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Superior efficacy with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira) compared with insulin degludec and liraglutide in insulin-naïve Japanese patients with type 2 diabetes in a phase 3, open-label, randomized trial

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Abstract

Aims: To investigate the efficacy and safety of insulin degludec/liraglutide (IDegLira) compared with its individual components in Japanese people with type 2 diabetes (T2D) uncontrolled on an oral antidiabetic drug (OAD).

Materials and methods: This 52-week, open-label, multicentre, treat-to-target trial randomized participants (n = 819) 1:1:1 to IDegLira, liraglutide 1.8 mg or degludec, as add-on to their pre-trial OAD. The maximum IDegLira dose was 50 dose steps (50 U degludec/1.8 mg liraglutide), there was no maximum dose for degludec, and both were titrated based on individual blood glucose measurements.

Results: After 52 weeks, glycated haemoglobin (HbA1c) decreased by 26 mmol/mol with IDegLira vs 20 mmol/mol with degludec and liraglutide: estimated treatment differences were −6.91 mmol/mol (95% confidence interval [CI] −8.18; −5.64) and −5.30 mmol/mol (95% CI −6.58; −4.03), confirming non-inferiority of IDegLira to degludec and superiority of IDegLira to liraglutide ($P < .0001$ for both [primary endpoint]). Mean body weight changes were 2.9 kg, 4.1 kg and −1.0 kg with IDegLira, degludec and liraglutide, respectively, showing superiority of IDegLira versus degludec ($P = .0001$), but a significant difference in favour of liraglutide ($P < .0001$). Rates of severe or blood glucose-confirmed hypoglycaemia for IDegLira were lower versus degludec (rate ratio 0.48 [95% CI 0.35; 0.68]; $P < .0001$), but higher versus liraglutide (rate ratio 37.58 [95% CI 19.80; 71.31]; $P < .0001$). Mean daily total insulin dose was lower with IDegLira (27.7 U) versus degludec (34.8 U; $P < .0001$). Overall adverse event (AE) rates were similar. In total, 34.9%, 22.9% and 41.8% of IDegLira-, degludec- and liraglutide-treated participants experienced gastrointestinal AEs.

Conclusion: IDegLira was superior to degludec and liraglutide in terms of HbA1c reduction and superior to degludec in terms of body weight change and rates of hypoglycaemia in Japanese people with T2D.

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

1 | INTRODUCTION

The prevalence of diabetes in Japan is expected to reach 8.3% in 2045, up from 7.7% in 2017,[1] with the majority of cases being type 2 diabetes (T2D).[2-4] This increase is attributable, at least in part, to Japan's ageing population and changes in lifestyle factors, including diet and physical activity.[5,6] Impaired insulin secretion is considered more common among Japanese people with T2D compared with white people, probably because of differences in body composition between these populations.[7,8]

Due to the progressive nature of T2D and associated deterioration of β-cell function, most patients will eventually require treatment intensification to maintain glycaemic targets. Japanese clinical practice guidelines emphasize treatment individualization and intensification with oral antidiabetic drugs (OADs), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and basal or premixed insulin.[9] Basal insulin is an effective therapy for reducing fasting plasma glucose (FPG) levels, but it is associated with considerable risk of hypoglycaemia and weight gain.[10-12] GLP-1RAs augment glucose-dependent insulin secretion, as well as preserving β-cell function, delaying gastric emptying, promoting weight loss and increasing insulin sensitivity.[13] The complementary actions of insulin and GLP-1RAs target multiple pathophysiological defects involved in T2D, and combining both therapies together can reduce glycated haemoglobin (HbA1c) levels with lower risk of hypoglycaemia and weight gain compared with basal insulin alone.[14-17] However, this burdens patients with two different treatment regimens, which may limit treatment adherence and intensification.[18,19]

Insulin degludec/liraglutide (IDegLira) is a fixed-ratio soluble combination of insulin degludec (degludec) and the GLP-1RA liraglutide (100 U and 3.6 mg/mL, respectively), which allows once-daily administration of both active ingredients with a single injection. The efficacy and safety of IDegLira has been investigated in a number of patient populations in the DUAL clinical trial programme.[20-28] Based on evidence from these trials, IDegLira received regulatory approval from the European Medicines Agency and the US Food and Drug Administration (FDA).[29,30]

The global DUAL I trial, which encompassed insulin-naïve participants with T2D, demonstrated that treatment with IDegLira results in improved glycaemic control compared with each component administered separately, whilst mitigating the side effects associated with each, including the gastrointestinal side effects associated with liraglutide.[20] The aim of the present study was to confirm the efficacy and safety of IDegLira compared with each of its components in Japanese people with T2D inadequately controlled on one OAD.

