Contribution of Liraglutide in the Fixed-Ratio Combination of Insulin Degludec and Liraglutide (IDegLira)

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OBJECTIVE

Insulin degludec/liraglutide (IDegLira) is a novel combination of insulin degludec (IDeg) and liraglutide. This trial investigated the contribution of the liraglutide component of IDegLira versus IDeg alone on efficacy and safety in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS

In a 26-week, double-blind trial, patients with type 2 diabetes (A1C 7.5–10.0% [58–86 mmol/mol]) on basal insulin (20–40 units) and metformin with or without sulfonylurea/glinides were randomized (1:1) to once-daily IDegLira + metformin or IDeg + metformin with titration aiming for fasting plasma glucose between 4 and 5 mmol/L. Maximum allowed doses were 50 dose steps (equal to 50 units IDeg plus 1.8 mg liraglutide) and 50 units for IDeg. The primary end point was change in A1C from baseline.

RESULTS

A total of 413 patients were randomized (mean A1C 8.8% [73 mmol/mol]; BMI 33.7 kg/m^2). IDeg dose, alone or as part of IDegLira, was equivalent (45 units). A1C decreased by 1.9% (21 mmol/mol) with IDegLira and by 0.9% (10 mmol/mol) with IDeg (estimated treatment difference −1.1% [95% CI −1.3, −0.8], −12 mmol/mol [95% CI −14, −9; $P < 0.0001$). Mean weight reduction with IDegLira was 2.7 kg vs. no weight change with IDeg, $P < 0.0001$. Hypoglycemia incidence was comparable (24% for IDegLira vs. 25% for IDeg). Overall adverse events were similar, and incidence of nausea was low in both groups (IDegLira 6.5% vs. IDeg 3.5%).

CONCLUSIONS

IDegLira achieved glycemic control superior to that of IDeg at equivalent insulin doses without higher risk of hypoglycemia and with the benefit of weight loss. These findings establish the efficacy and safety of IDegLira and the distinct contribution of the liraglutide component.

Basal insulin therapy, often in combination with oral agents, including metformin, is well established for the treatment of patients with type 2 diabetes. Once initiated, basal insulin is usually continued even when control is not achieved (1,2). Indeed, more than half of patients with type 2 diabetes treated with basal insulin do not achieve glycemic control (A1C ≤7.0% [53 mmol/mol]) (1,3,4) and are therefore at increased risk of developing diabetes complications. Delayed or suboptimal

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treatment intensification is often caused by common associated barriers, both from a patient perspective (fear of hypoglycemia and weight gain, increased regimen complexity) and from a physician perspective (lack of patient adherence, increased need for resources, reluctance to titrate insulin and add to additional insulin injections). Further treatment options for optimizing glycemic control are therefore needed, ideally without increasing complexity, the risk of hypoglycemia, or weight gain (5–8).

The American Diabetes Association and European Association for the Study of Diabetes have recommended the combination of basal insulin and a GLP-1 receptor agonist (9). In line with this, insulin degludec/liraglutide (IDegLira), a novel combination of basal insulin degludec (IDeg) and GLP-1 analog liraglutide, is being developed for the treatment of patients with type 2 diabetes as a once-daily, single subcutaneous injection. IDegLira combines the complementary effects of IDeg and liraglutide on glycemic control (10–12). The main pharmacologic effect of IDeg is to lower fasting plasma glucose (FPG) levels (13), while liraglutide targets FPG as well as modestly reducing postprandial glucose excursions (14). The effects of the liraglutide component of IDegLira on β-cell and α-cell function are glucose dependent and may counterbalance the risk of hypoglycemia seen with increasing doses of insulin. Furthermore, by reducing hunger and food intake, IDegLira has the potential to mitigate the weight gain associated with insulin therapy.

The aim of this trial was to determine the relative contribution of the liraglutide component of the combination product while examining the efficacy and safety of IDegLira, as recommended by regulatory authorities. This goal was achieved by conducting a comparison of IDegLira with IDeg in a double-blind fashion and with identical exposure to IDeg in both arms of the study. For achievement of this latter target, a patient population was recruited that was likely to require near-maximal doses of IDegLira (patients inadequately controlled on prior insulin therapy), and IDeg titration was limited to the maximal amount provided in full doses of IDegLira (50 units). A companion study, which will be reported separately, allowed for unlimited IDeg titration in comparison with IDegLira.

