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ORIGINAL RESEARCH

The Efficacy of IDegLira (Insulin Degludec/Liraglutide Combination) in Adults with Type 2 Diabetes Inadequately Controlled with a GLP-1 Receptor Agonist and Oral Therapy: DUAL III Randomized Clinical Trial

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ABSTRACT

Introduction: The progressive nature of type 2 diabetes necessitates treatment intensification. This often involves intensification with oral antidiabetic drugs (OADs) initially, followed by other agents, such as glucagon-like peptide-1 receptor agonists (GLP-1RAs), with the majority of patients eventually requiring insulin therapy. Therefore, this trial aimed to investigate the efficacy of IDegLira (combination of insulin degludec and liraglutide) in controlling glycemia in adults with type 2 diabetes who were inadequately controlled on a GLP-1RA and OADs.

Methods: In this 26-week open-label phase 3b trial, patients on maximum-dose GLP-1RA therapy (liraglutide once daily or exenatide twice daily) with metformin alone or with pioglitazone and/or sulfonylurea were randomized 2:1 to IDegLira once daily ($n = 292$) or to unchanged GLP-1RA therapy ($n = 146$), continuing OADs at the pre-trial dose.

Results: After 26 weeks, HbA_{1c} reductions were superior with IDegLira versus unchanged GLP-1RA; estimated treatment difference −0.94% (−10.3 mmol/mol), $p < 0.001$. Mean

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HbA_{1c} reduced from 7.8% to 6.4% (61.5 to 46.9 mmol/mol) with IDegLira and from 7.7 to 7.4% (60.8 to 57.1 mmol/mol) with unchanged GLP-1RA. With IDegLira, 75% and 63% of patients achieved HbA_{1c} <7% and ≤6.5%, compared with 36% and 23% on unchanged GLP-1RA, respectively. Fasting plasma glucose and 9-point self-monitored blood glucose profiles improved significantly more with IDegLira versus unchanged GLP-1RA. The mean change in weight was +2.0 kg with IDegLira, versus −0.8 kg with unchanged GLP-1RA. Rates of confirmed hypoglycemia were low, but higher with IDegLira versus unchanged GLP-1RA. The safety profile of IDegLira was consistent with previous findings; both treatments were well tolerated and the rate of nausea was low in both groups. IDegLira improved patient-reported outcomes versus unchanged GLP-1RA.

Conclusions: IDegLira provided superior glycemic control versus unchanged GLP-1RA and represents an efficacious intensification approach in patients inadequately controlled on GLP-1RAs.

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Keywords: Clinical trial; GLP-1 receptor agonist; IDegLira; Insulin therapy; Type 2 diabetes

INTRODUCTION

Due to the progressive nature of type 2 diabetes, current therapies, including glucagon-like peptide-1 receptor agonists (GLP-1RAs), usually do not provide sustained glycemic control, so treatment intensification is necessary in many patients [1, 2]. Insulin remains the most efficacious glucose-lowering therapy, and is typically initiated when patients are unable to achieve glycemic control with lifestyle changes, oral antidiabetic drugs (OADs), and GLP-1RAs [2, 3]. GLP-1RAs can offer significant reductions in HbA_{1c} with a low risk of hypoglycemia and significant weight loss [4]. Several studies have demonstrated the clinical benefits of using basal insulin and GLP-1RAs together [5–9], and their co-use is supported by treatment guidelines [2]. Thus, intensification with basal insulin is seen as a natural progression for patients whose blood glucose is not controlled by a GLP-1RA and OADs.

Insulin degludec/liraglutide (IDegLira) is the first combination of a basal insulin (insulin degludec) and a GLP-1RA (liraglutide). The complementary modes of action of the two molecules can help to control both fasting plasma glucose (FPG) and postprandial glucose (PPG). IDegLira is available as a single once-daily injection that can be taken at any time of day, but preferably at the same time each day [10]. IDegLira is administered and titrated in a treat-to-target manner as dose steps, with each dose step containing 1 unit (U) of insulin degludec and 0.036 mg of liraglutide, up to a maximum of 50 dose steps (50 U insulin degludec and 1.8 mg liraglutide) daily [10].

The DUAL phase 3 clinical trial program investigated the efficacy and safety of IDegLira in patients with type 2 diabetes. DUAL I and its 26-week extension showed that IDegLira provided clinical advantages and improved glycemic control compared with its monocomponents given alone in insulin-naïve patients [11, 12]. DUAL II investigated the contribution of liraglutide in IDegLira in insulin-experienced patients, with patients on IDegLira achieving superior glycemic control versus those on insulin degludec (which was capped at 50 U per day) [13]. DUAL IV

investigated the efficacy and safety of IDegLira in insulin-naïve patients inadequately controlled with sulfonylurea with or without metformin, where it demonstrated superior glycemic control versus placebo [14]. DUAL V compared IDegLira with the uptitration of insulin glargine 100 units/mL in patients who were inadequately controlled on 20–50 U of insulin glargine 100 units/mL, with IDegLira resulting in superior HbA_{1c}, a lower rate of hypoglycemia, and weight loss versus insulin glargine 100 units/mL [15].

