Insulin Degludec/Insulin Aspart Administered Once Daily at Any Meal, With Insulin Aspart at Other Meals Versus a Standard Basal-Bolus Regimen in Patients With Type 1 Diabetes

A 26-week, phase 3, randomized, open-label, treat-to-target trial

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OBJECTIVE—To evaluate efficacy and tolerability of a co-formulation of insulin degludec and insulin aspart (IDegAsp) with insulin aspart (IAsp) at other meals compared with basal-bolus therapy using insulin detemir (IDet) and IAsp.

RESEARCH DESIGN AND METHODS—Adults (n = 548) with type 1 diabetes (A1C 7.0–10.0%; BMI ≤35.0 kg/m2) were randomized 2:1 in a 26-week, multinational, parallel-group, treat-to-target trial to IDegAsp or IDet. IDegAsp was given with a meal, and IDet was given in the evening, with a second (breakfast) dose added if needed.

RESULTS—Non-inferiority for IDegAsp versus IDet was confirmed; A1C improved by 0.75% with IDegAsp and 0.70% with IDet to 7.6% in both groups (estimated treatment difference IDegAsp – IDet: –0.05% [95% CI –0.18 to 0.08]). There was no statistically significant difference between IDegAsp and IDet in the rates of severe hypoglycemia (0.33 and 0.42 episodes/patient-year, respectively) or overall confirmed (plasma glucose <3.1 mmol/L) hypoglycemia (39.17 and 44.34 episodes/patient-year, respectively). Nocturnal confirmed hypoglycemia rate was 37% lower with IDegAsp than IDet (3.71 vs. 5.72 episodes/patient-year, P < 0.05). Total insulin dose was 13% lower in the IDegAsp group (P < 0.0001). No treatment differences were detected in Health-Related Quality of Life, laboratory measurements, physical examination, vital signs, electrocardiograms, fundoscopy, or adverse events.

CONCLUSIONS—IDegAsp in basal-bolus therapy with IAsp at additional mealtimes improves overall glycemic control and was non-inferior to IDet, with a reduced risk of nocturnal hypoglycemia and fewer injections in comparison with IDet + IAsp basal-bolus therapy.

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Evaluation of IDegAsp-based basal-bolus therapy

over the likelihood of weight gain. In this respect, insulin detemir (IDet) has consistently shown reduced weight gain compared with other basal insulins in trials (11–14).

Insulin degludec/insulin aspart (IDegAsp) is a new insulin combination product in clinical development for the treatment of diabetes. The basal component, insulin degludec (IDeg), is formulated in the pharmaceutical product so as to form soluble, stable di-hexamers that reorganize, after injection, into multi-hexamer chains, forming a subcutaneous depot (15,16). The multi-hexamer subsequently releases monomers at a slow and steady rate, and these are readily absorbed into the circulation (15,16). The resulting ultra-long and stable action profile is characterized by a duration of action beyond 40 h (15) with a terminal half-life exceeding 25 h at a dose of 0.4 units/kg (17). IDeg has a lower day-to-day and hour-to-hour variability in glucose-lowering effect compared with insulin glargine (18). This distinct pharmacodynamic (PD) profile translates clinically into the ability to optimize glycemic control with a lower risk of nocturnal hypoglycemia compared with currently available basal insulins (19,20), as well as into the possibility of adjusting the injection time of both IDeg and IDegAsp from day to day to accommodate individual needs.

Another unique pharmacological property of IDeg is that it can be combined with insulin aspart (IAsp) without the risk of hybrid hexamers (mixed hexamers containing monomers of both IDeg and IAsp) forming, which lead to unpredictable and suboptimal pharmacokinetic/PD profiles being produced (21). IDegAsp is therefore designed to produce a PD profile that reflects the prandial insulin profile of IAsp (22) superimposed on the long-duration and stable profile of IDeg (15).

A clear separation of the PD effects of the bolus and basal components of IDegAsp was hypothesized to carry a lower risk of hypoglycemia than can be achieved with conventional premixed insulin products, and a proof-of-concept study has indeed demonstrated lower rates of confirmed and nocturnal hypoglycemia comparing IDegAsp to biphasic IAsp in type 2 diabetes (23).

