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ORIGINAL ARTICLE

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 people with uncontrolled type 2 diabetes

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Aim: To investigate the efficacy and safety of insulin degludec/liraglutide (IDegLira) versus insulin glargine 100 units/mL (IGlar U100) as add-on to sodium-glucose co-transporter-2 (SGLT2) inhibitor therapy.

Materials and methods: In this 26-week, phase IIIb, open-label, parallel-group, treat-to-target trial, conducted at 74 sites in 11 countries, insulin-naïve people aged ≥18 years with glycated haemoglobin (HbA1c) 53–97 mmol/mol (7.0–11.0%), body mass index 20–40 kg/m^2 and inadequately controlled type 2 diabetes (T2D) on SGLT2 inhibitor ± oral antidiabetic drugs were randomized 1:1 to once-daily IDegLira or IGlar U100, both as add-on to existing therapy. The primary endpoint was change in HbA1c from baseline to week 26.

Results: A total of 210 participants were randomized to each treatment arm. Mean HbA1c reductions were 21 mmol/mol (1.9%-points) with IDegLira and 18 mmol/mol (1.7%-points) with IGlar U100; confirming non-inferiority ($P < 0.0001$) and superiority of IDegLira (difference in HbA1c change −3.90 mmol/mol; 95% confidence interval [CI] −5.45; −2.35 (−0.36%-points; 95% CI −0.50, −0.21)). Superiority for IDegLira over IGlar U100 was also confirmed for: body weight (difference −1.92 kg; 95% CI −2.64, −1.19); severe or blood-glucose-confirmed symptomatic hypoglycaemia (rate ratio 0.42; 95% CI 0.23, 0.75); total daily insulin dose (difference −15.37 U; 95% CI −19.60, −11.13). The overall treatment-emergent adverse event rate was higher with IDegLira as a result of higher increased lipase and nausea rates.

Conclusions: The favourable safety and efficacy profile of IDegLira in people with uncontrolled T2D on SGLT2 inhibitors, and lower weight gain and hypoglycaemia risk versus IGlar U100, suggest that clinicians should consider IDegLira initiation in this population.

KEYWORDS

GLP-1 analogue, insulin therapy, liraglutide, randomized trial, SGLT2 inhibitor, type 2 diabetes

1 | INTRODUCTION

Clinicians now have access to treatment options for people with type 2 diabetes (T2D) that not only lower blood glucose, but also confer a lower risk of hypoglycaemia and weight gain. As T2D is a progressive disease, combining two or more therapies is frequently required to maintain glycaemic control.[1] Some therapeutic combinations, such as the addition of a dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-

like peptide-1 receptor agonist (GLP-1RA) or sodium-glucose co-transporter-2 (SGLT2) inhibitor to basal insulin, are well established.[1,2] IDegLira is a fixed-ratio combination of the basal insulin degludec and the GLP-1RA liraglutide; the safety and efficacy of IDegLira have been demonstrated in a variety of patient populations in the DUAL clinical trial programme.[3–9] In the DURATION-8[10] and AWARD-10[11] clinical trials, combined therapy with GLP-1RAs and SGLT2 inhibitors in patients failing to achieve glycaemic control on metformin and SGLT2 inhibitor ± metformin, respectively, resulted in improvements in glycaemic control, with no unexpected side effects. Treatments belonging to the GLP-1RA and SGLT2 inhibitor classes of medications exert their positive effects on patients by different, but complementary, modes of action. GLP-1RAs achieve reduction of glucose levels by stimulating insulin secretion and suppressing pancreatic glucagon secretion, reducing glucose output from the liver and reducing the gut-to-bloodstream glucose transfer rate by slowing gastric emptying. Inhibition of SGLT2 protein transporters in the proximal renal tubule, which have a role in ~90% of glucose reabsorption, increases urinary glucose secretion and indirectly increases glucagon concentration.

Current T2D treatment guidelines recommend the sequential addition of up to two further therapies if glucose remains uncontrolled within 3 months of metformin initiation, before initiating combination injectable therapy.[1] To determine if there are therapeutic advantages to initiating a fixed-ratio combination of a basal insulin and a GLP-1RA as first injectable therapy, the DUAL IX study (clinicaltrials.gov: NCT02773368) compared the efficacy and safety of IDegLira with insulin glargine 100 units/mL (IGlar U100), the most widely prescribed basal insulin worldwide and common next-step in care,[12,13] as an add-on to SGLT2 inhibitor therapy in insulin-naïve people with T2D inadequately controlled on SGLT2 inhibitors, in combination with other oral antidiabetic drugs (OADs).

2 | MATERIALS AND METHODS

2.1 | Study design

DUAL IX was a phase IIIb, open-label, two-arm parallel, treat-to-target, randomized trial, in insulin-naïve people with inadequately controlled T2D on a stable dose of an SGLT2 inhibitor, conducted at 74 sites in 11 countries between May 2016 and October 2017. It was conducted in accordance with International Conference on Harmonisation Good Clinical Practice[14] and the Declaration of Helsinki.[15] The 32-week trial comprised a 2-week screening period, a 26-week treatment period, and two follow-up safety assessments at 7 (+3) days and 30 days (+3 days) after last dose of randomized treatment. An interactive web response system was used to randomize participants 1:1 to IDegLira or IGlar U100. Existing DPP-4 inhibitor therapy was discontinued at randomization. Prior to trial initiation, the protocol, consent form, and participant information sheet were reviewed and approved according to local regulations by appropriate health authorities, and an independent ethics committee/institutional review board. Participants provided written informed consent prior to inclusion in the trial. Treatment assignment was masked for a safety committee, an independent external committee that adjudicated selected adverse events (AEs), and personnel involved in defining the analysis sets until the database was released for statistical analysis, but was not masked for patients and all other investigators.

