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ORIGINAL ARTICLE

A Novel Insulin Combination of Insulin Degludec and Insulin Aspart Achieves a More Stable Overnight Glucose Profile than Insulin Glargine: Results from Continuous Glucose Monitoring in a Proof-of-Concept Trial

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Abstract

Purpose:

Insulin degludec coformulated with insulin aspart (as IDegAsp) can cover 24 h basal insulin and postprandial insulin requirements after a main meal with one injection. We compared glycemic stability following IDegAsp or insulin glargine (IGlar) given before the evening meal in patients with type 2 diabetes.

Methods:

A subset of 112 insulin-naïve type 2 diabetes patients from a randomized, parallel-group trial (IDegAsp versus IGlar, each added to metformin) underwent 72 h continuous interstitial glucose (IG) monitoring after 16 weeks of treatment. End points included mean IG concentrations, 2 h postprandial IG increments and postprandial peak, IG fluctuation (summed area above and below mean IG), within-subject coefficient of variation (day-to-day variation) in mean nocturnal IG, and episodes of low (<3.5 mmol/liter) and high (>10 mmol/liter) IG. Values were derived for the entire 72 h, with the nocturnal interval (0001–0559 h) also assessed.

Results:

The postdinner IG increment observed with IGlar did not occur with IDegAsp [IDegAsp - IGlar, -1.42 (-2.15, -0.70) mmol/liter]. Nocturnal IG fluctuation was 21% lower with IDegAsp [IDegAsp/IGlar, 0.79 (0.66, 0.96) mmol/liter], with 48% fewer nocturnal high IG episodes [ratio IDegAsp/IGlar, 0.52 (0.32, 0.87)].

Conclusions:

IDegAsp given with the evening meal reduces postdinner glucose excursion and provides more stable nocturnal glycemia as compared with IGlar.

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Abbreviations: (CGM) continuous interstitial glucose monitors, (CI) confidence interval, (CV) coefficient of variation, (FPG) fasting plasma glucose, (HbA1c) hemoglobin A1c, (IAsp) insulin aspart, (IDeg) insulin degludec, (IDegAsp) insulin degludec and insulin aspart combined, (IG) interstitial glucose, (IGlar) insulin glargine, (OAD) oral antidiabetic drug

Keywords: continuous glucose monitoring, glucose excursion, insulin aspart, insulin degludec, insulin glargine

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Introduction

Insulin degludec (IDeg) is a novel basal insulin with an ultra-long duration of action due to postinjection formation of a subcutaneous depot of soluble multihexamer chains.[1] In the pharmaceutical formulation, IDeg exists as soluble and highly stable dihexamers that do not interact with the soluble and stable hexamers of insulin aspart (IAsp) when the two are combined (IDegAsp).[2,3] Once injected into the subcutaneous tissue, IAsp hexamers immediately split into monomers that are rapidly absorbed into the circulation, while the IDeg dihexamers form soluble multihexamers. These are of a molecular size too large to be absorbed, leading to a depot from which IDeg monomers are slowly and continuously absorbed into the circulation. This provides a way to obtain a clear separation between the pharmacodynamic effects of the basal (IDeg) and bolus (IAsp) components of IDegAsp.[2,3]

IDegAsp, comprising IDeg (70%) and IAsp (30%), is under development for the treatment of diabetes mellitus with the objective of combining the pharmacokinetic/pharmacodynamic characteristics of the two insulin components. Insulin degludec has an ultra-long duration of action, with a half-life (>25 h) that is twice as long as that of insulin glargine (IGlar)[4] and a duration of blood glucose-lowering action that extends beyond 42 h.[5] It also has a less variable pharmacodynamic profile compared with IGlar.[6] Insulin aspart has a rapid onset and short duration of action.[7] Thus, IDegAsp should cover the basal insulin requirements as well as the postprandial insulin requirement after the main meal with one injection. IDegAsp therefore has the potential for achieving flatter and less fluctuating blood glucose profiles than are possible with currently available insulin products as a result of the low variability in the pharmacodynamic effect of IDeg versus other basal insulins and the use of the IAsp component to limit the postprandial glucose excursion after the main meal.

