SUPPLEMENTARY DATA

Supplementary Table 1. Basal dose titration algorithm

mmol/L	mg/dL	Dose adjustment when current dose ≤15 U	Dose adjustment when current dose >15 U
≤3.9	≤70	−1	−2
4.0–8.0	71–145	0	0
8.1–10.0	146–180	+1	+2
10.1–15.0	181–270	+2	+4
>15.1	>271	+3	+6

SUPPLEMENTARY DATA

Supplementary Table 2. Bolus dose titration algorithm

Pre-breakfast and pre-lunch bolus insulin titration

mmol/L	mg/dL	Dose adjustment when current dose <5 U (U)	Dose adjustment when current dose ≥5 U (U)
≤3.9	≤70	−1	−2
4.0–8.0	71–145	No adjustment	No adjustment
≥8.1*	≥146	+½	+1

*At the investigator's discretion to use a higher dose increment.

Pre-dinner bolus insulin titration

mmol/L	mg/dL	Dose adjustment when current dose <5 U (U)	Dose adjustment when current dose ≥5 U (U)
≤6.6	≤119	–1	–2
6.7–10	120–180	No adjustment	No adjustment
≥10.1*	≥181	+½	+1

*At the investigator's discretion to use a higher dose increment.

SUPPLEMENTARY DATA

Supplementary Table 3. 8-point profile (SMBG)

Timepoint	Day −2	Day −1	Day of visit
Before breakfast	✓	✓*	✓
60 min after start of breakfast	✓	✓	
Before lunch	✓	✓	
60 min after start of lunch	✓	✓	
Before main evening meal	✓	✓	
60 min after start of evening meal	✓	✓	
At bedtime	✓	✓	

*The last SMBG value of the first 8-point profile was the first SMBG value of the last 8-point profile. In addition to date and SMBG values, the actual clock time had to be recorded in the diary for the 8-point profile. SMBG profiles are plasma equivalent glucose values.
SMBG, self-measured blood glucose.

SUPPLEMENTARY DATA

Supplementary Table 4. List of pre-specified endpoints*

Primary endpoint	• Change from baseline in HbA_{1c} 26 weeks after randomization
Supportive secondary efficacy endpoints	• Change from baseline to week 26 in: • Mean PPG and PPG increment over all three meals (8-point SMBG profile) • Individual meal (breakfast, lunch, and main evening meal) PPG and PPG increment (8-point SMBG profile) • Mean of the 8-point SMBG profile • FPG • 1,5-AG • Evaluated 26 weeks after randomization • Percentage of participants reaching $HbΛ_{1c}$ target <7.5% (58 mmol/mol) • Percentage of participants reaching HbA_{1c} target <7.5% (58 mmol/mol) without severe hypoglycemia • Evaluated during the 26-week treatment period • Insulin dose (total basal, total bolus, and individual meals insulin dose)
CGM related (subgroup)	• Change from baseline to week 26 in: • Time spent in low IG (IG ≤3.9 mmol/L [70 mg/dL]) • Mean time to the IG peak after a meal

	• Evaluated 26 weeks after randomization • Percentage of time spent within IG target range 4.0–10.0 mmol/L (71–180 mg/dL)
CGM and meal-characteristics (subgroup): individual meals and mean over all meals	• Change from baseline to week 26 in: – Mean IG increment (1-h and 2-h) – Mean IG peak after start of meal – Mean time to the IG peak after meal
Meal test-related (subgroup)	• Change from baseline to week 26 in: – PPG and PPG increment at 30-min, 1-h, and 2-h
Supportive secondary safety endpoints	• Number of treatment-emergent hypoglycemic episodes during the 26 weeks after randomization • Overall • Daytime and nocturnal (23:00–7:00) • Meal-related from start of meal until 1, 2, and 4 h after start of meal • Number of treatment-emergent AEs • Number of treatment-emergent injection-site reactions • Number of allergic reactions • Change from baseline in clinical evaluation: • Physical examination

	– Head, ears, eyes, nose, throat, neck, respiratory system, cardiovascular system, gastrointestinal system including mouth, musculoskeletal system, central and peripheral nervous system, skin and Tanner stage • Vital signs – Diastolic blood pressure, systolic blood pressure and pulse • Change from baseline in: • Body weight • BMI • Change from baseline in laboratory assessments: individual laboratory values were compared to their relevant reference range • Hematology (hemoglobin, hematocrit, erythrocytes, thrombocytes, and leucocytes) • Biochemistry (creatinine, ALT, AST, ALP, sodium, potassium, albumin, and total bilirubin) • Lipid profile (total cholesterol, HDL, LDL) • Change from baseline in anti-IAsp (specific and cross-reacting with human insulin) antibody development

*Non-exclusive list of pre-specified study endpoints. SMBG measurements are plasma equivalent glucose values. 1,5-AG, 1,5-anhydroglucitol; AE, adverse events; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FPG, fasting plasma glucose; HDL, high-density lipoprotein; IAsp, insulin aspart; IG, interstitial glucose; LDL, low-density lipoprotein; PPG, postprandial glucose; SD, standard deviation; SMBG, self-measured blood glucose.

SUPPLEMENTARY DATA

Supplementary Table 5. Stepwise hierarchical testing procedure for confirmatory endpoints

Position	Confirmatory endpoint
1st	Change from baseline in HbA_{1c}: non-inferiority of mealtime faster aspart versus mealtime IAsp
2nd	Change from baseline in HbA_{1c}: non-inferiority of post-meal faster aspart versus mealtime IAsp
3rd	Change from baseline in HbA_{1c}: superiority of mealtime faster aspart versus mealtime IAsp

The primary objective and the confirmatory secondary objectives were investigated using a hierarchical testing procedure on the primary endpoint.
Faster aspart, fast-acting insulin aspart; IAsp, insulin aspart.

SUPPLEMENTARY DATA

Supplementary Table 6. Confirmatory analysis

Endpoint [comparison]		Estimate [95%CI]	*P*-value*	Conclusion
PRIMARY				
Step 1	Change from baseline in HbA_{1c} 26 weeks after randomization (%) [mealtime faster aspart – IAsp]	–0.17 [–0.30;–0.03]	<0.001	Non-inferiority confirmed with one-sided *P*-value
CONFIRMATORY SECONDARY				
Step 2	Change from baseline in HbA_{1c} 26 weeks after randomization (%) [post-meal faster aspart – IAsp]	0.13 [–0.01;0.26]	<0.001	Non-inferiority confirmed with one-sided *P*-value
Step 3	Change from baseline in HbA_{1c} 26 weeks after randomization (%) [mealtime faster aspart – IAsp]	–0.17 [–0.30;–0.03]	0.007	Superiority confirmed with one-sided *P*-value

**P*-values are from the one-sided test for non-inferiority and superiority respectively evaluated at the 2.5% level.
Faster aspart, fast-acting insulin aspart; IAsp, insulin aspart.

