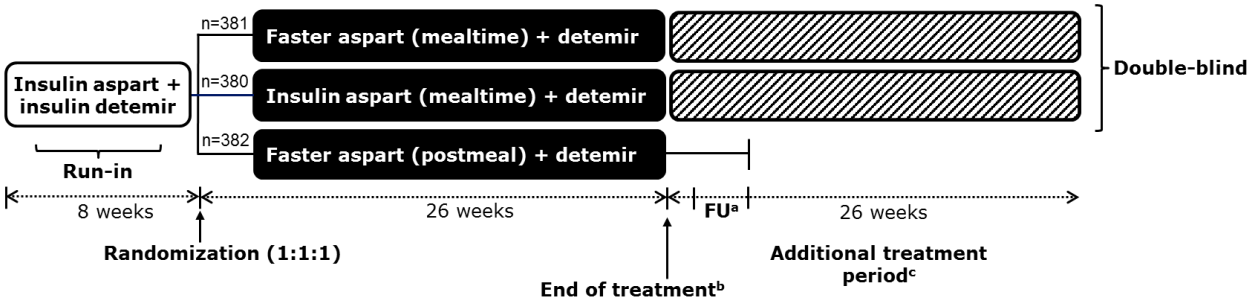
SUPPLEMENTARY DATA

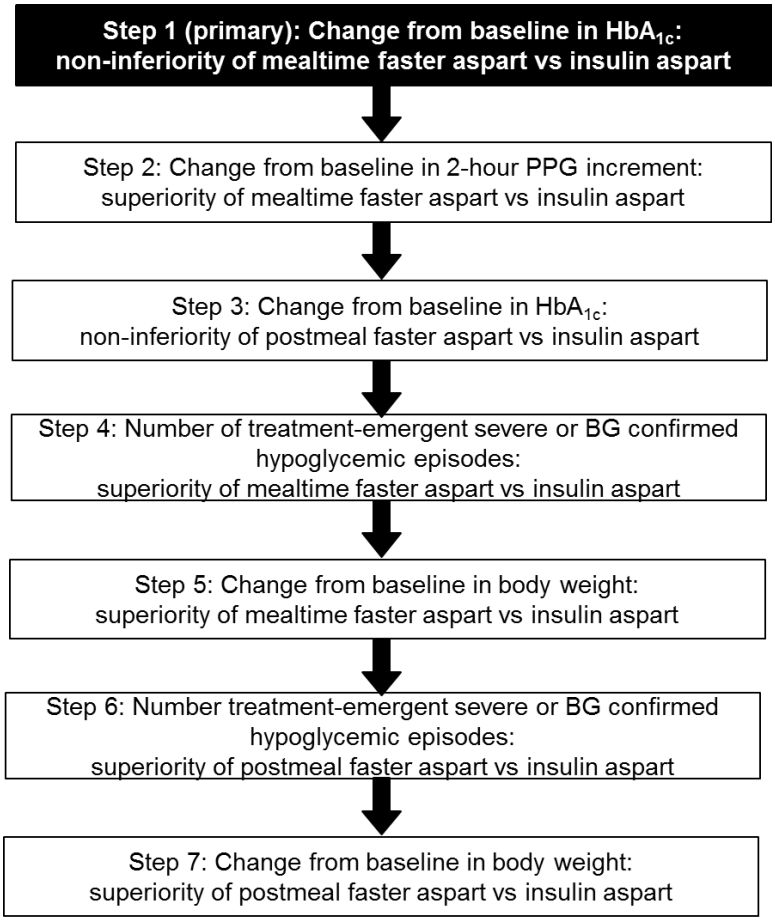
Supplementary Figure 1. Onset 1: a randomized, treat-to-target trial



This trial is registered at ClinicalTrials.gov: NCT01831765. [a]FU (7–30 days). [b]Primary endpoint. [c]Results from the additional treatment period will not be presented here. Faster aspart, fast-acting insulin aspart; FU, follow-up.

