Efficacy and safety of fast-acting insulin aspart compared with insulin aspart in combination with insulin degludec in Japanese adults with type 1 diabetes: a subgroup analysis of the randomized onset 8 trial

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Abstract. This study aimed to confirm the efficacy and safety of mealtime and post-meal fast-acting insulin aspart versus insulin aspart, both with basal insulin degludec, in Japanese patients with type 1 diabetes. This was a subgroup analysis of onset 8, a randomized multicenter, treat-to-target trial of mealtime fast-acting insulin aspart (subgroup \( n = 73 \)), mealtime insulin aspart (\( n = 83 \)), or open-label post-meal fast-acting insulin aspart (\( n = 89 \)), all for 26 weeks. Change from baseline in HbA\(_1c\) was considered the primary endpoint. After 26 weeks, the estimated treatment difference (ETD, 95% CI) for change from baseline in HbA\(_1c\) between mealtime fast-acting insulin aspart or post-meal fast-acting insulin aspart vs. insulin aspart was 0.01% (–0.16;0.19) and 0.10% (–0.07;0.27), respectively. Following a standardized meal test, ETD for change from baseline in postprandial glucose (PPG) increment at 1 hour was –16.91 mg/dL (–32.15;–1.68) for mealtime fast-acting insulin aspart and 40.16 mg/dL (25.46;54.87) for post-meal fast-acting insulin aspart, both versus insulin aspart. Mean self-measured blood glucose 1-hour PPG increments also showed a trend towards improved PPG control with mealtime fast-acting insulin aspart versus insulin aspart. Rates of overall hypoglycemia (35.56, 37.72 and 38.75 per patient-year of exposure with mealtime fast-acting insulin aspart, post-meal fast-acting insulin aspart and insulin aspart, respectively) and meal-related hypoglycemia were similar between treatment arms. Consistent with findings of onset 8, this analysis confirmed mealtime and post-meal fast-acting insulin aspart provided effective HbA\(_1c\) and PPG control versus insulin aspart, with similar safety profiles, in Japanese adults with type 1 diabetes.

Key words: Fast-acting insulin, Japan, Type 1 diabetes

FOR MANY PEOPLE with type 1 diabetes (T1D), basal–bolus insulin therapy is used to achieve glycemic control. For non-pregnant adults with diabetes, the Japanese Diabetes Society recommends a target HbA\(_1c\) value of <6.0% (42 mmol/mol) to attain normoglycemia, and <7.0% (53 mmol/mol) to prevent the development and progression of diabetes-associated micro- and macro-vascular complications [1]. As postprandial glucose (PPG) levels contribute markedly to overall HbA\(_1c\) control in patients approaching their glycemic target [2, 3], PPG excursions should be minimized, but this remains challenging in clinical practice [4]. Controlling PPG is particularly important for attaining glycemic targets in Asian (versus Caucasian) patients [5-7], which might be attributed to the high-carbohydrate, low-fat diet typically consumed in Asian countries [8]. Consequently, Asian people with diabetes may have to rely more on the prandial component of their basal–bolus insulin regimen to improve overall glycemic control compared with their Caucasian counterparts.

The aim of basal–bolus insulin therapy is to imitate physiological insulin secretion. Although rapid-acting insulin analogs (RAIAs), such as insulin aspart (IAsp), insulin glulisine and insulin lispro, improve PPG control versus regular human insulin when used in a basal–bolus
regimen, the time–action profiles of these RAIAs do not mimic the physiological insulin secretion pattern in healthy individuals. A new generation of ultra-fast-acting mealtime insulins, which include novel modifications to insulin formulations, provide accelerated absorption of insulin thereby improving insulin time–action and PPG-lowering profiles versus RAIAs [9-13].

Fast-acting insulin aspart (faster aspart), which has recently been approved for the treatment of diabetes in Japan, is an ultra-fast-acting mealtime insulin that is more rapidly absorbed into the bloodstream and exerts a glucose-lowering effect greater and earlier than conventional IAsp in adults with T1D [14, 15].

In a phase 3 trial (onset 1), faster aspart improved glycemic control versus IAsp when administered as part of a basal–bolus regimen with insulin detemir in adults with T1D [16]. Mealtime faster aspart was superior to IAsp after 26 weeks’ treatment with regards to improvements in HbA1c and a reduction in the 2-h PPG increment after a standardized meal test [16]. The reported efficacy of faster aspart was maintained after 52 weeks of treatment in the same trial population [17]. In a phase 3 trial (onset 8) in adults with T1D receiving insulin degludec (an ultra-long-acting basal insulin), both mealtime and post-meal faster aspart provided non-inferior HbA1c control versus mealtime IAsp (estimated treatment difference [ETD 95% CI]: –0.02% [–0.11;0.07] and 0.10% [0.004;0.19], respectively), with mealtime faster aspart providing a superior reduction in 1-h PPG increment compared with mealtime IAsp [18]. In both trials, safety profiles and overall rate of severe or blood glucose (BG)-confirmed hypoglycemia were similar between faster aspart and IAsp [16, 18].