SUPPLEMENTARY DATA

Supplementary Table 7. Summary of supportive endpoints

	Faster aspart (mealtime), % of participants	Faster aspart (post-meal), % of participants	Insulin aspart (mealtime), % of participants	Treatment comparison	Estimated OR [95%CI]
HbA_{1c} responders 26 weeks after randomization					
HbA_{1c} <7.5% (58.5 mmol/mol)	42.3	31.7	39.5	Mealtime faster aspart vs. IAsp	1.33 [0.87;2.01]
				Post-meal faster aspart vs. IAsp	0.66 [0.43;1.02]
HbA_{1c} <7.5% (58.5 mmol/mol) without severe hypoglycemia	41.9	30.9	38.4	Mealtime faster aspart vs. IAsp	1.37 [0.91;2.08]
				Post-meal faster aspart vs. IAsp	0.68 [0.44;1.04]
	Faster aspart (mealtime), mean	**Faster aspart (post-meal), mean**	**Insulin aspart (mealtime), mean**	**Treatment comparison**	**ETD [95%CI]**
Change from baseline 26 weeks after randomization					
Mean 8-point SMBG, mmol/L	–0.27	0.17	–0.05	Mealtime faster aspart vs. IAsp	–0.25 [–0.58;0.08]
				Post-meal faster aspart vs. IAsp	0.28 [–0.05;0.61]
1-h PPG (SMBG, breakfast), mmol/L	–1.11	0.16	0.04	Mealtime faster aspart vs. IAsp	–1.01 [–1.58;–0.45]***
				Post-meal faster aspart vs. IAsp	0.21 [–0.35;0.77]
1-h PPG (SMBG, lunch), mmol/L	–0.80	0.18	–0.24	Mealtime faster aspart vs. IAsp	–0.58 [–1.15;–0.02]*
				Post-meal faster aspart vs. IAsp	0.76 [0.20;1.33]**

SUPPLEMENTARY DATA

1-h PPG (SMBG, main evening meal), mmol/L	–0.74	0.61	–0.05	Mealtime faster aspart vs. IAsp	0.44 [–1.03;0.15]
				Post-meal faster aspart vs. IAsp	0.76 [0.16;1.36]*
1-h PPG (SMBG, all meals), mmol/L	–0.94	0.36	–0.21	Mealtime faster aspart vs. IAsp	–0.70 [–1.14;–0.27]**
				Post-meal faster aspart vs. IAsp	0.67 [0.23;1.12]**
1-h PPG increment (SMBG, breakfast), mmol/L	–0.82	0.46	0.10	Mealtime faster aspart vs. IAsp	–1.00 [–1.63;–0.37]**
				Post-meal faster aspart vs. IAsp	0.38 [–0.26;1.01]
1-h PPG increment (SMBG, lunch), mmol/L	–0.58	0.12	–0.11	Mealtime faster aspart vs. IAsp	–0.38 [–1.02;0.27]
				Post-meal faster aspart vs. IAsp	0.50 [–0.14;1.15]
1-h PPG increment (SMBG, main evening meal), mmol/L	–0.92	1.03	0.45	Mealtime faster aspart vs. IAsp	–0.90 [–1.57;–0.24]**
				Post-meal faster aspart vs. IAsp	0.34 [–0.34;1.01]
1-h PPG increment (SMBG, all meals), mmol/L	–0.92	0.56	0.14	Mealtime faster aspart vs. IAsp	–0.93 [–1.35;–0.52]***
				Post-meal faster aspart vs. IAsp	0.43 [0.02; 0.85]*
IG peak (breakfast), mmol/L	12.08	13.72	13.38	Mealtime faster aspart vs. IAsp	–1.29 [–2.22;–0.35]**
				Post-meal faster aspart vs. IAsp	0.43 [–0.49;1.35]
IG peak (lunch), mmol/L	12.20	13.21	13.30	Mealtime faster aspart vs. IAsp	–1.00 [–1.91;–0.08]*
				Post-meal faster aspart vs. IAsp	0.38 [–0.51;1.28]
IG peak (main evening meal), mmol/L	13.28	13.76	13.54	Mealtime faster aspart vs. IAsp	–0.27 [–1.17;0.64]
				Post-meal faster aspart vs. IAsp	0.70 [–0.19;1.58]
IG peak (all meals), mmol/L	12.62	13.57	13.41	Mealtime faster aspart vs. IAsp	–0.75 [–1.50;0.01]

SUPPLEMENTARY DATA

Time to IG peak (breakfast), min	100.36	100.32	108.22	Post-meal faster aspart vs. IAsp	0.52 [–0.22;1.27]
				Mealtime faster aspart vs. IAsp	–0.90 [–14.52;12.71]
				Post-meal faster aspart vs. IAsp	–8.32 [–21.60;4.95]
Time to IG peak (lunch), min	111.73	97.11	91.36	Mealtime faster aspart vs. IAsp	17.08 [4.23;29.92]*
				Post-meal faster aspart vs. IAsp	3.33 [–9.02;15.68]
Time to IG peak (main evening meal), min	110.39	97.74	111.13	Mealtime faster aspart vs. IAsp	0.84 [–13.43;15.11]
				Post-meal faster aspart vs. IAsp	–13.39 [–27.41;0.64]
Time to IG peak (all meals), min	106.78	98.37	104.08	Mealtime faster aspart vs. IAsp	3.42 [–5.19;12.04]
				Post-meal faster aspart vs. IAsp	–7.37 [–15.88;1.14]
1-h IG increment (breakfast), mmol/L	–0.31	0.19	0.09	Mealtime faster aspart vs. IAsp	–0.44 [–0.79;–0.08]*
				Post-meal faster aspart vs. IAsp	0.29 [–0.06;0.63]
1-h IG increment (lunch), mmol/L	–0.10	0.54	–0.05	Mealtime faster aspart vs. IAsp	–0.27 [–0.67;0.13]
				Post-meal faster aspart vs. IAsp	0.38 [–0.02;0.77]
1-h IG increment (main evening meal), mmol/L	–0.23	0.09	0.15	Mealtime faster aspart vs. IAsp	–0.39 [–0.73;–0.06]*
				Post-meal faster aspart vs. IAsp	0.12 [–0.21;0.45]
1-h IG increment (all meals), mmol/L	–0.19	0.26	0.07	Mealtime faster aspart vs. IAsp	–0.34 [–0.57;–0.10]**
				Post-meal faster aspart vs. IAsp	0.25 [0.02;0.48]*
2-h IG increment (breakfast), mmol/L	–0.48	0.30	0.09	Mealtime faster aspart vs. IAsp	–0.68 [–1.19;–0.17]**
				Post-meal faster aspart vs. IAsp	0.60 [0.10;1.11]*

SUPPLEMENTARY DATA

2-h IG increment (lunch), mmol/L	–0.29	0.91	0.07	Mealtime faster aspart vs. IAsp	–0.47 [–1.05;0.10]
				Post-meal faster aspart vs. IAsp	0.73 [0.17;1.29]*
2-h IG increment (main evening meal), mmol/L	–0.47	0.52	0.11	Mealtime faster aspart vs. IAsp	–0.61 [–1.22;–0.00]*
				Post-meal faster aspart vs. IAsp	0.58 [–0.02;1.18]
2-h IG increment (all meals), mmol/L	–0.35	0.55	0.09	Mealtime faster aspart vs. IAsp	–0.51 [–0.85; –0.17]**
				Post-meal faster aspart vs. IAsp	0.61 [0.27;0.95]***
1,5-AG, µg/mL	–0.06	–0.85	–0.63	Mealtime faster aspart vs. IAsp	0.52 [0.09;0.95]*
				Post-meal faster aspart vs. IAsp	–0.29 [–0.73;0.14]
FPG, mmol/L	0.41	–0.08	–0.13	Mealtime faster aspart vs. IAsp	0.46 [–0.38;1.30]
				Post-meal faster aspart vs. IAsp	0.25 [–0.58;1.08]
Variation in IG profile (CV, %)					
Baseline	42.61	41.72	39.67	–	–
Week 26	41.42	39.96	40.28	–	–

*P<0.05; **P<0.01; ***P<0.001.