SUPPLEMENTARY DATA

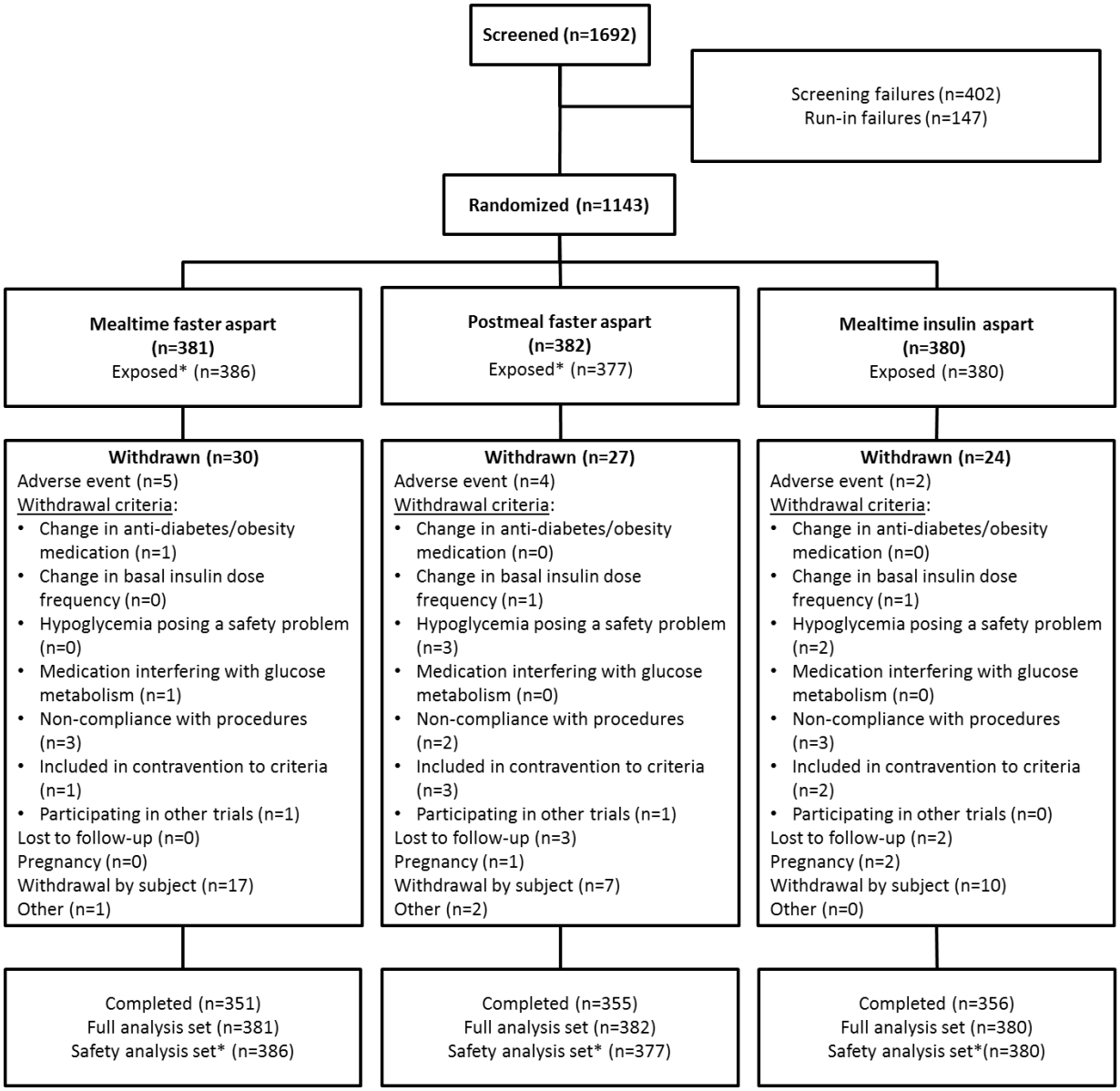
Supplementary Figure 2. Stepwise hierarchical testing procedure for confirmatory endpoints



