Faster Aspart Versus Insulin Aspart as Part of a Basal-Bolus Regimen in Inadequately Controlled Type 2 Diabetes: The onset 2 Trial

Keith Bowering,[1] Christopher Case,[2] John Harvey,[3] Michael Reeves,[4] Michael Sampson,[5] Robert Strzinek,[6] Ditte-Marie Bretler,[7] Rikke Beck Bang,[7] and Bruce W. Bode[8]

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OBJECTIVE

This multicenter, double-blind, treat-to-target, phase 3 trial evaluated the efficacy and safety of fast-acting insulin aspart (faster aspart) versus insulin aspart (IAsp) in adults with type 2 diabetes receiving basal insulin and oral antidiabetic agents.

RESEARCH DESIGN AND METHODS

The primary end point was HbA_{1c} change from baseline after 26 weeks' treatment. After an 8-week run-in to optimize basal insulin, subjects were randomized (1:1) to mealtime faster aspart (*n* = 345) or IAsp (*n* = 344), titrated using a simple daily patient-driven algorithm, plus insulin glargine U100 and metformin.

RESULTS

HbA_{1c} change was –1.38% (faster aspart) and –1.36% (IAsp); mean HbA_{1c} was 6.6% for both groups. Faster aspart demonstrated noninferiority versus IAsp in reducing HbA_{1c} (estimated treatment difference [ETD] [95% CI] –0.02% [–0.15; 0.10]). Both treatments improved postprandial plasma glucose (PPG) control; the PPG increment (liquid meal test) was statistically significant in favor of faster aspart after 1 h (ETD [95% CI] −0.59 mmol/L [−1.09; −0.09]; −10.63 mg/dL [−19.56; −1.69]; *P* = 0.0198), but not after 2–4 h. Change from baseline in fasting plasma glucose, body weight, and overall severe/blood glucose–confirmed hypoglycemia rates (rate ratio [RR] [95% CI] 1.09 [0.88; 1.36]) were similar between treatments. Postmeal hypoglycemia (0−2 h) rates were 2.27 (faster aspart) and 1.49 (IAsp) per patient-year of exposure (RR [95% CI] 1.60 [1.13; 2.27]).

CONCLUSIONS

Faster aspart and IAsp were confirmed noninferior in a basal-bolus regimen regarding change from baseline in HbA_{1c}. Faster aspart improved 1-h PPG with no differences in 2−4-h PPG versus IAsp. Overall hypoglycemia rates were similar except for an increase in 0−2-h postmeal hypoglycemia with faster aspart.

Basal insulins are one of the recommended steps in type 2 diabetes treatment intensification when oral antidiabetic drugs (OADs) no longer provide sufficient glycemic control (1). As β-cell function decreases further, maintaining target HbA_{1c} levels becomes challenging, even when target fasting plasma glucose (FPG) levels have been achieved (2), and further therapeutic intensification may be required (3). The aim of

[1]Division of Endocrinology and Metabolism, University of Alberta, Edmonton, Alberta, Canada
[2]Jefferson City Medical Group, Jefferson City, MO
[3]Gladstone Centre, Maelor Hospital, Bangor University, Wrexham, U.K.
[4]Diabetes Clinical Trials, Chattanooga, TN
[5]Diabetes, Endocrinology and General Medicine, Norfolk and Norwich University Hospitals NHS Foundation Trust, Norwich, U.K.
[6]Protenium Clinical Research, Hurst, TX
[7]Novo Nordisk A/S, Søborg, Denmark
[8]Atlanta Diabetes Associates, Atlanta, GA

Corresponding author: Keith Bowering, keith.bowering@ualberta.ca.

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such intensification is to prevent excessive postprandial plasma glucose (PPG) excursions, which contribute to overall hyperglycemia. Several studies have documented that in type 2 diabetes, the relative contribution of PPG to excess hyperglycemia increases as HbA_{1c} levels approach target (4,5).

Options for therapy intensification in type 2 diabetes include glucagon-like peptide-1 (GLP-1) receptor agonists or the addition of mealtime insulin as part of a basal-bolus regimen (1). Reduction of PPG excursions with the addition of bolus insulin has been clearly demonstrated in type 2 diabetes (6). First-generation rapid-acting insulin analogs represented a major step forward in reducing PPG excursions versus regular human insulin (RHI). However, there remains an unmet need for insulin analogs with an even faster onset of action than rapid-acting insulin analogs, which could potentially achieve better PPG control (7,8).

