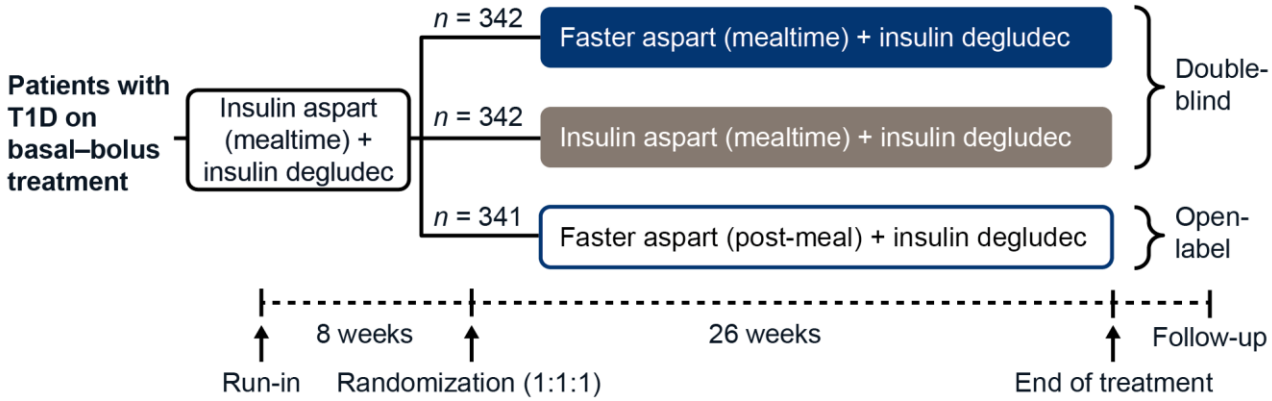
Supplementary Material

Fast-acting insulin aspart versus insulin aspart in the setting of insulin degludec-treated type 1 diabetes: efficacy and safety from a randomized double-blind trial

John B. Buse MD PhD, Anders L. Carlson MD, Mitsuhisa Komatsu MD PhD, Ofri Mosenzon MD, Ludger Rose MD, Bo Liang MD PhD, Kristine Buchholtz MD PhD, Hiroshi Horio MSc, Takashi Kadowaki MD PhD

Supplementary Figure 1. Trial design



ClinicalTrials.gov: NCT02500706. Baseline is at randomization. Follow-up was 30 days.

Faster aspart; fast-acting insulin aspart; T1D, type 1 diabetes

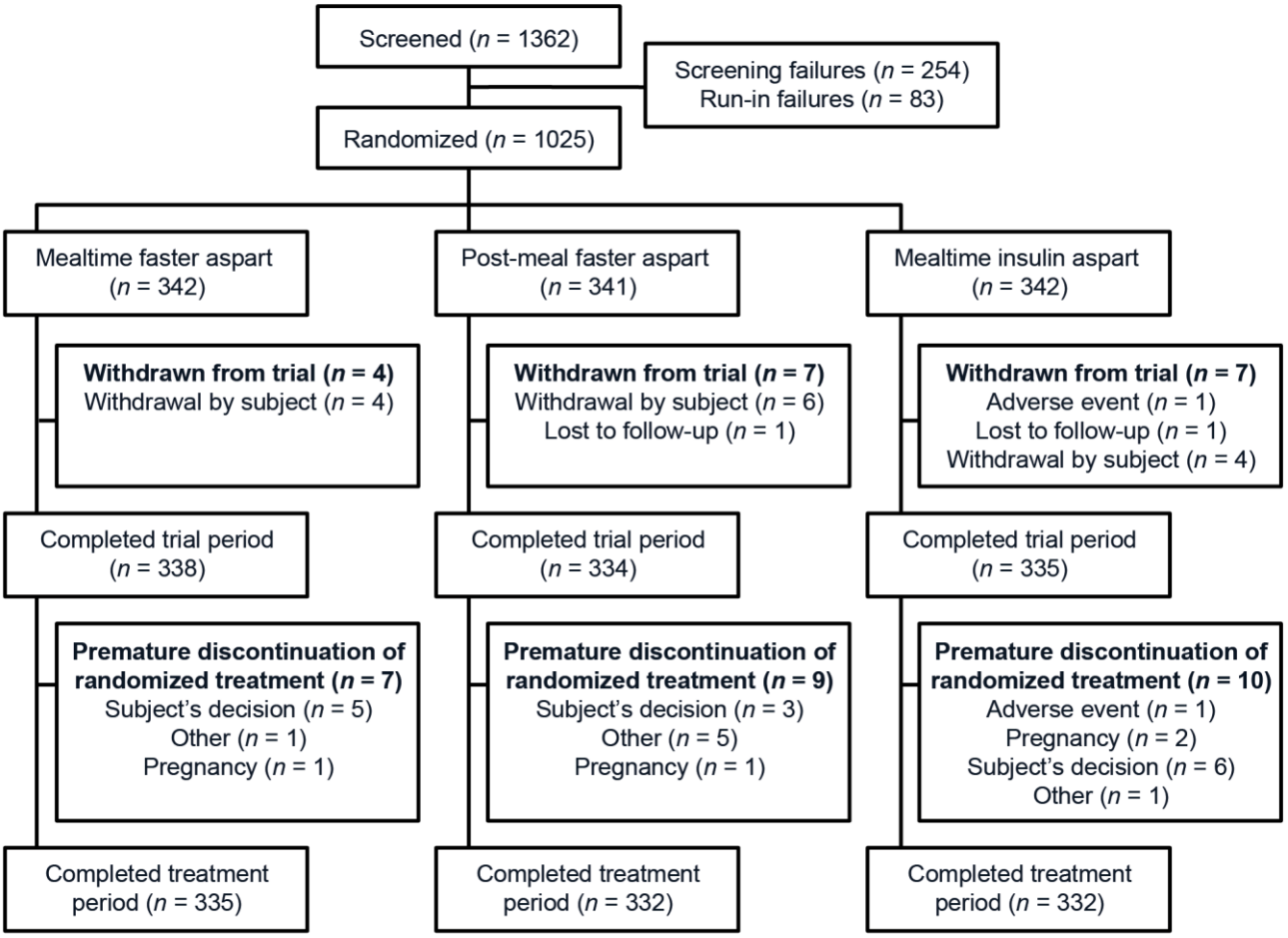
Supplementary Figure 2. Stepwise hierarchical testing procedure for confirmatory hypotheses