RESEARCH DESIGN AND METHODS

Trial Design and Participants

DUAL II was a phase 3, 26-week, randomized, parallel, two-arm, double-blind trial comparing the efficacy and safety of IDegLira + metformin with IDeg + metformin in patients with type 2 diabetes inadequately controlled on basal insulin + metformin with or without sulfonylurea/glinides.

Patients were screened at 75 trial sites across seven countries (Supplementary Table 1). The trial protocol, consent form, and information sheet were approved by appropriate health authorities and independent ethics committee/institutional review boards. Written informed consent was obtained from participants before enrollment. The trial was performed in accordance with the Declaration of Helsinki (15) and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice (16).

Eligible participants were ≥18 years of age, with inadequately controlled type 2 diabetes (A1C of 7.5−10.0% [58−86 mmol/mol], inclusive) and a BMI ≥27 kg/m^2 and treated for ≥90 days with basal insulin at a stable dose (20−40 units/day [±10%]) in combination with metformin with or without sulfonylurea or glinides. Supplementary Tables 2 and 3 provide full lists of eligibility criteria. Race/ethnicity was identified by the investigator, choosing between the following: race, white, black or African American, Asian Indian, Asian non-Indian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, other, or not applicable, and ethnicity, Hispanic or Latino, non-Hispanic, or Latino.

Randomization and Masking

Via a central interactive voice/web system, participants were randomly allocated 1:1 to receive once-daily, subcutaneous injections of either IDegLira (100 units/mL IDeg and 3.6 mg/mL liraglutide in a 3-mL prefilled FlexPen; Novo Nordisk, Bagsvaerd, Denmark) or IDeg (100 units/mL in a 3-mL prefilled FlexPen). Allocation was stratified with respect to pretrial treatment with or without sulfonylurea/glinide.

Novo Nordisk ensured continuous safety surveillance and monitoring of titration. An external independent event adjudication committee (EAC) performed ongoing adjudication of cardiovascular events, pancreatitis, neoplasms, and thyroid disease requiring thyroidectomy (Supplementary Table 4). An independent committee of thyroid experts regularly monitored plasma calcitonin levels.

Treatment was blinded for investigators and participants via use of visually identical trial drugs. Blinding was maintained for all involved in the trial (including titration, event adjudication, and calcitonin monitoring) until the database was released for statistical analyses.

Procedures

At randomization, participants discontinued all glucose-lowering drugs except for metformin (kept at pretrial dose and frequency) and transferred from current basal insulin to IDegLira or IDeg. Initiation dose was 16 units IDeg or 16 dose steps IDegLira (16 units IDeg plus 0.6 mg liraglutide). One dose step of IDegLira contains 1 unit IDeg plus 0.036 mg liraglutide.

Doses of IDeg and IDegLira were adjusted biweekly according to a predefined titration algorithm, based on self-measured prebreakfast FPG (mean of 3 consecutive days), striving for a mean prebreakfast glucose concentration of 4.0–5.0 mmol/L (72–90 mg/dL) (Supplementary Table 5). IDegLira and IDeg were to be dosed once daily, independent of meals but preferably at the same time every day. Maximum dose was 50 units IDeg or 50 dose steps IDegLira (50 units IDeg plus 1.8 mg liraglutide).

Participants performed blood glucose monitoring with a glucose meter (Abbott Diabetes Care, Abbott Park, IL), calibrated to plasma values.

Outcome Measures

The primary end point was change from baseline in A1C after 26 weeks of treatment. Secondary efficacy end points included doses of IDegLira and IDeg after 26 weeks, achievement of A1C levels of <7.0% (53 mmol/mol) and ≤6.5% (48 mmol/mol), and achievement of these A1C levels with or without confirmed hypoglycemia or weight gain, changes in laboratory-measured FPG, 9-point

plasma glucose (PG) profiles, and body weight.