The aim of this analysis was to confirm the efficacy and safety of faster aspart versus IAsp, both with basal insulin degludec, in the Japanese subgroup of the onset 8 trial.

Materials and Methods

Trial design

This study was a subgroup analysis of the Japanese population included in a phase 3b, multicenter, active-controlled, randomized, parallel-group, 26-week study (onset 8; ClinicalTrials.gov: NCT02500706) that evaluated the efficacy and safety of mealtime or post-meal faster aspart versus mealtime IAsp, both in combination with insulin degludec, in participants with T1D [18]. The design, inclusion/exclusion criteria and results of the primary trial have been reported previously [18]. Briefly, after an 8-week run-in period allowing for titration of basal insulin, participants, aged ≥20 years, with T1D, a body mass index (BMI) ≤35.0 kg/m² and an HbA1c ≤9.5% (80 mmol/mol), were randomized (1:1:1) to double-blind mealtime faster aspart, mealtime IAsp treatment or open-label post-meal faster aspart, all for 26 weeks. Faster aspart and IAsp were administered in a basal–bolus regimen in conjunction with once-daily insulin degludec. Participants were instructed to record the date, time and value of all SMBG measurements relating to 4-, 7-, and 9-point profiles with a supplied BG meter (Abbott Precision Neo or Precision; Abbott Laboratories, Chicago, Illinois, USA). Meal tests were carried out to measure 30-min to 4-hour PPG at Week 0 (randomization) and Week 26, using a standardized meal equivalent to 78 grams of carbohydrate. Follow-up assessments occurred 7 and 30 days after treatment. The protocol for this research was approved by Ethics Committees for the institutions involved in the trial and the trial was conducted in accordance with the Declaration of Helsinki and International Conference on Harmonization of Good Clinical Practice.

Assessments

The primary endpoint in onset 8 was change in HbA1c from baseline to Week 26 after randomization. Secondary endpoints included change from baseline to Week 26 after randomization in 30-min, 1-, 2, 3- and 4-h PPG and PPG increment (meal test), 1.5-anhydroglucitol (1,5-AG), fasting plasma glucose (FPG), mean 7-9-7-point SMBG profile, and PPG and PPG increment (mean at each meal and over all meals); insulin dose (basal, bolus, and total daily insulin dose [units and units/kg]), participants (%) achieving HbA1c targets (<7.0% [53 mmol/mol]) and HbA1c targets (<7.0% [53 mmol/mol]) without severe hypoglycemia (in conjunction with minimal weight gain), and participants achieving overall 1-hour PPG targets (<140 mg/dL [7.8 mmol/L]). Safety endpoints included treatment-emergent adverse events (TEAEs), treatment-emergent hypoglycemic episodes (overall and 1, 1–2, 2–3, and 2–4, 3–4 hours after a meal) and body weight. Hypoglycemia was defined as treatment-emergent if the onset of the episode occurred on or after the first day of treatment administration post-randomization and no later than 1 day after the last day of treatment. Severe hypoglycemia was defined according to the American Diabetes Association classification [19], and BG-confirmed hypoglycemia was defined as a plasma glucose value <56 mg/dL (Novo Nordisk A/S definition), with or without symptoms consistent with hypoglycemia.

Statistical methods

The full analysis set was used to describe the efficacy endpoints, and all results shown are those from a subset of all randomized Japanese participants over the entire...
trial period. This included data which were collected after participants discontinued trial product prematurely (in-trial observation period). The safety analysis set, which included those receiving at least 1 dose of IAsp or faster aspart, was used to describe the safety endpoints.

The statistical methods for each endpoint have been described previously [18]. Descriptive statistics based on the last available measurement are presented to summarize measurements at Week 26 for efficacy endpoints and body weight.

### Results

#### Trial population

Of the 1,025 randomized participants in the onset 8 trial, 245 were Japanese and included in this analysis. 73, 89, and 83 participants were randomized to mealtime faster aspart, post-meal faster aspart, and mealtime IAsp treatment, respectively, and all were exposed to their study medication. Of the Japanese population, 240 participants (98.0%) completed the trial period and 235 participants (95.9%) completed treatment without premature discontinuation (Supplementary Fig. 1). Baseline characteristics were similar between the three treatment arms (Table 1).