Position	Confirmatory hypotheses
1st	Change from baseline in HbA1c: non-inferiority of mealtime faster aspart versus insulin aspart
2nd	Change from baseline in HbA1c: non-inferiority of post-meal faster aspart versus insulin aspart
3rd	Change from baseline in 1-h PPG increment: superiority of mealtime faster aspart versus insulin aspart
4th	Change from baseline in HbA1c: superiority of mealtime faster aspart versus insulin aspart
5th	Change from baseline in 1,5-anhydroglucitol: superiority of mealtime faster aspart versus insulin aspart

All available information regardless of treatment discontinuation was used. Rejection of the null hypothesis was only confirmed for analyses where all previous null-hypotheses had been rejected in favour of faster aspart. The hierarchical statistical testing procedure was stopped after step 4 as HbA1c superiority of faster aspart versus insulin aspart could not be confirmed.

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

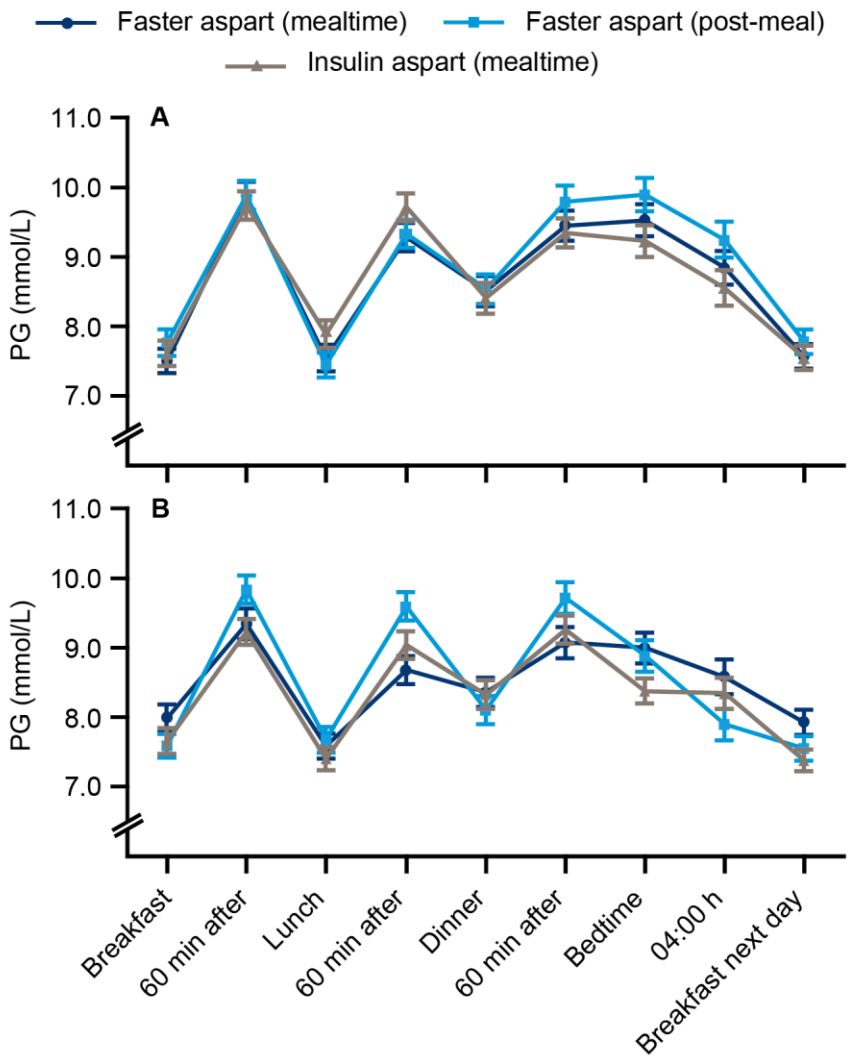
Supplementary Figure 3. Patient disposition



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.

Faster aspart, fast-acting insulin aspart.

Supplementary Figure 4. 9-point SMBG profiles at A) baseline and B) end of trial



Error bars: ± standard error (mean).