Safety assessments included adverse events (AEs), hypoglycemic episodes, laboratory analyses, physical examination, and electrocardiogram. Confirmed hypoglycemia consisted of episodes confirmed by a PG value <3.1 mmol/L (56 mg/dL) (regardless of symptoms) and severe episodes (requiring assistance of another person). Confirmed hypoglycemia with onset between 0001 and 0559 h (inclusive) was classified as nocturnal.

A central laboratory (Quintiles Limited, Livingston, U.K.) performed laboratory analyses.

Statistical Analyses

The primary objective was to confirm the superiority of IDegLira versus IDeg with respect to change from baseline in A1C after 26 weeks of treatment. Sample size was calculated using a two-sided *t* test of size 5%, assuming a mean treatment difference of 0.4% (4 mmol/mol) and SD of 1.2% (13 mmol/mol) for A1C. To obtain at least 90% power of meeting the primary objective, we required 382 participants. The primary end point was analyzed using an ANCOVA model with treatment, previous glucose-lowering drugs, and country as fixed factors and baseline value as covariate. Superiority was confirmed if the 95% CI for the treatment difference was entirely below 0%. All analyses of efficacy and safety end points, as well as summarized baseline values, were based on the full analysis set (subjects contributed to the analysis "as randomized"). The full analysis set comprised all randomized participants except for 15 (8 IDegLira and 7 IDeg) who were excluded from analysis before unmasking of trial results owing to a breach in Good Clinical Practice at a trial site. Sensitivity analyses were performed for the primary end point (Supplementary Table 6).

Mean daily insulin dose and change from baseline in FPG, body weight, mean 9-point PG profile, and mean prandial increment across meals were analyzed using the same model as used for the primary end point; for dose, baseline A1C was also included as covariate. Analysis of responder end points was based on a logistic regression model with treatment, region, and previous glucose-lowering drugs as fixed factors and baseline value(s) as covariate(s). Mean of the 9-point PG profile was defined as the area under the profile (calculated using the trapezoidal method) divided by the measurement time. The mean increment across meals (calculated as change from premeal to 90 min postmeal) was derived as the mean of all available meal increments. A mixed-effect model for repeated measures was fitted to the 9-point profile data. The model included treatment, time point, previous antidiabetes treatment, country, and treatment by time-point interaction as fixed factors and baseline 9-point profile value as covariate. The number of confirmed and nocturnal confirmed hypoglycemic episodes was analyzed using a negative binomial regression model with a log-link function and the logarithm of the time period in which a hypoglycemic episode was considered treatment emergent as offset. The model included treatment, previous antidiabetes treatment, and region as fixed factors.

RESULTS

Of 831 patients screened, 413 were randomized and treated between 28 November 2011 and 4 October 2012. Of ineligible patients, 90% failed to meet the requirement for A1C. Completion rates were 85% for IDegLira and 83% for IDeg. Withdrawal patterns were comparable between treatment groups; none withdrew owing to gastrointestinal AEs (Supplementary Fig. 1).

Baseline characteristics were similar between treatment groups and representative of a population with type 2 diabetes inadequately controlled on their current treatment (Table 1).

While doses were uptitrated, mean A1C concentration decreased over time with both treatments (Fig. 1*A*, *B*, and *E*). The decrease was observed earlier with IDegLira than with IDeg. At 26 weeks, mean A1C was reduced by 1.9% (21 mmol/mol) with IDegLira and by 0.9% (10 mmol/mol) with IDeg to 6.9% (52 mmol/mol) and 8.0% (64 mmol/mol), respectively (Fig. 1*A* and *B*). The estimated treatment difference (ETD) (IDegLira – IDeg) was −1.1% (95% CI −1.3, −0.8) (−12 mmol/mol [95% CI −14, −9]), $P < 0.0001$, confirming superiority of IDegLira over IDeg; again, note that IDeg titration in this protocol was limited to a maximal dose of 50 units per day. All sensitivity analyses confirmed this result (Supplementary Table 6).

After 26 weeks, the mean daily doses of IDeg, either alone or as part of IDegLira, were equivalent (45 units, *P* = NS) (Fig. 1*E*), thus allowing for a valid assessment of the contribution of the liraglutide component in IDegLira.