Once non-inferiority of mealtime faster aspart versus insulin aspart was confirmed in terms of change from baseline in HbA_{1c} after 26 weeks of treatment (Step 1), the confirmatory statistical analyses could proceed to the next step. The hierarchical (fixed-sequence) testing was based on a priority ordering of the null-hypotheses – testing using the two-sided 95% CI approach until an insignificant result appeared. As superiority of mealtime faster aspart in terms of number of treatment-emergent severe or BG confirmed hypoglycemic episodes from baseline until Week 26 (Step 4) could not be confirmed, the hierarchical statistical testing procedure was stopped. BG, blood glucose; CI, confidence interval; faster aspart, fast-acting insulin aspart; HbA_{1c}, glycosylated hemoglobin; PPG, postprandial plasma glucose.

SUPPLEMENTARY DATA

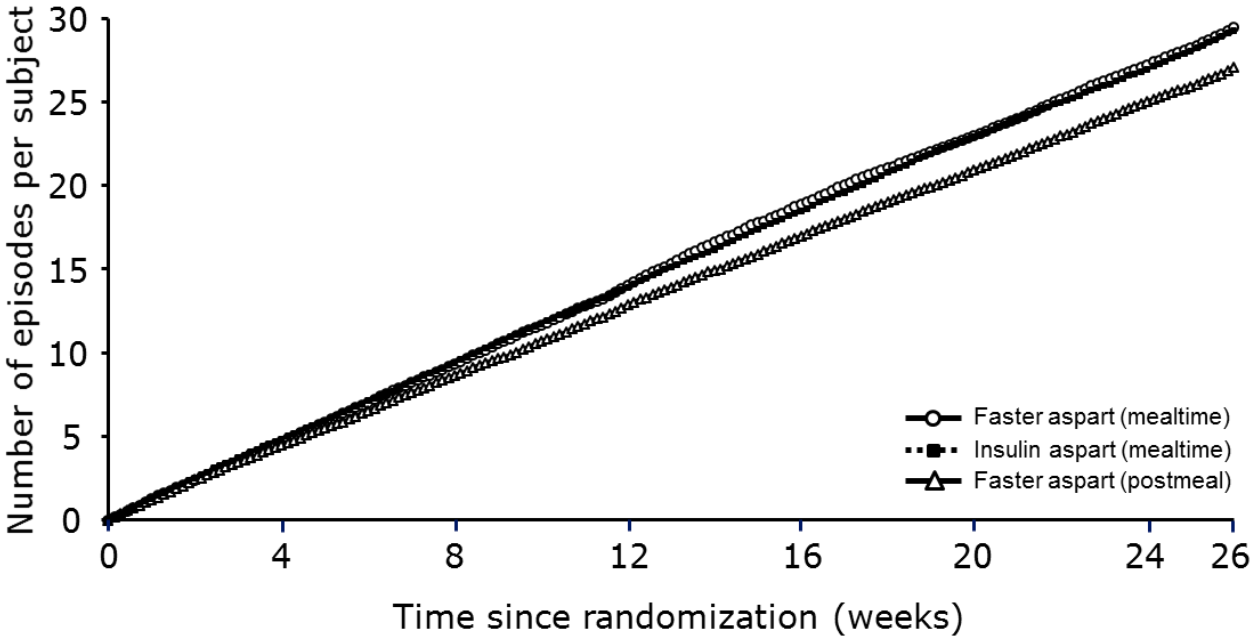
Supplementary Figure 3. Subject disposition



A total of 1,290 subjects entered the run-in period of the trial; the most common reason for failure during the run-in period was withdrawal by subject (n=64). *Five subjects were randomized to receive postmeal faster aspart but had consistently taken their bolus insulin before the meal, throughout the trial, so they were considered as having been treated with mealtime faster aspart. Faster aspart, fast-acting insulin aspart.

