Received: 20 November 2017 | Revised: 22 December 2017 | Accepted: 28 December 2017

DOI: 10.1111/dom.13205

WILEY

ORIGINAL ARTICLE

Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): A 52-week, randomized, treat-to-target, phase III trial

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Funding information
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Aims: To compare the safety and efficacy of fast-acting insulin aspart (faster aspart) with conventional insulin aspart (IAsp) in adults with type 1 diabetes (T1D).

Materials and methods: onset 1 was a randomized, multicentre, treat-to-target, phase III, 52-week (initial 26 weeks + additional 26 weeks) trial conducted at 165 sites across 9 countries. Adults with T1D were randomly allocated to double-blind mealtime faster aspart or IAsp, each with once- or twice-daily insulin detemir. The primary endpoint, change in glycated haemoglobin (HbA1c) from baseline after the initial 26 weeks, has been reported previously. In the present paper, we report data from the full 52-week study period.

Results: Between August 2013 and June 2015, 381 participants were assigned to double-blind faster aspart and 380 participants to IAsp. After 52 weeks, estimated mean changes from baseline in HbA1c levels were −0.08% (faster aspart) and +0.01% (IAsp); estimated treatment difference significantly favoured faster aspart (−0.10% [95% confidence interval {CI} −0.19;−0.00]; P = .0424). Changes from baseline in 1-hour postprandial plasma glucose (PPG) increment (meal test; faster aspart −1.05 mmol/L; IAsp −0.14 mmol/L) also significantly favoured faster aspart (estimated treatment difference −0.91 mmol/L [95% CI −1.40;−0.43]; −16.48 mg/dL [95% CI −25.17;−7.80]; P = .0002). There was no difference in overall severe or blood glucose-confirmed hypoglycaemic episodes or treatment-emergent adverse events between treatments.

Conclusions: At 52 weeks, overall glycaemic control had significantly improved with faster aspart vs IAsp, consistent with the 26-week study findings. Achieving an insulin profile closer to physiological insulin secretion with faster aspart translates into lower PPG and HbA1c levels compared with those achieved with IAsp in people with T1D.

KEYWORDS

insulin therapy, type 1 diabetes

1 | INTRODUCTION

Postprandial plasma glucose (PPG) excursions are an important contributor to elevated glycated haemoglobin (HbA1c) levels,[1,2] and limiting these excursions is challenging.[3] Rapid-acting insulin analogues (insulin aspart [IAsp], glulisine and lispro) were developed to more effectively control PPG excursions than regular human insulin,[4] and to have a faster onset and shorter duration of action,[3] providing more physiological PPG control when used in basal–bolus regimens.[5–7] Further improvements in PPG control may be achieved with novel insulin

formations and delivery methods that accelerate both insulin absorption and action profile.[8–14]

Fast-acting insulin aspart (faster aspart) is a new formulation of IAsp (NovoRapid/NovoLog, Novo Nordisk A/S, Bagsværd, Denmark) containing niacinamide; data suggest this promotes formation of IAsp monomers after subcutaneous injection,[15] leading to more rapid absorption of faster aspart into the bloodstream vs conventional IAsp.[16] In a pooled analysis of six randomized trials in participants with type 1 diabetes (T1D; *n* = 218), onset of appearance was twice as fast and early insulin exposure 2-fold greater, leading to a 74% greater early glucose-lowering effect with faster aspart vs IAsp.[16] The phase III onset 1 trial evaluated efficacy and safety of faster aspart as part of a basal–bolus regimen in T1D.[17] At 26 weeks, non-inferiority of mealtime faster aspart to mealtime IAsp was confirmed in terms of HbA1c change.[17] Compared with IAsp, faster aspart resulted in a significantly greater reduction in HbA1c, and provided superior mealtime PPG control, with no difference in overall rate of severe or blood glucose (BG)-confirmed hypoglycaemia.

Long-term follow-up data are helpful when judging the clinical value of new treatments; therefore, onset 1's initial 26-week treatment period was followed by an additional 26-week treatment period, the aim of which was to assess the long-term safety and efficacy of faster aspart. In the present paper, we report the results for 52 weeks of treatment.

2 | METHODS

2.1 | Study design and participants

onset 1 was a 26-week (initial treatment period) plus 26-week (additional treatment period), multicentre, randomized, parallel-arm trial comparing double-blind mealtime faster aspart with mealtime IAsp, both administered with once- or twice-daily insulin detemir (IDet), in adults with T1D (Figure S1 in File S1). The trial was conducted at 165 sites across 9 countries: Belgium (5 sites); Canada (12 sites); Czech Republic (5 sites); Finland (6 sites); Germany (25 sites); Hungary (5 sites); Poland (6 sites); the United Kingdom (9 sites); and the United States (92 sites). Results of the initial 26-week period have been reported previously[17]; in the present paper, we report results for the total 52-week period. Previously reported data from a third arm receiving open-label, post-meal faster aspart in the initial 26 weeks[17] are not presented, as these participants did not continue into the additional period.

The trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonisation of Good Clinical Practice. The 21 US Code of Federal Regulations parts 312, 50 and 56 were followed, and the trial was conducted in accordance with US Food and Drug Administration 21 US Code of Federal Regulations 312.120. The protocol, consent form and participant information sheet were approved according to local regulations by the appropriate health authorities and independent ethics committees. All participants provided written, informed consent before undergoing any trial procedures (Clinical trial registration: NCT01831765, ClinicalTrials.gov).

Participants were adults (aged ≥18 years) with clinically diagnosed T1D who received treatment with a basal–bolus insulin regimen for ≥12 months before screening (including any regimen of IDet or insulin glargine for ≥4 months before screening), had HbA1c levels ranging from 53 to 80 mmol/mol (7.0%-9.5%) and body mass index ≤35.0 kg/m^2. Key exclusion criteria were: any use of antidiabetic drugs other than insulin within the 3 months pre-screening; anticipated change in concomitant medications that interfere with glucose metabolism; cardiovascular disease within 6 months pre-screening; recurrent severe hypoglycaemia (>1 event during the previous 12 months); and hypoglycaemic unawareness (judged by investigators). Full exclusion criteria have been published previously.[17]

2.2 | Randomization and masking

Randomization was performed by the trial sponsor. At the randomization visit, participants with HbA1c ≤80 mmol/mol (9.5%) were randomly allocated 1:1:1 to receive double-blind pre-meal faster aspart or IAsp or open-label post-meal faster aspart using a telephone or web-based randomization system. Randomization was stratified by: method used for adjusting bolus insulin (i.e. carbohydrate counting or dosing algorithm); current basal treatment regimen (once or twice daily); and inclusion in the exploratory subgroup for continuous glucose monitoring and frequently sampled meal test (yes/no).[17] During the additional 26-week period, the blinded treatment allocation continued for the two mealtime arms. The investigator and participants remained blinded, but the sponsor was not blinded during the additional treatment period because the treatment randomization was unblinded to the sponsor for data analysis after the initial 26-week period.

2.3 | Procedures

The basal insulin provided throughout the study was IDet (100 U/mL; 3.0 mL FlexPen, Novo Nordisk A/S), optimized during an 8-week run-in. Participants not receiving IDet at the start of the run-in period were switched on a unit-to-unit basis from their previous basal insulin. Participants initially continued the dosing frequency (once or twice daily), but were permitted to change dosing frequency during the run-in if required. During run-in, IDet was titrated based on a weekly self-monitored plasma glucose (SMPG) target for once-daily (pre-breakfast target 4.0-5.0 mmol/L [71-90 mg/dL]) and twice-daily (pre-dinner target 4.0-6.0 mmol/L [71-108 mg/dL]) dosing. Titration regimens have been published previously.[17] After run-in, adjustments in dose were performed when considered necessary by the investigators. Changes to dose frequency after randomization were not permitted and resulted in trial withdrawal.

All bolus injections of faster aspart and IAsp were provided as 100 U/mL and administered 0-2 minutes before meals using a 3.0 mL FlexTouch (Novo Nordisk A/S) pen-injector. During run-in, all participants received mealtime IAsp. Participants previously receiving other mealtime insulins were switched on a unit-to-unit basis. Insulin dose was adjusted by participants as done before entering the trial. No adjustments in bolus insulin dose were performed during run-in unless needed for safety reasons. After standardized training in

carbohydrate counting, participants deemed by investigators to be proficient in flexible bolus dosing, based on carbohydrate content and preprandial plasma glucose (PG) levels, used this method to adjust bolus doses during the trial, with a weekly review performed by investigators based on SMPG values. The target level for preprandial PG was 4.0 to 6.0 mmol/L (71-108 mg/dL), although insulin dose could be reduced by investigators in the event of hypoglycaemia. All other participants were provided with a predefined titration algorithm for bolus adjustment (Table S1 in File S1).

All participants received a BG meter (calibrated to display PG values) and recorded the date, time and value of SMPG measurements from 7-9-7-point profiles (pre- and post-meal, bedtime and once at 4:00 AM) on 3 consecutive days before clinic visits at weeks 0, 12, 26, 40 and 52. Four-point profiles (preprandial and bedtime) were recorded daily for titration purposes.

Participants completing the run-in received a bolus dose of IAsp (0.1 U/kg, calculated by investigators) 0 to 2 minutes before a standardized mixed liquid meal test (80 g carbohydrate [Ensure, Abbott Nutrition, Columbus, OH, USA] consumed within 12 minutes). Participants were required to have fasting plasma glucose (FPG) 4.0 to 8.8 mmol/L (71-160 mg/dL) for the meal test to be performed. Blood samples were collected before the meal and at 1, 2, 3 and 4 hours afterwards for evaluation of 1- to 4-hour PPG levels. The meal test was repeated at weeks 26 and 52 with the inclusion of faster aspart, with participants self-administering the bolus dose (0.1 U/kg) 0 to 2 minutes before the test.

