A Randomized Trial Evaluating the Efficacy and Safety of Fast-Acting Insulin Aspart Compared With Insulin Aspart, Both in Combination With Insulin Degludec With or Without Metformin, in Adults With Type 2 Diabetes (ONSET 9)

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OBJECTIVE

To evaluate the efficacy and safety of fast-acting insulin aspart (faster aspart) compared with insulin aspart (IAsp), both with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

RESEARCH DESIGN AND METHODS

This multicenter, double-blind, treat-to-target trial randomized participants to faster aspart ($n = 546$) or IAsp ($n = 545$). All available information, regardless of treatment discontinuation or use of ancillary treatment, was used for evaluation of effect.

RESULTS

Noninferiority for the change from baseline in HbA_{1c} 16 weeks after randomization (primary end point) was confirmed for faster aspart versus IAsp (estimated treatment difference [ETD] −0.04% [95% CI −0.11; 0.03]; −0.39 mmol/mol [−1.15; 0.37]; $P < 0.001$). Faster aspart was superior to IAsp for change from baseline in 1-h postprandial glucose (PPG) increment using a meal test (ETD −0.40 mmol/L [−0.66; −0.14]; −7.23 mg/dL [−11.92; −2.55]; $P = 0.001$ for superiority). Change from baseline in self-measured 1-h PPG increment for the mean over all meals favored faster aspart (ETD −0.25 mmol/L [−0.42; −0.09]); −4.58 mg/dL [−7.59; −1.57]; $P = 0.003$). The overall rate of treatment-emergent severe or blood glucose (BG)–confirmed hypoglycemia was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]).

CONCLUSIONS

In combination with insulin degludec, faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen.

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The progressive deterioration of β-cell function in type 2 diabetes requires the intensification of treatment over time (1). There are a number of antihyperglycemic therapies available for treating type 2 diabetes, and current guidelines recommend a stepwise approach to treatment intensification taking into account patient factors and preferences (2). For many people with long-standing type 2 diabetes, control of fasting hyperglycemia on regimens that include basal insulin is necessary but often insufficient to achieve and maintain HbA_{1c} goals (3). Options for treatment intensification targeting postprandial glucose (PPG) include the addition of a glucagon-like peptide 1 receptor agonist, a sodium–glucose cotransporter 2 inhibitor, a dipeptidyl peptidase 4 inhibitor, a rapid-acting insulin analog (RAIA), or a premix insulin (2).

Studies indicate that targeting PPG excursions is important for achieving overall glycemic control and reducing the risk of the macrovascular and microvascular complications of diabetes (4). Postprandial hyperglycemia has been shown to be associated with adverse outcomes even in the absence of fasting hyperglycemia, including elevated intraocular pressure and cognitive dysfunction (5,6). Although further evidence is needed to fully demonstrate the benefits of lowering PPG on hard end points, careful consideration should be given to the treatment options available to physicians to limit PPG excursions in people with type 2 diabetes.

RAIAs aim to mimic the physiological action of endogenous insulin secreted in response to meals to reduce PPG excursions. However, current RAIAs have a delayed onset and a longer duration of action compared with endogenous insulin in individuals without diabetes and there is an unmet need for mealtime insulins that more closely mimic physiological prandial insulin secretion.

Fast-acting insulin aspart (faster aspart) is a novel formulation of insulin aspart (IAsp) containing the excipients niacinamide and L-arginine. In people with type 2 diabetes, faster aspart is associated with an ~9 min earlier onset of action and an ~150% greater glucose-lowering effect during the first 30 min after dosing compared with IAsp (7). In the ONSET 2 trial, faster aspart was confirmed to be noninferior to IAsp in terms of change from baseline in HbA_{1c} after 26 weeks of treatment in bolus-naive adults with type 2 diabetes treated with basal insulin and oral antidiabetes agents (OADs). Moreover, faster aspart improved 1-h PPG after a meal test, with no differences in overall hypoglycemia rates compared with IAsp (8).

