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Superior HbA1c control with the fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with a maximum dose of 50 units of insulin degludec in Japanese individuals with type 2 diabetes in a phase 3, double-blind, randomized trial

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Abstract

Aims: To investigate the efficacy and safety of insulin degludec/liraglutide (IDegLira) compared with 50 U insulin degludec (degludec) or less in Japanese individuals with type 2 diabetes (T2D).

Materials and methods: In this 26-week, double-blind, multicentre, treat-to-target trial, Japanese individuals with T2D that was uncontrolled with basal or pre-mix insulin (20–50 units) were randomized (1:1) to receive IDegLira or degludec, both with metformin. The maximum dose was 50 dose steps (IDegLira) or 50 units (degludec). The primary endpoint was change from baseline in HbA1c with IDegLira vs degludec after 26 weeks of treatment.

Results: In total, 210 Japanese individuals were randomized to IDegLira or degludec and completion rates were 100% and 93%, respectively. IDegLira was superior to degludec with respect to change from baseline in HbA1c: estimated treatment difference (ETD) (95% confidence interval), −13.98 mmol/Mol (−16.41; −11.55); $P < 0.0001$. The change in mean HbA1c was from 70.6 by −21.3 mmol/Mol with IDegLira and from 70.1 by −7.1 mmol/Mol with degludec. Mean change in body weight was −0.7 kg with IDegLira and 0.7 kg with degludec: ETD (95% CI) −1.41 kg (−2.26; −0.56); $P = 0.0012$. Mean daily total insulin dose was significantly lower with IDegLira (37.6 U) as compared to that with degludec (41.2 U) at Week 26. Overall rates of severe or blood glucose-confirmed hypoglycaemia and adverse events were comparable between treatment groups.

Conclusions: IDegLira provided superior reductions in HbA1c compared with ≤50 U degludec, with weight loss and similar hypoglycaemia rates and no unexpected safety or tolerability issues. These results suggest that this treatment could be an attractive intensification option for Japanese subjects with T2D that was uncontrolled with basal or pre-mixed insulin.

KEYWORDS

basal insulin, hypoglycaemia, liraglutide, randomized trial, type 2 diabetes

1 | INTRODUCTION

The prevalence of diabetes in the Japanese adult population is projected to increase from 7.7% in 2017 to 8.3% in 2045,[1] with the majority of cases being type 2 diabetes (T2D).[2-4] This increase in prevalence is attributed, in part, to changes in lifestyle such as diet and exercise.[5]

Many patients with T2D will require insulin therapy because of the progressive nature of the disease.[6] Basal or pre-mix insulin, in combination with oral agents such as metformin, are established treatments for T2D in Japan.[7] However, many patients fail to achieve adequate glycaemic control and, therefore, may be at higher risk of developing long-term complications,[8] possibly as a result of clinical inertia.[9]

Barriers to optimal initiation and titration of insulin can include the increased risk of hypoglycaemia and weight gain, as well as the burden of the number of injections necessary to titrate and administer complex insulin regimens that is experienced by patients.[10] To help overcome some of these barriers, combination therapy with basal insulin and a glucagon-like peptide-1 receptor agonist (GLP-1RA), administered as separate injections, has been recommended by the Japanese Diabetes Society following successful outcomes from recent global trials.[7] Basal insulin and GLP-1RAs, together, lower fasting plasma glucose (FPG) levels and reduce post-prandial glucose excursions, while limiting the risk of hypoglycaemia.[11] These effects may be particularly important in the ageing Japanese population.[12]

Insulin degludec/liraglutide (IDegLira) is a fixed-ratio combination of insulin degludec (degludec) and the GLP-1RA liraglutide, administered as a once-daily single injection.[13,14] The safety and efficacy of IDegLira has been investigated in a number of patient populations in the global DUAL clinical trial programme, including the global DUAL II study which confirmed the superiority of IDegLira over degludec alone in terms of glycaemic control and established the contribution of the liraglutide component in IDegLira in non-Japanese patients.[15] These trials led to the European approval of IDegLira in 2014 and to US approval in 2016. The aim of this study was to compare the efficacy and safety of IDegLira with that of degludec (≤50 units) in Japanese patients with T2D who were inadequately controlled with a basal or pre-mixed insulin regimen.

2 | RESEARCH DESIGN AND METHODS

This was a 26-week, multicentre, randomized, parallel, two-arm, treat-to-target, double-blind trial (ClinicalTrials.gov NCT02911948) to investigate the efficacy and safety of IDegLira as compared to degludec, both in combination with metformin (Figure 1). Degludec was capped at the same maximum dose (50 U) across treatment groups to allow for assessment of the contribution of the liraglutide component of IDegLira. The trial comprised a 2-week screening period and a 26-week treatment period. Participants were Japanese adults with a body mass index (BMI) of at least 23 kg/m^2 and HbA1c levels between 58 and 97 mmol/Mol (7.5%–11.0%), who had been diagnosed with T2D at least 6 months prior to screening, and who had been undergoing stable therapy with basal or pre-mix/combination insulin (20–50 U) in combination with metformin for at least 60 days prior to screening. In addition to metformin, participants could also be receiving one of the following oral anti-diabetic drugs (OADs): sulphonylureas (SU), glinides, α-glucosidase inhibitors (α-GI), sodium-glucose cotransporter-2 inhibitors (SGLT2i) or thiazolidinediones (TZD).