2 | MATERIALS AND METHODS

2.1 | Study design and participants

This 52-week, multicentre, randomized, open-label, three-arm parallel-group trial investigated the efficacy and safety of IDegLira versus each of its components, degludec and liraglutide (Figure 1). The trial consisted of a 2-week screening period and a 52-week treatment period. Participants were Japanese adults (aged ≥20 years) with HbA1c levels of 53–97 mmol/mol (7.0%–11.0%) and a body mass index (BMI) of ≥20 kg/m^2, who had been diagnosed with T2D ≥6 months prior to screening and who were on stable therapy with one of six OAD types for at least 60 days prior to screening. Permitted OADs were aligned with Japanese clinical practice guidelines: α-glucosidase inhibitors; thiazolidinediones; sodium-glucose co-transporter-2 inhibitors; glinides; metformin; or sulphonylureas.[9]

The protocol was approved by independent ethics committees or institutional review boards at all participating institutions, and the

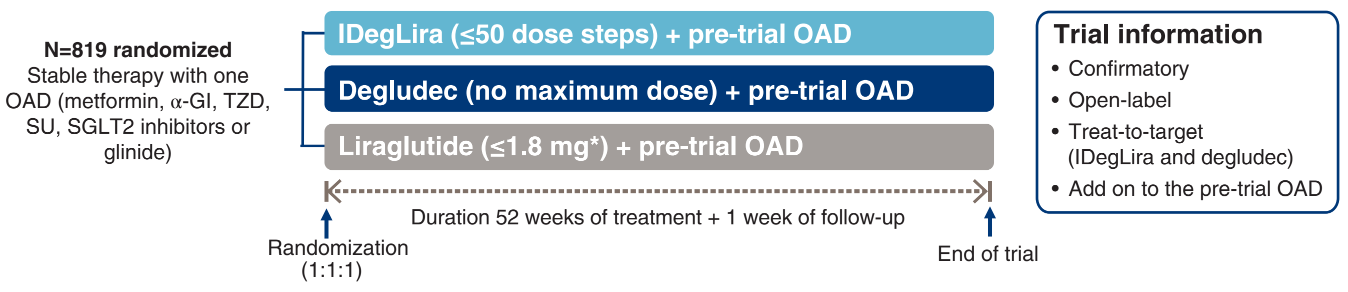

FIGURE 1 Trial design. *Maximum dose of liraglutide was 1.8 mg, double the maximum approved dose in Japan of 0.9 mg. α-GI, alpha-glucosidase inhibitor; IDegLira, insulin degludec/liraglutide; Lira, liraglutide; OAD, oral antidiabetic drug; SGLT2, sodium-glucose co-transporter-2; SU, sulphonylurea; TZD, thiazolidinedione

study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines. Written consent was obtained from all participants before enrolment.

2.2 | Treatment

IDegLira and degludec were administered once daily. Recommended starting doses were 10 dose steps of IDegLira (10 U degludec +0.36 mg liraglutide) or 10 U of degludec. Doses were adjusted twice weekly in increments of ±2 U, aiming for a mean pre-breakfast self-monitored blood glucose (SMBG; mean from 3 consecutive days) target range of 4.0–5.0 mmol/L (72–90 mg/dL; Table S1). SMBG was assessed using a glucose meter, calibrated to plasma equivalent values. The maximum dose of IDegLira was 50 dose steps, which delivers the maximum licensed liraglutide dose for diabetes (50 U degludec/1.8 mg liraglutide)[31]; there was no maximum dose for degludec.

Liraglutide was administered once daily. Liraglutide was initiated at 0.3 mg and increased by 0.3 mg each week over a 6-week period up to the maximum dose of 1.8 mg. Temporary dose reductions for <1 week were only allowed for safety reasons. OAD treatment continued unchanged at pre-trial doses; however, in case of safety concerns the dose could be reduced at the discretion of the investigator.

2.3 | Randomization and stratification

Participants were randomized 1:1:1, via a centralized allocation using an interactive web response system, to receive either IDegLira, degludec or liraglutide, each in combination with pre-trial OAD. Participants were stratified by type of pre-trial OAD treatment to ensure an even distribution of each of the six OAD types across the three treatment arms.

2.4 | Endpoints

The primary endpoint was change from baseline in HbA1c after 52 weeks of treatment for assessing superiority of IDegLira versus liraglutide and non-inferiority of IDegLira versus degludec. Secondary endpoints included: change from baseline in HbA1c after 52 weeks of treatment for assessing superiority of IDegLira versus degludec; percentages of participants reaching HbA1c <53 mmol/mol (<7.0%) and ≤48 mmol/mol (≤6.5%) after 52 weeks of treatment; change from baseline in body weight after 52 weeks of treatment; fasting lipid profile; and changes from baseline in FPG, nine-point SMBG profile, prandial plasma glucose increments (from before meal to 90 minutes after for breakfast, lunch and dinner) and blood pressure. Safety endpoints included number of treatment-emergent adverse events (AEs), number of treatment-emergent severe (defined according to the American Diabetes Association classification) or blood glucose-confirmed (plasma glucose <3.1 mmol/L [<56 mg/dL]) symptomatic hypoglycaemic episodes during 52 weeks of treatment, and pulse rate.