The aim of the ONSET 9 trial was to confirm the effect in terms of glycemic control of treatment with faster aspart compared with IAsp, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with a basal-bolus regimen. The trial also aimed to test superiority in terms of PPG regulation while evaluating the safety profile of both treatments. This was the first trial with faster aspart to recruit only participants with long-standing (≥10 years) type 2 diabetes treated with intensive (basal-bolus) insulin therapy for ≥1 year. The trial was designed to quantify a population average effect for participants with type 2 diabetes irrespective of adherence to randomized treatment and use of ancillary treatment. The primary objective was to estimate the effect based on difference in HbA_{1c} from baseline to 16 weeks under these circumstances.

RESEARCH DESIGN AND METHODS

Trial Design

In this phase 3b, multicenter, active-controlled, treat-to-target, randomized, parallel-group trial (ClinicalTrials.gov: NCT03268005), faster aspart was compared with IAsp, both in combination with insulin degludec with or without metformin, in adults with type 2 diabetes not optimally controlled with basal-bolus treatment (Supplementary Fig. 1). The trial consisted of a 12-week run-in period, a 16-week treatment period, and a 30-day follow-up period. At the start of the treatment period, participants were randomized 1:1 to double-blind treatment with either faster aspart or IAsp delivered in a basal-bolus regimen with once-daily insulin degludec with or without metformin. The trial included 165 sites across 17 countries (Supplementary Data). The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice.

Study Population

Adults (≥18 years old) were eligible for inclusion if they were diagnosed with type 2 diabetes for ≥10 years and had been treated with a basal-bolus insulin regimen for ≥1 year before screening (defined as basal insulin once or twice daily and bolus insulin analog taken with meals at least three times daily) with or without OADs. Participants were required to have an HbA_{1c} of 7.0–10.0% (53–86 mmol/mol) at screening and an HbA_{1c} ≤9.0% (75 mmol/mol) at randomization.

Key exclusion criteria were as follows: treatment with injectable glucagon-like peptide 1 receptor agonists within a period of 90 days before screening; any anticipated initiation or change in concomitant medications (for >14 consecutive days) known to affect weight or glucose metabolism; myocardial infarction, stroke, or hospitalization for unstable angina and/or transient ischemic attack within 180 days before screening; heart failure of New York Heart Association class IV; or planned coronary, carotid, or peripheral artery revascularization known on day of screening. Additional exclusion criteria included any known or suspected hypersensitivity to trial products or related products and being pregnant, planning to become pregnant, or breastfeeding (see Supplementary Appendix for full list of inclusion and exclusion criteria).

Treatment Interventions

Basal Insulin Dosing

After a 2-week screening period, a 12-week run-in allowed for basal insulin titration. Participants switched from their previous basal insulin to insulin degludec once daily (100 units/mL at any time of the day, preferably at the same time every day, using a 3-mL pen injector) with dose optimization based on protocol-specified guidelines. Basal insulin dose was titrated weekly by the investigator to a prebreakfast target of 4.0–5.0 mmol/L (71–90 mg/dL) (Supplementary Table 1). An increase in dose was based on the mean of three prebreakfast self-measured blood glucose (SMBG) values measured on the last 2 days prior to and on the day of contact, while a decrease was based on the lowest of three prebreakfast SMBG values measured on the last 2 days prior to and on the day of contact. During the treatment period, basal insulin adjustments were not performed by the investigators unless for safety reasons.

Bolus Insulin Dosing

During the run-in period, participants continued their pretrial bolus insulin

analog. The dose was not adjusted unless considered necessary for safety reasons by the investigator. During the 16-week treatment period, eligible participants with HbA_{1c} ≤9.0% (75 mmol/mol) were randomized 1:1 to receive double-blinded faster aspart or IAsp (both 100 units/mL, administered 0–2 min before each main meal using a 3-mL pen injector). Bolus insulin was titrated twice weekly in a treat-to-target approach to achieve a glycemic target of preprandial and bedtime blood glucose (BG) between 4.0 and 6.0 mmol/L (71 and 108 mg/dL). Participants titrated bolus insulin using a predefined bolus-dosing algorithm (Supplementary Table 2).