2.2 | Participants

Participants were aged ≥18 years, and had a glycated haemoglobin (HbA1c) concentration of 53–97 mmol/mol (7.0–11.0%), a body mass index (BMI) 20–40 kg/m^2 and T2D uncontrolled on SGLT2 inhibitors ± other OADs (metformin, DPP-4 inhibitors and/or pioglitazone). Full inclusion/exclusion criteria are provided in Table S1.

2.3 | Interventions

IDegLira and IGlar U100 were administered once daily subcutaneously, as add-on to existing therapy, both initiated at a dose of 10 units (U) and titrated twice-weekly to a fasting plasma glucose (FPG) target of 4.0–5.0 mmol/L (72–90 mg/dL) according to the titration algorithm (Table S2). The maximum approved IDegLira dose was 50 U; IGlar U100 had no maximum dose. IDegLira was supplied in a 3-mL pre-filled FlexTouch® pen with a fixed insulin degludec/liraglutide ratio of 100 U/3.6 mg per mL solution. IGlar U100 (100-U/mL solution) was supplied in a 3-mL pre-filled Solostar injection pen (Sanofi, Paris, France).

2.4 | Endpoints

The primary endpoint was change in HbA1c from baseline to week 26. Confirmatory secondary endpoints consisted of change from baseline in body weight, the number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes during the 26-week study, and total daily insulin dose at end of study. Supportive secondary endpoints were change from baseline to week 26 in FPG, nine-point self-measured blood glucose (SMBG) profile, blood pressure, fasting lipids, percentage of participants reaching HbA1c targets of <53 mmol/mol (<7%) and ≤48 mmol/mol (≤6.5%) without hypoglycaemia and/or weight gain, patient-reported outcomes (PROs) and safety outcomes. PROs were assessed using the previously validated Treatment Related Impact Measure – Diabetes (TRIM-D) questionnaire.[16] TRIM-D consists of five domains, each containing items that are scored on a one- to five-point scale. Domain scores are calculated by summing across items in the domain, and a total score is calculated by summing scores from all the domains. All domain scores and the total score are transformed to a 0–100 scale, with higher scores indicating better outcomes.

Hypoglycaemic events included in the analyses were either severe (requiring the assistance of another person) or blood glucose-confirmed symptomatic events (plasma glucose level <3.1 mmol/L with symptoms consistent with hypoglycaemia). Hypoglycaemia was considered nocturnal if occurring between 00:01 and 05:59 (both inclusive).

Treatment-emergent AEs (TEAEs) were defined as those with an onset on or after first exposure to randomized treatment and no later than 7 days after the last day of randomized treatment, or events that existed prior to exposure to randomized treatment if there was an

increase in severity during treatment or up to 7 days after the last day of exposure to randomized treatment. Major adverse cardiovascular events (MACE) were considered treatment-emergent until 30 days after the last day of treatment.

2.5 | Statistical analysis

2.5.1 | Sample size

The sample size was calculated using a one-sided *t*-test with α value of 0.025, a mean treatment difference of 0.0%, a standard deviation (SD) of 1.0%, a non-inferiority margin of 0.3% and an estimated 15% of randomized participants being excluded from the per-protocol analysis population, based on experience from the phase IIIa development programmes for IDegLira and insulin degludec. A total of 416 patients (208 per treatment arm) were required to achieve the primary objective with 80% power (per-protocol population).

2.5.2 | Efficacy and safety analyses

The full analysis set comprised all randomized participants and the safety analysis set included all participants who received at least one dose of trial product. The primary estimand in this study was the difference at 26 weeks between participants with T2D randomized to IDegLira or IGlar U100, regardless of whether participants remained on the initially assigned treatment or not. The results for the primary estimand include retrieved data at week 26 for participants who discontinued trial product prematurely.

The primary statistical analyses were performed based on the full analysis set. The primary endpoint was first evaluated in terms of non-inferiority (to a limit of 0.3%) of IDegLira versus IGlar U100. Subsequently, confirmatory secondary hypotheses tested the superiority of IDegLira versus IGlar U100 in terms of the confirmatory secondary endpoints and change from baseline in HbA1c. Family-wise type I error was controlled at 2.5% one-sided by applying a hierarchical testing approach. *P* values without multiplicity adjustment are considered nominal.

Continuous endpoints were assessed using analysis of covariance, with treatment, pre-trial OAD, and region as fixed factors, and the corresponding baseline value as covariate. Lipid endpoints and the corresponding baseline value were log-transformed before analysis. Missing data were imputed by unconditional reference-based multiple imputation,[17] based on 1000 imputations and assuming an immediate loss of treatment effect in the IDegLira arm. Retrieved data were available for confirmatory analyses; participants discontinuing trial product prematurely as a result of any of the rescue criteria, criteria for premature discontinuation of trial product, or at participants' own will had to attend a visit at week 26 to report HbA1c, body weight, and total insulin dose. The imputation method and use of retrieved data in analyses can equalize treatments, and could make it easier to demonstrate non-inferiority. To mitigate this potential bias, a penalty corresponding to the non-inferiority margin was added to the imputed IDegLira values when making the non-inferiority comparison.

Hypoglycaemic endpoints were analysed using a negative binomial regression model with treatment, pre-trial OAD, region and visit as fixed factors. Missing data were imputed by multiple imputation.

Responder endpoints were analysed by logistic regression with treatment, pre-trial OAD and region as fixed factors and baseline HbA1c (and baseline body weight when body weight was part of the composite) as covariates. Missing data were predicted from unconditional reference-based multiple imputation before applying the responder criterion.

The nine-point SMBG profile was analysed jointly via a mixed model for repeated measurements with an unstructured residual covariance structure with treatment, time point, pre-trial OAD, region and interaction between treatment and time point, and the interaction between pre-trial OAD and time as fixed factors, and participant as random effect.