SUPPLEMENTARY DATA

Supplementary Figure 4. Treatment-emergent hypoglycemia (severe or BG confirmed) mean cumulative function



Severe or BG confirmed hypoglycemia was defined as an episode that is severe according to the ADA classification (28) or BG confirmed by a PG value <3.1 mmol/L (56 mg/dL) with or without hypoglycemic symptoms. ADA, American Diabetes Association; BG, blood glucose; faster aspart, fast-acting insulin aspart; PG, plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 1. Adjustment of insulin detemir during the run-in period for subjects on a once-daily regimen

mmol/L	mg/dL	Dose adjustment for OD dosing (U)
<3.1	<56	–4 (or 10% if dose >45 U)*
3.1–3.9	56–70	–2 (or 5% if dose >45 U)*
4.0–5.0	71–90	No adjustment
5.1–10.0	91–180	+2
10.1–15.0	181–270	+4
>15.0	>270	+6

Dose adjustments at the evening meal were based on the mean of three pre-breakfast SMPG values measured on the 3 days prior to a dosing visit. *Dose reduction if one of the SMPG values was below target (<4.0 mmol/L [71 mg/dL]). During the 8-week run-in period, the subject was allowed to switch dosing frequency at the investigator's discretion; however, a switch after randomization constituted a withdrawal. OD, once-daily; SMPG, self-monitored plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 2. Adjustment of insulin detemir during the run-in period for subjects on a twice-daily regimen

mmol/L	mg/dL	Dose adjustment for BID dosing (U)
<3.1	<56	–4 (or 10% if dose >45 U)*
3.1–3.9	56–70	–2 (or 5% if dose >45 U)*
4.0–6.0	71–108	No adjustment
6.1–10.0	109–180	+2
10.1–15.0	181–270	+4
>15.0	>270	+6

Dose adjustments in the morning were based on the mean of three pre-dinner SMPG values measured on the 3 days prior to a dosing visit. *Dose reduction if one of the SMPG values was below target (<4.0 mmol/L [71 mg/dL]). During the 8-week run-in period, the subject was allowed to switch dosing frequency at the investigator's discretion; however, a switch after randomization constituted a withdrawal. BID, twice-daily; SMPG, self-monitored plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 3. Bolus dosing algorithm

Pre-prandial or bedtime plasma glucose mmol/L	mg/dL	Dose adjustment U	Rules for dose adjustments
<4.0	<71	–1	≥1 SMPGs below target
4.0–6.0	71–108	0	0–1 SMPG above targetNo SMPGs below target
>6.0	>108	+1	≥2 SMPGs above targetNo SMPGs below target

Insulin aspart and faster aspart adjustments were performed twice weekly (once by investigator, once by subjects), based on pre-prandial and bedtime SMPGs on the previous 3–4 days before each site visit/phone contact.Additional bolus dosing was allowed at the investigator's discretion. Faster aspart, fast-acting insulin aspart; SMPG, self-monitored plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 4. Trial endpoints (pre-specified)

Primary endpoint	• Change from baseline in HbA_{1c} after 26 weeks of randomized treatment
Confirmatory secondary endpoints	• Change from baseline in 2-hour PPG increment (meal test) after 26 weeks of randomized treatment • Number of treatment-emergent severe or BG confirmed hypoglycemic events from baseline until Week 26 • Change from baseline in body weight after 26 weeks of randomized treatment
Supportive secondary efficacy endpoints	• HbA_{1c} responder endpoints after 26 weeks of randomized treatment: – Percentage of subjects reaching HbA_{1c} <7% (53 mmol/mol/) or HbA_{1c} ≤6.5% (47.8 mmol/mol) • Change from baseline in PPG and PPG increments (meal test) after 26 weeks of randomized treatment • 7-9-7-point SMPG profiles after 26 weeks of randomized treatment: – Change from baseline in the mean of the 7-9-7-point SMPG profile – Change from baseline in PPG and PPG increment (7-9-7-point profile) • PPG responders (overall mean of daily PPG measurements in SMPG) after 26 weeks of randomized treatment: – Percentage of subjects reaching overall mean 2-hour PPG (SMPG) ≤7.8 mmol/L (140 mg/dL) • Change from baseline in 1,5-anhydroglucitol after 26 weeks of randomized treatment • Change from baseline in FPG after 26 weeks of randomized treatment • Insulin dose (basal insulin dose(s), total and individual mean bolus insulin dose) after 26 weeks of randomized treatment
Supportive secondary safety endpoints	• Number of adverse events during the trial • Number of treatment-emergent hypoglycemic episodes during the trial classified according to the ADA definition and an additional Novo Nordisk classification • Number of treatment-emergent hypoglycemic episodes related to a meal classified according to the ADA definition and an additional Novo Nordisk classification • Number of treatment-emergent injection-site reactions related to either basal or bolus insulin