The study protocol was approved by independent ethics committees or institutional review boards at all participating institutions. The study was performed in accordance with the Declaration of Helsinki and ICH Good Clinical Practice guidelines. Written consent was obtained from all participants before enrolment.

2.1 | Treatment

IDegLira and degludec were administered once daily at approximately the same time each day in a double-blind manner. The recommended starting doses were 10 dose steps of IDegLira (10 U degludec/0.36 mg liraglutide) or 10 U of degludec, with the option of a higher starting dose, up to 16 dose steps of IDegLira or 16 U of degludec, at the investigator's discretion depending on the condition of the patient. Both treatments were titrated twice weekly based on the mean of three consecutive pre-breakfast self-measured blood glucose (SMBG) values (Table S1). SMBG was assessed using a glucose meter calibrated to plasma equivalent values. The maximum dose was 50 dose steps (50 U degludec/1.8 mg liraglutide). All anti-diabetic treatments, with the exception of metformin, were discontinued at randomization. Metformin was continued at the pre-trial dose; however, in the case of safety concerns and at the investigator's discretion, the metformin dose could be reduced.

2.2 | Stratification and randomization

Participants were randomized 1:1, via a central interactive voice/web system, to receive either IDegLira or degludec, in combination with metformin. Particiants were stratified into four groups based on pre-trial anti-diabetic treatment regimen: metformin plus basal insulin; metformin plus basal insulin and one other OAD; metformin plus pre-mix/combination insulin; or metformin plus pre-mix/combination insulin and one other OAD.

2.3 | Endpoints

The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment to assess superiority of IDegLira vs degludec. Supportive secondary efficacy endpoints included: change from baseline after 26 weeks in body weight, laboratory-measured FPG, daily insulin dose, achievement of HbA1c less than 53 mmol/Mol (<7.0%) and up to 48 mmol/Mol (≤6.5%), achievement of HbA1c targets without hypoglycaemia or weight gain, SMBG nine-point profile, systolic and diastolic blood pressure, fasting lipid profiles and patient-reported outcomes (PROs). PROs were assessed using the Diabetes Therapy-Related Quality Of Life (DTR-QOL) and EuroQOL-5D-5 L (EQ-5D-5 L) questionnaires. Safety variables included number of treatment-emergent
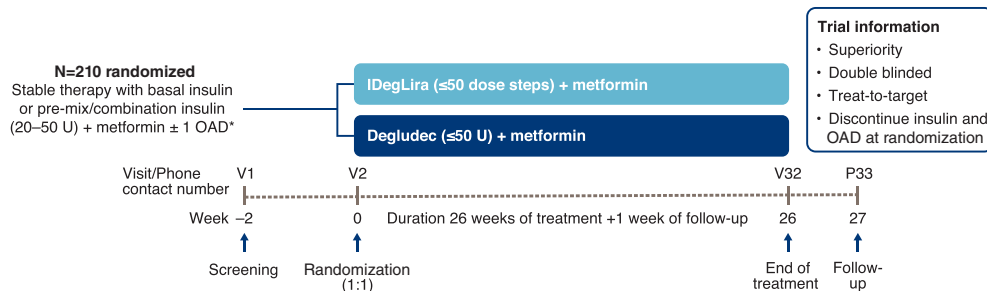
FIGURE 1 Trial design. *OAD, one of the following oral anti-diabetic drugs: sulphonylureas, glinides, α-glucosidase inhibitors, sodium-glucose co-transporter-2 inhibitors or thiazolidinediones. Maximum doses were 50 dose steps for IDegLira and 50 U for degludec. Metformin was continued at pre-trial doses. Abbreviations: IDegLira, insulin degludec/liraglutide; OAD, oral anti-diabetic drug; P, phone contact; V, site visit

adverse events (TEAEs), severe or blood glucose (BG)-confirmed (<3.1 mmol/L [<56 mg/dL]) hypoglycaemic events and pulse after 26 weeks of treatment.

2.4 | Statistical analysis

The primary objective was to confirm the superiority of IDegLira as compared to degludec in terms of change from baseline in HbA1c after 26 weeks of treatment. The sample size was determined using a t-statistic with α = 0.05 (two-sided test), a mean difference between treatments in change from baseline in HbA1c of −0.45% for IDegLira vs degludec for those who completed the study, a retained effect of 0.2% for withdrawals (assumed to be 15%) and a standard deviation of 1.0%. The above assumptions are based on experience from the global DUAL phase 3 development programme for IDegLira. From these assumptions, and based on 1:1 randomization, the sample size was determined to be 105 participants per treatment arm, a randomised population of at least 210 participants, which ensured a nominal power of at least 84.5%.