Fast-acting insulin aspart (faster aspart) is a new formulation of conventional insulin aspart (IAsp). Nonclinical data illustrate that the addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous (s.c.) injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood (9). In adults with type 1 diabetes, s.c. 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 versus IAsp (10). As part of a basal-bolus regimen in type 1 diabetes, mealtime faster aspart effectively improved HbA_{1c} (estimated treatment difference [ETD] [95% CI] –0.15% [–0.23; –0.07]), and noninferiority to IAsp was confirmed, with statistically superior 2-h PPG control versus IAsp (ETD [95% CI] −0.67 mmol/L [−1.29; −0.04]; –12.01 mg/dL [–23.33; –0.70]) (11). Statistically superior glycemic control versus basal-only therapy was observed in subjects with type 2 diabetes, where HbA_{1c} was reduced from 7.9% (63.2 mmol/mol) to 6.8% (50.7 mmol/mol) in the basal-bolus arm and from 7.9% (63.1 mmol/mol) to 7.7% (60.7 mmol/mol) in the basal arm (ETD [95% CI] –0.94% [–1.17; –0.72]; –10.29 mmol/mol [–12.75; –7.82]; $P < 0.0001$) (12).

The objective of this trial was to confirm the efficacy of mealtime faster aspart versus mealtime IAsp (NovoRapid/NovoLog), as part of a basal-bolus regimen in subjects with type 2 diabetes inadequately controlled with basal insulin and OADs.

RESEARCH DESIGN AND METHODS

Trial Design

This was a 26-week, multicenter, double-blind, active-controlled, treat-to-target randomized trial in subjects with type 2 diabetes comparing mealtime faster aspart with IAsp, both in combination with insulin glargine U100 (Lantus) and metformin. Subject follow-up occurred at 7 and 30 days after the end of trial (EOT). The trial was conducted in accordance with the Declaration of Helsinki (13) and the International Conference on Harmonization Good Clinical Practice (14).

Subjects

Subjects (≥18 years of age) with a BMI ≤40 kg/m^2 were eligible for inclusion if diagnosed with type 2 diabetes and treated with basal insulin for ≥6 months (current once-daily treatment with NPH insulin, insulin detemir, or insulin glargine U100 for ≥3 months) before screening. Eligible subjects had also been treated with metformin (stable dose ≥1,000 mg) alone or with a sulfonylurea, glinide, dipeptidyl peptidase 4 inhibitor, and/or an α-glucosidase inhibitor for ≥3 months before screening. Subjects receiving metformin monotherapy before enrollment were required to have an HbA_{1c} of 7.0–9.5% (53–80 mmol/mol) at screening or 7.0–9.0% (53–75 mmol/mol) if receiving OADs + metformin. Exclusion criteria specified no bolus insulin use, except short-term use because of intermittent illness (≤14 days' consecutive treatment), and no GLP-1 agonists and/or thiazolidinediones (all ≤3 months before screening); concomitant medications known to interfere significantly with glucose metabolism; cardiovascular (CV) disease ≤6 months before screening; recurrent severe hypoglycemia (>1 severe hypoglycemic event during the past 12 months), hypoglycemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis ≤6 months before screening. All inclusion/exclusion criteria are listed in the Supplementary Data.

Interventions

Basal Titration During the Trial

After an initial 2-week screening period, current OADs (except metformin) were discontinued, and subjects entered the 8-week run-in period, during which basal insulin glargine U100 (100 units/mL; administered s.c. once daily at approximately the same time in the evening using a 3.0 mL SoloStar pen injector) was optimized. Subjects were switched unit-for-unit from their previous basal insulin to once-daily insulin glargine U100. During run-in, basal insulin 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 Table 1). After run-in, basal adjustments were performed when required as judged by the investigator, but basal dose frequency could not be changed.