Sensitivity analyses were carried out for the primary and confirmatory secondary endpoints applying different assumptions for the missing data to evaluate the robustness of the results.

Post hoc analyses were performed using the same multiple imputation approach assessing the primary estimand, with the subgroup pre-trial DPP-4 inhibitor use included as an interaction term with randomized treatment.

3 | RESULTS

3.1 | Participants

In total, 554 participants were screened and 420 randomized to treatment (210 to each arm). One participant randomized to IDegLira in error (study entry criteria were not fulfilled), was withdrawn before administration of any study treatment. Participant disposition is shown in Figure S1. The rate of withdrawals was 4.8% (n = 10) for IDegLira and 1.9% (n = 4) for IGlar U100, with no obvious clustering of reason for withdrawal.

Baseline characteristics were similar for the two treatment arms (Table 1). All SGLT2 inhibitors marketed at study initialization were allowed in this study, the distribution at baseline being 44.5%, 34.8% and 20.5% for dapagliflozin, empagliflozin and canagliflozin, respectively.

3.2 | Primary endpoint

The mean HbA1c reductions from baseline to end of trial were 21 mmol/mol (1.9%-points) with IDegLira and 18 mmol/mol (1.7%-points) with IGlar U100 (Figure 1A). Non-inferiority of IDegLira versus IGlar U100 was confirmed ($P < 0.0001$). Superiority for IDegLira versus IGlar U100 for change in HbA1c was also confirmed with an estimated treatment difference (ETD) of −3.90 mmol/mol (95% confidence interval [CI] −5.45; −2.35; $P < 0.0001$); −0.36%-points (95% CI −0.50, −0.21; $P < 0.0001$ [Figure 1A]). A *post hoc* analysis, performed to assess whether the change in HbA1c from baseline differed between participants taking and not taking DPP-4 inhibitors at baseline found no statistically significant difference (test for treatment by subgroup interaction, $P = 0.7030$).

TABLE 1 Baseline characteristics (full analysis set)

Characteristic	IDegLira	IGlar U100
Full analysis set, n	210	210
Male, n (%)	121 (57.6)	126 (60.0)
Race, %		
White	83.3	81.4
Black	1.4	1.0
Asian	14.8	16.7
Other	0.5	1.0
Age, years	56.1 (10.4)	57.2 (10.2)
Weight, kg	89.3 (17.6)	87.2 (17.2)
BMI, kg/m^2	31.5 (4.8)	30.9 (4.8)
Duration of diabetes, years	9.8 (6.2)	9.3 (6.3)
HbA1c, mmol/mol	66.1 (10.2)	67.9 (11.8)
HbA1c, %	8.2 (0.9)	8.4 (1.1)
Fasting plasma glucose, mmol/L	9.5 (2.7)	9.6 (2.4)
Fasting plasma glucose, mg/dL	171.3 (48.4)	172.5 (43.3)
OAD at screening, n (%)		
SGLT2 inhibitor ± pioglitazone	4 (1.9)	7 (3.3)
SGLT2 inhibitor + metformin ± pioglitazone	141 (67.1)	132 (62.9)
SGLT2 inhibitor + DPP-4 inhibitor ± pioglitazone	1 (0.5)	7 (3.3)
SGLT2 inhibitor + metformin+ DPP-4 inhibitor ± pioglitazone	64 (30.5)	64 (30.5)

Abbreviations: BMI, body mass index; DPP-4, dipeptidyl peptidase-4; HbA1c, glycated haemoglobin; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; n, number of patients; OAD, oral antidiabetic drug; SGLT2, sodium-glucose co-transporter-2.
Data are mean (SD) unless otherwise stated. Baseline refers to week 0. The duration of diabetes is calculated as the time from date of diagnosis to the randomization date. DPP-4 inhibitor therapy was discontinued at randomization.

3.3 | Confirmatory secondary endpoints

After 26 weeks, there was no change from baseline in mean body weight for IDegLira; conversely, there was a mean increase of 2.0 kg for IGlar U100 (Figure 1B), confirming superiority for IDegLira (ETD −1.92 kg [95% CI −2.64, −1.19]; $P < 0.0001$).

The percentage of participants experiencing hypoglycaemia was 12.9% for IDegLira (0.37 episodes/participant-years of exposure [PYE]) and 19.5% for IGlar U100 (0.90 episodes/PYE). These findings confirmed superiority of IDegLira over IGlar U100 with an estimated rate ratio of 0.42 (95% CI 0.23, 0.75; $P = 0.0035$), corresponding to a 58% lower rate of hypoglycaemic episodes. The cumulative plot of hypoglycaemic episodes (Figure 1C) shows early separation of the two treatment arms that continued to diverge to the end of the trial. The low number of nocturnal hypoglycaemic episodes (six with IDegLira, 13 with IGlar U100) prevented statistical analysis of differences between the groups.

For both treatments, the mean total daily insulin dose gradually increased over the first 12 weeks of the study before stabilizing for IDegLira and continuing to increase, by ~1 U/week on average from week 12 to end of trial, for IGlar U100 (Figure 1D). The mean (SD) total daily insulin dose at end of study was 36.2 (13.4) U for IDegLira and 53.5 (26.1) U for IGlar U100, an ETD of −15.37 U (95% CI −19.60, −11.13; $P < 0.0001$), confirming superiority of IDegLira. By week 26, ~30% of participants were on the maximum permitted IDegLira dose, 83% of these participants reached the target of HbA1c <53 mmol/mol (<7%).

