients without a history of clinical CV disease, as guidelines recommend agents with proven CV benefit for such patients, which for GLP-1 RAs would be liraglutide 1.8 mg daily or semaglutide 1 mg once weekly. As individualization of care is the mainstay of T2DM management, IDegLira now provides another option for adding a GLP-1 RA to basal insulin-treated patients without a history of CV disease. Finally, the ADA and the European Association for the Study of Diabetes 2018 consensus statement[10] recommend GLP-1 RAs as the first injectable option in T2DM. As that approach becomes more common in clinical practice, IDegLira will be an option for initiating basal insulin for individuals not achieving target on a GLP-1 RA with or without other agents.

Conclusions

Four phase III RCTs (DUAL II, DUAL V, DUAL VII, and DUAL III) provided evidence on the efficacy and safety of IDegLira in adults with T2DM. In patients who had inadequate glycemic control with basal insulin plus MET, the therapy of titrated IDegLira with MET compared with titrated basal insulin plus MET was found to statistically significantly improve hemoglobin A1C and lower body weight with reduction or no increase in hypoglycemia. IDegLira plus MET was also shown to have noninferior glycemic efficacy to a basal-bolus insulin regimen (IGlar + IAsp), with less hypoglycemia. IDegLira demonstrated statistically significant improvement in hemoglobin A1C but with more hypoglycemia and weight increase when switching from a GLP-1 RA to IDegLira while continuing background MET with or without other agents in insulin-naive patients who had inadequate glycemic control with GLP-1 RA. The overall frequency of AEs was similar between treatment groups within trials. GI AEs were reported more frequently in the IDegLira group compared with the IDeg, IGlar, and IGlar + IAsp treatment groups, which was expected from the safety profile of liraglutide. The most frequent GI AEs were nausea, diarrhea, and vomiting.

The manufacturer-submitted ITC for patients with T2DM inadequately controlled with basal insulin suggested that there is a [redacted] However, due to the considerably high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain. For patients with T2DM inadequately controlled with liraglutide, the Bucher ITC provided only limited evidence for the comparative efficacy and safety of IDegLira due to the small number of included studies; in addition, there was a lack of evidence for the comparative efficacy and safety versus a number of relevant comparators (e.g., [redacted]).

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 Group(s) Supplying Input

Two patient groups, Diabetes Canada and Type 2 Diabetes Experience Exchange (T2DXX), provided patient input for this submission. Diabetes Canada is a national health charity representing 11 million Canadians living with diabetes or prediabetes. The priorities of Diabetes Canada's mission are diabetes prevention, care, and cure. Diabetes Canada focuses on research and policy initiatives for better prevention and treatment strategies. The organization received funding from multiple pharmaceutical companies and organizations, including Novo Nordisk Canada Inc., which was one of five companies that provided more than $350,000 over the past two years. T2DXX reported that they had no help from outside their organization to collect and analyze data, or to complete the submission.

T2DXX (http://www.t2dxx.com/) is a community of more than 1,600 Canadians living with type 2 diabetes mellitus (T2DM). T2DXX creates an open, safe, and non-judgmental space in which to share personal experiences. T2DXX is known for kick-starting new collaborative conversations in how patients with T2DM define, understand, and, most importantly, improve the outcomes and quality of life of the type 2 patient journey. T2DXX information is viewed by more than 50,000 people per month. T2DXX is creating new opportunities to share the stories of people living with T2DM, using social media, video, the Web, and other avenues, to influence, invite, and inspire a re-imagining of perceptions of the experience of patients with T2DM. Fifteen videos involving those with diabetes reflecting on their experiences can be accessed from the T2DXX patient input provided. T2DXX declared that it has not received any financial payment from any company or organization over the past two years. It did not receive help from outside its patient group to collect or analyze data or to complete the submission.

2. Condition-Related Information

Diabetes Canada collected patient input through online surveys conducted in October 2016 as well as in January and February 2019, using a self-administered questionnaire targeting people living with T2DM and their caregivers across Canada. The 2019 survey asked questions specific to insulin degludec (IDeg) + liraglutide (Xultophy). A total of 847 people responded to the 2016 survey, including 790 patients and 57 caregivers. Of those who responded to questions about age and time since diagnosis (n = 379), 70% were over the age of 55 years and 60% had been living with diabetes for more than 10 years. Nine patients with T2DM participated in the 2019 survey. Of the five people who provided age and date of diagnosis data, 100% of respondents were over the age of 40 years (two in the 40- to 54-year-old category, two in the 55- to 69-year-old category, and one in the 70 years and over category). Two respondents reported having lived with diabetes for three to five years and three respondents reported having lived 11 to 20 years with the disease.

The T2DXX group indicated the following sources of data for their submission: personal interviews and facilitated group discussion in T2DXX forums and social media conversation threads. In addition, for Xultophy, T2DXX found a relevant users' group on Facebook, created in March 2018, with 68 members who had experience with the drug. T2DXX identified themes emerging from community conversations by group users without directing the conversation.

The patient groups highlighted that diabetes is a chronic, progressive disease without cure. T2DM is very complex and has a striking burden on the physical, emotional, social, and economic status of the person. The common symptoms of diabetes include extreme fatigue, unusual thirst, frequent urination, and weight change (gain or loss). Diabetes requires considerable self-management, including eating well, engaging in regular physical activity, maintaining a healthy body weight, taking medications (oral and/or injectable) as prescribed, monitoring blood glucose (BG), and managing stress. Poor glucose control is serious and problematic. Low BG can precipitate an acute crisis, such as confusion, coma, or seizure. High BG over time can irreversibly damage blood vessels and nerves, resulting in blindness, heart disease, kidney problems, and lower limb amputations, among other issues. The goal of diabetes management is to keep glucose levels within a target range to minimize symptoms and avoid or delay complications.

Most patients surveyed talked about the adverse effect diabetes has had on their lives. Patients describe diabetes as a "horrendous experience," "manageable but a bother," an "awful disease," inconvenient, frustrating, and exhausting. Their diabetes affects all aspects of their lives, from eating and exercising to working and socialization. Patients are anxious and fearful of complications of the disease, and face stigma due to diabetes. Patients who responded to the surveys indicated that they experienced the following symptoms or comorbidities: hyperglycemia; hypoglycemia; high blood pressure; high cholesterol; heart problems; mental health problems; kidney symptoms or disease; foot problems; eye problems; nerve damage; damage to blood vessels, heart, or brain; liver disease, weight gain; and sexual dysfunction. The T2DXX patient group indicated that when patients are diagnosed as T2DM, sometimes they feel anger, depression, and shame.

The following are some quotes from survey respondents:

"It is part of every decision I make on a daily basis regarding general health, exercise, nutrition, social activities, work etc."

"I feel like my body is breaking down 25 years ahead of its time."

"The fact that I have to consistently monitor myself and wonder if I'm going to lose my eyes is something I wouldn't wish on my worst enemy."

"I am a…mother…and hate the fact that I have developed diabetes and have to take medications for it… My kids have to know what to do if I pass out…"

"I've had to change my entire way of life, the things I eat, the things I do. Some days I feel sick all day, others I'm just plain tired and can't get motivated."

3. Current Therapy-Related Information

In the Diabetes Canada input, patients who responded to the October 2016 survey (n = 647) reported that they use or have used (currently or in the past) the following antihyperglycemic agents: metformin (MET), glucagon-like peptide 1 receptor agonists, sodium-glucose cotransporter-2 inhibitors, a combination of sodium-glucose cotransporter-2 inhibitors and MET, dipeptidyl peptidase-4 (DPP-4) inhibitors, a combination of DPP-4 inhibitors and MET, sulfonylureas, thiazolidinediones (TZDs), a combination of TZDs and MET, a combination of TZDs and glimepiride, meglitinides, acarbose, and insulin. More than 60% of respondents from the October 2016 survey noted improvements in meeting target BG levels (fasting, postprandial, upon waking) and hemoglobin A1C levels after initiation on their current medication regimen, compared with before (when they were not on treatment). About 46% of patients said they were "better" or "much better" able to avoid

hypoglycemia, and 39% said their current regimen helped them maintain or lose weight more effectively than in the past. Gastrointestinal side effects were “neither better nor worse” than previously in 39% of respondents. About two-thirds indicated that they were either “satisfied” or “very satisfied” with the medication or combination of medications they were currently taking for their diabetes management. The factors that respondents considered “quite important” or “very important” in choosing diabetes medications were, among others, keeping BG at a satisfactory level, avoiding low blood sugar, avoiding weight gain or facilitating weight loss, reducing the risk of heart problems, and avoiding gastrointestinal issues (nausea, vomiting, diarrhea, pain) and urinary tract and/or yeast infections. Patients responded to questions about their medication use in the January and February 2019 survey: MET (n = 4), glucagon-like peptide 1 receptor agonists (n = 1), a combination of DPP-4 inhibitors and MET (n = 1), sulfonylureas (n = 1), meglitinides (n = 1) and orlistat (n = 1). A few respondents cited the use of certain medications in the past. These included sulfonylureas (n = 1) and MET (n = 1).

In the T2DXX submission, it was indicated that treatment options are often determined not by the most effective therapy for the individual, but by the patient’s insurance coverage and ability to afford the cost of a particular therapy.

4. Expectations About the Drug Being Reviewed

In the Diabetes Canada submission, of those who participated in the January and February 2019 survey and answered the questions specific to IDeg + liraglutide (Xultophy) (n = 5), no one reported taking the medication, either at the time of survey completion or in the past. However, 60% of respondents felt it is “somewhat beneficial” or “very beneficial” to have combination medications available for diabetes treatment (while 40% said they “don’t know”).

In the T2DXX submission, patients’ experience on Xultophy indicated that nausea and upset stomachs were reported as initial side effects that disappeared after tolerance developed. The method of starting at a low dose with slow, gradual increases delivers the best outcomes. The drug reduces appetite and lowers blood sugar, resulting in some weight loss. This affects social and emotional impacts of the condition in positive ways, equating to an improved quality of life, as well as reduced stress from stigma and bias. There is improved control of blood sugar, a reduced fear of hypoglycemia, and simplified dosage management, resulting in improved treatment adherence. Caregivers benefit from a reduced burden, improved emotional state, and restored balance in relationships. There continues to be an issue of affordability and coverage.

Both the Diabetes Canada and T2DXX groups indicated the desire for medications that have been proven safe and can normalize and stabilize BG levels and improve hemoglobin A1C levels without causing weight gain or hypoglycemia. They wish for new treatments to enhance weight loss and improve health outcomes at an affordable cost. Ideally, they’d like medications and diabetes devices to be covered in a timely manner by public and private plans. They want treatments that are easily administered, cause the least amount of disruption to lifestyle, and allow for flexibility with food intake and choices. They also want medications that will help avoid polypharmacy and eliminate the need for injections while minimizing risk of any short-term medication-related side effects or long-term disease-related side effects. Several respondents indicated that they hope future treatments will reverse or cure diabetes. In the October 2016 survey from Diabetes Canada, some respondents commented on the advantage of having combination medications available for diabetes treatment. Several spoke about how burdensome it is to take several oral and/or

injectable medications for their management, and that it would make a difference to their daily management and quality of life to reduce the number of agents they administer.

The following are a few examples of quotes from either the Diabetes Canada or T2DXX groups regarding their experience and expectations for new treatments:

"Help with A1c[sic], reduce weight gain, promote weight loss, supported by formulary to keep cost down."

"Manage diabetes effectively without needing such a large variety of medications."

"The less medication [I] have to take, the better it is on my mental health."

"This is why I'm on Xultophy. I got lazy and quit taking meds for months!. Lesson learned."

"I've been on Xultophy for about a year. Taking 17 to 18 units depending on what my carb count is and what time I had my last meal of the day. Seen some improvement on my morning glucose readings. They've been mainly in the 120s to 130s. The insurance I'm on now doesn't cover the medication. Looking for a way to obtain it cheaply as I don't want to rely on the doctor's office for samples."

"Hopefully easier attainment of targets, reduction of complication risks and less of a burden of disease."

"Expectations are that eventually there will be a medication that can be taken once a day that will help my pancreas produce the right amount of insulin to keep up with me (or possibly even cure the disease). I would hope that medications are made available to anyone living with diabetes and covered under by our government benefits."

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE All (1946-present) Embase (1974-present) PubMed **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 28, 2019
Alerts:	Biweekly search updates until project completion
Study Types:	No publication type filters were applied.
Limits:	Publication date limit: none Language limit: none Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical 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
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.pt	Publication type
.ot	Original title (MEDLINE)
.rn	Registry number
.dq	Candidate term word (Embase)
medall	Ovid database code: MEDLINE All, 1946 to present, updated daily
oemezd	Ovid database code; Embase, 1974 to present, updated daily

MULT-DATABASE STRATEGY	
Line #	**Search Strategy**
1	(Xultophy* or iDegLira* or "insulin degludec/liraglutide" or "liraglutide/insulin degludec" or nn 9068 or nn9068).ti,ab,kf,ot,hw,rn,nm.
2	(Tresiba* or degludec* or insulin degludec* or NN 1250 or NN1250 or 54Q18076QB).ti,ab,kf,ot,hw,rn,nm.
3	Liraglutide/
4	(Liraglutid* or Victoza* or Saxenda* or HSDB 8205 or HSDB8205 or NN 2211 or NN2211 or NNC 90 1170 or NNC 901170 or NNC901170 or NN 9924 or NN9924 or 839I73S42A).ti,ab,kf,ot,hw,rn,nm.
5	or/3-4
6	2 and 5
7	1 or 6

MULT-DATABASE STRATEGY	
Line #	**Search Strategy**
8	7 use medall
9	*insulin degludec plus liraglutide/
10	(Xultophy* or iDegLira* or "insulin degludec/liraglutide" or "liraglutide/insulin degludec" or nn 9068 or nn9068).ti,ab,kw,dq.
11	or/9-10
12	*insulin degludec/
13	(Tresiba* or degludec* or insulin degludec* or NN 1250 or NN1250).ti,ab,kw,dq.
14	or/12-13
15	*liraglutide/
16	(Liraglutid* or Victoza* or Saxenda* or HSDB 8205 or HSDB8205 or NN 2211 or NN2211 or NNC 90 1170 or NNC 901170 or NNC901170 NN 9924 or NN9924).ti,ab,kw,dq.
17	or/15-16
18	14 and 17
19	11 or 18
20	19 use oemezd
21	20 not conference abstract.pt.
22	8 or 21
23	remove duplicates from 22

CLINICAL TRIAL REGISTRIES	
ClinicalTrials.gov	Produced by the U.S. National Library of Medicine. Targeted search used to capture registered clinical trials. [Search -- Studies with results | Xultophy OR iDegLira OR (insulin degludec AND liraglutide)]
WHO ICTRP	International Clinical Trials Registry Platform, produced by the World Health Organization. Targeted search used to capture registered clinical trials. [Search terms -- Xultophy OR iDegLira OR (insulin degludec AND liraglutide)]
Health Canada Clinical Trails Database	Produced by Health Canada. Targeted search used to capture registered clinical trials. [Search terms -- Xultophy OR iDegLira OR (insulin degludec AND liraglutide)]

OTHER DATABASES	
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.

Grey Literature

Dates for Search:	February 15, 2019 – February 25, 2019
Keywords:	Xultophy, iDegLira, insulin degludec, liraglutide, and type 2 diabetes.
Limits:	Publication years: all

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- health technology assessment agencies
- health economics
- clinical practice guidelines
- drug and device regulatory approvals
- advisories and warnings
- drug class reviews
- clinical trial registries
- databases (free)
- health statistics
- Internet search
- up-to-date.

Appendix 3: Excluded Studies

Table 17: Excluded Studies

Reference	Reason for Exclusion
Philis-Tsimikas A, Billings LK, Busch R, et al. Superior Efficacy of Insulin Degludec/Liraglutide versus Insulin Glargine U100 as Add-on to Sodium-Glucose Co-Transporter-2 Inhibitor Therapy: a Randomized Clinical Trial in Patients with Uncontrolled Type 2 Diabetes. Diabetes Obes Metab. 2019;13:13. Rodbard HW, Bode BW, Harris SB, et al. Safety and efficacy of insulin degludec/liraglutide (IdegLira) added to sulphonylurea alone or to sulphonylurea and metformin in insulin-naive people with Type 2 diabetes: the DUAL IV trial. Diabet Med. 2017;34(2):189-196. Gough SC, Bode BW, Woo VC, et al. One-year efficacy and safety of a fixed combination of insulin degludec and liraglutide in patients with type 2 diabetes: results of a 26-week extension to a 26-week main trial. Diabetes Obes Metab. 2015;17(10):965-973. Holst JJ, Buse JB, Rodbard HW, et al. IDegLira Improves Both Fasting and Postprandial Glucose Control as Demonstrated Using Continuous Glucose Monitoring and a Standardized Meal Test. J Diabetes Sci Technol. 2015;10(2):389-397. Gough SC, Bode B, Woo V, et al. Efficacy and safety of a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with its components given alone: results of a phase 3, open-label, randomised, 26-week, treat-to-target trial in insulin-naive patients with type 2 diabetes. Lancet Diabetes Endocrinol. 2014;2(11):885-893.	Inappropriate background therapy
Dempsey M, Mocarski M, Langer J, Hunt B. Ideglira is Associated With Improved Short-Term Clinical Outcomes and Cost Savings Compared with Insulin Glargine U100 Plus Insulin Aspart in the U.S. Endocr Pract. 2018;24(9):796-804. Drummond R, Malkin S, Du Preez M, Lee XY, Hunt B. The management of type 2 diabetes with fixed-ratio combination insulin degludec/liraglutide (IDegLira) versus basal-bolus therapy (insulin glargine U100 plus insulin aspart): A short-term cost-effectiveness analysis in the UK setting. Diabetes Obes Metab. 2018;20(10):2371-2378. Khunti K, Mohan V, Jain SM, Boesgaard TW, Begtrup K, Sethi B. Efficacy and Safety of IDegLira in Participants with Type 2 Diabetes in India Uncontrolled on Oral Antidiabetic Drugs and Basal Insulin: Data from the DUAL Clinical Trial Program. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2017;8(3):673-682. Freemantle N, Mamdani M, Vilsboll T, Kongso JH, Kvist K, bain SC. IDegLira Versus Alternative Intensification Strategies in Patients with Type 2 Diabetes Inadequately Controlled on Basal Insulin Therapy. Diabetes Therapy Research, Treatment and Education of Diabetes and Related Disorders. 2015;6(4):573-591.	Not a randomized controlled trial
Buse JB, Vilsboll T, Thurman J, et al. Contribution of liraglutide in the fixed-ratio combination of insulin degludec and liraglutide (IDegLira). Diabetes Technology and Therapeutics. 2015;17(Supplement 1):S128-S129. Freemantle N, Lingvay I, Kongso JH, Abrahamsen TJ, Bjorner JB. Ideglira Improves Health Utility Compared With Insulin Glargine In Patients With Type 2 Diabetes. Value Health. 2015;18(7):A614.	Poster (not an article)
Lingvay I, Handelsman Y, Linjawi S, et al. Efficacy and Safety of Ideglira in Older Patients with Type 2 Diabetes. Endocr Pract. 2018;01:01.	Subgroup reported not of interest
Lingvay I, Manghi FP, Garcia-Hernandez P. Erratum: Effect of insulin glargine up-titration vs insulin degludec/liraglutide on glycated hemoglobin levels in patients with uncontrolled type 2 diabetes: The Dual V randomized clinical trial (JAMA - Journal of the American Medical Association (2016) 315: 9 (898-907)). JAMA - Journal of the American Medical Association. 2016;315(19):2125.	Erratum

Appendix 4: Detailed Outcome Data

Table 18: Hemoglobin A1C After 26 Weeks of Treatment (Sensitivity Analysis)

	DUAL II		DUAL V		DUAL VII			DUAL III
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)		IDegLira (N = 292)
N = 146								
Hemoglobin A1C (%) — Sensitivity Analysis (Completer Analysis Set)								
After 26 Weeks of Treatment								
N	175	171	250	265	238	233	276	117
LS mean (SEM)	6.72 (0.072)	7.73 (0.073)	6.43 (0.05)	7.08 (0.05)	6.70 (0.05)	6.74 (0.05)	6.38 (0.05)	7.23 (0.07)
Change From Baseline After 26 Weeks of Treatment								
N	175	171	250	265	238	233	276	117
LS mean (SEM)	−2.09 (0.072)	−1.07 (0.073)	−1.87 (0.05)	−1.22 (0.05)	−1.50 (0.05)	−1.47 (0.05)	−1.36 (0.05)	−0.51 (0.07)
LS mean difference after 26 weeks of treatment (95% CI)	−1.01 (−1.22 to −0.81)[a]		−0.65 (−0.79 to −0.51)[b]	−0.04 (−0.17 to 0.10)[c]		−0.85 (−1.02 to −0.68)[d]		
P value	< 0.0001[a]		< 0.001	< 0.0001[c]		< 0.001		
Hemoglobin A1C (%) — Sensitivity Analysis (Per-Protocol Analysis Set)								
After 26 Weeks of Treatment								
N	NR	NR	257	270	239	238	279	135
LS mean (SEM)	NR	NR	6.44 (0.05)	7.10 (0.05)	6.71 (0.05)	6.75 (0.05)	6.39 (0.05)	7.37 (0.07)
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	257	270	239	238	279	135
LS mean (SEM)	NR	NR	−1.85 (0.05)	−1.20 (0.05)	−1.50 (0.05)	−1.46 (0.05)	−1.36 (0.05)	−0.38 (0.07)
LS mean difference after 26 weeks of treatment (95% CI)	NR		−0.65 (−0.79 to −0.51)[b]	−0.04 (−0.17 to 0.10)[c]		−0.98 (−1.15 to −0.81)[d]		
P value	NR		< 0.001	< 0.0001[c]		< 0.001		
Hemoglobin A1C (%) — Sensitivity Analysis (Repeated Measurement Model, Full Analysis Set)								
After 26 Weeks of Treatment								
N	192	188	270	274	NR	NR	286	141
LS mean (SEM)	6.77 (0.07)	7.81 (0.07)	6.43 (0.05)	7.09 (0.05)	NR	NR	6.40 (0.05)	7.32 (0.07)
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	NR	NR	NR	NR	NR	NR
LS mean (SEM)	NR	NR	NR	NR	NR	NR	NR	NR
LS mean difference after 26 weeks of treatment (95% CI)	−1.04 (−1.25 to −0.84)[e]		−0.66 (−0.80 to −0.52)[f]	NR		−0.93 (−1.09 to −0.76)[g]		
P value	< 0.0001[e]		< 0.001	NR		< 0.001		
Hemoglobin A1C (%) — Sensitivity Analysis (Including Measurements Obtained After Premature Treatment Discontinuation, Full Analysis Set)								
After 26 Weeks of Treatment								
N	NR	NR	NR	NR	248	249	NR	NR

	DUAL II		DUAL V		DUAL VII			DUAL III
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)		IDegLira (N = 292)
N = 146								
LS mean (SEM)	NR	NR	NR	NR	6.78 (0.05)	6.79 (0.05)	NR	NR
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	NR	NR	248	249	NR	NR
LS mean (SEM)	NR	NR	NR	NR	−1.43 (0.05)	−1.42 (0.05)	NR	NR
LS mean difference after 26 weeks of treatment (95% CI)	NR		NR	−0.01 (−0.16 to 0.13)[h]		NR		
P value	NR		NR	< 0.0001[h]		NR		
Hemoglobin A1C (%) — Sensitivity Analysis (ANCOVA Model, Full Analysis Set)								
After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	6.87 (0.06)	6.87 (0.06)	NR	NR
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	−1.36 (0.06)	−1.36 (0.06)	NR	NR
LS mean difference after 26 weeks of treatment (95% CI)	NR		NR	0.00 (−0.15 to 0.16)[i]		NR		
P value	NR		NR	0.0002[i]		NR		
Hemoglobin A1C (%) — Sensitivity Analysis (ANCOVA Model, Multiple Imputation [Conditional], Full Analysis Set)								
After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	6.80 (0.05)	6.80 (0.05)	NR	NR
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	−1.42 (0.05)	−1.43 (0.05)	NR	NR
LS mean difference after 26 weeks of treatment (95% CI)	NR		NR	0.00 (−0.15 to 0.15)[jk]		NR		
P value	NR		NR	0.0001[jk]		NR		
Hemoglobin A1C (%) — Sensitivity Analysis (ANCOVA Model, Multiple Imputation [Unconditional], Full Analysis Set)								
After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	6.80 (0.05)	6.80 (0.05)	NR	NR
Change From Baseline After 26 Weeks of Treatment								
N	NR	NR	NR	NR	252	254	NR	NR
LS mean (SEM)	NR	NR	NR	NR	−1.42 (0.05)	−1.43 (0.05)	NR	NR

	DUAL II		DUAL V		DUAL VII		DUAL III
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)
N = 146							
LS mean difference After 26 weeks of treatment (95% CI)	NR		NR	0.00 (−0.15 to 0.15)[jl]	NR		
P value	NR		NR	0.0001[jl]	NR		

ANCOVA = analysis of covariance; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; NR = not reported; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. The change in hemoglobin A1C from baseline after 26 weeks of treatment was analyzed using an ANCOVA model with treatment, country, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as a covariate. *P* value for the difference between IDegLira and IDeg was test for superiority.

[b] Missing data were imputed using LOCF. The hemoglobin A1C change from baseline after 26 weeks of treatment was analyzed using an ANCOVA method with treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate.

[c] The response was analyzed using a MMRM with an unstructured covariance matrix. The model included treatment, visit, and regions as fixed factors and baseline hemoglobin A1C as a covariate. Interactions between visit and all factors and covariates were also included in the model. Two-sided *P* value is test for noninferiority.

[d] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors and baseline hemoglobin A1C value as a covariate.

[e] All hemoglobin A1C values available post baseline at scheduled measurement times were analyzed in a linear mixed normal model using an unstructured residual covariance matrix for hemoglobin A1C measurements within the same patient. The model included treatment, country, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as a covariate. Furthermore, the model included interaction terms between treatment and visit, between previous antidiabetes treatment and visit, between country and visit, and between baseline hemoglobin A1C and visit. *P* value for the difference between IDegLira and IDeg was test for superiority.

[f] All hemoglobin A1C values available post baseline at scheduled measurement times were analyzed in a linear mixed normal model using an unstructured residual covariance matrix for hemoglobin A1C measurements within the same patient. The model included treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. Furthermore, the model included interaction terms between treatment and visit, between region and visit, and between baseline hemoglobin A1C and visit.

[g] Hemoglobin A1C records available at scheduled time points after randomization were jointly analyzed in a linear mixed model with an unstructured residual covariance matrix, and with treatment, pretrial GLP-1 RA (Victoza or Byetta), and region as fixed factors and baseline HEMOGLOBIN A1C value as a covariate. Furthermore, interaction in terms of visit by treatment, visit by pretrial GLP-1 RA, visit by region, and visit by baseline HEMOGLOBIN A1C were included.

[h] All observed hemoglobin A1C measurements available post randomization at scheduled measurement times were analyzed with a MMRM with an unstructured covariance matrix. The model included treatment, visit, and regions as fixed factors and baseline HEMOGLOBIN A1C as a covariate. Interactions between visit and all factors and covariates were also included in the model. Two-sided *P* value was test for noninferiority.

[i] The hemoglobin A1C change from baseline after 26 weeks of treatment is analyzed using an ANCOVA method with treatment and region as fixed factors, and baseline response as a covariate. Missing data were imputed using LOCF. *P* value was two-sided test for noninferiority.

[j] The change from baseline after 26 weeks of treatment was analyzed using an ANCOVA method with treatment and region as fixed factors, and baseline response as a covariate. Four IDegLira patients and nine IGlar + IAsp patients have imputed end-of-treatment values. A noninferiority limit of 0.3% (3.279 mmol/mol) was added to both the withdrawn and prematurely discontinued IDegLira patients (14 patients in total). Two-sided *P* value was test for noninferiority.

[k] Missing data were imputed using conditional reference-based multiple imputation.