All available information regardless of treatment discontinuation was used.

PG, plasma glucose; SMBG, self-measured blood glucose.

Supplementary Table 1. Basal insulin dose conversion

Prior basal insulin dose and HbA1c	Initial insulin degludec dose
Once-daily basal insulin and HbA1c ≥8.0% (64 mmol/mol)	Switch to once-daily insulin degludec on a unit-to-unit basis at the investigator's discretion
Twice-daily basal insulin or HbA1c <8.0% (64 mmol/mol)	Switch to once-daily insulin degludec at a dose determined on an individual basis by the investigator, considering dose reduction

Supplementary Table 2. Basal insulin titration algorithm

Pre-breakfast blood glucose (mmol/L)	Insulin degludec dose adjustment (U)
<3.1	–4 (or 10% if dose >45 U)*
3.1–3.9	–2 (or 5% if dose >45 U)*
4.0–5.0	**No adjustment**
5.1–10.0	+2
10.1–15.0	+4
>15.0	+6

*Dose reduction if one of the SMBG values was below target (<4.0 mmol/L).

SMBG, self-measured blood glucose.

Supplementary Table 3. Bolus dose titration algorithm

Pre-prandial glucose (mmol/L)	Dose adjustment (U)	Rules for dose adjustments
<4.0	–1	≥1 SMBG below target
4.0–6.0	**No adjustment**	**0–1 SMBG above target** **No SMBG below target**
>6.0	+1	≥2 SMBG above target No SMBG below target

Adjustments were made twice weekly, once by the investigator and once by the participant.
SMBG, self-measured blood glucose.

Supplementary Table 4: Trial endpoints (pre-specified)

Primary endpoint	• Change from baseline in HbA1c after 26 weeks of randomized treatment
Confirmatory secondary endpoints	• Change from baseline in 1-h PPG increment (meal test) after 26 weeks of randomized treatment • Change from baseline in 1,5-anhydroglucitol 26 weeks after randomization
Supportive secondary efficacy endpoints	• Change from baseline in FPG after 26 weeks of randomized treatment • Percentage of participants reaching HbA1c targets: – <7.0% (53 mmol/mol) – <7.0% (53 mmol/mol) without severe hypoglycemia – <7.0% (53 mmol/mol) without severe hypoglycemia and with minimal weight gain (<3.0%) • Change from baseline in 30-min, 1-h, 2-h, 3-h and 4-h PPG and PPG increment (meal test) • Change from baseline in 7-9-7-point SMBG assessed by: – Mean of the 7-9-7-point profile – PPG and PPG increment (mean, breakfast, lunch, main evening meal) • Percentage of participants reaching PPG target (overall mean of daily postprandial glucose measurements in SMBG): – Overall postprandial glucose (1 h) ≤7.8 mmol/L • Change from baseline in lipids–lipoproteins profile (total cholesterol, high density lipoproteins, low density lipoproteins) • Insulin dose (basal insulin dose, total and individual meal insulin dose)

Supportive secondary safety endpoints	• Number of treatment-emergent adverse events during the 26 weeks after randomization • Number of treatment-emergent injection-site reactions during the 26 weeks after randomization • Number of hypoglycemic episodes during the 26 weeks after randomization – Overall – Following a meal (1, 1–2, 2–3, 3–4 h) • Change from baseline 26 weeks after randomization in clinical evaluations: – Physical examination – Vital signs – Electrocardiogram – Fundoscopy • Change from baseline 26 weeks after randomization in central laboratory assessments: – Hematology – Biochemistry – Urinalysis • Change from baseline in anti-insulin aspart (specific and cross-reacting with human insulin) • Change from baseline in body weight

FPG, fasting plasma glucose; PPG, postprandial glucose; SMBG, self-measured blood glucose.

Supplementary Table 5. Confirmatory statistical analysis

Endpoint [comparison]		Estimate [95% CI]	*P* value[†]	Conclusion
PRIMARY				
Step 1	**Change from baseline in HbA1c 26 weeks after randomization (%)** [mealtime faster aspart–mealtime insulin aspart]	–0.02 [–0.11; 0.07]	<0.001	*Non-inferiority confirmed with one-sided P-value*
CONFIRMATORY SECONDARY				
Step 2	**Change from baseline in HbA1c 26 weeks after randomization (%)** [post-meal faster aspart–mealtime insulin aspart]	0.10 [0.004; 0.19]	<0.001	*Non-inferiority confirmed with one-sided P-value*
Step 3	**Change from baseline in 1-h PPG increment 26 weeks after randomization (meal test) (mmol/L)** [mealtime faster aspart–mealtime insulin aspart]	–0.90 [–1.36; –0.45]	<0.001	*Superiority confirmed with one-sided P-value*
Step 4	**Change from baseline in HbA1c 26 weeks after randomization (%)** [mealtime faster aspart–mealtime insulin aspart]	–0.02 [–0.11; 0.07]	0.316	*Superiority not confirmed with one-sided P-value*
Step 5	**Change from baseline in 1,5-anhydroglucitol 26 weeks after randomization (µg/mL)** [mealtime faster aspart–mealtime insulin aspart]	0.02 [–0.31; 0.34]		*Testing procedure stopped*

[†]*P*-values are from the one-sided test for non-inferiority and superiority respectively evaluated at the 2.5% level.

