Research Article | Emerging Technologies and Therapeutics

Fast-Acting Insulin Aspart Improves Glycemic Control in Basal-Bolus Treatment for Type 1 Diabetes: Results of a 26-Week Multicenter, Active-Controlled, Treat-to-Target, Randomized, Parallel-Group Trial (onset 1)

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Abstract

OBJECTIVE This multicenter, treat-to-target, phase 3 trial evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) versus conventional insulin aspart (IAsp) in adults with type 1 diabetes.

RESEARCH DESIGN AND METHODS The primary end point was change from baseline in HbA_{1c} after 26 weeks. After an 8-week run-in, subjects were randomized (1:1:1) to double-blind mealtime faster aspart (n = 381), IAsp (n = 380), or open-label postmeal faster aspart (n = 382)—each with insulin detemir.

RESULTS HbA_{1c} was reduced in both treatment groups, and noninferiority to IAsp was confirmed for both mealtime and postmeal faster aspart (estimated treatment difference [ETD] faster aspart–IAsp, mealtime, –0.15% [95% CI –0.23; –0.07], and postmeal, 0.04% [–0.04; 0.12]); mealtime faster aspart statistically significantly reduced HbA_{1c} versus IAsp (P = 0.0003). Postprandial plasma glucose (PPG) increments were statistically significantly lower with mealtime faster aspart at 1 h (ETD –1.18 mmol/L [95% CI –1.65; –0.71], –21.21 mg/dL [–29.65; –12.77]; P < 0.0001) and 2 h (–0.67 mmol/L [–1.29; –0.04], –12.01 mg/dL [–23.33; –0.70]; P = 0.0375) after the meal test; superiority to IAsp for the 2-h PPG increment was confirmed. The overall rate of severe or blood glucose–confirmed (plasma glucose <3.1 mmol/L [56 mg/dL]) hypoglycemic episodes and safety profiles were similar between treatments.

CONCLUSIONS Faster aspart effectively improved HbA_{1c}, and noninferiority to IAsp was confirmed, with superior PPG control for mealtime faster aspart versus IAsp. Subjects randomized to postmeal faster aspart for all meals maintained HbA_{1c} noninferior to that obtained with mealtime IAsp.

Introduction

Postprandial glycemic control is an essential component for meeting HbA_{1c} target levels of 6.5–7% (48–53 mmol/mol) (1–3). Such targets are recommended by several guidelines to reduce the incidence and slow the progression of diabetes-related complications (4–6). Yet, limiting postprandial plasma glucose (PPG) excursions is one of the most challenging aspects in achieving adequate glycemic control (7).

Basal-bolus insulin therapy in type 1 diabetes aims to replace physiologic insulin secretion. Rapid-acting insulin analogs, insulins aspart, glulisine, and lispro, were developed to control PPG excursions more effectively than regular human insulin (RHI), primarily by offering a faster onset and shorter duration of action (8–10).

Innovative modifications of insulin formulations and delivery methods that offer ultrafast insulin time-action profiles (11–18) aim to further improve PPG control by accelerating insulin absorption and appearance in the bloodstream. Fast-acting insulin aspart (faster aspart; an ultrafast mealtime insulin) is conventional insulin aspart (IAsp; NovoRapid/NovoLog) in a new formulation; nonclinical data demonstrate that addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood (19). In adults with type 1 diabetes, subcutaneous injection of faster aspart was associated with twice-as-fast onset of appearance in the bloodstream (4 vs. 9 min), twofold higher insulin concentration, and 74% greater insulin action in the first 30 min compared with IAsp (20). Furthermore, in the recently completed phase 3 clinical trials, faster aspart improved 1-h PPG control versus IAsp when administered as part of a basal-bolus regimen (21) and demonstrated superior glycemic control versus basal-only therapy (22) in subjects with type 2 diabetes.

A large proportion (81.4%) of people with diabetes would like their insulin regimen to fit with their daily life changes (23), and the option to take their insulin dose after a meal when necessary may address this need.

The objective of this double-blind trial was to confirm the efficacy of faster aspart in terms of glycemic control compared with mealtime IAsp after 26 weeks of randomized treatment. An open-label postmeal faster aspart dosing arm was also compared with IAsp to evaluate whether postmeal administration could prove effective in achieving glycemic control and thereby offer a clinically acceptable treatment option.

