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Research: Treatment

Insulin degludec/insulin aspart once daily in Type 2 diabetes: a comparison of simple or stepwise titration algorithms (BOOST®: SIMPLE USE)

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Abstract

Aims To compare the efficacy and safety of two titration algorithms for insulin degludec/insulin aspart (IDegAsp) administered once daily with metformin in participants with insulin-naïve Type 2 diabetes mellitus.

Methods This open-label, parallel-group, 26-week, multicentre, treat-to-target trial, randomly allocated participants (1:1) to two titration arms. The Simple algorithm titrated IDegAsp twice weekly based on a single pre-breakfast self-monitored plasma glucose (SMPG) measurement. The Stepwise algorithm titrated IDegAsp once weekly based on the lowest of three consecutive pre-breakfast SMPG measurements. In both groups, IDegAsp once daily was titrated to pre-breakfast plasma glucose values of 4.0–5.0 mmol/l. Primary endpoint was change from baseline in HbA_{1c} (%) after 26 weeks.

Results Change in HbA_{1c} at Week 26 was $IDegAsp_{Simple}$ −14.6 mmol/mol (−1.3%) (to 52.4 mmol/mol; 6.9%) and $IDegAsp_{Stepwise}$ −11.9 mmol/mol (−1.1%) (to 54.7 mmol/mol; 7.2%). The estimated between-group treatment difference was −1.97 mmol/mol [95% confidence interval (CI) −4.1, 0.2] (−0.2%, 95% CI −0.4, 0.02), confirming the non-inferiority of $IDegAsp_{Simple}$ to $IDegAsp_{Stepwise}$ (non-inferiority limit of ≤ 0.4%). Mean reduction in fasting plasma glucose and 8-point SMPG profiles were similar between groups. Rates of confirmed hypoglycaemia were lower for $IDegAsp_{Stepwise}$ [2.1 per patient years of exposure (PYE)] vs. $IDegAsp_{Simple}$ (3.3 PYE) (estimated rate ratio $IDegAsp_{Simple}$/$IDegAsp_{Stepwise}$ 1.8; 95% CI 1.1, 2.9). Nocturnal hypoglycaemia rates were similar between groups. No severe hypoglycaemic events were reported.

Conclusions In participants with insulin-naïve Type 2 diabetes mellitus, the $IDegAsp_{Simple}$ titration algorithm improved HbA_{1c} levels as effectively as a Stepwise titration algorithm. Hypoglycaemia rates were lower in the Stepwise arm.

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Introduction

People with diabetes who require intensified (prandial and basal) insulin therapy can find it challenging to manage separate basal and bolus injections, which may become a barrier to adherence to treatment [1]. Regular self-monitored plasma glucose (SMPG) allows people with diabetes to adjust their insulin dose as necessary according to titration algorithms in order to maintain appropriate glycaemic control. However, SMPG can be perceived as burdensome and incurs significant healthcare costs [2,3]. In order to improve adherence to insulin treatments, and to reduce the burden associated with multidose insulin regimens, novel insulins designed to have a longer duration of action and lower variability with reduced episodes of hypoglycaemia may allow for a clinically simplified treatment regimen for physicians and people with diabetes alike [4]. Insulin

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What's new?

- The co-formulation, insulin degludec/insulin aspart (IDegAsp), provides basal and mealtime insulin coverage in a single injection.
- IDegAsp may be titrated using two titration algorithms, Simple (titrated twice weekly) or Stepwise (titrated once weekly). Both algorithms effectively reduce HbA_{1c} levels in participants with insulin-naïve Type 2 diabetes, with similar rates of nocturnal hypoglycaemia and no reported severe hypoglycaemic events. $IDegAsp_{Stepwise}$ leads to significantly lower rates of overall confirmed hypoglycaemia compared with $IDegAsp_{Simple}$.
- Optimizing titration may facilitate better disease management by healthcare professionals and people with diabetes.

