Supplementary Material

Trial Exclusion Criteria

Key exclusion criteria included a history of ketoacidosis, severe hypoglycemia, or cardiovascular disease, all within the last 6 months before the trial; impaired liver (alanine aminotransferase [ALAT/SGPT] ≥2.5 times upper limit of normal) or renal function (serum creatinine ≥180 μmol/l [≥2.0 mg/dl]); high blood pressure (systolic: ≥180 mmHg, diastolic: ≥100 mmHg); proliferative retinopathy or maculopathy; females who were pregnant, breast-feeding, or intending to become pregnant; and subjects suffering from life-threatening disease.

Assessments/Endpoints

HbA_{1c}, fructosamine, 7-9-7-point SMPG profiles, and FPG were measured to evaluate metabolic control and glucose profiles. '7-9-7-point SMPG profiles' are calculated from measurements taken on 3 consecutive days before a visit: on day -3 7 SMPG measurements are performed; on day -2 7 SMPG measurements are performed with additional measurements at 4am and before breakfast the following day; on day -–1, seven7 SMPG measurements are performed, with the last SMPG measurement (before breakfast) of the 9-point profile and the first SMPG measurement of day –-1 being the same.

Subjects were recommended to perform ≥4 SMPG measurements every day (before breakfast, before lunch, before dinner, and at bedtime), although only measurements taken over 3 consecutive days before each site visit were recorded.

PPG increment for each meal (breakfast, lunch, and dinner) was derived from the 7-9-7-point SMPG profile as the difference between plasma glucose values available 120 min after meal and before meal from each separate profile. 1,5-anhyhdroglucitol was measured to evaluate PPG fluctuations; a higher reported value reflects fewer episodes of high PPG. Severe hypoglycemia was defined as an event requiring third-party assistance to administer carbohydrates, glucagon, or take other corrective actions,[1] while BG-confirmed required a plasma glucose value <56 mg/dl with or without symptoms consistent with hypoglycemia. Hyper- and hypoglycemic episodes were defined as treatment-emergent if the onset of the episode occurred on or after the first day of trial product administration and no later than 1 day after the last day receiving the trial product. Hyperglycemic episodes could either be explained or unexplained (no apparent medical, dietary, insulin dosage reason, or pump problem). A TEAE was defined as an event that had an onset date on or after the first day of exposure to randomized treatment and no later than 7 days after the last day of randomized treatment. AEs were assessed based on severity (mild, moderate, or severe) and whether they were probably, possibly or unlikely to be associated the treatment. Other secondary safety endpoints included the number of infusion-site reactions, clinical evaluations (physical examination, vital signs), and change from baseline in central laboratory assessments (hemotology, biochemistry, lipids, and urine tests) after 6 weeks of treatment. Follow-up visits 30 days after the end of the treatment period collected information on potential major cardiovascular events (MACEs).

Statistical Analysis

Change from baseline in FPG, 1,5-anhydroglucitol, fructosamine, and HbA_{1c} were analyzed using an analysis of variance (ANOVA) model including treatment, region

(North America or Europe) and infusion set as fixed factors and each respective baseline variable as covariate.

Change from baseline in mean 2-h PPG over all meals was analyzed using a mixed-effect model for repeated measurements including treatment, region, and infusion set as fixed effects, subject as random effect, baseline response as covariate, and interaction between all fixed effects and visit, and between the covariate and visit.

An unstructured covariate matrix was used to describe the variability for the repeated measurements for a subject.

Treatment-emergent severe or BG-confirmed hypoglycemia was analyzed using a negative binomial regression model, with log-link function and the logarithm of the treatment-emergent period as offset. The model included treatment, region, and infusion set as fixed factors. As a *post hoc* analysis, the model was inflated to include the rate of severe or BG-confirmed hypoglycemia during the run-in period as a covariate.

Insulin Dosing Results

Mean total bolus and basal insulin doses were maintained throughout the study. At baseline and after 6 weeks of treatment, mean total bolus dose was 0.31 U/kg and 0.32 U/kg, respectively, in the faster aspart group, and 0.31 U/kg for both time points in the insulin aspart group. Mean total basal dose was maintained at

0.28 U/kg and 0.29 U/kg in the faster aspart and insulin aspart groups, respectively, throughout the trial. After 6 weeks of treatment, the mean total insulin dose ratio (faster aspart/insulin aspart) was 0.99.