Bolus Doses During the Trial

After the run-in, subjects with HbA_{1c} 7.0−9.5% (53−80 mmol/mol) were randomized 1:1 to receive mealtime faster aspart (100 units/mL) or IAsp (100 units/mL), both with basal insulin glargine U100 and metformin (stratified according to continuous glucose monitoring [CGM] subgroup participation). Faster aspart or IAsp was administered s.c. 0–2 min before each main meal using a 3.0 mL PDS290 prefilled pen injector. The timing of bolus insulin administration was in line with the IAsp label, which recommends administration immediately before a meal (15). The double-blind treatment period (bolus insulin titration) was 26 weeks. After randomization, bolus insulin dose adjustments were performed daily by the subject and reviewed weekly by the investigator. Bolus dose adjustments were made by subjects based on SMPG values from the previous day, according to the titration guideline (Supplementary Table 1). Subjects commenced 4 units of mealtime insulin at each meal, which was titrated by 1-unit increases or decreases to achieve the next premeal or bedtime target of 4.0–6.0 mmol/L (70–108 mg/dL). Additional bolus dosing was allowed at the investigator's discretion.

SMPG

Subjects were supplied with a blood glucose (BG) meter (factory calibrated to display plasma glucose [PG] values) and instructed to record the date, time, and value of all SMPG measurements for 7-9-7-point profiles (preprandial, postmeal, bedtime, and once at 4 A.M.) on three consecutive days before the scheduled clinic visits at weeks 0, 12, and 26; 4-point

profiles (preprandial and bedtime) were recorded daily for titration purposes.

Standardized Meal Test

PPG levels from 1 to 4 h were assessed in subjects completing the run-in period via a standardized liquid meal test containing ~80 g carbohydrate, consumed as quickly as possible and ≤12 min. To participate in the meal test, subjects had to be fasting with FPG levels within 4.0–8.8 mmol/L (72−160 mg/dL; SMPG measured before meal test). Blood samples were taken just before the meal and after 1, 2, 3, and 4 h. The same meal test was repeated at week 26, with the addition of the randomized treatment, a bolus insulin dose. The bolus insulin dose at the second meal test was calculated by dividing the carbohydrate content of the standardized liquid meal by the subject-specific insulin-to-carbohydrate ratio. This ratio was calculated using the "500 rule," whereby 500 was divided by the total daily insulin dose to determine the grams of carbohydrate covered by each unit of insulin (16).

Assessments

All end points reported were prespecified and are summarized in Supplementary Table 2.

Primary End Point

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

Secondary End Points

Confirmatory secondary end points included change from baseline in 2-h PPG increment (meal test) after 26 weeks' treatment, number of treatment-emergent severe or BG-confirmed hypoglycemic episodes from baseline to week 26, and change from baseline to week 26 in body weight. Hypoglycemic episodes were categorized as treatment emergent if the onset of the episode 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 (ADA) classification as an event requiring assistance of another person to actively administer carbohydrates or glucagon or take other corrective actions. PG concentrations may not be available during an event, but neurological recovery after the return of PG to normal is considered sufficient evidence that the event was induced by a low PG concentration (17). BG-confirmed hypoglycemia was defined by a PG value <3.1 mmol/L (56 mg/dL; Novo Nordisk definition) with or without symptoms consistent with hypoglycemia.

Supportive secondary efficacy end points included HbA_{1c} responders (subjects achieving HbA_{1c} <7.0% [53.0 mmol/mol] or ≤ 6.5% [47.5 mmol/mol], as well as the proportions who achieved these targets without severe hypoglycemia); change from baseline in PPG from the meal test (at 1, 2, 3, and 4 h separately) and PPG increment from the meal test (at 1, 3, and 4 h separately), both after 26 weeks' randomized treatment; change from baseline in mean SMPG profile and mean PPG increments (7-9-7-point profile); PPG responders (subjects achieving an overall mean 2-h PPG ≤7.8 mmol/L [140 mg/dL] and the same targets without severe hypoglycemia, derived from the 7-9-7-point SMPG profile); change from baseline to week 26 in 1,5-anhydroglucitol (1,5-AG), a marker for postprandial hyperglycemia; change from baseline to week 26 in FPG; and daily insulin dose (basal, bolus, and total).

Supportive secondary safety end points included the numbers of treatment-emergent adverse events (TEAEs), hypoglycemic episodes at 1, 2, 4, and 6 h postmeal, daytime (0600−2359 h) and nocturnal (0001−0559 h) hypoglycemic episodes, allergic reactions, and injection-site reactions. An adverse event was defined as treatment emergent if onset occurred on or after the first day of exposure to treatment and no later than 7 days after the last day of treatment. CV events and deaths occurring after randomization were sent for evaluation by an external, independent, clinical safety event adjudication committee. Additional safety assessments, physical examination, vital signs, fundoscopy, electrocardiograms, and laboratory parameters were recorded at baseline and week 26.