degludec/insulin aspart (IDegAsp) is a soluble insulin co-formulation of insulin degludec (IDeg, 70%), a basal insulin with a stable, ultra-long duration of action, combined with insulin aspart (IAsp, 30%), a rapid-acting bolus insulin [5,6], in a single injection. IDegAsp can be administered once or twice daily with main meal(s). The aim of this study (BOOST®: SIMPLE USE) was to compare the efficacy and safety of two self-titration algorithms (Simple – self-titration performed twice weekly with 3–4 days between titrations; and Stepwise – self-titration performed once weekly) for IDegAsp administered once daily with a main meal plus metformin in participants with insulin-naïve Type 2 diabetes mellitus, inadequately controlled on oral anti-diabetic drugs alone. This was done by comparing the difference in change from baseline in HbA_{1c} after 26 weeks of treatment between IDegAsp once daily using the Simple titration algorithm + metformin and IDegAsp once daily using the Stepwise algorithm + metformin to a non-inferiority limit of 0.4% (≤ 4 mmol/mol).

Participants and methods

The study (BOOST®: SIMPLE USE) was a 26-week, multinational, multicentre, randomized, open-label, stratified, two-arm, parallel-group, treat-to-target Phase 3b trial that compared the efficacy and safety of two titration algorithms for IDegAsp once daily, in combination with metformin (≥ 1000 mg/day) in participants with insulin-naïve Type 2 diabetes mellitus inadequately treated with oral anti-diabetic drugs alone. The study was conducted in accordance with the Declaration of Helsinki and with the International Conference on Harmonisation Guidelines for Good Clinical Practice. Approval was obtained from appropriate ethics committees and written consent was given by all participants before the start of any study-related procedures.

Eligible participants were insulin-naïve men and women aged ≥ 18 years with a diagnosis of Type 2 diabetes mellitus for ≥ 24 weeks prior to randomization, HbA_{1c} 53–86 mmol/mol (7.0–10.0%) (both inclusive), BMI ≤ 45.0 kg/m^2, and currently treated with metformin monotherapy or metformin in any combination with one or two additional oral anti-diabetic drugs, including sulfonylurea/glinide, dipeptidyl peptidase 4 inhibitors, α–glucosidase inhibitors, thiazolidinediones, all with unchanged dosing for at least 12 weeks prior to randomization. Key exclusion criteria included treatment with a glucagon-like peptide–1 receptor agonist in the previous 12 weeks or diagnosis of a life-threatening disease.

Eligible participants were randomized (1:1) to one of the two IDegAsp titration algorithms: Simple ($IDegAsp_{Simple}$) or Stepwise ($IDegAsp_{Stepwise}$). For $IDegAsp_{Simple}$, participants titrated their insulin dose twice weekly using 2–U increments or decrements based on a single pre-breakfast SMPG measurement on the day of titration (Table S1). For $IDegAsp_{Stepwise}$, participants titrated their insulin dose once weekly using increments or decrements of 2–8 U based on the lowest of three consecutive pre-breakfast SMPG readings (2 days before, and on the day of titration) (Table S2). In both groups, the IDegAsp dose was titrated to achieve pre-breakfast plasma glucose values of 4.0–5.0 mmol/l (71–90 mg/dl). IDegAsp was administered once daily with a main meal at a starting dose of 10 U in both titration groups. Any changes in injection schedule were guided by a physician during either a visit or telephone contact. Participants continued on the same dose of metformin; all other oral anti-diabetic drugs were discontinued before the start of the trial.

The primary endpoint was the change in HbA_{1c} (%) from baseline to after 26 weeks of treatment, using a non-inferiority limit of 0.4% (≤ 4 mmol/mol). Secondary efficacy endpoints included change in fasting plasma glucose from baseline, the proportion of participants who achieved HbA_{1c} targets and 8-point SMPG profiles. Secondary safety endpoints included insulin dose, body weight, adverse events and hypoglycaemic episodes. Confirmed hypoglycaemic episodes included those with a plasma glucose value < 3.1 mmol/l (56 mg/dl) and/or severe hypoglycaemic episodes (in which the participant required assistance). Hypoglycaemic episodes that occurred between 00.01 and 05.59 h (both inclusive) were classified as nocturnal. All endpoints were analysed as detailed in the Supporting Information (statistical analyses).

Results

Of 276 participants, 136 were randomly allocated to the $IDegAsp_{Simple}$ group and 140 to the $IDegAsp_{Stepwise}$ group. Baseline characteristics (Table 1) and participant disposition (Fig. S1) were similar in the two groups.