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

1,5-AG, 1,5-anhydroglucitol; CV, coefficient of variation; ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; IAsp, insulin aspart; IG, interstitial glucose; OR, odds ratio; PPG, postprandial glucose; SMBG, self-measured blood glucose.

SUPPLEMENTARY DATA

Supplementary Table 8. Baseline characteristics table in CGM subpopulation

	Faster aspart (mealtime) ***n*=43**	**Faster aspart (post-meal)** ***n*=48**	**Insulin aspart (mealtime)** ***n*=44**
Proportion of trial population, %	16.5	18.5	17.1
Sex, male, *n* (%)	28 (65.1)	25 (52.1)	25 (56.8)
Age, years	12.7 (2.6)	12.1 (2.5)	13.0 (2.4)
8 ≤ age <12 years, *n* (%)	16 (37.2)	21 (43.8)	14 (31.8)
12 ≤ age <18 years, *n* (%)	27 (62.8)	27 (56.3)	30 (68.2)
BMI, kg/m^2	20.7 (3.2)	19.8 (3.7)	20.6 (4.3)
Diabetes duration, years	5.1 (3.3)	3.8 (2.4)	4.8 (4.0)
HbA_{1c}, %	7.4 (0.8)	7.3 (0.7)	7.4 (0.9)
mmol/mol	57.8 (8.7)	56.3 (8.0)	57.7 (9.5)
FPG, mmol/L	7.1 (2.9)	7.2 (2.3)	6.2 (2.3)
mg/dL	127.2 (51.8)	130.4 (41.1)	112.2 (41.6)

Results are presented as arithmetic means (SD) unless otherwise stated.
BMI, body mass index; CGM, continuous glucose monitoring; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; SD, standard deviation.

SUPPLEMENTARY DATA

Supplementary Table 9. Daily bolus, basal, and total insulin dose (actual), basal/bolus ratios and change in body weight

Visit (week)	Treatment	Insulin dose					
		N*	Mean	SD	Median	Min	Max
Bolus dose (all meals), U							
Week 0	Faster aspart (meal)	261	20.9	12.3	18.3	3	75
	Faster aspart (post)	258	21.1	14.5	16.5	2	91
	Insulin aspart (meal)	258	20.5	12.4	16.9	2	71
Week 26	Faster aspart (meal)	261	23.3	14.5	20.0	3	84
	Faster aspart (post)	258	23.5	15.1	19.1	2	82
	Insulin aspart (meal)	258	22.5	13.0	19.1	1	80
Basal dose, U							
Week 0	Faster aspart (meal)	261	19.3	11.4	17.7	1	72
	Faster aspart (post)	258	19.2	12.8	17.0	1	78
	Insulin aspart (meal)	258	18.5	11.8	16.0	1	56
Week 26	Faster aspart (meal)	261	21.6	12.9	19.3	1.0	70
	Faster aspart (post)	258	21.5	14.5	18.0	1.0	101
	Insulin aspart (meal)	258	20.7	12.8	18.0	2.0	64.0
Total insulin dose, U							
Week 0	Faster aspart (meal)	261	40.2	21.4	37.2	4	102
	Faster aspart (post)	258	40.2	25.0	32.8	3	135
	Insulin aspart (meal)	258	39.0	22.4	34.7	6	124
Week 26	Faster aspart (meal)	261	44.8	24.4	41.5	6	147
	Faster aspart (post)	258	45.0	26.9	39.2	3	171
	Insulin aspart (meal)	258	43.2	23.6	38.8	7	144
Bolus dose (all meals), U/kg							
Week 0	Faster aspart (meal)	261	0.453	0.206	0.411	0.09	1.55
	Faster aspart (post)	258	0.452	0.218	0.409	0.03	1.55
	Insulin aspart (meal)	258	0.445	0.198	0.416	0.06	1.36
Week 26	Faster aspart (meal)	261	0.483	0.256	0.432	0.07	2.29

	Faster aspart (post)	258	0.491	0.241	0.438	0.03	1.49
	Insulin aspart (meal)	258	0.468	0.224	0.426	0.01	1.80
Basal dose, U/kg							
Week 0	Faster aspart (meal)	261	0.400	0.175	0.390	0.04	1.08
	Faster aspart (post)	258	0.395	0.182	0.364	0.03	1.10
	Insulin aspart (meal)	258	0.384	0.172	0.349	0.05	1.14
Week 26	Faster aspart (meal)	261	0.433	0.228	0.402	0.07	2.16
	Faster aspart (post)	258	0.425	0.196	0.399	0.03	1.29
	Insulin aspart (meal)	258	0.409	0.176	0.384	0.10	1.27
Total insulin dose, U/kg							
Week 0	Faster aspart (meal)	261	0.853	0.320	0.811	0.18	2.12
	Faster aspart (post)	258	0.847	0.341	0.780	0.07	2.31
	Insulin aspart (meal)	258	0.829	0.320	0.780	0.13	2.36
Week 26	Faster aspart (meal)	261	0.915	0.413	0.851	0.22	4.24
	Faster aspart (post)	258	0.916	0.373	0.839	0.07	2.58
	Insulin aspart (meal)	258	0.877	0.341	0.817	0.11	2.54

Basal/bolus ratio	Faster aspart (mealtime)	Faster aspart (post-meal)	Insulin aspart (mealtime)
Week 0	47/53	47/53	46/54
Week 26	47/53	46/54	47/53

Change from baseline in body weight 26 weeks after randomization, kg

	Faster aspart (mealtime), mean	Faster aspart (post-meal), mean	Insulin aspart (mealtime), mean	Treatment comparison	ETD[95%CI]

				Mealtime faster aspart vs. IAsp	0.06 [–0.39;0.51]
Week 26	+2.22	+1.93	+2.19		
				Post-meal faster aspart vs. IAsp	–0.24 [–0.68;0.21]

Safety analysis set. *One participant randomized to the post-meal faster aspart treatment arm was treated with mealtime faster aspart. Values at ‘week 26’ are the last ‘on-treatment’ values recorded.
CI, confidence interval; ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; IAsp, insulin aspart; meal, mealtime; N, number of participants; post, post-meal; SD, standard deviation.