Other Diabetes Treatment

All OADs, except for metformin, were stopped at the start of the run-in period. The dose and dosing frequency of metformin were not changed during the trial unless for safety reasons. Initiation of any other diabetes treatment was not allowed during the screening, run-in, or treatment period.

SMBG Measurements

Participants were supplied with a BG meter (MyGlucoHealth [Entra Health] and FreeStyle [Abbott]) calibrated to display plasma-equivalent glucose values and instructed to record the date, time, and value of all SMBG measurements for 7-9-7 point profiles (preprandial, postprandial, bedtime, and once at 4:00 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 8, and 16; four-point profiles (preprandial and bedtime) were recorded daily for titration purposes.

Meal Test Protocol

Participants were required to undergo a meal test with a fasting SMBG (adjusted to plasma glucose) of 4.0–8.8 mmol/L (71–160 mg/dL). The meal test was rescheduled if the participant's SMBG was outside of this range. Before randomization at week 0 (baseline), a bolus dose of the participant's pretrial insulin analog was administered followed by a mixed liquid-meal test (Ensure, Fortisip, or NutriDrink; all contained 78 g carbohydrate that needed to be consumed within 12 min). The bolus dose was calculated by dividing the digestible carbohydrate content of the liquid meal by an insulin:carbohydrate ratio. The insulin:carbohydrate ratio was calculated using the "500 rule," whereby 500 was divided by the participant's total daily dose (taken from the day before) of both basal and bolus insulin. Blood samples were taken 2 min before the meal and after 30 min and 1, 2, 3, and 4 h (0 h defined as start time of meal consumption). The meal test was repeated at week 16 with the participant's randomized trial product using the same bolus dose calculated at the baseline meal test. During the meal test, glucose rescue medication could be used if the participant experienced hypoglycemia (SMBG ≤3.9 mmol/L [70 mg/dL]).

Assessments

Primary End Point

The primary end point was change from baseline in HbA_{1c} 16 weeks after randomization.

Secondary End Points

Confirmatory secondary end points were change from baseline in 1-h PPG increment (meal test) and change from baseline in 1,5-anhydroglucitol 16 weeks after randomization. 1,5-anhydroglucitol was used as a surrogate marker for measuring PPG excursions (9).

Key supportive secondary efficacy end points included change from baseline 16 weeks after randomization in the following: fasting plasma glucose (FPG), PPG and PPG increment (meal test), PPG and PPG increment (7-9-7 point SMBG profile), mean of the 7-9-7 point SMBG profile, and the percentage of participants achieving HbA_{1c} <7.0% (53 mmol/L) and PPG ≤7.8 mmol/L (140 mg/dL) targets with and without severe hypoglycemia at 16 weeks.

Key supportive secondary safety end points included number of treatment-emergent adverse events, number of treatment-emergent hypoglycemic episodes, and change from baseline in body weight 16 weeks after randomization (end points are summarized in Supplementary Table 3).

Adverse events were defined as treatment emergent if the onset of the event occurred on or after the 1st day of exposure to randomized treatment and no later than 7 days after last day of treatment. Hypoglycemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the 1st day of treatment administration after randomization and no later than 1 day after the last day of treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (10), and BG-confirmed hypoglycemia was defined as a plasma glucose value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycemia.

Statistical Methods

All statistical analyses were prespecified. Efficacy end points were summarized and analyzed using the full analysis set, and results are presented based on data from all randomized participants for the entire trial period, which include data collected after participants prematurely discontinued treatment or initiated ancillary treatment. Safety end points (and insulin dose) were summarized using the safety analysis set (participants receiving one or more doses of IAsp or faster aspart) and are presented as either treatment emergent or based on data collected up to 7 days after the last dose of randomized treatment or the day before initiation of ancillary treatment.

Statistical analysis of the primary and secondary confirmatory end points followed a stepwise hierarchical procedure in order to control type 1 error (Supplementary Table 4). Noninferiority (primary end point) was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. One-sided *P* values are presented for noninferiority analysis and for the other confirmatory analyses, with two-sided *P* values for treatment differences presented for all other analyses. Supportive analyses were not corrected for multiplicity.