Continuous efficacy endpoints, including the primary endpoint, were analysed separately using an analysis of covariance (ANCOVA) model that included treatment and pre-trial anti-diabetic treatment as fixed effects and the baseline value of the parameter as a covariate. In the primary analysis of the primary endpoint, superiority was confirmed if the 95% CI for the treatment difference was entirely below 0.0%. Insulin dose was analysed using an ANCOVA model including the same fixed effects/covariate and baseline HbA1c as an additional covariate. Last observation carried forward (LOCF) was used to impute missing values for endpoints after 26 weeks of treatment. Responder endpoints were analysed separately using a logistic regression model with treatment and pre-trial anti-diabetic treatment as fixed effects and the associated baseline values (HbA1c and body weight, if relevant) as covariate(s). Number of treatment-emergent hypoglycaemic episodes was analysed using a negative binominal regression model with a log-link function, with treatment and pre-trial anti-diabetic treatment as fixed effects, and the logarithm of the treatment-emergent time period, on or after the first day of treatment and no later than 7 days after the last day of treatment, as offset. A linear mixed-effect model was fitted to the nine-point SMBG profile

data. The model included treatment, pre-trial anti-diabetic treatment, time, and treatment-time and pre-trial anti-diabetic treatment-time interactions as fixed factors and subject as random effect. For the fasting lipid profile, the endpoint and baseline covariates were log-transformed before analysis, and the estimated treatment difference on a logarithmic scale was back-transformed and shown as the estimated treatment ratio. All statistical analyses of efficacy and safety endpoints were carried out using the full analysis set (FAS), defined as all subjects randomized to IDegLira or degludec. Robustness of conclusions from the primary endpoint was assessed in sensitivity analyses using a mixed model for repeated measurements (MMRM) and a pattern mixture model approach, mimicking an intention-to-treat scenario.

3 | RESULTS

3.1 | Participants

Of 267 patients screened, 210 were randomized (105 to each treatment group). No participants in the IDegLira group withdrew from treatment, compared with seven participants (6.7%) in the degludec group who withdrew. Subject disposition and reasons for withdrawal are given in Figure S1. Baseline characteristics were similar between treatment groups and were representative of a T2D population that was inadequately controlled with their current treatment; treatment regimens at screening were comparable (Table 1 and Table S2).

3.2 | Primary endpoint

The primary endpoint was change from baseline in HbA1c after 26 weeks of treatment. After 26 weeks, mean HbA1c changed from 70.6 mmol/Mol (8.61%) at baseline by −21.3 mmol/Mol (−1.95%) with IDegLira, and from 70.1 mmol/Mol (8.56%) by −7.1 mmol/Mol (−0.65%) with degludec. The estimated treatment difference (ETD) was −13.98 mmol/Mol [−16.41; −11.55]$_{95\% CI}$, −1.28%-points [−1.50; −1.06]$_{95\% CI}$; $P < 0.0001$, confirming superiority of IDegLira vs degludec (Figure 2(A)). The conclusion from the primary analysis was supported by sensitivity analyses.

3.3 | Secondary endpoints

3.3.1 | Body weight

From baseline to end of trial, mean body weight decreased by −0.7 kg (from 73.9 kg to 73.2 kg) with IDegLira and increased by 0.7 kg (from 75.5 kg to 76.3 kg) with degludec, representing an ETD of −1.41 kg [−2.26; −0.56]$_{95\% CI}$, P = 0.0012 (Figure 2(B)).

3.3.2 | Fasting plasma glucose

Mean change from baseline in FPG after 26 weeks was −2.8 mmol/L (−50.6 mg/dL) in the IDegLira group and − 2.3 mmol/L (−41.3 mg/dL) in the degludec group (ETD after 26 weeks, −0.25 mmol/L [−0.81; 0.30]$_{95\%CI}$; −4.59 mg/dL [−14.62; 5.44]$_{95\%CI}$; P = 0.3678) (Figure 2(C)).

3.3.3 | Insulin dose

After 26 weeks, the mean daily total insulin dose was significantly lower with IDegLira than with degludec (37.6 U vs 41.2 U, respectively) with an ETD of −3.08 U [−6.08; −0.08]$_{95\%CI}$; P = 0.0444 (Figure 2(D)). At end of trial, 34 (32.4%) participants in the IDegLira group were receiving the maximum dose of 50 dose steps and 49 (46.7%) participants in the degludec group were receiving the maximum dose of 50 U.

3.3.4 | HbA1c responders

The odds of achieving HbA1c targets and composite endpoints at the end of the trial were significantly higher for participants who received IDegLira compared with those who received degludec (P < 0.0001 in all cases) (Figure 3). Of the participants receiving the maximum dose of IDegLira/degludec, 50%/18.4% achieved HbA1c less than 53 mmol/Mol (<7%), respectively.

3.3.5 | Nine-point SMBG profile

With the exception of the pre-breakfast period, SMBG values were significantly lower with IDegLira compared with degludec; P values ranged from less than 0.0001 to 0.024. After 26 weeks, mean nine-point SMBG decreased by 2.9 mmol/L (52.3 mg/dL) to 8.6 mmol/L (155.0 mg/dL) with IDegLira compared with −1.1 mmol/L (20.1 mg/dL) to 10.1 mmol/L (182.0 mg/dL) with degludec. The ETD was −1.61 mmol/L [−2.18; −1.05]$_{95\%CI}$, −29.04 mg/dL [−39.23; −18.85]$_{95\%CI}$ (P < 0.0001) (Figure S2). After 26 weeks, the mean prandial increment across all meals was smaller with IDegLira than with degludec (3.8 and 4.8 mmol/L [69.1 and 86.9 mg/dL], respectively) with an ETD of −1.08 mmol/L [−1.65; −0.50], −19.39 mg/dL [−29.77; −9.02]$_{95\%CI}$ (P = 0.0003). The mean prandial glucose increment at baseline and at Week 26, and statistical analyses of change from baseline in prandial glucose increments, are presented in Table S3.