SUPPLEMENTARY DATA

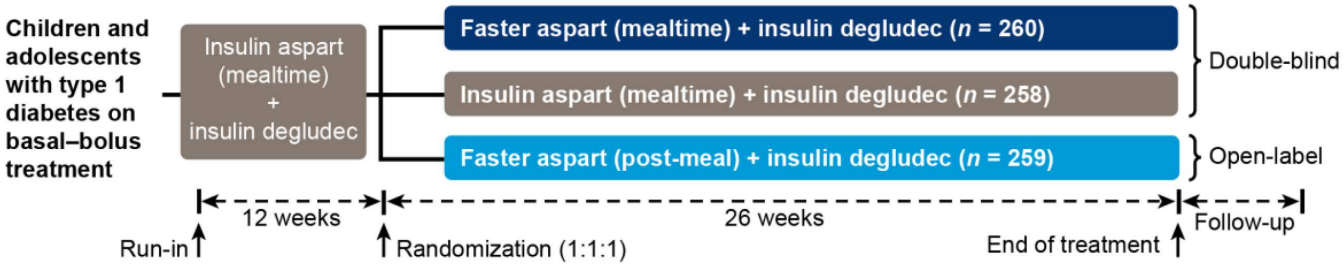
Supplementary Table 10. Treatment-emergent adverse events

	Faster aspart (mealtime)				Faster aspart (post-meal)				Insulin aspart (mealtime)			
	N	**%**	**E**	**R**	**N**	**%**	**E**	**R**	**N**	**%**	**E**	**R**
Treatment-emergent AEs	193	73.9	576	4.49	199	77.1	678	5.31	203	78.7	593	4.65
Serious AEs	5	1.9	7	0.05	13	5	15	0.12	9	3.5	13	0.1
Injection-site reactions	8	3.1	11	0.09	14	5.4	31	0.24	11	4.3	17	0.13
Allergic reactions	13	5.0	17	0.13	8	3.1	8	0.06	9	3.5	13	0.10

Treatment-emergent: events occur after trial product administration after randomization and no later than 7 days after last trial product administration. Serious AE is an experience that at any dose results in any of the following: death; a life-threatening experience; inpatient hospitalization or prolongation of existing hospitalization; a persistent or significant disability or incapacity; a congenital anomaly or birth defect; an event that may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
%, percentage of participants; AE, adverse event; E, events; faster aspart; fast-acting insulin aspart; N, number; R, rate per patient-year of exposure.

SUPPLEMENTARY DATA

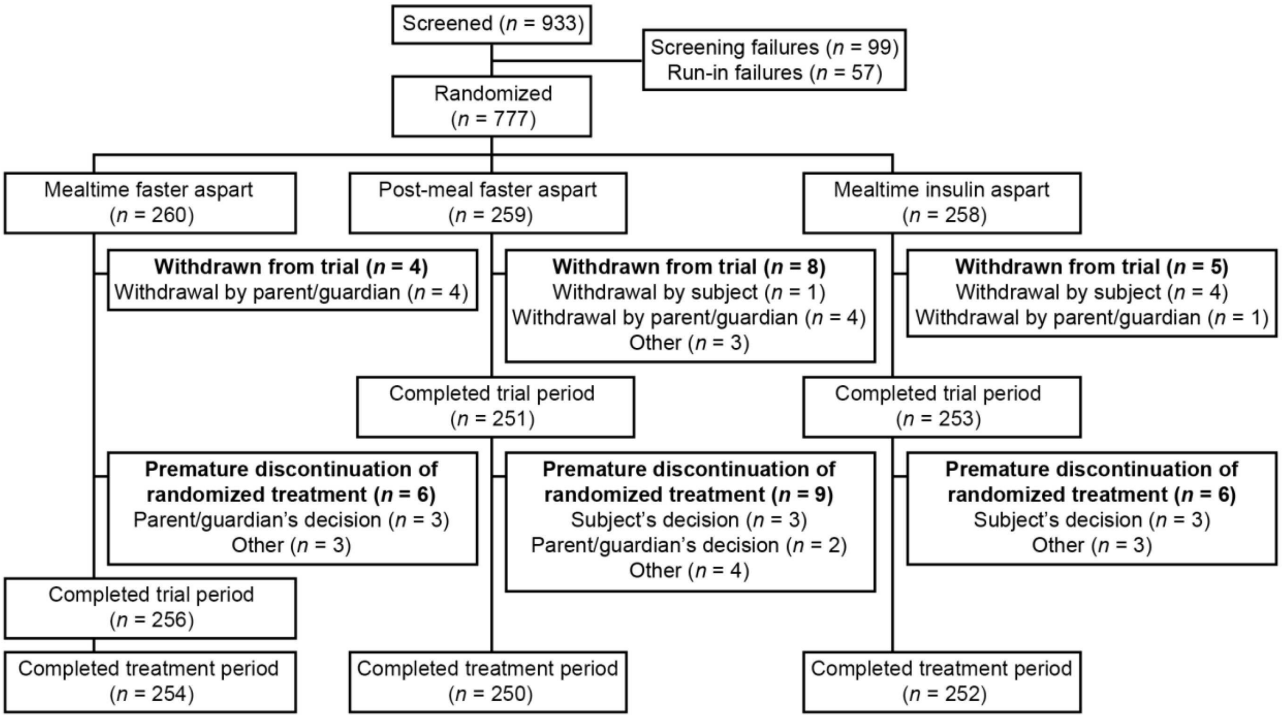
Supplementary Figure 1. Trial design



ClinicalTrials.gov: NCT02670915. Baseline is at randomization. Follow-up occurred 7 and 30 days after end of treatment.
Faster aspart, fast-acting insulin aspart; *n*, number of participants.

SUPPLEMENTARY DATA

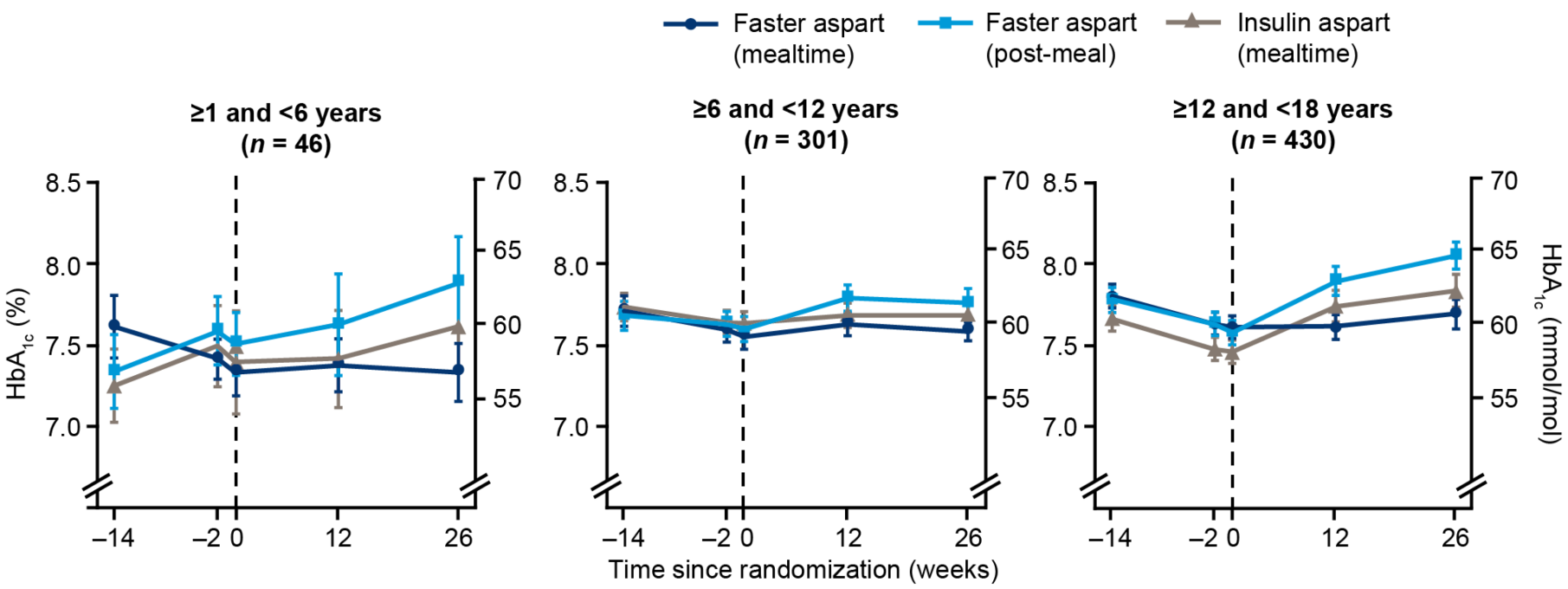
Supplementary Figure 2. Subject disposition