The primary objective of the DUAL III clinical trial was to confirm the superiority of IDegLira compared with continuing on unchanged GLP-1RA therapy in controlling glycemia in insulin-naïve adult patients with type 2 diabetes who were inadequately controlled with the maximum approved or tolerated dose of a GLP-1RA and OADs. The secondary objective of the trial was to compare the general efficacy and safety of IDegLira with unchanged GLP-1RA.

METHODS

Trial Design and Participants

This was a 26-week, multi-center, randomized, open-label, two-group parallel, treat-to-target trial conducted at 81 sites in five countries (Australia, France, Hungary, Slovakia, and the United States) between August 2012 and March 2014. The trial was registered at clinicaltrials.gov (NCT01676116), and was conducted in accordance with Declaration of Helsinki and ICH Good Clinical Practice [16, 17]. Informed consent was obtained from all patients before they were included in the trial.

Insulin-naïve patients with type 2 diabetes were enrolled if they were inadequately controlled with a GLP-1RA and OADs (metformin alone or in combination with pioglitazone and/or sulfonylurea). Pre-trial patients were treated with the maximum dose (according to the local label) or the maximum tolerated dose of either liraglutide once daily or exenatide twice daily, and OADs at stable dose for at least 90 days before screening. Patients were included if they were ≥18 years of age, had an HbA_{1c} of 7.0–9.0% (53–75 mmol/mol, both inclusive), and a body mass index (BMI) ≤40 kg/m^2. Patients were excluded if they had used any OADs except for metformin, pioglitazone, and sulfonylurea within 90 days prior to screening. Full inclusion and exclusion criteria are provided in the Table S1 in the Electronic supplementary material, ESM.

Randomization and Masking

Patients were stratified according to pre-trial type of GLP-1RA and randomized 2:1 to IDegLira or to continue on unchanged GLP-1RA therapy using an interactive voice/web response system. IDegLira was dosed once daily and could be administered at any time of the day, but preferably at the same time each day. Those on unchanged GLP-1RA continued on their pre-trial dosing regimen. Treatment assignment was masked for the safety committee and independent adjudication committee throughout the trial. No randomization codes were broken before database lock.

Procedures

IDegLira (100 units/mL insulin degludec and 3.6 mg/mL liraglutide in a 3 mL pre-filled PDS290 pen-injector, Novo Nordisk, Bagsværd, Denmark) was injected subcutaneously. The starting dose of IDegLira was 16 dose steps (16 U insulin degludec and 0.6 mg liraglutide).

Adjustment of IDegLira dose was performed twice weekly based on the three preceding pre-breakfast self-monitored blood glucose (SMBG) measurements. The IDegLira dose was titrated to an FPG target of 4.0–5.0 mmol/L (72–90 mg/dL) (Table S2 in the ESM). IDegLira could be titrated up to a maximum of 50 dose steps (50 U insulin degludec and 1.8 mg liraglutide).

Patients randomized to the unchanged GLP-1RA treatment continued their pre-trial treatment schedule without making any changes. Liraglutide (Victoza) was administered once daily using a 6.0 mg/mL solution provided in a 3-mL prefilled pen. Exenatide (Byetta) was administered twice daily using a 250 μg/mL solution provided in 1.2-mL or 2.4-mL prefilled pens. All previous OADs (metformin, pioglitazone, sulfonylurea) were continued at pre-trial doses in both groups unless there was a safety concern. OAD dose reduction was allowed for safety reasons (including hypoglycemic events) based on the judgment of the investigator.

At the screening visit, each patient was provided with a blood glucose monitoring meter in order to perform regular SMBG; this was used according to the manufacturer's instructions.

Outcomes

The primary endpoint was change in HbA_{1c} from baseline after 26 weeks of treatment. Key secondary efficacy endpoints included responders for HbA_{1c} [predefined targets of <7% (53 mmol/mol) and ≤6.5% (48 mmol/mol)] after 26 weeks of treatment, change from baseline in body weight, laboratory-measured FPG, and nine-point SMBG profile.

Safety variables included the number of treatment-emergent adverse events and episodes of confirmed hypoglycemia. Confirmed hypoglycemia was defined as plasma glucose ≤3.1 mmol/L (≤56 mg/dL) or severe hypoglycemia which required third-party assistance. Nocturnal confirmed hypoglycemia was defined as confirmed hypoglycemia occurring between 00:01 and 05:59, inclusive. Other safety endpoints included clinical evaluation (physical examination, fundoscopy, blood pressure, ECG, and pulse) and laboratory variables (including lipid profile, amylase, lipase, and calcitonin).