At trial end, 60% of participants in the IDegLira group had achieved A1C <7.0% (53 mmol/mol), compared with 23% in

Table 1—Baseline characteristics

Characteristic	IDegLira	IDeg
FAS, *n*	199	199
Female/male, %	44/56	47/53
Race: white/black/Asian/other#, %	79/5/17/0	76/5/18/1
Ethnicity: Hispanic or Latino/non-Hispanic or Latino, %	8/92	12/88
Age, years	57 ± 9	58 ± 11
Weight, kg	95.4 ± 19	93.5 ± 20
BMI, kg/m^2	33.6 ± 6	33.8 ± 6
Duration of diabetes, years	10 ± 6	11 ± 7
A1C, % (mmol/mol)	8.7 ± 0.7 (72 ± 8)	8.8 ± 0.7 (73 ± 8)
FPG, mg/dL	175 ± 52	173 ± 56
FPG, mmol/L	9.7 ± 2.9	9.6 ± 3.1
Basal insulin dose (units)	29 ± 8	29 ± 8
Treatment at screening		
Basal insulin + metformin, *n* (%)	95 (48)	98 (49)
Basal insulin + metformin + SU/glinides, *n* (%)	104 (52)	101 (51)

Data are mean ± SD unless otherwise stated. SU, sulfonylurea. #"Other" comprises "American Indian/Alaska Native" (*n* = 0), "Native Hawaiian/other Pacific Islander" (*n* = 1), and "Other" (*n* = 1).