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 30.
Faster aspart, fast-acting insulin aspart; *n*, number of participants.

SUPPLEMENTARY DATA

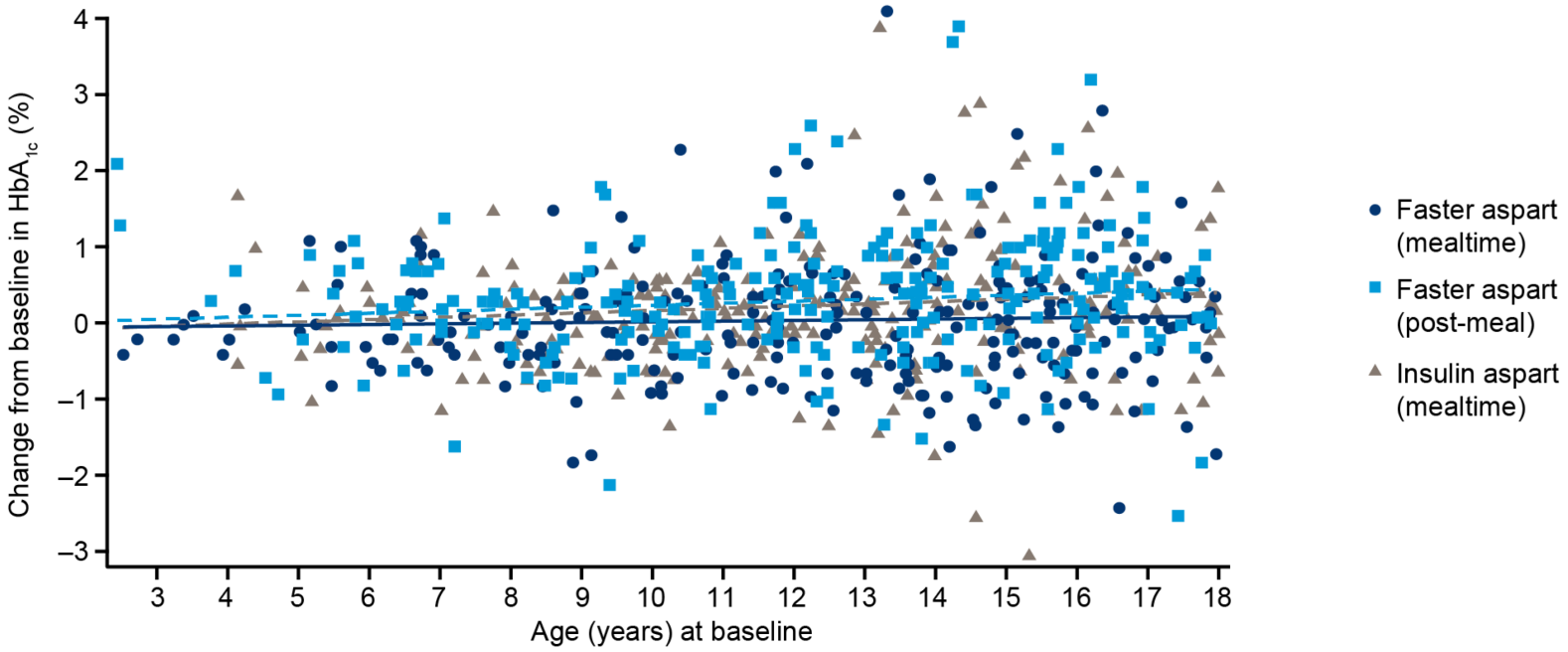
Supplementary Figure 3. HbA1c over time by age



Error bars: +/– standard error (mean). Faster aspart, fast-acting insulin aspart; *n*, number of participants.

SUPPLEMENTARY DATA

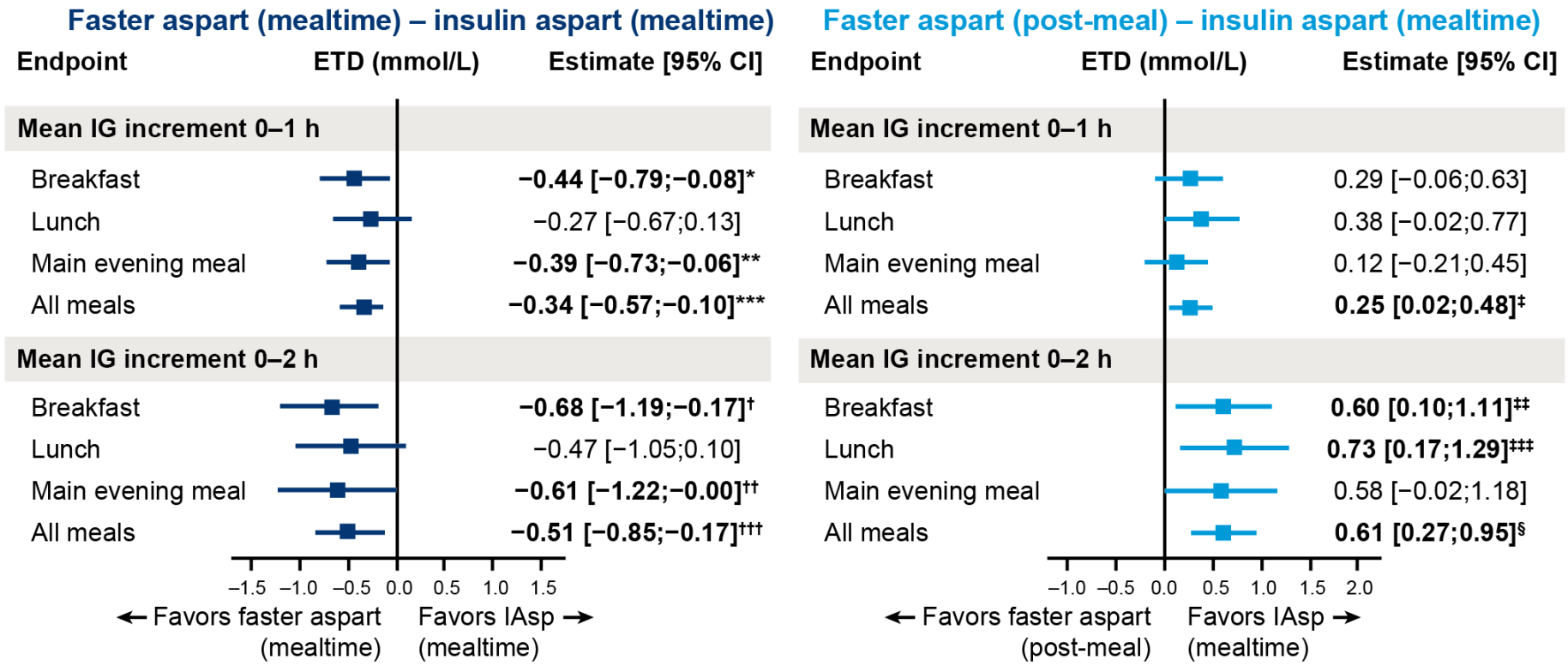
Supplementary Figure 4. Exploratory *post hoc* analysis: change from baseline in HbA1c by age