Patient-reported outcomes (PROs) were measured using the treatment-related impact measure—diabetes (TRIM-D) and diabetes treatment satisfaction questionnaire status (DTSQs) [18–20]. The TRIM-D questionnaire was used to measure the treatment-related impact of the diabetes medication, whereby a higher TRIM-D total score indicated a better health state [18, 19]. The DTSQs consisted of a questionnaire consisting of eight items; items 2 and 3 were perceived frequency of hyperglycemia and hypoglycemia, respectively, and were analyzed individually in the data analysis. A higher score for these items reflected a higher perceived frequency of hyperglycemia or hypoglycemia. The treatment satisfaction score was based on the sum of the remaining six items of the questionnaire. A higher score in the DTSQs treatment satisfaction scale total indicates higher patient satisfaction with treatment [20].

Statistics

The trial was powered to the primary objective of demonstrating superiority using a two-sided *t* test of size 5%, under the assumptions of a 0.4% treatment difference with a 1.2% standard deviation. From these assumptions, a total of 429 patients were randomized 2:1 to IDegLira

and unchanged GLP-1RA in order to obtain a nominal power of 90%.

The full analysis set (FAS) included all randomized subjects, and was used to analyze HbA_{1c}, FPG, SMBG, hypoglycemia, and body weight. The safety endpoints were summarized using the safety analysis set (SAS), which included all randomized subjects receiving at least one dose of the investigational product. Missing values were imputed using last observation carried forward (LOCF). The primary endpoint was also analyzed for the per protocol analysis set (all subjects in the FAS who fulfilled the inclusion criteria, had not violated any of the exclusion criteria, had HbA_{1c} values from screening, randomization and after 12 weeks of treatment, and were exposed to the trial product for at least 12 weeks), completers analysis set (all randomized subjects who completed the trial), and using a repeated measurement analysis (missing data were imputed using a mixed-model repeated measurement technique rather than utilizing LOCF, in order to evaluate the sensitivity of using LOCF).

Change in HbA_{1c} was analyzed using an analysis of covariance (ANCOVA) on the FAS. Treatment, pre-trial GLP-1RA, and region (Australia, Europe, or North America) were included as fixed effects with baseline HbA_{1c} as covariate. IDegLira was to be considered superior if the upper bound of the 95% confidence interval (CI) for the treatment difference was below 0.

Other continuous variables (mean of the nine-point SMBG profile, FPG, and body weight) were also analyzed by ANCOVA. Attainment of HbA_{1c} target $<7.0\%$ (53 mmol/mol) and $\leq 6.5\%$ (48 mmol/mol) was analyzed using a logistic regression model on the FAS population using LOCF, with treatment, pre-trial GLP-1 RA, and region as fixed factors and baseline HbA_{1c} value as covariate.

Hypoglycemia was analyzed using a negative binomial regression model based on the FAS population, with treatment, pre-trial GLP-1RA, and region included as fixed factors and the logarithm of the time period in which an episode was considered treatment emergent as offset.

TRIM-D and DTSQs questionnaires were completed at baseline, visit 14, and the end of the trial. Change from baseline score in each subdomain as well as the total score after 26 weeks of treatment were analyzed for the FAS population by ANCOVA, with treatment, pre-trial GLP-1 RA, and region as fixed effects and baseline value as covariate.

RESULTS

Of the 704 patients screened, 438 were randomized to receive trial product; 292 to IDegLira and 146 to unchanged GLP-1RA (Figure S1 in the ESM). Pre-trial, and in the unchanged GLP-1RA group, 79.5% of patients were treated with liraglutide and 20.5% with exenatide twice daily. A total of 94.5% of those randomized to IDegLira completed the trial versus 80.1% of those who were randomized to unchanged GLP-1RA. The baseline and demographic characteristics were similar for the treatment groups (Table 1). Patients continued with their pretrial OADs, with similar proportions of patients on one, two, or three OADs in each treatment group (Table 1). After 26 weeks, the mean IDegLira dose was 43 dose steps, equating to 43 U of insulin degludec and 1.5 mg of liraglutide.

Over the 26-week trial, the observed mean [standard deviation (SD)] HbA_{1c} decreased from a baseline of 7.8% (0.6) [61.5 mmol/mol (6.2)] to 6.4% (0.8) [46.9 mmol/mol (9.0)] with