#### Efficacy

**Change in HbA$_{1c}$**

Mean HbA$_{1c}$ over time in the Japanese subgroup is shown in Fig. 1. During the run-in period, a reduction in mean HbA$_{1c}$ from 8.02% (64.18 mmol/mol) to 7.41% (57.44 mmol/mol) was observed for participants subsequently randomized to mealtime faster aspart; from 7.89% (62.78 mmol/mol) to 7.27% (55.97 mmol/mol) for those randomized to post-meal faster aspart; and from 7.97% (63.56 mmol/mol) to 7.34% (56.73 mmol/mol) for those randomized to mealtime IAsp treatment. After 26-weeks’ treatment, mean HbA$_{1c}$ was 7.22% (55.42 mmol/mol), 7.11% (54.25 mmol/mol), and 7.26% (55.85 mmol/mol) in the mealtime faster aspart, mealtime IAsp, and post-meal faster aspart arms, respectively. Compared with mealtime IAsp, the ETD (95% CI) in change from baseline in HbA$_{1c}$ was 0.01% (–0.16; 0.19), 0.15 mmol/mol (–1.78; 2.09) with mealtime faster aspart, and 0.10% (–0.07; 0.27), 1.07 mmol/mol (–0.77; 2.92) with faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; n, number of participants; SD, standard deviation.

### Table 1  Baseline characteristics

| Parameter                          | Faster aspart (mealtime) $(n = 73)$ | Faster aspart (post-meal) $(n = 89)$ | Insulin aspart (mealtime) $(n = 83)$ | Total $(n = 245)$ |
|------------------------------------|-------------------------------------|--------------------------------------|-------------------------------------|------------------|
| Age, years                         | 46.08 (11.88)                      | 49.83 (15.21)                       | 47.51 (12.16)                      | 47.93 (13.31)    |
| Gender, n (% male)                 | 36 (49.3)                          | 45 (50.6)                           | 33 (39.8)                          | 114 (46.5)       |
| Body weight, kg                    | 64.73 (11.86)                      | 62.33 (11.12)                       | 61.00 (11.45)                      | 62.60 (11.51)    |
| BMI, kg/m$^2$                      | 23.80 (3.03)                       | 23.40 (3.52)                        | 22.99 (3.32)                       | 23.38 (3.31)     |
| Duration of diabetes, years        | 14.66 (10.57)                      | 12.57 (8.24)                        | 14.83 (9.61)                       | 13.96 (9.47)     |
| HbA$_{1c}$, %                      | 7.41 (0.61)                        | 7.34 (0.63)                         | 7.27 (0.60)                        | 7.34 (0.61)      |
| mmol/mol                           | 57.44 (6.64)                       | 56.73 (6.93)                        | 55.97 (6.53)                       | 56.69 (6.71)     |
| FPG, mg/dL                         | 131.03 (36.06)                     | 126.32 (34.05)                      | 124.47 (42.69)                     | 127.10 (37.70)   |
| mmol/L                             | 7.27 (2.00)                        | 7.01 (1.89)                         | 6.91 (2.37)                        | 7.05 (2.09)      |
| Bolus adjusting method, n (% carbohydrate counting) | 21 (28.8)                          | 28 (31.5)                           | 25 (30.1)                          | 74 (30.2)        |

Data are presented as means (SD) unless otherwise stated. BMI, body mass index; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; n, number of participants; SD, standard deviation.

![Fig. 1 Mean HbA$_{1c}$ over time](image-url)

Error bars: ±standard error. All available information, regardless of treatment discontinuation, was used. Faster aspart, fast-acting insulin aspart.
The percentages of participants achieving HbA1c <7.0% (53 mmol/mol) at Week 26 were similar between treatment arms (38.4% in the mealtime faster aspart arm, 36.1% in the mealtime IAsp arm and 39.3% in the post-meal faster aspart arm) (Supplementary Table 1).

Meal test

PPG increments after a standardized meal test at baseline and Week 26 are shown in Fig. 2. Error bars: ±standard error. Mealtime faster aspart and insulin aspart dosed immediately before the liquid meal; post-meal faster aspart dosed 20 min after the start of the liquid meal. All available information, regardless of treatment discontinuation, was used. Faster aspart, fast-acting insulin aspart; PPG, postprandial glucose.

For change from baseline in PPG, ETDs (95% CI) for mealtime faster aspart versus IAsp at 30 min and 1 h were −23.13 mg/dL (−38.20;−8.07) and −24.23 mg/dL (−43.55;−4.91), respectively. For the post-meal faster aspart versus IAsp comparison, ETDs (95% CI) at 30 min and 1 h were 28.18 mg/dL (13.84;42.53) and 43.63 mg/dL (25.09;62.18), respectively.