[l] Missing data were imputed using unconditional reference-based multiple imputation.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 19: Responder for Hemoglobin A1C After 26 Weeks of Treatment

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Responder for Hemoglobin A1C After 26 Weeks of Treatment								
Hemoglobin A1C < 7.0%								
Baseline (week 0), n (%)	0 (0.0)	0 (0.0)	8 (2.9)	15 (5.4)	7 (2.8)	14 (5.5)	11 (3.8)	10 (6.8)
Week 26, n (%)	120 (60.3)	46 (23.1)	199 (71.6)	131 (47.0)	157 (62.3)	162 (63.8)	220 (75.3)	52 (35.6)
Odds ratio (95% CI)	5.44 (3.42 to 8.66)[a]		3.45 (2.36 to 5.05)[b]		0.91 (0.62 to 1.33)[c]		6.84 (4.28 to 10.94)[d]	
P value	< 0.0001		< 0.001		0.6207		< 0.001	
Hemoglobin A1C < 6.5%								
Baseline (week 0), n (%)	0 (0.0)	0 (0.0)	1 (0.4)	3 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Week 26, n (%)	90 (45.2)	26 (13.1)	154 (55.4)	86 (30.8)	118 (46.8)	105 (41.3)	184 (63.0)	33 (22.6)
Odds ratio (95% CI)	5.66 (3.37 to 9.51)[a]		3.29 (2.27 to 4.75)[b]		1.26 (0.88 to 1.82)[c]		7.53 (4.58 to 12.38)[d]	
P value	< 0.0001		< 0.001		0.2116		< 0.001	
Responder for Hemoglobin A1C After 26 Weeks of Treatment Without Confirmed Hypoglycemia								
Hemoglobin A1C < 7.0%								
Week 26, n (%)	97 (48.7)	31 (15.6)	151 (54.3)	82 (29.4)	137 (54.4)	81 (31.9)	NR	NR
Odds ratio (95% CI)	5.57 (3.36 to 9.21)[e,f]		3.24 (2.24 to 4.70)[b,f]		2.58 (1.78 to 3.74)[c,g]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	
Hemoglobin < 6.5%								
Week 26, n (%)	72 (36.2)	14 (7.0)	115 (41.4)	53 (19.0)	105 (41.7)	59 (23.2)	NR	NR
Odds ratio (95% CI)	7.79 (4.11 to 14.76)[e,f]		3.39 (2.27 to 5.05)[b,f]		2.59 (1.73 to 3.87)[c,g]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	
Responder for Hemoglobin A1C After 26 Weeks of Treatment Without Weight Gain								
Hemoglobin A1C < 7.0%								
Week 26, n (%)	101 (50.8)	24 (12.1)	139 (50.0)	55 (19.7)	103 (40.9)	38 (15.0)	NR	NR
Odds ratio (95% CI)	7.65 (4.50 to 13.02)[h,i]		5.18 (3.43 to 7.83)[i,j]		4.46 (2.89 to 6.89)[i,k]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	
Hemoglobin A1C < 6.5%								
Week 26, n (%)	76 (38.2)	16 (8.0)	116 (41.7)	35 (12.5)	76 (30.2)	26 (10.2)	NR	NR
Odds ratio (95% CI)	7.32 (3.98 to 13.46)[h,i]		6.14 (3.90 to 9.68)[i,j]		4.15 (2.52 to 6.84)[i,k]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	
Responder for Hemoglobin A1C After 26 Weeks of Treatment Without Confirmed Hypoglycemia and Weight Gain								
Hemoglobin A1C < 7.0%								
Week 26, n (%)	80 (40.2)	17 (8.5)	108 (38.8)	34 (12.2)	91 (36.1)	16 (6.3)	NR	NR
Odds ratio (95% CI)	7.44 (4.08 to 13.57)[f,i,l]		5.53 (3.49 to 8.77)[f,i,m]		10.39 (5.76 to 18.75)[g,i,n]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Hemoglobin A1C < 6.5%								
Week 26, n (%)	59 (29.6)	9 (4.5)	88 (31.7)	21 (7.5)	68 (27.0)	12 (4.7)	NR	NR
Odds ratio (95% CI)	8.85 (4.15 to 18.89)[f,i,l]		6.76 (3.96 to 11.55)[f,i,m]		9.23 (4.68 to 18.20)[g,i,n]		NR	
P value	< 0.0001		< 0.001		< 0.0001		NR	

CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; MMRM = mixed-effects model for repeated measures; NR = not reported.

[a] Missing data were imputed using LOCF. The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment, region, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as a covariate.

[b] Missing data were imputed using LOCF. The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate.

[c] The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment and region as fixed factors and baseline hemoglobin A1C value as a covariate. Missing hemoglobin A1C assessments at week 26 were imputed from the primary analysis using MMRM.

[d] Missing data were imputed using LOCF. The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate.

[e] Missing data were imputed using LOCF. The binary end point was analyzed using a logistic regression model with treatment, region, and previous antidiabetes treatment as fixed factors and baseline hemoglobin A1C value as a covariate.

[f] Responder was defined as meeting the hemoglobin A1C target without confirmed hypoglycemic episodes during the last 12 weeks of treatment. Confirmed hypoglycemia was defined as patient being unable to treat himself or herself and/or having a plasma glucose < 3.1 mmol/L.

[g] Responder for hemoglobin A1C without hypoglycemia was defined as patient meeting the hemoglobin A1C target at the end of the trial without treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycemic episodes during the last 12 weeks of treatment. “Severe or blood glucose-confirmed symptomatic” was defined as an episode that is severe, according to the American Diabetes Association classification, or blood glucose confirmed by a plasma glucose value < 3.1 mmol/L with symptoms consistent with hypoglycemia.

[h] Missing data were imputed using LOCF. The binary end point was analyzed via a logistic regression model using a logit link. The model included treatment, region, and previous antidiabetes treatment as fixed factors, and baseline hemoglobin A1C value and baseline body weight as covariates.

[i] Responder for hemoglobin A1C without weight gain was defined as patient meeting the hemoglobin A1C target at the end of the trial with change in body weight from baseline to the end of the trial below or equal to zero.

[j] Missing data were imputed using LOCF. The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment and region as fixed factors and baseline hemoglobin A1C value and baseline body weight as covariates.

[k] The binary end point was analyzed in a logistic regression model using a logit link. The model included treatment and region as fixed factors and baseline hemoglobin A1C and baseline body weight as covariates. Missing hemoglobin A1C and/or weight assessments at week 26 were imputed using a mixed-effects model for repeated measurements.

[l] Missing data were imputed using LOCF. The binary end point was analyzed using a logistic regression model with treatment, region, and previous antidiabetes treatment as fixed factors, and baseline hemoglobin A1C value and baseline body weight as covariates.

[m] Missing data were imputed using LOCF. The binary end point is analyzed in a logistic regression model using a logit link. The model included treatment and region as fixed factors and baseline hemoglobin A1C value and baseline body weight as covariates.

[n] The binary end point is analyzed in a logistic regression model using a logit link.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 20: Fasting Plasma Glucose After 26 Weeks of Treatment

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
FPG (mmol/L)								
Baseline (Week 0)								
N	198	199	275	278	251	254	285	145
Mean (SD)	9.7 (2.9)	9.6 (3.1)	8.9 (2.6)	8.9 (2.9)	8.52 (2.65)	8.28 (2.53)	9.0 (2.1)	9.4 (2.3)
After 26 Weeks of Treatment								
N	198	199	275	278	243	245	285	145
LS mean (SEM)	6.24 (0.16)	6.97 (0.16)	6.09 (0.12)	6.09 (0.12)	6.14 (0.13)	6.44 (0.13)	6.05 (0.11)	8.69 (0.16)
Change From Baseline After 26 Weeks of Treatment								
N	198	199	275	278	243	245	285	145
LS mean (SEM)	−3.38 (0.16)	−2.66 (0.16)	−2.80 (0.12)	−2.79 (0.12)	−2.24 (0.13)	−1.93 (0.13)	−3.06 (0.11)	−0.42 (0.16)
LS mean difference after 26 weeks of treatment (95% CI)	−0.73 (−1.19 to −0.27)		−0.01 (−0.35 to 0.33)		−0.31 (−0.67 to 0.05)		−2.64 (−3.03 to −2.25)	
P value	0.0019		0.963		0.0936		< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, country, and previous antidiabetes treatment as fixed factors, and baseline response as a covariate.

[b] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[c] All observed FPG measurements available post randomization at scheduled measurement times were analyzed with a MMRM with an unstructured covariance matrix. The model included treatment, visit, and region as fixed factors and baseline response as a covariate. Interactions between visit and all factors and covariates were also included in the model.

[d] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 21: Treatment-Related Impact Measure for Diabetes Scores After 26 Weeks of Treatment in DUAL V, DUAL VII, and DUAL III Trials

	DUAL V[a]		DUAL VII[b]		DUAL III[c]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
TRIM-D Treatment Burden Score						
Baseline (Week 0)						
N	278	275	252	254	290	146
Mean (SD)	66.0 (21.4)	64.4 (18.6)	66.0 (19.3)	61.3 (19.7)	70.3 (17.5)	70.9 (17.5)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	75.6 (1.1)	71.9 (1.1)	77.88 (1.13)	67.38 (1.14)	81.3 (0.9)	76.3 (1.3)

	DUAL V[a]		DUAL VII[b]		DUAL III[c]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Change From Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	10.4 (1.1)	6.7 (1.1)	13.67 (1.13)	3.17 (1.14)	10.7 (0.9)	5.8 (1.3)
LS mean difference (95% CI)	3.7 (0.7 to 6.8)		10.50 (7.34 to 13.67)		5.0 (1.9 to 8.0)	
P value	0.017		< 0.0001		0.002	
TRIM-D Daily Life Score						
Baseline (Week 0)						
N	278	275	252	254	290	146
Mean (SD)	82.9 (17.0)	81.4 (16.9)	79.1 (17.9)	77.5 (17.2)	78.2 (18.3)	80.9 (15.4)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	85.0 (0.9)	83.7 (1.0)	82.44 (1.12)	78.21 (1.13)	84.8 (0.9)	81.1 (1.3)
Change From Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	2.9 (0.9)	1.6 (1.0)	3.77 (1.12)	−0.46 (1.13)	5.7 (0.9)	2.0 (1.3)
LS mean difference (95% CI)	1.3 (−1.3 to 4.0)		4.23 (1.09 to 7.37)		3.7 (0.5 to 6.8)	
P value	0.332		0.0083		0.022	
TRIM-D Diabetes Management Score						
Baseline (Week 0)						
N	278	275	252	254	290	146
Mean (SD)	57.5 (19.7)	56.3 (20.8)	55.8 (20.4)	54.3 (18.7)	61.0 (19.7)	63.2 (17.5)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS Mean (SEM)	71.0 (1.1)	63.8 (1.1)	72.69 (1.12)	61.93 (1.14)	72.2 (1.0)	66.6 (1.5)
Change From Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	14.1 (1.1)	6.9 (1.1)	17.20 (1.12)	6.44 (1.14)	10.5 (1.0)	4.8 (1.5)
LS mean difference (95% CI)	7.2 (4.2 to 10.2)		10.76 (7.62 to 13.90)		5.7 (2.2 to 9.2)	
P value	< 0.001		< 0.0001		0.002	
TRIM-D Compliance Score						
Baseline (Week 0)						
N	278	275	252	254	290	146
Mean (SD)	82.0 (17.9)	81.4 (16.9)	81.0 (18.0)	79.3 (17.0)	78.4 (17.3)	80.1 (17.0)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	88.3 (0.8)	87.2 (0.8)	89.78 (0.87)	83.52 (0.88)	87.5 (0.8)	84.0 (1.1)
Change from Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	6.6 (0.8)	5.5 (0.8)	9.58 (0.87)	3.33 (0.88)	8.5 (0.8)	5.0 (1.1)
LS mean difference (95% CI)	1.1 (−1.2 to 3.5)		6.25 (3.82 to 8.69)		3.5 (0.8 to 6.2)	
P value	0.342		< 0.0001		0.010	
TRIM-D Psychological Health Score						
Baseline (Week 0)						
N	278	275	252	254	290	146

	DUAL V[a]		DUAL VII[b]		DUAL III[c]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Mean (SD)	83.1 (16.4)	82.6 (16.4)	80.8 (17.1)	80.0 (15.5)	78.6 (16.4)	79.1 (16.4)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	88.2 (0.8)	86.7 (0.8)	86.46 (0.88)	83.70 (0.88)	85.9 (0.8)	80.5 (1.1)
Change From Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	5.3 (0.8)	3.8 (0.8)	5.81 (0.88)	3.05 (0.88)	7.1 (0.8)	1.7 (1.1)
LS mean difference (95% CI)	1.5 (−0.7 to 3.6)		2.77 (0.32 to 5.21)		5.4 (2.7 to 8.1)	
P value	0.176		0.0268		< 0.001	
TRIM-D Total Score						
Baseline (Week 0)						
N	278	275	252	254	290	146
Mean (SD)	74.6 (13.2)	73.6 (12.5)	72.9 (14.0)	70.9 (12.5)	73.6 (12.8)	75.0 (11.8)
After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	81.8 (0.7)	79.0 (0.7)	81.87 (0.74)	75.36 (0.75)	82.6 (0.6)	77.5 (0.9)
Change From Baseline After 26 Weeks of Treatment						
N	278	275	240	238	290	146
LS mean (SEM)	7.7 (0.7)	4.9 (0.7)	9.64 (0.74)	3.14 (0.75)	8.5 (0.6)	3.5 (0.9)
LS mean difference (95% CI)	2.8 (0.9 to 4.7)		6.50 (4.44 to 8.57)		5.0 (2.9 to 7.2)	
P value	0.003		< 0.0001		< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; SEM = standard error of the mean; SD = standard deviation; TRIM-D = treatment-related impact measure for diabetes.

[a] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[b] Change from baseline after 26 weeks of treatment was analyzed using a mixed-effects model for repeated measures with an unstructured covariance matrix. The model included treatment, visit, and region as fixed factors and baseline response as a covariate. Interactions between visit and all factors and covariates were also included in the model.

[c] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate.

Source: Clinical study reports of DUAL V, DUAL VII, and DUAL III.[12-14]

Table 22: Short Form (36) Health Survey Scores After 26 Weeks of Treatment in DUAL V and DUAL VII Trials

	DUAL V[a]		DUAL VII[b]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
Physical Component Score				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	47.4 (9.0)	47.7 (8.4)	47.2 (9.2)	46.7 (8.9)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	49.0 (0.4)	47.1 (0.4)	47.85 (0.43)	48.46 (0.43)

	DUAL V[a]		DUAL VII[b]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.5 (0.4)	−0.5 (0.4)	0.74 (0.43)	1.35 (0.43)
LS mean difference (95% CI)	1.9 (0.8 to 3.1)		−0.61 (−1.81 to 0.59)	
P value	< 0.001		0.3187	
Physical Functioning				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	47.0 (10.0)	47.5 (9.1)	46.5 (9.7)	45.8 (10.1)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	47.7 (0.5)	46.4 (0.5)	47.29 (0.46)	47.22 (0.46)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	0.5 (0.5)	−0.9 (0.5)	1.02 (0.46)	0.95 (0.46)
LS mean difference (95% CI)	1.4 (0.0 to 2.7)		0.07 (−1.22 to 1.35)	
P value	0.045		0.9186	
Role Physical				
Baseline (Week 0)				
N	277	277	252	254
Mean (SD)	46.6 (10.1)	47.2 (10.1)	45.9 (10.1)	46.2 (9.6)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	47.9 (0.5)	46.6 (0.5)	47.44 (0.51)	47.29 (0.52)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.0 (0.5)	−0.3 (0.5)	1.22 (0.51)	1.07 (0.52)
LS mean difference (95% CI)	1.3 (−0.0 to 2.6)		0.15 (−1.28 to 1.58)	
P value	0.051		0.8379	
Bodily Pain				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	49.4 (11.2)	50.0 (11.0)	49.4 (11.4)	49.4 (11.3)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	51.3 (0.6)	49.3 (0.6)	49.93 (0.58)	50.89 (0.58)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.6 (0.6)	−0.4 (0.6)	0.43 (0.58)	1.38 (0.58)
LS mean difference (95% CI)	2.0 (0.4 to 3.6)		−0.96 (−2.57 to 0.66)	
P value	0.012		0.2465	

	DUAL V[a]		DUAL VII[b]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
General Health				
Baseline (Week 0)				
N	278	276	252	254
Mean (SD)	42.9 (9.0)	43.6 (9.3)	43.5 (8.9)	43.6 (8.3)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	46.4 (0.4)	44.8 (0.4)	45.74 (0.47)	44.92 (0.47)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	3.2 (0.4)	1.5 (0.4)	2.06 (0.47)	1.23 (0.47)
LS mean difference (95% CI)	1.7 (0.4 to 2.9)		0.82 (−0.48 to 2.13)	
P value	0.008		0.2157	
Mental Component Score				
Baseline (Week 0)				
N	278	279	252	254
Mean (SD)	46.7 (11.4)	48.1 (9.9)	46.7 (10.7)	47.5 (10.2)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	48.7 (0.5)	48.7 (0.5)	49.22 (0.56)	47.39 (0.57)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.3 (0.5)	1.3 (0.5)	2.11 (0.56)	0.28 (0.57)
LS mean difference (95% CI)	−0.1 (−1.5 to 1.3)		1.83 (0.26 to 3.40)	
P value	0.928		0.0228	
Vitality				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	50.8 (10.3)	51.2 (9.8)	50.4 (9.3)	50.6 (9.8)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	53.0 (0.5)	52.6 (0.5)	52.29 (0.49)	51.11 (0.50)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	2.0 (0.5)	1.6 (0.5)	1.71 (0.49)	0.53 (0.50)
LS mean difference (95% CI)	0.4 (−0.8 to 1.7)		1.18 (−0.20 to 2.55)	
P value	0.498		0.0928	
Social Functioning				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	47.2 (10.4)	48.8 (8.9)	47.6 (10.2)	47.4 (9.8)
After 26 Weeks of Treatment				
N	278	277	240	238

	DUAL V[a]		DUAL VII[b]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)
LS mean (SEM)	49.0 (0.5)	48.6 (0.5)	49.02 (0.52)	48.53 (0.52)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.0 (0.5)	0.6 (0.5)	1.42 (0.52)	0.93 (0.52)
LS mean difference (95% CI)	0.4 (−0.9 to 1.8)		0.49 (−0.95 to 1.93)	
P value	0.546		0.5043	
Role Emotional				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	45.3 (11.6)	46.1 (10.8)	44.7 (11.5)	45.3 (11.3)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	46.3 (0.6)	45.3 (0.6)	46.53 (0.62)	45.99 (0.63)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	0.6 (0.6)	−0.4 (0.6)	1.45 (0.62)	0.91 (0.63)
LS mean difference (95% CI)	0.9 (−0.7 to 2.6)		0.54 (−1.19 to 2.28)	
P value	0.250		0.5392	
Mental Health				
Baseline (Week 0)				
N	278	277	252	254
Mean (SD)	45.9 (11.4)	47.6 (10.8)	46.0 (11.1)	46.8 (10.2)
After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	48.2 (0.5)	48.2 (0.5)	48.82 (0.60)	46.53 (0.60)
Change From Baseline After 26 Weeks of Treatment				
N	278	277	240	238
LS mean (SEM)	1.4 (0.5)	1.5 (0.5)	2.35 (0.60)	0.06 (0.60)
LS mean difference (95% CI)	−0.0 (−1.5 to 1.4)		2.29 (0.62 to 3.96)	
P value	0.949		0.0074	

ANCOVA = analysis of covariance; CI = confidence interval; IAsp = insulin aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; SD = standard deviation; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. The score and change in score from baseline after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline value as a covariate.

[b] Change from baseline after 26 weeks of treatment was analyzed using a mixed-effects model for repeated measures with an unstructured covariance matrix. The model included treatment, visit, and region as fixed factors and baseline response as a covariate. Interactions between visit and all factors and covariates were also included in the model.

Source: Clinical study reports of DUAL V and DUAL VII.[13, 14]

Table 23: Scores for Diabetes Treatment Satisfaction Questionnaire Status Version After 26 Weeks of Treatment in DUAL III Trial

	DUAL III[a]	
	IDegLira (N = 292)	GLP-1 RA (N = 146)
Treatment Satisfaction Scale Total		
Baseline (Week 0)		
N	290	146
Mean (SD)	29.4 (5.1)	29.7 (6.0)
After 26 Weeks of Treatment		
N	290	146
LS Mean (SEM)	32.6 (0.3)	30.6 (0.4)
Change From Baseline After 26 Weeks of Treatment		
N	290	146
LS mean (SEM)	3.1 (0.3)	1.1 (0.4)
LS mean difference (95% CI)	2.0 (1.1 to 2.8)	
P value	< 0.001	
Hyperglycemia		
Baseline (Week 0)		
N	290	146
Mean (SD)	3.2 (1.8)	3.2 (1.7)
After 26 Weeks of Treatment		
N	290	146
LS mean (SEM)	1.5 (0.1)	2.5 (0.1)
Change From Baseline After 26 Weeks of Treatment		
N	290	146
LS mean (SEM)	−1.7 (0.1)	−0.7 (0.1)
LS mean difference (95% CI)	−1.0 (−1.4 to −0.7)	
P value	< 0.001	
Hypoglycemia		
Baseline (Week 0)		
N	290	146
Mean (SD)	0.8 (1.4)	0.8 (1.4)
After 26 Weeks of Treatment		
N	290	146
LS mean (SEM)	1.1 (0.1)	0.7 (0.1)
Change From Baseline After 26 Weeks of Treatment		
N	290	146
LS mean (SEM)	0.3 (0.1)	−0.1 (0.1)
LS mean difference (95% CI)	0.4 (0.1 to 0.6)	
P value	0.006	

ANCOVA = analysis of covariance; CI = confidence interval; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; SD = standard deviation; SEM = standard error of the mean.

[a] The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate. Missing data were imputed using last observation carried forward. Out of eight items in the DTSQs, treatment satisfaction scale total was computed by adding items 1, 4, 5, 6, 7, and 8. Items 2 and 3 were "hyperglycemia" and "hypoglycemia," respectively.

Source: Clinical study report of DUAL III.[12]

Table 24: Body Weight After 26 Weeks of Treatment

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Body Weight (kg)								
Baseline (Week 0)								
N	199	199	278	279	252	254	292	146
Mean (SD)	95.4 (19.4)	93.5 (20.0)	88.3 (17.5)	87.3 (15.8)	87.2 (16.0)	88.2 (17.2)	95.6 (16.6)	95.5 (17.3)
After 26 Weeks of Treatment								
N	199	199	278	279	244	246	292	146
LS mean (SEM)	91.86 (0.25)	94.37 (0.25)	86.38 (0.20)	89.58 (0.20)	86.51 (0.22)	90.08 (0.22)	97.52 (0.21)	94.63 (0.30)
Change From Baseline After 26 Weeks of Treatment								
N	199	199	278	279	244	246	292	146
LS mean (SEM)	−2.59 (0.25)	−0.08 (0.25)	−1.39 (0.20)	1.81 (0.20)	−0.93 (0.22)	2.64 (0.22)	2.00 (0.21)	−0.89 (0.30)
LS mean difference after 26 weeks of treatment (95% CI)	−2.51 (−3.21 to −1.82)		−3.20 (−3.77 to −2.64)		−3.57 (−4.19 to −2.95)		2.89 (2.17 to 3.62)	
P value	< 0.0001		< 0.001		< 0.0001		< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, country, and previous antidiabetes treatment as fixed factors, and baseline response as a covariate.

[b] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[c] All observed body weight measurements available post randomization at scheduled measurement times were analyzed using a MMRM with an unstructured covariance matrix. The model included treatment, visit, and regions as fixed factors and baseline body weight as a covariate. Interactions between visit and all factors and covariates were also included in the model.

[d] Missing data were imputed using LOCF. Change in body weight was analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 25: Systolic Blood Pressure and Diastolic Blood Pressure After 26 Weeks of Treatment

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Systolic Blood Pressure (mm Hg)								
Baseline (Week 0)								
N	199	199	278	278	252	254	292	146
Mean (SD)	132.4 (14.8)	132.4 (15.5)	133.0 (13.8)	133.0 (12.5)	131.31 (13.08)	132.22 (13.68)	130.2 (13.5)[e]	131.3 (14.5)[e]
After 26 Weeks of Treatment								
N	199	199	278	278	240	238	292	146

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
LS mean (SEM)	127.02 (0.87)	130.73 (0.87)	129.30 (0.71)	132.86 (0.71)	126.99 (0.71)	130.69 (0.72)	129.78 (0.69)	130.53 (0.97)
Change From Baseline After 26 Weeks of Treatment								
N	199	199	278	278	240	238	292	146
LS mean (SEM)	−5.41 (0.87)	−1.70 (0.87)	−3.71 (0.71)	−0.15 (0.71)	−4.60 (0.71)	−0.90 (0.72)	−0.83 (0.69)	−0.08 (0.97)
LS mean difference after 26 weeks of treatment (95% CI)	−3.71 (−6.13 to −1.29)		−3.57 (−5.54 to −1.59)		−3.70 (−5.68 to −1.72)		−0.75 (−3.10 to 1.59)	
P value	0.0028		< 0.001		0.0003		0.529	
Diastolic Blood Pressure (mm Hg)								
Baseline (Week 0)								
N	199	199	278	278	252	254	292	146
Mean (SD)	79.1 (7.7)	79.1 (8.6)	79.4 (8.4)	78.7 (8.3)	76.75 (8.59)	76.96 (8.83)	77.5 (8.3)[a]	78.2 (8.2)[a]
After 26 Weeks of Treatment								
N	199	199	278	278	240	238	292	146
LS mean (SEM)	77.72 (0.49)	78.41 (0.49)	78.45 (0.43)	77.54 (0.43)	76.67 (0.50)	76.63 (0.50)	77.55 (0.45)	77.88 (0.64)
Change From Baseline After 26 Weeks of Treatment								
N	199	199	278	278	240	238	292	146
LS mean (SEM)	−1.38 (0.49)	−0.69 (0.49)	−0.61 (0.43)	−1.52 (0.43)	−0.13 (0.50)	−0.18 (0.50)	−0.19 (0.45)	0.14 (0.64)
LS mean difference after 26 weeks of treatment (95% CI)	−0.69 (−2.07 to 0.70)		0.91 (−0.28 to 2.10)		0.05 (−1.34 to 1.44)		−0.33 (−1.87 to 1.21)	
P value	0.3301		0.135		0.9439		0.673	

ANCOVA = analysis of covariance; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; SD = standard deviation; SEM = standard error of the mean.

[a] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, country, and previous antidiabetes treatment as fixed factors, and baseline response as a covariate.

[b] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment and region as fixed factors and baseline response as a covariate.

[c] All measurements available post randomization at scheduled measurement times were analyzed using a MMRM with an unstructured covariance matrix. The model included treatment, visit, and region as fixed factors and baseline response as a covariate. Interactions between visit and all factors and covariates were also included in the model.

[d] Missing data were imputed using LOCF. The response and change from baseline in the response after 26 weeks of treatment were analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and baseline response as a covariate.

[e] This measurement was at visit 1.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 26: Fasting Lipid Profile (Total Cholesterol; High-Density Lipoprotein, Low-Density Lipoprotein, and Very Low-Density Lipoprotein Cholesterol; Triglycerides) After 26 Weeks of Treatment

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Total Cholesterol, mmol/L								
Baseline (Week 0)								
N	199	197	278	279	252	252	292	146
Mean (SD)	4.71 (1.18)	4.73 (1.26)	4.70 (1.07)	4.68 (1.15)	4.43 (25.7)[e]	4.29 (25.2)[e]	4.23 (1.04)	4.35 (1.16)
After 26 Weeks of Treatment								
N	199	197	277	279	240	236	290	145
LS mean	4.25	4.49	4.42	4.65	4.20	4.39	4.14	4.29
Treatment ratio (95% CI)	0.95 (0.91 to 0.98)		0.95 (0.92 to 0.98)		0.96 (0.92 to 0.99)		0.96 (0.93 to 1.00)	
P value	0.0022		< 0.001		0.0120		0.025	
HDL Cholesterol (mmol/L)								
Baseline (Week 0)								
N	199	196	277	279	252	252	290	145
Mean (SD)	1.13 (0.29)	1.22 (0.32)	1.21 (0.28)	1.22 (0.31)	1.168 (28.8)[a]	1.158 (26.8)[a]	1.20 (0.34)	1.24 (0.32)
After 26 Weeks of Treatment								
N	199	196	277	279	240	236	290	145
LS mean	1.16	1.16	1.20	1.20	1.17	1.21	1.21	1.21
Treatment ratio (95% CI)	1.00 (0.97 to 1.03)		1.00 (0.97 to 1.03)		0.97 (0.94 to 0.99)		1.00 (0.97 to 1.03)	
P value	0.8474		0.835		0.0133		0.991	
LDL Cholesterol (mmol/L)								
Baseline (Week 0)								
N	199	196	277	278	252	252	290	145
Mean (SD)	2.64 (0.96)	2.57 (0.98)	2.63 (0.93)	2.54 (0.91)	2.30 (40.2)[a]	2.26 (39.3)[a]	2.11 (0.86)	2.23 (0.91)
After 26 Weeks of Treatment								
N	199	196	277	278	240	236	290	145
LS mean	2.19	2.43	2.32	2.51	2.24	2.33	2.06	2.10
Treatment ratio (95% CI)	0.90 (0.85 to 0.95)		0.92 (0.88 to 0.97)		0.96 (0.91 to 1.02)		0.98 (0.93 to 1.04)	
P value	0.0002		0.001		0.1600		0.541	
VLDL Cholesterol (mmol/L)								
Baseline (Week 0)								
N	199	197	278	279	252	252	290	145
Mean (SD)	0.95 (0.59)	0.94 (0.67)	0.86 (0.45)	0.91 (0.79)	0.744 (58.0)[a]	0.707 (54.4)[a]	0.93 (0.47)	0.87 (0.48)
After 26 Weeks of Treatment								
N	199	197	277	278	240	236	290	145
LS mean	0.712	0.713	0.71	0.75	0.65	0.67	0.69	0.77

	DUAL II[a]		DUAL V[b]		DUAL VII[c]		DUAL III[d]	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 254)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Treatment ratio (95% CI)	0.998 (0.93 to 1.08)		0.94 (0.88 to 1.00)		0.97 (0.91 to 1.03)		0.90 (0.85 to 0.96)	
P value	0.9656		0.070		0.3119		< 0.001	
Triglycerides (mmol/L)								
Baseline (Week 0)								
N	199	197	277	279	252	252	290	145
Mean (SD)	2.21 (1.66)	2.17 (2.48)	1.93 (1.23)	2.18 (2.98)	1.64 (61.0)[a]	1.56 (57.3)[a]	2.13 (1.30)	1.98 (1.38)
After 26 Weeks of Treatment								
N	199	197	277	279	240	236	290	145
LS mean	1.57	1.58	1.57	1.66	1.41	1.46	1.51	1.72
Treatment ratio (95% CI)	0.99 (0.92 to 1.07)		0.94 (0.88 to 1.01)		0.97 (0.91 to 1.03)		0.88 (0.82 to 0.94)	
P value	0.8924		0.098		0.2764		< 0.001	

ANCOVA = analysis of covariance; CI = confidence interval; CV = cardiovascular; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HDL = high-density lipoprotein; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LDL = low-density lipoprotein; LOCF = last observation carried forward; LS = least squares; MMRM = mixed-effects model for repeated measures; SD = standard deviation; VLDL = very low-density lipoprotein.

[a] Missing data were imputed using LOCF. The log-transformed response after 26 weeks of treatment was analyzed using an ANCOVA method with treatment, country, and previous antidiabetes treatment as fixed factors, and log-transformed baseline response as a covariate. Two-sided *P* values are presented.