2.4 | Outcomes

The primary endpoint (change in HbA1c from baseline) and all confirmatory endpoints for onset 1 were reported after 26 weeks.[17] Numerous supportive secondary endpoints were assessed at both 26 and 52 weeks; in the present paper, we report the 52-week results. Supportive secondary endpoints included: changes in HbA1c from baseline to 52 weeks; HbA1c responders (defined as HbA1c <53 mmol/mol [7.0%] or ≤47.8 mmol/mol [6.5%]) at week 52; changes from baseline in PPG levels and PPG increments (based on meal test) at week 52; changes from baseline in mean 7-9-7-point SMPG profile, mean 2-hour PPG level and mean 2-hour PPG increments (based on 7-9-7-point profile) at week 52; PPG responders (defined as overall mean 2-hour PPG ≤7.8 mmol/L [140 mg/dL]) at week 52; changes from baseline in 1,5-anhydroglucitol (1,5-AG) level, FPG level and body weight at week 52; total (basal + bolus) insulin doses; number of severe (classification according to the American Diabetes Association[18]) or BG-confirmed (PG <3.1 mmol/L [56 mg/dL]) treatment-emergent hypoglycaemic episodes during 52 weeks of randomized treatment; and numbers of treatment-emergent adverse events, injection-site reactions and allergic reactions. Laboratory efficacy variables (HbA1c, PG during meal test, FPG and 1,5-AG) were analysed by the central laboratory.

2.5 | Statistical analysis

All analyses were conducted with SAS (version 9.4) software. The sample-size calculation has been reported previously.[17] Efficacy data were summarized from the full analysis set (FAS), which included all participants randomly allocated to treatment. Safety data were summarized from the safety analysis set, which included all participants receiving at least 1 dose of trial medication. All analyses were undertaken with the FAS. Changes in HbA1c level from baseline were analysed using a mixed-effect model for repeated measurements. Responder endpoints (for HbA1c and PPG levels based on SMPG) were analysed separately using a logistic regression model. Changes from baseline in mean 7-9-7-point SMPG profiles, mean PPG levels (two separate endpoints based on meal test and 7-9-7-point SMPG profile) and mean PPG increments (two separate endpoints based on meal test and 7-9-7-point SMPG profile), 1,5-AG, FPG and body weight were analysed using a mixed-effect model for repeated measurements similar to that used for HbA1c. The numbers of overall treatment-emergent severe or BG-confirmed hypoglycaemic episodes were analysed using a negative binomial regression model. No interim analyses were performed during the trial and a Novo Nordisk safety committee performed ongoing safety surveillance during the trial. Further details of statistical methods are included in the Supporting Information.

3 | RESULTS

Between August 26, 2013 and June 11, 2015, participants were randomly allocated to mealtime faster aspart (n = 381) or mealtime IAsp (n = 380). Baseline characteristics were similar between treatment arms (Table 1). The full 52-week trial was completed by 675 participants (Figure S2 in File S1).

During run-in, observed mean HbA1c was reduced from 64.0 mmol/mol (8.0%) to 59.7 mmol/mol (7.6%) for participants subsequently randomized to receive mealtime faster aspart, and from 64.0 mmol/mol (8.0%) to 59.3 mmol/mol (7.6%) for participants subsequently randomized to receive mealtime IAsp (Figure 1). During the

TABLE 1 Demographics and disease characteristics at baseline

	Faster aspart (mealtime) n = 381	IAsp n = 380
Age, years	46.1 (13.8)	43.7 (14.0)
Sex, n (%)		
Men	215 (56.4)	238 (62.6)
Women	166 (43.6)	142 (37.4)
Body weight, kg	78.6 (14.9)	80.1 (15.2)
BMI, kg/m^2	26.4 (3.8)	26.7 (3.7)
Duration of diabetes, years	20.9 (12.9)	19.3 (11.8)
HbA1c		
%	7.6 (0.7)	7.6 (0.7)
mmol/mol	59.7 (7.7)	59.3 (7.4)
FPG		
mmol/L	8.4 (3.1)	7.9 (2.8)
mg/dL	151.4 (55.8)	141.8 (50.2)

Abbreviations: BMI, body mass index; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; HbA1c, glycated haemoglobin; IAsp, insulin aspart. Values expressed as mean (SD), unless otherwise stated, from the full analysis set.