Table 1 Baseline characteristics

Characteristic	IDegLira	Unchanged GLP-1RA
Full analysis set (FAS), *n*	292	146
Female/male, %	47.6/52.4	51.4/48.6
Race: white/black/Asian/American Indian (or Alaska native)/other, %	92.1/5.1/2.1/0.3/0.3	89.7/8.2/1.4/0.0/0.7
Ethnicity: Hispanic or Latin American, %	8.9	10.3
Age, years	58.3 ± 9.9	58.4 ± 8.8
Weight, kg	95.6 ± 16.6	95.5 ± 17.3
BMI, kg/m^2	32.9 ± 4.4	33.0 ± 4.1
Duration of diabetes, years	10.4 ± 5.8	10.4 ± 5.8
HbA_{1c}, %	7.8 ± 0.6	7.7 ± 0.6
mmol/mol[a]	61.5 ± 6.2	60.8 ± 6.7
FPG, mmol/L	9.0 ± 2.1	9.4 ± 2.3
mg/dL	161.7 ± 38.2	169.1 ± 41.7
Pretrial OADs, %		
Metformin	74.3	74.0
Metformin + sulfonylurea	20.9	21.9
Metformin + pioglitazone	2.4	2.7
Metformin + sulfonylurea + pioglitazone	2.4	1.4
Duration of treatment with GLP-1RA prior to randomization, days	468.1 ± 616.0	498.6 ± 525.1

Values are the mean ± SD unless otherwise stated

GLP-1RA glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *OAD* oral antidiabetic drug, *SD* standard deviation

[a] Calculated not measured

IDegLira and from 7.7% (0.5) [60.8 mmol/mol (6.7)] to 7.4% (1.0) [57.1 mmol/mol (10.9)] with unchanged GLP-1RA. The mean reductions in HbA_{1c} were 1.3% (0.8) [14.5 mmol/mol (9.3)] and 0.3% (0.9) [3.8 mmol/mol (10.0)] with IDegLira and unchanged GLP-1RA, respectively (Fig. 1a). IDegLira was superior to unchanged GLP-1RA, with an estimated treatment difference (ETD) of −0.94% (−1.11; −0.78)$_{95\%\ CI}$, [−10.3 mmol/mol (−12.2; –8.5)$_{95\%\ CI}$], $p < 0.001$. Furthermore, the robustness of the primary analysis was substantiated by three sensitivity analyses (the repeated measurement analysis, per protocol analysis, and completer analysis), all of which confirmed the superiority of IDegLira (data not shown).

Overall, 75% of patients on IDegLira achieved the HbA_{1c} target of <7.0% (53 mmol/mol) versus 36% on unchanged GLP-1RA therapy; estimated odds ratio (EOR) of 6.84 [4.28; 10.94]$_{95\%\ CI}$, $p < 0.001$. Similarly, significantly more patients on IDegLira (63%) versus those on unchanged GLP-1RA (23%) attained the HbA_{1c} target ≤6.5% (48 mmol/mol); EOR: 7.53 (4.58; 12.38)$_{95\%\ CI}$, $p < 0.001$ (Fig. 1b).