3.4 | Supportive secondary endpoints

A more rapid decline in FPG level was seen with IDegLira versus IGlar U100 (Figure 1E), with mean (SD) decreases from baseline after 26 weeks treatment of 3.59 (2.91) mmol/L and 3.39 (2.52) mmol/L, respectively. The ETD was −0.33 mmol/L (95% CI −0.64, −0.01; $P = 0.0400$) in favour of IDegLira. At baseline, nine-point SMBG values were similar for IDegLira and IGlar U100 at all time points. Both treatments were titrated according to the same algorithm (Table S2), with a target pre-breakfast SMBG of between 4.0 and 5.0 mmol/L, and at end of trial the pre-breakfast SMBG was similar, at 5.40 mmol/L for IDegLira versus 5.39 mmol/L for IGlar U100. Compared with the baseline profiles, both treatments displayed lower SMBG profiles at all time points at week 26 (Figure 1F); at all meal times postprandial glucose levels were significantly lower for IDegLira than for IGlar U100. At week 26, the prandial increments at every meal were statistically significantly lower with IDegLira versus IGlar U100 (Table 2). In line with the results for change in HbA1c, a *post hoc* analysis on change in FPG from baseline found there was no statistically significant difference between participants taking and not taking DPP-4 inhibitors at baseline (test for treatment by subgroup interaction, $P = 0.9939$).

A higher percentage of participants in the IDegLira treatment arm, versus IGlar U100, achieved the targets of HbA1c <53 mmol/mol (<7%) and HbA1c ≤48 mmol/mol (≤6.5%) (Figure 2). The triple composite endpoint of HbA1c <53 mmol/mol (<7%) without weight gain and without hypoglycaemia (Figure 2A) was achieved by a higher percentage of patients with IDegLira (42%) versus IGlar U100 (17%).

The change from baseline in systolic blood pressure was −3.0 mmHg in participants receiving IDegLira versus +0.6 mmHg in participants receiving IGlar U100 (ETD −2.87 mmHg [95% CI −5.01, −0.74]; $P = 0.0084$). There was no significant difference between IDegLira and IGlar U100 for the change in diastolic blood pressure. Pulse rate increased from baseline to end of trial for IDegLira and decreased for IGlar U100 (ETD +2.58 bpm [95% CI 1.12, 4.05]; $P = 0.0006$).

There were no statistically significant differences between treatments in any of the assessments of fasting lipid levels (Table S3).

Results for the TRIM-D PRO questionnaire demonstrated significantly greater improvements for IDegLira, versus IGlar U100, for total TRIM-D score ($P = 0.0052$) and the "treatment burden" ($P = 0.0414$) and "diabetes management" ($P < 0.0001$) domains. The greatest improvement for IDegLira versus IGlar U100 was observed in the diabetes management domain (change in score from baseline of 17.4 and 9.3, respectively).

