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IDegLira Improves Both Fasting and Postprandial Glucose Control as Demonstrated Using Continuous Glucose Monitoring and a Standardized Meal Test

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Abstract

Objective: IDegLira is a novel, fixed-ratio combination of the long-acting basal insulin, insulin degludec, and the long-acting glucagon-like peptide-1 analog liraglutide. We studied the effect of IDegLira versus its components on postprandial glucose (PPG) in type 2 diabetes.

Methods: In this substudy, 260 (15.6%) of the original 1663 patients with inadequate glycemic control participating in a 26-week, open-label trial (DUAL I) were randomized 2:1:1 to once-daily IDegLira, insulin degludec or liraglutide. Continuous glucose monitoring (CGM) for 72 hours and a meal test were performed.

Results: At week 26, IDegLira produced a significantly greater decrease from baseline in mean PPG increment (normalized $iAUC_{0\text{-}4h}$) than insulin degludec (estimated treatment difference [ETD] –12.79 mg/dl [95% CI: –21.08; –4.68], $P = .0023$) and a similar magnitude of decrease as liraglutide (ETD –1.62 mg/dl [95% CI: –10.09; 6.67], $P = .70$). CGM indicated a greater reduction in change from baseline in PPG increment ($iAUC_{0\text{-}4h}$) for IDegLira versus insulin degludec over all 3 main meals (ETD –6.13 mg/dl [95% CI: –10.27, –1.98], $P = .0047$) and similar reductions versus liraglutide (ETD –1.80 mg/dl [95% CI: –2.52, 5.95], $P = .4122$). Insulin secretion ratio and static index were greater for IDegLira versus insulin degludec ($P = .048$ and $P = .006$, respectively) and similar to liraglutide ($P = .45$ and $P = .895$, respectively).

Conclusions: Once-daily IDegLira provides significantly better PPG control following a mixed meal test than insulin degludec. The improvement is at least partially explained by higher endogenous insulin secretion and improved beta cell function with IDegLira. The benefits of liraglutide on PPG control are maintained across all main meals in the combination.

Keywords
diabetes therapy, insulin degludec, liraglutide, postprandial glucose, incretins, combination therapy, quality of glycemic control

Type 2 diabetes (T2D) is characterized by multiple pathophysiological deficits, which collectively foster a state of chronic hyperglycemia.[1,2] As T2D progresses, patients become increasingly insulin deficient and eventually require more intensive therapy, typically including a basal insulin and often a prandial insulin. Adherence to more complicated basal–bolus regimens may be challenging. These regimens have an increased risk of hypoglycemia and weight gain, and both patients and health care providers may be reluctant to intensify therapy despite being clinically indicated. Even adherent patients with seemingly adequate glycemic control measured by hemoglobin A1C (A1c) may experience significant glucose excursions over 24 hours, at least in part due to elevations in postprandial glucose

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(PPG). Although it is not yet established that reduction of postprandial glycemia alone is sufficient to reduce the risk of vascular disease in people with diabetes, the total amount of time spent under conditions of hyperglycemia is an important determinant for development of diabetes complications.[3-8] Thus, a treatment that helps address both fasting and postprandial control should be more effective in reducing the amount of time spent in the hyperglycemic state.

Accordingly, treatment incorporating several different classes of drugs with complementary modes of action may be the preferred strategy in T2D.[9,10] The combination product insulin degludec/liraglutide (IDegLira; Xultophy®, Novo Nordisk A/S, Bagsvaerd, Denmark) has been developed for the treatment of T2D to take clinical advantage of the complementary modes of action of its individual components, the once-daily basal insulin with long duration of action, insulin degludec, and the once-daily, long-acting human glucagon-like peptide-1 (GLP-1) analog liraglutide. In clinical trials, insulin degludec demonstrated similar improvements in A1c to insulin glargine but with fewer episodes of hypoglycemia, particularly nocturnal episodes, across a broad spectrum of patients with diabetes.[11] With a 24-hour duration of action, liraglutide improves glycemic control by lowering fasting plasma glucose (FPG) and PPG in patients with T2D.[12] When liraglutide is used in combination with basal insulin, improvements in glycemic control are achieved without increasing the risk of hypoglycemia and weight gain.[13-16]