[b] Missing data were imputed using LOCF. The log-transformed response after 26 weeks of treatment was analyzed using an ANCOVA method with treatment and region as fixed factors and log-transformed baseline response as a covariate.

[c] The log-transformed response after 26 weeks of treatment was analyzed using a MMRM model with unstructured covariance matrix. The model included treatment, visit, and region as fixed factors and the log-transformed baseline response as a covariate. Interactions between visit and all factors and the covariate were also included in the model. Two-sided *P* values are presented.

[d] Missing data were imputed using LOCF. The log-transformed response after 26 weeks of treatment was analyzed using an ANCOVA method with treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors, and log-transformed baseline response as a covariate.

[e] Geometric mean (CV [%]).

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 27: Efficacy Results for Patients With Pretrial Glucagon-Like Peptide 1 Receptor Agonist (Liraglutide) in DUAL III Trial

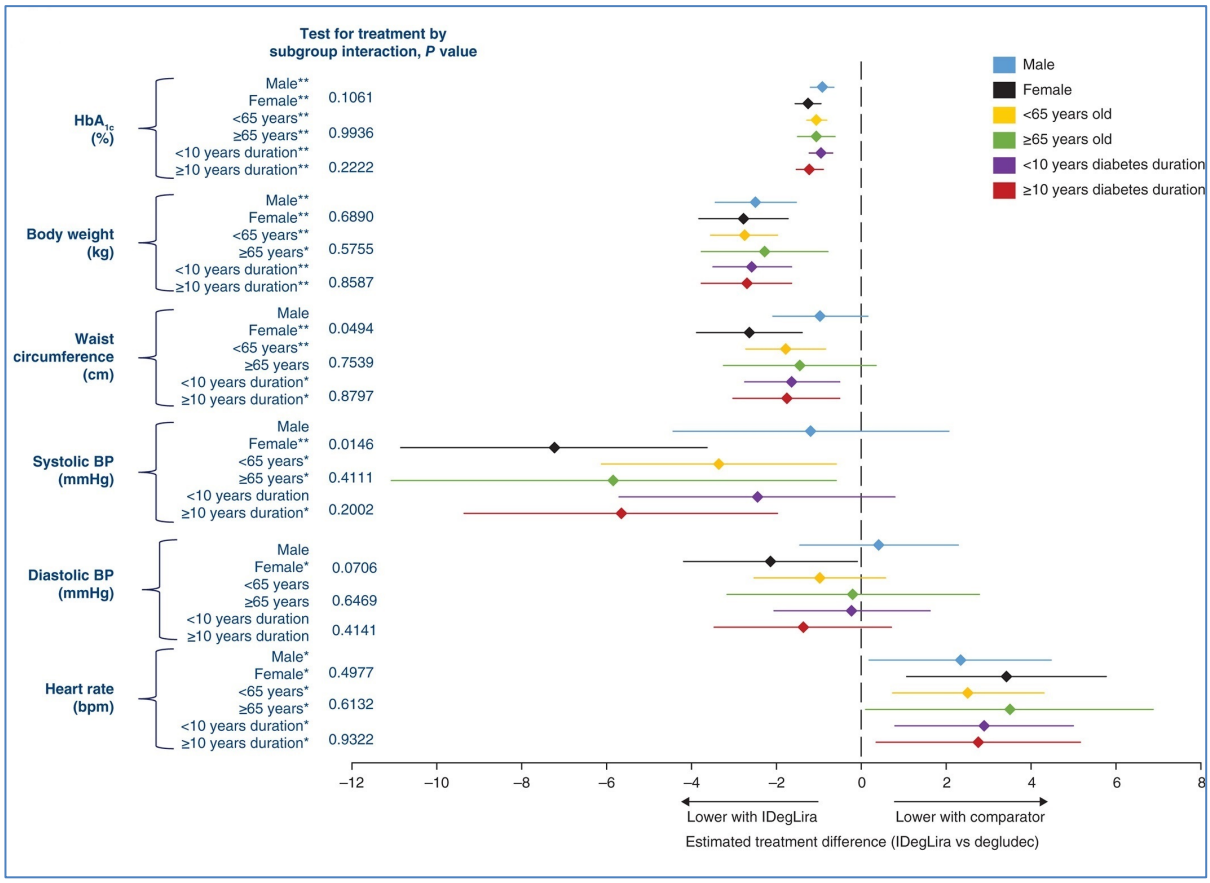
	DUAL III	
	IDegLira [redacted]	GLP-1 RA [redacted]
Hemoglobin A1C (%)		
Baseline (Week 0)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
Change From Baseline After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
LS mean difference after 26 weeks of treatment (95% CI)	[redacted]	
P value	[redacted]	
Responder for hemoglobin A1C After 26 Weeks of Treatment		
Hemoglobin A1C < 7.0%		
Week 26, n (%)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
P value	[redacted]	
hemoglobin A1C < 6.5%		
Week 26, n (%)	[redacted]	[redacted]
Odds ratio (95% CI)	[redacted]	
P value	[redacted]	
Body Weight (kg)		
Baseline (Week 0)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
After 26 Weeks of Treatment		
HN	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
Change From Baseline After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
LS mean difference after 26 weeks of treatment (95% CI)	[redacted]	
P value	[redacted]	
FPG (mmol/L)		
Baseline (Week 0)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
Change From Baseline After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]

	DUAL III	
	IDegLira [redacted]	GLP-1 RA [redacted]
LS mean difference after 26 weeks of treatment (95% CI)	[redacted]	
P value	[redacted]	
Systolic Blood Pressure (mm Hg)		
Baseline (Week 0)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change From Baseline After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
LS mean difference after 26 weeks of treatment (95% CI)	[redacted]	
P value	[redacted]	
Diastolic Blood Pressure (mm Hg)		
Baseline (Week 0)		
N	[redacted]	[redacted]
Mean (SD)	[redacted]	[redacted]
Change From Baseline After 26 Weeks of Treatment		
N	[redacted]	[redacted]
LS mean (SEM)	[redacted]	[redacted]
LS mean difference after 26 weeks of treatment (95% CI)	[redacted]	
P value	[redacted]	
Confirmed Hypoglycemic Episodes		
N	[redacted]	[redacted]
Number (%) of patients with confirmed hypoglycemia	[redacted]	[redacted]
Number of confirmed hypoglycemic episodes	[redacted]	[redacted]
Event rate per 100 PYE	[redacted]	[redacted]
LS means, events per 100 PYE	[redacted]	[redacted]
Treatment ratio (95% CI)	[redacted]	
P value	[redacted]	

CI = confidence interval; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; LS = least squares; PYE = patient-year of exposure; SD = standard deviation; SEM = standard error of the mean.

Source: Clinical study report of DUAL III.[12]

Figure 2: Changes in Hemoglobin A1C, Body Weight, and Systolic and Diastolic Blood Pressure in DUAL II Trial Grouped by Sex, Age, and Duration of Diabetes



BP = blood pressure; HbA = hemoglobin A1C; IDegLira = insulin degludec plus liraglutide in a fixed combination.

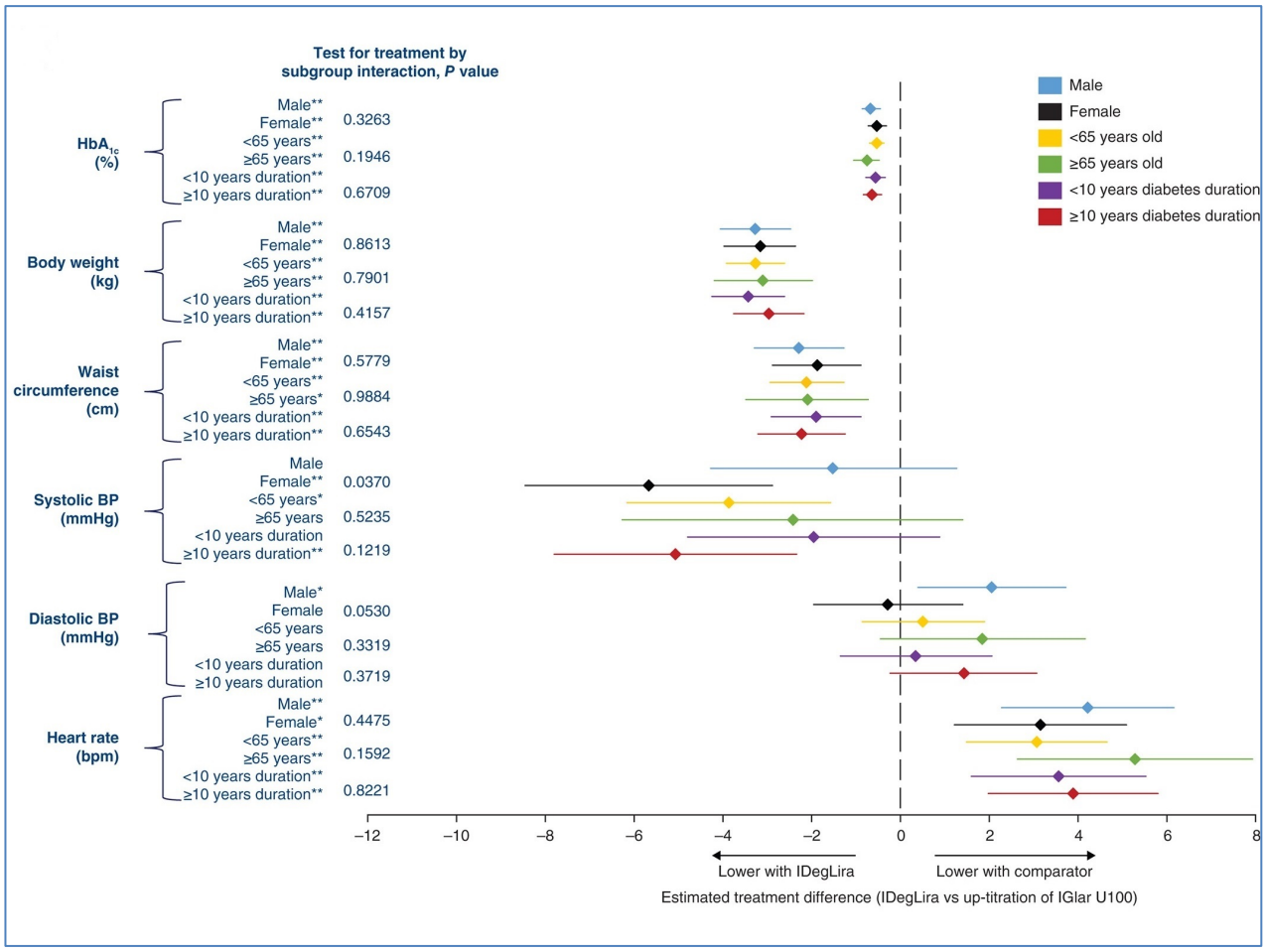
* $P < 0.05$.

** $P < 0.001$.

All analyses were based on the full analysis set. The end point was analyzed using analysis of covariance, with treatment, pretrial diabetes treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and baseline response as a covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 3: Changes in Hemoglobin A1C, Body Weight, and Systolic and Diastolic Blood Pressure in DUAL V Trial Grouped by Sex, Age, and Duration of Diabetes



BP = blood pressure; HbA = hemoglobin A1C; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL.

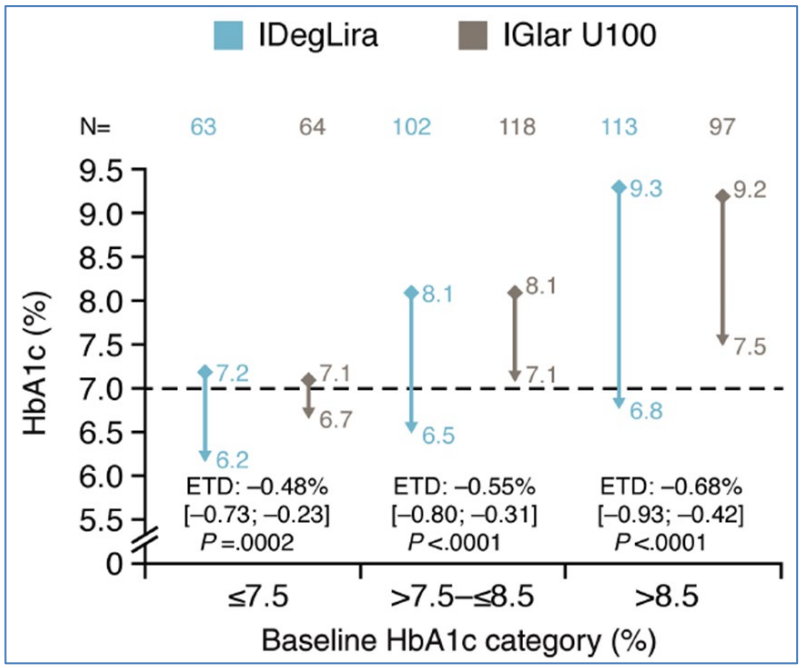
* $P < 0.05$.

** $P < 0.001$.

All analyses were based on the full analysis set. The end point was analyzed using analysis of covariance, with treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and baseline response as a covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 4: Change in Hemoglobin A1C With IDegLira vs. IGlar U100 Across Categories of Baseline Hemoglobin A1C in DUAL V Trial

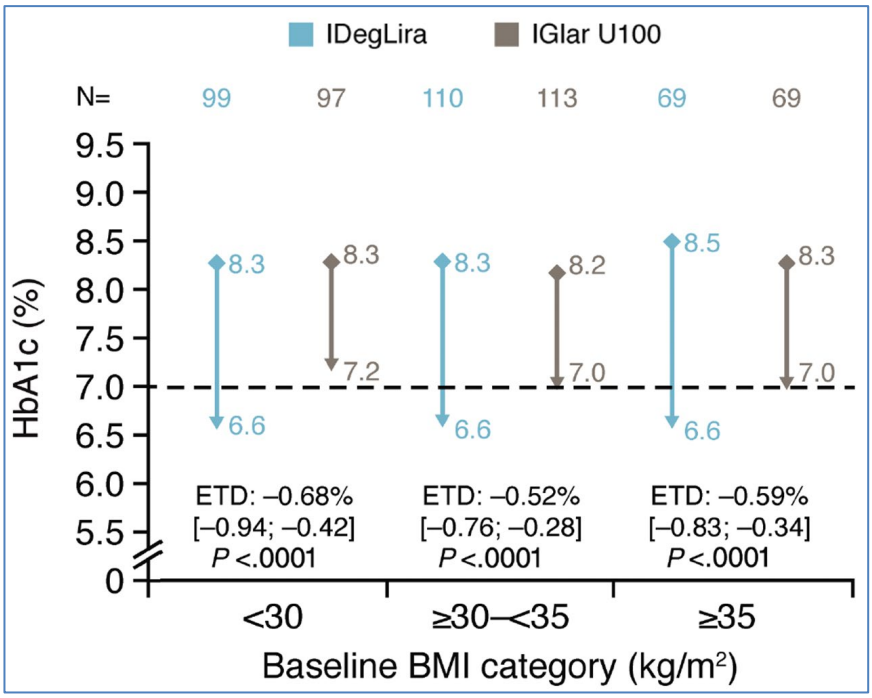


ETD = estimated treatment difference; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; vs. = versus.

Data based on the full analysis set, with missing data imputed by last observation carried forward. Data are mean values with ETD (95% confidence interval) based on analysis of covariance. Dotted line represents American Diabetes Association hemoglobin A1C target < 7.0%.

Source: Lingvay et al.[45]

Figure 5: Change in Hemoglobin A1C With IDegLira vs. IGlar U100 Across Categories of Baseline Body Mass Index in DUAL V Trial

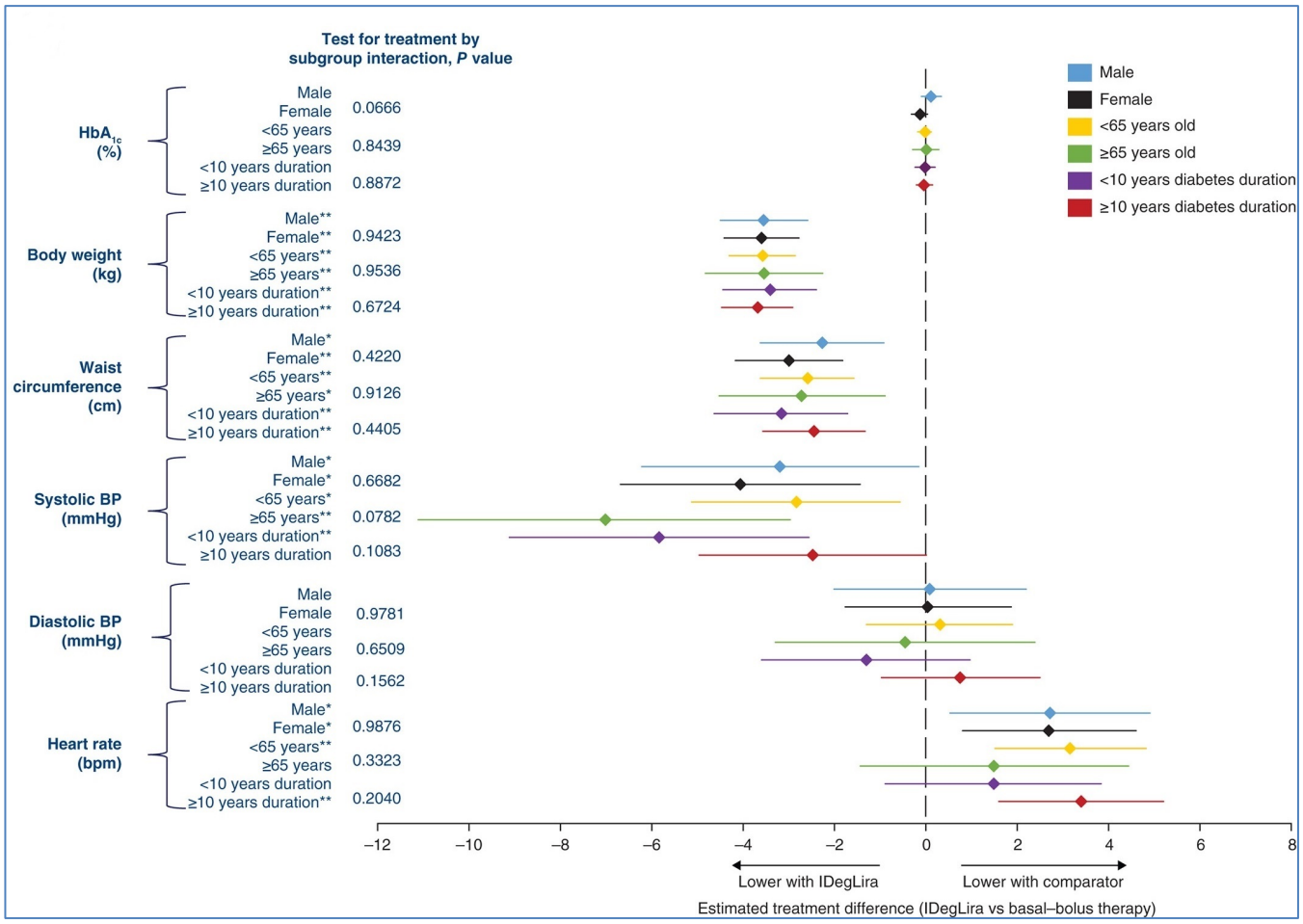


BMI = body mass index; ETD = estimated treatment difference; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; vs. = versus.

Data based on the full analysis set, with missing data imputed by last observation carried forward. Data are mean values with ETD (95% confidence interval) based on analysis of covariance. Dotted line represents American Diabetes Association hemoglobin A1C target < 7.0%.

Source: Lingvay et al.[45]

Figure 6: Changes in Hemoglobin A1C, Body Weight, and Systolic and Diastolic Blood Pressure in DUAL VII Trial Grouped by Sex, Age, and Duration of Diabetes



BP = blood pressure; HbA = hemoglobin A1C; IDegLira = insulin degludec plus liraglutide in a fixed combination.

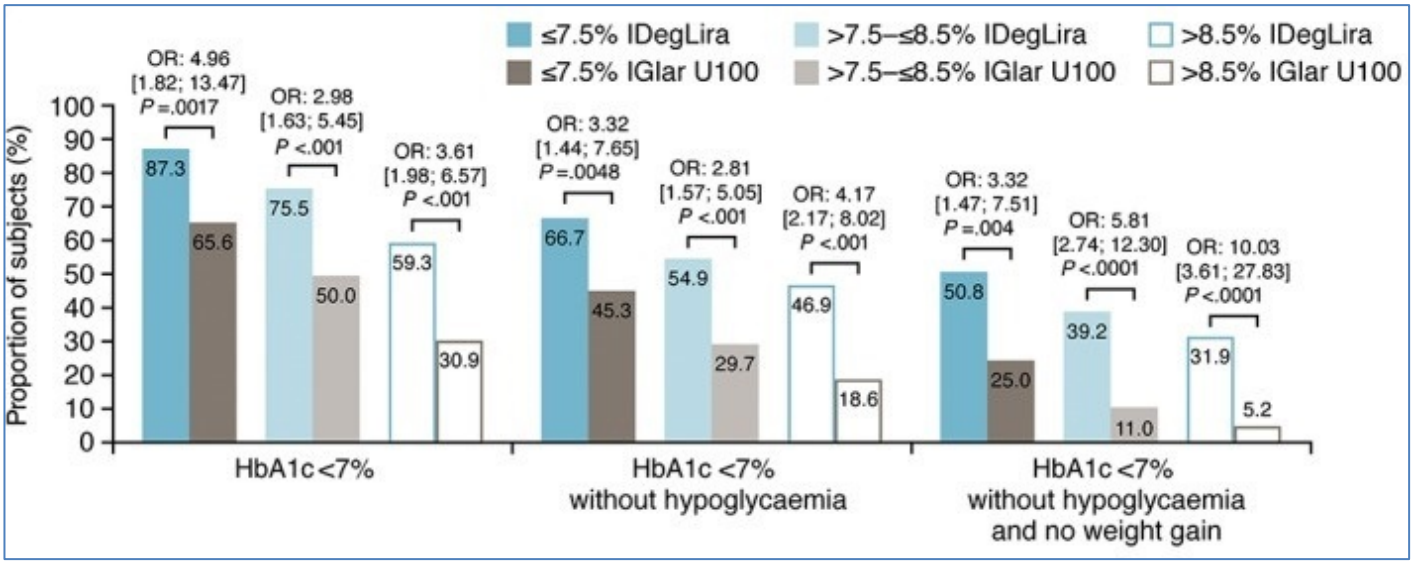
* $P < 0.05$.

** $P < 0.001$.

All analyses were based on the full analysis set. The end point was analyzed using a mixed-effects model for repeated measures including subgroup, visit, treatment, region and interaction between treatment, and subgroup as fixed factors, and baseline response as a covariate. Interactions between visit and all factors and covariates were also included.

Source: Vilsboll et al.[42]

Figure 7: Hemoglobin A1C Responders With IDegLira vs. IGlar U100 in Patients Stratified According to Baseline Hemoglobin A1C in DUAL V Trial

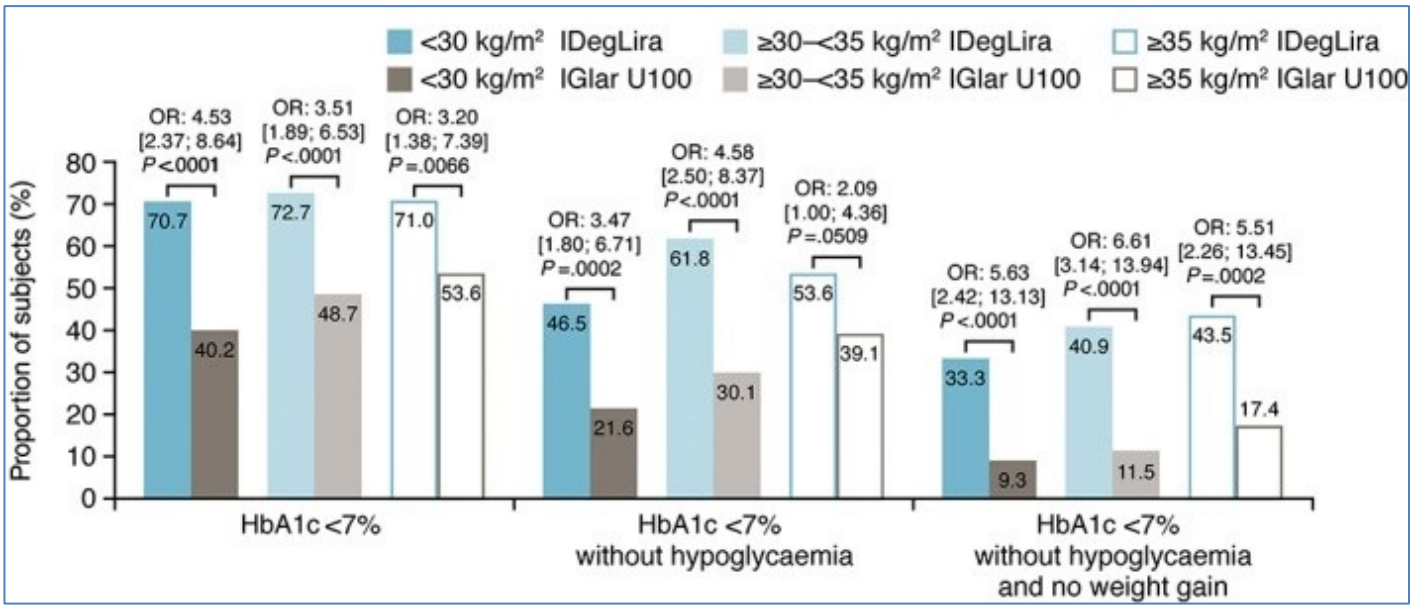


IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; OR = odds ratio; vs. = versus.

Data are percentage of patients reaching hemoglobin A1C target < 7% and composite end points at the end of the trial, based on the full analysis set with missing data imputed by last observation carried forward. Hypoglycemic events defined as patient unable to self-treat and/or plasma glucose < 3.1 mmol/L occurring during the last 12 weeks of treatment.

Source: Lingvay et al.[45]

Figure 8: Hemoglobin A1C Responders With IDegLira vs. IGlar U100 in Patients Stratified According to Baseline Body Mass Index in DUAL V Trial

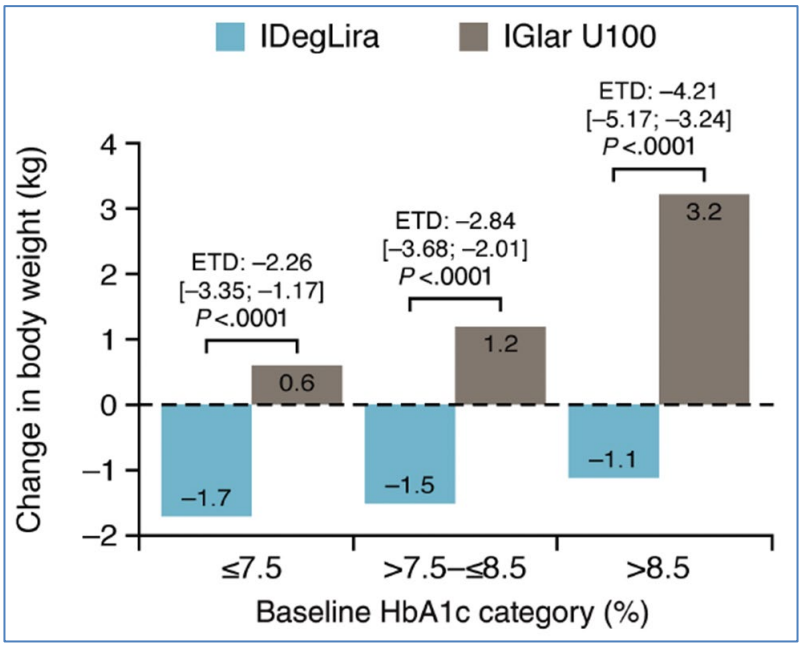


IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; OR = odds ratio; vs. = versus.

Data are percentage of patients reaching hemoglobin A1C target < 7% and composite end points at the end of the trial, based on the full analysis set with missing data imputed by last observation carried forward. Hypoglycemic events defined as patient unable to self-treat and/or plasma glucose < 3.1 mmol/L occurring during the last 12 weeks of treatment.

Source: Lingvay et al.[45]

Figure 9: Change in Body Weight With IDegLira vs. IGlar U100 Across Categories of Baseline Hemoglobin A1C in DUAL V Trial

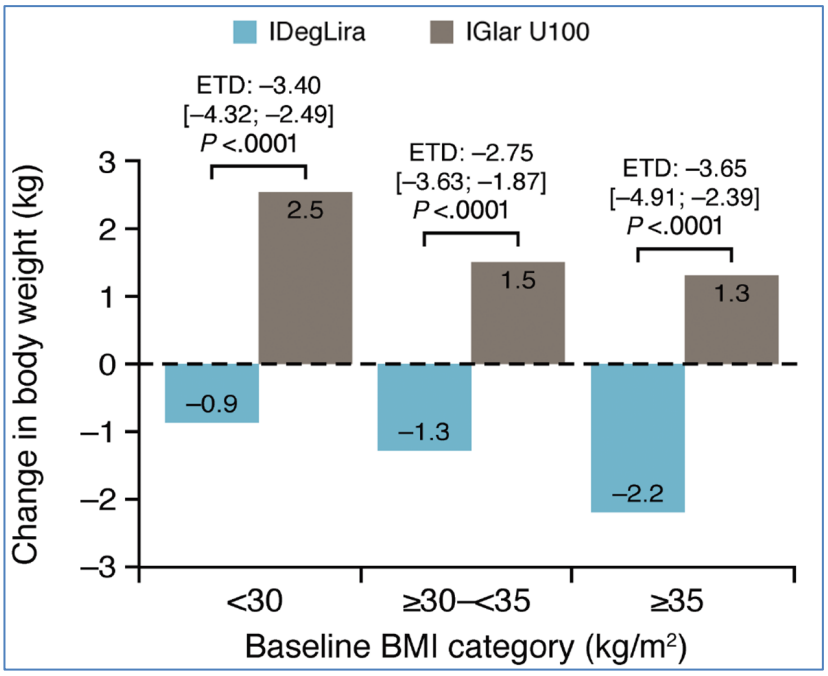


ETD = estimated treatment difference; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; vs. = versus.