Reference

1. Seaquist E, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R. Hypoglycemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care. 2013;36(5):1384–95.

Supplementary Table 1. MiniMed Paradigm pumps and infusion sets at randomization.

	Faster aspart *n* (%)	Insulin aspart *n* (%)
MiniMed Paradigm pump		
Model 522	1 (4.0)	1 (8.3)
Model 523	4 (16.0)	2 (16.7)
Model 554	5 (20.0)	1 (8.3)
Model 722	4 (16.0)	2 (16.7)
Model 723	3 (12.0)	1 (8.3)
Model 754	8 (32.0)	5 (41.7)
Infusion set		
Quick-Set	20 (80.0)	9 (75.0)
Silhouette	5 (20.0)	3 (25.0)

Supplementary Table 2. Evaluation of the infusion sets during the trial.

| Type of change	Faster aspart	Insulin aspart	Total	Evaluation
Routine at home	210	98	308	Macroscopic by subject
Routine at site visit	147	72	219	Macroscopic and microscopic by laboratory
Premature	21	4	25	Macroscopic by subject; plus macroscopic and microscopic by laboratory if shipped*
Unclassified	1	0	1	Macroscopic by subject
Total	*379*	*174*	*553*	

*Three of the seven infusion sets that were changed prematurely because of a possible occlusion were shipped to the laboratory for macroscopic and microscopic evaluation (all in the faster aspart group).

Supplementary Table 32. Treatment-emergent adverse events.

	Faster aspart (n = 25)		Insulin aspart (n = 12)	
	n (%)	R	*n* (%)	R
Number of events, *n* (%)	15 (60)	8.9	6 (50)	10.6
Serious, *n* (%)	0	0	0	0
Severe, *n* (%)	1 (4)	0.34	0	0
Probably related to an investigational product, *n* (%)	0	0	0	0
Probably related to a technical complaint, *n* (%)	0	0	0	0

A treatment-emergent adverse event was defined as one that has onset up to 7 days after last day of randomized treatment and excluding the events occurring in the run-in period. %, percentage of subjects; *n*, number of subjects with at least one event; R, number of events per patient-year of exposure.

Supplementary Figure 1. Subject disposition.
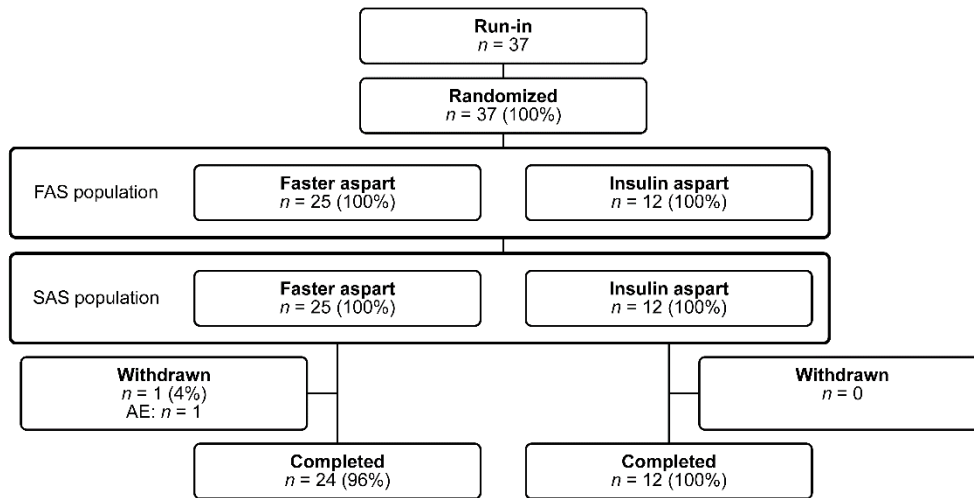
AE, adverse event; FAS, full analysis set; SAS, safety analysis set.