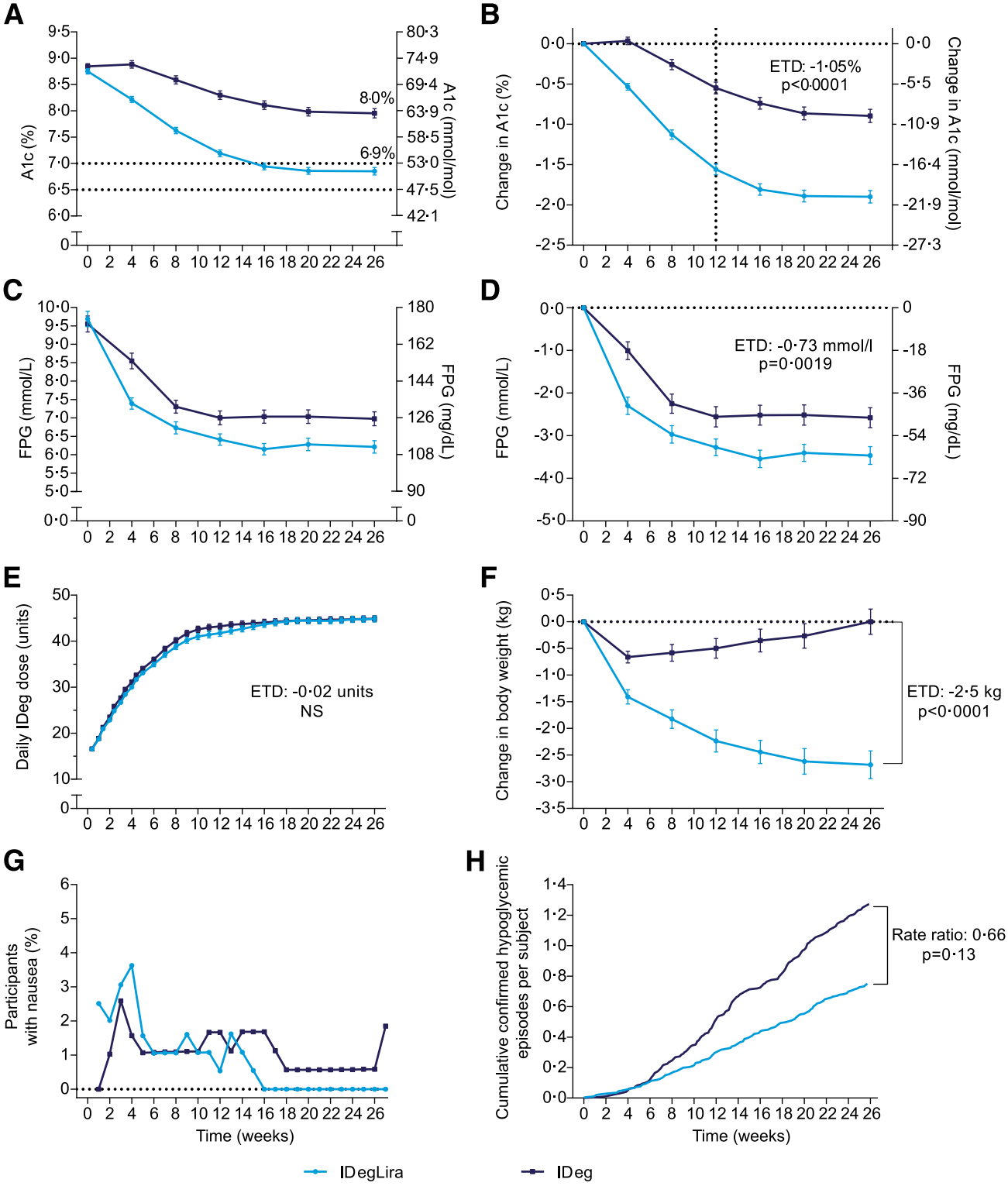

Figure 1—Glycemic efficacy, insulin dose, body weight, and AEs. Data are means (SE). *A*: A1C. *B*: Change in A1C. *C*: FPG. *D*: Change in FPG. *E*: Daily dose of IDeg alone or as part of IDegLira. *F*: Change in body weight. *G*: Proportion of subjects with nausea. *H*: Overall confirmed hypoglycemic episodes.

the IDeg group. The estimated odds of achieving A1C <7.0% (53 mmol/mol) after 26 weeks were statistically significantly higher for participants treated with IDegLira compared with IDeg ($P <$ 0.0001). With IDegLira, 40% of participants achieved A1C <7.0% (53 mmol/mol) without any confirmed hypoglycemic episodes during the last 12 weeks of treatment and without weight gain (change in body weight from baseline ≤0 kg), compared with 8.5% of participants treated with IDeg ($P < 0.0001$) (Supplementary Table 7). FPG decreased over time with both treatments, most pronouncedly with IDegLira. The greatest change in FPG was observed during the first 8 weeks, reaching a plateau at 12–16

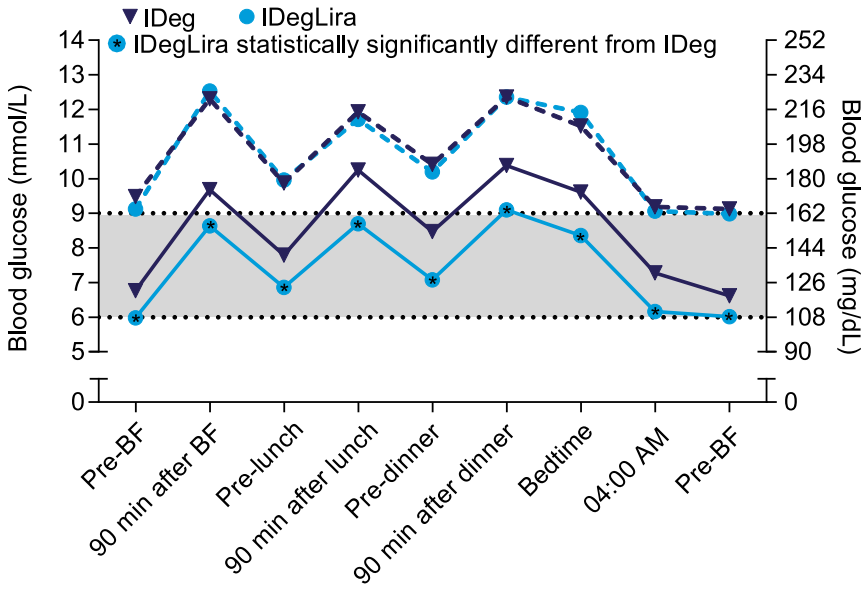

Figure 2—Mean 9-point self-monitored blood glucose profiles at baseline (dotted line) and after 26 weeks (full line). Mean values based on full analysis set and with missing profiles imputed from baseline; dotted line and gray area indicate the glycemic range of IDegLira. *At all 9 time points, self-monitored blood glucose values were statistically significantly lower with IDegLira compared with IDeg (*P* values ranged from <0.0001 to 0.0290). BF, breakfast.