2.5 | Statistical analyses

The main study objective was jointly confirming the non-inferiority of IDegLira to insulin degludec alone with an upper 95% confidence interval (CI) margin of 0.3%, and the superiority of IDegLira to liraglutide alone with a lower 95% CI margin of 0% (with respect to change in HbA1c at 26 weeks). The sample size was determined using a t-statistic under the assumption of a one-sided test with a type I error rate of 2.5% and a standard deviation of 1.0% for both the superiority and non-inferiority testing. For sample size calculations, the mean difference between treatments in change from baseline in HbA1c after 52 weeks was assumed to be −0.1% for non-inferiority and −0.3% for superiority testing. The per-protocol analysis set (assumed to be 85% of the randomized participant population) was used for the power calculation for non-inferiority, while the full analysis set was used for superiority. Based on these assumptions, a sample size of 807 participants would provide a non-inferiority power of 98.9% and a superiority power of 93.5%, giving an overall power for meeting the primary objective of 92.5%. A non-inferiority margin for the difference in the change from baseline in HbA1c after 52 weeks of treatment of 0.3% was selected based on existing FDA guidance, and is considered to be the minimal clinically significant change for HbA1c level.[32]

To ensure that the overall type I error rate was not inflated, a hierarchical testing procedure was used. If the primary hypotheses were confirmed in change in HbA1c (ie, IDegLira superiority to liraglutide and non-inferiority to degludec), the secondary confirmatory tests were performed for superiority of IDegLira versus degludec following a fixed sequence: (a) Change from baseline in body weight after 52 weeks of treatment, (b) Number of treatment-emergent severe or blood glucose-confirmed hypoglycaemic episodes during 52 weeks of treatment, and (c) Change in HbA1c after 52 weeks of treatment. Tests lower down the sequence in the hierarchy were only performed if the preceding test was statistically significant in favour of IDegLira.

Continuous efficacy endpoints including the primary endpoint were analysed separately using an analysis of covariance (ANCOVA) model including treatment, pre-trial OAD treatment as fixed factors and the baseline value of the parameter as a covariate. For the fasting lipid profile, the endpoint and baseline covariates were log-transformed before the analysis. Insulin dose was analysed using an ANCOVA model including the same fixed factors and baseline HbA1c as a covariate. Last observation carried forward was used to impute missing values for endpoints after 52 weeks of treatment. Attainment of glycaemic targets was analysed using a logistic regression model with treatment and pre-trial OAD treatment as fixed factors and baseline HbA1c as covariate.

Number of treatment-emergent hypoglycaemic episodes was analysed using a negative binominal regression model with a log-link function and the logarithm of the time period in which a hypoglycaemic episode was considered treatment-emergent as offset, with treatment and pre-trial OAD treatment as fixed factors.

The robustness of the conclusions from the primary and confirmatory secondary analyses were assessed in various sensitivity analyses, including analysis of different analysis sets (per-protocol and completer) and using a mixed model for repeated measurements and a pattern mixture model approach mimicking an intention-to-treat scenario.

3 | RESULTS

3.1 | Participants

A total of 819 participants were randomized and treated with either IDegLira (n = 275), degludec (n = 271) or liraglutide (n = 273), all in combination with pre-trial OAD (Figure S1). In total 54 participants withdrew from the trial; 21 (7.6%) in the IDegLira group, 23 (8.5%) in the IDeg group and 10 (3.7%) in the liraglutide group. The number of withdrawals due to AEs was low and similar across treatment groups (eight participants [2.9%] with IDegLira, six [2.2%] with degludec and six [2.2%] with liraglutide). Baseline characteristics were similar in the three treatment groups (Table 1).

TABLE 1 Baseline characteristics of participants

	IDegLira (N = 275)	Degludec (N = 271)	Liraglutide (N = 273)
Age, y			
Mean (SD)	56.9 (10.2)	57.8 (9.9)	56.8 (10.1)
Median (min.; max.)	57.0 (29.0; 81.0)	59.0 (22.0; 80.0)	57.0 (25.0; 79.0)
Sex, n (%)			
Female	81 (29.5)	76 (28.0)	81 (29.7)
Male	194 (70.5)	195 (72.0)	192 (70.3)
Body weight, kg			
Mean (SD)	70.7 (12.4)	72.6 (14.5)	72.2 (15.0)
Median (min.; max.)	68.7 (44.1; 113.3)	70.5 (44.8; 161.8)	70.4 (42.3; 142.4)
BMI, kg/m^2			
Mean (SD)	26.1 (3.7)	26.6 (4.8)	26.5 (4.5)
Median (min.; max.)	25.5 (19.9; 36.8)	25.5 (19.6; 56.0)	25.8 (19.8; 45.5)
HbA1c, mmol/mol			
Mean (SD)	69.6 (12.2)	69.7 (11.5)	67.4 (10.8)
Median (min.; max.)	67.2 (50.8; 98.9)	67.2 (51.9; 101.1)	63.9 (49.7; 101.1)
HbA1c, %			
Mean (SD)	8.5 (1.1)	8.5 (1.1)	8.3 (1.0)
Median (min.; max.)	8.3 (6.8; 11.2)	8.3 (6.9; 11.4)	8.0 (6.7; 11.4)
FPG, mmol/L			
Mean (SD)	9.9 (2.4)	10.0 (2.3)	9.7 (2.2)[a]
Median (min.; max.)	9.4 (5.1; 17.6)	9.6 (5.5; 17.0)	9.3 (5.1; 19.3)[a]
Fasting C-peptide, nmol/L			
Geometric mean (CV%)	0.49 (42.8)	0.51 (47.1)	0.50 (43.0)[a]
Median (min.; max.)	0.50 (0.20; 1.68)	0.49 (0.12; 2.19)	0.49 (0.16; 1.36)[a]
FPG, mg/dL			
Mean (SD)	178.7 (43.0)	179.9 (42.3)	175.4 (39.8)[a]
Median (min.; max.)	170.0 (92.0; 318.0)	173.0 (99.0; 307.0)	168.0 (92.0; 347.0)[a]
Duration of diabetes, y			
Mean (SD)	9.2 (6.2)	9.7 (6.0)	9.4 (5.9)
Median (min.; max.)	8.1 (0.6; 45.3)	8.7 (0.5; 30.7)	8.4 (0.8; 33.9)
OAD use at screening, n (%)			
Metformin	47 (17.1)	46 (17.0)	47 (17.2)
α-glucosidase inhibitors	41 (14.9)	40 (14.8)	41 (15.0)
Thiazolidinediones	43 (15.6)	43 (15.9)	42 (15.4)
Sulphonylureas	43 (15.6)	42 (15.5)	42 (15.4)
SGLT2 inhibitors	61 (22.2)	61 (22.5)	61 (22.3)
Glinides	40 (14.5)	39 (14.4)	40 (14.7)