All available information regardless of treatment discontinuation was used.

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

Supplementary Table 6. Summary of supportive endpoints

	Faster aspart (mealtime), %	Faster aspart (post-meal), %	Insulin aspart (mealtime), %	Treatment comparison	Estimated OR [95% CI]
HbA1c responders 26 weeks after randomization					
HbA1c <7.0% (58 mmol/mol)	28.7	28.2	32.7	Mealtime faster aspart vs. IAsp	0.88 [0.60; 1.29]
				Post-meal faster aspart vs. IAsp	0.80 [0.55; 1.17]
HbA1c <7.0 (58 mmol/mol) without severe hypoglycaemia	25.7	26.4	30.4	Mealtime faster aspart vs. IAsp	0.83 [0.56; 1.22]
				Post-meal faster aspart vs. IAsp	0.82 [0.56; 1.20]
HbA1c <7.0 (58 mmol/mol) without severe hypoglycaemia and minimal weight gain	16.4	17.9	19.3	Mealtime faster aspart vs. IAsp	0.87 [0.56; 1.34]
				Post-meal faster aspart vs. IAsp	0.95 [0.62; 1.45]
PPG responders 26 weeks after randomization					
PPG ≤7.8 mmol/L	27.8	19.9	21.6	Mealtime faster aspart vs. IAsp	1.54 [1.05; 2.26]
				Post-meal faster aspart vs. IAsp	0.98 [0.66; 1.47]

	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					
30-min PPG increment (meal test), mmol/L	–0.57	0.87	–0.05	Mealtime faster aspart vs. IAsp	–0.52 [–0.83; –0.20]*
				Post-meal faster aspart vs. IAsp	0.93 [0.61; 1.24]†
1-h PPG increment (meal test), mmol/L	–1.02	0.90	–0.12	Mealtime faster aspart vs. IAsp	–0.90 [–1.36; –0.45]†
				Post-meal faster aspart vs. IAsp	1.01 [0.56; 1.47]†

2-h PPG increment (meal test), mmol/L	–0.35	0.28	0.01	Mealtime faster aspart vs. IAsp	–0.35 [–0.98; 0.27]
				Post-meal faster aspart vs. IAsp	0.28 [–0.34; 0.90]
3-h PPG increment (meal test), mmol/L	–0.07	0.43	0.10	Mealtime faster aspart vs. IAsp	–0.16 [–0.82; 0.49]
				Post-meal faster aspart vs. IAsp	0.34 [–0.32; 0.99]
4-h PPG increment (meal test), mmol/L	–0.03	0.43	0.12	Mealtime faster aspart vs. IAsp	–0.14 [–0.74; 0.45]
				Post-meal faster aspart vs. IAsp	0.31 [–0.28; 0.90]
Mean 7-9-7-point SMBG, mmol/L	–0.30	–0.23	–0.31	Mealtime faster aspart vs. IAsp	0.07 [–0.17; 0.30]
				Post-meal faster aspart vs. IAsp	0.15 [–0.09; 0.39]
1-h PPG (SMBG, all meals), mmol/L	–0.65	–0.004	–0.25	Mealtime faster aspart vs. IAsp	–0.25 [–0.54; 0.04]
				Post-meal faster aspart vs. IAsp	0.34 [0.06; 0.63]‡
1-h PPG increment (SMBG, all meals), mmol/L	–0.72	0.08	–0.02	Mealtime faster aspart vs. IAsp	–0.48 [–0.74; –0.21]
				Post-meal faster aspart vs. IAsp	0.25 [–0.01; 0.52]
1,5-AG, µg/mL	0.23	–0.14	0.21	Mealtime faster aspart vs. IAsp	0.02 [–0.31; 0.34]
				Post-meal faster aspart vs. IAsp	–0.35 [–0.68; –0.03]§
FPG, mmol/L	0.17	0.46	0.56	Mealtime faster aspart vs. IAsp	–0.39 [–0.78; –0.0008]¶
				Post-meal faster aspart vs. IAsp	–0.10 [–0.49; 0.29]

*$P = 0.001$, †$P < 0.001$, ‡$P = 0.019$, §$P = 0.035$, ¶$P = 0.05$

All available information regardless of treatment discontinuation was used.

1,5-AG, 1,5-anhydroglucitol; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; OR, odds ratio; PPG, postprandial glucose; SMBG, self-measured blood glucose; IAsp, insulin aspart.