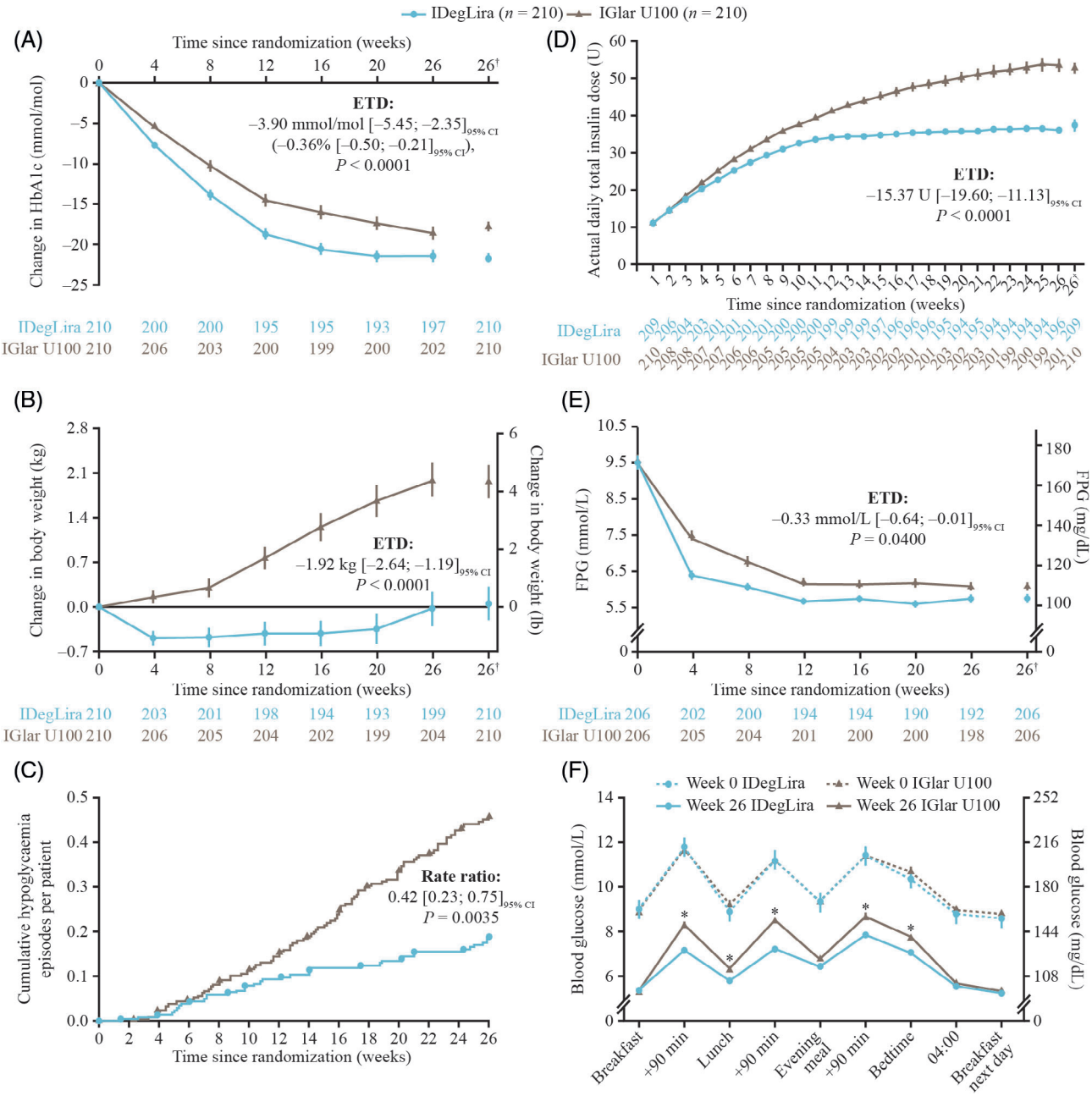

FIGURE 1 Results for **(A)**, change in glycated haemoglobin (HbA1c) over time, **(B)**, change in body weight, **(C)**, severe or blood glucose-confirmed hypoglycaemia, **(D)**, daily total insulin dose, **(E)**, FPG over time and **(F)**, nine-point self-measured blood glucose (SMBG) profile. (A) Mean observed values with error bars (SEM) based on full analysis set, including data obtained after premature discontinuation. *P* value is from the superiority test. (B) Mean observed values with error bars (SEM) based on full analysis set, including data obtained after premature treatment discontinuation. (C) Mean cumulative frequency based on safety analysis set. Severe or blood glucose-confirmed symptomatic: 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 (<56 mg/dL) with symptoms consistent with hypoglycaemia. (D–E) Mean observed values with error bars (SEM) based on full analysis set, including data obtained after premature treatment discontinuation. (F) Nine-point SMBG profile at baseline and week 26. *Statistically significant difference between end of trial means in favour of IDegLira versus IGlar U100. Mean observed values with error bars (standard error of the mean) based on full analysis set. 26†: estimated mean values and the corresponding error bars at week 26 with missing data derived using unconditional reference based multiple imputation. The response and change from baseline in response after 26 weeks for glycated haemoglobin (HbA1c) and body weight are assessed using an analysis of covariance (ANCOVA) model with treatment, pre-trial oral antidiabetic drug (OAD) and region as factors and corresponding baseline value as covariate. Data obtained after premature treatment discontinuation are included in the analysis. Number of treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemic episodes are analysed using a negative binomial regression model with a log link and the logarithm of the exposure time as offset. The model includes treatment and pre-trial OAD as fixed factors. Missing data are imputed using multiple imputation (conditioning on expected event rate before premature treatment discontinuation or withdrawal from trial as if treated with IGlar U100). The actual daily total insulin dose after 26 weeks is analysed using an ANCOVA model with treatment, pre-trial OAD and region as factors and baseline HbA1c as covariate. Data obtained after premature treatment discontinuation are included in the analysis. Missing data are imputed using unconditional reference based on multiple imputation. CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; N, number of patients

TABLE 2 Mean nine-point self-measured blood glucose and prandial increments at baseline and after 26 weeks

	Baseline		Week 26			
	Mean (SD)		Mean (SD)			
	IDegLira	IGlar U100	IDegLira	IGlar U100	ETD (95% CI)	*P*-value
Mean of nine-point SMBG						
n	204	207	180	188		
mmol/L	9.98 (2.17)	10.06 (2.04)	6.48 (1.05)	7.08 (1.20)	−0.46 (−0.68, −0.25)	< 0.0001
mg/dL	179.92 (39.12)	181.22 (36.84)	116.82 (18.98)	127.58 (21.67)	−8.33 (−12.20, −4.46)	
Prandial increments						
All meals						
n	210	207	182	188		
mmol/L	2.38 (1.73)	2.28 (1.88)	1.53 (1.32)	2.35 (1.60)	−0.70 (−0.99, −0.40)	< 0.0001
mg/dL	42.96 (31.11)	41.09 (33.89)	27.58 (23.75)	42.31 (28.87)	−12.58 (−17.87, −7.30)	
Breakfast						
n	209	207	182	187		
mmol/L	2.78 (2.68)	2.78 (2.62)	1.80 (1.81)	2.97 (2.21)	−0.97 (−1.39, −0.55)	< 0.0001
mg/dL	50.08 (48.32)	50.04 (47.22)	32.47 (32.66)	53.43 (39.79)	−17.54 (−25.13, −9.94)	
Lunch						
n	208	207	179	186		
mmol/L	2.32 (2.67)	2.02 (2.95)	1.39 (1.98)	2.15 (2.47)	−0.66 (−1.13, −0.20)	0.0055
mg/dL	41.81 (48.10)	36.39 (53.18)	24.97 (35.69)	38.76 (44.60)	−11.97 (−20.41, −3.52)	
Evening meal						
n	205	206	180	184		
mmol/L	2.06 (2.70)	2.04 (2.87)	1.40 (1.94)	1.90 (2.27)	−0.46 (−0.90, −0.02)	0.0421
mg/dL	37.20 (48.72)	36.79 (51.65)	25.27 (34.98)	34.22 (40.92)	−8.24 (−16.19, −0.29)	

Abbreviations: ANCOVA; analysis of covariance; CI, confidence interval; ETD, estimated treatment difference; IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL; *n*, number of patients; OAD, oral antidiabetic drug; SMBG, self-measured blood glucose.
Data are mean (SD). SMBG assessed with glucose meter as plasma equivalent values of capillary whole blood glucose, the mean profile value is defined as the area under the profile divided by measurement time and is calculated using the trapezoidal method. The response and change from baseline in response are analysed using an ANCOVA model with treatment, pre-trial OAD and region as factors and corresponding baseline value as covariate. Missing data were imputed by unconditional reference based multiple imputation.