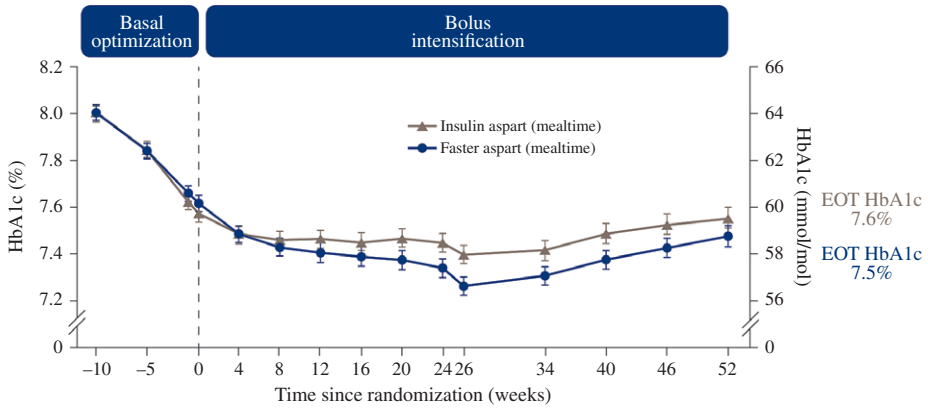

FIGURE 1 Mean glycated haemoglobin (HbA1c) level over time. Data are mean (SE) for the full analysis set. During run-in, observed mean HbA1c was reduced from 64.0 mmol/mol (8.0%) to 59.7 mmol/mol (7.6%) for participants subsequently randomized to receive mealtime faster aspart (n = 381), and from 64.0 mmol/mol (8.0%) to 59.3 mmol/mol (7.6%) for participants subsequently randomized to receive mealtime insulin aspart (n = 380). Following the 52-week treatment period, observed mean HbA1c was 58.5 mmol/mol (7.5%) with mealtime faster aspart and 59.6 mmol/mol (7.6%) with mealtime insulin aspart. EOT, end of trial; faster aspart, fast-acting insulin aspart

initial 26 weeks, observed mean HbA1c was reduced from baseline to 56.4 mmol/mol (7.3%) with faster aspart and to 57.6 mmol/mol (7.4%) with IAsp.[17]

At 52 weeks, observed mean HbA1c was 58.5 mmol/mol (7.5%) with faster aspart and 59.6 mmol/mol (7.6%) with IAsp (Figure 1); estimated mean changes from baseline of −0.08% and +0.01%, respectively. The estimated treatment difference (faster aspart – IAsp) was −1.04 mmol/mol (95% confidence interval [CI] −2.05;−0.04) or −0.10% (95% CI −0.19;−0.00; P = .0424 [Figure S3 in File S1]).

The percentages of participants achieving HbA1c targets of <53 mmol/mol (7.0%) and ≤47.8 mmol/mol (6.5%) increased from baseline to 52 weeks with faster aspart and IAsp. The estimated odds of achieving HbA1c targets with faster aspart were not significantly different from those with IAsp (Table S2 in File S1).

At baseline and week 52, mean PPG increased up to 2 hours after meal consumption in both arms and then started to decrease (Figure 2A). At 52 weeks, observed mean 1-hour PPG was reduced from 13.83 to 13.04 mmol/L (249.3 to 235.1 mg/dL) with faster aspart and increased from 13.54 to 13.81 mmol/L (244.1 to 248.9 mg/dL) with IAsp. Estimated changes from baseline to 52 weeks in 1-hour PPG were −0.79 mmol/L (−14.3 mg/dL) with faster aspart and +0.14 mmol/L (+2.5 mg/dL) with IAsp (treatment difference −0.93 mmol/L [95% CI −1.58;−0.27]; −16.7 mg/dL [95% CI −28.5;−5.0]; P = .0054 [Table S2 in File S1]). There were no statistically significant differences in 2-, 3- or 4-hour PPG levels between treatment arms.

Mean PPG increments were similar between treatment arms at baseline. After 52 weeks (Figure 2B), observed mean 1-hour PPG increment was reduced from 5.39 to 4.50 mmol/L (97.2 to 81.2 mg/dL) with faster aspart and from 5.65 to 5.44 mmol/L (101.9 to 98.1 mg/dL) with IAsp. Estimated changes from baseline in 1-hour PPG increment were −1.05 mmol/L (−18.9 mg/dL) with faster aspart and −0.14 mmol/L (−2.5 mg/dL) with IAsp (treatment difference −0.91 mmol/L [95% CI −1.40;−0.43]; −16.48 mg/dL [95% CI −25.17;−7.80]; P = .0002 [Table S2 in File S1]). There were no significant treatment differences at 2 hours (−0.42 mmol/L [95% CI −1.11;0.27], −7.60 mg/dL [95% CI −19.98;4.78]); 3 hours (0.15 mmol/L [95% CI −0.58;0.87], 2.64 mg/dL [95% CI −10.37;15.64]); or 4 hours (0.24 mmol/L [95% CI −0.45;0.92], 4.24 mg/dL [95% CI −8.11;16.59]; Table S2 in File S1).