Supplementary Table 7. Daily bolus, basal and total insulin dose (actual) and basal/bolus ratio at week 0 and after 26 weeks of treatment

Visit (week)	Treatment	Insulin dose					
		N	Mean	SD	Median	Min	Max
Bolus dose (all meals), U							
Week 0	Faster aspart (meal)	339	25.5	15.4	22.0	5.0	150.0
	Faster aspart (post)	336	25.4	14.3	21.8	3.7	113.7
	Insulin aspart (meal)	335	26.6	14.8	23.7	6.0	100.3
Week 26*	Faster aspart (meal)	341	31.1	19.4	27.0	6.7	167.0
	Faster aspart (post)	337	30.5	18.9	26.0	5.0	142.0
	Insulin aspart (meal)	340	33.5	22.5	27.0	5.7	133.0
Basal dose, U							
Week 0	Faster aspart (meal)	342	25.3	14.5	22.0	5.0	96.0
	Faster aspart (post)	339	26.7	15.6	22.7	2.0	148.0
	Insulin aspart (meal)	339	26.2	15.0	23.3	4.0	94.0
Week 26*	Faster aspart (meal)	342	26.7	16.6	23.0	6.0	120.0
	Faster aspart (post)	339	27.3	16.8	23.0	2.0	142.0
	Insulin aspart (meal)	340	27.2	17.3	24.0	5.0	146.0
Total insulin dose, U							
Week 0	Faster aspart (meal)	339	50.8	26.1	45.3	16.3	232.0
	Faster aspart (post)	335	52.2	25.2	46.0	12.0	224.0
	Insulin aspart (meal)	335	53.1	25.9	46.0	13.0	184.0
Week 26*	Faster aspart (meal)	341	57.7	31.4	50.0	16.0	243.0
	Faster aspart (post)	336	57.8	30.2	50.7	10.7	233.0
	Insulin aspart (meal)	340	60.4	34.0	49.5	14.5	202.0
Bolus dose (all meals), U/kg							
Week 0	Faster aspart (meal)	339	0.356	0.198	0.308	0.08	1.69
	Faster aspart (post)	336	0.360	0.189	0.313	0.06	1.43
	Insulin aspart (meal)	335	0.379	0.214	0.326	0.07	1.46
Week 26*	Faster aspart (meal)	341	0.426	0.252	0.385	0.09	1.88
	Faster aspart (post)	337	0.428	0.279	0.378	0.08	2.79
	Insulin aspart (meal)	340	0.469	0.331	0.359	0.06	2.26
Basal dose, U/kg							
Week 0	Faster aspart (meal)	342	0.341	0.148	0.316	0.07	0.96

	Faster aspart (post)	339	0.365	0.171	0.332	0.02	1.70
	Insulin aspart (meal)	339	0.358	0.174	0.316	0.07	1.26
Week 26*	Faster aspart (meal)	342	0.349	0.161	0.314	0.09	1.19
	Faster aspart (post)	339	0.364	0.177	0.327	0.04	1.70
	Insulin aspart (meal)	340	0.363	0.193	0.315	0.08	1.61
Total insulin dose, U/kg							
Week 0	Faster aspart (meal)	339	0.697	0.287	0.633	0.26	2.62
	Faster aspart (post)	335	0.725	0.287	0.674	0.14	2.59
	Insulin aspart (meal)	335	0.739	0.332	0.661	0.19	2.34
Week 26*	Faster aspart (meal)	341	0.773	0.345	0.705	0.21	2.66
	Faster aspart (post)	336	0.793	0.375	0.712	0.20	3.40
	Insulin aspart (meal)	340	0.828	0.455	0.699	0.22	3.61

Basal/bolus ratio	**Faster aspart (mealtime)**	**Faster aspart (post-meal)**	**Insulin aspart (mealtime)**
Week 0	49/51	50/50	48/52
Week 26	45/55	45/55	43/57

Safety analysis set. *End of trial contains last available measurement. Bolus is the sum of all bolus injections during a day, and an average over 3 days before a visit.

Faster aspart, fast-acting insulin aspart; meal, mealtime; N, number of participants; post, post-meal; SD, standard deviation.

Supplementary Table 8. 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	240	70.2	649	3.79	237	69.5	656	3.85	248	72.5	627	3.69
Serious AEs	20	5.8	27	0.16	17	5.0	23	0.14	17	5.0	19	0.11
Injection-site reactions	8	2.3	9	0.053	8	2.3	12	0.071	5	1.5	10	0.059
Allergic reactions	9	2.6	13	0.076	14	4.1	16	0.094	11	3.2	11	0.065
Dermatitis	1	0.3	3	0.018	4	1.2	4	0.024	0	0	0	–

Treatment-emergent: events occur after 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 Appendix

Full inclusion criteria

1. Informed consent 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.
2. Male or female, age ≥18 years (for Japan and Taiwan: age ≥20 years) at the time of signing informed consent.
3. Type 1 diabetes (based on clinical judgement and/or supported by laboratory analysis as per local guidelines) ≥12 months prior to screening.
4. Currently treated with a basal–bolus insulin regimen for at least 12 months prior to screening.
5. Currently treated with a basal insulin analogue for at least 4 months prior to screening
6. HbA1c 7.0–9.5% (53–80 mmol/mol) (both inclusive) as assessed by central laboratory
7. Body mass index ≤ 35.0 kg/m^2.
8. Ability and willingness to adhere to the protocol including performing of self-measured plasma glucose profiles and meal test.
9. Ability and willingness to take at least three mealtime boluses a day every day during the trial.
10. Not currently using flash glucose monitoring or real-time continuous glucose monitoring system and/or willing not to use flash glucose monitoring or a real-time continuous glucose monitoring system during the trial.

Full exclusion criteria

1. Known or suspected hypersensitivity to trial product(s) or related products.
2. Previous participation in this trial. Participation is defined as signed informed consent.
3. Female who is pregnant, breast-feeding 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 Austria, Germany and Italy only: Adequate contraceptive measures are defined as those which result in a less than 1% failure rate per year when used consistently and correctly such as implants, injectables, combined oral contraceptives, hormonal intrauterine devices, sexual abstinence or vasectomized partner.