Graph displays a scatter plot overlaid with a linear regression line for each treatment group.
Faster aspart, fast-acting insulin aspart.

SUPPLEMENTARY DATA

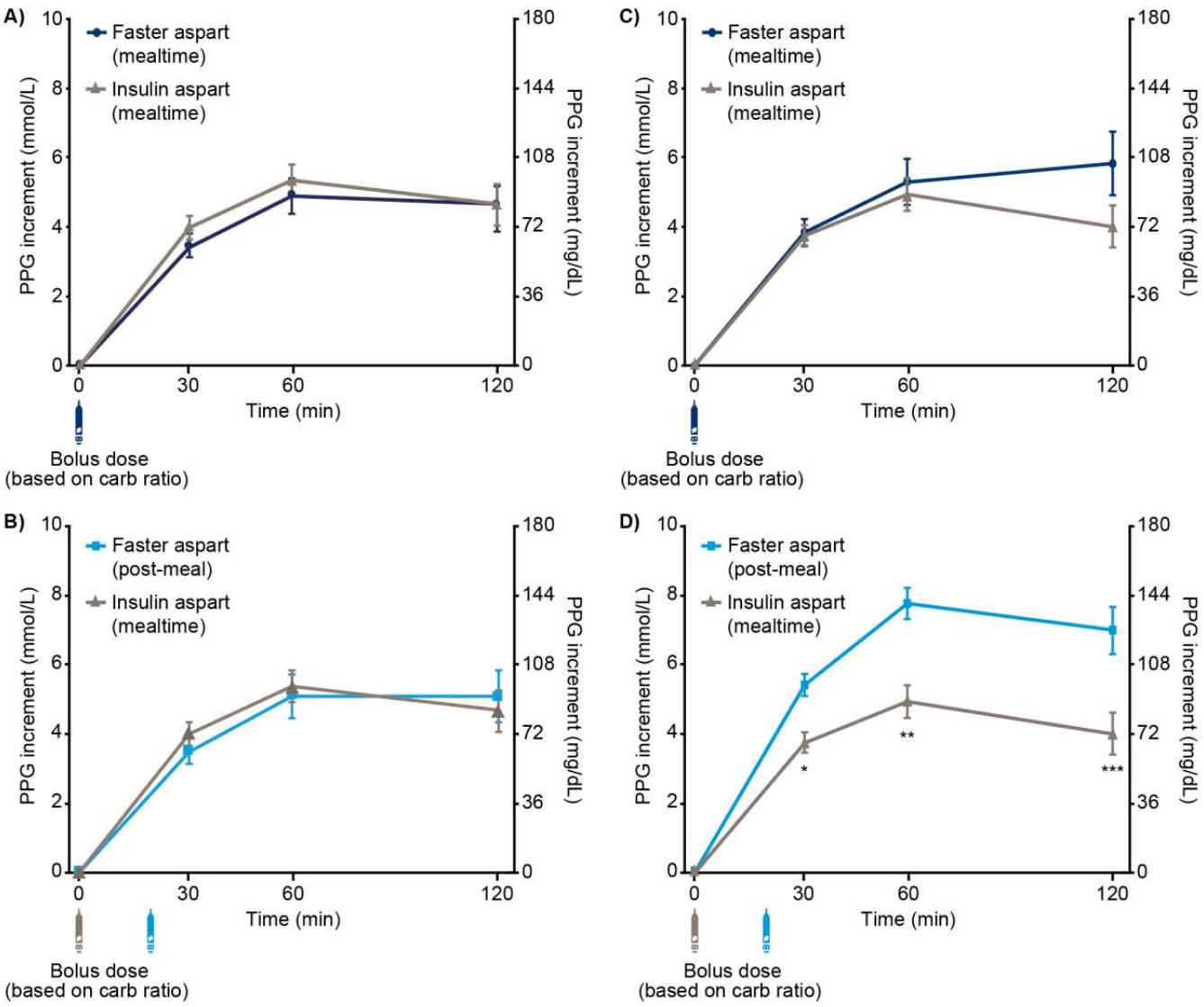
Supplementary Figure 5. Analysis of meal IG increment forest plot 26 weeks after randomization



*P=0.016, **P=0.021, ***P=0.006, †P=0.009, ††P=0.049, †††P=0.004, ‡P=0.034, ‡‡P=0.020, ‡‡‡P=0.011, §P<0.001. Change from baseline in IG increment was analyzed using an analysis of variance model. CI, confidence interval; ETD, estimated treatment difference; faster aspart; fast-acting insulin aspart; IG, interstitial glucose.

SUPPLEMENTARY DATA

Supplementary Figure 6. PPG increment results from a standardized meal test at baseline and week 26. Mealtime faster aspart versus IAsp (C); post-meal faster aspart versus IAsp (D)



A) and B) Baseline PPG increment values for all treatment arms. C) Mealtime comparison between faster aspart and insulin aspart. No statistically significant differences were observed between treatments at any time point: 30 min, *P*=0.567; 60 min, *P*=0.461; 120 min, *P*=0.074. D) Post-meal faster aspart comparison with mealtime insulin aspart. **P*=0.001, ***P*<0.001, ****P*=0.013, all in favor of IAsp.

Error bars: +/– standard error (mean). Mealtime insulin aspart dosed immediately before the liquid meal; post-meal faster aspart dosed 20 min after the start of the liquid meal.

Faster aspart, fast-acting insulin aspart; IAsp, insulin aspart; PPG, postprandial glucose.