Data based on the full analysis set, with missing data imputed by last observation carried forward. Data are mean values with ETD (95% confidence interval) based on analysis of covariance.

Source: Lingvay et al.[45]

Figure 10: Change in Body Weight With IDegLira vs. IGlar U100 Across Categories of Baseline Body Mass Index in DUAL V Trial

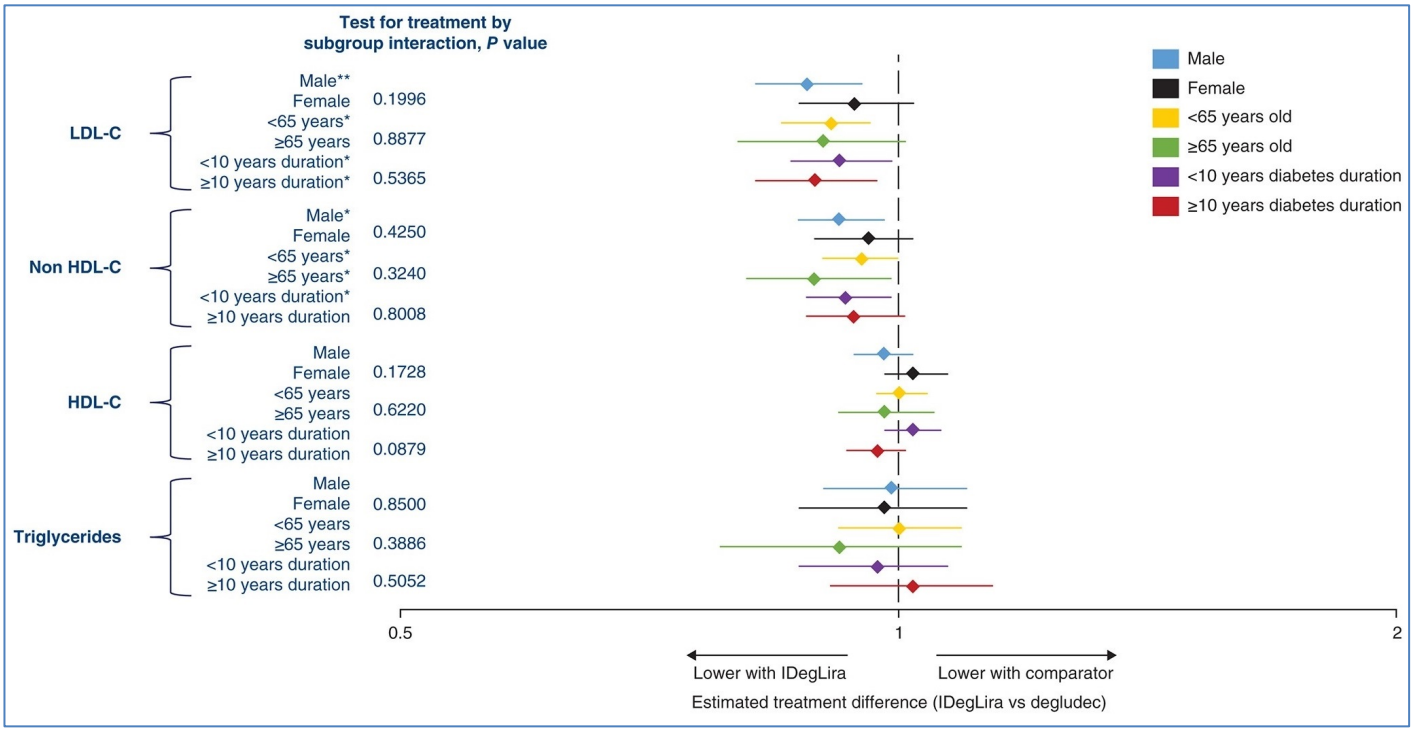


BMI = body mass index; ETD = estimated treatment difference; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; vs. = versus.

Data based on the full analysis set, with missing data imputed by last observation carried forward. Data are mean values with ETD (95% confidence interval) based on analysis of covariance.

Source: Lingvay et al.[45]

Figure 11: Lipids in DUAL II Trial Grouped by Sex, Age, and Duration of Diabetes



HDL-C = high-density lipoprotein cholesterol; IDegLira = insulin degludec plus liraglutide in a fixed combination; LDL-C = low-density lipoprotein cholesterol; vs. = versus.

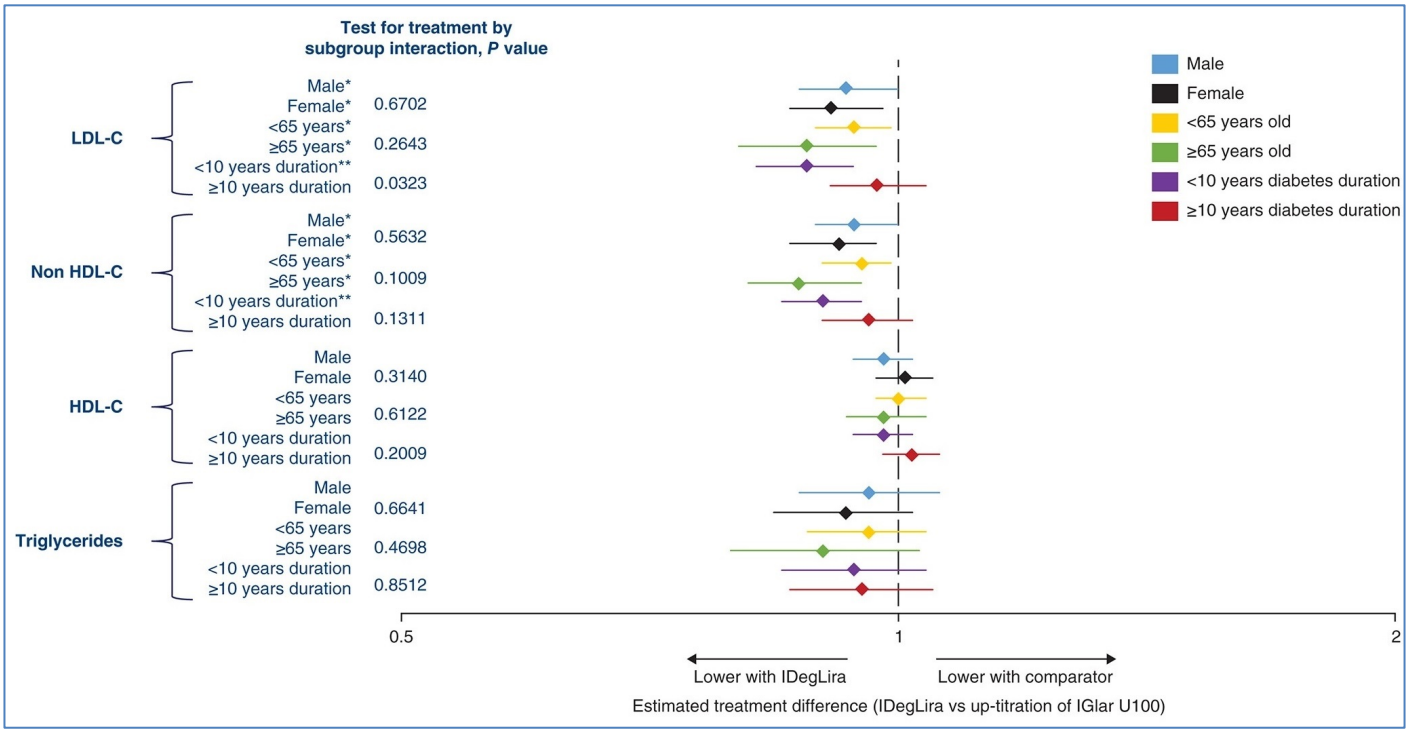
* $P < 0.05$.

** $P < 0.001$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using analysis of covariance, with treatment, pretrial diabetes treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and log-transformed baseline response as a covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 12: Lipids in DUAL V Trial Grouped by Sex, Age, and Duration of Diabetes



HDL-C = high-density lipoprotein cholesterol; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; LDL-C = low-density lipoprotein cholesterol; vs. = versus.

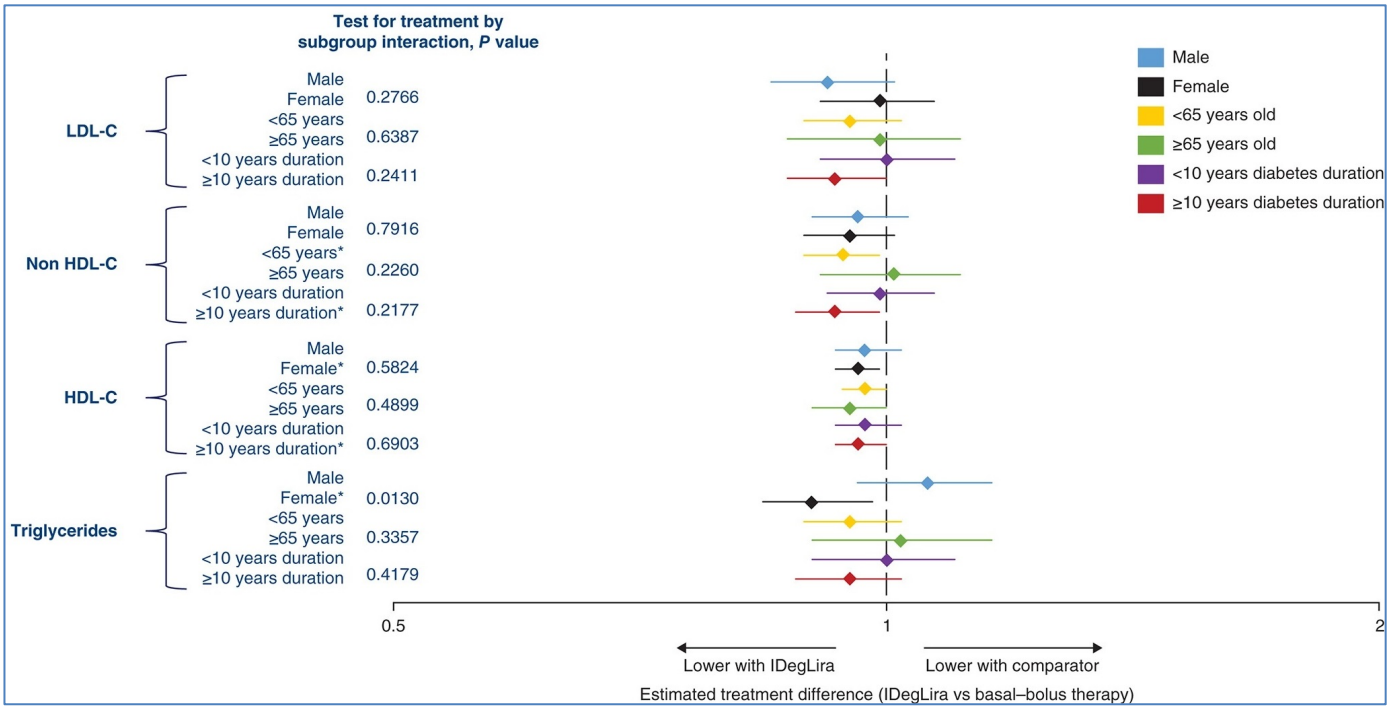
* $P < 0.05$.

** $P < 0.001$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using analysis of covariance, with treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and log-transformed baseline response as a covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 13: Lipids in DUAL VII Trial Grouped by Sex, Age, and Duration of Diabetes



HDL-C = high-density lipoprotein cholesterol; IDegLira = insulin degludec plus liraglutide in a fixed combination; LDL-C = low-density lipoprotein cholesterol; vs. = versus.

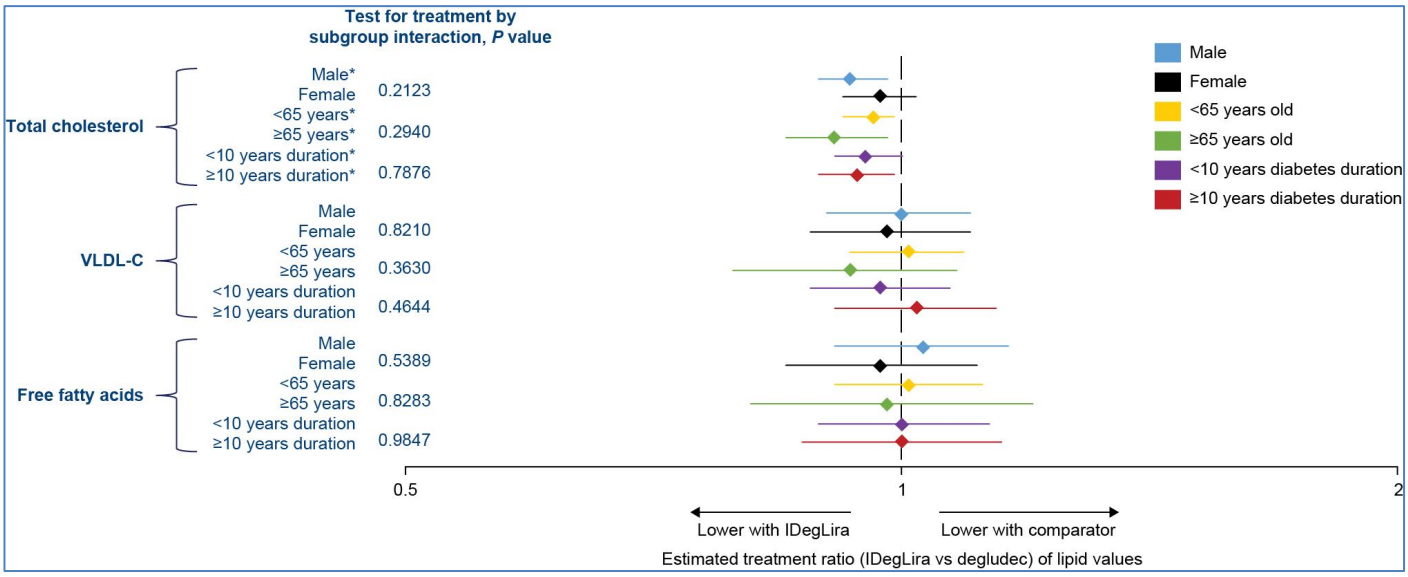
* $P < 0.05$

** $P < 0.001$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using a mixed-effects model for repeated measures including subgroup, visit, treatment, region, and interaction between treatment, and subgroup as fixed factors, and log-transformed baseline response as a covariate. Interactions between visit and all factors and covariates were also included.

Source: Vilsboll et al.[42]

Figure 14: Total Cholesterol, Very Low-Density Lipoprotein Cholesterol, and Free Fatty Acids in DUAL II Trial Grouped by Sex, Age, and Duration of Diabetes



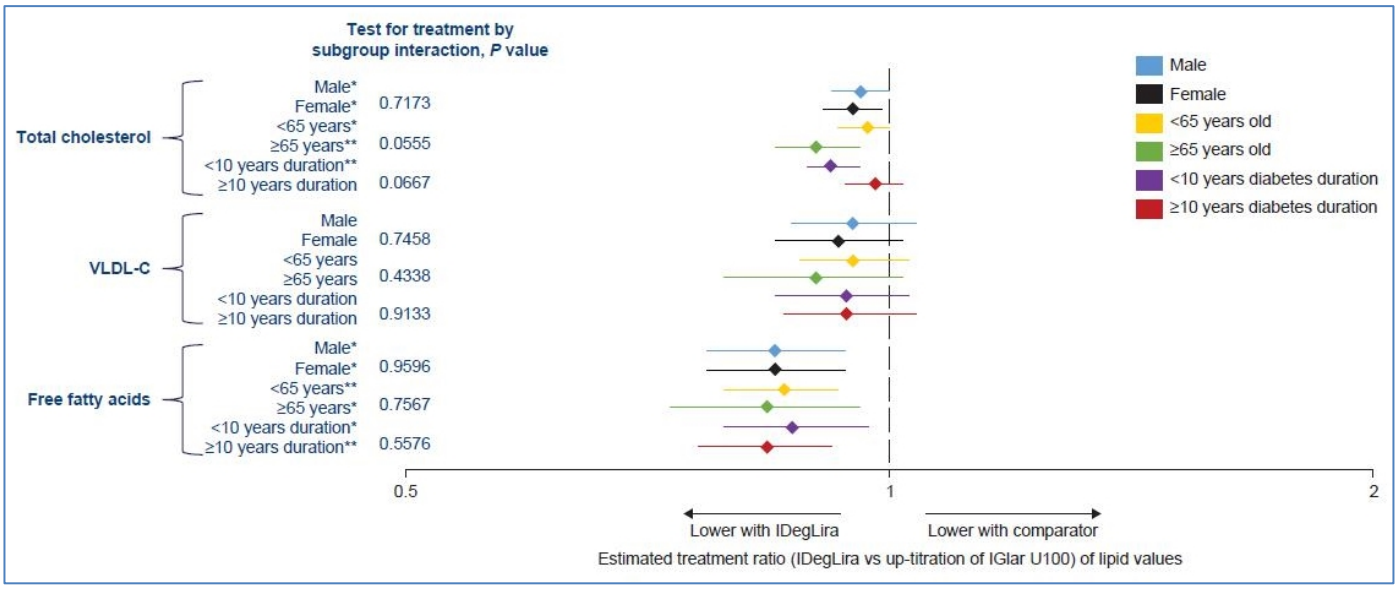
ANCOVA = analysis of covariance; IDegLira = insulin degludec plus liraglutide in a fixed combination; VLDL-C = very low-density lipoprotein cholesterol; vs. = versus.

* $P < 0.05$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using an ANCOVA model with treatment, pretrial diabetes treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and log-transformed baseline response as a covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 15: Total Cholesterol, Very Low-Density Lipoprotein Cholesterol, and Free Fatty Acids in DUAL V Trial Grouped by Sex, Age, and Duration of Diabetes



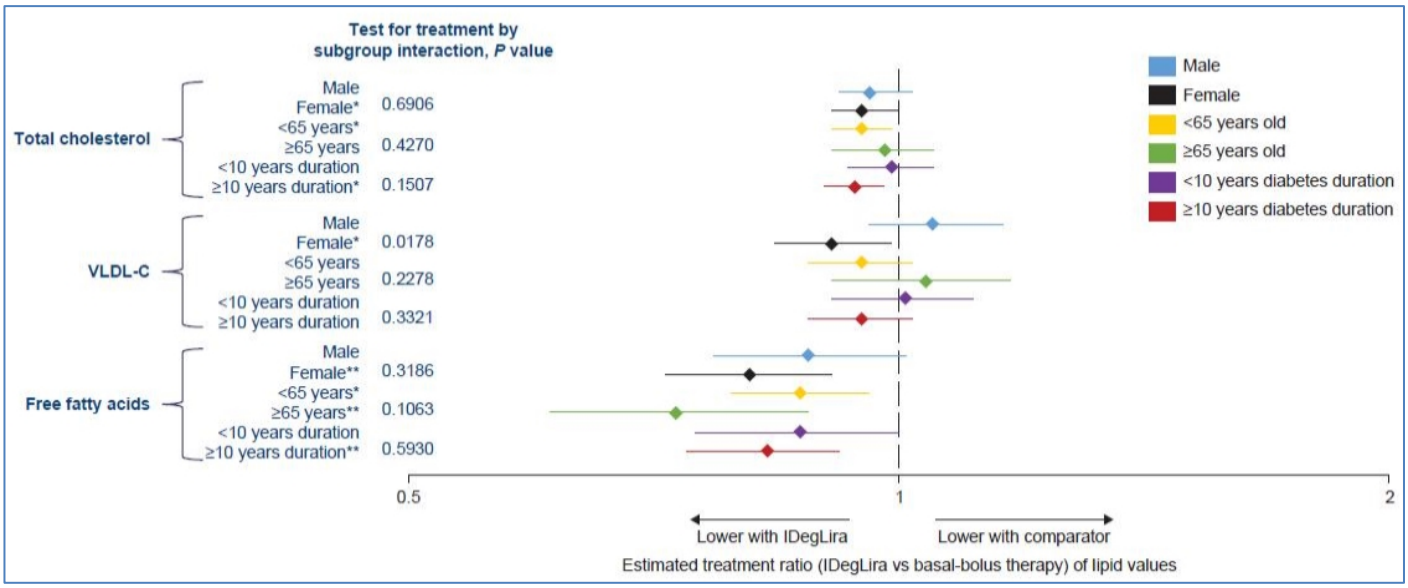
ANCOVA = analysis of covariance; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar U100 = insulin glargine 100 U/mL; VLDL-C = very low-density lipoprotein cholesterol; vs. = versus.

* $P < 0.05$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using an ANCOVA model with treatment, region, subgroup, and interaction between treatment and subgroup as fixed factors and log-transformed baseline response as covariate. Missing data were imputed using last observation carried forward.

Source: Vilsboll et al.[42]

Figure 16: Total Cholesterol, Very Low-Density Lipoprotein Cholesterol, and Free Fatty Acids in DUAL VII Trial Grouped by Sex, Age, and Duration of Diabetes



IDegLira = insulin degludec plus liraglutide in a fixed combination; VLDL-C = very low-density lipoprotein cholesterol; vs. = versus.

* $P < 0.05$.

All analyses were based on the full analysis set. The log-transformed end point was analyzed using a mixed-effects model for repeated measures including subgroup, visit, treatment, region, and interaction between treatment and subgroup as fixed factors and log-transformed baseline response as a covariate. Interactions between visit and all factors and covariates were also included.

Source: Vilsboll et al.[42]

Table 28: Hypoglycemic Episodes — Treatment Emergent After 26 Weeks of Treatment in DUAL V and DUAL III Trials

	DUAL V[a]		DUAL III[b]	
	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 292)	GLP-1 RA (N = 146)
Confirmed Hypoglycemic Episodes				
N	278	279	291	145
Number (%) of patients with confirmed hypoglycemia	79 (28.4)	137 (49.1)	93 (32.0)	4 (2.8)
Number of confirmed hypoglycemic episodes	289	683	397	8
Event rate per 100 PYE	223	505.4	281.7	12.1
LS means, events per 100 PYE	125.86	291.39	233.88	9.22
Treatment ratio (95% CI)	0.43 (0.30 to 0.61)		25.36 (10.63 to 60.51)	
P value	< 0.001		< 0.001	
Confirmed Nocturnal Hypoglycemic Episodes				
N	278	279	291	145
Number (%) of patients with confirmed nocturnal hypoglycemic episodes	17 (6.1)	68 (24.4)	32 (11.0)	1 (0.7)
Number of events	29	166	64	1
Event rate per 100 PYE	22.4	122.8	45.4	1.5
LS means, events per 100 PYE	12.83	74.27	36.39	1.11
Treatment ratio (95% CI)	0.17 (0.10 to 0.31)		32.82 (4.13 to 261.04)	
P value	< 0.001		< 0.001	

CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LS = least squares; PYE = patient-year of exposure.

[a] The number of confirmed hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment and region as fixed factors.

[b] The number of confirmed hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment, pretrial GLP-1 RA (Victoza [liraglutide] or Byetta [exenatide injection]), and region as fixed factors.

Source: Clinical study reports of DUAL V and DUAL III.[12,13]

Table 29: Hypoglycemic Episodes — Treatment Emergent After 26 Weeks of Treatment in DUAL VII Trial

	DUAL VII	
	IDegLira (N = 252)	IGlar + IAsp (N = 254)
Severe or BG-Confirmed Symptomatic Hypoglycemic Episodes[a]		
N	252	253
Number (%) of patients with severe or BG-confirmed symptomatic hypoglycemic episodes	50 (19.8)	133 (52.6)
Number of events	129	975
Event rate per 100 PYE	107.2	817.0
LS means, events per 100 PYE	90.16	784.43
Treatment ratio (95% CI)	0.11 (0.08 to 0.17)	
P value	< 0.0001	
Severe or BG-Confirmed Symptomatic Hypoglycemic Episodes (Sensitivity Analysis, Multiple Imputation [Method 1])[b]		
N	252	253
LS means, events per 100 PYE	100.87	780.53
Treatment ratio (95% CI)	0.13 (0.08 to 0.20)	
P value	< 0.0001	
Severe or BG-Confirmed Symptomatic Hypoglycemic Episodes (Sensitivity Analysis, Multiple Imputation [Method 1])[c]		
N	252	253
LS means, events per 100 PYE	122.66	779.94
Treatment ratio (95% CI)	0.16 (0.10 to 0.26)	
P value	< 0.0001	
Nocturnal Hypoglycemic Episodes (Severe or BG-Confirmed Symptomatic)[a]		
N	252	253
Number (%) of patients with nocturnal hypoglycemic episodes (severe or BG-confirmed symptomatic)[a]	12 (4.8)	49 (19.4)
Number of events	16	198
Event rate per 100 PYE	13.3	165.9
LS means, events per 100 PYE	12.68	156.32
Treatment ratio (95% CI)	0.08 (0.04 to 0.17)	
P value	< 0.0001	

BG = blood glucose; CI = confidence interval; IAsp = insulin aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; PYE = patient-year of exposure (1 PYE = 365.25 days).

[a] The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment and region as fixed factors. To control the overall type I error on a 5% level, a hierarchical testing procedure was used.

[b] The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment and region as fixed factors. Missing data were imputed using multiple imputation (conditioning on expected event rate before withdrawal if treated with IGlar + IAsp).

[c] The number of treatment-emergent severe or BG-confirmed symptomatic hypoglycemic episodes was analyzed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model included treatment and region as fixed factors. Missing data were imputed using multiple imputation (conditioning on expected event rate before withdrawal if treated with randomized treatment).

Source: Clinical Study Report of DUAL VII.[14]

Table 30: Serious Adverse Events and Withdrawal Due to Adverse Events

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
SAEs								
Patients with > 0 SAEs, N (%)[a]	7 (3.5)	11 (5.5)	5 (1.8)	9 (3.2)	12 (4.8)	10 (4.0)	9 (3.1)	3 (2.1)
Reasons								
Convulsion	0	1 (0.5)	0	0	0	0	0	0
Ischemic stroke	0	1 (0.5)	0	0	0	0	0	0
Transient ischemic attack	0	0	0	0	0	0	1 (0.3)	0
Mononeuropathy	0	1 (0.5)	0	0	0	0	0	0
VIIth nerve paralysis	1 (0.5)	0	0	0	0	0	0	0
Vertigo CNS origin	0	1 (0.5)	0	0	0	0	0	0
Acute myocardial infarction	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Atrial fibrillation	1 (0.5)	0	0	0	1 (0.4)	0	1 (0.3)	0
Ventricular fibrillation	1 (0.5)	0	0	0	0	0	0	0
Ventricular tachycardia	1 (0.5)	0	0	0	0	0	0	0
Pneumonia	1 (0.5)	1 (0.5)	0	0	0	1 (0.4)	0	0
Vestibular neuronitis	1 (0.5)	0	0	0	0	0	0	0
Acetabulum fracture	0	1 (0.5)	0	0	0	0	0	0
Foot fracture	0	1 (0.5)	0	0	0	0	0	0
Humerus fracture	0	1 (0.5)	0	0	0	0	0	0
Cholecystitis acute	1 (0.5)	0	0	1 (0.4)	0	0	1 (0.3)	0
Cholelithiasis	0	0	1 (0.4)	0	0	0	0	1 (0.7)
Hypoglycemia	1 (0.5)	0	0	1 (0.4)	1 (0.4)	0	0	0
Intervertebral disc protrusion	0	1 (0.5)	0	0	0	0	0	0
Pancreatic carcinoma, metastatic	0	1 (0.5)	0	0	0	0	0	0
Major depression	1 (0.5)	0	0	0	0	0	0	0
Renal failure, acute	1 (0.5)	0	0	0	0	0	0	0
Asthma	0	1 (0.5)	0	0	0	0	0	0
Coronary revascularization	0	1 (0.5)	0	0	0	0	0	0
Lacunar infarction	0	0	0	0	0	0	1 (0.3)	0
Sciatica	0	0	0	0	0	0	0	1 (0.7)
Foot fracture	0	0	0	0	0	0	0	1 (0.7)
Road traffic accident	0	0	0	0	0	0	1 (0.3)	0
Adrenal insufficiency	0	0	0	0	0	0	1 (0.3)	0
Non-cardiac chest pain	0	0	0	0	0	0	1 (0.3)	0
Spinal pain	0	0	0	0	0	0	1 (0.3)	0
Pituitary tumour	0	0	0	0	0	0	1 (0.3)	0

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
Chronic obstructive pulmonary disease	0	0	0	0	0	0	1 (0.3)	0
Thrombectomy	0	0	0	0	0	0	1 (0.3)	0
Peripheral artery thrombosis	0	0	0	0	0	0	1 (0.3)	0
Acute coronary syndrome	0	0	0	1 (0.4)	0	0	0	0
Arrhythmia	0	0	0	1 (0.4)	0	0	0	0
Cardiac failure	0	0	0	1 (0.4)	1 (0.4)	0	0	0
Biliary colic	0	0	0	1 (0.4)	0	0	0	0
Prostate cancer	0	0	1 (0.4)	0	0	0	0	0
Rectal adenocarcinoma	0	0	1 (0.4)	0	0	0	0	0
Hemorrhagic stroke	0	0	0	1 (0.4)	0	0	0	0
Vertebrobasilar insufficiency	0	0	1 (0.4)	0	0	0	0	0
Auricular perichondritis	0	0	0	1 (0.4)	0	0	0	0
Appendicitis	0	0	0	1 (0.4)	0	0	0	0
Postmenopausal hemorrhage	0	0	1 (0.4)	0	0	0	0	0
Angina, unstable	0	0	0	0	1 (0.4)	0	0	0
Atrial flutter	0	0	0	0	1 (0.4)	0	0	0
Silent myocardial infarction	0	0	0	0	0	1 (0.4)	0	0
Post-operative wound infection	0	0	0	0	1 (0.4)	1 (0.4)	0	0
Diabetic foot infection	0	0	0	0	1 (0.4)	0	0	0
Gastroenteritis	0	0	0	0	1 (0.4)	0	0	0
Staphylococcal bacteremia	0	0	0	0	1 (0.4)	0	0	0
Anal fistula	0	0	0	0	0	1 (0.4)	0	0
Gastritis	0	0	0	0	0	1 (0.4)	0	0
Musculoskeletal chest pain	0	0	0	0	0	1 (0.4)	0	0
Osteoarthritis	0	0	0	0	0	1 (0.4)	0	0
Retinal detachment	0	0	0	0	1 (0.4)	0	0	0
Chest pain	0	0	0	0	1 (0.4)	0	0	0
Hepatic cyst	0	0	0	0	1 (0.4)	0	0	0
Breast cancer	0	0	0	0	0	1 (0.4)	0	0
Staghorn calculus	0	0	0	0	1 (0.4)	0	0	0
Metrorrhagia	0	0	0	0	0	1 (0.4)	0	0
Diabetic foot	0	0	0	0	0	1 (0.4)	0	0
Embolism, arterial	0	0	0	0	0	1 (0.4)	0	0
WDAEs								
WDAEs, N (%)	1 (0.5)	3 (1.5)	7 (2.5)	1 (0.4)	1 (0.4)	0	1 (0.3)	2 (1.4)

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
Reasons								
Acute myocardial infarction	0	1 (0.5)	0	0	0	0	0	0
Cholelithiasis	0	1 (0.5)	0	0	0	0	0	0
Ischemic stroke	0	1 (0.5)	0	0	0	0	0	0
Major depression	1 (0.5)	0	0	0	0	0	0	0
Abdominal discomfort	0	0	0	0	0	0	0	1 (0.7)
Abdominal pain	0	0	2 (0.7)	0	0	0	0	0
Abdominal distension	0	0	1 (0.4)	0	0	0	0	0
Drug hypersensitivity	0	0	0	0	0	0	1 (0.3)	0
Foot fracture	0	0	0	0	0	0	0	1 (0.7)
Dyspepsia	0	0	2 (0.7)	0	0	0	0	0
Nausea	0	0	1 (0.4)	0	0	0	0	0
Vomiting	0	0	0	0	0	0	0	0
Gastrointestinal disorder	0	0	0	0	0	0	0	0
Blood creatinine increased	0	0	1 (0.4)	0	0	0	0	0
Lipase increased	0	0	1 (0.4)	0	0	0	0	0
Malaise	0	0	1 (0.4)	0	0	0	0	0
Hemorrhagic stroke	0	0	0	1 (0.4)	0	0	0	0
Nephropathy	0	0	1 (0.4)	0	0	0	0	0
Palpitations	0	0	0	0	0	0	0	0
Anxiety	0	0	0	0	0	0	0	0
Gastroenteritis	0	0	0	0	1 (0.4)	0	0	0

CNS = central nervous system; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] No SAEs occurred in ≥ 1% of patients.