SMBG

At baseline and Week 26, mean observed nine-point SMBG profiles were similar between treatments (Supplementary Fig. 2). The ETDs (95% CI) for change from baseline to Week 26 in 1-h PPG increment (SMBG) for mealtime faster aspart versus IAsp were −19.79 mg/dL (−34.77;−4.81) at breakfast and −14.92 mg/dL (−25.35;−4.49) over all meals. Estimated differences in 1-h PPG increment (SMBG) (95% CI) between mealtime faster aspart and IAsp were smaller at lunch (−10.95 mg/dL [−27.55;5.64]) and the main evening meal (−8.37 mg/dL [−26.12;9.37]). For the post-meal faster aspart versus IAsp comparison, ETDs (95% CI) for change from baseline in 1-h PPG increment were 7.86 mg/dL (−6.37;22.08) at breakfast, 9.07 mg/dL (−6.73;24.87) at lunch, 27.99 mg/dL (11.24;44.74) at the main evening meal and 14.29 mg/dL (4.47;24.12) over all meals (Supplementary Table 1).

Change from baseline in 1-hour PPG (SMBG) for any individual meal (breakfast, lunch, evening meal) or the mean over all meals was similar between mealtime faster aspart versus IAsp (Supplementary Table 1). For post-meal faster aspart versus IAsp, the ETD for change from baseline in 1-h PPG (95% CI) was 21.70 mg/dL (5.64;37.76) for the main evening meal, while ETDs were smaller after breakfast (1.26 mg/dL [−14.28;16.79]), lunch (4.17 mg/dL [−10.57;18.91]) and over all meals (8.61 mg/dL [−2.31;19.53]).

The percentage of participants achieving 1-h PPG ≤140 mg/dL (7.8 mmol/L) (SMBG) at Week 26 was 17.8%, 13.3% and 5.6% in the mealtime faster aspart, mealtime IAsp and post-meal faster aspart arm, respectively (Supplementary Table 1).

Other secondary endpoints

Change from baseline in 1,5-AG was similar between treatment arms (Supplementary Table 1). Change from baseline in FPG was also similar for mealtime or post-meal faster aspart and IAsp (Supplementary Table 1).

Insulin dosing

There were similar increases in mean and median daily bolus insulin doses from baseline to Week 26 with faster aspart (mealtime and post-meal) and IAsp (Supplementary Table 2). With regards to the basal/bolus splits at Week 26, all treatment arms reported a greater proportion of bolus, compared with basal insulin.

Post-meal faster aspart.

HbA1c responders

The percentages of participants achieving HbA1c <7.0% (53 mmol/mol) at Week 26 were similar between treatment arms (38.4% in the mealtime faster aspart arm, 36.1% in the mealtime IAsp arm and 39.3% in the post-meal faster aspart arm) (Supplementary Table 1).
safety of mealtime or post-meal faster aspart, both in

ences were seen with regard to vital signs, BMI, physical

examination, safety laboratory assessments (biochemis‐

try counting to adjust their bolus dose compared with

25.1

kg/m²), were older (48 vs. 41 years), and had a shorter
diabetes duration (14 vs. 17 years) at baseline [18]. A
lower percentage of Japanese participants used carbohy‐
drate counting to adjust their bolus dose compared with
the overall onset 8 population (30.2 vs. 41.8%). All other
demographic and baseline characteristics were similar
between the Japanese and entire trial populations.

Mealtime faster aspart was effective in reducing PPG
excursions in the Japanese participants, consistent with
the results from the overall onset 8 trial population and
the wider faster aspart clinical trial program [16, 18, 20-22]. In this analysis, the treatment difference for
change from baseline in 1-h-PPG increment (following a
standardized meal test) for mealtime faster aspart versus
IAsp was –16.91 mg/dL (95% CI –32.15;–1.68); –0.94
mmol/L (95% CI –1.78;–0.09). This was similar to that

combinations with insulin degludec, in the Japanese sub‐
group of the onset 8 trial. onset 8 demonstrated that
mealtime and post-meal faster aspart was non-inferior to
mealtime IAsp in respect of changes in HbA₁c after 26
weeks’ treatment in adults with T1D [18]. There were
similar estimated mean treatment differences for change
from baseline in HbA₁c across the three treatment arms
in the Japanese subgroup, and no noteworthy differences
between the Japanese population and the entire trial popu‐
lation, mealtime –0.02% [–0.11;0.07] and post-meal
0.10% [–0.07;0.27]; onset 8 overall popu‐
lation (18). There were
equally across the three treatment arms
respective), as were the rates 0–1, 1–2, 2–3 and 3–4 h
after a meal.

Change in body weight 26 weeks after randomization
was similar between treatment arms (1.24 kg, 1.21 kg
and 1.34 kg, with mealtime faster aspart, post-meal faster
aspart, and IAsp, respectively).