Research Design and Methods

Trial Design

This 26-week (plus additional 26 weeks) multicenter, active-controlled, randomized, parallel-group trial compared double-blind mealtime faster aspart with mealtime IAsp in adults with type 1 diabetes. A 26-week open-label treatment group with postmeal faster aspart provided a second comparison with IAsp (Supplementary Fig. 1). The additional 26-week treatment period was included to document long-term safety (not reported here). Faster aspart and IAsp were delivered in a basal-bolus regimen with once- or twice-daily insulin detemir (Levemir).

The trial was conducted in accordance with the Declaration of Helsinki (24) and International Conference on Harmonization of Good Clinical Practice (25) and is registered with ClinicalTrials.gov (reg. no. NCT01831765).

Subjects

Adults (≥18 years old) with type 1 diabetes (diagnosed clinically) were eligible for inclusion if treated with basal-bolus insulin for ≥12 months prior to screening and if treated with any regimen of insulin detemir or glargine for ≥4 months prior to screening, with an HbA_{1c} of 7.0–9.5% (53–80 mmol/mol) and BMI of ≤35.0 kg/m^2. Exclusion criteria included any use of an antidiabetes drug other than insulin within 3 months prior to screening, an anticipated change in concomitant medications known to interfere significantly with glucose metabolism, cardiovascular (CV) disease within 6 months prior to screening, recurrent severe hypoglycemia (>1 event during the past 12 months), hypoglycemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis within 6 months prior to screening. Full criteria are listed in Supplementary Data.

Interventions

Basal Titration During the Trial

After an initial 2-week screening period, an 8-week run-in allowed for the optimization of basal insulin detemir (100 units/mL; 3.0-mL FlexPen). At the start of the run-in period, subjects switched unit for unit from their previous basal insulin (if required). The same once- or twice-daily dosing frequency that was used prior to screening was maintained initially, but subjects were permitted to switch dosing frequency during the run-in period if required.

During run-in, insulin detemir was titrated using a weekly treat-to-target approach, with a prebreakfast self-monitored plasma glucose (SMPG) target of 4.0–5.0 mmol/L (71−90 mg/dL) (Supplementary Tables 1 and 2). Subjects on a twice-daily regimen used a predinner SMPG target of 4.0–6.0 mmol/L (71−108 mg/dL) (Supplementary Table 2). After run-in, basal adjustments were only performed when required as judged by the investigator; changing the dose frequency after randomization was a withdrawal reason, according to the protocol.

Bolus Doses During the Trial

At the start of the 8-week run-in, all subjects commenced mealtime IAsp (all bolus insulins supplied at 100 units/mL; 3.0-mL PDS290 Pen injector). After run-in, subjects (with HbA_{1c} ≤9.5% [80 mmol/mol]) were randomized 1:1:1 to receive double-blind mealtime faster aspart, IAsp, or open-label postmeal faster aspart while continuing with insulin detemir. Mealtime bolus insulins were injected 0–2 min before a meal; postmeal faster aspart was injected at a fixed time of 20 min after the start of the meal. Randomization was stratified by the method used by the subject for adjusting bolus insulin (carbohydrate counting [flexible dosing] or dosing algorithm), current basal treatment regimen (once or twice daily), and continuous glucose monitoring and frequently sampled meal test subgroup participation.

At the beginning of the run-in period, subjects commenced mealtime IAsp (requiring subjects on other bolus insulins to switch unit for unit) and adjusted insulin doses as they had done before the trial. No titration of bolus insulin dose was performed by the investigator during run-in unless adjustments were necessary for safety reasons. At the randomization visit, subjects commenced the bolus regimen to which they had been randomized. It was the investigator's responsibility to ensure adequate education of each subject following the principles of flexible bolus dosing based on carbohydrate content (recommending additional local training, if required); subjects deemed proficient in carbohydrate counting were to continue using this method for bolus adjustments during the treatment period. All other subjects used a predefined bolus-dosing algorithm (Supplementary Table 3).

Meal carbohydrate content and preprandial plasma glucose (PG) values were used to determine bolus insulin doses for subjects following the principles of flexible dosing. Adjustments were made several times daily by the subject in accordance with the insulin-to-carbohydrate ratio and the PG correction (sensitivity) factor. A weekly review of the ratio and correction factor was performed by the investigator, based on individual subject SMPG values. The target preprandial PG range was 4.0–6.0 mmol/L (71−108 mg/dL); in case of hypoglycemic episodes, the dose could be reduced at the investigator's discretion.