Abbreviations: BMI, body mass index; CV, coefficient of variation; FPG, fasting plasma glucose; OAD, oral anti-diabetic drug; SGLT2, sodium-glucose co-transporter-2 inhibitor.
[a]N = 272.

3.2 | Efficacy

After 52 weeks of treatment, mean HbA1c decreased from 69.6 mmol/mol (8.52%) to 43.1 mmol/mol (6.10%) with IDegLira, 69.7 mmol/mol (8.53%) to 50.1 mmol/mol (6.73%) with degludec, and 67.4 mmol/mol (8.32%) to 47.7 mmol/mol (6.52%) with liraglutide (Figure 2A). Mean HbA1c was reduced to a significantly greater extent with IDegLira compared with liraglutide (−26.5 mmol/mol [−2.42%] vs −19.7 mmol/mol [−1.80%], estimated treatment difference [ETD] −5.30 mmol/mol [95% CI −6.58; −4.03; −0.48% {95% CI −0.60; −0.37}]; $P < .0001$), confirming superiority for IDegLira versus liraglutide. Mean HbA1c was also significantly reduced with IDegLira compared with degludec (−26.5 mmol/mol [−2.42%] vs −19.6 mmol/mol [−1.80%], ETD −6.91 mmol/mol [95% CI −8.18; −5.64; −0.63% {95% CI −0.75; −0.52}]; $P < .0001$) confirming non-inferiority of IDegLira versus degludec. The superiority of IDegLira versus degludec was confirmed as a part of confirmatory hierarchical testing procedure (−0.63% [95% CI −0.75; −0.52]; $P < .0001$).

The level of glycaemic control demonstrated with IDegLira was supported by the secondary endpoint, achievement of predefined HbA1c targets (Figure S2). The odds of achieving HbA1c <53 mmol/mol (<7.0%) and ≤ 48 mmol/mol (≤6.5%) were significantly higher with IDegLira compared with either degludec (estimated odds ratios for <53 mmol/mol and ≤48 mmol/mol: 4.70 [95% CI 2.82; 7.82] and 4.76 [95% CI 3.12; 7.25], respectively) or liraglutide (estimated odds ratios for <53 mmol/mol and ≤48 mmol/mol: 3.90 [95% CI 2.31; 6.59] and 2.94 [95% CI 1.93; 4.50], respectively; $P < .0001$ for all).

3.3 | Body weight

After 52 weeks, there was a significantly smaller increase in body weight with IDegLira (2.9 kg) versus degludec (4.1 kg; Figure 2B) with an ETD of −1.19 kg (95% CI −1.80; −0.59; $P = .0001$ [P-value for superiority]). The mean change from baseline in body weight was −1.0 kg with liraglutide versus 2.9 kg with IDegLira (Figure 2B), representing an ETD of 3.89 kg (95% CI 3.29; 4.49; $P < .0001$).

An exploratory analysis showed there was no significant interaction between background OAD therapy and treatment for the