The efficacy and safety of IDegLira was demonstrated in the DUAL I trial. DUAL I was a 26-week, randomized, open-label trial involving 1663 adults with T2D (mean age 55 ± 10 years, BMI ≤40 kg/m^2) with unsatisfactory glycemic control (A1c 7-10%) on metformin ± pioglitazone.[17] In the full population, glycemic control was assessed by A1c, FPG, and 9-point self-monitored blood glucose (SMBG) profiles. At 26 weeks, A1c with IDegLira was shown to be significantly better than insulin degludec (estimated treatment difference [ETD] –0.47% [95% CI: –0.58; –0.36], $P < .0001$) and superior to liraglutide (ETD –0.64% [95% CI: –0.75; –0.53], $P < .0001$). There was no significant difference in FPG reduction between IDegLira and insulin degludec ($P = .16$). However, IDegLira reduced FPG more than liraglutide ($P < .0001$). As assessed by 9-point SMBG profiles, IDegLira reduced the PPG increment more than insulin degludec, and equally well as liraglutide used alone, both for individual meals and across all main meals.[17]

This preplanned, prospective substudy from DUAL I[17] was conducted to more precisely characterize the postprandial glycemic control provided by IDegLira, in comparison with each of its components. Postprandial glycemic control was assessed using 2 different approaches: by measuring glucose profiles after a single, standardized meal test, where we also measured hormone profiles and beta cell function, and by measuring interstitial glucose profiles across all 3 main meals via continuous glucose monitoring (CGM).

Methods

The study reported here involved a subpopulation of 260 (15.6%) of the original 1663 participants from the DUAL I trial, who underwent a standardized meal test. Among the substudy participants, 131 were randomized to IDegLira, 64 to insulin degludec and 65 to liraglutide. Patient recruitment and eligibility, treatment, and statistical analyses have been described elsewhere.[17] The study was conducted in accordance with Declaration of Helsinki[18] and Good Clinical Practice guidelines.[19] Countries invited to participate in this substudy (Australia, Finland, France, Germany, Hungary, India, Ireland, Italy, Russian Federation, Spain, United Kingdom, and United States) were selected based on experience with the meal test and CGM. Recruitment began May 23, 2011, and follow-up continued until October 31, 2011.

IDegLira was administered as dose steps, with each step containing 1 unit of insulin degludec and 0.036 mg of liraglutide. IDegLira was initiated at 10 dose steps (10 units insulin degludec plus 0.36 mg liraglutide) and insulin degludec was initiated at 10 units. On the basis of prebreakfast SMBG measurements (mean of 3 consecutive days), IDegLira and insulin degludec doses were titrated stepwise twice a week to an FPG target of 72-90 mg/dl; if blood glucose was <72 or >90 mg/dl, the IDegLira dose was decreased or increased by ± 2 dose steps, respectively, and the insulin degludec dose was decreased or increased by ± 2 units. IDegLira could be titrated to a maximum of 50 dose steps (50 units insulin degludec and 1.8 mg liraglutide), but there was no dose limit for insulin degludec. Liraglutide was initiated at 0.6 mg/day and increased by 0.6 mg per week, with the goal of eventually reaching 1.8 mg/day for all participants in this substudy by week 3. All 3 treatments could be administered at any time of day as long as the chosen time was used consistently. Similar proportions of patients administered their treatment in the morning in all 3 arms.

Postprandial Glucose and Hormone Profiles During a Standardized Meal Test

The meal test was conducted in the morning after fasting for ≥8 hours, at baseline and at week 26. Subjects consumed a single, standardized, liquid mixed meal containing ~675 calories with 14.8% protein, 57.0% carbohydrates, 28.2% fat (Ensure Plus®, Abbot Laboratories, Columbus, Ohio). Trial products and oral antidiabetic drugs (OADs) were withheld on the day of the meal test until blood sampling had been completed (meal test duration of 4.5-5 hours). Blood samples for determination of plasma glucose (PG), insulin, C-peptide, and glucagon levels were taken at 9 time points in relation to the start of the test meal: –10, +15, +30, +45, +60, +90, +120, +180, and + 240 minutes.

A central laboratory (Quintiles Limited, Kingston, UK) performed laboratory analyses for glucose, insulin, C-peptide, and glucagon. Insulin and C-peptide were analyzed in serum

using chemiluminescence immunoassay methods. Plasma glucagon was measured using the Millipore Glucagon radioimmunoassay (Ref GL-32K; Millipore, Billerica, MA, USA).

Postprandial Interstitial Glucose Profiles

CGM[20] was used to characterize interstitial glucose excursions over a 24-hour period encompassing all 3 main meals, at baseline and at week 26. Subjects wore the CGM device (iPro1 [United States] and iPro2 [Europe and Australia], Medtronic International, Tolochenaz, Switzerland) for a minimum of 72 hours for each recording, performed 3-4 days just before site visits. Subjects were instructed not to change their diet, OAD dose, or product treatment dose during the 72-hour period.