3.3.6 | Blood pressure

Change in systolic and diastolic blood pressure was similar in the IDegLira and degludec groups, with ETDs of −0.57 mmHg [−4.17; 3.04]$_{95\% CI}$; P = 0.7575 and 0.89 mmHg [−1.37; 3.14]$_{95\% CI}$; P = 0.4381, respectively (Table S4).

TABLE 1 Baseline characteristics of participants

	IDegLira	Degludec	Total
Full analysis set	105	105	210
Age (years)	56.6 (10.4)	55.5 (10.0)	56.0 (10.2)
Duration of diabetes (years)	14.33 (7.79)	13.77 (7.46)	14.05 (7.61)
Male (%)	66.7	60.0	63.3
Weight (kg)	73.9 (11.9)	75.5 (14.0)	74.7 (13.0)
BMI (kg/m^2)	27.3 (3.1)	28.1 (4.4)	27.7 (3.8)
FPG (mmol/L)	8.95 (2.61)	8.64 (2.52)	8.79 (2.56)
FPG (mg/dL)	161.31 (46.95)	155.62 (45.37)	158.47 (46.15)
HbA1c (mmol/Mol)	70.57 (9.67)	70.06 (8.70)	70.32 (9.18)
HbA1c (%)	8.61 (0.88)	8.56 (0.80)	8.58 (0.84)
Metformin dose at screening (mg)	1171 (567)	1200 (566)	1186 (565)
Diabetes regimen at screening, n (%)			
Metformin and basal insulin	46 (43.8)	46 (43.8)	92 (43.8)
Metformin, basal insulin and one other OAD	20 (19.0)	21 (20.0)	41 (19.5)
Metformin and pre-mix/combination insulin	26 (24.8)	25 (23.8)	51 (24.3)
Metformin, pre-mix/combination insulin and one other OAD	13 (12.4)	13 (12.4)	26 (12.4)

Data are given as mean (SD) unless otherwise stated.
Abbreviations: BMI, body mass index; degludec, insulin degludec; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide; OAD, oral anti-diabetic drug.
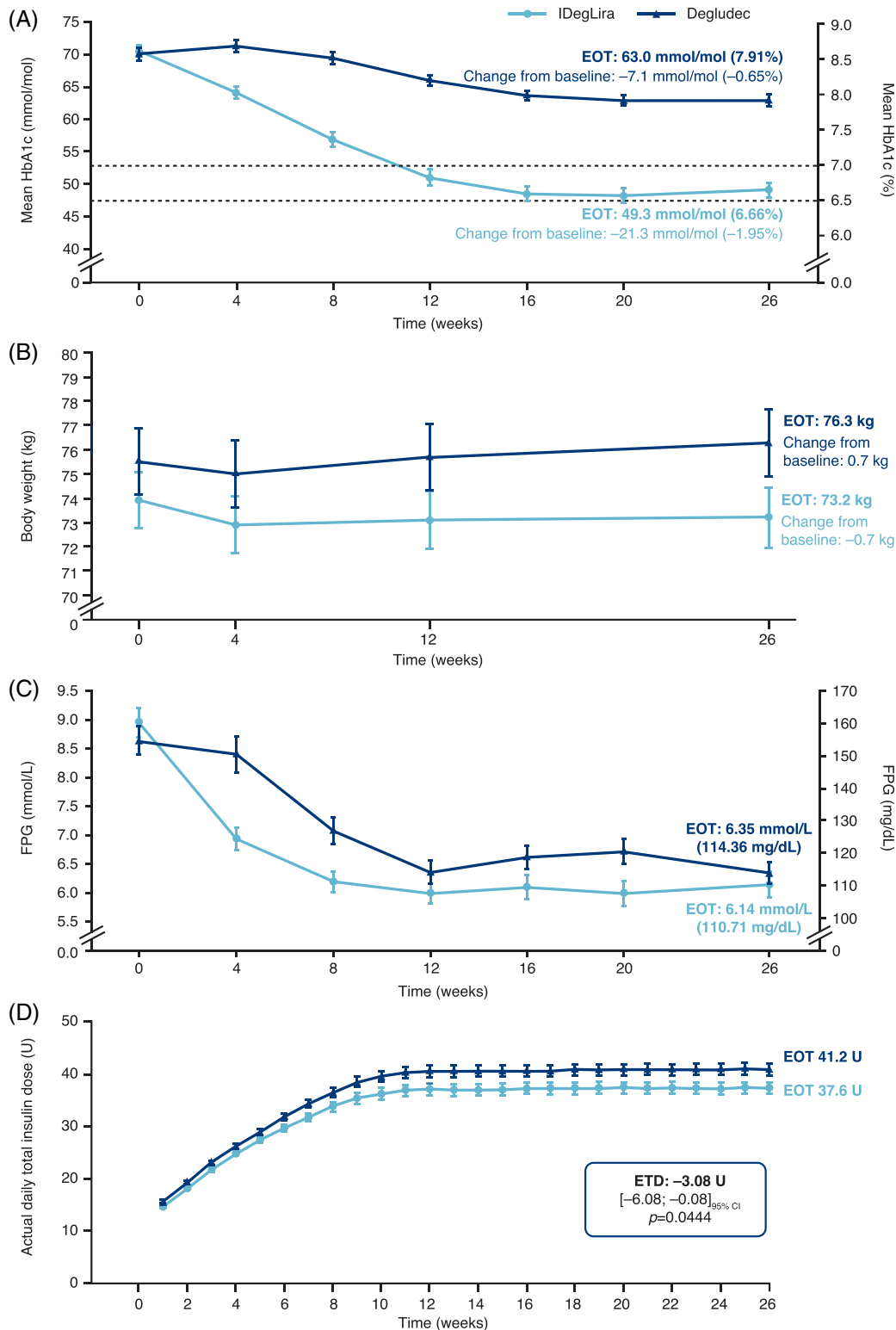
FIGURE 2 Mean change from baseline in HbA1c (A), body weight (B), fasting plasma glucose (C) and total daily insulin dose (D) over time. (A), (B) and (C): Full analysis set. (D): Safety analysis set. Missing values are imputed by last observation carried forward. Error bars are standard error of the mean. Abbreviations: EOT, end of trial; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide

3.3.7 | Fasting lipid profiles

After 26 weeks, a statistically significant treatment difference was seen in total cholesterol (favouring IDegLira), in low-density lipoprotein (favouring IDegLira) and in high-density lipoprotein (favouring degludec), while all other lipid endpoints were not statistically significant between treatment arms (Table S5).
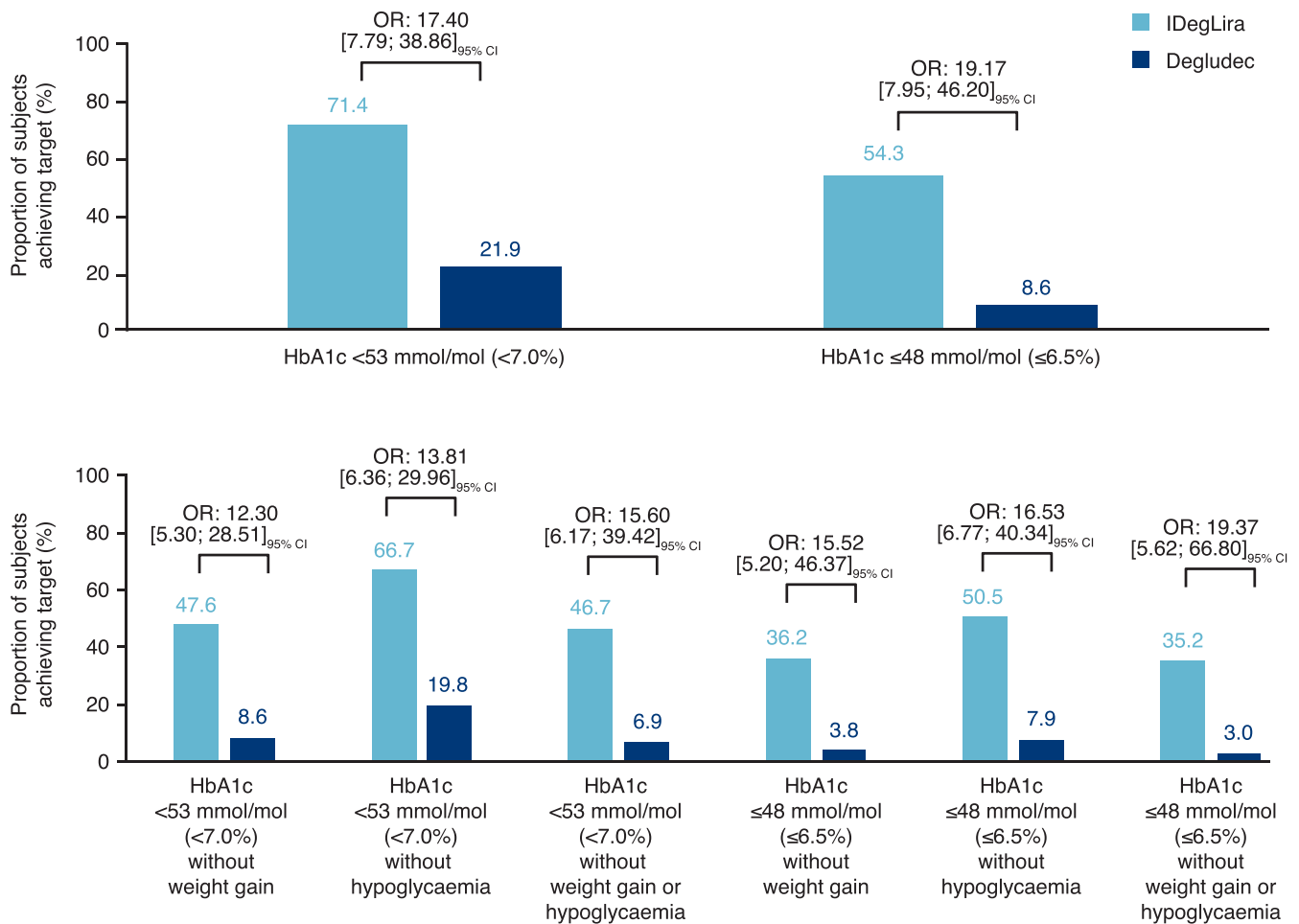
FIGURE 3 Participants achieving HbA1c outcomes of <53 mmol/Mol (<7.0%) and ≤ 48 mmol/Mol (≤6.5%) (A); participants achieving composite outcomes with HbA1c <53 mmol/Mol (<7.0%) and ≤ 48 mmol/Mol (≤6.5%) without weight gain, without hypoglycaemia and without weight gain or hypoglycaemia (B). Hypoglycaemia was defined as severe according to ADA criteria or blood glucose-confirmed (<3.1 mmol/L [<56 mg/dL]) episodes. Based on full analysis set. Logistic regression model with treatment and pre-trial anti-diabetic treatment as factors and HbA1c baseline value (and weight) as covariate(s). Hypo: Severe or blood glucose-confirmed symptomatic hypoglycaemia during last 12 weeks of treatment. Missing values were imputed by last observation carried forward. Abbreviations: ADA, American Diabetes Association; CI, confidence interval; hypo, hypoglycaemia; IDegLira, insulin degludec/liraglutide; OR, odds ratio