Change from baseline in HbA_{1c} 16 weeks after randomization was analyzed using an ANOVA model after multiple imputation, where participants with missing data at scheduled visits had their HbA_{1c} values imputed using available information from the treatment arm to which the participant had been randomized. The model included treatment, region, and metformin use at baseline as factors and baseline HbA_{1c} as a covariate. A similar statistical model was used to analyze change from baseline to 16 weeks in PPG and PPG increments (meal test), 1,5-anhydroglucitol, FPG, PPG and PPG increment (7-9-7 point SMBG profile), mean of the 7-9-7 point SMBG profile, and body weight. For change from baseline in PPG and PPG increments (meal test), participants with missing data had their PPG values at week 16 imputed based on information from the IAsp arm.

HbA_{1c} and PPG responder end points were analyzed using a logistic regression model. The number of treatment-emergent severe or BG-confirmed hypoglycemic episodes was analyzed using a negative binomial regression model.

Further details on the statistical methods for the primary and secondary end points and the sample-size calculation are provided in Supplementary Data.

Data and Resource Availability

The data sets generated during the current study are available from the corresponding author on reasonable request.

RESULTS

Trial Participants

Participants (n = 1,091) were randomized to faster aspart (n = 546) or IAsp (n = 545), and 99.6% (n = 544) and 99.8% (n = 544) of participants, respectively, were exposed to randomized trial product. A total of 1,062 participants (97.3%) completed the trial, while 1,053 participants (96.5%) completed the 16-week treatment period without premature discontinuation of randomized treatment (Supplementary Fig. 2). Premature discontinuation of randomized treatment occurred in 23 participants in the faster aspart arm and 15 in the IAsp arms (Supplementary Fig. 2). The number of participants who withdrew from the trial was distributed similarly across treatment arms (Supplementary Fig. 2). Baseline characteristics were similar between treatment arms (Table 1). There were no marked differences in antihyperglycemic treatment at screening between treatment arms.

Efficacy

HbA_{1c}

During the run-in period, observed mean HbA_{1c} was reduced from 8.25% (66.69 mmol/mol) to 7.15% (54.64 mmol/mol) for participants subsequently randomized to faster aspart and from 8.28% (67.01 mmol/mol) to 7.05% (53.54 mmol/mol) for those randomized to IAsp (Fig. 1). At the end of the 16-week treatment period, observed mean HbA_{1c} was 7.00% (52.96 mmol/mol) and 6.96% (52.59 mmol/mol) in the faster aspart and IAsp arms, respectively. Noninferiority of faster aspart to IAsp in change from baseline in HbA_{1c} after 16 weeks was confirmed (estimated treatment difference [ETD] −0.04% [95% CI −0.11; 0.03]; −0.39 mmol/mol [−1.15; 0.37]; $P < 0.001$ for noninferiority [0.4% margin]). Superiority of faster aspart versus IAsp regarding change from baseline in HbA_{1c} could not be confirmed (hierarchical testing was stopped after step 3 [Supplementary Table 4]).

At 16 weeks, the proportion of subjects achieving HbA_{1c} <7.0% (53 mmol/mol) was 49.6% in the faster aspart group and 51.7% in the IAsp group. The odds of achieving HbA_{1c} <7.0% (53 mmol/mol) were not statistically significantly different between faster aspart and IAsp (Supplementary Table 5).

Meal Test

PPG increment profiles at baseline and week 16 are shown in Fig. 2. The observed change from baseline in 1-h PPG increment after 16 weeks was −0.43 mmol/L (−7.72 mg/dL) in the faster aspart arm and 0.08 mmol/L (1.52 mg/dL) in the IAsp arm. Superiority of faster aspart to IAsp in terms of change from baseline in 1-h PPG increment was confirmed (ETD −0.40 mmol/L [95% CI −0.66; −0.14]; −7.23 mg/dL [−11.92; −2.55]; P = 0.001 for superiority) (Fig. 2). There were no statistically significant differences between treatment arms for change from baseline in 30-min or 2-, 3-, or 4-h PPG increment (Supplementary Table 5). Change from baseline in PPG favored faster aspart at 1 h and 2 h with ETDs of −0.47 mmol/L (95% CI −0.81; −0.13) (−8.47 mg/dL [−14.68; −2.27]) (P = 0.007) and −0.39 mmol/L (−0.78; −0.002) (−7.02 mg/dL [−14.00; −0.04]) (P = 0.049), respectively. There was no statistically significant difference between treatment arms for change from baseline in 30-min or 3- or 4-h PPG (Supplementary Table 5).