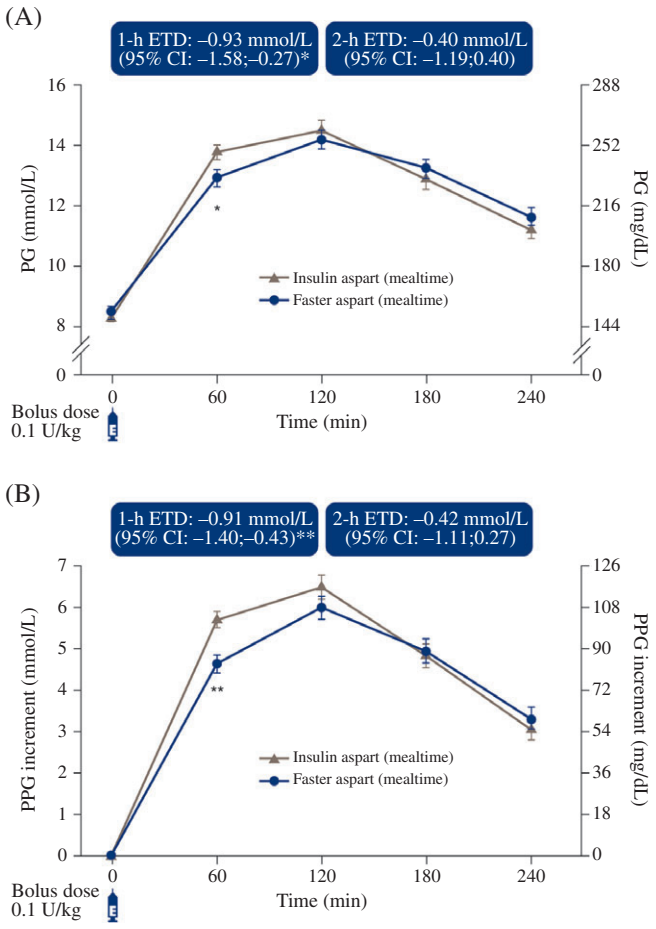

FIGURE 2 A, Postprandial plasma glucose (PPG) levels and B, PPG increments based on the meal test at week 52. Data are mean (SE) for the full analysis set. *P = .0054, **P = .0002. Changes from baseline in PPG levels and PPG increments were analysed using a mixed-effect model for repeated measurements. ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; PG, plasma glucose; PPG, postprandial plasma glucose

At baseline, the mean of the 7-9-7-point SMPG profile was ~8.7 mmol/L (156.8 mg/dL) in both treatment arms. At 52 weeks, the observed mean of the 7-9-7 point SMPG profile was 8.33 mmol/L (150.1 mg/dL) and 8.44 mmol/L (152.1 mg/dL) with faster aspart and IAsp, respectively. Estimated changes from baseline were −0.41 mmol/L (−7.37 mg/dL) with faster aspart and −0.18 mmol/L (−3.23 mg/dL) with IAsp, significantly favouring faster aspart (treatment difference −0.23 mmol/L [95% CI −0.46;−0.00]; −4.14 mg/dL [95% CI −8.23;−0.06]; *P* = .047 [Table S2 in File S1]).

At 52 weeks, 153/363 participants (42.1%) receiving faster aspart and 127/372 (34.1%) receiving IAsp achieved the 2-hour PPG target of ≤7.8 mmol/L (140 mg/dL). The estimated odds ratio for achieving target PPG was 1.57 (95% CI 1.12;2.20; *P* = .0085). Participants receiving faster aspart were significantly more likely to achieve the 2-hour PPG target of ≤7.8 mmol/L (140 mg/dL) without severe hypoglycaemia (estimated odds ratio 1.47 [95% CI 1.05;2.06]; *P* = .0254; Figure S4 in File S1).

Based on 7-9-7-point SMPG profiles, mean PPG levels over all meals at week 52 were reduced with faster aspart, and after all individual meals except breakfast with IAsp (Figure 3). Significant treatment differences in favour of faster aspart over IAsp were seen in 2-hour PPG and 2-hour PPG increments for all meals except lunch (Figure S5 in File S1).