IDegAsp is the first analog co-formulation that contains both long- and rapid-acting insulins, thereby providing the total daily basal insulin requirement as well as the bolus insulin requirement for one main meal. Administration of IDegAsp at a single meal, with additional bolus injections at the remaining meals, facilitates a treatment regimen that requires fewer daily injections than standard basal-bolus therapy, which typically requires 4-5 daily injections. The current study was therefore undertaken to confirm the efficacy and tolerability of basal-bolus therapy with IDegAsp administered once daily (OD) at a main meal in combination with IAsp at other meals in patients with type 1 diabetes compared with full basal-bolus therapy using IDet and IAsp.

RESEARCH DESIGN AND METHODS

Trial design
This was a 26-week, multinational, multicenter, open-labeled, two-arm, parallel, randomized, treat-to-target trial comparing the efficacy and safety of OD IDegAsp plus mealtime IAsp for remaining meals to OD IDet with mealtime IAsp in patients with type 1 diabetes. This trial was conducted at 79 sites in nine countries (Denmark, Poland, Romania, France, U.K., Russian Federation, Israel, Australia, and U.S.) between 25 August 2009 and 31 May 2010.

The protocol, protocol amendments, consent form, and patient information sheet were reviewed and approved by health authorities, according to local regulations, and by the local independent ethics committee prior to trial initiation. The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation Good Clinical Practice guidelines. Written informed consent was obtained from patients prior to entry and any trial-related activities.

Trial population
Men and women (≥18 years of age) with type 1 diabetes for at least 12 months, A1C 7.0–10.0% (inclusive), BMI ≤35.0 kg/m², and currently treated with insulin (using basal-bolus, premixed insulin, or self-mix regimens) for at least 12 months were eligible for inclusion. Patients were excluded if they were using insulin regimens other than those listed above within 3 months of trial initiation or a basal-bolus regimen with a basal insulin injected twice daily. Other exclusion criteria included anticipated change in concomitant medications known to interfere with glucose metabolism, recurrent severe hypoglycemia or hypoglycemic unawareness, proliferative retinopathy or maculopathy requiring treatment, pregnancy, breastfeeding, renal or hepatic dysfunction, significant cardiovascular disease or cancer, and other conditions considered by the investigator as likely to interfere with the trial results.

Randomization
Eligible patients were randomized 2:1 to receive OD IDegAsp (100 units/mL, 3 mL FlexPen; Novo Nordisk) or OD IDet (100 units/mL, 3 mL FlexPen; Novo Nordisk), both in combination with IA (NovoRapid/NovoLog; 100 units/mL, 3 mL FlexPen; Novo Nordisk). Randomization was stratified based on previous insulin regimen at screening: basal-bolus regimen or another insulin regimen. The unequal randomization ratio was to ensure an adequate number of patients were exposed to IDegAsp to fulfill regulatory requirements. An open-label trial design was chosen as the two treatment regimens required a different number and timing of daily injections. In addition, trials conducted with an insulinpen injection device cannot be blinded.

A safety committee from Novo Nordisk performed ongoing safety surveillance and was blinded to treatment but could recommend unblinding of the data to be assessed by an independent ad hoc group, if appropriate. The external cardiovascular Event Adjudication Committee was masked to treatment. The titration of insulin doses was monitored by Quintiles and reviewed by a blinded titration committee.

Treatment administration and titration
IDegAsp is a soluble co-formulation consisting of 70% ultra-long-acting basal insulin, IDeg, and 30% rapid-acting insulin, IA. IDegAsp was administered OD with a main meal, and the dosing time could be moved to another main meal at any time during the trial at the patient’s and/or physician’s discretion. IA was administered at the remaining meals with the instruction given to inject immediately before commencing the meal (both treatment groups).

Patients randomized to IDet plus IA were prescribed the same number of basal and bolus units as prior to randomization. IDet was administered OD at the evening meal or at bedtime, according to local practice, and at the same time each day. In the case of inadequate glycemic control after 8 weeks of treatment, the investigator could add a second morning dose of...
IDet. Consideration of this was recommended if mean pre-dinner plasma glucose (PG) was >6.0 mmol/L (108 mg/dL), and when patients with baseline A1C <8% showed any deterioration of A1C, or when patients with baseline A1C 8–10% inclusive showed less than a 0.5%-point drop in A1C. The second dose of IDet was to be started at 4 units at breakfast. Insulin aspart was administered at all meals.