Bolus titration (for subjects using the algorithm) was to the next preprandial target of 4.0–6.0 mmol/L (71–108 mg/dL) for both breakfast and lunch doses and to the same target at bedtime for the dinner dose. Adjustments were made twice weekly: once by the investigator and once by the subject (Supplementary Table 3).

SMPG

At the run-in visit, subjects were supplied with a blood glucose (BG) meter, factory calibrated to display PG values, and instructed to record the date, time, and value of all SMPG measurements from 7-9-7-point profiles (pre- and postmeal, bedtime, and once at 4:00 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 12, and 26; 4-point profiles (preprandial and at bedtime) were recorded daily for titration purposes.

Standardized Meal Test

Subjects completing the run-in period had their 1- to 4-h PPG levels assessed after a bolus dose of IAsp (0.1 units/kg, calculated by the investigator) administered 0–2 min before a standardized mixed liquid meal test (80 g carbohydrate [Ensure] consumed within 12 min). Subjects attended the meal visit with a fasting PG (FPG) level within 4.0–8.8 mmol/L (71–160 mg/dL) for the test to be performed. Blood samples were drawn just before the meal and after 1, 2, 3, and 4 h. The meal test was repeated at week 26, with subjects administering the bolus dose (0.1 units/kg body weight, chosen as an approximation of a clinically relevant bolus dose needed for the given size of a standardized meal for subjects with type 1 diabetes) either 0–2 min before (mealtime faster aspart and IAsp) or 20 min after (postmeal faster aspart) the meal test.

Assessments

Primary End Point

The primary end point was change from baseline in HbA_{1c} after 26 weeks of treatment.

Secondary End Points

Confirmatory secondary end points included the following: change from baseline after 26 weeks of treatment in 2-h PPG increments (meal test) and body weight, and number of treatment-emergent severe or BG-confirmed hypoglycemic episodes. Hypoglycemic episodes were categorized as treatment emergent if the onset occurred on the first day of exposure to and no later than 1 day after the last day of randomized treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification (26) and BG-confirmed hypoglycemia by a PG value <3.1 mmol/L (56 mg/dL; Novo Nordisk A/S definition) with/without symptoms consistent with hypoglycemia (Supplementary Table 4).

Supportive secondary end points included the following: HbA_{1c} responders (subjects achieving HbA_{1c} <7% [53 mmol/mol] or ≤6.5% [47.8 mmol/mol]); change from baseline in PPG and PPG increments (meal test); change from baseline in mean SMPG 7-9-7-point profile and mean 2-h PPG and mean 2-h PPG increments (7-9-7-point profile); PPG responders (subjects achieving overall mean 2-h PPG ≤7.8 mmol/L [140 mg/dL] in SMPG); change from baseline in 1,5-anhydroglucitol (1,5-AG) (a marker for postprandial hyperglycemia), FPG, and body weight; and total (basal + bolus) insulin doses. Analyses of laboratory efficacy parameters (HbA_{1c}, PG during the meal test, FPG, and 1,5-AG) were carried out by central laboratory (Supplementary Table 4).

Supportive secondary safety end points included the following: the numbers of treatment-emergent adverse events (TEAEs), hypoglycemic episodes, and injection-site and allergic reactions (Supplementary Table 4). All presented adverse events (except CV events) are TEAEs (i.e., with onset up to 7 days after the last day of treatment, excluding any events during run-in). Information on CV events and deaths occurring after randomization was sent for evaluation by an external event adjudication committee. Additional safety assessments, including physical examination, vital signs, fundoscopy, and electrocardiograms, were recorded at screening, baseline, and week 26. Laboratory parameters were recorded at various time points throughout the 26-week trial. Subject follow-up occurred at 7 and 30 days after the end of treatment.

Statistical Methods

All statistical analyses were based on the full analysis set (all randomized subjects) and prespecified. Safety end points were summarized using the safety analysis set (subjects receiving ≥1 dose of investigational products). Statistical analysis of the primary and secondary confirmatory hypotheses followed a stepwise hierarchical procedure (Supplementary Fig. 2). Noninferiority (primary end point) was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. For analyses of noninferiority, one-sided *P* values are presented, and for all other analyses, two-sided *P* values for treatment differences are presented.