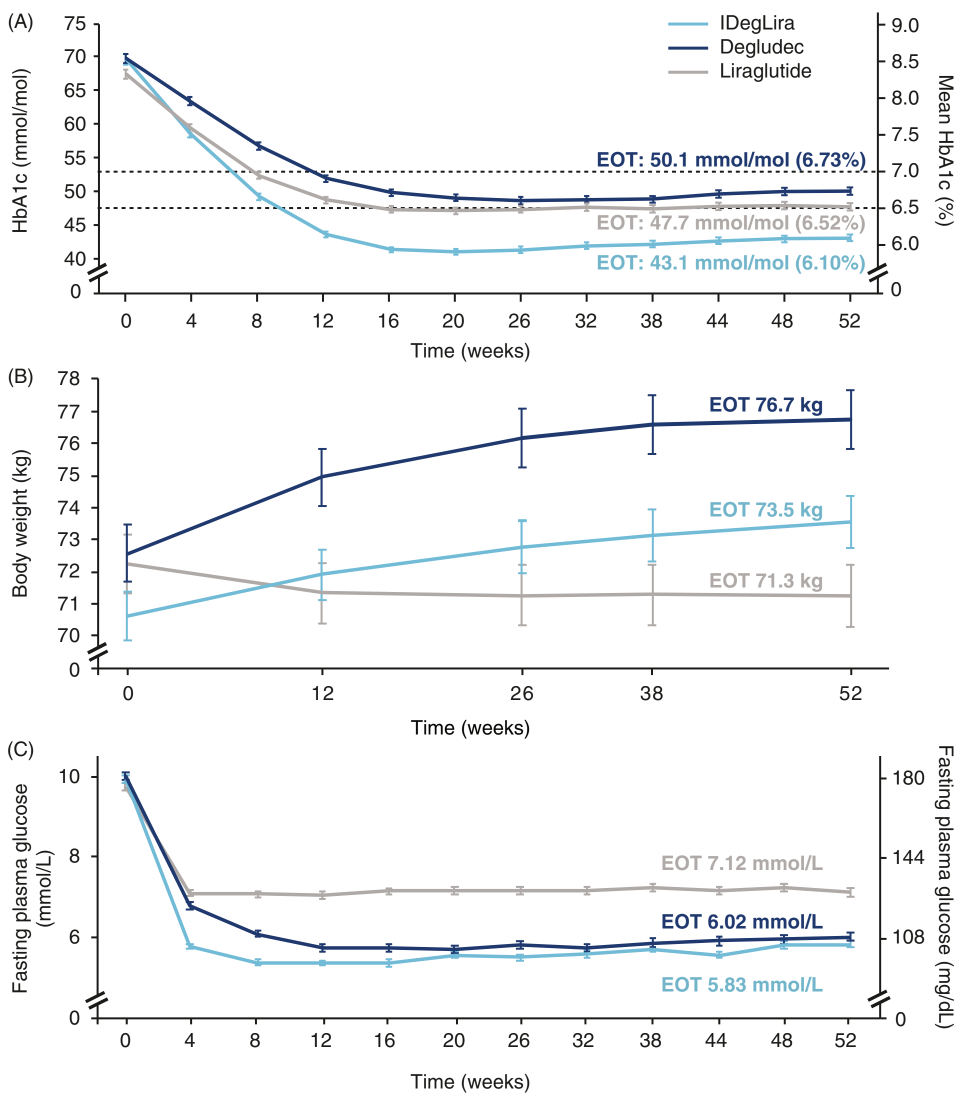

FIGURE 2 Mean A, HbA1c, B, body weight and C, fasting plasma glucose over 52 weeks. Full analysis set. Missing values are imputed using last observation carried forward. Error bars represent standard error. EOT, end of trial; FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide

endpoint change in body weight; there was no effect of pre-trial OAD treatment on the differences between IDegLira and comparator.

3.4 | Hypoglycaemic episodes

The cumulative incidence of severe or blood glucose-confirmed hypoglycaemia is shown in Figure 3. After 52 weeks, rates of severe or blood glucose-confirmed hypoglycaemia were 174.3, 331.9 and 4.8 events/100 participant-years of exposure [PYE] for IDegLira, degludec and liraglutide, respectively, with 38.5% of IDegLira-treated participants, 54.6% of degludec-treated participants and 2.2% of liraglutide-treated participants experiencing ≥1 event (Table 2). The treatment rate ratio of severe or blood glucose-confirmed hypoglycaemic episodes was significantly lower for IDegLira versus degludec (0.48 [95% CI 0.35; 0.68]; $P < .0001$), confirming superiority, and significantly higher for IDegLira versus liraglutide (rate ratio 37.58 [95% CI 19.80; 71.31]; $P < .0001$). The percentage of participants who experienced severe or blood glucose-confirmed symptomatic hypoglycaemia was 19.3% (IDegLira), 29.5% (degludec) and 1.1% (liraglutide), with rates of 50.4, 138.3 and 1.5 events/100 PYE, respectively (Table 2).

3.5 | Dose

The mean insulin doses during the first week were similar in the IDegLira (10.5 dose steps) and degludec (10.4 U) groups. After 52 weeks of treatment, the mean daily total insulin dose was significantly lower with IDegLira than degludec (27.7 vs 34.8 U; ETD −7.01 U [95% CI −10.52; −3.50]; $P < .0001$ [Figure S3A]). Mean liraglutide doses were lower in the IDegLira group compared with the liraglutide group throughout the trial, and at week 52 were 1.0 mg and 1.8 mg, respectively (Figure S3B). Of the participants randomized to IDegLira, 17.1% (n = 47) were on the maximum dose of 50 dose steps, and 74.5% of these participants achieved the target of HbA1c <53 mmol/mol (<7.0%) at end of trial.

3.6 | Fasting plasma glucose

The mean FPG levels over time are shown in Figure 2C. After 52 weeks of treatment, change from baseline in mean FPG was similar for IDegLira and degludec (−4.1 mmol/L [−73.6 mg/dL] and −4.0 mmol/L [−71.5 mg/dL], respectively) but greater for IDegLira versus liraglutide (−4.1 mmol/L [−73.6 mg/dL] vs −2.6 mmol/L [−47.1 mg/dL]).

3.7 | Self-monitored blood glucose

The mean nine-point SMBG profiles decreased across all groups throughout the trial (Figure S4). After 52 weeks, SMBG profiles showed statistically significantly lower pre- and post-prandial glucose concentrations for IDegLira compared with degludec and liraglutide at all timepoints (except for pre-breakfast and at 4:00 AM, which were similar between IDegLira and degludec).