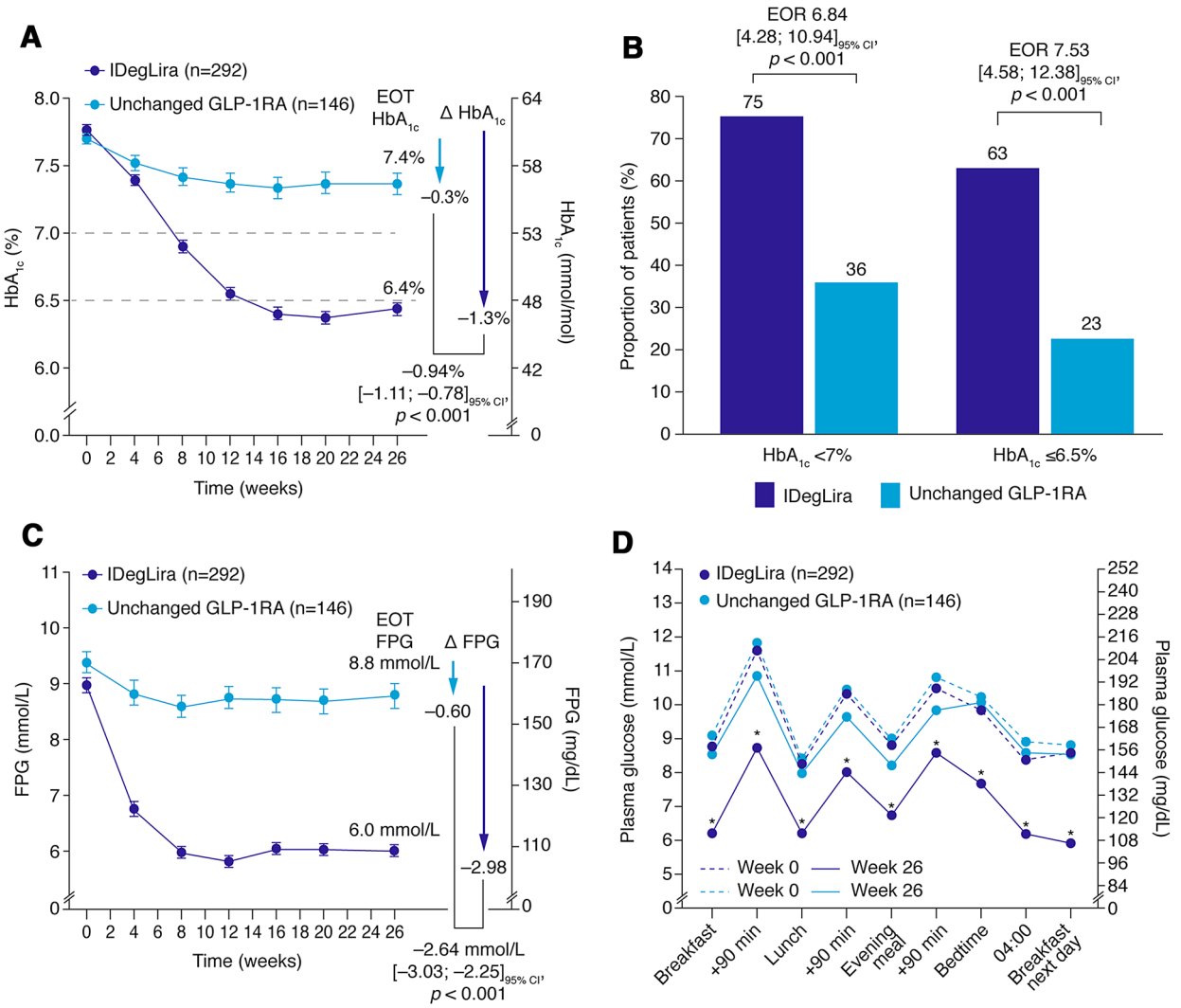

Fig. 1 **a** Glycemic efficacy HbA_{1c} over time. Mean observed values with *error bars* (standard error of the mean) based on FAS and LOCF imputed data. ETD is from ANCOVA analysis, and change in HbA_{1c} (Δ) values are observed; both are based on FAS and LOCF imputed data. *Dotted lines* represent ADA/EASD and AACE HbA_{1c} targets of <7.0% and ≤6.5%, respectively. **b** Patients achieving the HbA_{1c} target. Treatment comparisons are from a logistic regression model based on FAS and LOCF imputed data. **c** FPG over time. Mean observed values with *error bars* (standard error of the mean) based on FAS and LOCF imputed data. ETD is from ANCOVA analysis, and change in FPG (Δ) values are observed; both are based on FAS and LOCF imputed data. **d** Mean nine-point SMBG profile at weeks 0 and 26. $^{*}p < 0.001$ (post hoc analysis). Mean values are based on FAS, with missing profiles imputed using LOCF; SMBG was assessed with a glucose meter as plasma-equivalent values of capillary whole blood glucose. *ANCOVA* analysis of covariance, *EOR* estimated odds ratio, *EOT* end of trial, *FAS* full analysis set, *FPG* fasting plasma glucose, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *LOCF* last observation carried forward, *SMBG* self-monitored blood glucose

During the trial, there was a statistically significantly greater improvement in laboratory-measured FPG from baseline with IDegLira versus unchanged GLP-1RA, resulting in end-of-trial mean (SD) values of 6.0 mmol/L (1.6) and 8.8 mmol/L (2.7), respectively. The

mean (SD) reductions in FPG were 2.98 mmol/L (2.28) with IDegLira and 0.60 mmol/L (2.74) with unchanged GLP-1RA, ETD: −2.64 mmol/L $(-3.03; -2.25)_{95\%\ CI}$, $p < 0.001$ (Fig. 1c).

After 26 weeks, the mean nine-point SMBG profile had decreased with both treatments versus baseline. The end-of-trial mean of the nine-point SMBG profile was statistically significantly lower with IDegLira versus unchanged GLP-1RA, with an ETD of −1.78 mmol/L $(-2.13; -1.43)_{95\%\ CI}$, $p < 0.001$. At all nine time points, measured SMBG values were statistically significantly lower with IDegLira versus unchanged GLP-1 RA (Fig. 1d, post hoc analysis). Importantly, glucose control did not deteriorate during the first 4 weeks with IDegLira after transfer from the pre-trial GLP-1RA dose (Fig. 2) [1.2 or 1.8 mg liraglutide (mean daily dose at baseline 1.7 mg) or 5 or 10 μg exenatide twice daily (mean daily dose at baseline 18.4 μg) maximum dose, depending on local label or maximum tolerated dose] to the IDegLira starting dose of 16 dose steps (16 U insulin degludec and 0.6 mg liraglutide).