Change from baseline in HbA_{1c} after 26 weeks of treatment was analyzed using a mixed-effect model for repeated measurements where all changes in HbA_{1c} from baseline at trial visits were included in the analysis. Change from baseline in PPG and PPG increments (meal test) was analyzed separately using an ANOVA model. Responder end points (for HbA_{1c} and PPG) were analyzed separately based on a logistic regression model.

Change from baseline in mean 7-9-7-point profiles; mean PPG; mean PPG increments (7-9-7-point profiles); 1,5-AG; FPG; and body weight were analyzed using a mixed-effect model for repeated measurements similar to the model used for the primary end point.

The number of treatment-emergent severe or BG-confirmed hypoglycemic episodes was analyzed using a negative binomial regression model.

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

Results

Trial Subjects

In total, 1,143 subjects were randomized to mealtime faster aspart (n = 381), IAsp (n = 380), or postmeal faster aspart (n = 382). All 1,143 randomized subjects were exposed to randomized trial product (Supplementary Fig. 3), and 92.9% of subjects completed the trial. Baseline characteristics were similar between the three groups (Table 1).

Table 1

View inline

Baseline characteristics

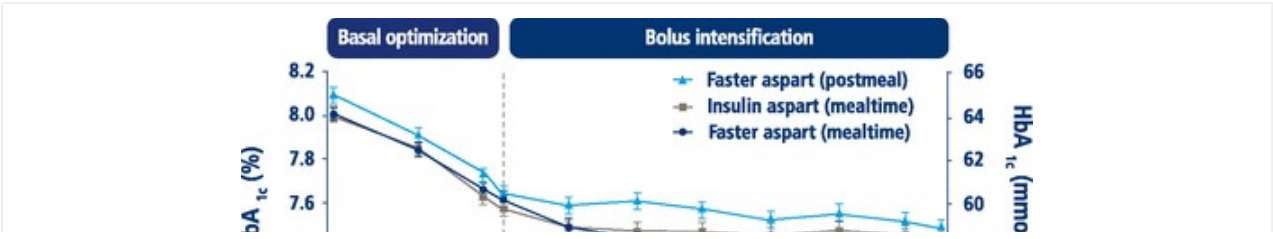
Hierarchical Testing Procedure

Steps 1–3 (which are described in more detail below) were confirmed. As step 4 could not be confirmed, the hierarchical statistical testing procedure was stopped (Supplementary Table 5).

Efficacy

Change in HbA_{1c}

Noninferiority of faster aspart, both mealtime and postmeal dosing, to mealtime IAsp in terms of change from baseline in HbA_{1c} was confirmed (estimated treatment difference [ETD] mealtime –0.15% [95% CI –0.23; –0.07], –1.62 mmol/mol [–2.50; –0.73]); postmeal 0.04% [–0.04; 0.12], 0.47 mmol/mol [–0.41; 1.36]; P < 0.0001 for noninferiority) (Fig. 1, steps 1 and 3). The reduction in HbA_{1c} was statistically significantly greater for mealtime faster aspart than for IAsp (P = 0.0003); however, superiority could not be considered confirmed, as this was not part of the hierarchical testing procedure (Supplementary Fig. 2).



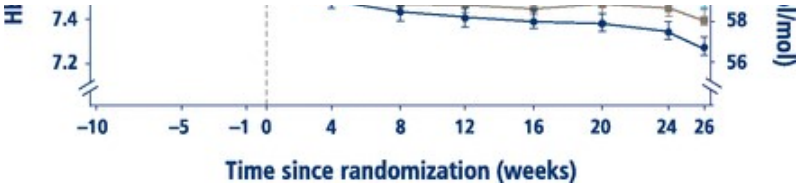


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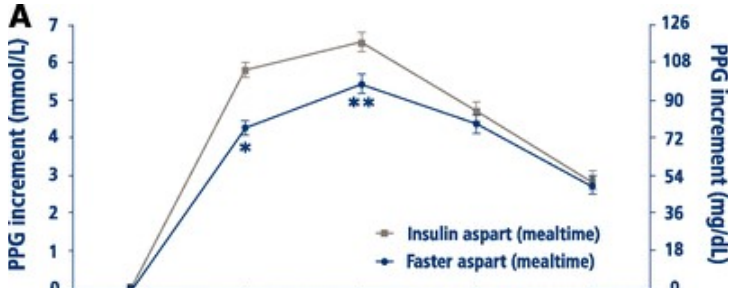
Figure 1