After 52 weeks of treatment, the reduction from baseline in prandial glucose increments was statistically significantly greater with IDegLira compared with degludec for breakfast (ETD −0.81 mmol/L [95% CI −1.24; −0.38; −14.58 mg/dL {95% CI −22.27; −6.88}]; $P = .0002$), dinner (ETD, −0.66 mmol/L [95% CI −1.17; −0.15; −11.94 mg/dL {95% CI −21.15; −2.73}]; $P = .0111$) and mean of all meals (ETD −0.64 mmol/L [95% CI −0.96; −0.32; −11.51 mg/dL {95% CI −17.26; −5.76}]; $P < .0001$), but not significant for lunch (ETD −0.49 mmol/L [95% CI −1.02; 0.04; −8.86 mg/dL {95% CI −18.44; 0.72}]; $P = .0699$). However, although a treatment difference for IDegLira compared with liraglutide was observed for breakfast (ETD 0.48 mmol/L [95% CI 0.06; 0.91]; 8.70 mg/dL {95% CI 1.03; 16.36}]; $P = .0263$), a significant difference was not observed for dinner (ETD 0.16 mmol/L [95% CI −0.35; 0.67; 2.84 mg/dL {95% CI −6.33; 12.02}]; $P = .5430$), lunch (ETD 0.09 mmol/L [95% CI −0.44; 0.61; 1.55 mg/dL {95% CI −7.97; 11.08}]; $P = .7488$) or mean of all meals (ETD 0.24 mmol/L [95% CI −0.08; 0.56; 4.33 mg/dL {95% CI −1.40; 10.06}]; $P = .1385$).

3.8 | Vital signs

After 52 weeks, there was a statistically significant reduction in systolic blood pressure with IDegLira versus degludec (ETD −2.05 mmHg [95% CI −4.02; −0.08]; $P = .0412$). However, systolic blood pressure was significantly higher with IDegLira versus liraglutide (ETD 2.88 mmHg [95% CI 0.91; 4.85]; $P = .0042$). There was no significant

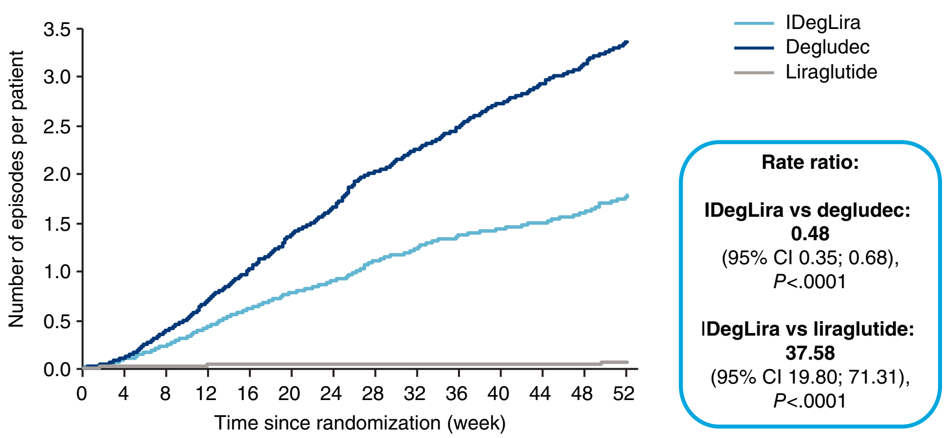

FIGURE 3 Cumulative incidence of severe or blood glucose-confirmed hypoglycaemia (with or without symptoms). Safety analysis set. Observed data. Severe or blood glucose-confirmed: An episode that is severe according to the American Diabetes Association classification or blood glucose-confirmed by a plasma glucose value <3.1 mmol/L (<56 mg/dL) with or without symptoms consistent with hypoglycaemia. IDegLira, insulin degludec/liraglutide

TABLE 2 Adverse events

Event	IDegLira(N = 275)				Degludec (N = 271)				Liraglutide (N = 273)			
	n	%	E	R	n	%	E	R	n	%	E	R
AE	229	83.3	873	325.7	216	79.7	829	316.6	229	83.9	885	325.6
AE possibly or probably related to treatment	88	32.0	152	56.7	55	20.3	84	32.1	108	39.6	210	77.3
Most frequent AE (≥5% of participants)												
Infections and infestations												
Viral upper respiratory tract infection	106	38.5	166	61.9	91	33.6	161	61.5	94	34.4	155	57.0
Pharyngitis	11	4.0	13	4.9	15	5.5	18	6.9	9	3.3	9	3.3
Influenza	15	5.5	15	5.6	9	3.3	9	3.4	9	3.3	9	3.3
Gastrointestinal disorders												
Constipation	27	9.8	28	10.4	12	4.4	12	4.6	38	13.9	42	15.5
Diarrhoea	15	5.5	20	7.5	12	4.4	14	5.3	24	8.8	31	11.4
Nausea	9	3.3	13	4.9	5	1.8	7	2.7	23	8.4	30	11.0
Investigations												
Weight increased	4	1.5	4	1.5	19	7.0	19	7.3	1	0.4	1	0.4
Lipase increased	6	2.2	8	3.0	0	-	-	-	15	5.5	15	5.5
Eye disorders												
Diabetic retinopathy	17	6.2	17	6.3	12	4.4	14	5.3	11	4.0	11	4.0
Skin and subcutaneous tissue disorders												
Eczema	16	5.8	18	6.7	6	2.2	6	2.3	9	3.3	10	3.7
Nervous system disorders												
Headache	7	2.5	11	4.1	7	2.6	12	4.6	15	5.5	17	6.3
SAE	17	6.2	18	6.7	13	4.8	16	6.1	14	5.1	14	5.2
SAE possibly or probably related to trial product	2	0.7	2	0.7	1	0.4	1	0.4	1	0.4	1	0.4
Severe or blood glucose-confirmed symptomatic hypoglycaemia	53	19.3	135	50.4	80	29.5	362	138.3	3	1.1	4	1.5
Severe or blood glucose-confirmed hypoglycaemia	106	38.5	467	174.3	148	54.6	869	331.9	6	2.2	13	4.8