Table 1 Baseline characteristics of participants (full analysis set)

Characteristic	$IDegAsp_{Simple}$ (n = 136)	$IDegAsp_{Stepwise}$ (n = 140)
Female/male, %	43.4/56.6	60.0/40.0
Race: white/black/ Asian/other, %	55.9/10.3/ 33.8/0.0	59.3/15.0/ 23.5/2.1
Ethnicity: Hispanic or Latin American, %	27.2	28.6
Age, years (SD)	57.0 (± 9.4)	55.8 (± 9.7)
Weight, kg (SD)	85.1 (± 17.3)	83.2 (± 21.5)
BMI, kg/m^2 (SD)	31.0 (± 5.0)	30.8 (± 6.0)
Duration of diabetes, years (SD)	10.1 (± 6.5)	10.2 (± 6.5)
HbA_{1c}, mmol/mol (SD)	66.9 (± 8.9)	66.6 (± 8.9)
HbA_{1c}, % (SD)	8.3 (± 0.8)	8.2 (± 0.8)
Fasting plasma glucose, mmol/l (SD)	8.9 (± 2.4)	9.0 (± 2.3)
Fasting plasma glucose, mg/dl (SD)	159.7 (± 44.1)	162.1 (± 42.0)

IDegAsp, insulin degludec/insulin aspart.

Efficacy

The observed mean HbA_{1c} decreased from 67.2 (± 8.7) mmol/mol [8.3 (± 0.8)%] to 52.4 (± 10.7) mmol/mol [6.9 (± 1.0)%] in the $IDegAsp_{Simple}$ group and from 66.9 (± 8.9) mmol/mol [8.2 (± 0.8)%] to 54.7 (± 10.3) mmol/mol [7.2 (± 0.9)%] in the $IDegAsp_{Stepwise}$ group after 26 weeks of treatment. The mean reductions in HbA_{1c} from baseline to 26 weeks (primary endpoint) were −14.6 mmol/mol (−1.3%; $IDegAsp_{Simple}$) and −11.9 mmol/mol (−1.1%; $IDegAsp_{Stepwise}$) (full analysis set; Fig. 1a). The estimated between-group treatment difference (ETD) was −2.0 mmol/mol [95% confidence interval (CI) −4.1, 0.2] [−0.2% (95% CI −0.4, 0.02)], confirming non-inferiority of $IDegAsp_{Simple}$ vs. $IDegAsp_{Stepwise}$.

There were no significant differences in the mean reduction in fasting plasma glucose between the two groups [ETD −0.4 mmol/l; 95% CI −0.9, 0.09 (−7.6 mg/dl; 95% CI −16.7, 1.6)] (Fig. 1b). The statistical analyses of the 8-point SMPG showed no statistically significant differences between groups at any of the measured time points. Similarly, the prandial glucose increment after 26 weeks showed no statistically significant differences between groups at any of the measured time points (Figs S2 and S3). The mean daily insulin dose was similar in both groups at baseline; however, by Week 26, the mean daily insulin dose was 0.7 U/kg in the $IDegAsp_{Simple}$ group vs. 0.7 U/kg in the $IDegAsp_{Stepwise}$ group (mean dose ratio of 1.11 U/kg) (Fig. 1c). The observed proportion of participants who achieved the American Diabetes Association-recommended HbA_{1c} target of < 7% at the end of the trial was 58.1% in the $IDegAsp_{Simple}$ group and 49.3% in the $IDegAsp_{Stepwise}$ group. The proportion of participants who achieved HbA_{1c} targets of < 53 mmol/mol (< 7.0%) without confirmed hypoglycaemia in the last 12 weeks of the trial was 39.5% for $IDegAsp_{Simple}$ and 30.7% for $IDegAsp_{Stepwise}$, a difference that was statistically not significant.

Safety

At Week 26, mean increase in body weight from baseline was higher for $IDegAsp_{Simple}$ than for $IDegAsp_{Stepwise}$, but this was not statistically significant (2.6 and 1.9 kg, respectively; ETD 0.9 kg; 95% CI −0.1, 1.8).