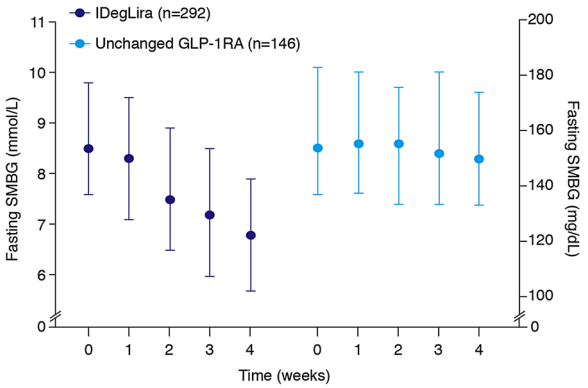

Fig. 2 Glycemic control during the first 4 weeks of the trial. Values are the median with interquartile range, based on FAS and with missing values imputed using LOCF. *FAS* full analysis set, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *LOCF* last observation carried forward, *SMBG* self-monitored blood glucose

After 26 weeks, observed mean (SD) body weight increased by 2.0 kg (3.9) from baseline with IDegLira and decreased by 0.8 kg (3.0) with unchanged GLP-1RA, corresponding to a statistical significant ETD of 2.89 kg $(2.17; 3.62)_{95\%\ CI}$, $p < 0.001$, in favor of unchanged GLP-1RA (Fig. 3). Body weight was also summarized according to whether patients were treated with concomitant sulfonylurea therapy. With IDegLira, the increase from baseline in body weight was more pronounced in the sulfonylurea-treated (3.3 kg) compared with the non-sulfonylurea-treated patients (1.6 kg). With unchanged GLP-1RA, the change from baseline in body weight was −0.7 versus −0.8 kg in sulfonylurea-treated versus non-sulfonylurea-treated patients, respectively.

With IDegLira there were 2.82 episodes of confirmed hypoglycemia per patient-years of exposure (PYE) versus 0.12 episodes per PYE with unchanged GLP-1RA, corresponding to an estimated rate ratio (ERR) of 25.36 (10.6;

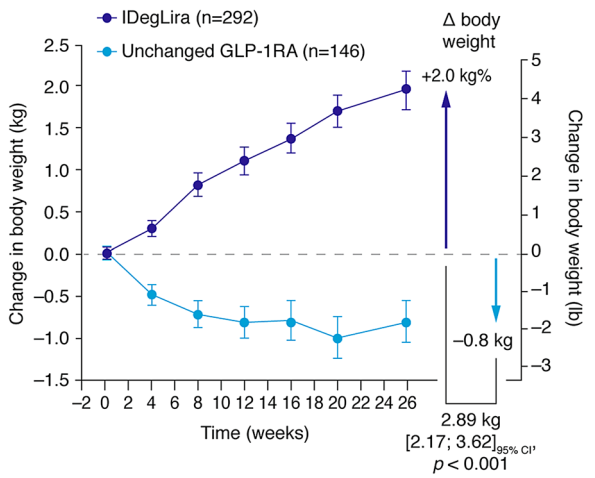

Fig. 3 Body weight over time. Values are the mean with error bars (standard error of the mean), based on FAS and with missing values imputed using LOCF. Estimated treatment differences are from an ANCOVA analysis. *ANCOVA* analysis of covariance, *FAS*, full analysis set, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *LOCF* last observation carried forward

60.5)$_{95\%\ CI}$, $p < 0.001$ (Table 3 in the ESM). One episode of severe hypoglycemia was reported in the IDegLira group. The rate of nocturnal confirmed hypoglycemia was statistically significantly higher with IDegLira (0.454 episodes per PYE) compared with unchanged GLP-1RA (0.015 episodes per PYE), ERR: 32.82 (4.13; 261.04)$_{95\%\ CI}$, $p < 0.001$ (Table S3 in the ESM). Hypoglycemic episodes were also summarized according to whether patients were receiving concomitant sulfonylurea therapy. With IDegLira, the rate of confirmed hypoglycemia was 6.34 events per PYE in sulfonylurea-treated patients ($n = 68$) versus 1.75 events per PYE in non-sulfonylurea-treated patients ($n = 223$). With unchanged GLP-1RA, the event rate was 0.51 events per PYE in sulfonylurea-treated patients ($n = 34$) and 0 events per PYE in non-sulfonylurea-treated patients ($n = 111$) (Table S4 in the ESM).

Overall, the proportions and rates of treatment-emergent adverse events and serious adverse events reported with IDegLira and unchanged GLP-1RA were similar (Table 2). The overall rates of adverse events were 410.1 events per 100 PYE with IDegLira and 364.3 events per 100 PYE with unchanged GLP-1RA; the majority of these events were non-serious and were evaluated as mild in severity by the investigator. The most frequently reported adverse events were nasopharyngitis, upper respiratory tract infection, lipase increased, headache and diarrhea. The rates of serious adverse events were nine and five events per 100 PYE with IDegLira and unchanged GLP-1RA, respectively (Table 2); none were reported as possibly or probably related to the trial product. No deaths were reported during the trial.