SMBG

Observed mean 7-9-7 point SMBG profiles at baseline and 16 weeks after randomization were similar between treatment arms (Supplementary Fig. 4). There was no statistically significant difference in the change from baseline in mean of the 7-9-7 point SMBG profile between faster aspart and IAsp (Supplementary Table 4). The observed change from baseline in the 1-h PPG increment mean over all main meals was −0.48 mmol/L (−8.66 mg/dL) with faster aspart and −0.23 mmol/L (−4.14 mg/dL) with IAsp, with a statistically significant ETD in favor of faster aspart (ETD −0.25 mmol/L [95% CI −0.42; −0.09]; −4.58 mg/dL [−7.59; −1.57]; P = 0.003). There were also significant treatment differences in 1-h PPG increment after lunch (−0.32 mmol/L [−0.57; −0.07]; −5.73 mg/dL [−10.19; −1.27]; P = 0.012) and the main evening meal (−0.27 mmol/L [−0.51; −0.03]; −4.80 mg/dL [−9.14; −0.47]; P = 0.030). There was no statistically significant difference between treatments after breakfast. Change from baseline in 1-h PPG for each individual meal or for the mean over all meals was not statistically significantly different for faster aspart versus IAsp (Supplementary Table 5).

The proportion of subjects achieving PPG ≤7.8 mmol/L (140 mg/dL) (based on SMBG values) 16 weeks after randomization was 34.1% in the faster aspart group and 35.2% in the IAsp group. The odds of achieving PPG ≤7.8 mmol/L (140 mg/dL) were not statistically significantly different between treatments (Supplementary Table 5).

1,5-anhydroglucitol

The observed mean change from baseline in 1,5-anhydroglucitol at 16 weeks was 1.38 μg/mL in the faster aspart arm and 0.89 μg/mL in the IAsp arm (Supplementary Fig. 5). The change from baseline in 1,5-anhydroglucitol 16 weeks after randomization was statistically significantly greater with faster aspart compared with IAsp (ETD 0.50 μg/mL [95% CI 0.11; 0.89]).

FPG and Insulin Dose

There was no statistically significant difference in change from baseline in FPG between treatment arms (Supplementary Table 5).

During the run-in period, the mean daily basal insulin dose increased from 41.35 units to 64.47 units with faster aspart and from 40.83 units to 64.81 units with IAsp. During the treatment period, the mean daily bolus insulin dose increased over time with both faster aspart and IAsp. Observed mean total daily insulin doses at week 16 were similar between treatments arms (118.52 units [1.23 units/kg] for faster aspart and 115.63 units [1.19 units/kg] for IAsp) (Supplementary Table 6). The basal and bolus splits at baseline and week 16 were similar in both treatment arms (baseline 62% and 38% and week 16 54% and 46%, respectively).

Safety

Treatment-emergent hypoglycemia rates are presented in Table 2. The overall rate of severe or BG-confirmed hypoglycemic

Table 1—Baseline characteristics

Parameter	FA (n = 546)	IAsp (n = 545)	Total (n = 1,091)
Age, years	62.6 (8.6)	62.1 (8.8)	62.3 (8.7)
Sex, n (% male)	265 (48.5)	289 (53.0)	554 (50.8)
Body weight, kg	94.36 (19.96)	95.06 (21.46)	94.71 (20.72)
Body weight, lb	208.02 (44.01)	209.56 (47.32)	208.79 (45.68)
BMI, kg/m^2	33.43 (6.10)	33.25 (6.52)	33.34 (6.31)
Duration of diabetes, years	19.4 (7.0)	19.4 (7.5)	19.4 (7.3)
HbA_{1c}, %	7.15 (0.77)	7.05 (0.70)	7.10 (0.74)
HbA_{1c}, mmol/mol	54.64 (8.39)	53.54 (7.66)	54.09 (8.05)
FPG, mmol/L	6.52 (1.87)	6.38 (1.82)	6.45 (1.84)
FPG, mg/dL	117.51 (33.62)	114.89 (32.73)	116.20 (33.19)
Metformin use at baseline, n (% yes)	322 (59.0)	329 (60.4)	651 (59.7)