We have shown that, compared with IGlar, IDegAsp was as effective and well tolerated when used as initial insulin therapy for type 2 diabetes, added to metformin.[8] The two insulin treatments achieved equivalent hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG) reductions, with low hypoglycemia rates. IDegAsp showed lower postdinner glucose excursions compared with IGlar, and the mean total insulin dose was lower with IDegAsp than with IGlar.

In this article, we report the interstitial glucose (IG) profiles derived by ambulatory continuous interstitial glucose monitors (CGMs) to further characterize the time course of glucose concentrations overnight and postdinner with IDegAsp.

Patients and Methods

This study was conducted according to International Conference on Harmonisation Good Clinical Practice[9] and requirements in the Declaration of Helsinki[10] and was a randomized, open-label, parallel-group, treat-to-target trial involving 22 European centers (in France, Germany, Norway, Romania, and Spain) for which the methodology has been described previously.[8] Briefly, patients were included if they were insulin-naïve adults (18–75 years of age) with type 2 diabetes, had HbA1c of 7–11% and body mass index of 25–37 kg/m^2, and were treated with up to two oral antidiabetic drugs (OADs; excluding thiazolidinediones) in the 2 months prior to trial at stable maximum doses or at least half maximum allowed doses. Fuller details on the inclusion and exclusion criteria have been reported previously.[8] The patients were randomized in a 1:1:1 ratio to add a once-daily evening injection of IDegAsp, IGlar, or an alternative formulation of IDeg/IAsp. Except for metformin, all OADs were discontinued. The alternative IDeg/IAsp formulation, which contained a higher percentage of IAsp (45%), has since been discontinued from further development because of higher hypoglycemia rates than the 30% formulation, so data from this arm are not presented. In total, 59 and 60 subjects were randomized to IDegAsp and IGlar, respectively.

Insulin was continuously titrated, aiming for an FPG target of 4.0–6.0 mmol/liter (72–108 mg/dl), and if this goal was achieved, a postdinner plasma glucose target of 8.0 mmol/liter (145 mg/dl) was additionally set. Interstitial glucose profiles were measured by CGM (Medtronic MiniMed CGMS® System Gold™, a Food and Drug Administration-approved and European Union Communauté Européenne-labeled plasma-calibrated CGM system) after 8 and 16 weeks of treatment. The CGM system was fitted 3–4 days before scheduled clinic visits and early enough in the day to allow

three calibrations before midnight. Staff and patients were fully trained in the use of CGM, which was performed on normal weekdays, with subjects instructed to eat normally and regularly (thus, meal content was not standardized) and not to change their insulin dosage during the 72 h data-collection period, unless absolutely necessary. Subjects were instructed to report the timing of meals and insulin injections during the 72 h CGM data-collection periods, after which data from the monitor were downloaded to a personal computer at the investigation site. Patients were blind to these CGM data. This report presents data from the analyses at 16 weeks only since insulin doses were still being actively adjusted at 8 weeks. All IG profiles were included in the analyses, except for one where the subject had been taking nonstudy insulin during the CGM period.

Continuous Glucose Monitor End Points and Statistical Analysis

The following end points were predefined for analysis:

End Points Related to the Mean Interstitial Glucose Profile

Mean IG concentrations were derived from both the entire 72 h profiles as well as the nocturnal profiles, defined as the intervals from 0001–0559 h (inclusive). In addition, the day-to-day within-subject variation in mean nocturnal IG was assessed in terms of the coefficient of variation (CV).

End Points Related to Meal-Related Changes in Interstitial Glucose

Meal-related end points were derived separately for breakfast, lunch, and dinner. The derived end points were

- The mean 2 h postprandial increment in IG level (difference from premeal value to value obtained 2 h after the start of meals) and
- The mean postprandial peak level of IG, based on data collected within 4 h from the start of meals.