Statistical Methods

Efficacy analysis was based on the full analysis set, following the intention-to-treat principle. Confirmatory end points were tested using a hierarchical (fixed-sequence) procedure (Supplementary Fig. 1). The primary end point was analyzed using a mixed-effect model for repeated measurements, where all calculated changes in HbA_{1c} from baseline at trial visits were included in the analysis. This model included treatment, region, and CGM strata as fixed effects; subject as a random effect; HbA_{1c} at baseline as a covariate; and interactions between all fixed effects and visit and between the covariate and visit. Noninferiority was confirmed if the upper boundary of the two-sided 95% CI was ≤0.4%. PPG and PPG increments (meal test) were based on an ANOVA model. Target end points were analyzed separately based on a logistic regression model. Body weight, FPG, 1,5-AG, and PPG increment (SMPG) were analyzed using a mixed-effect model for repeated measurements similar to the model used for the primary end point. For the primary analysis, the one-sided *P* value for noninferiority is presented; for the remaining analyses, the two-sided *P* value for treatment difference is presented. Additional details on the sample size, power determination, statistical methods for the secondary efficacy end points, and stepwise hierarchical test (Supplementary Fig. 1) are in the Supplementary Data.

Safety end points were summarized using the safety analysis set and analyzed using the full analysis set. Hypoglycemic episodes were summarized by severity, using Novo Nordisk and ADA hypoglycemia definitions, and by category and total number of events in relation to the time since the start of a meal (Supplementary Data).

RESULTS

Trial Subjects

The trial randomized 689 subjects to receive faster aspart (*n* = 345) or IAsp (*n* = 344). Overall, 682 subjects were exposed to randomized treatment (*n* = 341 in each group) (Supplementary Fig. 2), and 606 (88%; *n* = 301, faster aspart; *n* = 305, IAsp) completed the trial. Baseline characteristics were similar between groups (Table 1).

Hierarchical Testing Procedure

Step 1 was confirmed. Because step 2 was not confirmed, the stepwise testing procedure was stopped (Supplementary Table 3).

Efficacy

Change in HbA_{1c}

Mean HbA_{1c} in subjects subsequently randomized to the faster aspart and IAsp groups were, respectively, 8.2% and 8.1% (65.6 mmol/mol and 65.2 mmol/mol) before the 8-week run-in period and

Table 1—Baseline characteristics at randomization

Parameter	Faster aspart *n* = 345	IAsp *n* = 344	Total *N* = 689
Age, years	59.6 (9.3)	59.4 (9.6)	59.5 (9.4)
Gender, *n* (%)			
Male	163 (47)	173 (50)	336 (49)
Female	182 (53)	171 (50)	353 (51)
Race, *n* (%)			
White	277 (80)	281 (82)	558 (81)
Asian	40 (12)	42 (12)	82 (12)
Black or African American	22 (6)	18 (5)	40 (6)
American Indian or Alaska Native	3 (1)	0 (0)	3 (0)
Native Hawaiian or other Pacific Islander	2 (1)	0 (0)	2 (0)
Other	1 (0)	3 (1)	4 (1)
Body weight			
kg	89.0 (16.9)	88.3 (16.7)	88.7 (16.8)
lb	196.3 (37.3)	194.7 (36.9)	195.5 (37.1)
BMI, kg/m^2	31.5 (4.7)	31.0 (4.5)	31.2 (4.6)
Duration of diabetes, years	13.2 (6.7)	12.3 (6.3)	12.7 (6.5)
HbA_{1c}			
%	8.0 (0.7)	7.9 (0.7)	7.9 (0.7)
mmol/mol	63.5 (7.5)	62.7 (7.7)	63.1 (7.6)
FPG			
mmol/L	6.8 (1.8)	6.8 (2.0)	6.8 (1.9)
mg/dL	121.7 (32.7)	122.7 (35.1)	122.2 (33.9)
Antidiabetic treatment at screening, *n* (%)			
Basal + OAD	345 (100.0)	344 (100.0)	689 (100.0)
Basal OD + 1 OAD	187 (54.2)	184 (53.5)	371 (53.8)
Basal OD + 2 OADs	149 (43.2)	152 (44.2)	301 (43.7)
Basal OD + >2 OADs	9 (2.6)	8 (2.3)	17 (2.5)

Values for baseline characteristics are arithmetic means (SD), unless stated otherwise. The conversion factor between mmol/L and mg/dL is 18. OD, once daily.