Statistical Analysis

For data from the standardized meal test, at 26 weeks of treatment, the incremental area under the curve from 0 to 4 hours ($iAUC_{0\text{-}4h}$) for PPG, C-peptide, insulin, and glucagon was calculated using the trapezoidal method divided by the actual measurement time, using the available valid observations and the associated actual elapsed time point. AUC endpoints were log-transformed and analyzed separately using an ANCOVA model (hereafter the standard ANCOVA model), with treatment, country, baseline A1c stratum, and previous OAD treatment as fixed factors and the relevant log-transformed baseline value used as covariate. The resulting AUC provided the (normalized) prandial increment. The mean increment for all meals was calculated as the mean of all available meal increments.

In addition, beta cell function was assessed by the insulin secretion ratio ($AUC_{0\text{-}4h\ insulin}/AUC_{0\text{-}4h\ glucose}$), which expresses the insulin release over the 4-hour postprandial period relative to the concomitant PG levels; and by the static index, which also expresses the meal-derived estimate of the beta cell response to a change in glucose, but uses C-peptide levels that are modeled by means of the minimal model.[21] Units for the insulin secretion ratio and static index are presented as described by Breda et al.[21]

For interstitial glucose, due to technical issues with the iPro1 CGM device used in the USA, many of the CGM profiles were uploaded without any data (26% data missing and lost from uploads at baseline and 50% missing and lost from uploads at week 26). In Europe and Australia, where the iPro2 was used, almost all profiles contained data. Due to the magnitude and nature of missing data from iPro1 (which are assumed to be missing completely at random), the CGM results are based on observed values rather than imputing missing values, such as with using last observation carried forward (LOCF). Mean postprandial increment in interstitial glucose ($iAUC_{0\text{-}4h}$) was calculated as the AUC above the premeal value from t = 0 to 4 hours (calculated using the trapezoidal method) divided by measurement time. Treatments were compared using the standard ANCOVA model.

Results

Baseline characteristics (Table 1) including A1c and FPG were similar to those of the full trial population as previously reported.[17] The actual (LOCF) mean ± SD dose after 26 weeks of treatment for 129 patients treated with IDegLira was 43 dose steps (43 ± 11 units insulin degludec [range: 8-50 units] and 1.5 ± 0.4 mg liraglutide [range: 0.3-1.8 mg]; 60 ± 29 units for 64 patients treated with insulin degludec [range: 12-124 units] and 1.8 ± 0.2 mg for 64 patients treated with liraglutide [range: 0.6-1.8 mg]). Patient disposition is shown in Figure 1.

Glucose and Hormone Profiles during Standardized Meal Test

Mean PG levels were similar for all 3 treatment groups at baseline, and markedly lower in all treatment groups at 26 weeks. Comparing treatments, at 26 weeks, mean prandial glucose levels for the IDegLira and insulin degludec treatment group values were similar (156.0 mg/dl and 163.2 mg/dl, respectively), and lower than observed with liraglutide (179.3 mg/dl) (Figure 2, top row). IDegLira was associated with a greater decrease from baseline in mean ± SD PPG increment (normalized $iAUC_{0\text{-}4h\ glucose}$) than insulin degludec (–15.7 ± 29.7 vs –3.1 ± 35.7 mg/dl; ETD –12.8 mg/dl [95% CI: –21.1; –4.68], $P = .0023$), for a decrease of 21.6% and 4.1%, respectively; there was no significant difference in the reduction observed for IDegLira versus liraglutide (–15.7 ± 29.7 vs –14.1 ± 29.2 mg/dl; ETD –1.6 mg/dl [95% CI: –10.1; 6.7], $P = .7000$), a decrease of 21.6% and 18.4%, respectively.

The baseline insulin values for normalized $iAUC_{0\text{-}4h\ insulin}$ were similar with IDegLira and insulin degludec, and were higher than observed with liraglutide at baseline as shown in Figure 2 (second row). Changes in postprandial insulin increment ($iAUC_{0\text{-}4h\ insulin}$) from baseline to week 26 were 20.6 ± 127.0 versus –26.7 ± 197.5 pmol/l for IDegLira versus insulin degludec, and 20.6 ± 127.0 versus 64.8 ± 119.2 pmol/l for IDegLira versus liraglutide. At week 26, ETD for $iAUC_{0\text{-}4h\ insulin}$ were 39.3 pmol/l (95% CI: –4.2; 82.8) for IDegLira–insulin degludec ($P = .0765$), representing an increase of 7.7% for IDegLira versus a decrease of 12.4% for insulin degludec, and –38.5 pmol/l (95% CI: –81.9; 5.0) for IDegLira–liraglutide ($P = .0827$), representing an increase of 7.7% for IDegLira versus an increase of 27.4% for liraglutide.