Mean HbA_{1c} over time. During run-in, observed mean HbA_{1c} was reduced from 8.1% (64.9 mmol/mol) to 7.6% (59.9 mmol/mol) for subjects subsequently randomized to receive postmeal faster aspart (n = 382), from 8.0% (64.0 mmol/mol) to 7.6% (59.7 mmol/mol) for subjects subsequently randomized to receive mealtime IAsp (n = 380), and from 8.0% (64.0 mmol/mol) to 7.6% (59.3 mmol/mol) for subjects subsequently randomized to receive mealtime faster aspart (n = 381). During the 26-week treatment period, the observed mean HbA_{1c} decreased to 7.5% (58.6 mmol/mol) with postmeal faster aspart, 7.4% (57.6 mmol/mol) with mealtime IAsp, and 7.3% (56.4 mmol/mol) with mealtime faster aspart. Error bars: ±SEM.

Results for subjects who achieved the HbA_{1c} targets of <7.0% (53.0 mmol/mol) and ≤6.5% (47.8 mmol/mol) after 26 weeks' treatment are summarized in Supplementary Table 6. The odds of achieving HbA_{1c} <7.0% (53.0 mmol/mol) were statistically significantly higher with mealtime faster aspart compared with IAsp (estimated odds ratio 1.47 [95% CI 1.02; 2.13]; P = 0.0405) and not statistically significantly different between postmeal faster aspart and IAsp (0.73 [0.49; 1.07]) (Supplementary Table 6).

Meal Test

The estimated change from baseline in the 2-h PPG increment (meal test) was –0.3 mmol/L (–5.2 mg/dL) with mealtime faster aspart and 0.4 mmol/L (6.8 mg/dL) with IAsp (ETD mealtime faster aspart–IAsp –0.67 mmol/L [95% CI –1.29; –0.04], –12.01 mg/dL [–23.33; –0.70]; P = 0.0375), and superiority of mealtime faster aspart versus IAsp was confirmed for this end point (**Fig. 2*A***, step 2, and Supplementary Fig. 2). The estimated change from baseline in 1-h PPG increment was –0.8 mmol/L (–15.1 mg/dL) for mealtime faster aspart and 0.3 mmol/L (6.1 mg/dL) for IAsp (ETD mealtime faster aspart–IAsp –1.18 mmol/L [95% CI –1.65; –0.71], –21.21 mg/dL [–29.65; –12.77]; P < 0.0001) (**Fig. 2*A***). There was no statistical difference in ETD for change from baseline in 3-h or 4-h PPG increments (**Fig. 2*A***).