8.0% and 7.9% (63.5 mmol/mol and 62.7 mmol/mol) at baseline. By EOT, mean HbA_{1c} had decreased to 6.6% (49 mmol/mol) in both groups (Fig. 1). The estimated mean change in HbA_{1c} from baseline to EOT was –1.38% (–15.1 mmol/mol) for faster aspart and –1.36% (–14.9 mmol/mol) for IAsp. The ETD was –0.02% (95% CI –0.15; 0.10) (–0.24 mmol/mol [–1.60; 1.11]), confirming noninferiority of faster aspart to IAsp ($P < 0.0001$; hierarchical testing step 1) (Supplementary Fig. 1). By week 26, 74.8% of subjects in the faster aspart group and 75.9% in the IAsp group had achieved HbA_{1c} <7.0% (53 mmol/mol), and 71.9% and 72.7%, respectively, achieved this target without severe hypoglycemia (Supplementary Fig. 3*A* and Supplementary Table 4). By week 26, 54.5% and 56.4% of subjects had achieved HbA_{1c} ≤6.5% (47.5 mmol/mol), and 52.2% and 53.5% had achieved this target without severe hypoglycemia in the faster aspart and IAsp groups, respectively (Supplementary Fig. 3*B* and Supplementary Table 4).

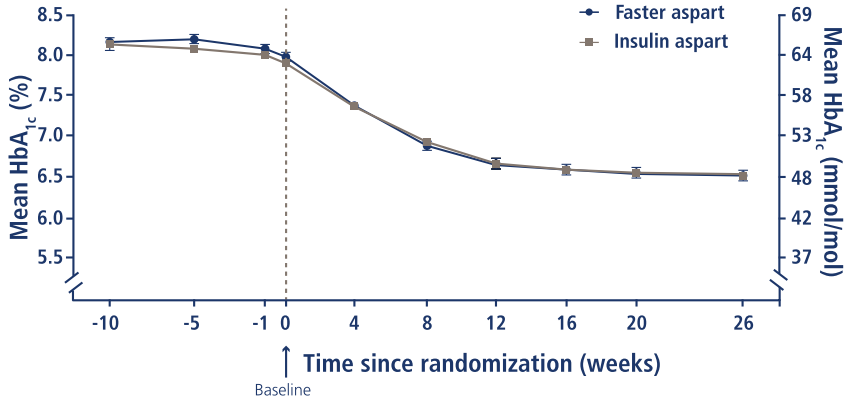

Figure 1—Mean HbA_{1c} over time. Error bars: ± SEM.

Meal Test

Estimated change from baseline in 2-h PPG increment was –3.2 mmol/L (–58.3 mg/dL) with faster aspart versus –2.9 mmol/L (–51.8 mg/dL) for IAsp. The ETD was –0.36 mmol/L (95% CI –0.81; 0.08) (−6.57 mg/dL [−14.54; 1.41]) (Fig. 2), which did not reach statistical significance. The estimated change from baseline in 1-h PPG increment was −2.1 mmol/L (−38.5 mg/dL) for faster aspart and −1.6 mmol/L (−27.9 mg/dL) for IAsp. The ETD was −0.59 mmol/L (95% CI −1.09; −0.09) (−10.63 mg/dL [−19.56; −1.69]), which was statistically significantly in favor of faster aspart ($P = 0.0198$) (Fig. 2 and Supplementary Table 4).

Statistical superiority of treatment with faster aspart versus IAsp could not be confirmed for change from baseline in 2-h PPG increment (Supplementary Fig. 1). There were no statistical differences between groups for change from baseline in 3-h or 4-h PPG increments or in PPG at any time point (Supplementary Table 4).