Patients randomized to IDegAsp plus IAsp from a basal-bolus regimen received the same number of basal units as prior to randomization. For the meals not covered by IDegAsp, similar bolus doses were prescribed as given prior to randomization. Patients switching from a premix/self-mix regimen were instructed to start treatment with IDegAsp at a dose corresponding to 70% of their total daily insulin dose prior to randomization. The remaining 30% was split and given as IAsp at the other meals.

Insulin dose adjustments were performed once weekly according to protocol-specified titration guidelines, with the overall treatment goal of achieving an A1C of <7%. A treat-to-target approach was applied, which is expected to result in parity between treatment arms in glycemic control. The IDegAsp and IDet doses were adjusted to a pre-breakfast PG target of 4–5 mmol/L (72–90 mg/dL), whereas morning doses of IDet were titrated based on the mean pre-dinner PG levels, again aiming for 4–5 mmol/L. Adjustments were based on the mean self-measured PG (SMPG) value from the preceding 3 days.

Titration of bolus insulin (IAsp) aimed to achieve a pre-meal PG target of 4–5 mmol/L at the following meal; hence, the breakfast bolus dose was titrated based on mean pre-lunch PG values, the lunch bolus dose was titrated based on mean pre-dinner PG values, and the dinner bolus dose was titrated based on the mean bedtime PG values.

**Trial end points**
The primary end point was the change from baseline in A1C after 26 weeks of treatment. Secondary end points included percent of patients reaching A1C <7.0%, change from baseline in fasting PG (FPG), 9-point SMPG including pre- and postprandial values and the prandial PG increment, time to meet pre-breakfast SMPG titration target, and Health-Related Quality of Life (HRQoL) (Short-Form 36 [SF-36] Version 2) questionnaire (24).

The SF-36 has eight domains (physical functioning, bodily pain, role-physical, general health, vitality, social functioning, role-emotional, and mental health) that can be combined to give two summary component scores. The first four domains give a physical component score representing predominantly physical wellbeing, with the latter four providing a mental component score comprising aspects of mental health.

Safety assessments included adverse events (AEs), hypoglycemic events, insulin doses (total insulin dose and basal and bolus doses), body weight, laboratory tests, and vital signs. Confirmed hypoglycemia was defined as those events with a PG value <3.1 mmol/L (56 mg/dL) regardless of symptoms) or considered severe (patient requiring assistance). Hypoglycemic events that occurred between midnight and 6:00 A.M. (inclusive) were classified as nocturnal.

**Statistical analysis**
This trial’s primary objective was to confirm the non-inferiority of IDegAsp to IDet, as assessed by change in A1C from baseline after 26 weeks, with a non-inferiority limit of 0.4%. If non-inferiority was confirmed, the trial also aimed to show superiority of IDegAsp on selected end points based on a hierarchical testing procedure.

The full analysis set included all randomized patients. These patients were included in all analyses of efficacy endpoints, including HRQoL and hypoglycemia. Safety end points were evaluated for all patients exposed to treatments (safety analysis set). Missing values were imputed using the last observation carried forward (LOCF) method. Change from baseline in A1C after 26 weeks of treatment was analyzed using an ANOVA model, with treatment, antidiabetic therapy at screening, sex, and region as fixed factors, and age and baseline values as covariates. Change from baseline in FPG, body weight, prandial increments, PG, and HRQoL, were analyzed using an ANOVA method similar to that applied to the primary end point. The number of hypoglycemic episodes was analyzed using a negative binomial regression model including treatment, antidiabetic therapy, sex, and region as fixed factors, age as a covariate, and exposure as offset. Other AEs are presented as descriptive statistics.

**RESULTS**

**Baseline characteristics and patient disposition**
A total of 548 patients were randomized to IDegAsp (n = 366) or IDet (n = 182). The disposition of patients during the trial is summarized in Fig. 1. Similar proportions completed the trial in each treatment arm (87.4% IDegAsp; 85.7% IDet).

Demographic and baseline characteristics are presented in Table 1 and appeared well matched between the two treatment groups. Overall, the patients had an average age of 41.3 years, with a diabetes duration of 17.4 years, an A1C of 8.3%, and a BMI 26.4 kg/m². At screening, the majority of patients had been previously treated with a basal-bolus insulin regimen (Table 1).