Interstitial Glucose Fluctuation

Fluctuation in IG concentration was assessed as an end point to describe the flatness of the glucose profile over time (as opposed to the within-subject variation, which describes how mean IG varies from one day to the next). Fluctuation was calculated (separately for the entire 72 h period and for the nocturnal portion of the profiles) as the sum of the areas above and below the mean IG level, normed by the length of the profile.

End Points Related to Episodes of Low and High Interstitial Glucose

End points related to episodes of low glucose levels (defined as IG < 3.5 mmol/liter) and episodes of high glucose levels (defined as IG > 10 mmol/liter) were derived separately based on the entire 72 h profiles as well as the nocturnal parts of the profiles. The derived end points were

- Number of episodes (the number of times a profile crossed the given thresholds),
- Time in state (the accumulated time a profile was below or above the given thresholds, normed by the length of the profile) expressed as hours/day and hours/night for the nocturnal period, and
- Incidence of episodes (a binary end point indicating whether a subject has experienced at least one episode).

It should be noted that episodes of low glucose values based on IG is a different end point from the previously reported safety end point of patient-reported confirmed hypoglycemic episodes verified by plasma glucose measurements (of <3.1 mmol/liter).[8]

Analyses of Continuous Glucose Monitor End Points

Statistical assessments were prespecified in the protocol. The mean IG and the log-transformed fluctuation in IG from each day were analyzed jointly using a linear mixed model, including treatment, gender, country, previous OAD therapy, and day as fixed factors; subjects as random factor; and age and baseline HbA1c as covariates.

The postprandial mean IG, the mean IG meal increment, the mean IG meal peak, and the duration of episodes of low/high glucose readings were compared between treatments by fitting a linear model, including treatment, gender, country, and previous OAD therapy as fixed factors and age and baseline HbA1c as covariates. When analyzing the postprandial mean IG, mean IG meal peak, and mean IG meal increments, the model also included the mean IG level before the meal as a covariate to adjust for the premeal value.

The number of low and high glucose episodes were analyzed using a negative binomial regression model, with the number of events as the dependent variable; the log-transformed measurement time as an offset; treatment, gender, country, and previous OAD therapy as fixed factors; and age and baseline HbA1c as continuous covariates. Separate analyses were done for each threshold value and per time interval.

The day-to-day variation in mean nocturnal IG expressed as CV was estimated in terms of residual variances in a mixed-effects model, where the mean nocturnal IG was log-transformed. The model included treatment, gender, country, previous OAD therapy, and day as fixed factors; subject as a random factor; and age and baseline HbA1c as covariates. The covariance parameters describing the between- and within-subject variability were estimated separately for each treatment.

A 5% significance level was used for all end points. No correction for multiple testing was performed, as this analysis was of exploratory nature. Missing values after 16 weeks of treatment were imputed using last observation carried forward

Results

Baseline demographic data, patient disposition, and clinical outcomes have been reported previously.[8] The two treatment groups were comparable for all demographic characteristics, except for a higher percentage of males in the IGlar group than the IDegAsp group (73% versus 63%). Data from CGM were evaluable from most of the original study cohort: 55 of 59 patients randomized to IDegAsp and 57 of 60 randomized to IGlar.

Mean of Interstitial Glucose Profiles

The observed mean IG concentration across the three 24 h intervals was 8.10 mmol/liter with IDegAsp and 8.31 mmol/literwith IGlar (IDegAsp - IGlar, -0.10 [95% confidence interval (CI) -0.71, 0.50] mmol/liter). While the observed mean nocturnal IG concentration tended to be lower with IDegAsp (7.26 versus 7.75 mmol/liter), this difference was not statistically significant [estimated treatment difference (IDegAsp - IGlar, -0.43 [95% CI -1.12, 0.25] mmol/liter)].

The overnight IG profile evaluated 0–12 h postdinner showed a small postmeal glucose increment with IDegAsp followed by a gradual decline to a stable IG level. With IGlar, the postdinner glucose level was elevated in the first 4 h following dinner and showed a small but steady decline from 4 h after the start of meal and onward (**Figure 1**).