%, percentage of participants with one or more events; AE, adverse event; E, number of adverse events; n, number of participants with one or more events; R, rate (number of AEs divided by participant-years of exposure [365.25 days] multiplied by 100); SAE, serious adverse event. Treatment emergent was defined as 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.

difference in diastolic blood pressure between IDegLira and either of its components. After 52 weeks of treatment, mean changes in pulse rate were 3.9, 0.8 and 4.2 beats/min with IDegLira, degludec and liraglutide, respectively; the difference between IDegLira and degludec was statistically significant (ETD IDegLira – degludec: 2.87 beats/min [95% CI 1.43; 4.30]; $P < .0001$), but a difference was not observed between IDegLira and liraglutide (ETD IDegLira – liraglutide: −0.43 beats/min [95% CI −1.86; 1.00]; $P = .5546$).

3.9 | Lipid profile

There was a statistically significant difference, in favour of IDegLira, for total cholesterol (vs. degludec and liraglutide), LDL cholesterol (vs. degludec) and free fatty acids (vs. liraglutide), and a statistically significant difference in HDL cholesterol in favour of liraglutide versus IDegLira (Table S2).

3.10 | Adverse events

The percentage of participants experiencing at least one AE was similar in each treatment group. The most frequently reported AEs were infections, with viral upper respiratory tract infection experienced by over one-third of participants in each treatment group (Table 2). Gastrointestinal events were reported by 34.9%, 22.9% and 41.8% of participants in the IDegLira, degludec and liraglutide groups, respectively. The overall rate of AEs per 100 PYE was similar between treatments groups. The majority of AEs were non-serious and judged unlikely to be related to trial products. In total, 24 participants experienced 31 AEs that led to dose reductions during the trial; eight events in six participants with IDegLira, 16 events in 13 participants with degludec and seven events in five participants with liraglutide. There were no confirmed events of thyroid disease. The event rate per 100 PYE of elevated lipase or amylase was 4.1, 7.4 and 0.0 with IDegLira, liraglutide and degludec, respectively. There were three events of elevated calcitonin (one with IDegLira and two with liraglutide).

3.11 | Serious adverse events

The percentage of participants experiencing at least one serious adverse event (SAE) was 6.2% in the IDegLira group, 4.8% in the degludec group and 5.1% in the liraglutide group. The majority of SAEs were considered unlikely to be related to trial product (Table 2). The most frequently reported SAEs were in the cardiac disorder System Organ Class: three events in three participants in the IDegLira and degludec groups and one event in the liraglutide group. All other SAEs were single events with no apparent difference in distribution between treatment groups. The event adjudication committee classified five cardiovascular AEs (three with IDegLira and two with degludec) as major adverse cardiovascular events. There was one event adjudication committee-confirmed cardiovascular death in the IDegLira group, which was considered unlikely to be related to the trial product. The event adjudication committee also confirmed one event of mild acute pancreatitis in the IDegLira group, which was considered unlikely to be related to trial product, and 14 neoplasms (four with IDegLira including one malignant [local, gastric intestinal], three with degludec including one malignant [metastatic lung/bronchus] and seven with liraglutide including two malignant [local, breast and skin]).

4 | DISCUSSION

This open-label, treat-to-target trial investigated the efficacy and safety of IDegLira, in combination with an OAD, in Japanese patients with T2D. After 52 weeks of treatment, the superiority of IDegLira over both liraglutide and degludec in terms of reduction in HbA1c was confirmed. The improvement in HbA1c was reflected by the fact that a significantly higher percentage of participants achieved HbA1c targets (<53 mmol/mol [<7.0%] or ≤ 48 mmol/mol [≤6.5%]) at end of trial with IDegLira compared with degludec or liraglutide, consistent with the results from the global DUAL I trial.[21] The −6.91 mmol/mol (−0.63%) HbA1c treatment difference with IDegLira versus degludec was achieved with a significantly lower daily total insulin dose with IDegLira (27.7 vs 34.8 U, respectively), showing the contribution of the liraglutide component. Only ~17% of the participants randomized to IDegLira reached the maximum allowed dose (50 dose steps) and the majority of these participants (74.5%) achieved the target of HbA1c <53 mmol/mol (<7.0%) after 52 weeks.