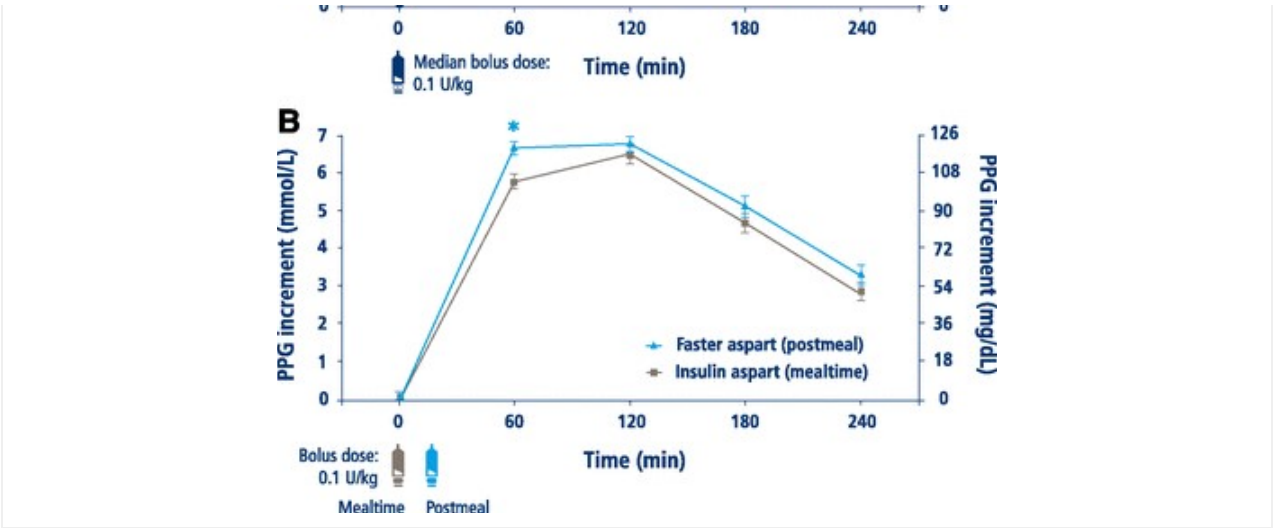


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Figure 2

A: PPG increment at week 26 for mealtime faster aspart versus IAsp. Observed data. One-hour and 2-h PPG increments statistically significantly in favor of mealtime faster aspart: **P* < 0.0001 and ***P* = 0.0375, respectively. *B*: PPG increment at week 26 for postmeal faster aspart versus IAsp. Observed data. Mealtime IAsp dosed 0 to 2 min before meal; postmeal faster aspart dosed 20 min after meal. Change in 1-h PPG increment significantly in favor of IAsp: **P* = 0.0001. Error bars: ±SEM. The conversion factor between mmol/L and mg/dL is 18.

The estimated change from baseline in 1-h PPG increment (meal test) was 1.3 mmol/L (22.9 mg/dL) with postmeal faster aspart (ETD postmeal faster aspart–IAsp 0.93 mmol/L [95% CI 0.46; 1.40], 16.75 mg/dL [8.26; 25.24]; *P* = 0.0001) (Fig. 2*B*), but by 2 h, PPG increments for postmeal faster aspart versus mealtime IAsp were not statistically significantly different (ETD 0.30 mmol/L [95% CI –0.34; 0.93], 5.32 mg/dL [–6.05; 16.68]) (Fig. 2*B*).

The difference in mean 1- and 2-h PPG change from baseline between mealtime faster aspart and IAsp (after the meal test) was statistically significant in favor of mealtime faster aspart (ETD mealtime faster aspart–IAsp, 1 h, –1.41 mmol/L [95% CI –2.00; –0.82], –25.44 mg/dL [–36.12; –14.76], *P* < 0.0001; 2 h, –0.93 mmol/L [–1.62; –0.23], –16.73 mg/dL [–29.26; –4.20], *P* = 0.0089). The difference in mean PPG change from baseline after 1 h between postmeal faster aspart and IAsp was statistically significant in favor of IAsp (ETD postmeal faster aspart–IAsp 0.69 mmol/L [95% CI 0.09; 1.28], 12.38 mg/dL [1.65; 23.11], *P* = 0.0238), while after 2 h there was no statistically significant difference between treatments (Supplementary Table 6).

SMPG

After 26 weeks, the mean of the 7-9-7-point profile was reduced in the two faster aspart treatment groups, with no statistically significant treatment differences versus IAsp (Supplementary Table 6). Reductions in 2-h PPG

and 2-h PPG increments from baseline (7-9-7-point profiles) were observed at all main meals; however, there were no statistically significant treatment differences between faster aspart (mealtime or postmeal) and IAsp (Supplementary Table 6).

The proportions of subjects achieving the 2-h PPG target ≤7.8 mmol/L (140 mg/dL; 7-9-7-point profiles) by week 26 were 42.7% with mealtime faster aspart, 39.6% with postmeal faster aspart, and 38.6% with IAsp. The odds of achieving the target PPG level was not statistically significantly different between faster aspart (mealtime or postmeal) and IAsp (Supplementary Table 6).

Other Secondary Efficacy End Points

Treatment with mealtime faster aspart for 26 weeks resulted in a statistically significantly greater increase from baseline in 1,5-AG compared with IAsp (ETD 0.50 μg/mL [95% CI 0.24; 0.76]; $P = 0.0001$), whereas increases in 1,5-AG from baseline were not statistically significantly different between postmeal faster aspart and IAsp (Supplementary Table 6).

In both faster aspart treatment groups, mean FPG showed an increase from baseline until week 12 and thereafter a decrease until week 26, with no statistically significant differences versus IAsp (Supplementary Table 6). The mean body weight increase from baseline in all three treatment groups was <1 kg over the 26-week treatment period; there was no statistically significant difference between faster aspart (mealtime or postmeal) and IAsp in terms of body weight increase (ETD faster aspart–mealtime IAsp, mealtime, 0.12 kg [95% CI –0.30; 0.55]; postmeal, 0.16 kg [–0.27; 0.58]).