weeks (Fig. 1*C* and *D*). At 26 weeks, mean (SD) FPG had decreased by 3.5 (2.9) mmol/L [62 (53) mg/dL] with IDegLira and 2.6 (3.3) mmol/L [46 (60) mg/dL] with IDeg to 6.2 mmol/L (112 mg/dL) and 7.0 mmol/L (126 mg/dL), respectively. ETD was −0.73 mmol/L (95% CI −1.19, −0.27) (−13 mg/dL [95% CI −21, −5]), *P* = 0.0019, demonstrating statistically significantly greater reduction in FPG for IDegLira compared with IDeg.

The 9-point profiles were similar at baseline (Fig. 2). After 26 weeks, PG concentrations had decreased with both treatments, and the 9-point profile for IDegLira revealed statistically significantly lower glucose concentrations compared with IDeg at all 9 time points (*P* value ranged from <0.0001 to 0.0290). The mean of the 9-point profiles decreased by 3.2 mmol/L (58 mg/dL) with IDegLira and by 2.0 mmol/L (36 mg/dL) with IDeg to end-of-trial values of 7.5 mmol/L (135 mg/dL) and 8.7 mmol/L (157 mg/dL), respectively. ETD was −1.1 mmol/L (95% CI 1.4, 0.7) (−19 mg/dL [95% CI −26, −13]), *P* < 0.0001, demonstrating statistically significantly greater reduction in mean glucose concentration with IDegLira compared with IDeg. At trial end, the mean prandial increment across meals was smaller with IDegLira (2.2 mmol/L [40 mg/dL]) than with IDeg (2.4 mmol/L [43 mg/dL]); ETD −0.4 mmol/L (95% CI −0.7, −0.0) (−7 mg/dL [95% CI −12, −1]), *P* = 0.0260.

After initiation of IDegLira at 16 dose steps, an immediate decline in mean prebreakfast glucose concentration was observed. In contrast, a transient increase occurred upon initiation of IDeg at 16 units (Supplementary Fig. 2*A–C*). A fraction of participants had a prebreakfast glucose increase >5.0 mmol/L (91 mg/dL) 3 days after transfer (IDegLira 2.6%, IDeg 5.2%), while a greater proportion had an increase >2.0 mmol/L (36 mg/dL) (IDegLira 19%, IDeg 29%). Notably, there were no withdrawals due to ineffective therapy during the first 2 weeks of treatment (Supplementary Table 8).

Mean body weight decreased from baseline by 2.7 kg in the IDegLira arm compared with no weight change with IDeg (Fig. 1*F*), resulting in an ETD between IDegLira and IDeg of 2.5 kg (95% CI −3.2, −1.8), *P* < 0.0001.

At lower mean A1C level with IDegLira at trial end, the incidence of confirmed hypoglycemia was comparable (IDegLira 24% vs. IDeg 25%). The rate of confirmed hypoglycemic episodes with IDegLira was numerically, though not statistically significantly, lower at trial end (Fig. 1*H*). One case of severe hypoglycemia was reported in the IDegLira treatment group: the event occurred during exercise (mountain climbing), and the participant recovered fully after administration of a sweet beverage. Rates of confirmed nocturnal hypoglycemia were low and similar for IDegLira and IDeg (Supplementary Table 9).

Rates of AEs were similar for IDegLira and IDeg (4.0 vs. 3.6 events per patient-years of exposure). The rate and frequency of serious AEs was also similar between treatments, and there were no treatment-specific patterns or clustering (Supplementary Table 10). One major adverse cardiovascular event in the IDegLira group (myocardial infarction) and two in the IDeg group (myocardial infarction and stroke) were confirmed by the EAC. One event of metastatic pancreatic carcinoma was reported in the IDeg group. No AEs related to medullary thyroid carcinomas, thyroid neoplasms, or pancreatitis were confirmed.