The estimated day-to-day variation in mean nocturnal IG as evaluated by the CV (percentage) was 19.3% for IDegAsp and 20.2% for IGlar, with no statistically significant difference.

Meal-Related Changes in Interstitial Glucose

The distribution of the times at which main meals were taken during the CGM assessment period did not differ between the treatment groups. In subjects treated with IDegAsp, the mean postprandial glucose increment was significantly lower following dinner compared with subjects treated with IGlar [estimated treatment difference, IDegAsp - IGlar, -1.42 mmol/liter (95% CI -2.15, -0.70)]. While IGlar was associated with a postdinner glucose increment (observed mean increment 1.15 mmol/liter), this was not seen with IDegAsp (observed mean increment -0.38 mmol/liter), with which glucose levels actually declined in the 4 h following start of dinner (**Figures 1** and **2**). There were no statistically significant differences in terms of prandial glucose increments between the treatment groups following breakfast [IDegAsp - IGlar, -0.04 (95% CI -0.92, 0.84)] and lunch [IDegAsp – IGlar, 0.23 (95% CI -0.75, 1.22); **Figure 2**].

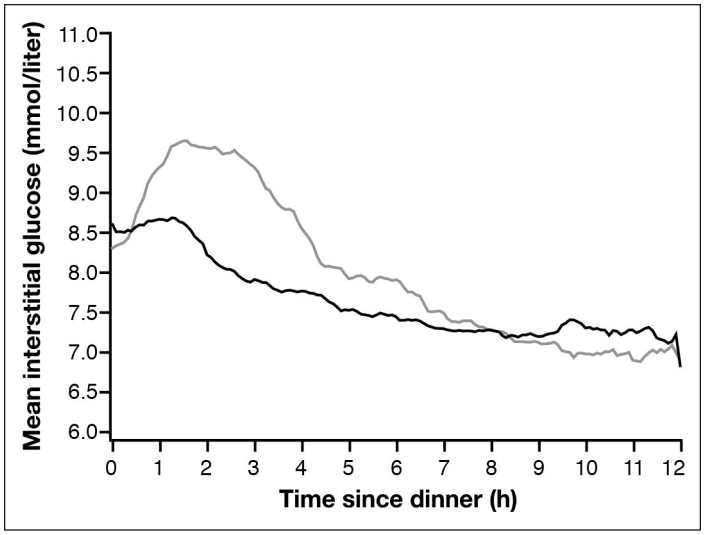

Figure 1. Mean IG profiles over 12 h following the start of the evening meal. Black line, IDegAsp; grey line, IGlar.

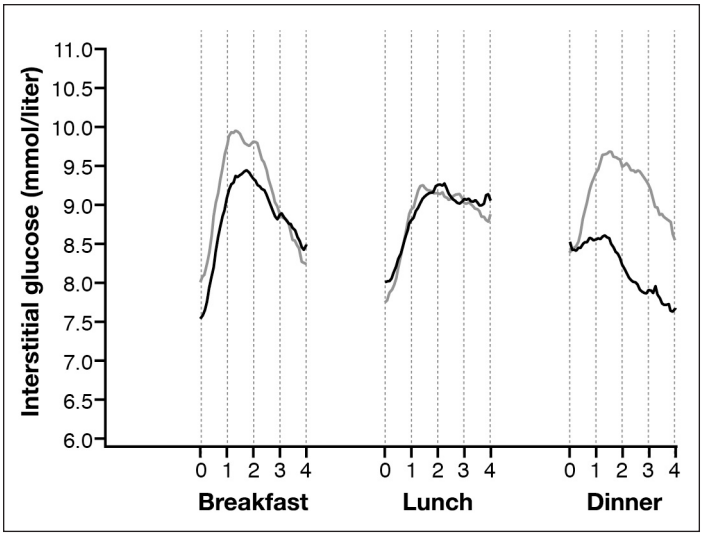

Figure 2. Mean IG profiles over 4 h following the start of each main meal. Black line, IDegAsp; grey line, IGlar.