3.3.8 | Patient reported outcomes

The change from baseline in total DTR-QOL score after 26 weeks was significantly in favour of IDegLira compared with degludec (ETD, 7.39 [3.82; 10.97]$_{95\%CI}$; P < 0.0001) (Table S6). The change from baseline in three of the four DTR-QOL domain scores was significantly in favour of IDegLira compared with degludec, with the largest ETDs between groups being in the "anxiety and dissatisfaction with treatment" and "satisfaction with treatment" domains, with ETDs of 11.65 [6.92; 16.38]$_{95\%CI}$ and 14.82 [9.59; 20.05]$_{95\%CI}$, respectively (both P < 0.0001). No significant difference was seen between treatment groups in the hypoglycaemia domain (ETD, 0.84 [−5.09; 6.77]$_{95\%CI}$; P = 0.7807). The change from baseline in EQ-5D-5 L VAS and EQ-5D-5 L index scores was also significantly in favour of IDegLira vs degludec. The ETDs were 4.67 ([0.91; 8.43]$_{95\%CI}$; P = 0.0151) and 0.03 ([0.01; 0.05]$_{95\%CI}$; P = 0.0136), respectively.

3.4 | Safety

3.4.1 | Adverse events

A summary of adverse events (AE) is given in Table 2. The percentage of participants experiencing at least one AE was similar in each treatment group (78.1% with IDegLira and 76.2% with degludec), with the overall rate of events per 100 patient years of exposure (PYE) being 515.9 with IDegLira compared with 401.8 with degludec. There were more participants who experienced constipation, nausea (Figure S3), diarrhoea and vomiting (AEs within the System Organ Class [SOC] gastrointestinal disorders) and decreased appetite (AE within the SOC metabolism and nutrition) with IDegLira compared with degludec. The most frequently reported AEs in both treatment groups were viral upper respiratory tract infection and diabetic retinopathy. The majority of AEs, in both groups, were considered by the investigator to be mild, non-serious and unlikely to be related to the trial product. The

TABLE 2 Adverse events during 26 weeks of treatment

Event	IDegLira (n = 105)				Degludec (n = 105)			
	n	%	E	R	n	%	E	R
AE	82	78.1	280	515.86	80	76.2	210	401.79
AE possibly or probably related to treatment	38	36.2	72	132.65	26	24.8	41	78.45
Most frequent AE (≥5% of participants in either group)								
Gastrointestinal disorders								
Diarrhoea	15	14.3	20	36.85	5	4.8	6	11.48
Nausea	10	9.5	12	22.11	4	3.8	5	9.57
Constipation	9	8.6	10	18.42	4	3.8	4	7.65
Vomiting	9	8.6	11	20.27	2	1.9	2	3.83
Abdominal discomfort	8	7.6	8	14.74	5	4.8	5	9.57
Infections and infestations								
Viral upper respiratory tract infection	21	20.0	27	49.74	24	22.9	30	57.40
Eye disorders								
Diabetic retinopathy	17	16.2	18	33.16	17	16.2	18	34.44
Metabolism and nutrition disorders								
Decreased appetite	8	7.6	8	14.74	0	-	-	-
SAE	3	2.9	4	7.37	4	3.8	6	11.48
SAE possibly or probably related to treatment	0	-	-	-	2	1.9	3	5.74

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. Data based on safety analysis set.

%, percentage of participants with one or more events.

Abbreviations: AE, adverse event; E, number of adverse events; n, number of participants with one or more events; R, rate (number of adverse events divided by patient years of exposure [365.25 days] multiplied by 100); SAE, serious adverse event.

percentage of participants with gastrointestinal AEs and AEs relating to metabolism and nutrition was higher with IDegLira (42.9% and 14.3%, respectively) compared with degludec (22.9% and 2.9%, respectively). Elevated lipase levels were reported for two participants, both in the IDegLira arm. These events were non-serious, mild or moderate in severity, and were assessed by the investigator as possibly related to trial product. There were no reported AEs of increased amylase or calcitonin levels (≥20 ng/L). In the degludec treatment group there was one event of pancreatic carcinoma, which led to permanent discontinuation of trial product after 2 weeks of treatment; this event was considered by the investigator to be unrelated to degludec. Eight (7.6%) participants experienced an AE, which resulted in a dose reduction of IDegLira, at the investigator's discretion, whereas there were no dose reductions of degludec because of AEs.