**Analysis of efficacy**
After 26 weeks of treatment, A1C decreased in both treatment groups to 7.6% (Fig. 2A). The estimated mean change from baseline to week 26 was −0.75% with IDegAsp and −0.70% with IDet (estimated treatment difference [ETD] IDegAsp−IDet: −0.05% [95% CI −0.18 to 0.08]), confirming the non-inferiority of IDegAsp to IDet. The proportion of patients achieving the A1C target of <7.0% at week 26 was 24.6% with IDegAsp and 20.3% with IDet (not significant [NS]). FPG was reduced after 26 weeks of treatment to 8.7 mmol/L (157 mg/dL) with IDegAsp and to 8.6 mmol/L (155 mg/dL) with IDet (ETD IDegAsp−IDet: 0.23 [−0.46 to 0.91] mmol/L, NS; −4.1 [−8.3 to 16.4] mg/dL) (Fig. 2B).

At week 26, 16.9 and 16.0% of IDegAsp- and IDet-treated patients, respectively, had self-measured fasting PG values <5 mmol/L (90 mg/dL) based on LOCF data. At baseline, the 9-point SMPG profiles were similar between treatment groups, and PG decreased across the profile after 26 weeks of treatment with both IDegAsp and IDet (Fig. 2C). After 26 weeks, the SMPG profiles were similar between the two treatment groups except before lunch (ETD IDegAsp−IDet: −1.08 [−1.73 to −0.43] mmol/L, P < 0.05) and before breakfast the next day (ETD IDegAsp−IDet: −0.72 [−1.28 to −0.15] mmol/L, P < 0.05), where PG was lower with IDegAsp than with IDet. The respective changes in prandial increment (mmol/L) from baseline to the end of the trial for IDegAsp and IDet were 0.0 and −0.3 (averaged for all meals), 0.0 and 0.2 (for breakfast), −0.2 and −1.4 (for lunch), and 0.2 and 0.2 (for the evening meal), respectively. Only the prandial increment at lunch was significantly higher with IDegAsp than with IDet (ETD IDegAsp−IDet: 0.92 [0.17–1.68], P < 0.05), this being the result of a lower
prelunch rather than a higher post-lunch PG value (Fig. 2C).

The disparity between the 26-week FPG and pre-breakfast SMPG values likely reflects the fact that the former was a central laboratory measurement and the latter was based on patient self-assessment. Furthermore, as the FPG was measured in the clinic, this occurred later in the morning than the pre-breakfast SMPG, which was measured earlier at home.

**Insulin dose**

The majority of patients randomized to IDegAsp selected the main evening meal as their administration time, with the remaining patients evenly split between taking IDegAsp at breakfast and lunch. These proportions were maintained throughout the trial. During the trial, 17% of patients in the IDegAsp group changed their injection time to another main meal, and 26% of patients randomized to IDet added a second dose.

At baseline, the total daily insulin doses (basal plus bolus) were similar (56 units [0.74 units/kg]) between treatment groups. After 26 weeks of treatment, the total insulin dose was 13% lower in the IDegAsp group (69 units [0.86 units/kg]; basal, 29 units [0.37 units/kg]; bolus, 39 units [0.49 units/kg]) than in the IDet group (79 units [1.00 units/kg]; basal, 36 units [0.46 units/kg]; bolus, 43 units [0.54 units/kg]) (ETD: 0.87 units [0.82–0.92], \(P\), 0.0001). Whereas the bolus insulin dose was not significantly different between treatment groups, the basal insulin dose was 15% lower in the IDegAsp group compared with the IDet group (ETD: 0.85 units [0.80–0.90], \(P\) < 0.0001). The basal-to-bolus split was 43%/57% after 26 weeks of treatment with IDegAsp + IAsg, and 46%/54% with IDet + IAsg. Overall, IDegAsp comprised 61% of the total daily insulin dose.

At 26 weeks, the basal insulin dose was numerically higher in patients treated with IDet twice daily (BID) (47 units [0.56 units/kg]) compared with the subgroup using IDet OD (33 units [0.43 units/kg]). The bolus insulin dose, however, was numerically lower in IDet BID users (37 units [0.44 units/kg]) compared with IDet OD users (45 units [0.58 units/kg]); hence, the total insulin dose was similar between the IDet subgroups. Average bolus insulin doses by meal at baseline and week 26 are presented in Supplementary Table 1.