The proportion of participants who reported TEAEs
was similar across treatments (Supplementary Table 3).
The majority of TEAEs were mild in severity and judged
to be unlikely related to the randomized trial product.
Two participants reported injection site-reactions during
the trial, one in the post-meal faster aspart arm and one
in the IAsp arm. Allergic reactions were low in number
and occurred equally across the three treatment arms
(Supplementary Table 3). No clinically significant differ‐
ences were seen with regard to vital signs, BMI, physical
examination, safety laboratory assessments (biochemis‐
try, hematology, lipids and urinalysis), electrocardio‐
grams, and eye examination.

Discussion

This post hoc analysis investigated the efficacy and
safety of mealtime or post-meal faster aspart, both in

| Safety analysis set. Hypoglycemia was defined as treatment-emergent if the onset of the episode occurred on or after the first day of
treatment administration post-randomization and no later than 1 day after the last day of treatment. Severe hypoglycemia was defined
glucose values
<56 mg/dL (Novo Nordisk A/S definition), with or without symptoms consistent with hypoglycemia. %, percentage of participants; BG,
blood glucose; E, events; N, number; R, rate per patient-year of exposure.

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, et al. (2013) Hypoglycemia and diabetes: a report of a workgroup of the
American Diabetes Association and the Endocrine Society. Diabetes Care 36: 1384–1395.

Table 2  Treatment-emergent hypoglycemia

| Treatment-emergent hypoglycemia | Faster aspart (mealtime) | Faster aspart (post-meal) | Insulin aspart (mealtime) |
|---------------------------------|-------------------------|--------------------------|--------------------------|
|                                 | N  | %  | E  | R  | N  | %  | E  | R  | N  | %  | E  | R  |
| Severe                          | 4  | 5.5| 4  | 0.11| 4  | 4.5| 4  | 0.09| 6  | 7.2| 6  | 0.15|
| Severe or BG-confirmed          | 68 | 93.2| 1,302| 35.56| 81 | 91.0| 1,659| 37.72| 75 | 90.4| 1,562| 38.75|
| Meal-related severe or BG-confirmed hypoglycemia | | |
| Within 1 h after a meal         | 13 | 17.8| 29 | 0.79| 23 | 25.8| 41 | 0.93| 23 | 27.7| 37 | 0.92|
| Between 1 and 2 h after a meal  | 30 | 41.1| 80 | 2.18| 29 | 32.6| 89 | 2.02| 32 | 38.6| 136| 3.37|
| Between 2 and 3 h after a meal  | 30 | 41.1| 138| 3.77| 43 | 48.3| 164| 3.73| 39 | 47.0| 162| 4.02|
| Between 3 and 4 h after a meal  | 38 | 52.1| 161| 4.40| 53 | 59.6| 165| 3.75| 41 | 49.4| 188| 4.66|

1. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, et al. (2013) Hypoglycemia and diabetes: a report of a workgroup of the
American Diabetes Association and the Endocrine Society. Diabetes Care 36: 1384–1395.
reported in onset 8, where superiority to IAsp was confirmed (ETD –16.24 mg/dL [95% CI –24.42;–8.05]; –0.90 mmol/L [95% CI: –1.36;–0.45]; p < 0.001 for superiority). Change from baseline in 1-h PPG increment was in favor of IAsp compared with post-meal faster aspart in the Japanese subgroup (ETD 40.16 mg/dL [95% CI 25.46;54.87]; 2.23 mmol/L [95% CI 1.41;3.04]). This was consistent with the results of the overall onset 8 trial population (ETD 18.26 mg/dL [10.08;26.45]; 1.01 mmol/L [95% CI 0.56;1.47]), however this change was greater in the Japanese subgroup, potentially due to the lower 1-h PPG increments reported for the post-meal faster aspart arm at the baseline meal test. Improved PPG control with mealtime faster aspart versus IAsp, indicated by changes in SMBG-derived 1-h PPG increments, was observed in both the Japanese and entire trial populations.

The mean bolus insulin dose and the total insulin dose in all three treatment arms increased over the trial period in both the Japanese subgroup and overall onset 8 population. In the overall onset 8 population, the basal/bolus splits at Week 26 was 45%/55% in both mealtime and post-meal faster aspart arms, and 43%/57% in the IAsp arm. In comparison, the Japanese subgroup had a higher percentage of bolus insulin, with basal/bolus splits of 37%/63% in the mealtime faster aspart arm, and 38%/62% in the post-meal faster aspart and IAsp arms.

Rates of severe or BG-confirmed hypoglycemia were similar between the faster aspart (mealtine or post-meal) and IAsp arms in both the Japanese subgroup and entire trial population. Rates of meal-related severe or BG-confirmed hypoglycemia were also similar between treatments in this analysis. However, in the entire onset 8 population, a significant reduction in meal-related hypoglycemia was observed in favor of mealtime faster aspart 3–4 h after a main meal [18], potentially reflecting a shift in the concentration–time curve, for faster aspart relative to IAsp, to the left [14].