Data are means (SD) unless otherwise stated. Baseline is at randomization. FA, fast-acting insulin aspart.

episodes was statistically significantly lower for faster aspart versus IAsp (estimated treatment ratio 0.81 [95% CI 0.68; 0.97]; P = 0.019). Both daytime and nocturnal rates were lower for faster aspart versus IAsp (0.83 [0.70; 0.99], P = 0.038, and 0.66 [0.49; 0.88], P = 0.004, respectively). There was no statistically significant difference in the rate of severe or BG-confirmed hypoglycemic episodes observed within 1 or 2 h after the start of the meal (1.16 [0.78; 1.71] and 0.97 [0.71; 1.32], respectively). However, a significant difference favoring faster aspart was observed within 4 h after the start of the meal (0.78 [0.63; 0.98]; P = 0.030).

After the 16-week treatment period, the observed change from baseline in body weight was 1.19 kg and 1.12 kg with faster aspart and IAsp, respectively. There was no statistically significant difference in change from baseline between treatment arms.

No clinically relevant differences were observed in the treatment-emergent adverse event profiles (including injection site and allergic reactions) for faster aspart and IAsp during the 16-week treatment period (Supplementary Table 7). Wrong product administered (mainly a mix-up between basal and bolus insulin or vice versa) was reported more often with faster aspart (4.8% of participants) than with IAsp (2.2% of participants) (Supplementary Table 8). No clinically significant differences were seen with regard to vital signs, BMI, physical examination, safety laboratory assessments (biochemistry and hematology), electrocardiogram, and eye examination.

CONCLUSIONS

In this trial, intensified insulin titration with faster aspart or IAsp, both in combination with insulin degludec with or without metformin, improved glycemic control in patients with long-standing type 2 diabetes not optimally controlled on a basal-bolus regimen, and faster aspart was confirmed to be noninferior to IAsp in terms of the change from baseline in HbA_{1c} following 16 weeks of randomized treatment. Switching patients to, and optimization of, insulin degludec during the 12-week run-in period resulted in a considerable and sustained improvement in HbA_{1c} (~1.0%) in both treatment arms. Compared with the IAsp treatment arm, PPG regulation 1 h after a meal was significantly improved in the faster aspart treatment arm, demonstrated by the difference in change from baseline in 1-h PPG increment 16 weeks after randomization using either a meal test or SMBG measurement profiles and supported by a significantly greater increase in 1,5-anhydroglucitol with faster aspart. Together, these findings are encouraging given that patients with advanced type 2 diabetes (~19 years in the reported study population) treated with a basal-bolus regimen represent a difficult patient population to manage, with PPG control being particularly challenging.

The glycemic findings of ONSET 9 generally align with previous studies comparing the efficacy and safety of faster aspart in patients with type 2 diabetes. In ONSET 2, after a 12-week run-in period to optimize basal insulin glargine, faster aspart was found to be noninferior to IAsp in terms of change from baseline in HbA_{1c} after a 26-week treatment period; however, the reduction in HbA_{1c} (1.4%) by end of trial was numerically greater compared with that reported here (8). This difference is likely to reflect the difference in study population, as well as the basal insulin analog (glargine versus degludec) and run-in period duration; in ONSET 2, patients were bolus insulin naive prior to commencing the study and thus would have been more likely to experience a greater change in glycemic control with the addition of bolus insulin, while in our bolus-experienced population most of the change in HbA_{1c} occurred during the run-in period when switching basal insulin to insulin degludec.