SMPG

Mean 9-point SMPG values (observed data) were reduced after the addition of bolus insulin doses (Supplementary Fig. 4). The observed mean of the 7-9-7-point profile was ~9.0 mmol/L (162.1 mg/dL) in both groups at baseline compared with ~6.9 mmol/L (124.4 mg/dL) by EOT (Supplementary Table 4). The change from baseline in 2-h PPG increment (7-9-7-point profile) was numerically greater with faster aspart versus IAsp at all meals, but this difference only reached statistical significance after lunch (–1.2 mmol/L [–21.4 mg/dL] vs. –0.8 mmol/L [–15.0 mg/dL]; ETD [95% CI] –0.35 mmol/L [–0.65; –0.05]; 6.36 mg/dL [–11.81; –0.92]; $P = 0.0219$) (Supplementary Table 4).

Overall, 71.2% and 67.2% of subjects achieved the 2-h PPG target of ≤7.8 mmol/L (140 mg/dL) at week 26 (7-9-7-point SMPG profile) in the faster aspart and IAsp groups, respectively (Supplementary Fig. 3*C* and Supplementary Table 4), with 69.4% and 64.5% of subjects, respectively, achieving the target without experiencing severe

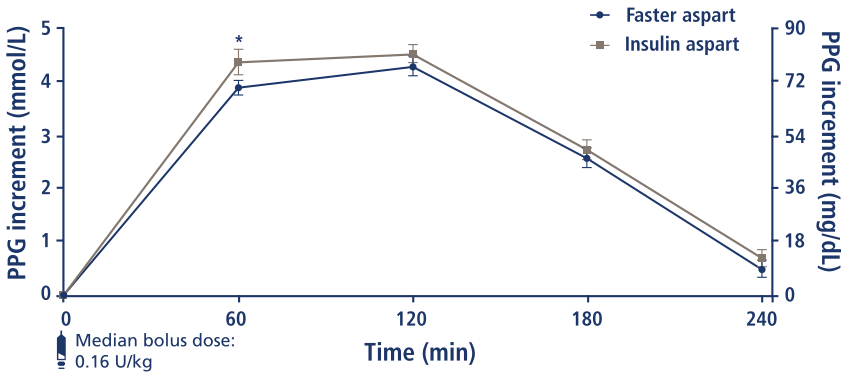

Figure 2—PPG increment (meal test) at week 26. *Change in 1-h PPG increment statistically significant in favor of faster aspart: ETD (95% CI): –0.59 (–1.09; –0.09) mmol/L; −10.63 (−19.56; −1.69) mg/dL; *P* = 0.0198. Observed data. Error bars: ± SEM. The conversion factor between mmol/L and mg/dL is 18.

hypoglycemia (Supplementary Fig. 3*C* and Supplementary Table 4).

Other Secondary Efficacy End Points

At EOT, increases in mean 1,5-AG levels were observed in both groups (to 12.8 μg/mL in faster aspart and 13.2 μg/mL in IAsp), with no difference in change from baseline between groups (Supplementary Table 4).

FPG remained similar from baseline to EOT in both groups (Supplementary Table 4). Body weight increased by ∼2.7 kg in both groups (ETD [95% CI] 0.00 kg [–0.60; 0.61]; 0.01 lb [–1.33; 1.35]).

Insulin Dosing

The total daily insulin dose increased during the treatment period for both groups due to the bolus intensification. Median total daily insulin dose increased from 0.56 units/kg to 1.02 units/kg in the faster aspart group and from 0.51 units/kg to 1.02 units/kg in the IAsp group (Supplementary Table 5). Observed insulin doses were similar between the faster aspart and IAsp groups. For both groups, the proportion of bolus daily insulin relative to total daily insulin was 56% after 26 weeks' treatment (Supplementary Table 5).

Safety (TEAEs)

The difference in overall rate of severe or BG-confirmed hypoglycemia was not statistically significant between treatment groups (treatment rate ratio [RR] 1.09 [95% CI 0.88; 1.36]) (Table 2). The number of severe or BG-confirmed hypoglycemic episodes per subject increased at a similar rate in both groups (Supplementary Fig. 5). The observed rates of severe hypoglycemic episodes were low in both groups (0.17 and 0.11 episodes per patient-year of exposure for, respectively, faster aspart and IAsp) (Table 2). The proportion of subjects who experienced severe hypoglycemia was 3.2% (faster aspart) and 3.8% (IAsp). The relative difference in the observed rates of severe hypoglycemic episodes between groups was not statistically significant.