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Table 31: Detailed Notable Harms

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
Adjudicated Major Cardiovascular Events, n (%)								
Myocardial infarction	1 (0.5)	1 (0.5)	0	0	0	0	0	0
Stroke	0	1 (0.5)	1 (0.4)	0	0	0	2 (0.7)	0
Death	0	0	0	1 (0.4)	0	0	0	0
Cardiac Arrhythmia, n (%)	5 (2.5)	4 (2.0)	5 (1.8)	2 (0.7)	6 (2.4)	0	6 (2.1)	2 (1.4)
Sinus tachycardia	1 (0.5)	2 (1.0)	0	0	0	0	1 (0.3)	0
Palpitations	1 (0.5)	1 (0.5)	1 (0.4)	0	1 (0.4)	0	1 (0.3)	0
Atrial fibrillation	1 (0.5)	0	0	0	1 (0.4)	0	2 (0.7)	0

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
Bundle branch block, right	1 (0.5)	0	0	0	0	0	0	0
Ventricular extrasystoles	0	1 (0.5)	1 (0.4)	0	0	0	1 (0.3)	0
Supraventricular extrasystoles	0	0	0	0	0	0	1 (0.3)	0
Ventricular fibrillation	1 (0.5)	0	0	0	0	0	0	0
Ventricular tachycardia	1 (0.5)	0	0	0	0	0	0	0
Heart rate increased	1 (0.5)	0	0	0	1 (0.4)	0	0	0
Syncope	0	0	1 (0.4)	0	0	0	1 (0.3)	1 (0.7)
Heart rate irregular	0	0	0	0	0	0	0	1 (0.7)
Heart rate abnormal	0	0	0	0	1 (0.4)	0	0	0
Tachycardia	0	0	2 (0.7)	1 (0.4)	1 (0.4)	0	0	0
Arrhythmia	0	0	0	1 (0.4)	0	0	0	0
Atrial flutter	0	0	0	0	1 (0.4)	0	0	0
Atrioventricular block first degree	0	0	0	0	1 (0.4)	0	0	0
Pancreatitis, n (%)	0	0	0	0	0	0	0	0
Altered Renal Function, n (%)								
Renal failure	1 (0.5)	0	0	0	0	1 (0.4)	0	0
Renal failure, acute	1 (0.5)		1 (0.4)	0	0	0	0	0
Renal impairment	0	1 (0.5)	0	0	0	0	0	0
Protein urine present	0	0	0	0	0	0	1 (0.3)	0
Blood creatinine increased	0	0	1 (0.4)	0	1 (0.4)	1 (0.4)	0	0
Confirmed Hypoglycemia,[a] n (%)	48 (24.1)	49 (24.6)	79 (28.4)	137 (49.1)	79 (31.3)	154 (60.9)	93 (32.0)	4 (2.8)
Hypoglycemia as Defined by ADA, n (%)								
Severe hypoglycemia	1 (0.5)	0	0 (0.0)	1 (0.4)	3 (1.2)	4 (1.6)	1 (0.3)	0
Documented symptomatic	71 (35.7)	62 (31.2)	137 (49.3)	182 (65.2)	109 (43.3)	187 (73.9)	112 (38.5)	12 (8.3)
Asymptomatic	94 (47.2)	93 (46.7)	167 (60.1)	195 (69.9)	155 (61.5)	192 (75.9)	169 (58.1)	16 (11.0)
Probable symptomatic	8 (4.0)	3 (1.5)	2 (0.7)	4 (1.4)	4 (1.6)	12 (4.7)	15 (5.2)	0
Relative	12 (6.0)	7 (3.5)	3 (1.1)	17 (6.1)	4 (1.6)	14 (5.5)	24 (8.2)	3 (2.1)
ADA unclassifiable hypoglycemic	10 (5.0)	10 (5.0)	7 (2.5)	12 (4.3)	1 (0.4)	0	12 (4.1)	2 (1.4)
Allergic Reaction (Immunogenicity), n (%)	0	2 (1.0)	7 (2.5)	7 (2.5)	3 (1.2)	5 (2.0)	8 (2.7)	7 (4.8)
Anaphylactic reaction	0	1 (0.5)	0	0	0	0	0	0
Gastrointestinal AEs, n (%)	42 (21.1)	23 (11.6)	70 (25.2)	27 (9.7)	59 (23.4)	28 (11.1)	45 (15.5)	22 (15.2)
Diarrhea	13 (6.5)	7 (3.5)	20 (7.2)	7 (2.5)	16 (6.3)	10 (4.0)	13 (4.5)	8 (5.5)
Nausea	13 (6.5)	7 (3.5)	26 (9.4)	3 (1.1)	28 (11.1)	4 (1.6)	9 (3.1)	(4.1)

	DUAL II		DUAL V		DUAL VII		DUAL III	
	IDegLira (N = 199)	IDeg (N = 199)	IDegLira (N = 278)	IGlar (N = 279)	IDegLira (N = 252)	IGlar + IAsp (N = 253)	IDegLira (N = 291)	GLP-1 RA (N = 145)
Vomiting	7 (3.5)	0	14 (5.0)	5 (1.8)	9 (3.6)	6 (2.4)	4 (1.4)	4 (2.8)
Constipation	0	0	0	0	9 (3.6)	1 (0.4)	7 (2.4)	0
Dyspepsia	0	0	10 (3.6)	2 (0.7)	10 (4.0)	0	7 (2.4)	0
Abdominal distension	0	0	9 (3.2)	1 (0.4)	3 (1.2)	2 (0.8)	0	0
Gastritis	0	0	7 (2.5)	3 (1.1)	4 (1.6)	3 (1.2)	0	0
Injection Site Reactions, n (%)	1 (0.5)	5 (2.5)	1 (0.4)	2 (0.7)	0	1 (0.4)	8 (2.7)	1 (0.7)
Injection site hemorrhage	0	1 (0.5)	0	0	0	0	0	0
Injection site pain	0	4 (2.0)	0	1 (0.4)	0	0	3 (1.0)	0
Injection site pruritus	0	2 (1.0)	0	0	0	0	0	0
Injection site reaction	1 (0.5)	1 (0.5)	0	0	0	1 (0.4)	1 (0.3)	0
Injection site urticaria	0	1 (0.5)	1 (0.4)	0	0	0	0	0
Injection site bruising	0	0	1 (0.4)	0	0	0	5 (1.7)	0
Injection site nodule	0	0	0	0	0	0	1 (0.3)	0
Vessel puncture site hematoma	0	0	0	0	0	0	0	1 (0.7)
Injection site extravasation	0	0	0	1 (0.4)	0	0	0	0
Injection site inflammation	0	0	1 (0.4)	0	0	0	0	0
Antibody Formation, n (%)	NR	NR	0	0	0	0	0	0

ADA = American Diabetes Association; AE = adverse event; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IAsp = insulin aspart; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; NR = not reported; PG = plasma glucose.

[a] Confirmed hypoglycemia: Patient unable to treat himself or herself and/or has a recorded PG < 3.1 mmol/L (minor: PG < 3.1 mmol/L).

Source: Clinical study reports of DUAL II, DUAL V, DUAL VII, and DUAL III.[11-14]

Appendix 5: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Short Form (36) Health Survey (SF-36) version 2
- Treatment-related impact measure for diabetes (TRIM-D)
- Diabetes Treatment Satisfaction Questionnaire status version (DTSQs)

Findings

A focused literature search was conducted to identify the psychometric properties and minimum clinically important difference (MCID) of each of the stated outcome measures. Table 32 summarizes the findings.

Table 32: 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 capture a full range of health states	Yes	MIDs for diabetes have been investigated and are discussed under the SF-36 subheading. General (non-disease specific) MID: 2 points in PCS, 3 points in MCS, 2 to 4 points for individual dimensions	Bjorner et al. (2013)[62] SF-36v2 user's manual[56]
TRIM-D	Disease-specific tool designed to evaluate the impact of treatment in both type 1 and type 2 diabetes	Yes	No MCID	Brod et al. (2009)[48] Brod et al. (2011)[63]
DTSQs DTSQc	Both forms of the DTSQ are 8-item, diabetes-specific measures of patient satisfaction with treatment.	Yes	Unknown	Bradley et al. (2007)[57]

DTSQ = Diabetes Treatment Satisfaction Questionnaire; DTSQc = Diabetes Treatment Satisfaction Questionnaire change version; DTSQs = Diabetes Treatment Satisfaction Questionnaire status version; MCS = mental component summary; MCID = minimal clinically important difference; MID = minimally important difference; PCS = physical component summary; SF-36 = Short Form (36) Health Survey; SF-36v2 = Short Form (36) Health Survey version 2; TRIM-D = treatment-related impact measure for diabetes.

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. There are two versions of SF-36, including the original version of SF-36[64] and version 2 of SF-36.[56,65] Compared with the original version of SF-36,[64] version 2 of SF-36 contains minor changes to the original survey, including changes to instructions (reduced ambiguity), questions and answers (better layout), item-level response choices (increased), cultural and language comparability (increased), and elimination of a response option from the items in the mental health and vitality dimensions.[56,65] The SF-36 consists of 36 items representing eight dimensions: physical functioning (PF), role physical (RP), bodily pain (BP), general health

(GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). Item response options are presented on a three- to six-point, Likert-like scale. All items are scored so that a high score defines a more favourable health state. In addition, each item is scored on a zero to 100 range so that the lowest and highest possible scores are zero and 100, respectively. Scores represent the percentage of total possible score achieved. Item scores are averaged together to create the eight domain scores. The SF-36 also provides two component summaries, the physical component summary (PCS) and the mental component summary (MCS), which are created by aggregating the eight domains according to a scoring algorithm. The PCS, MCS, and eight dimensions are each measured on a scale of zero to 100. The domain and summary scores (PCS and MCS) are standardized t scores to the US population with a mean equal to 50 and a standard deviation equal to 10.[56] 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.[56] On any of the scales, an increase in score indicates improvement in health status. In general use of version 2 of the SF-36, the user's manual[56] proposes the following minimally important differences (MID): a change of two points on the PCS, and three points on the MCS. The manual also proposes the following minimal mean group differences, in terms of t score points, for SF-36 version 2 individual dimension scores: PF = 3, RP = 3, BP = 3, GH = 2, VT = 2, SF = 3, RE = 4, and MH = 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.[56] MID values do not represent patient-derived scores. The MIDs for version 2 of the SF-36 are based on clinical and other non-patient–reported anchors.[56]

One study has investigated benchmarks for MIDs for one-point lower SF-36 scores in populations with diabetes.[62] 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, 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 one-point changes in SF-36 dimension and component scores. For example, using the US Medicare Health Outcomes Survey, one-point lower dimension and component scores were associated with increased risks of two-year mortality ranging from 1.8% to 6.4%, while the US Medical Outcomes Study data generated increased risks of seven-year mortality ranging from 2.0% to 9.0%. One-point lower scores using the 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%.[62] While MID benchmarks can be helpful in interpreting SF-36 scores in the absence of MCIDs, the magnitude of the increased risk, while statistically significant, can be difficult to interpret from a clinical and patient perspective. Furthermore, the one-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).[62] As such, the validity of these one-point score difference benchmarks remains unclear.

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

Validation of the SF-36 has been performed in a number of studies in T1DM and T2DM combined populations[52,53,66,67] and in T2DM: general populations in Germany (N = 144)[49] and in the UK (N = 131),[50] Pima Indian adults (N = 54),[51] older Chinese adults (N = 182),[55] and US veterans (N = 331; 98% male).[68] 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 following sections.

Reliability

Cronbach's alpha correlation coefficients measure of internal consistency and reliability conveys 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,[50,67] while others found some dimensions to have lower reliability: SF,[51,52] RE, RP, VT,[49] and GH.[49,55,66] Internal reliability discrepancies (dimensions with alpha lower than 0.7) may relate 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 a range of coefficients was reported for the different dimensions: PF: 0.902; SF > 0.6 to 0.9; RP; RE; MH; energy; GH perception; BP: 0.433. 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.[53] 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 RE and RP (lower), and GE (higher).[49]

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 five points across all dimensions of the SF-36 and used Cohen's effect size to evaluate responsiveness (effect size ranges were defined as "trivial" [effect size < 0.20], "small" [effect size ≥ 0.20 and < 0.50], "moderate" [effect size ≥ 0.50 and < 0.80], or "large" [effect size ≥ 0.80]).[68] Six of the SF-36 dimensions (GH, PF, SF, RP, BP, VT) were found to be responsive when patients who developed ≥ two complications were compared with those who were stable or improved (ES 0.31 to 0.66), and an increase of > 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 (GH, PF, SF, RP, VT) or to any neuropathy complication in four of these six dimensions (GH, PF, RP, VT).[68]

Validity

Two cross-sectional studies conducted in Taiwan[52] and mainland China[55] primarily studying T2DM patients (mean ages 63[52] and 69[55]) evaluated the internal validity of the SF-36 by factor analysis (eigenvalues ≥ 1.0; factor loadings ≥ 0.4 were significant). In one study, all dimensions were loaded onto their hypothesized component summary (PCS or MCS).[52] In the other study, factor analysis revealed appropriate loading except for GH on MCS and RP on both MCS and PCS. Item-dimension correlations ranged from 0.27 to 0.81 across all dimensions and summary scores. Only the PF dimension had a scaling success rate < 100% (PF: 99%).[55] In a large observational cohort study of chronic disease in the US (T1DM and T2DM subgroup, N = 624), item-dimension correlations ranged from 0.62 to 0.76 in all but the GH dimension (0.38 to 0.71) and PF dimension (0.52 to 0.82).[67] Scaling success rates from 280 tests, based on item correlation with hypothesized dimension exceeding that with all others by more than two standard errors, were 100% in all but GH (90%) and PF (99%).[67] GH was found to correlate with both PCS and MCS during SF-36 development.[56]

Inter-dimension correlations of the SF-36 in a T1DM and T2DM patient population ranged from 0.179 (MH correlation with PF) to 0.637 (RP with BP),[53] suggesting that different dimensions are measuring somewhat different constructs.

One challenge when validating a pre-established, generic health-related quality of life (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 hemoglobin A1C, a known surrogate marker in both forms of diabetes, and SF-36 dimensions, or have performed known-group comparisons based on hemoglobin A1C level stratification. These studies have established that there is no clear relationship between dimensions of the SF-36 and hemoglobin A1C levels, reporting unexpected, poor, or negligible correlations,[51,54] or an inability of the SF-36 to discriminate between known groups based on hemoglobin A1C levels.[52,53] 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).[52] Construct validity testing was based on exploratory and a priori hypotheses. The SF-36 showed evidence of measuring effects of diabetic complications,[50] treatment type, and changes following diabetes interventions,[49,51] but it was also influenced by non-diabetic comorbidity[50,51] and other non-diabetes–specific factors such as age:[50,51]

- age: PF, RP, SF, and MH deteriorated in older age groups (Spearman rank correlation coefficients = −0.52 to −0.40, $P < 0.005$);[51] PF and RP were impaired in older age groups ($P < 0.05$),[50] while RE was impaired in younger age groups ($P < 0.01$)[50]
- sex: no statistically significant differences;[50,51] women had lower scores on multiple dimensions ($P < 0.05$)[49]
- education level: no correlation[51]
- socioeconomic status and income: no statistically significant differences[50,51]
- diabetes-related laboratory markers: no correlation[51]
- diabetic complications: these were associated with lower dimension scores for SF, RE, VT ($P < 0.01$), and RP ($P < 0.05$);[50] all dimensions of the SF-36 were lower with > one late complication ($P < 0.01$)[49]

- non-diabetic comorbidities: lower scores — PF, RP ($P = 0.001$); VT, GH ($P < 0.01$); MH ($P < 0.05$)[50]
- comorbidities: lower scores — PF, RP, RE, MH, SF (Spearman rank correlation coefficients = −0.42 to −0.32, $P < 0.02$)[51]
- diabetic treatment: insulin was associated with lower scores than non-insulin treatment — PF, RP, SF, GH (Spearman rank correlation coefficients = 0.31 to 0.40, $P < 0.03$)[51] and VT, MH ($P < 0.01$)[49]
- response to diabetes intervention (treatment and/or education): RP, GH, VT, and SF ($P < 0.05$ or less).[49]

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 audit in patients without any other disease or comorbidity than in those with comorbidities (Spearman rank coefficients: 0.30 to 0.44) across five domains: SF, RP, MH, VT, and GH ($P < 0.05$).[50] Another study compared validation of the SF-36 with Diabetes-39 (D-39), a five-dimension measure consisting of 39 items that probe diabetes-related HRQoL.[52] The SF-36 performed better than D-39 on some dimensions and in the PCS for cardiovascular (CV) 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 (0.38) compared with D-39 summary score (0.15). The D-39 had discriminative power over the SF-36 (based on C-statistic): two-hour postprandial glucose (0.7 versus 0.63; $P < 0.05$). SF-36 generally performed better than the D-39 for complication known groups. SF-36 dimensions performed better at a statistically significant level than D-39 subscales for CV disease and the all-complication known groups,[52] and in the German T2DM population, SF-36 showed statistically significant multidimensional changes after diabetes intervention, when the D-39 did not.[49] Based on a priori hypotheses, known-group comparisons of self-reported high blood pressure, heart problems, and measured depression levels known-group comparison 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).[55]

Critical Appraisal

As SF-36 was developed as a generic instrument, it has been suggested that the tool be evaluated and possibly re-validated 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.[52,55] Furthermore, in the CADTH Common Drug Review search of the literature, few studies were identified that attempted to validate the test-retest reliability,[49,53] responsiveness,[68] or MCID of the SF-36 in the general diabetic population, in separate T1DM and T2DM populations, and in more specific diabetic subgroups. The SF-36 has shown evidence of measuring effects of diabetic complications,[49,50] but it is also influenced by non-diabetic comorbidity[50,51] and other non-diabetes–specific factors such as age.[50,51] It does not demonstrate evidence of association with surrogate markers of disease severity,[51-54] but does respond to treatment type and changes following diabetes interventions.[49,51] The SF-36 and diabetes-specific instruments likely provide some degree of overlap, but also address different features of a patient's overall HRQoL.[52,55] 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 diabetic patients, but it can provide useful insight

when used in combination with the appropriate, complementary diabetes-specific treatment evaluation and HRQoL instruments. No MCID specifically in diabetes has been established.

Treatment-Related Impact Measure for Diabetes

TRIM-D is a diabetes-specific instrument designed to measure the treatment-related impact of diabetes medications on patients.[47,48] TRIM-D was developed in English by The Brod Group and by Novo Nordisk as a questionnaire appropriate for both patients with T1DM and patients with T2DM.[48] 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 five-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.[48] No MCID has been determined for TRIM-D.

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

Content validity was addressed during instrument development. Item development was initially extracted from literature and input from patients with T1DM or T2DM, and clinical experts. Then it was compiled and assembled into an early version of the survey measuring the multifaceted impact of diabetes.[48,69] Five individual telephone interviews of pre-filled early surveys were conducted, findings were reviewed, and decisions were 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 patients with diabetes ranging from 18 to 80 years (mean of 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.[48] 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), ranging from 0.86 to 0.91 (for the subscale scores);[48] follow-up internal reliability alphas exceeded 0.7 and fell within 0.1 of those found in the development study.[63] 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[48] (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 outcome measures (validated and not validated in diabetes). Convergent validity was reported based on a priori hypotheses using a two-tailed Pearson's correlation coefficient, significance: < 0.05, with coefficients > 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:[48]

- r = 0.63: global satisfaction scale of the Treatment Satisfaction Questionnaire for Medication
- r = 0.45: burden subscale of the Diabetes Medication Satisfaction Measure
- r = −0.67: Activity Impairment Assessment total score
- r = 0.66 and 0.60: efficacy scale of the Diabetes Medication Satisfaction Measure and effectiveness scale of the Treatment Satisfaction Questionnaire for Medication, 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 covariance (groups as fixed factors; ANOVA F-value (F); significance: *P* values < 0.05).[48]

- The total TRIM-D distinguished between willingness of respondents to change diabetes treatment (F = 83.7; *P* < 0.001) and between those compliant versus those 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 management domain distinguished between hemoglobin 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, one to two times, or > three, 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 the participation of 242 patients with T1DM or T2DM, aged 18 years or older.[63] The author indicated that a confirmatory factor analysis was conducted using the Bentler comparative fit index and root mean square error of approximation to determine the goodness of fit between the models previously identified.[63] It was reported that the 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).[63] External responsiveness using the Insulin Treatment Satisfaction Questionnaire score change found a strong association with the TRIM-D total score (r = 0.72; *P* < 0.001). The change of the Insulin Treatment Satisfaction Questionnaire summary score showed the following correlations with the changes of TRIM-D domain items: treatment burden items (r ranging between 0.32 and 0.53), daily life items (0.37 to 0.45), diabetes management items (0.22 to 0.38), psychological health items (0.35 to 0.51), and compliance domain items (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; 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.[63]

Preliminary, exploratory estimates of MIDs in this study[63] 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 (SD) of the TRIM-D domain score differences (Δ) corresponding with the minimally 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:[48] (1) treatment burden: Δ = 10.6, ½ SD = 9.5, (2) daily life: Δ = 16.0, ½ SD = 9.2, (3) diabetes management: Δ = 12.0, ½ SD = 8.2, (4) psychological: Δ = 17.8, ½ SD = 8.7, (5) TRIM-D total score: Δ = 17.6, ½ SD = 7.8.[63]

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 was supported by a priori hypotheses (demonstrating moderate to strong associations) and known-group methods. Most items of the TRIM-D were responsive in a RCT setting of patients with T1DM and patients with T2DM, 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.

Diabetes Treatment Satisfaction Questionnaire

The Diabetes Treatment Satisfaction Questionnaire is a diabetes-specific measure of patient satisfaction with treatment.[57,70] The original "status" version, the DTSQs, contains eight items: six items measuring treatment satisfaction (satisfaction with current treatment, convenience, flexibility, satisfaction with own understanding of diabetes, likelihood of continuing on, and recommending current treatment), and two items measuring perceived frequency of hyperglycemia and frequency of hypoglycemia. The items are scored on seven-point response scales ranging from zero ("very satisfied") to six ("very unsatisfied"). A lower score indicates improved satisfaction. The psychometric properties of different language versions of the DTSQs were assessed in a study of patients with T1DM and patients with T2DM treated with insulin or poorly controlled on sulfonylureas, who then started on insulin treatment.[71] The DTSQs was shown to be consistently reliable in all languages studied and significantly sensitive to change in patients with T1DM at week 8, week 20, week 24, and at last available visit.[71]

However, it has also been observed that because patients tend to report satisfaction with current treatment in the absence of experience with alternatives for comparison, the DTSQs often exhibits a ceiling effect.[57,72] The Diabetes Treatment Satisfaction Questionnaire change version (DTSQc) was developed to better capture change in treatment satisfaction and address the ceiling effect for those patients who have high scores on the DTSQs at baseline.[57] The DTSQc also contains eight items that ask about current satisfaction relative to preceding treatment, and is scored on a seven-point scale with responses ranging from "much more satisfied now" to "much less satisfied now."[73] Psychometric analyses of the DTSQc in patients with T1DM and patients with T2DM showed that the six-item treatment satisfaction component was highly reliable, with a Cronbach's alpha of 0.92.[57] This study

also found that the DTSQc identified significantly more improvement in treatment satisfaction than the DTSQs, particularly when patients had high baseline DTSQs scores; this suggests a reduction in ceiling effect and better responsiveness to change with the DTSQc. The authors recommended using the DTSQc in conjunction with the DTSQs to adequately capture changes in treatment satisfaction over the course of a clinical trial.[57] A MCID for the DTSQ in patients with T2DM was not identified.

Summary

The SF-36 was developed as a generic HRQoL measure and has shown good validity and reliability in diabetic 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 diabetic 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 a RCT setting of patients with T1DM and patients with T2DM, but five items did not respond as expected. No MCID has been determined for the TRIM-D. The DTSQs and DTSQc are measures of patient satisfaction with current treatment at baseline and changes in treatment satisfaction over time, respectively. Both questionnaires have been shown to be reliable in several languages for patients with T1DM and patients with T2DM, and should be used together to reduce the ceiling effect observed with the DTSQs alone. MCIDs for patients with T2DM were not identified the DTSQ.

Appendix 6: Summary of Other Studies

Aim

To summarize the safety findings of:

- DUAL I — extension study at week 52[74]
- DUAL VIII at week 104.[75]

Findings

Study Design

DUAL I Extension

DUAL I was a 26-week, randomized, parallel, three-arm, open-label, multi-centre, multinational treat-to-target trial comparing Xultophy, a fixed-ratio combination of insulin degludec (IDeg) and liraglutide (IDegLira), versus IDeg or liraglutide alone (2:1:1), in patients with type 2 diabetes mellitus (T2DM) treated with one or two oral antidiabetes drugs with a 26-week extension, during which patients remained on their randomized treatment assignment.[74]

DUAL VIII

DUAL VIII was a 104-week (two-year), randomized, parallel, two-arm, open-label, multi-centre, multinational, treat-to-target trial comparing a fixed-ratio combination of IDeg and liraglutide versus insulin glargine (IGlar) (1:1) in patients with T2DM inadequately controlled with oral antidiabetes drugs. Inadequate control was defined as hemoglobin A1C of 7.0% to 11.0% (53 mmol/mol to 97 mmol/mol), inclusive. The study included a two-week screening period, a 104-week treatment period, and two follow-up visits after the last dose of trial product — at seven days (+ three days) to collect all treatment-emergent adverse events (AEs), and at 30 days (+ three days) to collect potential major cardiovascular (CV) event. The first 26 weeks of the trial were focused on reaching the treatment target: hemoglobin A1C < 7.0%; the following 78 weeks were allotted for treatment intensification and assessment of durability. Patients were screened at visit 1, randomized within two weeks of screening (visit 2), started on treatment within one week (± three days) of randomization (visit 3), and followed at increasing intervals (one-week to 14-week intervals) until the end of the treatment period (visit 3 to visit 13). Trial participation ended after the two follow-up visits.[75]

Population Demographics and Baseline Disease Characteristics

DUAL I Extension

DUAL I inclusion criteria included male and female patients with T2DM; ≥ 18 years; body mass index (BMI) ≤ 40 kg/m^2 and hemoglobin A1C of 7.0% to 10.0%, both inclusive; and patients on a stable daily dose of one or two oral antidiabetes drugs (metformin [≥ 1,500 mg or maximum tolerated dose] or metformin [≥ 1,500 mg or maximum tolerated dose] + pioglitazone [≥ 30 mg]) for at least 90 days prior to screening.[74]

Exclusion criteria included, but were not limited to:

- use of any drug (except for oral antidiabetes drugs) that, in the investigator's opinion, could interfere with the glucose level (e.g., systemic corticosteroids)

- treatment with insulin (except for short-term treatment due to intercurrent illness at the discretion of the investigator)
- treatment with glucagon-like peptide 1 receptor agonists (GLP-1 RAs) (e.g., exenatide, liraglutide), sulfonylurea, or dipeptidyl peptidase-4 (DPP-4) inhibitors within 90 days prior to trial
- females of child-bearing potential who were pregnant, breastfeeding, or intended to become pregnant or were not using adequate contraceptive methods
- impaired liver function, defined as alanine aminotransferase ≥ 2.5 times the upper limit of the normal range
- impaired renal function defined as serum creatinine ≥ 133 µmol/L for males and ≥ 125 µmol/L for females
- contraindications or restrictions to use of pioglitazone (according to local labelling)
- patients with a clinically significant, active (during the past 12 months) disease of the gastrointestinal (GI), pulmonary, neurological, genitourinary, or hematological system (except for conditions associated with T2DM) that, in the opinion of the investigator, may confound the results of the trial or pose additional risk in administering the trial drug
- patients who used any investigational product within 30 days prior to this trial
- cardiac disorder defined as congestive heart failure, diagnosis of unstable angina pectoris, cerebral stroke, and/or myocardial infarction within the last 12 months and planned coronary, carotid, or peripheral artery revascularization procedures
- severe uncontrolled treated or untreated hypertension (systolic blood pressure ≥ 180 mm Hg or diastolic blood pressure ≥ 100 mm Hg)
- Acute treatment required proliferative retinopathy or maculopathy (macular oedema)
- history of chronic pancreatitis or idiopathic acute pancreatitis
- cancer.