Compared with IAsp, faster aspart has been shown to improve PPG control 1 h after a meal test in bolus-naive patients treated with basal insulin and OADs (8). In the current trial, changing the insulin in bolus-experienced patients to faster aspart significantly reduced 1-h PPG increments compared with IAsp, indicating

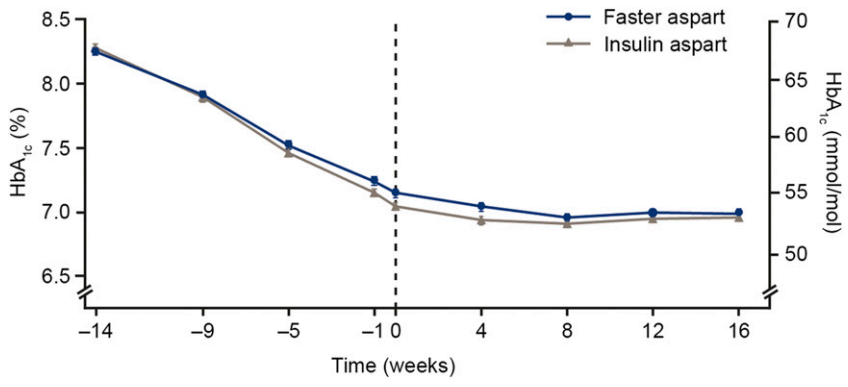

Figure 1—Mean HbA_{1c} over time. Error bars: ±SE (mean). All available information regardless of treatment discontinuation or use of ancillary treatment was used. ETD after 16 weeks for the change in HbA_{1c} from baseline was −0.04% (95% CI −0.11; 0.03); −0.39 mmol/mol (−1.15; 0.37). Noninferiority confirmed at 0.4% level (P value from the one-sided test for noninferiority evaluated at the 2.5% level: $P < 0.001$).

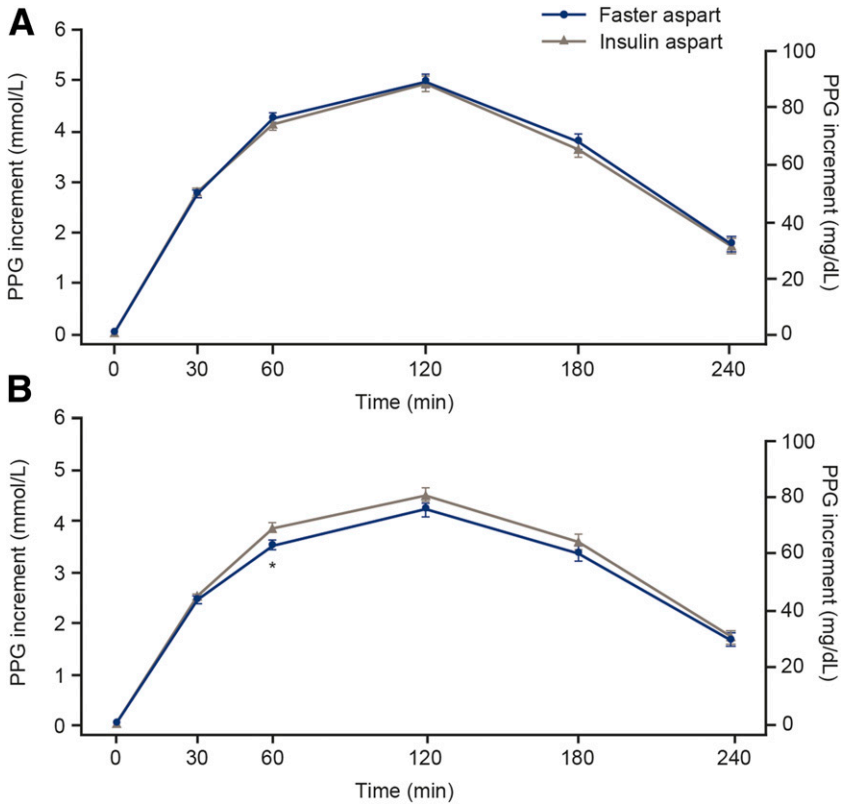

Figure 2—PPG increment after a meal test at baseline (*A*) and week 16 (*B*). Error bars: ±SE (mean). All available information regardless of treatment discontinuation or use of ancillary treatment was used. *ETD was −0.40 mmol/L (95% CI −0.66; −0.14); −7.23 mg/dL (−11.92; −2.55), and superiority was confirmed ($P = 0.001$).

that improvement in mealtime glucose control can be achieved in this clinically challenging population.