The observed mean IG peak concentrations following dinner were 10.3 and 10.9 mmol/liter for IDegAsp and IGlar, respectively. The estimated mean IG peak concentration after dinner was significantly lower for IDegAsp compared with IGlar [-1.05 mmol/liter (95% CI -1.67, -0.44)]. It should be noted that these data do not correspond to the apparent peak values in **Figures 1** and **2** since these images depict mean values as a function of time and the peak value does not occur simultaneously in all patients. There was no statistically significant treatment difference following breakfast and lunch, nor were there any statistically significant differences between the treatment groups in terms of the mean time to reach IG peak following any of the meals.

Fluctuation in Interstitial Glucose

The observed mean fluctuation for the whole 72 h profiles was 1.70 mmol/liter with IDegAsp and 1.84 mmol/liter with IGlar [estimated treatment ratio, IDegAsp/IGlar, 0.96 (95% CI 0.85, 1.08)]. The observed mean fluctuation in nocturnal IG was 1.13 versus 1.30 mmol/liter with IDegAsp and IGlar, respectively [estimated treatment ratio, IDegAsp/IGlar, 0.79 (95% CI 0.66, 0.96)], hence the fluctuation in nocturnal IG levels was a statistically significant 21% lower with IDegAsp. While there was no statistically significant difference in the fluctuation in IG in the 0–4 h period following dinner, there was significantly less fluctuation in IG in the 4–12 h period following dinner with IDegAsp compared with IGlar [estimated treatment ratio, IDegAsp/IGlar, 0.80 (95% CI 0.66, 0.96)].

Episodes of Low and High Glucose Values

Data for episodes where IG was <3.5 or >10.0 mmol/liter are presented in **Table 1**.

The number and percentages of subjects experiencing at least one episode of low and high IG were comparable between the treatment groups, both based on the entire 72 h period as well as the nocturnal period. Although numerically the observed rate of episodes and mean total duration of episodes of both low and high IG were lower for IDegAsp, these differences did not attain statistical significance. IDegAsp was, however, associated with a statistically significant 48% lower rate of nocturnal episodes of high IG compared with subjects treated with IGlar [estimated rate ratio, IDegAsp/IGlar, 0.52 (95% CI 0.32, 0.87)]. The rate of nocturnal episodes of low IG and the total duration of nocturnal episodes of low and high IG did not differ between the treatment groups.

Discussion

This secondary analysis shows that, compared with IGlar, treatment with IDegAsp results in a lower postdinner glucose peak, fewer episodes of nocturnal hyperglycemia, and less fluctuation in the overnight IG profile. The lower rise in

postdinner IG was consistent with the results of the nine-point self-monitored plasma glucose profiles derived for the original analysis of this study.[8] Little difference was discernible between the two insulins during the daytime, but this is not unexpected, as glucose concentration during the day is influenced by many factors that are unrelated to the insulin absorption profile, such as meals, variability in mealtimes, and exercise. At nighttime, the influence of the insulins on glucose profile is stronger, as it is minimally affected by exercise, food intake, and other behavioral variables.

Table 1.
Episodes of Low and High Interstitial Glucose

	IG < 3.5 mmol/liter			IG > 10.0 mmol/liter		
	IDegAsp	IGlar	Difference (95% CI)	IDegAsp	IGlar	Difference (95% CI)
Patient number[a]						
24 h interval	25 (46%)	30 (53%)	0.75 (0.35, 1.61)	51 (93%)	50 (88%)	1.72 (0.43, 6.95)
Nocturnal interval	14 (26%)	11 (20%)	1.51 (0.60, 3.82)	24 (44%)	31 (55%)	0.64 (0.28, 1.46)
Number episodes reported[b]						
24 h interval	69	97	Not assessed	392	488	Not assessed
Nocturnal interval	23	31	Not assessed	56	126	Not assessed
Rate of episodes per interval[c]						
24 h interval	0.46	0.65	0.58 (0.31, 1.11)	2.61	3.26	0.83 (0.64, 1.07)
Nocturnal interval	0.15	0.21	0.84 (0.33, 2.10)	0.37	0.83	0.52 (0.32, 0.87)
Time in state[d]						
24 h interval	0.29	0.35	-0.39 (-1.16, 0.39)	5.23	5.91	-0.65 (-2.30, 1.00)
Nocturnal interval	0.08	0.09	-0.01 (-0.11, 0.09)	0.74	1.08	-0.25 (-0.66, 0.17)