For Japan only: Adequate contraceptive measures are abstinence (not having sex), diaphragm, condom (by the partner), intrauterine device, sponge, spermicide or oral contraceptives.

4. Receipt of any investigational medicinal product within 4 weeks before screening.
5. Anticipated change in lifestyle (e.g. eating, exercise or sleeping pattern) during the trial.
6. Within the past 180 days any of the following: myocardial infarction, stroke or hospitalization for unstable angina and/or transient ischemic attack.
7. Participants presently classified as being in New York Heart Association Class IV.
8. Currently planned coronary, carotid or peripheral artery revascularization.
9. Inadequately treated blood pressure as defined as Class 2 hypertension or higher (systolic ≥160 mmHg or diastolic ≥100 mmHg).
10. Impaired liver function, defined as alanine aminotransferase ≥2.5 times upper limit of normal.
11. Renal impairment estimated glomerular filtration rate ≤60 mL/min/1.73 m^2 as assessed by central laboratory.
12. Anticipated initiation or change in concomitant medications in excess of two weeks known to affect weight or glucose metabolism, such as weight loss/modifying (e.g. sibutramine, orlistat, thyroid hormones, corticosteroids).
13. Proliferative retinopathy or maculopathy requiring acute treatment as verified by fundus photography or dilated fundoscopy performed within three months before screening.
14. Diabetic ketoacidosis requiring hospitalization within the last 180 days prior to screening.

15. Treatment with any medication for the indication of diabetes or obesity other than stated in the inclusion criteria in a period of 3 months before screening.
16. Diagnosis of malignant neoplasms within the last 5 years (except basal and squamous cell skin cancer, polyps and in-situ carcinomas) prior to screening.
17. Any condition which, in the opinion of the Investigator might jeopardize participant's safety or compliance with the protocol.
18. Anticipated initiation in use of real-time continuous glucose monitoring system during the trial.
19. For Austria, Germany and Italy only: Known hypoglycaemic unawareness as judged by the Investigator.
20. For Austria, Germany and Italy only: Participants with gastroparesis as judged by the Investigator.

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 treatment).

Hypoglycaemia was defined as treatment-emergent if the onset of the episode occurred on or after first day of treatment administration after randomization and no later than 1 day after the last day on treatment.

Severe hypoglycaemia was defined according to the American Diabetes Association (ADA) classification. Severe or BG-confirmed hypoglycaemia was defined as an episode that is severe according to the ADA classification* or BG-confirmed by a PG <3.1 mmol/L with or without symptoms consistent with hypoglycaemia.

*American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2018. *Diabetes Care* 2018; **41**(Suppl 1): S55–S64.

Statistical methods

Sample size calculations

The sample size was determined to ensure a sufficient power for the first step and the second step in the hierarchical testing procedure. The following assumptions were used for the sample size calculations:

	Significance level	Non-inferiority margin	SD	Mean difference
Step 1	One-sided 2.5%	0.4% (absolute)	1.2	0.0
Step 2	One-sided 2.5%	0.4% (absolute)	1.2	0.1

SD, standard deviation.

As trials in this population, where participants discontinuing treatment are followed up, is limited, a conservative estimate of the standard deviation (SD) in change from baseline in HbA1c of 1.2% was chosen. Based on t-statistics under the above assumptions, a total of 333 participants per arm gives 99.0% power to conclude HbA1c non-inferiority for the first step. This sample size gives 89.6% marginal power to conclude HbA1c non-inferiority for the second step.

Confirmatory analyses

The primary analysis was based on all participants included in the FAS using the in-trial observation period and implemented as a statistical model using multiple imputation where the participants without HbA1c measurements at scheduled visits would have their change from baseline HbA1c value(s) imputed from the available information from the treatment to which the participant had been randomized. The analysis was implemented as follows:

- In the first step, intermittent missing values were imputed using a Markov Chain Monte Carlo (MCMC) method, in order 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 bolus adjusting method at randomization (principles of flexible dosing based on the carbohydrate content of the meal or using bolus dosing algorithms) as factors, and baseline HbA1c as a covariate was fitted to the change in HbA1c from baseline to week 4 for each treatment group separately. The estimated parameters, and their variances, from these models were used to impute missing values at week 4 for participants in each treatment group, based on region, bolus adjusting method and baseline HbA1c.
- In the third step, for each of the 100 copies of the dataset, missing values at week 8 were imputed in the same way as for week 4. The imputations were based on an analysis of variance model with region and bolus adjusting method as factors and baseline HbA1c and change from baseline in HbA1c at week 4 as covariates.
- This stepwise procedure was then to be repeated sequentially for week 12, 16, 20, 24 and 26.
- For each of the complete data sets, the change from baseline to week 26 was analysed using an analysis of variance model with treatment, region, and bolus adjusting method as factors, and baseline HbA1c as a covariate.

The estimates and SDs for the 100 data sets were pooled using Rubin's formula:

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

where m_i and SD_i were the estimated means and SDs for the 100 copies of the dataset, and m_{MI} and SD_{MI} were the pooled estimates.