The mean age of study participants was 55.1 years in the IDegLira group, 54.9 years in the IDeg group, and 55 years in the liraglutide group, respectively, as outlined in Table 33. The treatment groups were similar in their baseline characteristics of body weight, BMI, duration of diabetes, hemoglobin A1C, fasting plasma glucose, race distribution, and oral antidiabetes treatment at screening.[74] Population demographics and baseline disease characteristics for the DUAL I trial are presented in Table 33.[74]

Table 33: DUAL I — Demographics and Baseline Characteristics (Summary, Full Analysis Set)

	IDegLira N	IDeg N	Lira N
Number of Patients, N	833	413	414
Age Group			
N (%)	833 (100.0)	413 (100.0)	413 (100.0)
18 to 40 years	64 (7.7)	24 (5.8)	34 (8.2)
40 to 65 years	651 (78.2)	328 (79.4)	322 (78.0)
65 to 75 years	107 (12.8)	52 (12.6)	48 (11.6)
> 75 years	11 (1.3)	9 (2.2)	9 (2.2)
Sex			
N (%)	833 (100.0)	413 (100.0)	414 (100.0)

	IDegLira N	IDeg N	Lira N
Female	398 (47.8)	213 (51.6)	206 (49.8)
Male	435 (52.2)	200 (48.4)	208 (50.2)
Race			
N (%)	833 (100.0)	413 (100.0)	414 (100.0)
White	513 (61.6)	257 (62.2)	258 (62.3)
Black or African-American	72 (8.6)	23 (5.6)	28 (6.8)
Asian Indian	176 (21.1)	97 (23.5)	88 (21.3)
Asian Non-Indian	52 (6.2)	23 (5.6)	28 (6.8)
American Indian or Alaska Native	2 (0.2)	2 (0.5)	0 (0.0)
Native Hawaiian or other Pacific Islander	0 (0.0)	0 (0.0)	1 (0.2)
Other	18 (2.2)	11 (2.7)	11 (2.7)
Smoker Status			
N (%)	833 (100.0)	413 (100.0)	414 (100.0)
Current smoker	132 (15.8)	42 (10.2)	56 (13.5)
Never smoked	504 (60.5)	282 (68.3)	261 (63.0)
Previous smoker	197 (23.6)	89 (21.5)	97 (23.4)
Age (Years)			
N	833	413	413
Mean (SD)	55.1 (9.9)	54.9 (9.7)	55.0 (10.2)
Median	55.7	55.0	55.3
Min., Max.	27.8, 83.8	24.0, 79.1	24.4, 81.6
Height (m)			
N	833	413	414
Mean (SD)	1.67 (0.10)	1.67 (0.11)	1.67 (0.10)
Median	1.67	1.66	1.67
Min., max.	1.35, 1.94	1.43, 1.98	1.40, 2.06
Body Weight (kg)			
N	833	413	414
Mean (SD)	87.2 (19.0)	87.4 (19.2)	87.4 (18.0)
Median	85.6	86.6	87.1
Min., max.	41.0, 147.1	43.5, 156.9	45.5, 143.8
BMI (kg/m^2)			
N	833	413	414
Mean (SD)	31.2 (5.2)	31.2 (5.3)	31.3 (4.8)
Median	31.3	31.0	31.3
Min., max.	17.3, 45.2	16.8, 41.8	19.9, 40.5
Duration of Diabetes (Years)			
N	833	413	413
Mean (SD)	6.62 (5.13)	6.98 (5.30)	7.15 (6.09)
Median	5.2	5.5	5.6
Min., max.	0.03, 35.07	0.01, 32.34	0.01, 53.86
Hemoglobin A1C (%)			
N	833	413	414
Mean (SD)	8.3 (0.9)	8.3 (1.0)	8.3 (0.9)
Median	8.2	8.2	8.2
Min., max.	6.0, 11.0	6.6, 11.3	6.4, 12.6

	IDegLira N	IDeg N	Lira N
FPG (mmol/L)			
N	809	409	409
Mean (SD)	9.2 (2.4)	9.4 (2.7)	9.0 (2.6)
Median	8.8	8.7	8.4
Min., max.	2.7, 18.5	4.7, 19.4	3.1, 23.4
Oral Antidiabetes Drug at Screening			
N (%)	833 (100.0)	413 (100.0)	414 (100.0)
Metformin	691 (83.0)	343 (83.1)	338 (81.6)
Metformin + pioglitazone	142 (17.0)	70 (16.9)	75 (18.1)
Metformin + glimepiride	0 (0.0)	0 (0.0)	1 (0.2)

BMI = body mass index; FAS = full analysis set; FPG = fasting plasma glucose; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; Lira = liraglutide; max. = maximum; min. = minimum; SD = standard deviation.

Note: The FAS included all randomized patients. The statistical evaluation of the FAS followed the intention-to-treat principle and patients contributed to the evaluation "as randomized."

Source: Clinical Study Report of DUAL I (main and extension trials).[74]

DUAL VIII

DUAL VIII inclusion criteria included male and female patients; ≥ 18 years; with a clinical diagnosis of T2DM prior to screening; BMI ≥ 20 kg/m^2 and hemoglobin A1C of 7.0% to 11.0% (53 mmol/mol to 97 mmol/mol), both inclusive; insulin naive (short-term insulin treatment for a maximum of 14 days prior to the day of screening and/or treatment during gestational diabetes were exempted); and on stable oral antidiabetes drug treatment (excluding DPP-4 inhibitors or glinides as monotherapy, or the combination of DPP-4 inhibitors and glinides) within 90 days of screening.[75]

Exclusion criteria included, but were not limited to:[75]

- females of child-bearing potential who were pregnant, breastfeeding, or intended to become pregnant or were not using adequate contraceptive methods
- renal impairment estimated glomerular filtration rate < 60 mL/minute/1.73 m^2 as per Chronic Kidney Disease Epidemiology Collaboration value to be defined as listed in the classification Chronic Kidney Disease Epidemiology Collaboration using isotope dilution mass spectrometry for serum-creatinine measurement on the day of screening
- (screening calcitonin ≥ 50 ng/L)
- impaired liver function, defined as Alanine aminotransferase or aspartate aminotransferase ≥ 2.5 times the upper limit of the normal range
- acute decompensation of glycemic control requiring immediate intensification of treatment to prevent severe metabolic dysregulation (e.g., diabetic ketoacidosis) in the 90 days prior to the screening date
- history of pancreatitis (acute or chronic)
- cardiac disorder defined as congestive heart failure (New York Heart Association class IV), stroke, or hospitalization for unstable angina and/or transient ischemic attack and/or myocardial infarction within the last 180 days prior to screening and/or planned coronary, carotid, or peripheral artery revascularization procedures
- inadequately treated blood pressure defined as Class II hypertension or higher (systolic blood pressure ≥ 160 mm Hg or diastolic blood pressure ≥ 100 mm Hg) at screening

- treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before the screening date
- proliferative retinopathy or maculopathy requiring acute treatment as verified by fundus photography or dilated fundoscopy performed within 90 days prior to randomization
- history or presence of malignant neoplasms within the last five years (except basal and squamous cell skin cancer and in-situ carcinomas); family or personal history of multiple endocrine neoplasia type 2 or medullary thyroid carcinoma

[redacted]

Table 34: DUAL VIII — Summary of Baseline Characteristics

	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Intervention

DUAL I Extension

Twenty-six weeks after randomization, all patients were eligible to enter the additional 26-week open-labelled treatment extension phase. The patients continued the same treatment at unchanged dose (liraglutide group) or regimen of doses. During the trial, IDegLira was injected subcutaneously (N = 833). The IDegLira unit for doses was defined as a dose step. One IDegLira dose step contains 1 U IDeg and 0.036 mg liraglutide. Treatment with IDegLira was initiated at 10 U (containing 10 U IDeg and 0.36 mg liraglutide). Adjustment of IDegLira was performed twice weekly based on the mean of three preceding daily fasting self-monitored plasma glucose measurements on three consecutive days prior to each dose adjustment. Adjustments occurred in 2 U (2 U IDeg and 0.072 mg liraglutide) to the fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L (72 mg/dL to 90 mg/dL). IDeg was injected subcutaneously (N = 413). IDeg treatment was initiated with 10 U, and titrated twice weekly to the fasting glycemic target of 4.0 mmol/L to 5.0 mmol/L (72 mg/dL to 90 mg/dL) based on the mean self-monitored plasma glucose (fasting) from three preceding measurements as described earlier for IDegLira. There was no maximum dose limit. Liraglutide was injected subcutaneously (N = 414). Liraglutide treatment was started at 0.6 mg/day and subsequently increased by 0.6 mg in weekly dose escalation steps to a maximum dosage of 1.8 mg/day. Liraglutide dose was to remain unchanged after dosage escalation to 1.8 mg/day.[74]

DUAL VIII

[redacted]

Patient Disposition and Exposure

DUAL I Extension

Patient disposition for the DUAL I extension trial is presented in Table 35: 665 (79.7%) of the main trial IDegLira randomized participants were included in the extension, and 621 (74.5%) completed the 26-week extension period. Withdrawals during the extension trial included 44 participants (5.3%) in the IDegLira group, of whom five (0.6%) withdrew due to AEs. In the IDeg group, 80.4% of participants entered the extension phase. Among participants, 6.8% withdrew (of these, 0.2% withdrew due to AEs and 73.7% completed the study). Fewer participants from the liraglutide group entered the extension (75.4%); of these, 6.7% withdrew (0.5 % due to AEs). The remaining 68.7% completed the extension phase.[74]

Total exposure during the DUAL I combined main and extension periods (see Table 36) was 705.6 patient-years for the IDegLira group, with the majority (627 participants, 76.0%) exposed to the trial drug for 49 weeks to 56 weeks. Total exposure in the other two groups was lower: 350.1 patient-years and 334.3 patient-years in the IDeg and liraglutide groups, respectively. The average exposure for individual patients was 0.9 years, 0.8 years, and 0.8 years for the IDegLira, IDeg, and liraglutide groups, respectively.[74]

DUAL VIII

The DUAL VIII trial screened [redacted]

Exposure in the DUAL VIII trial is presented in Table 38. Total exposure for the IDegLira group was [redacted]

Table 35: DUAL I (Main and Extension Periods) — Patient Disposition

	IDegLira	IDeg	Lira
Randomized in Main Trial, N (%)	**834 (100.0)**	**414 (100.0)**	**415 (100.0)**
Exposed in main trial	826 (99.0)	413 (99.8)	413 (99.5)
Completed main trial	734 (88.0)	366 (88.4)	342 (82.4)
Not screened for extension	69 (8.3)	33 (8.0)	29 (7.0)
Included in Extension, N (%)	**665 (79.7)**	**333 (80.4)**	**313 (75.4)**
Withdrew during extension, n (%)	44 (5.3)	28 (6.8)	28 (6.7)
Adverse event	5 (0.6)	1 (0.2)	2 (0.5)
Ineffective therapy	0 (0.0)	0 (0.0)	0 (0.0)
Nonadherence	2 (0.2)	0 (0.0)	1 (0.2)
Withdrawal criteria	19 (2.3)	14 (3.4)	16 (3.9)
Other	18 (2.2)	13 (3.1)	9 (2.2)
Completed extension, n (%)	621 (74.5)	305 (73.7)	285 (68.7)
FAS, N (%)	833 (99.9)	413 (99.8)	414 (99.8)
PP, N (%)	755 (90.5)	374 (90.3)	362 (87.2)
SAS, N (%)	825 (98.9)	412 (99.5)	412 (99.3)
Extension Trial Set, N (%)	665 (79.7)	332 (80.2)	313 (75.4)

FAS = full analysis set; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; Lira = liraglutide; PP = per-protocol; SAS = safety analysis set.

Source: Clinical Study Report of DUAL I (main and extension trials).[74]

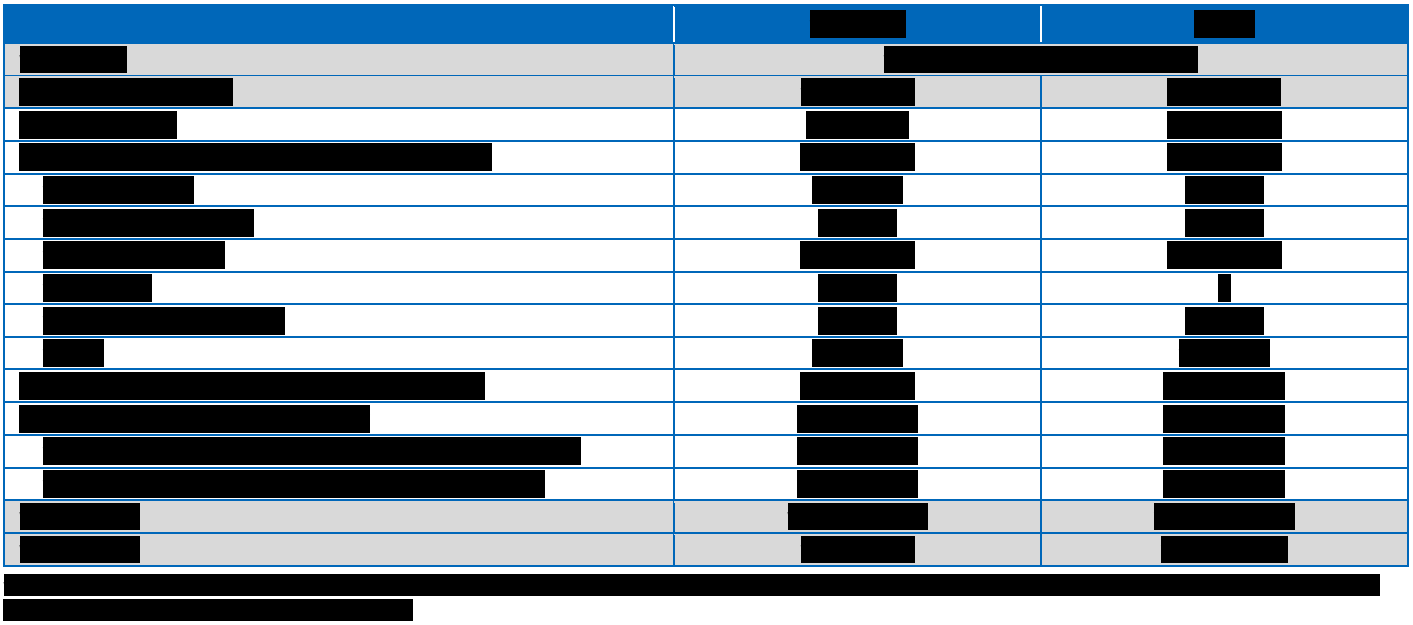
Table 36: DUAL I Main and Extension Periods (Safety Population) — Treatment Exposure

	IDegLira	IDeg	Lira
Number of Patients Receiving ≥ 1 Dose	**825**	**412**	**412**
PYE, Years	705.6	350.1	334.3
Individual Exposure (Years)			
N	**825**	**412**	**412**
Mean (SD)	0.9 (0.3)	0.8 (0.3)	0.8 (0.3)
Median (min., max.)	1.0 (0.0, 1.1)	1.0 (0.0, 1.1)	1.0 (0.0, 1.1)

IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; Lira = liraglutide; max. = maximum; min. = minimum; PYE = patient-year of exposure (1 PYE = 365.25 days); SD = standard deviation.

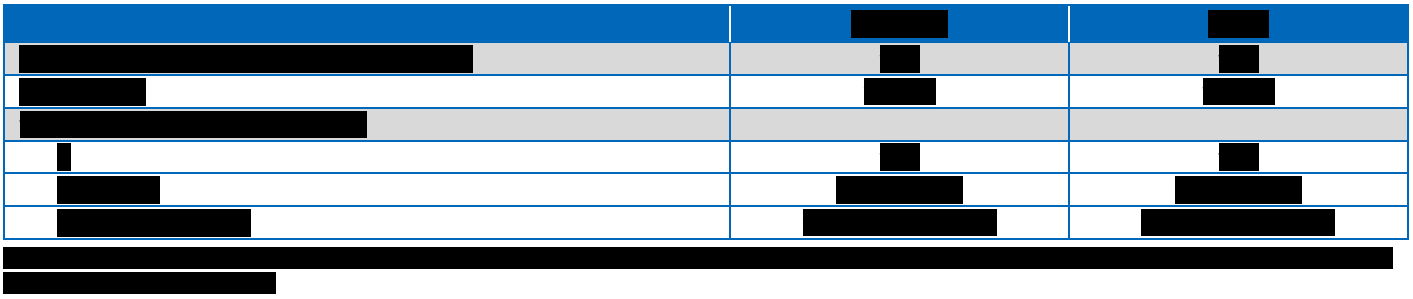
Source: Clinical Study Report of DUAL I (main and extension trials).[74]

Table 37: DUAL VIII — Patient Disposition



Source: Clinical Study Report of DUAL VIII.[75]

Table 38: DUAL VIII (Safety Population) — Treatment Exposure



Source: Clinical Study Report of DUAL VIII.[75]

Harms

Harm outcomes from the DUAL I main and extension periods (52-week treatment period) and the DUAL VIII trial are presented in Table 39 and in Table 40. Generally, [redacted]. A brief summary of the harms for each trial follows.

DUAL I Extension

In the DUAL I main and extension periods (52-week treatment period), the most frequent treatment-emergent AEs across treatment groups, in ≥ 5% of patients, were in the System Organ Classes of GI disorders (diarrhea, nausea, and vomiting), infections and infestations (nasopharyngitis and upper respiratory tract infection), and headaches. The non-GI AEs were more similar between treatment groups, while GI-related AEs appeared more

frequently in the IDegLira group than in the IDeg group, but had the highest incidence in the liraglutide group, especially diarrhea and nausea (diarrhea: 10.3%, 6.8%, and 16.3%, respectively, and nausea: 10.3%, 3.9%, and 22.3%, respectively).[74]

In the DUAL I main and extension periods (52-week treatment period), withdrawal due to AEs were highest in the liraglutide group at 6.3%, followed by the IDeg group (2.2%) and the IDegLira group (1.7%). The only reason for withdrawal that occurred at an incidence ≥ 1% was nausea, in the liraglutide group of the study.[74]

Few serious AEs in any System Organ Class occurred in proportions ≥ 1% of the safety population. Notably, GI disorders occurred in 0.5% of participants (four patients) in the IDegLira group and 1.2% (five patients) in the liraglutide group. Serious cardiac disorders occurred in 0.8%, 1.0%, and 0.7% of participants in the IDegLira, IDeg, and liraglutide groups, respectively. Two treatment-emergent deaths occurred, both in the IDegLira group: one of undetermined cause, the other due to septic shock following a urinary tract infection. Both were adjudicated and confirmed as cardiovascular deaths.[74]

The proportion of patients having AEs related to altered renal function were IDegLira (1.0%) compared with IDeg (2.9%) and liraglutide (1.9%).[74]

Pancreatitis events were either confirmed by the investigator or by the event adjudication committee. These included two events in the IDegLira group and two events of acute pancreatitis in the liraglutide group.[74]

No cases of anaphylaxis or antibody formation were reported in the main and extension periods (52-week treatment period) of the DUAL I trial.[74]

Injection site reactions occurred in all three groups of the trial at similar frequencies, in proportions ranging from 3.4% to 4.6%. The most common cause among these was injection site hematoma (2.1%, 2.2%, and 2.4% in the IDegLira, IDeg, and liraglutide groups, respectively).[74]

The proportions of participants experiencing confirmed hypoglycemia as defined by the American Diabetes Association were 75.8%, 81.3%, and 32.3% in the IDegLira, IDeg, and liraglutide groups, respectively. The event rate per 100 patient-years was highest in the IDeg group (2,115.2) compared with the IDegLira group (1,635.4), with the lowest rate in the liraglutide group (145.1). Documented symptomatic events occurred in 43.6%, 56.6%, and 11.7% of patients in the IDegLira, IDeg, and liraglutide groups, at event rates per 100 patient-years of 419.7, 639.0, and 36.8 (IDegLira, IDeg, and liraglutide groups, respectively). The IDeg group consistently had the highest proportion of patients with hypoglycemic events, followed by the IDegLira group, while the liraglutide group had lower proportions. Proportions of patients experiencing severe hypoglycemic events were low, ranging from 0.4% to 0.5%, with similar event rates across treatment groups.[74]

DUAL VIII

During the 104-week treatment period of DUAL VIII, [redacted]

[redacted]

Table 39: Harms — Total Study Duration for Safety Populations

	DUAL I — Main and Extension Periods (52-Week Treatment Period)			[redacted]	
	IDegLira (N = 825)	IDeg (N = 412)	Lira (N = 412)	[redacted]	[redacted]
AEs					
Patients with ≥ 1 AEs, n (%)	587 (71.2)	291 (70.6)	318 (77.2)	[redacted]	[redacted]
Most common AEs[a]					
Diarrhea	84 (10.3)	28 (6.8)	67 (16.3)	[redacted]	[redacted]
Nausea	85 (10.3)	16 (3.9)	92 (22.3)	[redacted]	[redacted]
Vomiting	41 (5.0)	10 (2.4)	38 (9.2)	[redacted]	[redacted]
Dyspepsia	28 (3.4)	5 (1.2)	22 (5.3)	[redacted]	[redacted]
Constipation	26 (3.2)	4 (1.0)	21 (5.1)	[redacted]	[redacted]
Nasopharyngitis	115 (13.9)	52 (12.6)	55 (13.3)	[redacted]	[redacted]
Upper respiratory tract infection	64 (7.8)	34 (8.3)	33 (8.0)	[redacted]	[redacted]
Influenza	29 (3.5)	18 (4.4)	12 (2.9)	[redacted]	[redacted]
Urinary tract infection	23 (2.8)	15 (3.6)	21 (5.1)	[redacted]	[redacted]
Headache	106 (12.8)	45 (10.9)	60 (14.6)	[redacted]	[redacted]
Dizziness	24 (2.9)	10 (2.4)	22 (5.3)	[redacted]	[redacted]
Arthralgia	30 (3.6)	15 (3.6)	22 (5.3)	[redacted]	[redacted]
Back pain	45 (5.5)	20 (4.9)	23 (5.6)	[redacted]	[redacted]
Lipase increased	48 (5.8)	18 (4.4)	35 (8.5)	[redacted]	[redacted]
Appetite decreased	22 (2.7)	2 (0.5)	30 (7.3)	[redacted]	[redacted]
SAEs					
Patients with ≥ 1 SAEs, n (%)	38 (4.6)	22 (5.3)	24 (5.8)	[redacted]	[redacted]
Reasons, SOCs[b] (≥ 1%)					
Cardiac disorders	7 (0.8)	4 (1.0)	3 (0.7)	[redacted]	[redacted]
Infections and infestations	5 (0.6)	3 (0.7)	2 (0.5	[redacted]	[redacted]
Gastrointestinal disorders	4 (0.5)	NR	5 (1.2)	[redacted]	[redacted]
Injury, poisoning, and procedural complications	3 (0.4)	3 (0.7)	1 (0.2)	[redacted]	[redacted]
Musculoskeletal and connective tissue disorders	4 (0.5)	1 (0.2)	4 (1.0)	[redacted]	[redacted]
Vascular disorders	1 (0.1)	NR	NR	[redacted]	[redacted]
Hepatobiliary disorders	2 (0.2)	3 (0.7)	1 (0.2)	[redacted]	[redacted]
Nervous system disorders	4 (0.5)	1 (0.2)	NR	[redacted]	[redacted]
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	5 (0.6)	2 (0.5)	2 (0.5)	[redacted]	[redacted]
Respiratory, thoracic, and mediastinal disorders	NR	4 (1.0)	NR	[redacted]	[redacted]
WDAEs					
WDAEs, n (%)	14 (1.7)	9 (2.2)	26 (6.3)	[redacted]	[redacted]
Reasons (≥ 1%)					
Nausea	1 (0.1)	0	9 (2.2)	[redacted]	[redacted]
Deaths					
Number of deaths, n (%)	2 (0.2)	0	0	[redacted]	[redacted]
Undetermined (CV death)	1 (0.1)	0	0	[redacted]	[redacted]
Septic shock	1 (0.1)	0	0	[redacted]	[redacted]
Cardiorespiratory arrest	0	0	0	[redacted]	[redacted]
Malignant lung neoplasm	0	0	0	[redacted]	[redacted]

	DUAL I — Main and Extension Periods (52-Week Treatment Period)			[redacted]	
	IDegLira (N = 825)	IDeg (N = 412)	Lira (N = 412)	[redacted]	[redacted]
Cardiac arrest	0	0	0	[redacted]	[redacted]
Acute myocardial infarction	0	0	0	[redacted]	[redacted]
Road traffic accident	0	0	0	[redacted]	[redacted]
Pulmonary hypertension, cardiac arrest	0	0	0	[redacted]	[redacted]
Cerebral infarction, hypertensive crisis	0	0	0	[redacted]	[redacted]

AE = adverse event; CV = cardiovascular; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; Lira = liraglutide; NR = not reported; SAE = serious adverse event; SOC = System Organ Class; WDAE = withdrawal due to adverse event.

[a] Proportion of patients ≥ 5%.

[b] SAEs are grouped by System Organ Class; no SAEs occurred in ≥ 1% of patients.