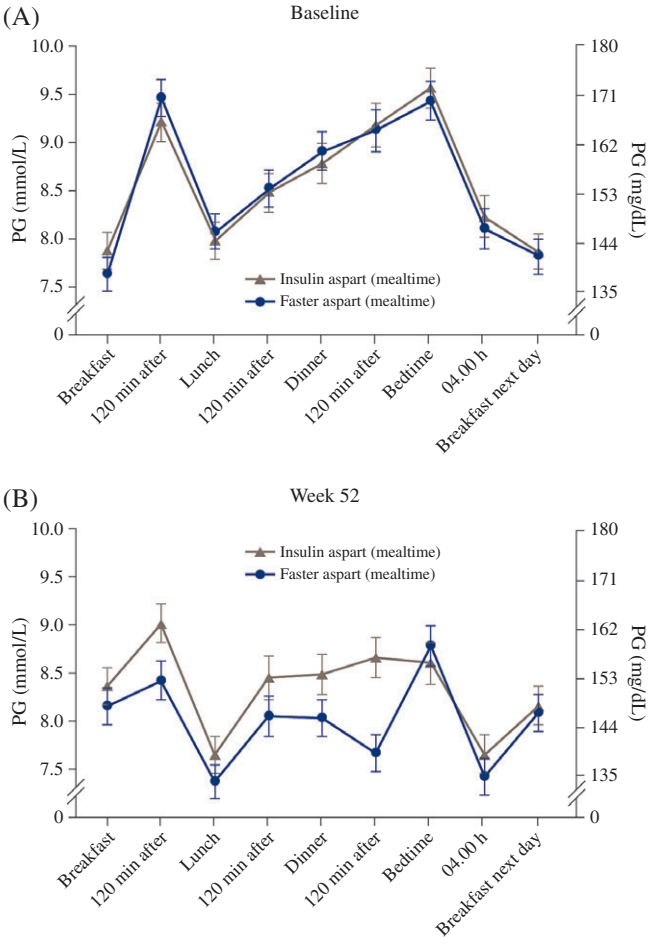

FIGURE 3 Nine-point self-monitored plasma glucose profile at A, baseline and B, week 52. Data are observed mean (SE) for the full analysis set. Faster aspart, fast-acting insulin aspart; PG, plasma glucose

Observed mean 1,5-AG increased from 4.18 to 4.67 μg/mL at 52 weeks with faster aspart and from 3.80 to 4.01 μg/mL with IAsp. Estimated changes from baseline to 52 weeks (+0.50 and +0.15 μg/mL, respectively) were significantly different (treatment difference 0.35 μg/mL [95% CI 0.05;0.65]; *P* = .0243 [Table S2 in File S1]).

Mean observed FPG increased slightly from baseline to week 52, with similar changes in both treatment arms (faster aspart: 8.40 to 8.59 mmol/L [151.4 to 154.7 mg/dL]; IAsp: 7.87 to 8.50 mmol/L [141.8 to 153.2 mg/dL]). The estimated treatment difference at week 52 was 0.07 mmol/L (95% CI −0.39;0.53) or 1.18 mg/dL (95% CI −7.11;9.46) (Table S2 in File S1).

Mean observed body weight increased from 78.6 to 79.7 kg at 52 weeks with faster aspart, and from 80.2 to 81.2 kg with IAsp. The increase in weight was not significantly different between treatment arms (treatment difference 0.13 kg [95% CI −0.38;0.65]).

Median daily bolus insulin doses increased during the 52 weeks, and were 0.38 and 0.39 U/kg at 52 weeks with faster aspart and IAsp, respectively (Table S3 in File S1). The median basal insulin dose remained similar between treatment arms throughout the trial. The median daily total insulin dose increased during the 52 weeks and remained similar between arms, with a basal/bolus dose ratio (%) of 52/48 and 50/50 with faster aspart and IAsp, respectively, at week 52 (Table S3 in File S1).

Overall, 97.7% (377/386) and 99.5% (378/380) of participants experienced treatment-emergent hypoglycaemic episodes with faster aspart and IAsp, respectively, during the 52 weeks. The percentages of participants reporting overall severe or BG-confirmed hypoglycaemic episodes were similar between arms (faster aspart 93.8% [362]; IAsp 97.4% [370]; Table 2), with observed rates of 53.3 and 53.2 events per patient-year of exposure (PYE) for faster aspart and IAsp, respectively. The rate of overall severe or BG-confirmed hypoglycaemic episodes was not statistically significantly different between arms (estimated rate ratio 1.01 [95% CI 0.88;1.15]; Table 2).

Within 1 hour of the start of the meal, there were 441 (2.32% of overall severe or BG-confirmed hypoglycaemic episodes) and 312 (1.62% of overall severe or BG-confirmed hypoglycaemic episodes) severe or BG-confirmed hypoglycaemic episodes in the faster aspart and IAsp arms, respectively. The corresponding event rate was 1.24 per PYE (observed value) for faster aspart and 0.86 per PYE (observed value) for IAsp (Table 2). The rate of severe or BG-confirmed hypoglycaemia within 1 hour of the start of the meal was significantly higher for faster aspart compared with IAsp (estimated rate ratio 1.37 [95% CI 1.06;1.76]; *P* = .0157). There were no statistically significant differences between arms in terms of rate of severe or BG-confirmed hypoglycaemia at later time points in relation to the start of the meal.