Overall, 46.3% and 38.6% of participants reported confirmed hypoglycaemia in the $IDegAsp_{Simple}$ and $IDegAsp_{Stepwise}$ groups, respectively. The rates of overall confirmed hypoglycaemia were significantly lower for $IDegAsp_{Stepwise}$ than for $IDegAsp_{Simple}$ [2.1 and 3.3 episodes/patient years of exposure (PYE), respectively; estimated rate ratio (ERR) 1.8; 95% CI 1.1, 2.9]. Similar proportions of participants reported nocturnal confirmed hypoglycaemic episodes for $IDegAsp_{Simple}$ and $IDegAsp_{Stepwise}$ (13.4% and 12.9%, respectively; 0.5 and 0.4 episodes/PYE, respectively; ERR 1.1; 95% CI 0.5, 2.4). No severe hypoglycaemic episodes were reported.

The proportions of participants in each group with reported treatment-emergent adverse events were 53.7% for $IDegAsp_{Simple}$ and 63.6% for $IDegAsp_{Stepwise}$ (Table S3).

Discussion

This 26-week study demonstrated that IDegAsp administered once daily and titrated twice weekly using a simple algorithm effectively improved HbA_{1c} levels, and was non-inferior to IDegAsp once daily titrated once weekly using a stepwise titration algorithm. Effective glycaemic control was achieved according to current treatment guidelines [7], including achievement of target HbA_{1c} levels of 52.4 mmol/mol (6.9%) and 54.7 mmol/mol (7.2%) for $IDegAsp_{Simple}$ and $IDegAsp_{Stepwise}$, after 26 weeks of treatment, a reduction from 66.9 mmol/mol (8.3%) and 66.6 mmol/mol (8.2%) at baseline for $IDegAsp_{Simple}$ and $IDegAsp_{Stepwise}$, respectively. Fewer than half of the participants in both arms achieved HbA_{1c} < 53 mmol/mol (< 7.0%) without confirmed hypoglycaemia during the trial. The reduction in HbA_{1c} from baseline was similar to that seen in people with Type 2 diabetes mellitus naïve to insulin, where twice-daily IDegAsp was non-inferior in lowering HbA_{1c}, compared with twice-daily biphasic insulin aspart 30 (BIAsp 30), but was superior in lowering fasting plasma glucose from baseline after 26 weeks, and significantly reduced overall confirmed hypoglycaemia [8]. This was also consistent with recent reports in Japanese people with Type 2 diabetes mellitus, demonstrating the superiority of IDegAsp once daily in lowering mean HbA_{1c} vs. insulin glargine (IGlar) [9]. When administered once or twice daily in people with Type 2 diabetes mellitus previously treated with insulin, IDegAsp demonstrated non-inferiority to BIAsp 30 in lowering HbA_{1c} from baseline at 26 weeks,