[a] The difference between treatments is expressed in terms of estimated odds ratio with 95% CI.
[b] The number of events were analyzed with the length of the profiles, i.e., the amount of information in each profile was included as an offset in the statistical model. Therefore, the numbers of events are presented as the observed rate (not assessed) but with the estimated treatment difference expressed as a rate ratio.[c]
[c] Rates for each treatment are derived as the total number of episodes divided by the total length of the profiles. The rates are expressed as episodes per day for the 24 h interval and as episodes per night for the nocturnal interval. The difference between treatments is expressed in terms of estimated rate ratio with 95% CI.
[d] The mean time in state is expressed as hours per day for the 24 h interval and as hours per night for the nocturnal interval. The difference between treatments is expressed in terms of estimated mean difference with 95% CI.

A CGM enables more refined and detailed assessment of glucose fluctuation over time, glucose profile variability from day to day, or variation of glucose concentration at fixed times of the day. The IG profile and how the glucose level changes over time is a potentially important end point for a number of reasons. First, some *in vitro* and preclinical studies suggest that short-duration oscillations in plasma glucose may adversely influence parameters of cardiovascular risk, and this possibility is supported by epidemiological data showing a correlation between cardiovascular events and post-oral glucose challenge plasma glucose excursions.[11] Therefore, insulin regimens associated with reduced oscillations in glucose level, as well as a reduced overall exposure to hyperglycemia, might be considered advantageous, although it must also be noted that proof for a prognostic advantage for interventions specifically targeting improved glycemic stability is currently lacking.[11,12] Perhaps more important is that, with increasing fluctuation in glucose level (and increasing variability in the day-to-day profile), the risk of hypoglycemia will increase, leading to difficulties in titrating insulin doses to desirable fasting glucose targets because the risk of nocturnal hypoglycemia will increase with the extent of fluctuation and unpredictability in nocturnal glycemia. Indeed, the ability to monitor glucose fluctuation using CGM technology may, in the future, permit more thorough assessment of the quality of glycemic control,[13] perhaps guiding the choice of insulin and regimen and the titration targets used.

As noted, the postprandial IG data are consistent with those reported from nine-point plasma profiling in the original report, but they build on these by illustrating the dynamic changes over time. The greatest difference between the treatment groups was, predictably, observed with respect to postdinner IG, for which IDegAsp effectively abolished the glucose increment seen with IGlar, presumably via the IAsp component of the product. The implications of this observation are worthy of further consideration; basal-only insulin added to OADs is a popular insulin initiation option

for type 2 diabetes because of its simplicity and tolerability and its consequent value in establishing acceptance of insulin injection therapy.[14] Basal insulin, however, does not directly address the high postprandial plasma glucose levels that characterize type 2 diabetes. An often-used counterargument is that basal insulin supplementation can help relieve both the secretory demand placed upon surviving beta cells and glucotoxicity, thereby helping to restore endogenous insulin responses.[14] Nonetheless, our results show clear postprandial increments in glucose levels and hence illustrate a remaining deficit in postprandial insulin secretion. The provision of a rapid-acting component after the main meal at least partly restores this defect. Additionally, the effect of current basal insulins often wanes over 24 h, resulting in potentially low levels of supplementary basal insulin in the postdinner interval with a once-daily evening IGlar regimen,[15] and this clearly does not occur with IDeg. Whether the addition to the starting insulin regimen of a component that addresses postprandial hyperglycemia will extend the time until insulin intensification is needed remains to be determined.