– From m_{MI} and SD_{MI}, 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

$$H_0: D > 0.4\% \text{ against } H_A: D \leq 0.4\%$$

was less than or equal to 2.5%, where D was the mean treatment difference (mealtime faster aspart minus mealtime IAsp).

Provided that the hierarchical testing allowed, the evaluation of HbA1c non-inferiority of post-meal faster aspart and HbA1c superiority of mealtime faster aspart (steps 2 and 4 in the hierarchical testing procedure) was to be based on the same statistical model as the primary analysis.

Rationale for using a non-inferiority margin of 0.4%: placebo-controlled trials conducted in people with type 1 diabetes are considered unethical. In people with type 2 diabetes, the addition of bolus insulin to a basal-only insulin regimen resulted in an HbA1c improvement of ~1.0%.[17] Assuming a similar effect in people with type 1 diabetes, ~0.6% of the effect would be preserved when using a non-inferiority margin of 0.4%.

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

Confirmatory secondary endpoints

Change from baseline in 1-h PPG increments 26 weeks after randomization (meal test)

Step 3 in the hierarchical testing procedure is to confirm superiority of changes from baseline in 1-h PPG increments (meal test) 26 weeks after randomization with mealtime faster aspart compared with mealtime IAsp using FAS. The 1-h PPG increment was derived using the 1-h PPG measurement minus the pre-prandial PG. Change from baseline in 1-h PPG increment 26 weeks after randomization was analysed using an analysis of variance model (ANOVA)

including treatment, region, and bolus adjusting method as factors and 1-h PPG increment at baseline as covariate.

Change from baseline in 1,5-anhydroglucitol 26 weeks after randomization

Step 5 in the hierarchical testing procedure is to confirm superiority of changes from baseline in 1,5-anhydroglucitol 26 weeks after randomization with mealtime faster aspart compared with mealtime IAsp using FAS. Change from baseline in 1,5-anhydroglucitol 26 weeks after randomization was analysed using a model similar to the primary analysis except with the corresponding baseline value as a covariate.

<u>Supportive secondary efficacy endpoints</u>

All efficacy endpoints except insulin dose were assessed using the FAS and the in-trial observation period. In-trial observation period was determined as the observation period from date of randomization and until last trial-related participant site contact. The in-trial observation period included data collected after treatment discontinuation. Insulin dose was presented based on the safety analysis set.

Change from baseline in PPG and PPG increment endpoints (meal test) 26 weeks after randomization were analysed separately using an ANOVA including treatment, region, and bolus adjusting method as factors and the corresponding baseline value as covariate.

Participants who achieved the HbA1c and PPG responder endpoints were analysed separately based on a logistic regression model using treatment, region, and bolus adjusting method as factors, and corresponding baseline value as covariate. In the analysis of each endpoint, participants without a measurement at week 26 were treated as non-responders.

The mean of the 7-9-7-point SMBG profile was defined as the area under the profile divided by the measurement time, and was calculated using the trapezoidal method. Change from baseline in the mean of the 7-9-7-point profile 26 weeks after randomization was analysed

using a model similar to primary analysis except with the corresponding baseline value as covariate.

Change from baseline in mean PPG and PPG increment overall three meals 26 weeks after randomization was analysed separately using a model similar to primary analysis, except with the corresponding baseline value as covariate.

Change from baseline in PPG and PPG increment endpoints 26 weeks after randomization for the individual meals (breakfast, lunch, main evening meal) was analysed separately using a model similar to the primary analysis except with the corresponding baseline value as covariate.

Change from baseline in FPG and 1,5-anhydroglucitol 26 weeks after randomization were analysed separately using a model similar to primary analysis except with the corresponding baseline value as covariate.

<u>Supportive secondary safety endpoints</u>

Treatment emergent adverse endpoints, physical examination, vital signs, fundoscopy, electrocardiograms and other laboratory assessments were subject to descriptive statistics using the safety analysis set. Data were collected from the date of first dose of randomized treatment up to and including 7 days after treatment discontinuation.

Treatment-emergent severe or BG-confirmed hypoglycaemic episodes were categorized in relation to time since start of meal.

- During first 1, 2, and 4 h after start of meal
- Between 1 (exclusive) to 2 h (inclusive) after start of meal
- Between 2 (exclusive) to 3 h (inclusive) after start of meal
- Between 3 (exclusive) to 4 h (inclusive) after start of meal
- Between 2 (exclusive) to 4 h (inclusive) after start of meal

The number of treatment-emergent severe or BG-confirmed hypoglycaemic episodes (all, daytime, nocturnal, 1 h, 2 h, 4 h, 1 [exclusive] to 2 h [inclusive], 2 [exclusive] to 3 h [inclusive], 3 [exclusive] to 4 h [inclusive], and from 2 h [exclusive] to 4 h [inclusive] after start of meal) were analysed using a negative binomial regression model with a log–link function and the logarithm of the time period for which a hypoglycaemic episode was considered treatment-emergent as offset. The model includes treatment, region, and bolus adjusting method as factors.

Change from baseline in body weight 26 weeks after randomization was analysed using a model similar to the primary analysis, except with the corresponding baseline value as covariate. The analysis was to be based on the safety analysis set and data collected from date of first dose of randomized treatment up to and including 7 days after treatment discontinuation.