For C-peptide, baseline values for normalized $iAUC_{0\text{-}4h\ C\text{-}peptide}$ were similar across treatments and increased for all treatments at week 26 (Figure 2, third row). Mean change in postprandial C-peptide increment ($iAUC_{0\text{-}4h\ C\text{-}peptide}$) from baseline to week 26 was 0.11 ± 0.54 versus 0.10 ± 0.60 nmol/l for IDegLira and insulin degludec, respectively, and 0.11 ± 0.54 versus 0.25 ± 0.51 nmol/l for IDegLira and liraglutide, respectively. At week 26, ETDs for $iAUC_{0\text{-}4h\ C\text{-}peptide}$ were 0.02 (95% CI: –0.13; 0.18) for IDegLira versus insulin degludec ($P = .7949$), representing an increase of 8.5% and 8.0%, respectively, and –0.11 (95% CI: –0.26; 0.05)

Table 1. Baseline Characteristics and End-of-Trial Values (Week 26) for n = 260 Patients Participating in the Standardized Meal Test During a Substudy of the DUAL I Trial, by Treatment.

	IDegLira	Insulin degludec	Liraglutide
Full analysis set (n)	131	64	65
Female (n, (%))	59 (45.0)	28 (43.8)	35 (53.8)
Race (n, (%))			
White	117 (89.3)	59 (92.2)	58 (89.2)
Black or African American	9 (6.9)	2 (3.1)	3 (4.6)
Other	5 (3.8)	3 (4.7)	4 (6.2)
Age (years)	54.4 (9.3)	55.0 (8.5)	55.0 (10.3)
Body weight (kg)	92.0 (15.7)	94.1 (18.3)	93.8 (20.1)
Body mass index (kg/m^2)	32.5 (4.4)	32.4 (4.5)	32.3 (4.8)
Duration of diabetes (years)	7.5 (5.7)	7.5 (4.9)	8.1 (5.1)
A1c (%)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)
A1c (mmol/mol)	66 (9.8)	66 (9.8)	67 (10.9)
FPG (mg/dl)	165.8 (41.4)	164.0 (48.6)	165.8 (43.2)
OAD at screening (n (%))			
Metformin	106 (80.9)	51 (79.7)	51 (78.5)
Metformin + pioglitazone	25 (19.1)	13 (20.3)	13 (20.0)
Metformin + glimepiride	0 (0.0)	0 (0.0)	1 (1.5)
End of trial values			
A1c (%)	6.3 (1.0)	6.6 (0.8)	7.0 (0.9)
A1c (mmol/mol)	45 (10.9)	49 (8.7)	53 (9.8)
FPG (mg/dl)	99.1 (30.6)	97.3 (34.2)	124.3 (34.2)
Insulin dose (U)	43 (11)	60 (29)	NA
Body weight (kg)	91.6 (15.7)	95.7 (19.5)	91.4 (20.5)

For this substudy, baseline characteristics as well as end of trial values in A1c and FPG corresponded closely with the full trial population.[17] Full analysis set. Data are mean (SD), unless otherwise noted. FPG, fasting plasma glucose; IDegLira, insulin degludec/liraglutide combination; OAD, oral antidiabetic drug.

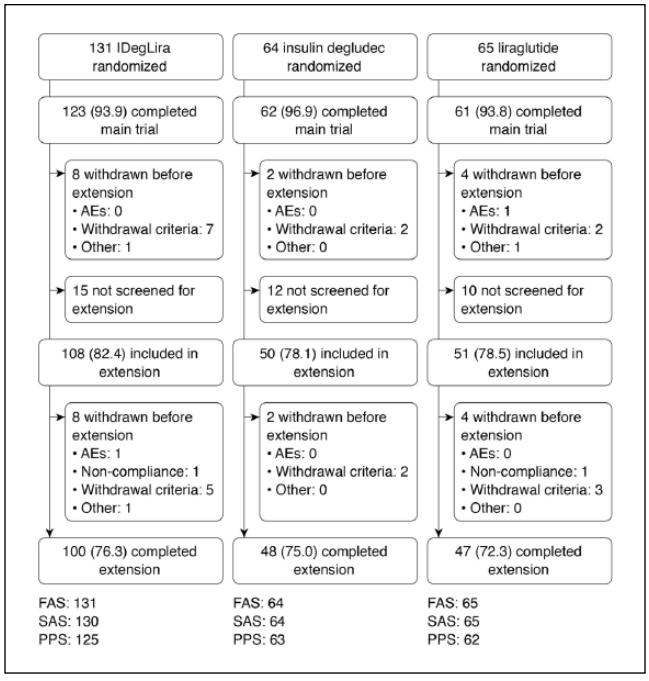

Figure 1. Patient disposition. FAS, full analysis set; PPS, per-protocol set; SAS, safety analysis set.

for IDegLira versus liraglutide (P = .1695), representing increases of 8.5% for IDegLira and 21.8% for liraglutide.