Insulin Dosing

During the trial, mean and median daily bolus insulin doses increased in all three treatment groups. By week 26, the doses were comparable between faster aspart (mealtime or postmeal) and IAsp (median total insulin dose [units/kg]: mealtime faster aspart, 0.801; postmeal faster aspart, 0.842; mealtime IAsp, 0.833), and the basal/bolus ratio was ~50/50 throughout the trial (Supplementary Table 7).

Safety

The overall rate of treatment-emergent severe or BG-confirmed hypoglycemic episodes, as well as the event rate of treatment-emergent severe hypoglycemic episodes, was comparable between faster aspart (mealtime or postmeal) and IAsp (**Table 2**). There were no statistically significant differences in the number of treatment-emergent severe or BG-confirmed hypoglycemic episodes between faster aspart (mealtime or postmeal) and IAsp, and superiority could not be confirmed (rate ratio faster aspart/IAsp, mealtime, 1.01 [95% CI 0.88; 1.15]; postmeal, 0.92 [0.81; 1.06]) (step 4).

Table 2

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Treatment-emergent hypoglycemic events

	Faster aspart mealtime			Faster aspart postmeal			IAsp mealtime			
	N (%)	E	R	*N* (%)	E	R	*N* (%)	E	R	Rate ratio (95% CI)
Treatment-emergent hypoglycemia										
Severe	26 (6.7)	46	0.25	30 (8.0)	47	0.26	32 (8.4)	51	0.27	
Severe or BG confirmed	358 (92.7)	10,993	58.99	358 (95.0)	9,961	54.43	370 (97.4)	11,078	58.65	
Meal-related severe or BG confirmed										
Within 1 h after a meal	131 (33.9)	275	1.476	85 (22.5)	131	0.716	108 (28.4)	182	0.964	
Within 2 h after a meal	258 (66.8)	1,391	7.464	231 (61.3)	969	5.295	251 (66.1)	1,108	5.866	
Severe or BG confirmed										
Faster aspart (mealtime)/IAsp*										1.01 (0.88; 1.15)
Faster aspart (postmeal)/IAsp										0.92 (0.81; 1.06)

Safety analysis set. Severe hypoglycemia was defined according to the American Diabetes Association classification (26). BG-confirmed hypoglycemia was defined as an episode with a PG value <3.1 mmol/L (56 mg/dL) with or without symptoms consistent with hypoglycemia (Novo Nordisk A/S definition). E, number of events; *N* (%), number (percentage) of subjects; R, event rate per patient-year of exposure.

*Confirmatory analysis (step 4) not statistically significant.

The distribution of hypoglycemic episodes at 1 and 2 h after meals (Table 2) revealed that the rate of severe or BG-confirmed hypoglycemic episodes during the first hour after the start of a main meal was statistically significantly higher for mealtime faster aspart than for IAsp (rate ratio faster aspart/IAsp 1.48 [95% CI 1.11; 1.96]; $P < 0.0073$); however, the observed number of hypoglycemic episodes reported with mealtime faster aspart during the first hour after a meal (events per patient-year of exposure: 1.476) constituted a small fraction (~1 of 40) of all severe or BG-confirmed hypoglycemic episodes reported for mealtime faster aspart (Table 2).

The proportion of subjects reporting TEAEs and the rate of TEAEs were comparable between faster aspart (mealtime or postmeal) and IAsp. All injection-site reactions (22 events reported in 19 subjects) were nonserious and of mild or moderate severity. A total of 123 allergic reactions were reported by 107 (9.4%) subjects and evenly distributed across all three treatment groups; all were of mild or moderate severity (further details on TEAEs may be found in Supplementary Table 8).

Five subjects experienced six CV adverse events (one with mealtime faster aspart, three with postmeal faster aspart, and one with IAsp) that were positively adjudicated (of 10 that qualified for adjudication) by the event

adjudication committee (Supplementary Table 9). During the trial, there were two deaths, both judged unlikely to be related to trial product (see Supplementary Data).

There were no clinically relevant differences from baseline to week 26 between faster aspart (mealtime or postmeal) and IAsp in physical examinations, vital signs, fundoscopy, electrocardiogram, or other laboratory assessments.

Conclusions

The current trial confirmed that, in subjects with type 1 diabetes on a basal-bolus regimen, both mealtime and postmeal faster aspart are noninferior to mealtime IAsp regarding HbA_{1c} change from baseline. Switching to mealtime or postmeal faster aspart was effective in improving glycemic control: the reduction in HbA_{1c} with mealtime faster aspart was moderately, yet statistically significantly, greater than with IAsp. After 26 weeks of treatment, subjects receiving mealtime faster aspart were almost 1.5 times as likely to achieve the HbA_{1c} target of <7.0% (53 mmol/mol) than those receiving IAsp.