For the interval 0−2 h after meals, a statistically significantly higher rate of meal-related hypoglycemia was reported for faster aspart (estimated RR 1.60 [95% CI 1.13; 2.27]; *P* = 0.0082), but there was no statistically significant difference between treatment groups for any other time frame or for daytime or nocturnal episodes of hypoglycemia (Table 2). The proportion of subjects reporting TEAEs and the rate of TEAEs was similar between groups (Supplementary Table 6). The most frequently reported TEAEs (≥1% of subjects; by preferred terms) across the treatment groups were nasopharyngitis and upper respiratory and urinary tract infections. Most events were nonserious and mild or moderate in severity. In total, 58 allergic reactions in 51 (7.5%) subjects were reported and evenly distributed across groups; most were nonserious. The event rate for injection-site reactions was low in this trial and similar between groups. All injection-site reactions were nonserious and did not recur, with the exception of two events of injection-site hematoma reported for one subject in the IAsp group.

The event adjudication committee positively adjudicated 12 adverse events as CV events (Supplementary Table 7). Six of these events were identified as major adverse CV events: two in the faster aspart group and four in the IAsp group. In the subjects with positively adjudicated CV events, most recovered/resolved and were judged by the investigator as unlikely to be related to trial products.

Table 2—Treatment-emergent hypoglycemic events

Treatment-emergent hypoglycemia	Faster aspart			IAsp			Treatment RR (faster aspart-to-IAsp)
	n (%)	E	R	*n* (%)	E	R	Estimate (95% CI)
Severe	11 (3.2)	27	0.17	13 (3.8)	17	0.11	1.25 (0.44; 3.55)
Severe or BG confirmed	262 (76.8)	2,857	17.9	250 (73.3)	2,692	16.6	1.09 (0.88; 1.36)
Meal-related severe or BG-confirmed hypoglycemia							
Within 1 h	45 (13.2)	78	0.49	39 (11.4)	62	0.38	1.29 (0.78; 2.15)
Within 2 h	112 (32.8)	362	2.27	96 (28.2)	241	1.49	1.60 (1.13; 2.27)*
Within 4 h	208 (61.0)	1,248	7.81	179 (52.5)	1,092	6.73	1.18 (0.91; 1.53)
Within 6 h	238 (69.8)	2,036	12.74	217 (63.6)	1,987	12.25	1.07 (0.84; 1.36)
Daytime and nocturnal severe or BG-confirmed hypoglycemia							
Daytime	257 (75.4)	2,572	16.09	245 (71.8)	2,475	15.25	1.07 (0.86; 1.33)
Nocturnal	104 (30.5)	285	1.78	84 (24.6)	217	1.34	1.38 (0.96; 2.00)

Severe hypoglycemia was defined according to the ADA classification (17). 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 definition). E, number of events; R, event rate per patient-year of exposure. *P = 0.0082.

There were no clinically relevant differences from baseline to EOT or between treatment groups in physical examinations, vital signs, fundoscopy, electrocardiograms, or laboratory assessments.

CONCLUSIONS

In this trial, treatment intensification with mealtime faster aspart or IAsp improved glycemic control in subjects with type 2 diabetes inadequately controlled on basal insulin and OADs, with faster aspart confirmed as noninferior to IAsp for HbA_{1c} change over 26 weeks. In both treatment groups, HbA_{1c} decreased during the first 16 weeks of treatment, stabilizing at ~6.6% thereafter until EOT, demonstrating that subjects were able to maintain tight glycemic control, as recommended by current guidelines (1), which is predicted to reduce the risk of long-term diabetes-associated complications (18–20). These results were achieved with a simple daily patient-driven algorithm that titrated mealtime insulin by 1-unit increases or decreases, as necessary, to achieve the next premeal or bedtime target of 4.0–6.0 mmol/L (70–108 mg/dL). The improvement in HbA_{1c} (~6.6%) over time was reflected in the high proportion of subjects who met the target HbA_{1c} level (<7.0% [53 mmol/mol]), including those without severe hypoglycemia, which is generally recommended by the European Association for the Study of Diabetes and ADA for type 2 diabetes (1). The degree of improvement in HbA_{1c} from baseline with the addition of prandial bolus insulin is notable and demonstrates the contribution of excessive PPG excursions to overall glycemic control. The final HbA_{1c} achieved in this trial (through a simple self-titration algorithm) is one of the lowest attained in a large randomized trial of basal-bolus insulin in type 2 diabetes (21).