Results

Safety endpoints

Rate of treatment-emergent severe or BG-confirmed hypoglycaemic episodes

There were no significant differences between the faster aspart (mealtime or post-meal) and IAsp arms. The estimated rate ratio [95%CI] was 0.84 (0.70;1.01) for mealtime faster aspart versus IAsp, and 0.97 (0.81;1.16) for post-meal faster aspart versus mealtime IAsp.

Change from baseline in body weight

There were no statistically significant differences between mealtime faster aspart and IAsp (ETD [95%CI] 0.19 kg [-0.22;0.60]) or post-meal faster aspart and mealtime IAsp (-0.08 kg [-0.49;0.33]).

Injection site and allergic reactions

In total, 31 were reported in 21 participants, and 40 allergic reactions were reported in 34 participants (Table 2).

Vital signs, physical examination, safety laboratory assessments

No significant clinical differences in biochemistry, haematology, lipids and urinalysis, fundoscopy, anti-IAsp antibody development (specific and cross-reacting with human insulin) and electrocardiogram, across the three treatment arms.

List of participating investigators

Austria: Rudolf Prager, Bernhard Ludvik, Thomas Pieber, Bernhard Paulweber; **Bulgaria:** Ivona Daskalova, Antoanela Slavcheva Petrova-Gancheva, Nikolay Botushanov, Katya Todorova, Zdravko Kamenov, Zhulieta Prakova-Teneva, Kiril Hristozov, Maria Orbetsova; **Canada:** Remi Rabasa-Lhoret, Thomas Peter Patrick Ransom, Buki Ajala, Martin D'Amours, Ronald M Goldenberg, Isabelle Labonté; **Germany:** Thomas Behnke, Ralf Jordan, Jörg Lüdemann, Andrea Mölle, Joachim Müller, Ludger Rose, Andreas Staudenmeyer, Uta Dorothea Stephan; **Israel:** Ofri Mosenzon, Moshe Phillip, Naim Shehadeh, Josef Cohen, Julio Wainstein, Anat Tsur; **India:** P Rao, Riddhi das Gupta, RM Anjana, Chandni R, Abhay A Mutha, Nikhil Tandon, Alok Kanungo, CS Yajnik, Tiven Marwah, Sanjeev Ratnakar Phatak, Sandeep Julka, Jaiganesh Muruganandam, Rajesh Rajput, Anil Bhansali, Vivekanand Bongi, Sunil M Jain; **Italy:** PierMaco Piatti, Roberto Trevisan, Dario Pitocco, Massimo Boemi, Agostino Gnasso, Stefano Genovese; **Japan:** Yuri Ono, Hidenori Bando, Takashi Sasaki, Hiroaki Seino, Takeshi Osonoi, Yukiko Onishi, Shinichiro Shirabe, Kiyokazu Matoba, Shizuka Kaneko, Ryoya Komatsu, Tomoyuki Kawamura, Toshikazu Takahashi, Hideaki Jinnouchi, Nobuyuki Abe, Shuji Nakamura, Rimei Nishimura, Mitsuhisa Komatsu, Yasuko Uchigata, Junnosuke Miura, Fuji Ikeda, Hiroki Ikeda, Katsuya Yamazaki, Hideo Takahashi, Eiji Kawasaki, Nobuyuki Sato; **Serbia:** Nebojsa Lalic, Katarina Lalic, Aleksandra Kendereski; **Russia:** Diana N Alpenidze, Alexandr S Ametov, Lidia V Belousova, Vadim V Klimontov, Maria A Kunitsyna, Olga E Lantseva, Tatiana A Lysenko, Nina A Petunina, Olga Sazonova, Lyudmila A Suplotova, Gulnar R Vagapova, Alexey V Zilov; **Taiwan:** Shih-Tzer Tsai, Sung-Chen Liu, Chia-Hung Lin; **USA:** John Chip Hamilton Reed, Mark P Christiansen, Carl Vance, Harold E Bays, James W Chu, Ronald Graf, David Huffman, Daniel A Nadeau, Steven Nagelberg, Leonard Ross Zemel, Elizabeth Barranco-Santana, Sumana Gangi, Phillip A Levin, John Charles Parker, Hemant Tuljaram Thawani, Kenneth Cohen, Tira Chaicha-Brom, Jackson M Rhudy, Syed WH Rizvi, John J Shelmet, Craig S Stump, Mark L Warren, Sady Alpizar, Carlos Jesus Arauz-Pacheco, Stephen L Aronoff, Anders Carlson, William C Biggs, Peter Bressler, Elizabeth Hackman Harris, Christopher Case, Harold Cathcart, Seth Charatz, John Gilbert, Priscilla Hollander, David M Kayne, Patrick McCarthy, Helena W Rodbard, Paul Rosenblit, Stephanie Shaw, Larry Stonesifer, Leslie J Klaff, Michael Valitutto, Jesus L Penabad, Alan Wynne, Michael Adams, Robert Hood, James Wood, Jack Wahlen, Gregg Gerety, Lyle Myers, Paul C Norwood, Julio

Rosenstock, Kristin Castorino, Anna Chang, Robert Ferraro, Samer N Nakhle, Robert J Silver, Timothy S Bailey, Valerie Espinosa.