3.5 | Safety outcomes

The overall TEAE rates were numerically higher with IDegLira than IGlar U100 (Table 3), mainly as a result of higher rates with IDegLira for increased lipase (Table S4) and nausea (the percentage of participants experiencing nausea with IDegLira was never above 3% at any time point [data not shown]). The majority of AEs were non-serious, mild in severity, and unlikely to be related to trial products as judged by the investigator. Four participants in the IDegLira treatment arm and one participant in the IGlar U100 treatment arm experienced an AE that led to permanent discontinuation of trial product. There was no clustering of events in any of the system organ classes and there were no events of diabetic ketoacidosis in either treatment arm. With the exception of headache, the number of TEAEs associated with vascular or nervous system disorders were very low in both treatment arms, including those associated with low blood pressure: hypotension occurred in three participants (one with IDegLira, two with IGlar U100), syncope in two participants (one in each treatment arm), and dizziness in six participants (two with IDegLira, four with IGlar U100). There were five adjudicated confirmed cardiovascular events in four participants; two in the IDegLira group (myocardial infarction and haemorrhagic stroke) and three in the IGlar U100 group (myocardial infarction and cardiovaacular death [in the same participant] and chronic cardiac failure). The myocardial infarction and haemorrhagic stroke seen with IDegLira and the cardiovascular death with IGlar U100 were confirmed as MACE. There were three adjudicated confirmed treatment-emergent neoplasms; one large intestine polyp (IDegLira), one colon adenoma (IGlar U100) and one malignant gastrointestinal stromal tumour (IGlar U100). There were no adjudicated confirmed pancreatitis or thyroid events.

4 | DISCUSSION

Previous trials have established the efficacy and safety of the combination of GLP-1RAs and SGLT2 inhibitors;[10,11] we have demonstrated the same in participants with T2D uncontrolled on SGLT2 inhibitors, albeit with a fixed-ratio combination of GLP-1RA and basal insulin, versus basal insulin, as an add-on to SGLT2 inhibitor ± OADs.

Consistent with previous reports from the DUAL programme,[3,4,6–9] the results profiled in DUAL IX illustrate the efficacy of IDegLira with regard to HbA1c, body weight and hypoglycaemia, confirming that the effects of IDegLira are preserved in people already on a SGLT2 inhibitor treatment regimen. IDegLira was superior to IGlar U100 in four main prespecified endpoints: HbA1c; body weight; rate of hypoglycaemia; and total daily insulin dose. Notably, this was achieved in a population who were inadequately controlled on up to four OADs at baseline and had a mean duration of diabetes of >9 years. In clinical practice, therapy intensification for this group of patients would typically be basal insulin initiation;[18–20] however, our results indicate that addition of IDegLira is a superior treatment option. Furthermore, a previous cost-effectiveness analysis identified that treatment with IDegLira versus continued uptitration of IGlar U100 demonstrates a lower cost per patient achieving treatment targets.[21] Weight gain and hypoglycaemia are well-known barriers for insulin initiation for both patients and healthcare providers,[22] therefore IDegLira should be considered at the point of insulin initiation, as