For glucagon, normalized $iAUC_{0\text{-}4h\ glucagon}$ responses at week 26 appeared similar to baseline, as shown in Figure 2 (bottom row). Postprandial glucagon increments ($iAUC_{0\text{-}4h\ glucagon}$) were similar for IDegLira and insulin degludec (ETD 0.00 pg/ml [95% CI: –3.5; 3.5], P = .9980), representing decreases of 33.3% and 32.8%, respectively, but significantly lower for IDegLira than for liraglutide (ETD –5.4 pg/ml [95% CI: –8.9; –1.9], P = .0029), representing a decrease of 33.3% for IDegLira versus an increase of 11.0% for liraglutide.

Beta Cell Function

At week 26, beta cell function was evaluated by the insulin secretion ratio—which, as described above, represents insulin release over the 4-hour postprandial period relative to concomitant PG levels—and was higher in the IDegLira group compared to the insulin degludec group (33.8 [pmol/l*min]/[mmol/l*min] vs 25.7 [pmol/l*min]/[mmol/l*min]; P = .048) and was similar in the IDegLira and liraglutide treatment groups (33.8 and 36.8 [pmol/l*min]/[mmol/l*min], respectively; P = .45) (Figure 3, top). Beta cell function as

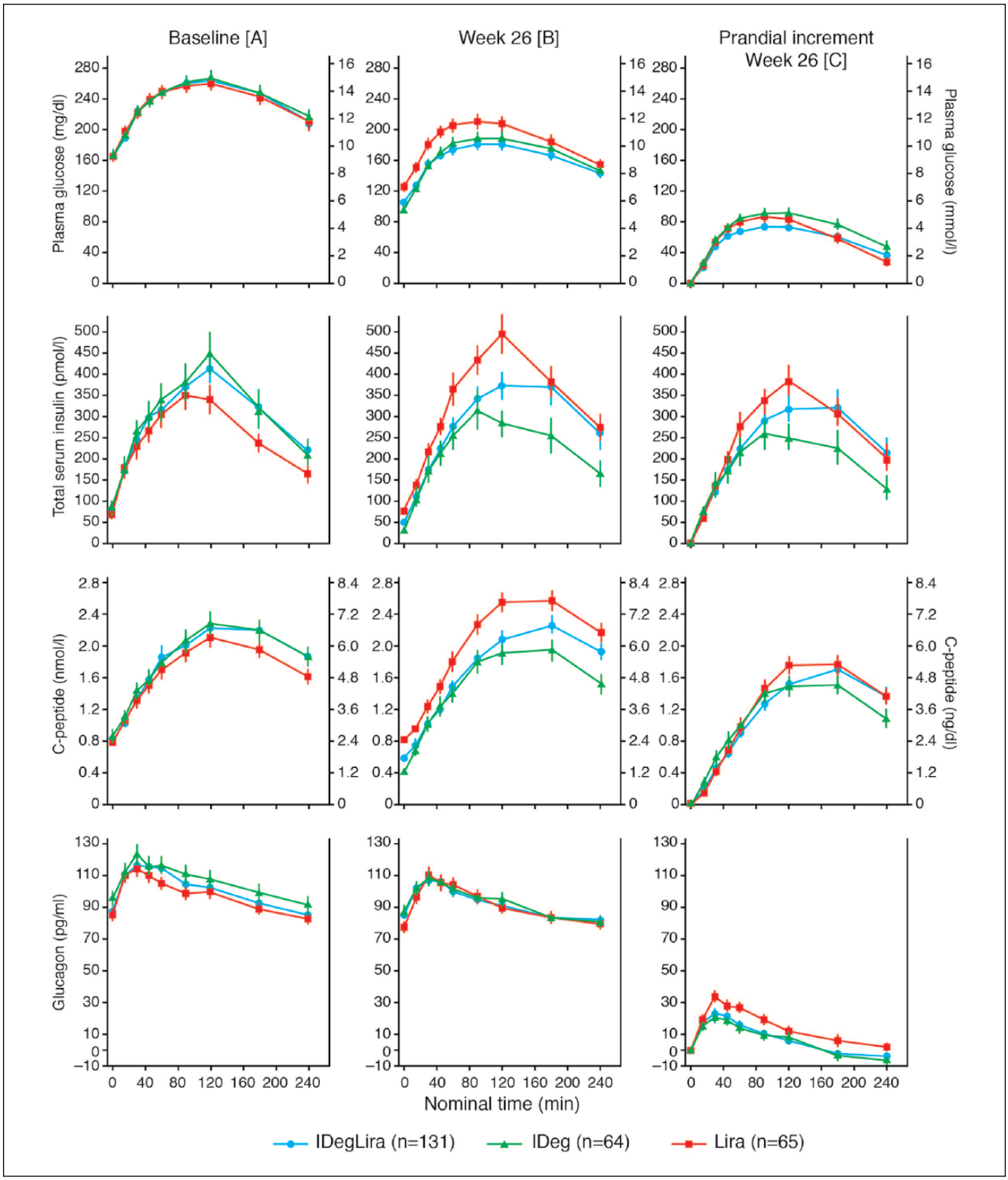

Figure 2. Mean plasma glucose (top row), mean serum insulin (second row), mean serum C-peptide (third row), and mean plasma glucagon (bottom row) profiles, for 260 patients with type 2 diabetes participating in a standardized meal test as part of the DUAL I trial, by treatment. IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; Lira, liraglutide. Labels for vertical axes carry through for all panels in a row.

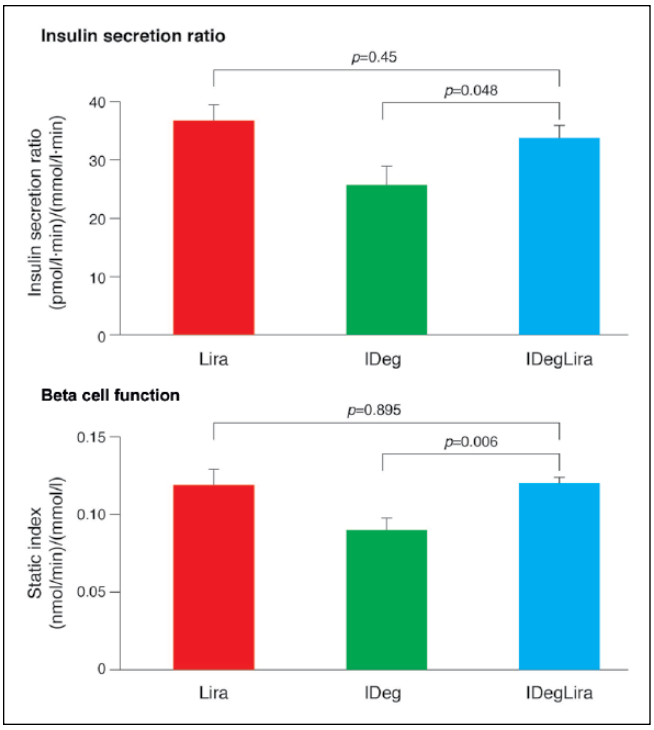