Mean lipase increased during the trial in the IDegLira group; mean change from baseline to week 26 was 14.4 units/L for IDegLira (range −124 to 405) and −3.6 units/L for IDeg (range −536 to 133). During the trial, 19 participants had plasma lipase levels three or more times above the upper-normal range (12 IDegLira, 7 IDeg). Of these, only one (IDegLira) presented with symptoms (nausea, abdominal pain) qualifying for event adjudication owing to suspicion of pancreatitis. The EAC did not confirm the event to be related to

pancreatitis. Similarly to lipase, but less pronounced, a mean increase in amylase was observed for IDegLira (mean change at week 26: 9.3 units/L [range −51 to 164]). Mean amylase remained unchanged for IDeg (−0.2 units/L [range −147 to 90]). Seven participants had plasma amylase three or more times above the upper-normal range (five IDegLira, two IDeg). None of these reported symptoms of pancreatitis. Overall, the incidences of gastrointestinal AEs (nausea, vomiting, and diarrhea) were low but slightly higher with IDegLira compared with IDeg (Table 2). With IDegLira, nausea was more frequent during the first 12 weeks of the treatment period compared with the last 12 weeks (Fig. 1*G*). Vomiting and diarrhea were less frequent (Supplementary Fig. 3). No participants discontinued the study owing to gastrointestinal AEs.

CONCLUSIONS

This 26-week, randomized, controlled, parallel, two-arm double-blind trial in insulin-treated patients with type 2 diabetes was designed to determine the relative contribution of the liraglutide component of the IDegLira combination product to glycemic control while examining the efficacy and safety of IDegLira. The study achieved insulin dose equivalence between the two arms allowing assessment of the added effects of liraglutide to those of IDeg in this setting. As the dose of IDeg was limited to 50 units, this study does not fully reflect the glucose lowering or other effects of fully titrated basal insulin.

Superiority of IDegLira over IDeg (limited to 50 units) in terms of change in A1C was confirmed with an observed reduction of 1.9% (21 mmol/mol) for IDegLira and a difference between the two treatments of −1.1% (−12 mmol/mol). In addition, from a baseline value of 8.7% (72 mmol/mol), IDegLira brought 60% of participants to A1C <7.0% (53 mmol/mol), and 40% achieved A1C <7.0% (53 mmol/mol) without confirmed hypoglycemic episodes during the last 12 weeks and without weight gain. The secondary glycemic end points supported the results of the primary end point: IDegLira was associated with significantly greater reductions in FPG and mean 9-point PG profiles compared with IDeg. Remarkably, at an A1C level 1.1% (12 mmol/mol) lower with IDegLira, the rate of confirmed hypoglycemia trended lower with IDegLira than IDeg (Fig. 1*H*).

In line with results of previous trials with liraglutide alone (17–20), a significant reduction in mean body weight after 26 weeks was seen when liraglutide was combined with IDeg in the IDegLira group compared with IDeg alone. The reduced insulin dose (from pretrial mean insulin doses of ~30 units to a starting trial insulin dose of 16 dose steps/16 units), combined with the fact that ~50% of subjects discontinued sulfonylureas at randomization, may to some extent explain the initial body weight reduction in both treatment groups. In the IDegLira arm, further weight reduction was attributed to the effect of the liraglutide component.

A 50-unit limit to the maximum dose in the IDeg arm was implemented in this trial in order to balance insulin exposure between arms to allow isolation of the contribution of the liraglutide component of IDegLira. The dose restrictions stipulated for IDeg in this trial design limit the conclusions that can be drawn in terms of direct comparisons with real-life treatment with IDeg. Another study comparing IDegLira with IDeg in patients with type 2 diabetes inadequately controlled on metformin with or without pioglitazone supports the benefits of IDegLira compared with IDeg as well as liraglutide (21).