There were significantly fewer severe or blood glucose-confirmed hypoglycaemic episodes with IDegLira compared with degludec, reinforcing the contribution of the liraglutide component of IDegLira to the lower rate of hypoglycaemia seen with IDegLira in comparison with degludec in previous trials.[26] There was a significantly lower rate of severe or blood glucose-confirmed hypoglycaemic episodes with liraglutide compared with IDegLira. This outcome was expected, because of the presence of the insulin component and the glucose-dependent mode of action of GLP-1RAs.[33]

A significantly smaller increase in body weight was seen with IDegLira (2.9 kg) compared with degludec (4.1 kg), probably as a result of the weight-reducing effect of liraglutide.[20] This significant difference is in alignment with findings from the global trial programme.[20] The weight gain associated with IDegLira treatment is in contrast to the modest weight loss (−0.5 kg) observed with IDegLira in the global DUAL I trial,[20] which could be attributed to differences in background OAD therapy between the global DUAL I extension trial and the present trial, and/or the difference in the relationship between BMI, insulin resistance and diabetes development in Japanese and white people.[7,34-36]

When IDegLira was used, the mean daily doses of liraglutide and degludec were both lower compared with using the respective monotherapies after 52 weeks. In the liraglutide group, the daily dose reached the maximum licensed dose for diabetes of 1.8 mg by week 6, whereas in the IDegLira group, the actual daily liraglutide dose remained stable from week 9 onwards at ~1.0 mg. This demonstrates a clinical advantage of using the fixed-dose combination injection compared with the monotherapies alone.

There were no unexpected safety or tolerability issues identified with IDegLira, and the reported AEs were consistent with those of liraglutide or degludec.[37,38] Treatment with IDegLira also resulted in fewer gastrointestinal side effects compared with liraglutide treatment alone.

The DUAL I Japan trial aimed to compare the efficacy and safety of IDegLira with its components given alone in Japanese patients with T2D. Comparing IDegLira with the free combination of its components was beyond the scope of the present trial and may be perceived as a study limitation. Nonetheless, co-administration of degludec and liraglutide within a single daily injection provides a simpler regimen than administering these components separately, and may help to overcome clinical inertia with respect to intensifying therapy.

In conclusion, in comparison with the individual components of IDegLira, the fixed-ratio combination offers Japanese participants with T2D who have been on stable OAD therapy a simplified treatment regimen with the benefits of improved glycaemic control, a low risk of hypoglycaemia and less weight gain than insulin treatment alone.

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CONFLICT OF INTEREST

K.K. has received honoraria or consulting fees from Astellas Pharma, AstraZeneca, Kowa Pharmaceutical, Mitsubishi Tanabe Pharma, MSD,

Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Sanwa Kagaku Kenkyusho, Dainippon Sumitomo Pharma, Taisho Toyama Pharmaceutical, Takeda. E.A. has participated on advisory panels for Alcon, Astellas Pharma, Astra Zeneca, Eli Lilly, Kowa Pharmaceutical, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Sanofi and Terumo Corporation, has received honoraria for lectures from Astellas Pharma, MSD, Ono Pharmaceutical, Novo Nordisk Pharma and Sanofi, and scholarship grants from Astellas Pharma, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Ono Pharmaceutical, Sanofi, Shionogi, Sumitomo Dainippon Pharma and Takeda Pharmaceutical. Y.T. has participated on advisory panels for Kowa Pharmaceutical, Novo Nordisk Pharma, and Terumo Corporation, has received honoraria for lectures from Astellas Pharma, MSD, Ono Pharmaceutical, Novo Nordisk Pharma, Sanofi and Takeda Pharmaceutical, and scholarship grants from Astellas Pharma, Eli Lilly, Daiichi Sankyo, Mitsubishi Tanabe Pharma, Nippon Boehringer Ingelheim, Novo Nordisk Pharma, Ono Pharmaceutical, Sanofi, Shionogi, Sumitomo Dainippon Pharma and Takeda Pharmaceutical. B.R.A., T.N. and M.R. are employees and shareholders in Novo Nordisk. N.I. has acted as a speaker for MSD, ARKRAY, Inc., Astellas Pharma, Kissei, Sanofi, Novartis Pharma, Novo Nordisk Pharma, Bayer, Kowa Pharma, Ono Pharma, Kyowa Hakko Kirin, Sumitomo Dainippon Pharma, Daiichi Sankyo, Eli Lilly Japan, Nippon Boehringer Ingelheim, Takeda Pharma, Mitsubishi Tanabe Pharma, Medtronic Japan, Taisho Toyama Pharma, Pfizer Japan, FUJIFILM Pharma, Saishin-igaku, Toyooka Hospital, Terumo, Olympus, Sunstar Foundation, Japan Tobacco, ILSI Japan, University of Occupational and Environmental Health, Japanese Red Cross Wakayama Medical Center, AstraZeneca, Tsumura, Chugai Pharma, Wakayama Medical University, Hokkaido University, Boehringer Ingelheim and MSD Life Science Foundation, and has received grants from Shionogi, Pfizer Japan, Eli Lilly Japan, Tsumura, Taisho Toyama Pharma, Novo Nordisk Pharma, the Japan China Medical Association and Teijin Pharma.

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. K.K. 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.

DATA-SHARING STATEMENT

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

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