Figure 3. Insulin secretion to glucose ratio (top) and beta cell function (bottom) at week 26 for a subset of patients (n = 260) with type 2 diabetes participating in a standardized meal test during the DUAL I trial. IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; Lira, liraglutide. Top panel: Insulin secretion ratio,[8] which expresses the insulin release over the 4-hour postprandial period adjusted for the concomitant plasma glucose levels, was calculated as $AUC_{0\text{-}4h\ insulin}$ / $AUC_{0\text{-}4h\ glucose}$. Bottom panel: Estimates of overall static insulin secretion during the meal test were calculated as the static index.[21] The static index also expresses the meal-derived estimate of the beta cell response to a change in glucose, but uses C-peptide levels that are analyzed using the minimal model.[21] Units for the insulin secretion ratio and static index are presented as described by Breda et al.[21]

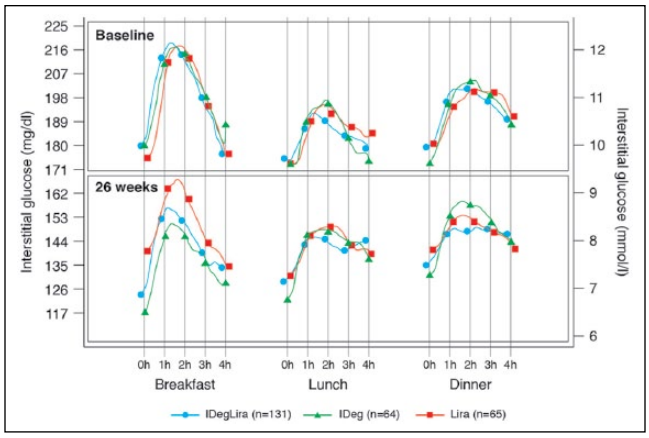

Figure 4. Mean postprandial interstitial glucose profiles after breakfast, lunch, and dinner, measured using CGM, in a subgroup of 260 patients with type 2 diabetes participating in the DUAL I trial, at baseline (upper panel) and week 26 (lower panel), by treatment. Last observation carried forward was used to impute missing data. Although all 260 patients (full analysis set) were included in the analysis, data were not available at all time points at every meal for each patient. See Figure 1 for patient disposition. CGM, continuous glucose monitoring, based on observed rather than estimated values; IDeg, insulin degludec; IDegLira, insulin degludec/liraglutide combination; Lira, liraglutide.

further evaluated using the static index was significantly higher for IDegLira versus insulin degludec (0.120 [nmol/min]/[mmol/l and 0.090 [nmol/min]/[mmol/l], respectively, $P = .006$) and similar in the IDegLira and liraglutide treatment groups (0.120 and 0.119 [nmol/min]/[mmol/l], respectively, $P = .895$) (Figure 3, bottom).