All participants in onset 8 received a once-daily injection of insulin degludec as the basal component of the basal–bolus regimen. There was an improvement in glycemic control with weekly titration of insulin degludec over the 8-week run-in period in both the Japanese subgroup and the entire trial population. Compared with conventional long-acting basal insulins, insulin degludec had been shown previously to provide similar glycemic control, with significantly reduced insulin dose and hypoglycemia in Japanese adults with T1D [23].

The onset 8 trial benefits from a high proportion of participants completing the study, individual optimization of basal insulin dose during the run-in period and the inclusion of a post-meal dosing arm for faster aspart. One limitation was that participants received the same meal test insulin dose (0.1 U/kg) without adjusting for individual insulin:carbohydrate ratio, so it was therefore only an estimation of the participant’s normal dose. Limitations of the subgroup analysis were that the standardized meal test may not have accurately represented the typical Asian diet, and that there were relatively small numbers of participants in each treatment arm.

**Conclusion**

This analysis confirmed that mealtime and post-meal faster aspart provided effective HbA\textsubscript{1c} control in Japanese adults with T1D. Consistent with the onset 8 trial, mealtime faster aspart also provided slightly improved control over early PPG excursions when compared with mealtime IAsp in this population. Faster aspart and IAsp were similar with regards to safety, and faster aspart did not increase the risk of hypoglycemia compared with IAsp.

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Data Availability

The subject-level analysis datasets for the research presented in the publication are available from the corresponding author on reasonable request.
### Supplementary Table 1  Summary of supportive endpoints

| HbA1c responders 26 weeks after randomization, % | Faster aspart (mealtime) | Faster aspart (post-meal) | Insulin aspart (mealtime) | Treatment comparison | Estimated OR [95% CI] |
|---|---|---|---|---|---|
| HbA1c <7.0% (58 mmol/mol) | 38.4 | 39.3 | 36.1 | Mealtime faster aspart vs. IAsp | 1.51 (0.71;3.22) |
| HbA1c <7.0% (58 mmol/mol) without severe hypoglycemia | 35.6 | 36.0 | 34.9 | Mealtime faster aspart vs. IAsp | 1.39 (0.65;3.00) |
| HbA1c <7.0% (58 mmol/mol) without severe hypoglycemia and minimal weight gain† †† | 26.0 | 21.3 | 18.1 | Mealtime faster aspart vs. IAsp | 2.34 (0.99;5.55) |

| PPG responders 26 weeks after randomization, % | Faster aspart (mealtime) | Faster aspart (post-meal) | Insulin aspart (mealtime) | Treatment comparison | Estimated OR [95% CI] |
|---|---|---|---|---|---|
| PPG ≤140 mg/dL (7.8 mmol/L) † † † | 17.8 | 5.6 | 13.3 | Mealtime faster aspart vs. IAsp | 1.82 (0.72;4.55) |

| 30-min PPG increment (meal test) | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | −19.04 | 23.23 | −2.67 | Mealtime faster aspart vs. IAsp | −16.37 (−26.33;−6.40) |
| mmol/L | −1.06 | 1.29 | −0.15 | Mealtime faster aspart vs. IAsp | −0.91 (−1.46;−0.36) |

| 1-h PPG increment (meal test) | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | −27.79 | 29.29 | −10.88 | Mealtime faster aspart vs. IAsp | −16.91 (−32.15;−1.68) |
| mmol/L | −1.54 | 1.63 | −0.60 | Mealtime faster aspart vs. IAsp | −0.94 (−1.78;−0.09) |

| Mean 7-9-7-point SMBG profiles | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | −5.52 | −2.89 | −1.96 | Mealtime faster aspart vs. IAsp | −3.55 (−13.50;6.39) |
| mmol/L | −0.31 | −0.16 | −0.11 | Mealtime faster aspart vs. IAsp | −0.93 (−10.47;8.61) |

| 1-h PPG (SMBG, all meals) | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | −13.16 | 6.85 | −1.76 | Mealtime faster aspart vs. IAsp | −11.40 (−22.93;0.13) |
| mmol/L | −0.73 | 0.38 | −0.10 | Mealtime faster aspart vs. IAsp | −0.63 (−1.27;0.01) |

| 1-h PPG increment (SMBG, all meals) | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | −18.96 | 10.25 | −4.04 | Mealtime faster aspart vs. IAsp | −14.92 (−25.35;−4.49) |
| mmol/L | −1.05 | 0.57 | −0.22 | Mealtime faster aspart vs. IAsp | −0.83 (−1.41;−0.25) |

| 1,5-AG | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| μg/mL | 0.30 | −0.19 | −0.05 | Mealtime faster aspart vs. IAsp | 0.34 (−0.36;1.05) |

| FPG | Faster aspart (mealtime) Estimated values | Faster aspart (post-meal) Estimated values | Insulin aspart (mealtime) Estimated values | Treatment comparison | ETD [95% CI] |
|---|---|---|---|---|---|
| mg/dL | 5.07 | 19.03 | 17.29 | Mealtime faster aspart vs. IAsp | −12.22 (−27.1;1.64) |
| mmol/L | 0.28 | 1.06 | 0.96 | Mealtime faster aspart vs. IAsp | −0.68 (−1.50;0.15) |

All available information, regardless of treatment discontinuation, was used. SMBG measurements are plasma-equivalent glucose values.