It is noteworthy that, while IDegAsp eliminates the postdinner glucose excursion, this is not at the cost of increased nocturnal hypoglycemia versus IGlar. Instead, the analysis of near-hypoglycemic IG is consistent with the safety assessment of hypoglycemia in the original analysis of this study, which did not show any excess in nocturnal events with IDegAsp (in fact, only one event versus three with IGlar).[8] These observations might relate to the smaller fluctuation in nocturnal IG in the 4–12 h postdinner interval for IDegAsp. This outcome is at least partly explained by the higher initial IG values at 4 h postdinner in the IGlar group, but a smaller fluctuation in the 4–12 h postdinner interval could, in theory, also relate to a lower level of pharmacodynamic variability from the IDeg component. Indeed, a repeat euglycemic clamp study of within-patient variability showed IDeg to produce a lower variation around the mean glucose infusion rate value across a 24 h period compared with IGlar (CV values 31% versus 73%; $p < .0001$).[6] Interestingly, when the analysis was repeated looking at sequential 2 h intervals along the glucose infusion rate curves, this reduced level of variability was consistent over time with IDeg, whereas, for IGlar, variability was higher throughout and tended to increase greatly after 8 h. That said, the present analysis did not find any significant differences in the one parameter we used to assess day-to-day variability (predictability)—i.e., CV of mean nocturnal glucose. However, this parameter might have been confounded by the uncontrolled content and time of the evening meals, the between-treatment difference in mean nocturnal IG level, the precision of the CGM system, and the small size of our type 2 diabetes cohort. Some of these issues are elaborated under study limitations discussed later.

Clinical studies comparing IDeg with IGlar have consistently shown reduced rates of nocturnal hypoglycemia with IDeg,[16–18] which we therefore suggest could also reflect reduced nocturnal glucose fluctuation. A more stable nocturnal pharmacodynamic effect should facilitate titration to more ambitious FPG targets and reduce the risk of both hyperglycemia and hypoglycemia.

While our data illustrate that IDegAsp was able to prevent the postdinner glucose increment without increasing the risk of nocturnal hypoglycemia in our study cohort, a corollary to be noted is that the IAsp component of IDegAsp therefore exerts a powerful glucose-lowering effect that may not be required in all patients. Use of IDegAsp in patients with highly variable eating patterns or in patients who eat only a light evening meal could result in an increased risk of hypoglycemia (or poorer fasting glucose control if compensatory low doses are used). Drug prescribers therefore need to consider the eating behavior of the patient and the timing of administration.

There are a number of limitations to this study that need to be considered when interpreting the data. There was an imbalance in the proportion of males/females between the two study groups, and meal content was neither standardized nor recorded. These factors could potentially confound the between-group differences investigated. The CGM system used has considerably less precision than conventional blood glucose meters, in particular, in the hypoglycemic range.[19] Nevertheless, the same CGM system has been used in all patients, so while absolute numbers might not be entirely correct, relative differences should be maintained. The study was done in patients with type 2 diabetes. Although this is the appropriate target group for study interventions, any differences between the pharmacodynamic profiles of exogenous insulin regimens can be partly buffered by the preserved endogenous responses of patients with type 2 diabetes. Under these circumstances, differences of potential clinical significance in advanced type 2 diabetes may not emerge, or may be underestimated, in the mean data of a relatively small-scale study. It is of

note that this was a secondary analysis from a proof-of-concept study that was not specifically powered for these end points. A larger study, or a study in a type 1 diabetes cohort, would likely show more distinct treatment differences in some of the end points explored here.

In conclusion, IDegAsp was associated with a flatter, more stable nocturnal IG profile than IGlar in previously insulin-naïve patients with type 2 diabetes. The prevention of a postdinner glucose excursion was achieved without the cost of increased risk of nocturnal hypoglycemia. It is likely that this may be explained, at least partly, by the smaller fluctuation in nocturnal glucose levels, which we suggest is attributable to the consistent pharmacodynamic effect of IDeg. The clinical potential of IDegAsp is being investigated in larger-scale phase 3 studies as an add-on treatment to OADs in comparison with premixed insulin or IGlar, as well as a basis for basal–bolus therapy with supplementary mealtime IAsp injections.

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