Interstitial Glucose Profiles Using CGM

With respect to observed change from baseline ($iAUC_{0\text{-}4h\ glucose}$) for interstitial glucose following individual meals, there was a greater reduction for IDegLira versus insulin degludec at breakfast (ETD –6.7 mg/dl [95% CI: –13.0; –0.4], $P = .0373$) and evening meal (ETD –7.4 mg/dl [95% CI: –13.2; –1.6], $P = .0130$); the lunch value was numerically lower but not significantly different for IDegLira and insulin degludec (ETD –3.6 mg/dl [95% CI: –9.9; 2.5], $P = .2430$). There were no differences at any meal between IDegLira and liraglutide (Figure 4). Observed change from baseline in postprandial interstitial glucose increment ($iAUC_{0\text{-}4h\ glucose}$) averaged over all 3 main meals was also significantly different for IDegLira versus insulin degludec (ETD –6.1 mg/dl [95% CI: –10.3; –2.0], $P = .0047$) but similar for IDegLira and liraglutide (ETD –1.8 mg/dl [95% CI: –2.5; 6.0], $P = .4122$).

Safety

As previously reported for all patients participating in DUAL I,[17] IDegLira was well tolerated, and the profile of adverse events (AEs) reflected those of the components insulin degludec and liraglutide. In this substudy population, serious AEs were reported for a minority of subjects across treatment groups (n = 1/130 [0.8%] for IDegLira, n = 2/64 [3.1%] for insulin degludec, n = 2/65 [3.1%] for liraglutide) and deemed unlikely to be related to trial products. The number of confirmed hypoglycemic events (ie, episodes confirmed by a PG of <56 mg/dl and severe episodes) per patient-year was 1.33 for IDegLira, 3.38 for insulin degludec, and 0.22 for liraglutide. No clustering or unexpected patterns in the reported AEs were observed, and frequencies were generally similar to the full population[17] (Table 2).

Discussion

In this preplanned, prospective substudy of 260 subjects participating in DUAL I, using more detailed PPG assessments (CGM plus meal test) compared with the main trial, which

Table 2. Treatment-Emergent Adverse Events That Occurred in at Least 5% of Patients in Any Treatment Group (or in ≥1% of Patients for Increased Lipase) for 260 Patients Participating in a Preplanned Substudy of the DUAL I Trial, by Treatment.

	IDegLira (n = 130)		Insulin degludec (n = 64)		Liraglutide (n = 65)	
	n (%)	Rate	n (%)	Rate	n (%)	Rate
Nausea	10 (7.7)	17.4	1 (1.6)	3.2	10 (15.4)	44.7
Diarrhea	8 (6.2)	14.3	4 (6.3)	12.6	7 (10.8)	25.5
Vomiting	4 (3.1)	7.9	0 (0)	0.0	5 (7.7)	16.0
Headache	12 (9.2)	23.8	6 (9.4)	44.2	9 (13.8)	60.7
Nasopharyngitis	16 (12.3)	34.9	5 (7.8)	18.9	7 (10.8)	22.3
Increased lipase concentration[a]	6 (4.6)	9.5	3 (4.7)	9.5	3 (4.6)	12.8
Decreased appetite	5 (3.8)	7.9	0 (0)	0.0	4 (6.2)	12.8

Safety analysis set; n, number of subjects; rate, per 100 person-years exposure.
[a]Elevated lipase, 3× upper limit of normal.

reported SMBG findings, we show that the effect of liraglutide on postprandial glycemic control was preserved when used in conjunction with insulin degludec in the combination product, IDegLira. This is demonstrated by lower blood glucose levels with IDegLira during a standardized meal test following a single meal and by improved interstitial glucose profiles measured using CGM over 3 main meals. Compared to insulin degludec alone, which demonstrated a 4.1% decrease from baseline in PPG increment, the decrease with IDegLira was 21.6% versus 18.4% with liraglutide. These data are consistent with the 9-point SMBG profile results from the full analysis set for all (n = 1663) subjects in the main trial, which showed a greater reduction in PPG increment for IDegLira versus insulin degludec for each main meal as well as across all 3 meals, and a similar reduction compared to liraglutide used alone.[17] These results are consistent with those from a study using a standardized meal test, at which both absolute and incremental PPG were reduced for liraglutide versus placebo.[22] In this substudy (as in the main trial population), the more gradual titration with IDegLira was associated with a reduced incidence of gastrointestinal side effects compared to liraglutide alone.