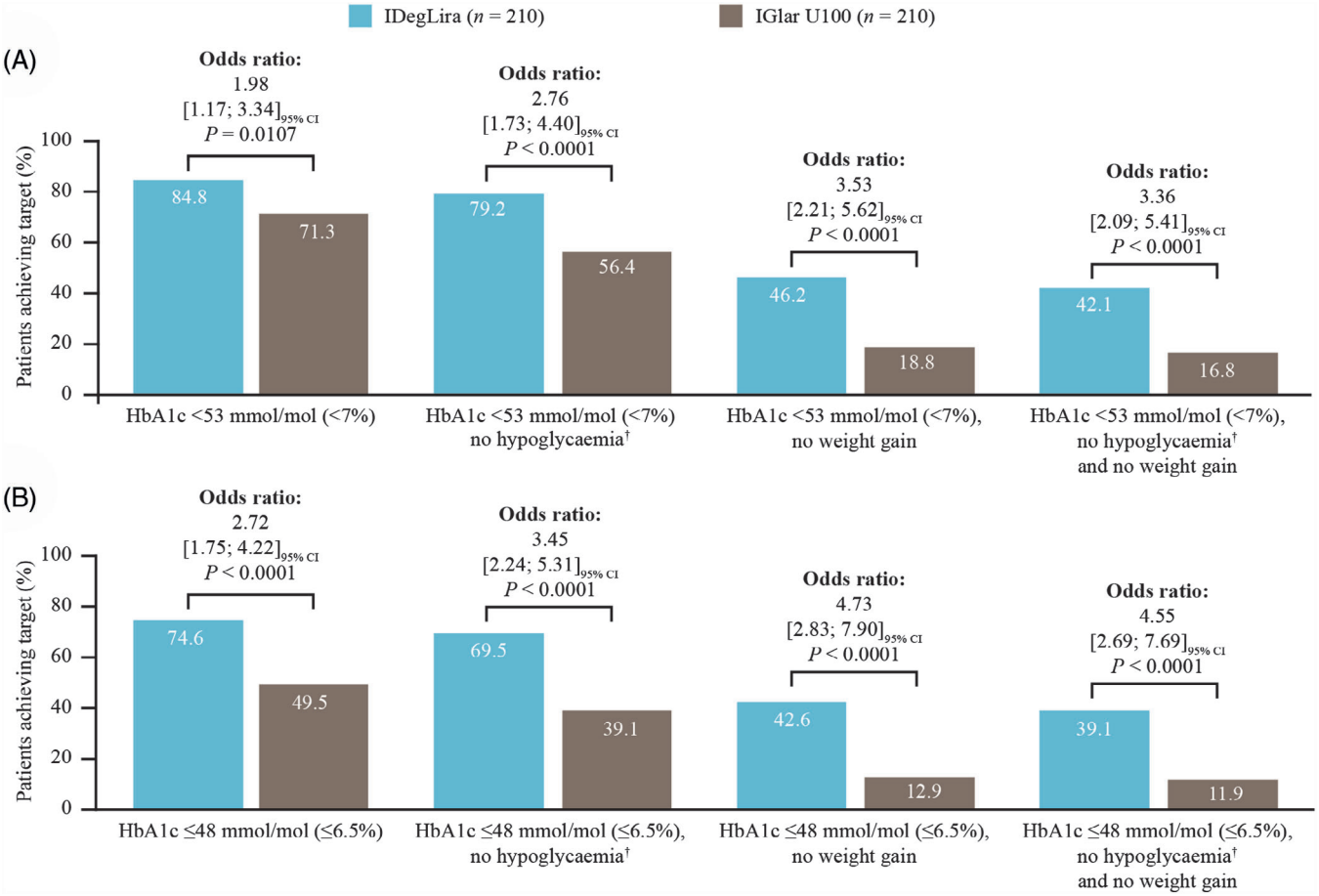

FIGURE 2 Patients achieving composite outcomes with **(A),** glycated haemoglobin (HbA1c) <53 mmol/mol (<7%) and **(B),** HbA1c ≤48 mmol/mol (≤6.5%) at week 26. †Treatment-emergent severe or blood glucose-confirmed symptomatic hypoglycaemia episodes in the last 12 weeks of treatment. The response after 26 weeks was analysed using a logistic regression model with treatment, pre-trial oral antidiabetic drug (OAD) and region as factors and HbA1c baseline value as covariate. Data obtained after premature treatment discontinuation were included in the analysis. Missing data were imputed using unconditional reference based multiple imputation. *P* value: two-sided *P* value for test of no difference. No correction for multiplicity testing. IDegLira, insulin degludec/liraglutide; IGlar U100, insulin glargine 100 units/mL

patients will have the potential benefits of superior glycaemic control, with lower weight gain and a lower risk of hypoglycaemia, as well as lower perceived treatment burden and easier diabetes management, which could improve treatment compliance and satisfaction.[22,23] The results of DUAL IX show that the odds of achieving HbA1c <53 mmol/mol (<7% were significantly higher with IDegLira versus IGlar U100. Specifically of interest, a higher percentage of participants achieved the clinically relevant composite endpoint of HbA1c <53 mmol/mol (<7%) without weight gain and hypoglycaemia (42% vs 17% for IDegLira and IGlar U100, respectively), highlighting the additional benefits beyond glycaemic control associated with IDegLira. The superior HbA1c reductions with IDegLira are probably attributable to lower prandial excursions in mean nine-point SMBG at week 26. This benefit, together with the low risk of weight gain and hypoglycaemia, can be attributed to the liraglutide component of IDegLira.

The greater improvements in PROs with initiating IDegLira versus IGlar U100 are consistent with the clinical outcomes observed in DUAL IX. Superiority of IDegLira versus IGlar U100 regarding HbA1c reductions, hypoglycaemia rates and change in body weight is likely to contribute to the substantial and significant improvement observed in the diabetes management domain of TRIM-D, which consists of the following items: (i) help you control your diabetes; (ii) help you avoid hyperglycaemia; (iii) help you avoid hypoglycaemia; (iv) help you manage your weight; and (v) help prevent you feeling tired/lack of energy. The reasons for a greater improvement in the treatment burden domain of TRIM-D with IDegLira versus IGlar U100 are not clear, as both treatment arms require one injection daily, but they may relate to other differences in product convenience or willingness to deal with the treatment burden, considering the perceived positive clinical benefits of IDegLira.

Limitations of the present trial include the open-label design, which may have introduced a bias with regard to reporting of hypoglycaemia and AEs, such as nausea, which is known to be a common side effect of GLP-1RA therapy. The trial's open-label design may also introduce a PRO bias; participants assigned to IDegLira may acknowledge they are receiving a newer drug with a favourable clinical outcome and PRO profile; however, IDegLira and IGlar U100 could not be compared in a blinded trial without limiting the maximum IGlar U100 dose. Although using IGlar U100/lixisenatide as a comparator would have enabled a head-to-head comparison of IDegLira with another fixed-ratio combination of a basal insulin and a GLP-1RA, the comparison would not have addressed whether a fixed-ratio

TABLE 3 Treatment-emergent adverse events

	IDegLira (*n* = 209)				IGlar U100 (*n* = 210)			
Event	***n***	**%**	**E**	**R**	***n***	**%**	**E**	**R**
AEs	129	61.7	450	436.0	123	58.6	386	364.7
Serious	6	2.9	8	7.75	7	3.3	9	8.50
Cardiac disorders	1	0.5	1	0.97	2	1.0	2	1.89
Myocardial infarction	1	0.5	1	0.97	0	–	–	–
Cardiac failure chronic	0	–	–	–	1	0.5	1	0.94
Coronary artery disease	0	–	–	–	1	0.5	1	0.94
Gastrointestinal disorders	0	–	–	–	1	0.5	1	0.94
Abdominal pain	0	–	–	–	1	0.5	1	0.94
Infections and infestations	2	1.0	2	1.94	3	1.4	3	2.83
Pneumonia	2	1.0	2	1.94	1	0.5	1	0.94
Infected skin ulcer	0	–	–	–	1	0.5	1	0.94
Urinary tract infection	0	–	–	–	1	0.5	1	0.94
Investigations	2	1.0	2	1.94	0	–	–	–
Blood potassium increased	1	0.5	1	0.97	0	–	–	–
CV evaluation	1	0.5	1	0.97	0	–	–	–
Neoplasms benign, malignant and unspecified (including cysts and polyps)	0	–	–	–	1	0.5	1	0.94
Gastrointestinal stromal tumours	0	–	–	–	1	0.5	1	0.94
Nervous system disorders	1	0.5	1	0.97	0	–	–	–
Haemorrhagic stroke	1	0.5	1	0.97	0	–	–	–
Product issues	1	0.5	2	1.94	0	–	–	–
Device failure	1	0.5	2	1.94	0	–	–	–
Renal and urinary disorders	0	–	–	–	2	1.0	2	1.89
Acute kidney injury	0	–	–	–	1	0.5	1	0.94
Chronic kidney disease	0	–	–	–	1	0.5	1	0.94
Fatal	0	–	–	–	1[a]	0.5	1	0.9
Severe	5	2.4	6	5.8	5	2.4	7	6.6
Cardiac disorders	0	–	–	–	1	0.5	1	0.94
Gastrointestinal disorders	0	–	–	–	1	0.5	1	0.94
Infections and infestations	2	1.0	2	1.94	3	1.4	3	2.83
Investigations	1	0.5	1	0.97	0	–	–	–
Metabolism and nutrition disorders	1	0.5	1	0.97	0	–	–	–
Musculoskeletal and connective tissue disorders	1	0.5	1	0.97	0	–	–	–
Nervous system disorders	1	0.5	1	0.97	0	–	–	–
Renal and urinary disorders	0	–	–	–	2	1.0	2	1.89
Probably related to treatment	28	13.4	77	74.6	6	2.9	22	20.8
EAC confirmed CV AE	2	1.0	2	1.9	2	1.0	3	2.8
EAC confirmed neoplasm AE	1	0.5	1	1.0	2	1.0	2	1.9