At trial drug initiation, participants transferred from their pretrial basal insulin to IDegLira or IDeg. The start dose of 16 dose steps for IDegLira ensured that patients discontinuing their pretrial basal insulin (20–40 units) were transferred to the highest possible insulin dose while taking into account the recommended starting dose of liraglutide in GLP-1–naïve patients (0.6 mg). A considerable reduction in basal insulin could potentially lead to transiently worsened glucose control in both arms. In the IDegLira group, mean prebreakfast glucose declined after the first treatment week in the majority of individuals, indicating early onset of the effect of the liraglutide component. No withdrawals due to ineffective therapy occurred during the first 2 weeks of treatment, thus indicating a safe transfer of patients from basal insulin to IDegLira. As would be expected, a larger proportion of the individuals who switched from their baseline dose of basal insulin to 16 units IDeg demonstrated a transient increase in prebreakfast PG levels. Nevertheless, glycemic escape was not a clinical problem in this trial.

In this double-blinded study, IDegLira was generally well tolerated and the types of AEs reported for IDegLira were not different from what was expected from the components IDeg and liraglutide (22–25). No events of pancreatitis or thyroid disease were observed. Notably, while incidences of nausea, vomiting, and diarrhea were slightly higher in the IDegLira group than in the IDeg group, the percentage of participants experiencing gastrointestinal AEs during titration was markedly lower with IDegLira compared with what was seen in previous trials with liraglutide alone (24). We speculate that this is related to slower titration and smaller dose increments in this protocol than in prior studies with liraglutide.

While insulin therapy is still one of the most effective ways to reduce A1C, significant barriers to therapy intensification, including hypoglycemia, weight gain, and regimen complexity, reduce the likelihood of patients achieving target levels of glycemic control.

Table 2—Treatment-emergent AEs occurring with a frequency of ≥5%

	IDegLira (*N* = 199)		IDeg (*N* = 199)	
AE	%	R	%	R
Nausea	6.5	21.8	3.5	7.8
Diarrhea	6.5	22.8	3.5	8.9
Headache	6.0	25.0	2.0	6.7
Nasopharyngitis	2.5	5.4	6.0	15.6
Lipase increased	6.0	13.1	3.5	7.8

%, percentage of subjects; *N*, number of subjects in the safety analysis set; R, event rate per 100 exposure-years.

The current Position Statement by American Diabetes Association and European Association for the Study of Diabetes is more patient-centered and less prescriptive than previous versions and emphasizes that the recommendations should be considered within the context of the needs, preferences, and tolerance of each patient; individualization of treatment is the cornerstone of success (9). For patients inadequately controlled on OADs and basal insulin treatment, intensification with IDegLira could be considered as a future treatment option in the context of individual treatment goals and patient characteristics. The benefits of improved glycemic control and weight loss when transferring from basal insulin to IDegLira should therefore be balanced against the risk profile associated with GLP-1 receptor agonist treatment, including (primarily transient) moderately increased risk of gastrointestinal AEs such as nausea associated with the liraglutide component of IDegLira.

This trial demonstrates that, at equivalent doses of IDeg, the liraglutide component of IDegLira provides additional glycemic control by reducing both FPG and, to a lesser extent, postprandial excursions in addition to promoting weight loss and a low rate of hypoglycemia. Indeed, the substantial reduction in A1C with a single daily injection of IDegLira in patients inadequately controlled on basal insulin therapy demonstrates the potential role of this combination in the treatment of type 2 diabetes. Furthermore, IDegLira has a low rate of gastrointestinal AEs. IDegLira may therefore offer clinical advantages in patients with type 2 diabetes inadequately controlled with basal insulin and in need of further treatment optimization.

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Author Contributions. J.B.B. developed the study concept and design; acquired, analyzed, and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; provided administrative, technical, or material support; and supervised the study. T.V. acquired, analyzed, and interpreted data; critically revised the manuscript for important intellectual content; provided administrative, technical, or material support; and supervised the study. J.T. acquired data; critically revised the manuscript for important intellectual content; and provided administrative, technical, or material support. T.C.B. acquired, analyzed, and interpreted data; critically revised the manuscript for important intellectual content; and provided administrative, technical, or material support. I.H.L. acquired, analyzed, and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; and provided administrative, technical, or material support. S.G.B. acquired, analyzed, and interpreted data; drafted the manuscript; critically revised the manuscript for important intellectual content; provided administrative, technical, or material support; and performed statistical analysis. H.W.R. acquired, analyzed, and interpreted data; critically revised the manuscript for important intellectual content; and provided administrative, technical, or material support. J.B.B. 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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