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Supplementary Appendix

Full inclusion criteria

1. Informed consent and child assent, as age-appropriate, obtained before any trial-related activities. Trial-related activities are any procedures that are carried out as part of the trial, including activities to determine suitability for the trial. Legally Acceptable Representative (LAR) of the Subject must sign and date the Informed Consent Form (according to local requirements). The child must sign and date the Child Assent Form or provide oral assent, if required according to local requirements.
2. Male or female aged 1 to 17 years at the time of signing informed consent and <18 years at the time of randomization. For Serbia only: male or female, 2 to 17 years of age at the time of signing informed consent and <18 years at the time of randomization.
3. Diagnosed with type 1 diabetes mellitus (based on clinical judgement and supported by laboratory analysis as per local guidelines).
4. Ongoing daily treatment with a basal–bolus insulin regimen using a basal insulin analogue or NPH insulin for at least 90 days prior to the screening visit.
5. Ability and willingness to take at least three daily mealtime-related bolus insulin injections throughout the trial (Subject and LAR(s) should be evaluated as a unit).
6. Total daily dose of insulin ≤2.0 U/kg prior to the screening visit.
7. HbA1c ≤9.5% (80 mmol/mol) analyzed by the central laboratory at the screening visit.

Full exclusion criteria

For an eligible subject, all exclusion criteria must be answered "no".
1. Known or suspected hypersensitivity to trial products or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breastfeeding or intends to become pregnant or is of child-bearing potential and not using adequate contraceptive methods (adequate contraceptive measures as required by local regulation or practice).
For EU only: Adequate contraceptive measures are implants, injectable, combined oral contraceptives, hormonal IUD, sexual abstinence, or vasectomized partner.
For Bulgaria, Czech Republic, Lithuania, Latvia, Poland, Estonia, and Finland only: Adequate contraceptive measures also include double barrier method (condom or diaphragm with spermicide) in addition to the measures listed under EU.
For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide, or oral contraceptives.
4. Participation in another clinical trial within 28 days before the screening visit (Note: Clinical trials do not include non-interventional studies).
5. Anticipated initiation or change in concomitant medication in excess of 14 days known to affect weight or glucose metabolism (e.g., orlistat, thyroid hormones, corticosteroids).
6. Any condition, which, in the opinion of the Investigator, might jeopardize the Subject's safety or compliance with the protocol (Subject and LAR(s) should be evaluated as a unit).
7. Diagnosis of malignant neoplasms within the last 5 years prior to the screening visit.
8. Known hypoglycemic unawareness or recurrent severe hypoglycemic episodes as judged by the Investigator.
9. More than one episode of diabetic ketoacidosis requiring hospitalization within the last 90 days prior to the screening.
10. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 90 days before screening.

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Statistical Appendix

Analysis sets

The full analysis set (FAS) includes all randomized participants. Participants in the FAS contributed to the evaluation ‘as randomized’. The safety analysis set (SAS) includes all participants receiving at least one dose of the investigational product (faster aspart) or its comparator (IAsp). Participants in the SAS contributed to the evaluation ‘as treated.

Observation periods

Two observation periods were defined. The ‘in-trial’ period refers to the observation period from date of randomization until last trial-related subject-site contact, and includes data collected after treatment discontinuation. The ‘on-treatment’ period relates to the observation period from date of first dose of randomized IAsp/faster aspart and no later than 7 days after the day of last dose of IAsp/faster aspart. The on-treatment observation period includes data collected up to and including 7 days after treatment discontinuation.

Hierarchical testing procedure

Step 1 (primary analysis): HbA1c non-inferiority of mealtime faster aspart versus mealtime IAsp, both in combination with insulin degludec.
Step 2: HbA1c non-inferiority of post-meal faster aspart versus mealtime IAsp, both in combination with insulin degludec.
Step 3: HbA1c superiority of mealtime faster aspart versus mealtime IAsp, both in combination with insulin degludec.

Sample size calculations

The sample size is determined to ensure a sufficient power for the first step and the second step in the hierarchal testing procedure using a non-inferiority limit of 0.4%. Power for the non-inferiority steps are based on a t-statistic under the assumption of a one-sided test of size 2.5%. A zero mean treatment difference for the comparison between mealtime faster aspart and mealtime IAsp is expected, and for the comparison of post-meal faster aspart and mealtime IAsp a mean difference of 0.05% in favor of mealtime IAsp is expected.
Based on results published from previous trials and considering the in-trial observation period included data collected after treatment discontinuation, the standard deviation (SD) for change in HbA1c was assumed to be 1.3%. With this SD, a sample size of 250 participants per group (750 participants in total) ensured more than 93% power to show non-inferiority, given that the actual treatment difference was 0%. This sample size ensured a power of 85% to show non-inferiority of post-meal faster aspart compared to IAsp.

Confirmatory analyses

The primary analysis (step 1 of the hierarchical testing procedure listed above) was based on all participants included in the FAS using the in-trial observation period. Using a multiple imputation model, missing data were imputed for the primary analysis using the available information from the treatment to which the participant had been randomized as follows:

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- In the first step, intermittent missing values were imputed using a Markov Chain Monte Carlo (MCMC) method to obtain a monotone missing data pattern. This imputation was done for each group separately and 100 copies of the dataset were generated.

- In the second step, for each of the 100 copies of the dataset, an analysis of variance model with region and strata (age group at randomization [≥1 to <3 years, ≥3 to <6 years, ≥6 to <12 years, ≥12 to <18 years]) as factors and baseline HbA1c as covariate was fitted to the change in HbA1c from baseline to week 12 for each treatment group separately. The estimated parameters, and their variances, from these models were used to impute missing values at week 12 for participants in each treatment group, based on region, strata, and baseline HbA1c.

- In the third step, for each of the 100 copies of the dataset, missing values at week 26 were imputed in the same way as for week 12. The imputations were based on an analysis of variance model with region and strata as factors and baseline HbA1c and HbA1c at week 12 as covariates.

- For each of the complete data sets, the change from baseline to week 26 was analyzed using an analysis of variance model with treatment, region, and strata as factors, and baseline HbA1c as a covariate.

- The estimates and SD for the 100 data sets were pooled to one estimate and associated SD using Rubin's formula, where mi and SDi were the estimated means and SDs for the 100 copies of the dataset, and mMI and SDMI were the pooled estimates:

$$m_{MI} = \frac{1}{100}\sum_{i=1}^{100} m_i, \quad SD_{MI} = \sqrt{\frac{1}{100}\sum_{i=1}^{100} SD_i^{\,2} + \left(1+\frac{1}{100}\right)\left(\frac{1}{100-1}\right)\sum_{i=1}^{100}(m_i - m_{MI})^2},$$

- From mMI and SDMI, the 95% CI for the treatment differences was calculated.