Abbreviations: AE, adverse event; CV, cardiovascular; E, number of adverse events; EAC, Event Adjudication Committee; MACE, major adverse cardiovascular events, n, number of patients with one or more event; PYE, participant-years of exposure (1 PYE = 365.25 days); R, rate (number of adverse events divided by patient-years of exposure multiplied by 100).

[a]The event was a major CV event (CV death), following a myocardial infarction that occurred >7 days but <30 days after the last day of randomized treatment, therefore the myocardial infarction was not regarded as a treatment-emergent AE but the subsequent CV death met criteria for treatment-emergent MACE. Treatment-emergent: onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment. %, percentage of participants with one or more events.

combination of basal insulin/GLP-1RA is a better therapeutic option for first injectable therapy than basal insulin alone. An additional limitation is DPP-4 inhibitor discontinuation at randomization, required to compare the intervention effect in an equally treated population; this contrasts with normal clinical practice, in which DPP-4 inhibitors would not be discontinued when initiating basal insulin. *Post hoc* subgroup analyses between participants taking and not taking DPP-4 inhibitors at baseline found no differences in the glycaemic variables.

In conclusion, in people who were inadequately controlled on SGLT2 inhibitor and up to three other OADs, initiation of IDegLira was superior to IGlar U100 in terms of glycaemic control, body weight, hypoglycaemia and total daily insulin dose. There were no

apparent or unexpected safety and tolerability issues identified for IDegLira.

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AUTHOR CONTRIBUTIONS

A.P.-T. has had full access to all the data in the study, was involved with trial conduct and data collection, analysis of results, writing of the manuscript and had final responsibility for the decision to submit for publication. L.K.B. was involved with trial conduct and data collection, analysis of results and writing of the manuscript. R.B. contributed to analysis and writing of the manuscript. R.S. contributed to data collection and writing of the manuscript. S.H. contributed to the trial design and conduct, data collection, analysis and writing of the manuscript. C.M.P. contributed to trial conduct, data collection and writing of the manuscript. K.B. contributed to design, analysis and writing the manuscript. S.E. contributed to analysis and writing manuscript. N.H. contributed to conduct/data collection, analysis and writing the manuscript.

DATA-SHARING STATEMENT

Individual participant data will be shared in datasets in a de-identified/anonymized format. Datasets from Novo Nordisk-sponsored clinical research completed after 2001 for product indications approved in both the European Union (EU) and USA will be shared. The study protocol and redacted clinical study report will be available according to Novo Nordisk data-sharing commitments. The data will be available permanently after research completion and approval of product use in both the EU and USA with no end date. Data will be shared with bona fide researchers submitting a research proposal requesting access to data, for analyses approved by the Independent Review Board (IRB) according to the IRB charter (see novonordisk-trials.com). Request proposal forms and the access criteria can be found at novonordisk-trials.com. The data will be made available on a specialized SAS data platform.

CONFLICT OF INTEREST

A.P.-T. reports advisor and educational grants with no direct or indirect reimbursement to advisor from Sanofi; advisor and research supplies with no direct or indirect reimbursement to advisor from Dexcom, advisor and educational grants with no direct or indirect reimbursement to advisor from Lilly, advisor and educational grants with no direct or indirect reimbursement to advisor from Novo Nordisk, and being a stockholder of Ionis, during the conduct of the study. L.K.B. reports personal fees from Novo Nordisk, personal fees from Sanofi and personal fees from Dexcom, outside the submitted work. R.B. reports personal fees from Novo Nordisk, grants from Novo Nordisk, grants from Sanofi, grants from AstraZeneca, grants from Lilly, grants from Lexicon Pharmaceuticals and grants from Bayer during the conduct of the study. C.M.P. reports no relevant conflicts of interest. R.S. reports personal fees from Novo Nordisk, personal fees from Sanofi, personal fees from Eli Lilly, personal fees from Boehringer Ingelheim and personal fees from AstraZeneca, outside the submitted work. N.H. is an employee of Novo Nordisk. S.E. is an employee of Novo Nordisk. K.B. reports employment by Novo Nordisk. S.H. reports financial relationships with Sanofi, Eli Lilly, Novo Nordisk, Janssen, Merck, AstraZeneca, Abbott, Boehringer Ingelheim, JDRF, Lawson, Medtronic, Amgen and Health Canada/First Nations and Inuit Health Branch.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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