Hypoglycemia often impedes the achievement of optimal glycemic control in patients with type 2 diabetes treated with insulin. However, noninferior HbA_{1c} reduction and an improvement in PPG control were achieved alongside a significantly lower rate of overall, daytime, and nocturnal hypoglycemia with faster aspart versus IAsp. This aligns with a recent post hoc analysis of two large trials in adults with type 1 diabetes, which reported a lower rate of nocturnal hypoglycemia with faster aspart versus insulin aspart treatment (11).

Table 2—Treatment-emergent hypoglycemic episodes

	FA				IAsp			
Hypoglycemia	*n*	%	E	R	*n*	%	E	R
Severe	16	2.9	18	0.11	10	1.8	14	0.08
Severe or BG confirmed								
Overall	367	67.5	2,227	13.40	391	71.9	2,749	16.52
Daytime	354	65.1	2,032	12.23	382	70.2	2,454	14.75
Nocturnal	116	21.3	195	1.17	136	25.0	295	1.77
Total	495	91.0	9,033	54.37	500	91.9	10,006	60.14
Meal-related severe or BG confirmed								
Within 1 h after a meal	57	10.5	74	0.45	55	10.1	65	0.39
Within 2 h after a meal	116	21.3	235	1.41	122	22.4	247	1.48
Within 4 h after a meal	232	42.6	768	4.62	269	49.4	974	5.85

Hypoglycemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the 1st day of exposure to randomized treatment and no later than 1 day after the last day of exposure to randomized treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (10), and BG-confirmed hypoglycemia was defined as an episode with a plasma glucose value <3.1 mmol/L (<56 mg/dL) with or without symptoms consistent with hypoglycemia. Nocturnal was defined as occurring in the period between 00:01 and 05:59 h (both included). Episodes with missing time stamps were considered daytime episodes. Total episodes included episodes where subjects were able to self-treat and that were not BG confirmed as well as episodes where subjects were able to self-treat but could not be classified due to missing data. %, percentage of participants; E, number of events; FA, fast-acting insulin aspart; *n*, number of participants; R, event rate per patient-year of exposure.

These findings demonstrate that these next-generation insulins, faster aspart and insulin degludec, can provide important clinical value in tailoring of complex basal-bolus regimens to limit the incidence of hypoglycemia for patients with advanced type 2 diabetes.

Collectively, strengths of this trial include the positive efficacy and safety findings in a difficult-to-treat population of people with a mean diabetes duration of >19 years, along with a relatively high trial completion rate (>95%). The study also employed a double-blind design and used a meal test, which, although not fully representative of a real-life setting, standardized macronutrient composition between participants, to measure PPG control at baseline and 16 weeks. A limitation of the trial was the need for participants to perform frequent capillary BG monitoring for dose titration, which, in the real-world setting, many patients may be unwilling to do.

In conclusion, with use of a treat-to-target approach, intensive insulin titration with faster aspart provided effective overall glycemic control, superior PPG control, and a lower rate of severe or BG-confirmed hypoglycemia versus IAsp, both in combination with insulin degludec with or without metformin, in adults with advanced type 2 diabetes not optimally controlled with a basal-bolus regimen.

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Author Contributions. W.S.L. and E.Fr. were the principal investigators of this clinical trial. E.Fa. and N.R. were the medical specialists for the trial and had the medical responsibility on a clinical trial level. M.I.S.K. was the responsible statistician. All authors had access to the study data, take responsibility for the accuracy of the analysis, contributed to data interpretation, reviewed and contributed to the content of the manuscript, and had authority in the decision to submit the manuscript. W.S.L. and E.Fr. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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