Non-inferiority of mealtime faster aspart was considered confirmed if the upper boundary of the two-sided 95% CI was below or equal to 0.4% or equivalent if the *P*-value for the one-sided test of H0: D >0.4% against HA: D ≤0.4% was less than or equal to 2.5%, where D was the mean treatment difference (mealtime faster aspart minus mealtime IAsp).
If the primary objective was confirmed, the effect of treatment with post-meal faster aspart in terms of glycemic control was investigated to show that post-meal faster aspart is non-inferior to IAsp both in combination with insulin degludec in terms of glucose-lowering effect, as assessed by change from baseline in HbA1c 26 weeks after randomization. This was determined in the same way as above where treatment difference was set to (post-meal faster aspart minus mealtime IAsp). Finally, if both the primary and the first secondary confirmatory hypotheses were fulfilled, the superiority of the mealtime faster aspart as compared to mealtime IAsp was tested in terms of glycemic control. This was assessed by comparing the upper limit of the 95% CI from the primary analysis to 0. If the upper 95% CI was below 0 then superiority was confirmed.

Supportive secondary endpoints

The supportive secondary (efficacy and safety) endpoints addressed the 2 secondary objectives:

1. To compare the effect and safety of treatment with mealtime faster aspart vs. mealtime IAsp, both in combination with insulin degludec, in children and adolescents with type 1 diabetes
2. To compare the effect and safety of treatment with post-meal faster aspart vs. mealtime IAsp, both in combination with insulin degludec, in children and adolescents with type 1 diabetes

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For all supportive secondary endpoints, mealtime faster aspart was compared to mealtime IAsp, and post-meal faster aspart was compared to mealtime IAsp. Change from baseline refers to the change from randomization to 26 weeks after randomization. Supportive secondary efficacy and safety endpoints are listed in **Table S4**.

Supportive secondary safety endpoint definitions

Treatment-emergent adverse events (TEAEs) are defined as adverse events that had an onset date on or after first day of exposure to treatment, and no later than 7 days after last day of randomized treatment. Hypoglycemic episodes were defined as treatment emergent if the onset of the episode occurred on or after the first day of treatment administration after randomization, and no later than 1 day after the last day of treatment. Nocturnal hypoglycemic episodes were episodes occurring between 23:00 and 07:00, both inclusive. Severe hypoglycemia was defined according to the ISPAD classification* as a hypoglycemic episode associated with severe neuroglycopenia, usually resulting in coma or seizure and requiring parenteral therapy (glucagon or intravenous glucose). Severe or BG-confirmed hypoglycemia was defined as an episode that is severe according to the ISPAD classification* or BG-confirmed by a PG value <3.1 mmol/L (56 mg/dL) with symptoms consistent with hypoglycemia.

*International Society for Pediatric and Adolescent Diabetes (ISPAD) Clinical Practice Consensus Guidelines 2014 Compendium. *Pediatr Diabetes* 2014;15 Suppl. 20:1–290

The treatment effect was also addressed in this trial as if all participants had taken the treatment as directed and continued on-treatment for the 26-week treatment period (data not shown). The results were similar to the primary analysis due to the high retention in this trial; therefore, this manuscript does not present the results for this different target of estimation

SUPPLEMENTARY DATA

List of participating investigators

Bulgaria: Violeta Iotova, Maia Konstantinova, Chayka Petrova, Galina Popova; **Czech Republic:** Barbora Červíčková, Martina Honková, David Neumann, Jaroslav Škvor, Jiří Strnadel, Jan Vosahlo; **Germany:** Thomas Behnke, Thomas Danne, Hans-Peter Kempe, Eggert Lilienthal, Thomas Schaum, Ulf Schimmel, Karl Otfried Schwab, Alexander Segner, Ralph Ziegler; **Estonia:** Ülle Einberg, Aleksandr Peet; **Finland:**
Taina Mustila, Mari Pulkkinen, Riitta Veijola; **Israel:** Ori Eyal, Orit Hamiel, Eli Hershkovitz, Zohar Landau, Moshe Phillip, Marianna Rachmiel, Naim Shehadeh; **India:** Sunil M Jain, Vaman Khadilkar, Jaiganesh Muruganandan, P V Rao, Banshi Saboo Vijay Sheker Reddy, Praveen V.P; **Italy:** Valentino Cherubini, Agostino Gnasso, Claudio Maffeis, Enza Mozzillo, Stefano Tumini; **Japan:** Yuki Abe, Ikuma Fujiwara, Naoaki Hori, Reiko Horikawa, Masaru Inoue, Kazuhiko Jinno, Masahiko Joo, Tomoyuki Kawamura, Toru Kikuchi, Yoichi Kondo, Toshihide Kubo, Tateo Kuno, Kenji Kurata, Junnosuke Miura, Tomoyuki Miyamoto, Mie Mochizuki, Jun Mori, Hisakazu Nakajima, Toshihiro Nakajima, Kimitoshi Nakamura, Shoji Nakayama, Yohei Ogawa, Yoshiaki Ohtsu, Kayo Ozaki, Tomohiro Saito, Hiroaki Seino, Yasuhiko Sera, Kentaro Shiga, Shigeru Suga, Toshikazu Takahashi, Masaro Takesue, Hiroyuki Tanaka, Masakuni Tokuda, Goro Tsuruta, Hideaki Yagasaki, Yukiyo Yamamoto, Shuichi Yatsuga, Koji Yokoyama, Yasuko Uchigata, Tatsuhiko Urakami; **Latvia:** Iveta Dzivite-Krisane; **Lithuania:** Rasa Verkauskiene; **Poland**: Malgorzata Mysliwiec, Anna Noczynska, Ewa Pankowska, Mieczyslaw Szalecki; **Serbia:** Dragan Katanic, Tatjana Milenkovic, Silvija Sajic, Ljiljana Saranac, Sasa Zivic; **Russia:** Nina Bolotova, Tatiana Dubinina, Galina Galkina, Margarita Kovarenko, Oleg Malievskiy, Evgeniia Mikhailova, Valentina Peterkova, Yulia Samoylova, Lubov Samsonova, Yulia Skorodok, Svetlana Zyangirova; **Turkey:** Murat Aydın, Firdevs Baş, İffet Bircanleft, Ece Böber, Damla Gökşen, Bahar Özcabi, Mesut Parlak, Bilgin Yüksel; **Ukraine:** Olena Budreiko, Olena Bolshova, Nataliya Chorna, Oksana Fishchuk, Oksana Khyzhnyak, Dmytro Logvinov, Yuriy Reznichenko, Olena Slepyan, Yurii Yerin, Natalia Zelinska; **USA:** Siham Accacha, Stephen Aronoff, Silva Arslanian, Kathleen Bethin, Thomas C. Blevins, Bruce W. Bode, Sureka Bollepalli, Mario Brakin, Jose Atilio Canas, Luis Casas, Ronald H. Chochinov, Amy Criego, Tala Dajani, Larry C. Deeb, Santhosh Eapen, Rachel Edelen, Lynda K. Fisher, Daniel P. Flynn, Carol Foster, Michael Gottschalk, Rebecca Green, Kurt Griffin, Ellen Kaizer Grishman, Robert P. Hoffman, David H. Jelley, Lori Laffel, Hillary Lockemer, Alison Lunsford, Lyle Myers, Samer N. Nakhle, Brandon Nathan, Francisco Nieves-Rivera, 31

Gnanagurudasan Prakasam, Barry Reiner, Judith Ross, Janet Silverstein, Carl Vance, Raj Paul Wadwa, Mark Wheeler, Steven M. Willi, Nancy Wright, Joshua Yang.