**Quality of life**

There were no significant differences between treatment groups in the change from baseline in the physical or mental scores from the HRQoL questionnaire (SF-36) (IDegAsp vs IDet: Physical score 0.3 [−0.6 to 1.3], NS; Mental score −0.1 [−1.6 to 1.3], NS).

**Hypoglycemic episodes**

Cumulative rates of overall confirmed and nocturnal confirmed hypoglycemia are
shown in Fig. 3, with data summarized in Supplementary Table 2. The observed rates of overall confirmed hypoglycemia were 39.17 episodes per patient-year of exposure (PYE) with IDegAsp and 44.34 episodes per PYE with IDet (estimated rate ratio [ERR] IDegAsp/IDet: 0.91 [0.76–1.09], NS). The rate of nocturnal confirmed hypoglycemia was significantly lower in the IDegAsp treatment group compared with the IDet group, corresponding to a 37% lower rate, with 3.71 and 5.72 episodes per PYE, respectively (ERR 0.63 [0.49–0.81], P < 0.05). The observed rates of nocturnal confirmed hypoglycemia were 4.82 and 8.23 episodes per PYE in patients completing on IDet OD or BID, respectively. The rates for severe hypoglycemia were 0.33 episodes per PYE with IDegAsp and 0.42 episodes per PYE with IDet (ERR 1.19 [0.58–2.41], NS). The rate of severe nocturnal hypoglycemia was low for both treatment groups; 0.06 IDegAsp and 0.17 IDet episodes per PYE.

### Safety evaluation

At week 26, the observed mean weight gain was 1 kg greater with IDegAsp (2.3 kg) than with IDet (1.3 kg) (ETD IDegAsp–IDet: 1.04 [0.38–1.69], P < 0.05). No differences were observed in laboratory measurements (hematology, lipids, biochemistry, and antibodies), physical examination, vital signs, electrocardiograms, or fundoscopy. The rate of treatment-emergent AEs per PYE was similar between the two treatment arms (5.00 IDegAsp; 5.20 IDet) (Supplementary Table 3). The most frequently reported AEs in both groups were nasopharyngitis, headaches, hypoglycemia, and upper respiratory tract infections (Supplementary Table 4). A total of seven patients withdrew from the trial due to an AE (1.1% IDegAsp; 1.6% IDet). The majority of AEs were mild or moderate and the rates of injection-site reactions were low; 0.04 reactions per PYE (1.4% of patients) in the IDegAsp group and 0.43 reactions per PYE (4.4% of patients) in the IDet group.

The rate of serious AEs was also similar between the IDegAsp and IDet treatment groups (0.27 and 0.20 events per PYE, respectively) (Supplementary Table 3). The serious AE possibly/probably related to treatment with the highest rate was hypoglycemia at 0.11 events per PYE for IDegAsp and 0.05 events per PYE for IDet (Supplementary Table 5). There were no fatal events and no major adverse cardiovascular events reported in the trial.

### CONCLUSIONS

This study demonstrates the efficacy and tolerability of a new insulin co-formulation, IDegAsp, combined with additional mealtime bolus insulin in the treatment of type 1 diabetes. Treatment with once-daily IDegAsp plus IAsp at remaining meals improved glycemic control and was non-inferior to a standard basal-bolus regimen, comprised of IDet + IAsp, in terms of lowering A1C. The efficacy of IDegAsp was established with fewer daily injections (3 vs. 4–5) and a lower insulin dose, and IDegAsp was also associated with a significantly lower risk of nocturnal hypoglycemia.

Taking into account the similar effectiveness of the two regimens, the 37% lower risk of nocturnal hypoglycemic episodes observed with IDegAsp seems to be a very important finding. It is all the more remarkable given that the ratio of the evening bolus and basal components is fixed with IDegAsp, and that the comparator basal insulin, IDet, has itself been consistently shown to reduce the risk of nocturnal hypoglycemia versus NPH insulin in trials in both type 1 (25–29) and type 2 diabetes (30–32). It should be noted that risk differences between basal insulins are expected to be greater with regard to nocturnal hypoglycemic episodes, because their influence on risk is less confounded during the night by other factors, such as inadequate carbohydrate intake or exercise. IDet is characterized by a reduced intra-patient variability in the PD action profile compared with earlier basal insulins (33,34). This is thought to be mediated via its solubility and reversible plasma albumin binding, and it is also thought that this contributes to a low risk of nocturnal hypoglycemia (35). It is therefore encouraging that this risk appears to be further reduced with IDegAsp, and this finding is also consistent with comparative studies of IDeg (the basal component of IDegAsp) versus insulin glargine when used in basal-bolus therapy (19) or as initial basal insulin therapy in type 2 diabetes (36).