In three patients, adverse events resulted in withdrawal: one with IDegLira (drug hypersensitivity) and two with unchanged GLP-1RA (abdominal discomfort and foot fracture). Nausea occurred in 3.1% of patients with IDegLira compared with 4.1% of patients with unchanged GLP-1RA, with 7.8 versus 10.6 events per 100 PYE, respectively. Two major adverse cardiovascular events (MACE) were sent for adjudication; both were confirmed by the external blinded event adjudication committee as stroke and they occurred in the IDegLira group. Seven potential neoplasms occurred during the trial and were sent for adjudication. Three of these were confirmed events of neoplasm, two events with IDegLira, and one with unchanged GLP-1RA. No medullary thyroid carcinoma events were reported. An additional event (lymphadenopathy) was also sent for adjudication but was not confirmed as a neoplasm. No pancreatitis or thyroid-related adverse events occurred in either treatment group.

Overall, the changes from baseline to week 26 in fasting lipid levels were small for both treatment groups. At the end of the trial, total cholesterol [estimated treatment ratio (ETR): 0.96 (0.93; 1.00)$_{95\%\ CI}$, $p = 0.025$], very low density lipoprotein cholesterol [ETR: 0.90 (0.85; 0.96)$_{95\%\ CI}$, $p < 0.001$], triglycerides [ETR: 0.88 (0.82; 0.94)$_{95\%\ CI}$, $p < 0.001$], and free fatty acids [ETR: 0.71 (0.65; 0.77)$_{95\%\ CI}$, $p < 0.001$] were statistically significantly lower with IDegLira versus unchanged GLP-1RA. A decrease in lipase activity from baseline to the end of the trial was observed both with IDegLira (mean change −1.0 units/L) and unchanged GLP-1RA (mean change −1.8 units/L) (Table S5 in the ESM). An increase in amylase activity was observed with IDegLira (mean change 6.2 units/L) compared with a decrease with unchanged GLP-1RA (mean change −1.0 units/L) (Table S5 in the ESM). No clinically relevant differences were observed between treatment groups in mean calcitonin levels, physical examination, or

Table 2 Adverse events

	IDegLira				Unchanged GLP-1RA			
	N	(%)	*E*	*R*	*N*	(%)	*E*	*R*
Adverse events	191	65.6	578	410	92	63.4	240	364
Serious	9	3.1	12	9	3	2.1	3	5
Deaths	0	–	–	–	0	–	–	–
Severe	9	3.1	14	10	3	2.1	3	5
Probably related to investigational product	11	3.8	12	9	3	2.1	3	5
Related to device	0	–	–	–	0	–	–	–

% percentage of subjects, *E* number of events, *N* number of subjects with ≥1 event, *R* rate of events per 100 PYE, *GLP-1RA* glucagon-like peptide-1 receptor agonist, *IDegLira* insulin degludec/liraglutide combination, *PYE* patient years of exposure

fundoscopy during the trial. There were no statistically significant differences in systolic or diastolic blood pressure between treatment groups. After 26 weeks of treatment, there was a statistically significant difference in mean pulse between IDegLira and unchanged GLP-1RA; ETD of 1.78 beats/min $(0.22; 3.33)_{95\%\ CI}$, $p = 0.025$.

The PRO scores improved with both treatments from baseline to the end of the trial, but to a greater extent with IDegLira. After 26 weeks of treatment with IDegLira, the TRIM-D total score was statistically significantly higher (indicating a better health state/outcome) than with unchanged GLP-1 RA, with an ETD of 5.0 units $(2.9; 7.2)_{95\%\ CI}$, $p < 0.001$ (Table S6 in the ESM). In both treatment groups, all TRIM-D subdomain scores and the total score increased throughout the trial. In all subdomains, the score increases were statistically significantly higher with IDegLira versus unchanged GLP-1RA (Table 6 in the ESM). After 26 weeks of treatment, the DTSQs treatment satisfaction score was statistically significantly higher with IDegLira compared with unchanged GLP-1RA, with an ETD of 2.0 units $(1.1; 2.8)_{95\%\ CI}$, $p < 0.001$. Hypoglycemia and hyperglycemia were scored significantly higher and lower, respectively, by patients treated with IDegLira versus unchanged GLP-1RA, indicating a higher perceived frequency of hypoglycemia and a lower perceived frequency of hyperglycemia with IDegLira (Table S6 in the ESM).

DISCUSSION

Due to the progressive nature of type 2 diabetes, many patients need to intensify their treatment in order to maintain glycemic control. A commonly used approach is the initiation of a GLP-1RA after one or more OADs fail to keep a patient at the target HbA_{1c} [21]. There are currently several options for treatment intensification in patients on a GLP-1RA, and the addition of basal insulin is a recognized option in the ADA/EASD guidelines [2]. Initiating basal insulin, and therefore the use of IDegLira, is a natural progression in the treatment of type 2 diabetes for those uncontrolled on a GLP-1RA, where beta-cell failure continues and endogenous insulin secretion declines. This trial investigated the efficacy and safety of IDegLira in patients with type 2 diabetes uncontrolled on a GLP-1RA. It demonstrates that when transferring from

maximum dose GLP-1RA to the IDegLira starting dose of 16 dose steps, there was no deterioration in blood glucose during the first 4 weeks of treatment. After 26 weeks, patients on IDegLira achieved superior HbA_{1c}, and had a statistically significant reduction in FPG and nine-point SMBG profile compared with those who continued unchanged GLP-1RA therapy. IDegLira also enabled significantly more patients to reach the HbA_{1c} targets of <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol).