3.4.2 | Serious adverse events

Three participants (2.9%) reported a total of four serious adverse events (SAEs) with IDegLira compared with four participants (3.8%) who reported a total of six SAEs with degludec. In the IDegLira group, one SAE (acute myocardial infarction) was confirmed by the Event Adjudication Committee (EAC) to be a major adverse cardiovascular event; however, this did not lead to changes in dosing. The EAC also confirmed two neoplasms (colorectal) in the IDegLira group, which were non-serious, of moderate severity and unlikely to be related to

trial product. All four SAEs reported in the IDegLira group were considered unlikely to be related to treatment. In the degludec group, there was one EAC-confirmed neoplasm (pancreatic carcinoma), which was considered serious, of mild severity and unlikely to be related to trial product. Three of the SAEs reported in the degludec group were considered to be possibly related to treatment; these included two events of loss of consciousness, both related to excessive alcohol consumption, in the same participant and one event of acute cholecystitis. There were no deaths and no events of pancreatitis reported in this trial.

3.4.3 | Hypoglycaemia

The cumulative events of severe or BG-confirmed symptomatic hypoglycaemia are described in Figure S4. The percentage of participants who experienced severe or BG-confirmed hypoglycaemic episodes was similar between groups (28.6% [IDegLira] vs 30.5% [degludec]; corresponding rates were 228.45 and 208.55 episodes per 100 PYE, respectively). The percentage of participants who experienced severe or BG-confirmed symptomatic hypoglycaemic episodes was 14.3% in the IDegLira group and 17.1% in the degludec group; corresponding rates were 95.80 and 82.27 episodes per 100 PYE, respectively. There was no statistically significant difference in the rate of severe or BG-confirmed hypoglycaemic episodes or severe or BG-confirmed symptomatic hypoglycaemic episodes between

treatment groups (estimated rate ratios 1.16 [0.57; 2.34]$_{95\%CI}$; P = 0.6853 and 1.05 [0.40; 2.77]$_{95\%CI}$; P = 0.9184, respectively).

3.4.4 | Pulse

After 26 weeks, the change in pulse rate was significantly greater in the IDegLira group as compared to the degludec group (6.1 vs −0.2 beats/min; ETD: 7.73 beats/min [5.45; 10.01]$_{95\% CI}$; P < 0.0001.

4 | DISCUSSION

The relative contribution of the liraglutide component of IDegLira was assessed while comparing the efficacy and safety of IDegLira and degludec (≤50 U) in Japanese patients with T2D that was uncontrolled with basal insulin or pre-mix/combination insulin plus metformin, with or without one additional OAD. In this trial, IDegLira proved superior to degludec in terms of change in HbA1c levels, consistent with results from the global DUAL II trial.[15] Despite this, the rates of severe or BG-confirmed hypoglycaemia were similar between groups. The difference in HbA1c levels observed with IDegLira was achieved at a significantly lower insulin dose than the dose of degludec, supporting a clinically significant contribution of the liraglutide component to overall glycaemic control.

Treatment effect on body weight was consistent with previous findings,[15-19] a review of which may be found in Wysham et al. 2018 and Aroda et al. 2018,[20,21] and demonstrates that the benefits of IDegLira extend beyond glycaemic control. The initial weight loss observed in both treatment groups may be the result of the decrease in insulin dose from pre-trial doses of approximately 28 U to starting doses of 10 dose steps/U, or up to 16 dose steps/U in some cases.[22] The additional weight loss seen in the IDegLira group is attributed to the weight-lowering effect of liraglutide, which has been described in previous trials,[23] whereas mean weight gain was observed with degludec from Week 4 as the dose was titrated to achieve glycaemic control. A lower magnitude of weight loss was seen in the DUAL II Japan trial, as compared with the DUAL global trials; for instance, in the global DUAL II trial, a mean weight reduction of 2.7 kg was observed with IDegLira, compared with no change in weight with degludec, while in the DUAL II Japan trial, a weight reduction of 0.7 kg was seen with IDegLira. This may be attributable to the lower mean baseline BMI of the Japanese study population (27.3 kg/m^2 vs 33.6 kg/m^2 in the IDegLira arm of DUAL II Japan and global DUAL II, respectively).[15]

A higher percentage of participants achieved HbA1c targets below 53 mmol/Mol (<7.0%) or up to 48 mmol/Mol (≤6.5%) and reached the triple composite endpoints of achieving HbA1c targets without weight gain and without hypoglycaemia with IDegLira than with degludec alone after 26 weeks. This is in alignment with findings from the global DUAL II trial, in which a higher percentage of participants achieved HbA1c below 53 mmol/Mol (<7.0%) with IDegLira than with degludec alone.[15] The mean prandial increment across all meals was smaller with IDegLira than with degludec, supporting the notion that GLP1-RA helps reduce post-prandial glucose excursions. Altogether, these results demonstrate that the liraglutide component of IDegLira (maximum dose: 50 dose steps IDegLira, comprising 1.8 mg of liraglutide) provides additional glycaemic control, with the benefit of weight loss and no increase in rates of hypoglycaemia in patients who were uncontrolled with basal insulin or pre-mix/combination insulin, as compared with degludec (maximum dose: 50 U) alone.