No statistically significant differences were observed between treatment arms in the rates of daytime or nocturnal severe or BG-confirmed hypoglycaemia. Daytime rates were 46.9 and 45.7 per PYE with faster aspart and IAsp, respectively (estimated rate ratio 1.03 [95% CI 0.90;1.19]); nocturnal rates were 6.4 and 7.5 per PYE with faster aspart and IAsp, respectively (estimated rate ratio 0.84 [95% CI 0.69;1.01]).

TABLE 2 Treatment-emergent hypoglycaemic episodes

	Faster aspart (*n* = 386)		IAsp (*n* = 380)		
	n (%)	Events (rate per PYE)	*n* (%)	Events (rate per PYE)	Rate ratio (95% CI)
Overall hypoglycaemic episodes					
Severe	37 (9.6)	66 (0.18)	46 (12.1)	82 (0.23)	0.79 (0.46;1.36)
Severe or BG-confirmed	362 (93.8)	19 028 (53.29)	370 (97.4)	19 247 (53.19)	1.01 (0.88;1.15)
Nocturnal hypoglycaemic episodes					
Severe or BG-confirmed	287 (74.4)	2273 (6.4)	297 (78.2)	2708 (7.5)	0.84 (0.69;1.01)
Daytime hypoglycaemic episodes					
Severe or BG-confirmed	358 (92.7)	16 755 (46.9)	370 (97.4)	16 539 (45.7)	1.03 (0.90;1.19)
Severe or BG-confirmed meal-related hypoglycaemic episodes					
Time since start of meal, within:					
1 hour	166 (43.0)	441 (1.24)	148 (38.9)	312 (0.86)	
2 hour	279 (72.3)	2400 (6.72)	284 (74.7)	1971 (5.45)	

Abbreviations: BG, blood glucose; CI, confidence interval; IAsp, insulin aspart; PYE, patient-year of exposure.

Treatment-emergent adverse events were reported in 324 participants (83.9%) receiving faster aspart and in 320 (84.2%) receiving IAsp (event rates per PYE 4.46 and 4.11, respectively), with similar adverse event profiles with both treatments (Table S4 in File S1). Most treatment-emergent adverse events were mild or moderate in severity, with the most common being nasopharyngitis – observed in 128 (33.2%) and 120 (31.6%) participants receiving faster aspart and IAsp, respectively.

Injection-site reactions were reported in 8 participants (2.1%) receiving faster aspart and 5 (1.3%) receiving IAsp (Table S4 in File S1). Seven reactions (5 with faster aspart, 2 with IAsp) were judged as possibly or probably related to bolus insulin, of which 5 were also judged as possibly or probably related to basal insulin.

During the 52-week treatment period, 15 suspected cardiovascular events were referred to an independent external adjudication committee; of these, 5 events in 4 participants were positively adjudicated (Table S5 in File S1). Two events were considered major adverse cardiovascular events (MACE; 1 participant each with stroke and cardiovascular death [both in the IAsp arm]). Two participants in the faster aspart arm had 3 non-MACE events (heart failure, percutaneous revascularization and unstable angina pectoris).

Mean total anti-IAsp (specific and cross-reacting to human insulin) antibody development was similar at baseline and after 12, 26, 40 and 52 weeks of treatment in both treatment arms (Figure S6 in File S1). No clinically significant differences were seen with regard to vital signs, physical examination, safety laboratory assessments (biochemistry, haematology and lipids) or ECG findings.

4 | DISCUSSION

In patients with T1D, the insulin profile induced by exogenous rapid-acting insulin does not fully control glucose excursions induced by meals, and this mismatch can be exacerbated with varying daily schedules.[4] With regular human insulin, patients are advised to inject at least 30 minutes before meals, but many struggle to adhere to this regimen.[19] Rapid-acting insulin analogues improve control of PPG excursions,[20] can be administered immediately before mealtimes[7] and help improve patients' quality of life[21]; however, patients often inject rapid-acting insulin analogues during or after meals,[22–24] even though the action profile of rapid-acting insulin analogues is not fast enough to optimally cover PPG excursions under these circumstances. This has led to development of ultra-fast insulins, for which minor improvements in time of onset can lead to improvements in glycaemic control and treatment flexibility.[8–14] Overall, the 52-week results from onset 1 are consistent with the initial 26 weeks of the trial,[17] in which faster aspart was associated with significant improvements in HbA1c and improved PPG control in a large patient population. The improvement in PPG control observed with faster aspart relative to IAsp is of particular clinical importance, due to the proposed independent link between PPG and diabetes-related complications.[25]

There was no significant difference in overall rates of severe or BG-confirmed hypoglycaemia between treatments; however, as expected, given the faster onset of action with faster aspart,[16] a significantly higher rate of severe or BG-confirmed hypoglycaemia for faster aspart was observed within 1 hour of the start of a meal compared with IAsp. There was no difference at later time points up to 6 hours after starting a meal. Interestingly, there was a trend toward lower incidence of nocturnal hypoglycaemia with faster aspart compared with IAsp.