Sources: Clinical study reports of DUAL I (main and extension trials)[74] and DUAL VIII.[75]

Table 40: Notable Harms for Safety Populations

	DUAL I — Extension			[redacted]	
	IDegLira (N = 825)	IDeg (N = 412)	Lira (N = 412)	[redacted]	[redacted]
Adjudicated Major Cardiovascular Events, n (%)	4 (0.5)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Acute coronary syndrome	2 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Acute myocardial infarction				[redacted]	[redacted]
Myocardial infarction	2 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Stroke	0	0	0	[redacted]	[redacted]
CV death	2 (0.2)	0	0	[redacted]	[redacted]
Undetermined death	0	0	0	[redacted]	[redacted]
Confirmed Adjudicated Fatal Cardiovascular Events, n (%)				[redacted]	[redacted]
Myocardial infarction	0	0	0	[redacted]	[redacted]
Sudden cardiac death	0	0	0	[redacted]	[redacted]
Stroke	0	0	0	[redacted]	[redacted]
Undetermined or unknown causes	1 (0.1)	0	0	[redacted]	[redacted]
Septic shock	1 (0.1)	0	0	[redacted]	[redacted]
Cardiac Disorders, n (%)	23 (2.8)	16 (3.9)	12 (2.9)	[redacted]	[redacted]
Palpitations	3 (0.4)	0	4 (1.0)	[redacted]	[redacted]
Angina, unstable				[redacted]	[redacted]
Pancreatitis, Acute and Chronic, n (%)	2 (0.2)	0	2 (0.5)	[redacted]	[redacted]
Altered Renal Function, n (%)	8 (1.0)	12 (2.9)	8 (1.9)	[redacted]	[redacted]
Renal and urinary disorders	5 (0.6)	9 (2.2)	4 (1.0)	[redacted]	[redacted]
Proteinuria	5 (0.6)	5 (1.2)	2 (0.5)	[redacted]	[redacted]
Acute kidney injury	NR	NR	NR	[redacted]	[redacted]
Renal failure	0	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Renal failure, acute	0	2 (0.5)	0	[redacted]	[redacted]
Renal impairment	0	0	1 (0.2)	[redacted]	[redacted]
Albuminuria	0	1 (0.2)	0	[redacted]	[redacted]

	DUAL I — Extension			[redacted]	
	IDegLira (N = 825)	IDeg (N = 412)	Lira (N = 412)	[redacted]	[redacted]
Investigations	3 (0.4)	3 (0.7)	4 (1.0)	[redacted]	[redacted]
Blood creatinine increased	1 (0.1)	1 (0.2)	3 (0.7)	[redacted]	[redacted]
Protein urine present	0	2 (0.5)	1 (0.2)	[redacted]	[redacted]
Blood urea increased	1 (0.1)	0	0	[redacted]	[redacted]
Glomerular filtration rate decreased	1 (0.1)	0	0	[redacted]	[redacted]
Renal and Urinary Disorders, n (%)	35 (4.2)	27 (6.6)	18 (4.4)	[redacted]	[redacted]
Microalbuminuria	3 (0.4)	2 (0.5)	1 (0.2)	[redacted]	[redacted]
Proteinuria	5 (0.6)	5 (1.2)	2 (0.5)	[redacted]	[redacted]
Renal failure	0	1 (0.2)	1 (0.2)	[redacted]	[redacted]
Renal failure, acute	0	2 (0.5)	0	[redacted]	[redacted]
Renal impairment	0	0	1 (0.2)	[redacted]	[redacted]
Blood creatinine increased	0	0	1 (0.2)	[redacted]	[redacted]
Confirmed Hypoglycemia as Defined by ADA[a], n (%)	625 (75.8)	335 (81.3)	133 (32.3)	[redacted]	[redacted]
Severe hypoglycemia	3 (0.4)	2 (0.5)	2 (0.5)	[redacted]	[redacted]
Documented symptomatic	360 (43.6)	233 (56.6)	48 (11.7)	[redacted]	[redacted]
Asymptomatic	583 (70.7)	314 (76.2)	103 (25.0)	[redacted]	[redacted]
Probably symptomatic	39 (4.7)	20 (4.9)	5 (1.2)	[redacted]	[redacted]
Relative	43 (5.2)	23 (5.6)	13 (3.2)	[redacted]	[redacted]
Pseudo	NR	NR	NR	[redacted]	[redacted]
ADA unclassifiable hypoglycemic	95 (11.5)	54 (13.1)	5 (1.2)	[redacted]	[redacted]
Allergic Reaction (Immunogenicity), n (%)	6 (0.7)	5 (1.2)	6 (1.5)	[redacted]	[redacted]
Anaphylactic reaction	NR	NR	NR	[redacted]	[redacted]
Antibody Formation	NR	NR	NR	[redacted]	[redacted]
Gastrointestinal AEs, n (%)	269 (32.6)	81 (19.7)	195 (47.3)	[redacted]	[redacted]
Diarrhea	84 (10.3)	28 (6.8)	67 (16.3)	[redacted]	[redacted]
Nausea	85 (10.3)	16 (3.9)	92 (22.3)	[redacted]	[redacted]
Vomiting	41 (5.0)	10 (2.4)	38 (9.2)	[redacted]	[redacted]
Constipation	26 (3.2)	4 (1.0)	21 (5.1)	[redacted]	[redacted]
Dyspepsia	28 (3.4)	5 (1.2)	22 (5.3)	[redacted]	[redacted]
Abdominal distension	10 (1.2)	3 (0.7)	11 (2.7)	[redacted]	[redacted]
Abdominal pain, upper	10 (1.2)	7 (1.7)	9 (2.2)	[redacted]	[redacted]
Abdominal pain	15 (1.8)	10 (2.4)	10 (2.4)	[redacted]	[redacted]
Gastroesophageal reflux disease	12 (1.5)	4 (1.0)	13 (3.2)	[redacted]	[redacted]
Gastritis	18 (2.2)	5 (1.2)	10 (2.4)	[redacted]	[redacted]
Injection Site Reactions, n (%)	34 (4.1)	14 (3.4)	19 (4.6)	[redacted]	[redacted]
Injection site hematoma	17 (2.1)	9 (2.2)	10 (2.4)	[redacted]	[redacted]
Injection site pain	5 (0.6)	0	2 (0.5)	[redacted]	[redacted]
Injection site pruritus	0	2 (0.5)	1 (0.2)	[redacted]	[redacted]
Injection site reaction	4 (0.5)	2 (0.5)	3 (0.7)	[redacted]	[redacted]
Injection site mass	2 (0.2)	0	1 (0.2)	[redacted]	[redacted]

	DUAL I — Extension			[redacted]	
	IDegLira (N = 825)	IDeg (N = 412)	Lira (N = 412)	[redacted]	[redacted]
Injection site rash	2 (0.2)	0	0	[redacted]	[redacted]
Injection site bruising	NR	NR	NR	[redacted]	[redacted]
Injection site erythema	1 (0.1)	0	1 (0.2)	[redacted]	[redacted]
Injection site atrophy	NR	NR	NR	[redacted]	[redacted]
Injection site nodule	0	0	1 (0.2)	[redacted]	[redacted]
Vessel puncture site hematoma	1 (0.1)	0	0	[redacted]	[redacted]
Vessel puncture site bruise	NR	NR	NR	[redacted]	[redacted]
Other	2 (0.2)	1 (0.2)	1 (0.2)	[redacted]	[redacted]

ADA = American Diabetes Association; AE = adverse event; CV = cardiovascular; IDeg = insulin degludec; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; Lira = liraglutide; NR = not reported; PG = plasma glucose.

[a] Confirmed hypoglycemia: Patient unable to treat himself or herself and/or has a recorded PG < 3.1 mmol/L (56mg/dL). Minor: PG < 3.1 mmol/L (56mg/dL).

Sources: Clinical study reports of DUAL I (main and extension trials)[74] and DUAL VIII.[75]

Limitations

The purpose of this supplemental issue was to monitor safety signals in the IDegLira treatment groups over extended treatment periods not afforded in the pivotal trials. No statistically significant clinical differences should be interpreted from the information presented within this section.

Both DUAL I and DUAL VIII were open-label studies, which can bias the reporting of subjective outcomes and AEs, such as hypoglycemia. Knowing their treatment randomization assignment may also bias the participant's experience and their level of participation in — and commitment to — the study. Furthermore, DUAL I was an extension study, having lost more than 20% of participants at the entry point into the extension phase.[74] The loss of study participants can favour a treatment group when patients are withdrawing from the trial due to tolerability, safety, effectiveness, or treatment regime issues. Results may suggest a more advantageous outcome or safety profile than a study in which full participation was maintained.

Summary

DUAL I was a 52-week study, which included a 26-week extension, while DUAL VIII was a 104-week duration study. Both were open-label studies comparing IDegLira to either IDeg and liraglutide individually (DUAL I) or to IGlar (DUAL VIII). These two studies were reported in this supplemental issue to record safety data not afforded by the shorter pivotal trials in the main report.[74,75]

[redacted][74,75]

Appendix 7: Summary of Indirect Comparisons by Batson (2019)

Introduction

The objective of this summary is to review, summarize, and critically appraise the manufacturer-submitted indirect treatment comparisons (ITCs) by Batson (2019)[76] that compared insulin degludec (IDeg) plus liraglutide in a fixed combination (IDegLira) with relevant treatment regimens (specified in the CADTH Common Drug Review protocol) for patients with type 2 diabetes mellitus (T2DM) inadequately controlled with either basal insulin or liraglutide in combination with metformin (MET) (± sulfonylurea [SU]).

The manufacturer submitted another ITC by Evans et al. (2018).[77,78] However, after a thorough assessment, it was found that there were several methodological limitations with the ITC (e.g., not being based on a systematic review, lack of information to allow the reader to better assess the validity of the reported results, potential heterogeneity) that would prevent any interpretation or conclusions from the data. [redacted][76] As a result, this ITC was excluded from this report.

Methods of the Indirect Treatment Comparison

Systematic Review

The primary objective of the ITC was to assess the [redacted] with inadequately controlled T2DM with either basal insulin therapy (stratum 1) or glucagon-like peptide 1 receptor agonist (GLP-1 RA) (stratum 2) in combination with MET or other oral antidiabetes drugs.[76] [redacted]

Study Eligibility and Selection Process

The ITC was conducted in [redacted]

Relevant studies were identified by searches of MEDLINE; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations; Embase; and the Cochrane Library on September 26, 2018. Records were reviewed based on title and abstract in the first instance. Those included were reviewed based on the full publication. This procedure complied with Health Technology Assessment guidelines for conducting a robust

systematic review.[79] The study selection process was conducted by two independent analysts. Any disputes were referred to the third party and resolved by consensus.

Table 41: Inclusion Criteria for the Stratum 1 Systematic Review

	Eligibility Criteria for the Stratum 1 Systematic Review
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Table 42: Inclusion Criteria for the Stratum 2 Systematic Review

	Eligibility Criteria for the Stratum 2 Systematic Review
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

	Eligibility Criteria for the Stratum 2 Systematic Review
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Data Extraction

Data extraction was conducted by an analyst and all data inputs were independently checked against the source document by a second analyst.

Comparators

[redacted]

Outcomes

[redacted]

Quality Assessment of Included Studies

[redacted]

[redacted]

Figure 17: Graphical Depiction of the Bias Assessment of the [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Indirect Comparison Methods

[redacted]

[redacted]

Results

The evidence synthesis results were presented in an Excel sheet in the manufacturer-submitted technical report.

Summary of Included Studies

[redacted]

Figure 18: Overall Evidence Network for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Table 43: Randomized Controlled Trials Identified in the [redacted]

RCTs	Prior Therapy	[redacted]	[redacted]	[redacted]
[redacted]				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

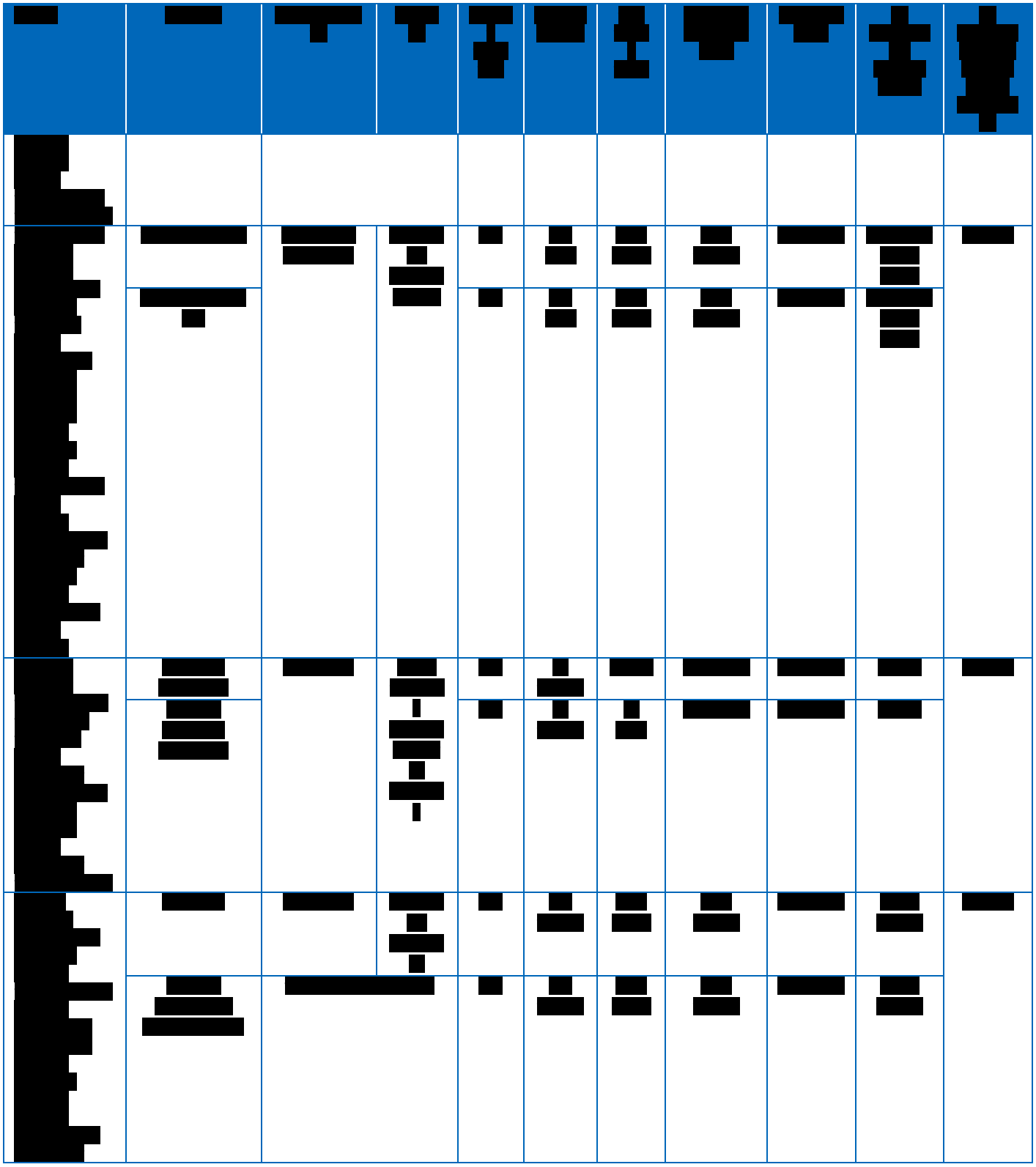
RCTs	Prior Therapy	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]				

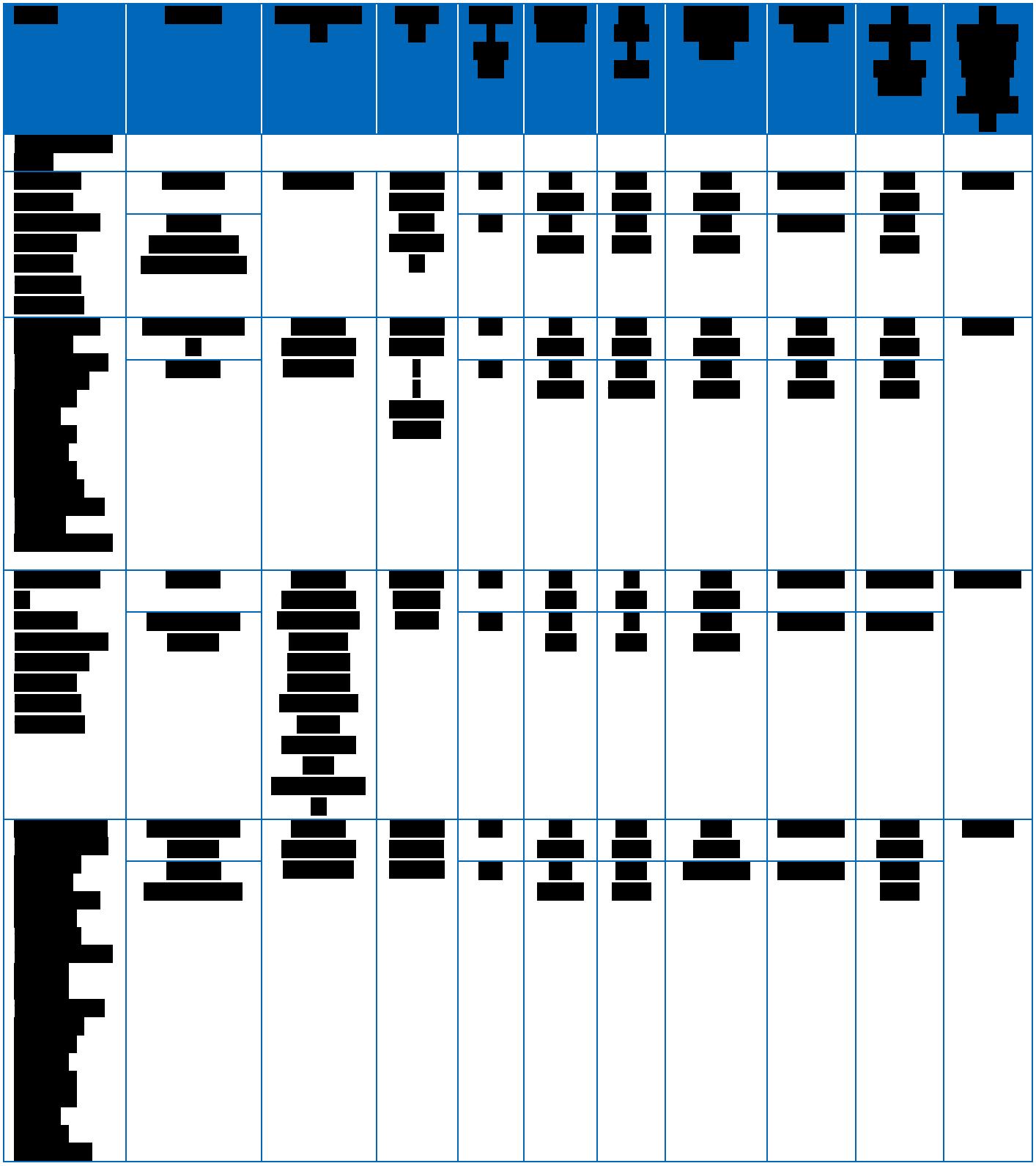
RCTs	Prior Therapy	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

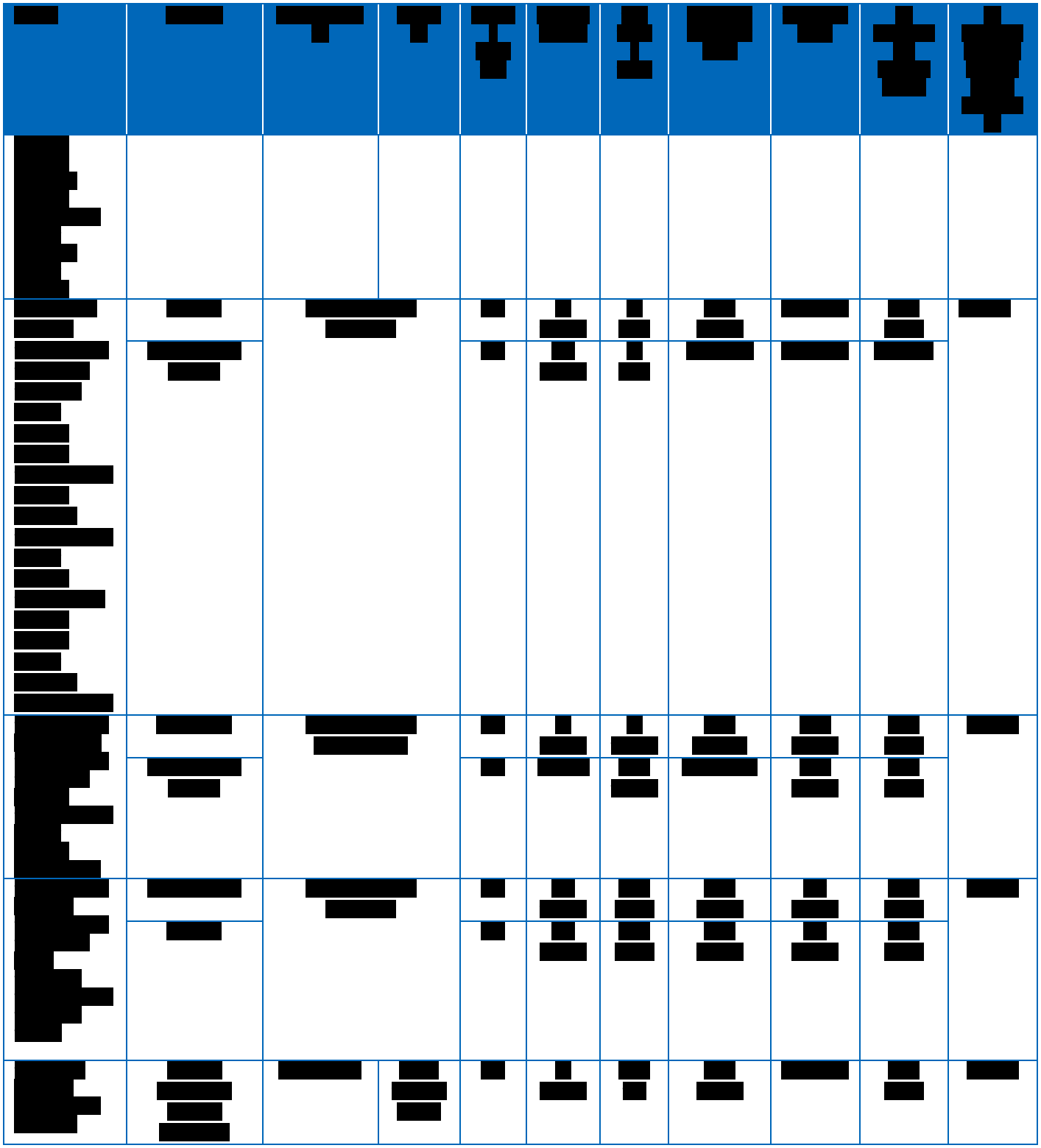
[redacted]

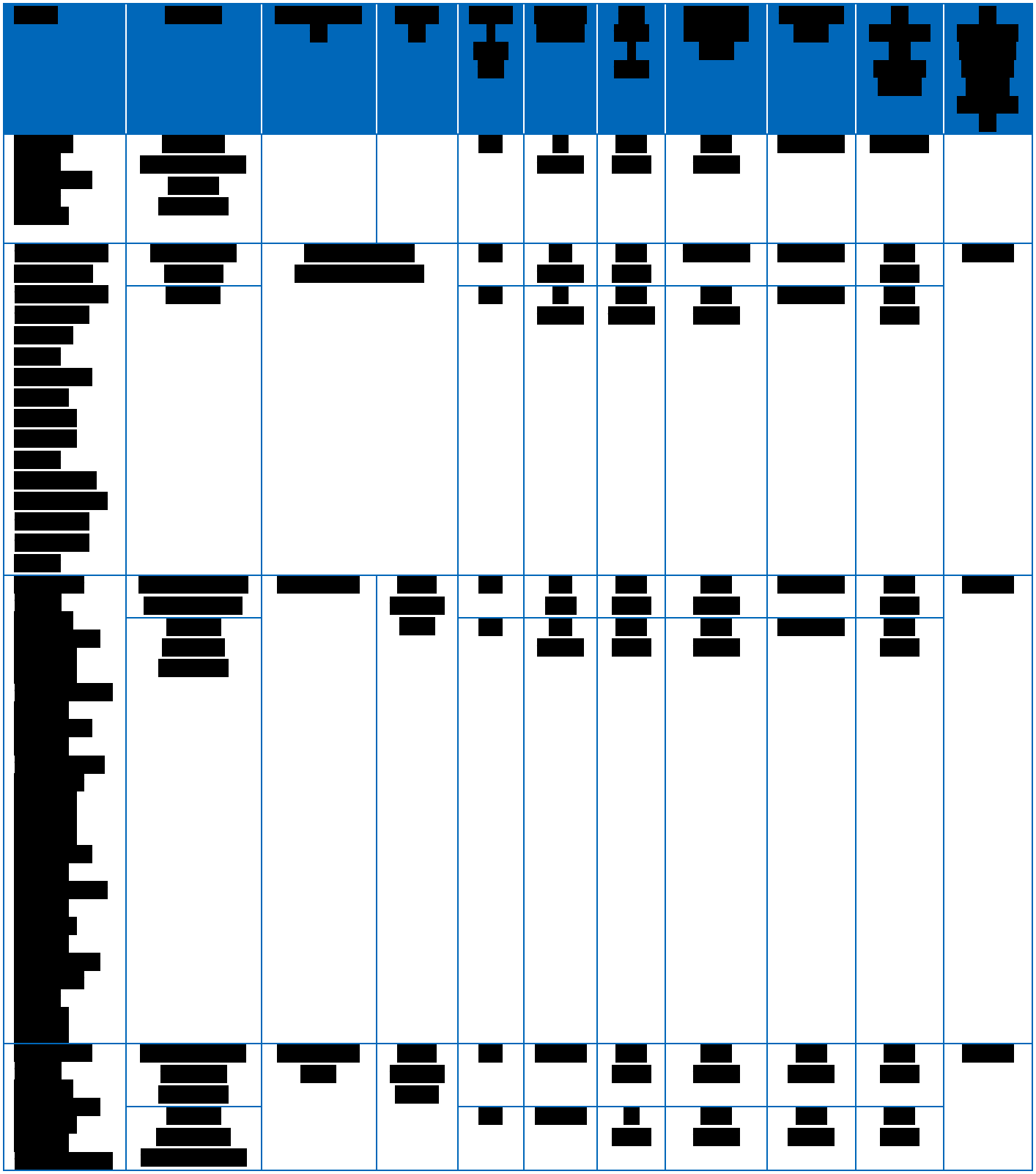
Table 44: Overview of Study Design and Baseline Characteristics [redacted]

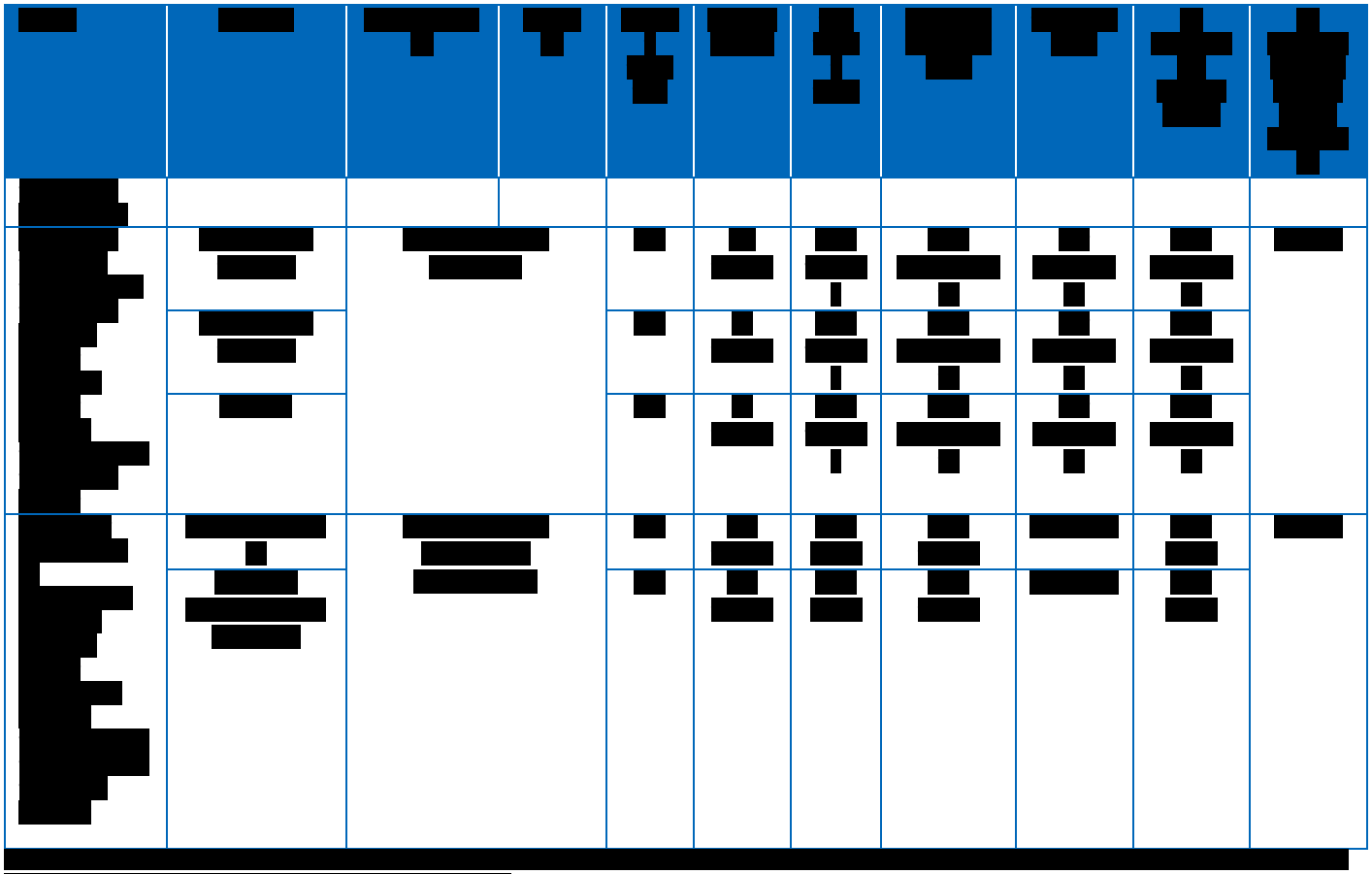
[redacted]										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]











Outcomes

ITC networks are presented from Figure 21 to Figure 26 for each specific outcome.

The ITC results of all outcomes of interest are summarized in Table 45.