Overall, the safety and tolerability profile of IDegLira was consistent with previous findings [11–14]. Initiation of IDegLira resulted in a statistically significantly increase in weight and a higher rate of hypoglycemia compared with unchanged GLP-1RA, however, this is to be expected following the introduction of insulin, and has been observed in other trials of insulin-naïve patients [22–25]. Moreover, the rate of hypoglycemia was low in both groups. The concomitant use of sulfonylurea in ~23% of the patients in the IDegLira group may have also contributed to the hypoglycemia and weight gain. A post hoc summary showed that hypoglycemia was more frequent in the IDegLira plus sulfonylurea-treated patients versus those on IDegLira without sulfonylurea; this was also observed with unchanged GLP-1RA. This is consistent with the results of the DUAL IV clinical trial, where IDegLira was investigated as an add-on to sulfonylurea therapy and the rate of hypoglycemia was higher [14] compared with other IDegLira trials where concomitant sulfonylurea treatment was not part of the background OAD therapy [11, 13]. It is recognized that insulin and sulfonylurea is a frequently used combination [26]. According to the IDegLira prescribing information, a reduction in the dose of sulfonylurea should be considered when IDegLira is added to sulfonylurea therapy [10], whereas pre-trial doses were maintained during this trial unless there was a safety concern. The DUAL III trial had an FPG target of 4–5 mmol/L. In DUAL IV, the FPG target was 4–6 mmol/L (72–108 mg/dL) and the rate of confirmed hypoglycemia with IDegLira plus sulfonylurea was 3.5 versus 1.4 episodes per PYE with placebo [14]. The ADA have recently raised their glycemic target from 3.9–7.2 to 4.4–7.2 mmol/L (70–130 to 80–130 mg/dL) [27]. Therefore, we can speculate that lower rates of hypoglycemia may be observed in real-life clinical practice with IDegLira, where sulfonylurea doses would be reduced and glycemic targets individualized if the patient experienced hypoglycemia. The frequency of nausea was low with both treatments (occurring in 3.1% with IDegLira and 4.1% with unchanged GLP-1RA); a low frequency of nausea has also been observed with IDegLira in other clinical trials [28].

Overall, IDegLira treatment had a positive impact on PROs compared with unchanged GLP-1RA. The change from baseline score for TRIM-D in the IDegLira group was greater than that in the unchanged GLP-1RA group. In the DTSQ, patients treated with IDegLira reported greater treatment satisfaction versus those on unchanged GLP-1RA. According to the DTSQs, patients on IDegLira perceived the frequency of hypoglycemia to be higher and hyperglycemia to be lower than in patients on unchanged GLP-1RA. This is in line with the clinical results of the trial.

A limitation of this trial is that IDegLira was compared to an unchanged pre-trial comparator, and it would be interesting to compare the initiation of IDegLira in patients uncontrolled on a GLP-1RA with an active comparator, e.g., basal insulin. Also, due to the open-label nature of the trial, an improvement in PRO may be expected in the patients receiving the trial product compared with those continuing their existing therapy.

CONCLUSIONS

In conclusion, in patients inadequately controlled on maximum dose GLP-1RA and OADs, IDegLira resulted in a superior HbA_{1c} reduction and enabled patients to achieve a lower FPG and nine-point SMBG profile compared with patients continuing unchanged GLP-1RA therapy. Patients treated with IDegLira gained more weight and experienced more hypoglycemia versus unchanged GLP-1RA therapy; these results are consistent with previous findings on GLP-1RA intensification with insulin-containing therapy. Treatment with IDegLira resulted in a low rate of nausea and improved PROs versus unchanged GLP-1RA. IDegLira represents an efficacious and simple approach to intensifying therapy in patients uncontrolled on GLP-1RAs.

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All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published. SL, BWB, LBC, JPC, YH, and RWS were principal investigators on this trial and contributed to data collection, analysis, and interpretation. RWS was appointed as the signatory investigator for the trial. LML was medically responsible for the trial and AM was the trial statistician. All authors confirm that they meet the International Committee of Medical Journal Editors (ICJME) requirements for authorship and that they have contributed to the critical analysis and interpretation of the data as well as the drafting/critical revision of the manuscript, and they share in the final responsibility for the content of the manuscript and the decision to submit it for publication. SL is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with Ethics Guidelines. The trial was registered at clinicaltrials.gov: NCT01676116, and all procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients before they were included in the trial.

Data Availability. The datasets obtained and/or analyzed during the current study are available from the corresponding author on reasonable request.

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