One of the pathophysiological deficits in T2D is chronic hyperglucagonemia during fasting and postprandial states.[23] Liraglutide, like other GLP-1 analogs, has a stimulating effect on insulin secretion and an inhibitory effect on glucagon secretion, both in a glucose-dependent manner.[12] In this substudy, the postprandial glucagon response was similar in the IDegLira and insulin degludec groups. The glucagon response for IDegLira was statistically significantly lower compared to liraglutide, which may explain part of the glycemic superiority. However, the underlying mechanism for the improved PPG control with IDegLira versus insulin degludec observed in this substudy seems to be a stimulatory effect on endogenous insulin secretion, rather than enhanced glucagon suppression (since glucagon responses were similar). This notion is supported by indices of beta cell function (such as insulin secretion ratio and static index), which were improved for IDegLira versus insulin degludec but were similar compared with liraglutide at 26 weeks. The reason for the difference in glucagon responses between IDegLira and liraglutide could be the combination of 2 potential inhibitors of glucagon secretion in IDegLira. However, the precise interaction between the 2 cannot be determined from these experiments because of the varying dosing of the individual components in the 3 groups. Interestingly, analysis of the data from the placebo-controlled LIBRA trial indicated that the postprandial glucagonostatic effect of liraglutide observed after short-term treatment was lost with chronic administration in patients with a short duration of diabetes.[24] However, the overall glycemic effects on insulin secretion, C-peptide response and reduction of glycemic excursion were accompanied with an expected improvement of glycemic control (as assessed by A1c and 2-hour glucose) in line with the well-established glycemic efficacy of liraglutide. More trials are needed to further explore these findings.

Demonstrating the PPG-lowering effect of liraglutide (alone or as part of IDegLira) after all meals and after individual meals throughout the day, in conjunction with showing indices of improved beta cell function (ie, static index and insulin secretion ratio), reinforce results previously reported using SMBG profiles.[17] The long duration of action of liraglutide (half-life 11-15 hours) contributes to blood glucose lowering across all main meals when administered once daily,[25] as opposed to short-acting GLP-1 receptor agonists, including exenatide (half-life 2.4 hours[26]) and lixisenatide (half-life 2-3 hours[27]) which, because of their rapid elimination, primarily target the meal immediately following product administration. Clinically, these results have implications for the total time spent under conditions of hyperglycemia, a known risk factor for the development of diabetes complications.[3] The reduction of the extent and duration of hyperglycemia across all meals combined with the concomitant reduction of FPG provided by the combined action of the components, liraglutide and insulin degludec, provides a greater opportunity to improve the overall glycemic control.

This study focuses on the PPG control observed with IDegLira compared to each of the monocomponents (insulin

degludec and liraglutide) and reports results using both CGM and a meal test. Due to the maintained benefits of liraglutide when used in a combination product with insulin degludec, IDegLira provides significantly better postprandial glycemic control following a mixed meal test than insulin degludec, which is at least partially explained by a higher endogenous insulin secretion and improved beta cell function with IDegLira. Because of the long duration of action of the liraglutide component of IDegLira, the effect on PPG is evident across all main meals, and IDegLira is able to achieve tighter glycemic control compared with either insulin degludec or liraglutide used alone.

Conclusions

The improved control of PPG described for patients in this substudy is consistent with results from the full analysis set from the main DUAL I trial, which showed 81% of patients using IDegLira achieved A1c <7.0%, compared with 65% of patients using insulin degludec and 60% using liraglutide (both $P < .0001$ vs IDegLira).[17] That analysis also reported that more patients using IDegLira achieved glucose targets without increasing hypoglycemia and/or weight gain, compared to insulin degludec. Improved tolerability of IDegLira compared to its monocomponents, in conjunction with improved glycemic control during fasting as well as after meals, and the convenience of administering both drugs in a single injection, should be appealing to patients and providers alike.

Abbreviations

AE, adverse event; AUC, area under the curve; CGM, continuous glucose monitoring; ETD, estimated treatment difference; FPG, fasting plasma glucose; GLP-1, glucagon-like peptide-1; IDegLira, insulin degludec/liraglutide combination; LOCF, last observation carried forward; OAD, oral antidiabetic drug; PG, plasma glucose; PPG, postprandial glucose; SMBG, self-monitored blood glucose; T2D, type 2 diabetes.

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Declaration of Conflicting Interests

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