[redacted]

Figure 19: Evidence Networks for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Table 45: Indirect Treatment Comparison Results for [redacted]

[redacted]	[redacted]				
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					
[redacted]					

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

[redacted]

Figure 20: Evidence Networks for [redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

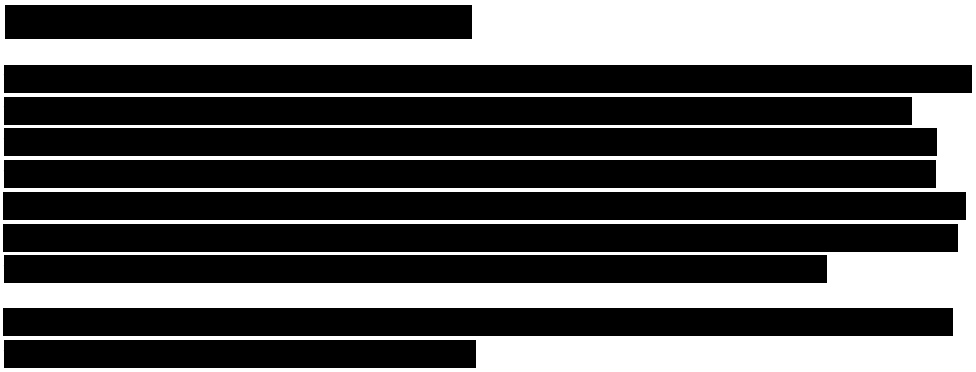


Figure 21: Evidence Networks [redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

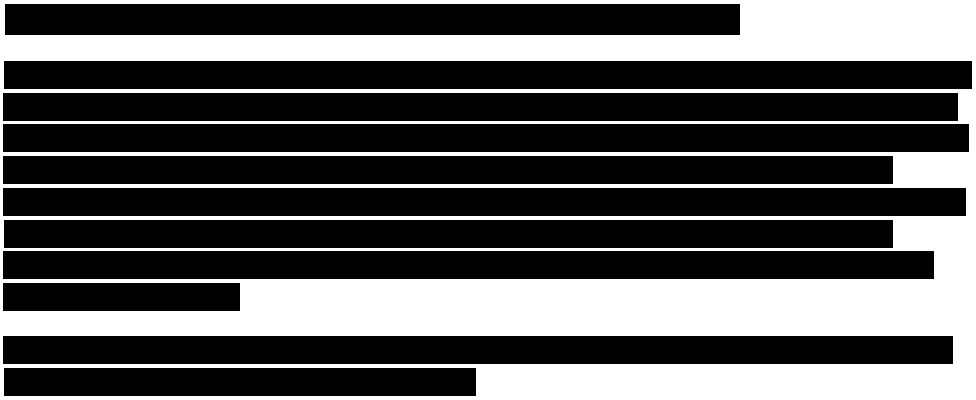


Figure 22: Evidence Networks [redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

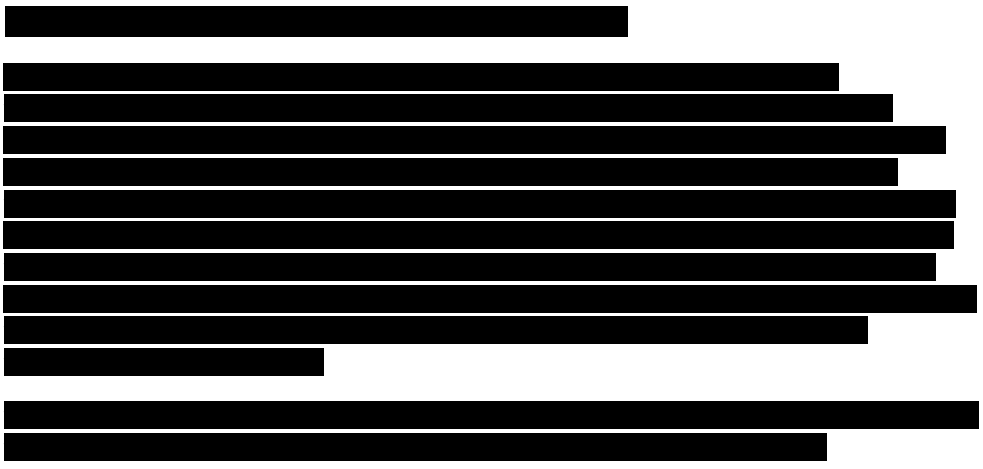


Table 46: Overview of the Types [redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Figure 23: Evidence Networks for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

[redacted]

Figure 24: Evidence Networks for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Figure 25: Evidence Network for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

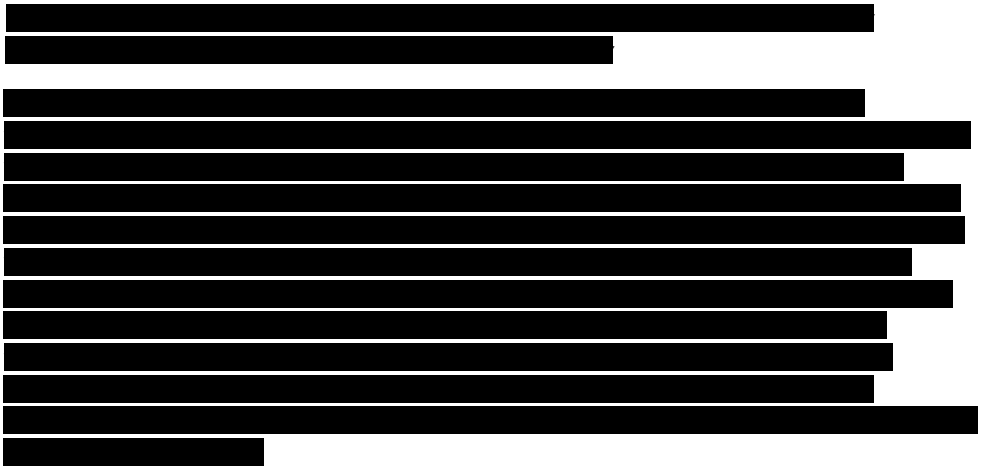


Figure 26: Evidence Networks for [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Figure 27: Evidence Networks [redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

[redacted]

Table 47: [redacted] Results [redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

[redacted]

Source: Technical report of indirect treatment comparison by Batson (2019).[76]

Critical Appraisal of Manufacturer-Submitted Indirect Treatment Comparison by Batson (2019)

The methodological quality (risk of bias) of the ITC by Batson (2019) submitted by the manufacturer was assessed by the CADTH Common Drug Review according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons.[82] Commentary for each of the relevant items identified by the Task Force are provided in Table 48.

Strengths

[redacted]

Limitations

In the ITC for patients with T2DM inadequately controlled on basal insulin (in combination with MET ± SU), several potential limitations of the methodology and/or the overall body of evidence (evidence gap) are discussed as follows. First, the most important limitation of the ITC was that there was a high amount of heterogeneity across the included studies in terms of [redacted]

[redacted] The high level of heterogeneity [redacted]; therefore, it was uncertain whether the assumption of transitivity in the ITC analysis was justified. [redacted]

For patients inadequately controlled with liraglutide (in combination with MET ± SU), the ITC using Bucher method provided only limited evidence for the comparative efficacy and safety of IDegLira, due to the small number of included studies and lack of evidence for a number of relevant comparators ([redacted]).

[redacted]

Discussion

For Patients With T2DM Inadequately Controlled on Basal Insulin (in Combination with MET ± SU)

[redacted]

[redacted]

For patients with T2DM inadequately controlled on liraglutide (in combination with MET ± SU)

[redacted]

Conclusion

For patients with T2DM inadequately controlled with basal insulin, the reviewed ITC suggested [redacted]. However, due to the high level of heterogeneity across the included studies, the reported ITC estimates are highly uncertain, especially for the comparison [redacted]

For patients with T2DM inadequately controlled with liraglutide, [redacted]

[redacted]However, the findings from the Bucher ITC should also be interpreted with caution, due to the small number of included studies. In addition, there is a lack of evidence for comparing [redacted]

[redacted]

Table 48: Appraisal of Indirect Treatment Comparison by Batson (2019) Using International Society for Pharmacoeconomics and Outcomes Research Criteria

	ISPOR Checklist Item[82]	Details and Comments
1.	Are the rationales for the study and objectives stated clearly?	• The rationale for conducting a network meta-analysis and the study objectives were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual randomized controlled trials were clearly stated. • Information sources and search strategy were reported. • Study selection process was conducted by 2 independent analysts. Any disputes were referred to the project manager and resolved by consensus. • The data extraction process was not sufficiently described. • Methods for quality assessment (assessment of risk of bias for individual study) were clearly reported. Risk of bias was assessed using CRD systematic reviews, CRD's guidance for undertaking reviews in health care (CRD, 2009).
3.	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly stated. • Justification of the outcome measures was provided.
4.	Is there a description of methods for analysis and synthesis of evidence? • Description of analyses methods and models • Handling of potential bias and inconsistency • Analysis framework	• A description of the statistical model was provided. • An analysis framework was provided for all analyses.
5.	Are sensitivity analyses presented?	• Sensitivity analysis was not performed. • Meta-regression sensitivity analyses were not performed.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• A detailed table with study and patient characteristics was provided. • Figures showing the network of studies were provided.
7.	Does the study describe an assessment of model fit?	• The fixed-effects or random-effects model was considered based on the model fit. ITC results from both fixed-effects or random-effects model were presented.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% credible intervals as a measure of uncertainty.
9.	Sensitivity and scenario analyses	• No sensitivity analyses were performed.

CRD = Centre for Reviews and Dissemination; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; ITC = indirect treatment comparison.

Appendix 8: Summary of Pooled Analysis (Novo Nordisk, 2015)

Introduction

The objective of this summary is to review, summarize, and critically appraise the manufacturer-submitted pooled analysis (indirect treatment comparisons [ITCs], Novo Nordisk, 2015)[89,90] that compared IDegLira with basal-bolus, or glucagon-like peptide 1 receptor agonist (GLP-1 RA) added to basal insulin or up-titration of basal insulin-only therapy in the treatment of patients with type 2 diabetes mellitus (T2DM) uncontrolled on basal insulin (with or without metformin).

Methods of the Pooled Analysis

The pooled analysis was not based on a systematic review. Trials were identified only from Novo Nordisk's "TrialTrove" database of clinical trials.[89,90] The inclusion criteria is summarized in Table 49. Briefly, trials were included if they met the following criteria: diabetes multinational randomized controlled trial (RCT) conducted by Novo Nordisk, where individual patient-level data were available; completed phase III or phase IV RCT; patients with T2DM on basal insulin; study with similar titration goals to DUAL II (i.e., fasting plasma glucose of 4.0 mmol/L to 5.0 mmol/L [72 mg/dL to 90 mg/dL]); intervention and comparators included insulin degludec plus liraglutide in a fixed combination (IDegLira), insulin glargine, insulin detemir, or liraglutide as the intervention drug, either alone or in combination with another intervention drug. To evaluate the efficacy of IDegLira compared with commonly used basal insulin intensification strategies, a pooled multivariable analysis using treatment groups from five different trials was applied. For these analyses, individual patient-level data were used.

The author indicated that the methodology used in the pooled analysis was supported by the European Network for Health Technology Assessment guidelines on how to conduct indirect analyses (however, the author did not provide a reference). Clinically relevant baseline differences between patients were adjusted by using standard multivariable and multivariate statistical methods (similar to DUAL II) with the addition of the following variables to account for potential systematic differences between trial populations: sex, disease duration, baseline hemoglobin A1C, and baseline body mass index (BMI). The baseline hemoglobin A1C and baseline BMI were included as explanatory variables in analyses of all the outcomes. Continuous outcomes were analyzed using an analysis of covariance model, hypoglycemic events were analyzed with a negative binomial model, and responder end points (binary) were analyzed using a logistic regression model. The regression coefficients from the multivariable and multivariate models were sufficiently reported.

Table 49: Inclusion Criteria in the Pooled Analysis (Novo Nordisk, 2015)

	Inclusion criteria
Database source	• All RCTs conducted within diabetes care in the Novo Nordisk clinical trial database, where individual patient-level data were available (the "TrialTrove" database of clinical trials intelligence)
Study design	• Completed phase III or phase IV RCT
Population	• Patients with T2DM on basal insulin (including basal-bolus, up titrating of basal insulin, or GLP-1 RA in combination with basal insulin)
Intervention and comparator	• IDegLira, insulin glargine, insulin detemir, or liraglutide as the intervention drug, either alone or in combination with bolus insulin or oral antidiabetes drugs • Study with similar titration goals to DUAL II i.e., FPG 4.0 mmol/L to 5.0 mmol/L (72 mg/dL to 90 mg/dL)
Outcomes	• Hemoglobin A1C, body weight, BMI, SBP, lipids, daily insulin dose at the end of treatment

BMI = body mass index; FPG = fasting plasma glucose; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; RCT = randomized controlled trial; SBP = systolic blood pressure; T2DM = type 2 diabetes mellitus.

Source: Pooled analysis technical report by Novo Nordisk (2015).[90]

Results of Manufacturer-Submitted Pooled Analysis by Novo Nordisk (2015)

Trials and Patient Characteristics

Five trials that met all these criteria (described in Table 49) were identified and were selected for the pooled analysis. Trial characteristics were briefly reported in Table 50. Baseline clinical and demographic characteristics of the selected treatment group from each included study are briefly summarized in Table 51. Briefly, all trials were RCTs. Two were double blind and three were open-label RCTs. All trial durations were 26 weeks except one (BEGIN BB Type 2), which was 52 weeks. The sample size reported in each selected group ranged from 56 to 225, mean age ranged from 57 to 59 years old, percentage female patients in each group ranged from 43% to 48%, body weight in each group ranged from 83 kg to 95 kg, baseline mean hemoglobin A1C (%) in each group ranged from 8.2% to 8.7%, mean duration of diabetes history in each group ranged from 10.3 years to 12.3 years, and the trial duration was not reported in the ITC (pooled analysis) report.

Table 50: Characteristics of the Five Trials Selected for the Pooled Analysis

Trial Name	Reference	Description	Arm and Sample Size Used in Pooled Analysis
DUAL II	Buse et al. (2014)	A 26-week randomized, parallel, 2-arm, double-blind trial comparing IDegLira to IDeg in basal insulin failures. There was a dose cap of 50 U in the IDeg group, corresponding to an insulin dose of 50 U in the maximum dose of IDegLira (50 U).	IDegLira (N = 199)
LIRA-ADD2BASAL	Ahmann et al. (2014)	A 26-week randomized, parallel, 2-arm, double-blind trial comparing Lira added to basal insulin with placebo added to basal insulin in patients previously treated with IGlar (66.7%) or IDet (33.3%). Insulin adjustments above pretrial dose were not allowed post randomization.	IGlar/IDet once daily + Lira (N = 225)
BEGIN BB Type 2	Garber et al. (2012)	A 52-week randomized, parallel, 2-arm, open-label trial comparing IDeg OD with IGlar OD in patients previously treated with basal insulin. (Only subset of patients who had failed basal insulin therapy)	Basal-bolus: IGlar once daily + IAsp t.i.d. (N = 56) Supplementary analysis: IGlar once daily + IAsp t.i.d. plus IDeg once daily + IAsp t.i.d. (N = 210)
BEGIN FLEX	Meneghini et al. (2013)	A 26-week randomized, parallel, 3-arm, open-label trial comparing IGlar and IDeg. IDeg was given in a flexible regimen of doses and as OD in combination with the evening meal. For the current analysis, the population is restricted to patients previously treated with basal insulin.	Basal only: Up-titrated IGlar groups from both trials combined (N = 329)
BOOST: INTENSIFY BASAL	Novo Nordisk, data on file	A 26-week randomized, parallel, 2-arm, open-label trial comparing IDegAsp with IGlar OD in patients previously treated with basal insulin.	

IAsp = insulin aspart; IDeg = insulin degludec; IDegAsp = insulin degludec aspart; IDegLira = insulin degludec plus liraglutide in a fixed combination; IDet = insulin detemir; IGlar = insulin glargine; Lira = liraglutide; t.i.d. = three times daily.

Source: Pooled analysis technical report by Novo Nordisk (2015).[90]

Table 51: Baseline Characteristics of Comparator Treatment Groups in the Pooled Analysis

	DUAL II (Buse et al., *Diabetes Care* [2014])	LIRA ADD-2BASAL (Ahmann et al., ADA [2014])	BEGIN BB Type 2 (Garber et al., The *Lancet* [2012])	BEGIN FLEX (Meneghini et al., *Diabetes Care* [2013]) and BOOST: INTENSIFY BASAL (Data on File, Novo Nordisk)
Arm selected	IDegLira (N = 199)	Liraglutide 1.8 mg Added to Basal Insulin (IGlar/ IDet) (N = 225)[a]	Basal-Bolus (IGlar + IAsp) (N = 56)	Up-Titrated IGlar (N = 329)
Sex (M/F %)	56.3/43.7	53.3/46.7	57.1/42.9	52.3/47.7
Age (years), mean (SD)	56.8 (8.9)	59.3 (9.2)	57.7 (10.9)	58.3 (9.4)
Body weight (kg), mean (SD)	95.4 (19.4)	90.2 (20.0)	93.4 (16.0)	83.3 (18.3)
BMI (kg/m^2), mean (SD)	33.6 (5.7)	32.3 (5.6)	32.4 (4.5)	30.0 (5.0)
Disease duration (years)	10.30 (6.01)	12.14 (7.12)	12.30 (6.52)	11.88 (7.23)

	DUAL II (Buse et al., *Diabetes Care* [2014])	LIRA ADD-2BASAL (Ahmann et al., ADA [2014])	BEGIN BB Type 2 (Garber et al., The *Lancet* [2012])	BEGIN FLEX (Meneghini et al., *Diabetes Care* [2013]) and BOOST: INTENSIFY BASAL (Data on File, Novo Nordisk)
Hemoglobin A1C (%), mean (SD)	8.7 (0.7)	8.2 (0.8)	8.5 (0.9)	8.4 (0.9)
SBP (mm Hg), mean (SD)	132.4 (14.8)	134.2 (13.6)	132.1 (16.1)	133.5 (16.1)
Total cholesterol (mg/dL), mean (SD)	182.0 (45.5)	178.7 (43.0)	168.0 (40.7)	170.3 (42.0)
HDL cholesterol (mg/dL), mean (SD)	43.4 (11.0)	49.4 (13.9)	44.8 (12.4)	46.0 (12.7)
LDL cholesterol (mg/dL), mean (SD)	101.9 (37.1)	96.9 (36.9)	91.7 (34.2)	96.8 (36.8)
Triglycerides (mg/dL), mean (SD)	196.8 (148)	169.1 (102)	164.8 (105)	138.7 (73.6)
Race, n (%)				
White	157 (78.9)	172 (76.4)	45 (80.4)	212 (64.4)
Other	42 (21.1)	53 (23.6)	11 (19.6)	117 (35.6)
Insulin dose at screening (U), mean (SD)	29.0 (7.7)	48.3 (33.6)	43.0 (25.5)	31.0 (21.9)

BMI = body mass index; F = female; HDL = high-density lipoprotein; IAsp = insulin aspart; IdegLira = insulin degludec plus liraglutide in a fixed combination; Idet = insulin detemir; IGlar = insulin glargine; LDL = low-density lipoprotein; M = male; SBP = systolic blood pressure; SD = standard deviation.

[a] A total of 66.7% of patients received IGlar and 33.3% of patients received Idet.

Source: Pooled analysis technical report by Novo Nordisk (2015).[90]

Efficacy

The results of the pooled analysis are presented in Table 52.

Hemoglobin A1C (%) — Change From Baseline

The author reported that there was a statistically significantly greater reduction in hemoglobin A1C with IDegLira compared with basal-bolus, GLP-1 RA added to basal insulin, or up-titration of basal insulin-only therapy. The mean treatment group difference of change from baseline were −0.30 (95% confidence interval [CI]) −0.58 to −0.01) between IDegLira and basal-bolus, −0.35 (95%, −0.56 to −0.14) between IDegLira and GLP-1 RA added to insulin, as well as −0.65 (95%, −0.83 to −0.47) between IDegLira and up-titration of basal only, respectively (see Table 52).

It was also reported that statistically significantly more patients treated with IDegLira achieved hemoglobin A1C < 7.0% at the end of treatment than patients treated with up-titration of basal insulin-only therapy or those adding a GLP-1 RA to basal insulin. Statistically significantly more patients treated with IDegLira achieved hemoglobin A1C < 7.0% without hypoglycemia at the end of treatment than patients treated with a basal-bolus regimen or up-titration of basal insulin-only therapy. Statistically significantly more patients treated with IDegLira achieved hemoglobin A1C < 7.0% without hypoglycemia and without weight gain at the end of treatment than patients treated with up-titration of basal insulin-only therapy (see Table 53).

Body Weight (kg) — Change From Baseline

The pooled analysis showed there was a statistically significantly greater reduction in body weight with IDegLira compared with basal-bolus or up-titration of basal insulin-only therapy. The mean treatment group difference of change from baseline were −6.89 (95% CI, −7.92 to −5.86) between IDegLira and basal-bolus, or −4.04 (95% CI, −4.69 to −3.40) between IDegLira and up-titration of basal insulin only, respectively. No statistically significant difference of 0.65 (95% CI, −0.11 to 1.40) in terms of body weight reduction was observed between IDegLira and GLP-1 RA added to insulin regimen.

BMI (kg/m^2) — Change From Baseline

There was a statistically significantly greater reduction in BMI with IDegLira versus basal-bolus or up-titration of basal insulin-only therapy. The mean treatment group difference of change from baseline were −2.44 (95% CI, −2.80 to −2.07) between IDegLira and basal-bolus, and −1.44 (95% CI, −1.67 to −1.21) between IDegLira and up-titration of basal insulin only, respectively. No statistically significant difference (0.26 [95% CI, −0.01 to 0.52]) in terms of body weight reduction were observed between IDegLira and GLP-1 RA added to insulin.

Overall Confirmed Hypoglycemia (Rate Ratio)

In the pooled analysis, severe hypoglycemia was defined as an episode requiring the assistance of another person to actively administer carbohydrate, glucagons, or other resuscitative actions. A minor hypoglycemic episode was defined as an episode biochemically confirmed by a plasma glucose value of < 3.1 mmol/L (56 mg/dL), with or without symptoms consistent with hypoglycemia. Confirmed hypoglycemia was defined as an episode that was classified as being a minor episode or a severe episode.

IDegLira was associated with a statistically significantly lower rate of overall confirmed hypoglycemia than treatment with either basal-bolus regimen (rate ratio, 0.12 [95% CI, 0.07 to 0.20]) or up-titration of basal insulin-only therapy (0.43 [95% CI, 0.30 to 0.62]). No statistically significant difference (0.99 (95% CI, 0.63 to 1.54)) in terms of confirmed hypoglycemia were observed between IDegLira and GLP-1 RA added to insulin.

Lipids (mmol/L)

IDegLira was associated with a statistically significantly greater reduction of lower total cholesterol (−0.19 [95% CI, −0.34 to −0.05]) or low-density lipoprotein (−0.12 [95% CI, −0.24 to −0.01]) compared with up-titration of basal insulin regimen. No statistically significant difference was reported between IDegLira and basal-bolus or between IDegLira and GLP-1 RA added to insulin in terms of total cholesterol or low-density lipoprotein. No statistically significant difference was observed between IDegLira and basal-bolus or between IDegLira and GLP-1 RA added to insulin or up-titration of basal in terms of total cholesterol, low-density lipoprotein, high-density lipoprotein, and triglycerides (see Table 52).

Insulin Dose at End of Treatment (Units per Day)

At the end of the trial, the daily basal insulin dose was statistically significantly lower with IDegLira than with either a basal-bolus regimen or up-titration of basal-only therapy (see Table 52).

Table 52: Results (Analysis of Covariance Model)

	IDegLira vs. Basal-Bolus (IGlar as Basal Insulin) (N = 56)	IDegLira vs. GLP-1 RA Add-On to Basal Insulin (N = 225)	IDegLira. vs. Basal Only (Up-Titrated IGlar) (N = 329)
	Mean (95% CI; *P* Value)	Mean (95% CI; *P* Value)	Mean (95% CI; *P* Value)
Δ hemoglobin A1C, %	−0.30 (−0.58 to −0.01; *P* = 0.040)	−0.35 (−0.56 to −0.14; *P* = 0.0009)	−0.65 (−0.83 to −0.47; *P* < 0.0001)
Δ body weight, kg	−6.89 (−7.92 to −5.86; *P* = < 0.0001)	0.65 (−0.11 to 1.40; *P* = 0.092)	−4.04 (−4.69 to −3.40; *P* < 0.0001)
Δ BMI (kg/m^2)	−2.44 (−2.80 to −2.07; P < 0.0001)	0.26 (−0.01 to 0.52; *P* = 0.058)	−1.44 (−1.67 to −1.21; *P* < 0.0001)
Δ SBP (mm Hg)	−8.67 (−12.58 to −4.77; *P* < 0.0001)	−2.16 (−5.01 to 0.69; *P* = 0.14)	−3.37 (−5.80 to −0.94; *P* = 0.0065)
Δ total cholesterol (mg/dL)	−4.64 (−13.60 to 4.31; *P* = 0.31)	2.82 (−3.71 to 9.34; *P* = 0.40)	−7.56 (−13.16 to −1.97; *P* = 0.0081)
Δ total cholesterol (mmol/L)[a]	−0.12 (−0.35 to 0.11)	0.07(−0.09 to 0.24)	−0.19 (−0.34 to −0.05)
Δ LDL (mg/dL)	−4.43 (−11.68 to 2.83; *P* = 0.23)	2.30 (−3.00 to 7.60; *P* = 0.39)	−4.82 (−9.35 to −0.30; *P* = 0.037)
Δ LDL (mmol/L)[a]	−0.11 (−0.30 to 0.073)	0.06 (−0.07 to 0.19)	−0.12 (−0.24 to −0.01)
Δ HDL (mg/dL)	0.07 (−1.96 to 2.10; *P* = 0.94)	1.21 (−0.27 to 2.70; *P* = 0.11)	−0.59 (−1.86 to 0.67; *P* = 0.36)
Δ HDL (mmol/L)[a]	0.00 (−0.05 to 0.05)	0.03 (−0.01 to 0.07)	−0.02 (−0.05 to 0.02)
Δ triglycerides(mg/dL)	−2.46 (−26.20 to 21.27; *P* = 0.84)	−2.05 (−19.36 to 15.26; *P* = 0.82)	−9.18 (−24.10 to 5.74; *P* = 0.23)
Δ triglycerides (mmol/L)[a]	−0.03 (−0.29 to 0.24)	−0.02 (−0.21 to 0.17)	−0.10 (−0.27 to 0.06)
Daily basal dose at end of treatment (U)	−24.64 (−32.79 to −16.49; *P* < 0.0001)	1.17 (−4.75 to 7.09; *P* = 0.70)	−22.86 (−27.94 to −17.78; *P* < 0.0001)

Δ = change from baseline; BMI = body mass index; CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; HDL = high-density lipoprotein; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; LDL = low-density lipoprotein; SBP = systolic blood pressure; vs. = versus.

[a] Unit converted by CADTH.

Source: Pooled analysis technical report by Novo Nordisk (2015).[90]

Table 53: Responder or Hypoglycemia for IDegLira vs. Comparators (Logistic Regression Model)

	IDegLira vs. Basal-Bolus With IGlar as Basal Component	IDegLira vs. GLP-1 RA Add-On to Basal Insulin	IDegLira. vs. Basal Only (Up-Titrated IGlar)
In all subjects	Odds Ratio (95% CI; *P* Value)	Odds Ratio (95% CI; *P* Value)	Odds Ratio (95% CI; *P* Value)
Hemoglobin A1C < 7.0% (53 mmol/mol)	1.64 (0.86 to 3.12; *P* = 0.13)	2.06 (1.28 to 3.31; *P* = 0.003)	3.91 (2.58 to 5.93; *P* < 0.0001)
Hemoglobin A1C < 7.0%, no hypoglycemia	16.05 (4.71 to 54.66; *P* < 0.0001)	1.53 (0.95 to 2.47; *P* = 0.084)	4.53 (2.87 to 7.14; *P* < 0.0001)
Hemoglobin A1C < 7.0%, no hypoglycemia, no weight gain	Not estimated	1.29 (0.77, 2.14; *P* = 0.33)	7.71 (4.50, 13.19; *P* < 0.0001)
Hypoglycemia	Rate Ratio (95% CI; *P* Value)	Rate Ratio (95% CI; *P* value)	Rate Ratio (95% CI; *P* Value)
Overall confirmed hypoglycemia	0.12 (0.07 to 0.20; *P* < 0.0001)	0.99 (0.63 to 1.54; *P* = 0.95)	0.43 (0.30 to 0.62; *P* < 0.0001)
Severe hypoglycemia	0.18 (0.01 to 2.77; *P* = 0.22)	Not estimated	0.16 (0.01 to 1.81; *P* = 0.14)
Non-severe hypoglycemia	0.12 (0.07 to 0.20; *P* < 0.0001)	0.98 (0.63 to 1.54; *P* = 0.94)	0.43 (0.30 to 0.63; *P* < 0.0001)

CI = confidence interval; GLP-1 RA = glucagon-like peptide 1 receptor agonist; IDegLira = insulin degludec plus liraglutide in a fixed combination; IGlar = insulin glargine; vs. = versus.

Note: Confirmed hypoglycemia was defined as the occurrence of severe episodes (i.e., requiring assistance) or episodes in which plasma glucose concentration (confirmed by self-monitored blood glucose) was less than 56 mg/dL (3.1 mmol/L), irrespective of symptoms.

Source: Pooled analysis technical report by Novo Nordisk (2015).[90]

Critical Appraisal of Pooled Analysis

The pooled analysis was not based on a systematic review. Although the author indicated that the methodology used in the pooled analysis was supported by the European Network for Health Technology Assessment guidelines on how to conduct indirect analyses (reference not provided by the author), this was not a conventional ITC; therefore, typical International Society for Pharmacoeconomics and Outcomes Research appraisal tools could not be implemented. Several methodological limitations are discussed as follow. First, only five studies from the Novo Nordisk database were selected, which meant that there was a major risk of selection bias. It was not expected to be representative of all available studies in the area. Secondly, the use of treatment groups from different trials raised the potential for systematic differences in patient populations. Despite the author having reported that clinically relevant baseline differences between patients were adjusted by using standard multivariable and multivariate statistical methods (similar to DUAL II, i.e., region and previous oral antidiabetes drug treatment) with the addition of the following variables to account for potential systematic differences between trial populations such as sex, disease duration, baseline hemoglobin A1C, and baseline BMI, and insulin dose regimen, trial duration and outcome definitions, it is unclear if balance between the studies was sufficiently achieved with the use of multivariate regression. Therefore, those adjustments were unlikely to make the study populations sufficiently comparable in the highly selected data. In addition, the methodological quality (risk of bias) of individual studies was not assessed; therefore, the potential risk of bias of individual study was not considered in the ITC, i.e., no sensitivity or subgroup analyses were completed by removing studies with poor methodological quality of study (with high risk of bias). Taken together,

due to the substantial methodologic limitations, high uncertainty remains in the interpretation of the findings. Furthermore, sodium-glucose cotransporter-2 inhibitors (i.e., canagliflozin, dapagliflozin, empagliflozin, ertugliflozin) or dipeptidyl peptidase-4 inhibitors (i.e., alogliptin, linagliptin, sitagliptin, saxagliptin) used alone or in combination with insulin or GLP-1 RAs are commonly used options for patients with T2DM inadequately controlled basal insulin (or GLP-1 RA) in combination with metformin (or other oral antidiabetes drugs). The author did not include sodium-glucose cotransporter-2 or dipeptidyl peptidase-4 in the ITC. The author did not include the clinically important outcomes (e.g., mortality, diabetes-related morbidity, quality of life) in the ITC, which suggest the potential gaps of evidence.

Conclusion

In treatment of patients with T2DM, the pooled analysis showed a statistically significantly greater reduction in hemoglobin A1C with IDegLira compared with basal-bolus, GLP1-RA in combination with basal insulin, and basal insulin up-titration regimens; it also indicated a statistically significantly greater reduction in body weight with IDegLira compared with basal-bolus and basal insulin up-titration regimen. A statistically significantly greater reduction in total cholesterol, low-density lipoprotein, and overall confirmed hypoglycemia were also observed with IDegLira compared with basal insulin up-titration regimen. However, due to the considerable methodological limitations discussed earlier, the findings of the pooled analysis should be interpreted with caution. No credible conclusions can be drawn based on the pooled analysis.

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