† Subjects without an HbA1c measurement at Week 26 were treated as non-responders.

†† Subjects without an HbA1c measurement at Week 26 or without body weight measurement at Week 26 were treated as non-responders.

† † † Subjects without an overall mean 1-hour PPG at Week 26 were treated as non-responders.

1,5-AG, 1-5, anhydroglucitol; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; IAsp, insulin aspart; OR, odds ratio; PPG, postprandial glucose; SMBG, self-measured blood glucose.
### Supplementary Table 2  Daily bolus, basal, and total insulin dose (actual) and basal/bolus ratio at Week 1 and Week 26

| Visit (week) | Treatment | Insulin dose | N | Mean | SD | Median | Min | Max |
|-------------|-----------|--------------|----|------|----|--------|-----|-----|
|             |           | Bolus dose (all meals), U |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 70 | 25.9 | 10.4 | 24.3 | 7.0 | 53.7 |
|             | Faster aspart (post) | 86 | 24.6 | 9.7 | 22.0 | 6.0 | 54.7 |
|             | Insulin aspart (meal) | 81 | 22.5 | 9.3 | 22.0 | 6.0 | 54.0 |
|             | Faster aspart (meal) | 70 | 31.3 | 14.5 | 30.0 | 7.3 | 80.0 |
| Week 26†    | Faster aspart (post) | 83 | 29.9 | 13.9 | 28.0 | 5.0 | 82.3 |
|             | Insulin aspart (meal) | 76 | 27.5 | 13.4 | 25.5 | 8.0 | 84.0 |
|             | Basal dose, U |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 72 | 18.6 | 7.8 | 17.5 | 5.0 | 43.0 |
|             | Faster aspart (post) | 87 | 18.8 | 9.4 | 17.0 | 4.0 | 45.0 |
|             | Insulin aspart (meal) | 82 | 17.5 | 9.2 | 15.5 | 4.0 | 41.0 |
|             | Faster aspart (meal) | 71 | 18.6 | 8.3 | 18.0 | 6.0 | 48.0 |
| Week 26†    | Faster aspart (post) | 84 | 18.5 | 9.7 | 16.0 | 2.0 | 52.0 |
|             | Insulin aspart (meal) | 78 | 17.2 | 9.2 | 15.0 | 5.0 | 41.0 |
|             | Total insulin dose, U |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 70 | 44.4 | 14.9 | 42.3 | 18.0 | 93.0 |
|             | Faster aspart (post) | 86 | 43.3 | 16.0 | 40.8 | 13.3 | 87.7 |
|             | Insulin aspart (meal) | 81 | 40.2 | 15.6 | 38.0 | 16.0 | 86.0 |
|             | Faster aspart (meal) | 70 | 49.7 | 19.2 | 48.0 | 16.3 | 113.0 |
| Week 26†    | Faster aspart (post) | 83 | 48.2 | 20.7 | 43.7 | 10.7 | 120.3 |
|             | Insulin aspart (meal) | 76 | 44.7 | 19.3 | 42.0 | 16.0 | 117.0 |
|             | Bolus dose (all meals), U/kg |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 70 | 0.405 | 0.159 | 0.393 | 0.12 | 0.77 |
|             | Faster aspart (post) | 86 | 0.395 | 0.139 | 0.383 | 0.10 | 0.74 |
|             | Insulin aspart (meal) | 81 | 0.368 | 0.133 | 0.356 | 0.11 | 0.81 |
|             | Faster aspart (meal) | 70 | 0.471 | 0.194 | 0.476 | 0.14 | 0.94 |
| Week 26†    | Faster aspart (post) | 84 | 0.463 | 0.173 | 0.428 | 0.09 | 0.92 |
|             | Insulin aspart (meal) | 76 | 0.434 | 0.183 | 0.394 | 0.15 | 1.22 |
|             | Basal dose, U/kg |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 72 | 0.286 | 0.102 | 0.269 | 0.07 | 0.60 |
|             | Faster aspart (post) | 87 | 0.296 | 0.121 | 0.287 | 0.07 | 0.65 |
|             | Insulin aspart (meal) | 82 | 0.278 | 0.114 | 0.263 | 0.08 | 0.54 |
|             | Faster aspart (meal) | 71 | 0.277 | 0.101 | 0.257 | 0.13 | 0.52 |
| Week 26†    | Faster aspart (post) | 84 | 0.283 | 0.118 | 0.257 | 0.04 | 0.56 |
|             | Insulin aspart (meal) | 78 | 0.265 | 0.107 | 0.239 | 0.08 | 0.52 |
|             | Total insulin dose, U/kg |        |      |    |        |     |     |
| Week 1      | Faster aspart (meal) | 70 | 0.691 | 0.197 | 0.662 | 0.33 | 1.12 |
|             | Faster aspart (post) | 86 | 0.691 | 0.202 | 0.674 | 0.25 | 1.26 |
|             | Insulin aspart (meal) | 81 | 0.647 | 0.180 | 0.614 | 0.37 | 1.21 |
|             | Faster aspart (meal) | 70 | 0.746 | 0.224 | 0.724 | 0.30 | 1.35 |
| Week 26†    | Faster aspart (post) | 83 | 0.745 | 0.239 | 0.711 | 0.20 | 1.37 |
|             | Insulin aspart (meal) | 76 | 0.699 | 0.219 | 0.645 | 0.35 | 1.69 |