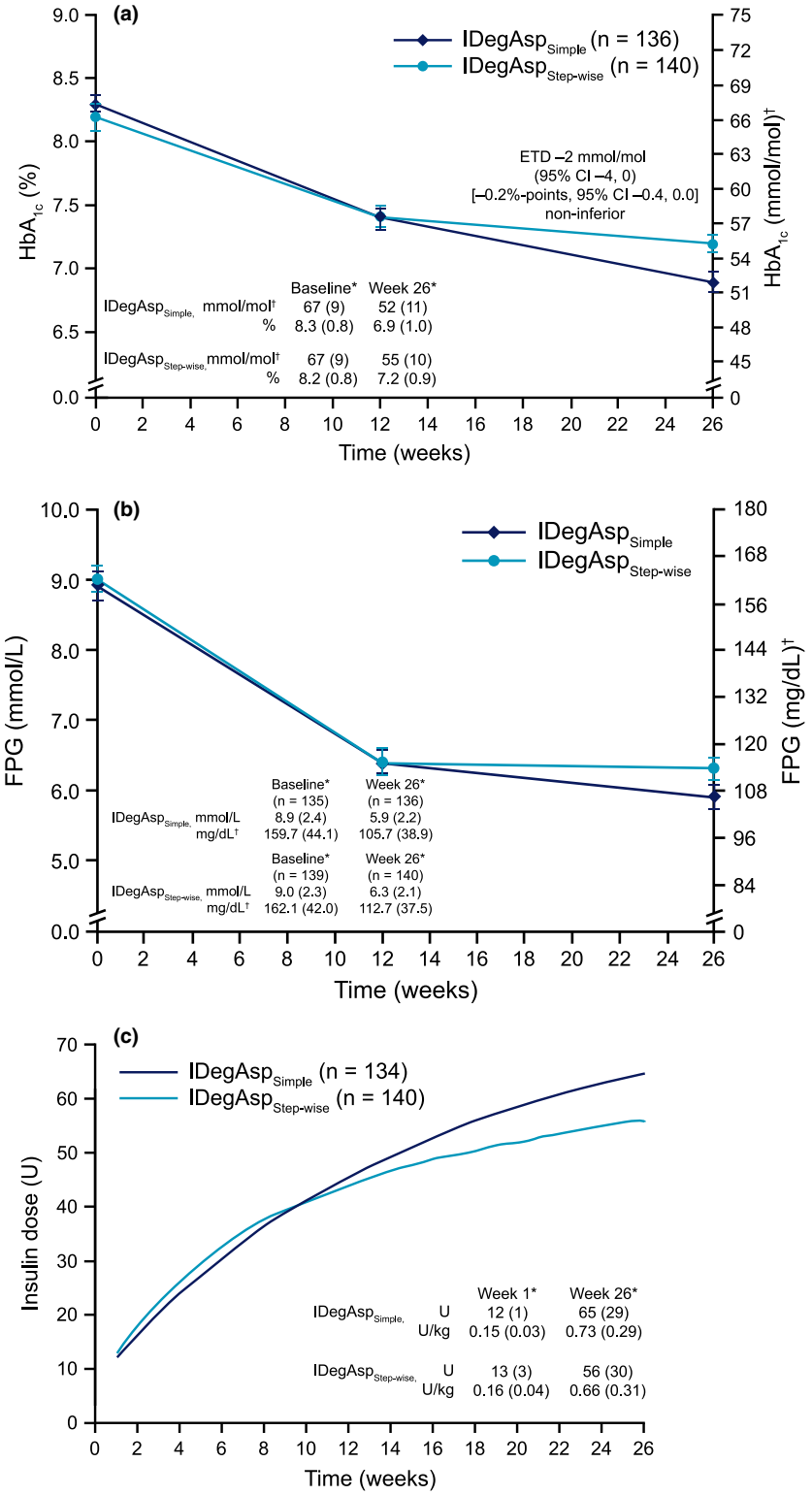

FIGURE 1 Efficacy of treatment with IDegAsp in people with Type 2 diabetes mellitus titrated using either a Simple (IDegAsp$_{Simple}$) or a Stepwise (IDegAsp$_{Stepwise}$) dose-titration algorithm measured in terms of: (a) mean HbA$_{1c}$ with IDegAsp$_{Simple}$ and IDegAsp$_{Stepwise}$ over 26 weeks (full analysis set), (b) mean fasting plasma glucose (FPG) with IDegAsp$_{Simple}$ and IDegAsp$_{Stepwise}$ over 26 weeks (full analysis set), and (c) daily insulin dose by treatment week (safety analysis set). The full analysis set included all participants randomized and the safety analysis set included all participants who received at least one dose of IDegAsp. Missing data were imputed using the last observation carried forward approach. *Data are mean (SD); treatment differences are derived from an LS means-based model. †Calculated, not measured. CI, confidence interval; ETD, estimated treatment difference; FPG, fasting plasma glucose; HbA$_{1c}$, glycated haemoglobin; IDegAsp, insulin degludec/insulin aspart; LS, least squares; SD, standard deviation; U, unit.

with the proportion of participants achieving HbA_{1c} targets of < 53 mmol/mol (< 7.0%) being 50.4% in the IDegAsp group and 48.6% in the BIAsp 30 group [10]. The odds of achieving an HbA_{1c} target of < 53 mmol/mol (< 7.0%) without hypoglycaemic episodes during the last 12 weeks of the study were higher for IDegAsp (21% of patients) than for BIAsp 30 (14% of participants) [10].