Strengths of the present trial include its duration, its randomized, double-blind design and the number of participants maintained on therapy for the full 52 weeks. Optimization of basal insulin during the run-in period allowed the impact of the two different bolus regimens to be more clearly evaluated. This is the first trial examining long-term treatment in T1D using faster aspart as part of a basal–bolus insulin regimen. Such long-term studies are able to support safety findings of initial trials and indicate the durability of treatment efficacy, and also better reflect clinical practice. Potential limitations include the artificiality of the meal test for the evaluation of PPG levels/increments and the lack of individualization of insulin doses. Generalizing data from the standardized meal test to a real-world context, in which more variable dietary habits are observed, should therefore be carried out with caution. Improvements in PPG control were, however, consistently reflected in the meal test, SMPG and 1,5-AG results.

In conclusion, the overall safety profile after 52 weeks, including adverse events, immunogenicity, and standard safety variables, was similar between treatment arms and was as expected for IAsp. A statistically significant difference in favour of faster aspart regarding changes in HbA1c level from baseline was maintained over 52 weeks. Approaching an insulin profile closer to physiological insulin secretion with faster aspart achieves lower PPG and HbA1c levels compared with IAsp, with these clinical improvements achieved alongside increased flexibility in mealtime insulin administration in patients with T1D.

ACKNOWLEDGMENTS

The onset 1 trial, including study design, data collection, analysis and interpretation, was funded by Novo Nordisk A/S. Medical writing and submission support were provided by Liam Gillies PhD and Helen Marshall of Watermeadow Medical – an Ashfield company, part of UDG Healthcare PLC, funded by Novo Nordisk A/S.

Conflict of interests

C.M.: *Advisory panel*: Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme Ltd., Eli Lilly and Company, Novartis, AstraZeneca LP, Jansen Pharmaceuticals, Hanmi Pharmaceuticals, Intrexon, Boehringer Ingelheim; *research support:* Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme Ltd., Boehringer Ingelheim; *speakers' bureau*: Novo Nordisk, Sanofi-Aventis, Merck Sharp & Dohme, Eli Lilly and Company, Novartis, AstraZeneca. B.B.: *Advisory panel*: Novo Nordisk, Sanofi, Adocia; *consultant:* Medtronic, Sanofi, Novo Nordisk; *research support:* Abbott, BI/lilly, BD, DexCom, Janssen, Lexicon, Medtronic, Novo Nordisk, Sanofi, Senseonics; *speakers' bureau*: AstraZeneca, Insulet, Janssen, Medtronic, Novo Nordisk, Sanofi; *stocks/shareholder*: Glytec. E.F.: *Advisory panel*: AstraZeneca, Boehringer Ingelheim, Merck Sharp & Dohme, Novo Nordisk; *speakers' bureau*: AstraZeneca/BMS, Boehringer Ingelheim, Eli Lilly, Merck, Merck Sharp & Dohme, Novo Nordisk, Servier. A.P.-T.: *Advisory panel*: AstraZeneca, DexCom, Lilly, Merck, Novo Nordisk, Sanofi (no direct or indirect reimbursement); *research support:* DexCom, Janssen, Lilly, Novo Nordisk, Sanofi (no direct or indirect reimbursement); *stocks/shareholder*: Esperion, Novo Nordisk, Ionis, Gilead. L.R.: *Advisory panel*: Eli Lilly, Novo Nordisk. T.G.: *Employee:* Novo Nordisk; *stocks/shareholder*: Novo Nordisk. A.B.O.: *Employee:* Novo Nordisk; *stocks/shareholder*: Novo Nordisk. D.R.-J.: *Advisory panel*: AstraZeneca, Sanofi-Aventis, Lilly, Novo Nordisk; *board member*: AstraZeneca, Sanofi-Aventis, Lilly, Novo Nordisk; *consultant:* AstraZeneca, Sanofi-Aventis, Lilly, Novo Nordisk; *research support:* AstraZeneca, Sanofi-Aventis, Novartis, Novo Nordisk; *speakers' bureau*: AstraZeneca, Sanofi-Aventis, Lilly, Novo Nordisk, Janssen, Takeda, Boehringer Ingelheim.

Author contributions

C.M., B.B., E.F., A.P.-T., L.R., T.G., A.B.O. and D.R.-J. all provided critical input into revised versions of the manuscript and approved the final manuscript for submission. T.G. carried out the statistical analysis.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

How to cite this article: Mathieu C, Bode BW, Franek E, et al. Efficacy and safety of fast-acting insulin aspart in comparison with insulin aspart in type 1 diabetes (onset 1): A 52-week, randomized, treat-to-target, phase III trial. *Diabetes Obes Metab*. 2018;20:1148–1155. https://doi.org/10.1111/dom.13205