It is reassuring to note that the absolute rates for overall and nocturnal hypoglycemia in our study were numerically similar (29) or reduced (37,38) compared with previous treat-to-target studies in type 1 diabetes in which less ambitious glycemic targets have been used for both basal and bolus insulin titration. This difference in bolus titration and the fact that this global study included study participants with diverse eating patterns might account for the lower final ratios of basal-to-bolus insulin dose in our study: 43.57 and 46.54 for IDegAsp and IDet, respectively.
Although these values do not differ greatly from the 50:50 split generally recommended with basal-bolus therapy, previous treat-to-target studies in adult type 1 diabetes cohorts of similar BMI to ours have tended to report 50–60% of the total insulin dose constituting basal insulin (29,37,38). In these studies, bolus insulin was titrated to 2-h postprandial glucose targets (~7.7 or ~9 mmol/L), whereas our study targeted preprandial normoglycemia. Another study involving IDeg in type 1 diabetes also titrated bolus insulin to a preprandial glucose target of 4–5 mmol/L, and here the basal-to-bolus ratio was 47:53 for both IDeg and insulin glargine (20).

The lower overall insulin dose used by the IDegAsp group was primarily driven by a lower basal insulin dose. The observation that 26% of patients in the IDet treatment arm changed to BID dosing is consistent with previous reports that a substantial proportion of patients with type 1 diabetes achieve improved glycemic profiles when they switch from once- to twice-daily use of IDet (38,39,40).

The IDet treatment arm had, on average, 1 kg less weight gain than the IDegAsp treatment arm. This weight advantage of IDet has been a consistent finding in many clinical trials versus NPH insulin and insulin glargine (11,41–43). Previous comparisons of IDegAsp or IDeg versus insulin glargine have not observed differences in weight outcome (19,44,45). Therefore, despite some structural similarities between IDeg and IDet (notably the presence of a fatty acid chain acylated to the B29 amino acid residue), this effect appears to be unique to IDet. The underlying mechanism responsible for this remains unproven although a number of pharmacological hypotheses have been articulated in previous publications (11–14).

As well as lowering the PG values over the study, both insulin regimens caused a flattening of the 9-point SMPG profile (Fig. 2C). It is possible that these profiles reflect titration of the basal insulin against a low FPG target, and/or that the ambitious titration algorithm used for IAsp was successful in suppressing postprandial increments in glucose. In the case of IDet, the rather flat profile partly reflected the PG level being sustained at the post-breakfast value across the remainder of the daytime, whereas with IDegAsp, PG declined after breakfast to a significantly lower pre-lunch value. This subtle between-treatment disparity in the glucose profiles is difficult to explain, but it is noteworthy that some patients were taking IDet BID, some patients were taking IDegAsp at meals other than dinner, and the total and basal insulin doses were lower in the IDegAsp group; hence, minor differences in the glucose trajectories might be expected. Similar flat SMPG profiles have been reported previously with insulin analog basal-bolus therapy using a titrate-to-target approach (37), and therefore this observation is worth investigating further.

The ambitious FPG target applied in this study was ~1 mmol/L lower than that of most previous treat-to-target type 1 diabetes studies, and both insulin regimens lowered FPG substantially. The proportions of patients achieving the target of 4–5 mmol/L (and A1C <7%), however, were low, but it should be noted that the achievement of such excellent levels of glycemic control is expected to be uncommon in type 1 diabetes cohorts. Thus, the target achievement results are
consistent with previous studies in type 1 diabetes where treat-to-target protocols (using less ambitious FPG targets) have been applied (29,38,40).

In summary, OD treatment with the new insulin combination IDegAsp at any main meal plus IAsp for the remaining meals is as efficacious and well tolerated as a standard basal-bolus regimen, with the added benefits of a significantly lower risk of nocturnal hypoglycaemia and fewer daily injections in patients with type 1 diabetes.

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