Given that participants entering the trial were insulin-naïve, the percentage of participants with overall confirmed hypoglycaemia observed in both titration groups was not unexpected ($IDegAsp_{Stepwise}$ 38.6% vs. $IDegAsp_{Simple}$ 46.3%). A similar number has been observed in a previous trial in participants with insulin-naïve Type 2 diabetes mellitus treated with IDegAsp once daily, where the proportion of participants reporting at least one confirmed hypoglycaemia episode during the treatment period was 44% (with both IDegAsp and IGlar) [9]. Notably, however, no participants experienced severe hypoglycaemia in this trial. Together, these findings highlight the effectiveness and safety of treatment with IDegAsp once daily in people with insulin-naïve Type 2 diabetes mellitus.

The rate of confirmed hypoglycaemia was numerically lower for $IDegAsp_{Simple}$ (3.3 events/PYE; 46.3% of participants) vs. $IDegAsp_{Stepwise}$ (2.1 events/PYE; 38.6% of participants). This reduction with IDegAsp once daily was previously reported in the aforementioned trial in Japanese people with Type 2 diabetes mellitus in which IDegAsp once-daily treatment was associated with numerically lower rates of overall confirmed hypoglycaemia vs. IGlar (IDegAsp: 1.9 events/PYE vs. IGlar 2.7 events/PYE) [9]. As mentioned above, in a population with uncontrolled Type 2 diabetes mellitus previously treated with once- or twice-daily insulin, IDegAsp administration (twice daily) reduced confirmed hypoglycaemia vs. BIAsp 30 [9.7 vs. 14.0 episodes/PYE for IDegAsp and BIAsp 30 groups, respectively; ERR 0.7 (95% CI 0.5–0.9), $P = 0.0049$] [10].

The more conservative nature of the Stepwise algorithm may explain the lower rates of overall confirmed hypoglycaemia and the lower mean daily insulin dose in the Stepwise arm. According to the Simple algorithm, dose adjustment was based on a single SMPG measurement rather than the lowest of three measurements required by the Stepwise algorithm, meaning that there was always a possibility that dose adjustments in the Simple arm were made based on a random high SMPG value.

The percentage of participants with adverse events in both groups was 53.7% for the $IDegAsp_{Simple}$ group vs. 63.6% for the $IDegAsp_{Stepwise}$ group. IDegAsp was well tolerated in both titration groups and no safety issues were identified during the trial.

These results provide insights into two possible titration methods that may be suitable for use with IDegAsp. For people with diabetes who are inadequately controlled on oral anti-diabetic drugs alone, and who require transition to insulin therapy, these methods potentially offer physicians the option to administer a personalized insulin titration regimen that is tailored to individual needs.

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Competing interests

S.W. Park has received research support from Novo Nordisk. R. de la Rosa has been a member of speaker bureaux for Novo Nordisk, Sanofi-Aventis, AstraZeneca, Boehringer Ingelheim, and AbbVie. He has also received clinical research support from Novo Nordisk, Sanofi-Aventis, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, and GlaxoSmith-Kline. S. Macura is an employee of Novo Nordisk A/S. W.M.W. Bebakar has been a member of advisory panels and speaker bureaux for Novo Nordisk. P.G. Hernandez has been a consultant for Amgen and Eli Lilly. He has also received clinical research support from Novo Nordisk, Amgen, Eli Lilly, Bristol-Myers Squibb, and MSD. M.L. Hersløv is an employee of Novo Nordisk A/S.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Disposition of participants.
Figure S2. Efficacy of IDegAsp using either a simple ($IDegAsp_{Simple}$) or a Stepwise ($IDegAsp_{Stepwise}$) dose-titration algorithm, as measured by an 8-point self-monitored plasma glucose profile at baseline and Week 26.
Figure S3. Efficacy of IDegAsp using either a Simple ($IDegAsp_{Simple}$) or a Stepwise ($IDegAsp_{Stepwise}$) dose-titration algorithm as measured by prandial glucose increments at Week 26.
Table S1. $IDegAsp_{Simple}$ titration algorithm.
Table S2. $IDegAsp_{Stepwise}$ titration algorithm.
Table S3. Summary of adverse events.