Treatment with IDegLira significantly improved quality of life compared with degludec, as demonstrated by the DTR-QOL scores, with the biggest differences being observed in the domains relating to treatment satisfaction. There was no significant difference in the hypoglycaemia domain, which is fully compatible with the similar rates of hypoglycaemia observed in this trial. PROs were not investigated in the global DUAL II study; however, these results are aligned with those of the DUAL V trial, which also compared the safety and efficacy of IDegLira with that of a basal insulin, namely continued titration of insulin glargine 100 units/mL (IGlar U100) with no maximum dose.[17] Greater improvements in treatment burden and diabetes management were observed with IDegLira, indicating higher treatment satisfaction.[17]

As per the protocol, the recommended starting dose was 10 dose steps/U of IDegLira/degludec, with the option of choosing a higher dose of up to 16 dose steps/U, at the investigator's discretion depending on the condition of the patient, for example, the risk of hyperglycaemia or hypoglycaemia. Pre-trial insulin products could be administered in up to 50 units/day; therefore, a potential concern might be that this considerable decrease in dose could cause uncontrolled glycaemia. However, in the IDegLira group, FPG levels began to decrease from baseline after the first week of treatment, confirming the safety of switching to IDegLira from a higher dose of pre-trial insulin. Furthermore, although some participants received a starting dose above 10 dose steps, this did not lead to a high rate of gastrointestinal AEs and no participants in the IDegLira group withdrew. This is consistent with results of other clinical trials, which reported no loss of glycaemic control and no safety concerns when switching to a starting dose of 16 U of IDegLira from any pre-trial insulin dose between 20 and 50 U.[17,24,25]

Overall, there were no unexpected safety or tolerability issues identified with treatment with IDegLira. The AE profile of IDegLira was consistent with that of liraglutide or degludec alone. This includes the higher incidence of gastrointestinal AEs such as diarrhoea, vomiting and nausea that was observed in the IDegLira group, which is expected according to the safety profile of liraglutide. The majority (four of seven) of gastrointestinal AEs leading to dose reduction occurred in the early period of the study, within 10 days of treatment randomization.

An increase in resting pulse was also observed with treatment with IDegLira, which is consistent with previous trials of IDegLira.[18] The clinical significance of this elevation is unknown but appears to be a class effect of long-acting GLP-1RAs.[26] Of note, cardiovascular benefits as compared to placebo have been reported for GLP-1RAs, including liraglutide.[27,28]

As with all randomized clinical trials, the findings of this trial may not be applicable to clinical practice or to patients who do not fit the specified inclusion and exclusion criteria. It is unclear if patients switching from more than 50 U of basal or pre-mix insulin to IDegLira would experience the same outcomes. In addition, it was necessary to cap the maximum dose of degludec at 50 U, to assess the contribution of the liraglutide component. Consequently, we cannot come to firm conclusions concerning the glucose-lowering or other effects of degludec, as a sub-group of participants in this trial may have required more than 50 U of insulin. However, in a previous trial comparing IDegLira to liraglutide and degludec, IDegLira had superior efficacy over degludec, despite no maximum dose.[29]

Results from this trial confirm the safety and superior control over HbA1c of IDegLira as compared to degludec in Japanese patients with T2D treated with basal or pre-mix insulin plus metformin, and one other OAD if required. In conclusion, IDegLira resulted in superior reductions in HbA1c as compared with up to 50 U degludec, with weight loss and similar rates of hypoglycaemia, and no unexpected safety or tolerability issues. Additionally, post-prandial increases were better controlled with IDegLira compared with degludec. These results suggest that this treatment could be an attractive intensification option for Japanese individuals with T2D that is uncontrolled with basal or pre-mixed insulin.

AUTHOR CONTRIBUTIONS

All authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) uniform requirements for authorship and that they have contributed to: critical analysis and interpretation of the data, drafting/critically revising the article and sharing in the final responsibility for the content of the manuscript and the decision to submit it for publication. H. W. was signatory investigator of this clinical trial, the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data.

CONFLICT OF INTEREST

H. W. has acted as an advisory board member for Novo Nordisk and as a speaker for Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk, Kowa Pharmaceutical, AstraZeneca, Takeda Pharmaceutical, Novartis, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Sanwa Kagaku Kenkyusho, Ono Pharmaceutical, Kissei Pharmaceutical and Fujifilm Pharma; and has received grants from Astellas Pharma, Sanofi, Mitsubishi Tanabe Pharma, Novo Nordisk Pharma, AstraZeneca, Takeda Pharmaceutical, Novartis Pharma, Nippon Boehringer Ingelheim, Merck Sharp & Dohme, Sumitomo Dainippon Pharma, Eli Lilly Japan, Ono Pharmaceutical, Kyowa Hakko Kirin, Daiichi Sankyo, Terumo, Pfizer Japan, Mochida Pharmaceutical, Taisho Toyama Pharmaceutical, Johnson & Johnson and Kowa.

S. K. has received honoraria for lectures from Sumitomo Dainippon Pharma Co., Ltd., Novo Nordisk Pharma Ltd., Eli Lilly Japan K.K., AstraZeneca K.K., Takeda Pharmaceutical Company Limited and Mitsubishi Tanabe Pharma Corporation.

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B. R. A., T. N. and M. R. are employees of and shareholders in Novo Nordisk.

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DATA SHARING STATEMENT

The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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