|               | Basal/bolus split, % | Faster aspart (mealtime) | Faster aspart (post-meal) | Insulin aspart (mealtime) |
|---------------|----------------------|--------------------------|---------------------------|--------------------------|
| Week 1        | 42/58                | 44/56                    | 44/56                     |
| Week 26†      | 37/63                | 38/62                    | 38/62                     |

Safety analysis set.

† Week 26 contains last available measurement.

Faster aspart, fast-acting insulin aspart; meal, mealtime; N, number of participants; post, post-meal; SD, standard deviation.
Supplementary Table 3  Treatment-emergent adverse events

|                      | Faster aspart (mealtime) | Faster aspart (post-meal) | Insulin aspart (mealtime) |
|----------------------|--------------------------|---------------------------|---------------------------|
|                      | N  | %  | E  | R  | N  | %  | E  | R  | N  | %  | E  | R  |
| Treatment-emergent AEs | 54 | 74.0 | 139 | 3.796 | 67 | 75.3 | 174 | 3.957 | 68 | 81.9 | 167 | 4.143 |
| Serious AEs          | 5  | 6.8 | 10  | 0.273 | 2  | 2.2 | 2   | 0.045 | 5  | 6   | 5   | 0.124 |
| Injection-site reactions | 0  | 0   | 0   | —   | 1  | 1.1 | 1   | 0.023 | 1  | 1.2 | 1   | 0.025 |
| Allergic reactions   | 5  | 6.8 | 9   | 0.246 | 4  | 4.5 | 4   | 0.091 | 3  | 3.6 | 3   | 0.074 |
| Dermatitis           | 1  | 1.4 | 3   | 0.082 | 2  | 2.2 | 2   | 0.045 | 0  | 0   | 0   | —   |

AEs were considered treatment-emergent if they occurred following trial product administration after randomization and no later than 7 days after last trial product administration. Serious AE was defined as any of the following: suspicion of infectious agents; death; life-threatening experience; inpatient hospitalization/prolonging of existing hospitalization; persistent or significant disability or incapacity; congenital anomaly or birth defect; or another event that, based on appropriate medical judgment, may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed in this definition. All injection-site reactions include: injection site reaction, injection-site bruising, injection-site hypertrophy, injection-site erythema, injection-site hematoma, and injection-site irritation.

%, percentage of participants; AE, adverse event; E, events; N, number; R, rate per patient-year of exposure.

Supplementary Fig. 1  Patient disposition

Treatment period: the period from Week 0 to Week 26 without premature discontinuation of randomized treatment. Trial period: the period from Week 0 to Week 26.

*Includes randomized patients who withdrew from the trial.

Faster aspart, fast-acting insulin aspart.
Supplementary Fig. 2 Nine-point SMBG profiles at baseline (A) and Week 26 (B)
Error bars: ±standard error (mean). All available information regardless of treatment discontinuation was used. SMBG profiles are plasma-equivalent glucose values.
Faster aspart, fast-acting insulin aspart; PG, plasma glucose; SMBG, self-measured blood glucose.

Supplementary Fig. 3 Frequency of treatment-emergent severe or BG-confirmed hypoglycemia over time
Hypoglycemia was defined as treatment-emergent if the onset of the episode occurred on or after the first day of treatment administration post-randomization and no later than 1 day after the last day of treatment. Severe hypoglycemia was defined according to the ADA classification, and BG-confirmed hypoglycemia was defined as a plasma glucose value <56 mg/dL (Novo Nordisk A/S definition), with or without symptoms consistent with hypoglycemia.
ADA, American Diabetes Association; BG, blood glucose; faster aspart, fast-acting insulin aspart.

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