Mealtime faster aspart was effective in controlling PPG excursions, and superiority versus IAsp in 2-h PPG increments (meal test) was confirmed. A statistically significant difference was demonstrated for the 1-h PPG increment (meal test) in favor of mealtime faster aspart; mean 7-9-7-point SMPG profiles and associated 2-h PPG and 2-h PPG increments showed modest trends toward improvement in PPG. Treatment with mealtime faster aspart for 26 weeks resulted in a statistically significantly greater increase from baseline in 1,5-AG compared with IAsp. This finding indicates that there were fewer recent hyperglycemic excursions, signifying that although the difference between mealtime faster aspart and IAsp was small, PPG control was improved. These results suggest that faster aspart, which has an improved action profile (20), produces the same glycemic improvements over IAsp in type 1 diabetes (0.15% statistically significantly lower HbA_{1c} and 0.7–1.2 mmol/L lower PPG increments) as reported previously with IAsp versus RHI (0.15% statistically significantly lower HbA_{1c} [27] and 1.1–1.3 mmol/L lower PPG increments [28,29]).

In certain situations, postmeal dosing of insulin may offer increased flexibility compared with mealtime dosing—for instance, when an individual is unable to predict the exact timing or carbohydrate content of a meal in advance (e.g., on social occasions), when experiencing lack of appetite or nausea (e.g., the very elderly or frail), when appetite is unpredictable (e.g., children), if an injection is forgotten, or if an individual is anxious about severe hypoglycemia (30,31). Subjects randomized to dosing faster aspart postmeal for all meals maintained overall glycemic control noninferior to that obtained with mealtime IAsp, indicating that flexibility in timing of dose with faster aspart does not lead to worsening of glycemic control.

Treatment with faster aspart was well tolerated by the subjects in this trial, and no safety concerns were raised. Overall, there were no clinically relevant differences in the TEAE profiles across all three treatment groups (Supplementary Table 8). No statistically significant difference was seen in overall rate of severe or BG-confirmed hypoglycemic episodes between faster aspart (mealtime or postmeal) and IAsp. The timing of

hypoglycemia in relation to a meal usually reflects the time-action profile of the administered insulin formulation. Thus, as expected, there was a higher rate of hypoglycemia in the first hour after a meal in the mealtime faster aspart arm than in the IAsp arm. This observation is consistent with the differing clinical pharmacology profiles of faster aspart and IAsp (20). Similar observations were reported when IAsp was compared with RHI in previous trials (28). Despite the higher rate of severe or BG-confirmed hypoglycemic episodes in the first hour (representing <3% of the overall episodes reported in this treatment group), there was no overall increase in severe or BG-confirmed hypoglycemia in the mealtime faster aspart arm compared with the IAsp arm.

The strengths of this trial include the number of subjects, the double blinding of subjects enrolled in the mealtime groups, and the additional 26-week period to document long-term safety and compare efficacy (which includes follow-up of subjects achieving target HbA_{1c} levels). Additionally, basal insulin dose was optimized on an individual basis prior to randomization with limited adjustments during the trial, thus allowing a clearer evaluation of the effect of the different bolus regimens. The bolus insulin dose of 0.1 units/kg used in this standardized meal test was in line with the median breakfast bolus dose measured at the end of the 26-week treatment period in each of the treatment groups. However, the meal test protocol was a potential limitation of the trial, as all subjects received the same 0.1 units/kg body weight bolus, and no adjustment was made for individual insulin-to-carbohydrate ratios: for all subjects, therefore, the insulin dose was an approximation of their usual dose.

Together with the results of previous studies (32,33,34), this trial has demonstrated that faster aspart given at mealtimes is noninferior to IAsp in terms of HbA_{1c} reduction while offering superior control of PPG excursions, without increased risk of overall hypoglycemia. Additionally, faster aspart offers the option of dosing up to 20 min postmeal while retaining overall glycemic control and without increased rates of overall hypoglycemia. This is an incremental step in more closely replicating the physiologic response of endogenous insulin release after a meal.

Article Information

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Footnotes

- Clinical trial reg. no. NCT01831765, clinicaltrials.gov.
- This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc16-1771/-/DC1.
- See accompanying articles, pp. 832 and 951.

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