Mealtime faster aspart and IAsp were effective in controlling PPG (assessed by both the meal test and SMPG) and improved levels of 1,5-AG, a marker for postprandial hyperglycemia (22,23). In studies of basal-bolus therapy in type 2 diabetes, changes in HbA_{1c} are often small and nonsignificant (~0.09%) (21). Given the heterogeneity of type 2 diabetes, both in regard to insulin resistance and residual β-cell function (24), that similar overall glycemic control was achieved with both faster aspart and IAsp is unsurprising. This similar control occurred despite a statistically significant improvement in the 1-h PPG increment (meal test) and a lower lunchtime 2-h PPG increment (7-9-7-point SMPG profile) with faster aspart. Here we report a 0.59 mmol/L (10.63 mg/dL) lower increment (meal test) in 1-h PPG with faster aspart versus IAsp. A previous meta-analysis of randomized clinical trials in type 1 and type 2 diabetes comparing IAsp and RHI reported a significant difference in PPG improvement between regimens in favor of IAsp, with overall estimates of –0.47 mmol/L (90-min PPG value); analysis of average change in PPG increment gave similar results (25). Faster aspart demonstrated statistically superior 2-h PPG control versus IAsp when used as part of a basal-bolus regimen in type 1 diabetes (11). Conceivably, in day-to-day clinical practice, people with type 2 diabetes who have marked reductions in endogenous insulin secretion might be the ones to most benefit from a faster-acting mealtime insulin.

After 26-weeks' treatment, 56% of the total insulin dose was provided by mealtime insulin in both groups. Use of CGM has previously shown that existing approaches for calculating basal-bolus doses may overestimate total insulin dose required and underestimate mealtime insulin requirements (26). Recommending a regimen in which the basal dose comprises <50% of the overall insulin dose is preferable for achieving optimal glycemic control in basal-bolus treatment (27). The results from the current trial broadly support this ratio.

Body weight gain was ~2.7 kg over 26 weeks for both treatment groups, which is typical of the weight gain associated with intensive insulin regimens (28).

The overall safety profiles for faster aspart and IAsp were similar and as expected for IAsp. Many people with diabetes fear hypoglycemia; however, although a high proportion of subjects achieved HbA_{1c} <7%, hypoglycemia rates were comparable with those previously reported (21), and no statistically significant differences were observed between the two treatments. The timing of hypoglycemia is usually indicative of the time-action profile of the administered insulin. The higher rate of overall hypoglycemic episodes within the first 2 h after a meal for faster aspart versus IAsp (absolute difference of ~0.8 events per patient-year of exposure) is consistent with the clinical pharmacology profiles of faster aspart and IAsp, wherein a greater early glucose-lowering effect with faster aspart was demonstrated versus IAsp (10). Similar observations were made previously when IAsp was compared with RHI (29). There were no statistically significant differences in hypoglycemic episodes between faster aspart and IAsp within 1, 4, and 6 h of a meal.

Strengths of the current trial include the double-blind design, use of a standardized meal test at baseline and after 26 weeks, and the relatively high (88%) completer rate. A limitation was the need for subjects to perform frequent finger-prick tests to record SMPG values, which, in the real-world setting, many patients may be unwilling to do. Advances in needle-free technology to measure glucose may, however, improve the practicality of intensive insulin self-management regimens in everyday life. Other limitations are the inclusion of subjects with relatively good glycemic control, who are not usually representative of subjects encountered in clinical practice, initiation of three bolus doses simultaneously, and the liquid meal test, which standardizes macronutrient composition between subjects but is not fully representative of a real-life setting. However, a treat-to-target trial of well-controlled subjects with type 2 diabetes showed that ~75% of subjects initiated with one bolus injection eventually required a full basal-bolus regimen (30), so it is of value to assess faster aspart in the same regimen.

In adults with type 2 diabetes inadequately controlled on basal insulin and OADs, insulin intensification with faster aspart or IAsp improved overall glycemic and PPG control, with statistically significantly improved 1-h PPG control with faster aspart. Overall hypoglycemia (severe or BG confirmed) rates were similar between treatment groups, with an increase in hypoglycemia rates during the 0−2 h postmeal interval with faster aspart. Thus, faster aspart and IAsp are both effective, well-tolerated treatment options for patients requiring mealtime insulin.

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