- Change from baseline in laboratory safety parameters after 26 weeks of randomized treatment
- Change from baseline in clinical safety parameters from baseline after 26 weeks of randomized treatment

ADA, American Diabetes Association; BG, blood glucose; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; SMPG, self-monitored plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 5. Confirmatory statistical analysis

Endpoint [comparison]		Estimate [95% CI]	*P* value[a]	Conclusion
PRIMARY				
Step 1	**Change from baseline in HbA_{1c} after 26 weeks of treatment** [mealtime faster aspart–mealtime insulin aspart]	–0.15 [–0.23; –0.07]	<0.0001	*Non-inferiority confirmed*
CONFIRMATORY SECONDARY				
Step 2	**Change from baseline in 2-hour PPG increment after 26 weeks of treatment (meal test)** [mealtime faster aspart–mealtime insulin aspart]	–0.67 [–1.29; –0.04]	0.0375	*Superiority confirmed*
Step 3	**Change from baseline in HbA_{1c} after 26 weeks of treatment** [postmeal faster aspart–mealtime insulin aspart]	0.04 [–0.04; 0.12]	<0.0001	*Non-inferiority confirmed*
Step 4	**Number of treatment emergent severe or BG confirmed hypoglycemic episodes** [mealtime faster aspart–mealtime insulin aspart]	1.01 [0.88; 1.15]	0.9191	*Superiority not confirmed*
Step 5	**Change from baseline in body weight after 26 weeks of treatment** [mealtime faster aspart–mealtime insulin aspart]	0.12 [–0.30; 0.55]	0.5648	*Testing procedure stopped*
Step 6	**Number of treatment emergent severe or BG confirmed hypoglycemic episodes** [postmeal faster aspart–mealtime insulin aspart]	0.92 [0.81; 1.06]	0.2435	
Step 7	**Change from baseline in body weight after 26 weeks of treatment** [postmeal faster aspart–mealtime insulin aspart]	0.16 [–0.27; 0.58]	0.4691	

[a]P values for non-inferiority are from the 1-sided test, evaluated at the 2.5% level; all other P values for superiority are from the 2-sided test, evaluated at the 5% level. BG, blood glucose; CI, confidence interval; PPG, postprandial plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 6. Summary of supportive endpoints

	Faster aspart (mealtime)	Faster aspart (postmeal)	Insulin aspart (mealtime)	Treatment arm	Estimated OR [95% CI]
HbA_{1c} responders after 26 weeks of treatment, %					
HbA_{1c} <7.0% (58.0 mmol/mol)	33.3	23.3	28.2	Mealtime faster aspart	1.47 [1.02; 2.13]*
				Postmeal faster aspart	0.73 [0.49; 1.07]
HbA_{1c} ≤6.5% (47.8 mmol/mol)	14.4	7.9	12.4	Mealtime faster aspart	1.26 [0.78; 2.03]
				Postmeal faster aspart	0.52 [0.30; 0.91]**
PPG responders after 26 weeks of treatment, %					
PPG ≤7.8mmol/L (140mg/dL)	42.7	39.6	38.6	Mealtime faster aspart	1.33 [0.95; 1.84]
				Postmeal faster aspart	1.02 [0.73; 1.42]
					ETD [95% CI]
Change from baseline after 26 weeks of treatment					
1-h PPG (meal test)					
mmol/L	–1.00	1.10	0.42	Mealtime faster aspart	–1.41 [–2.00; –0.82]†
mg/dL	–17.96	19.86	7.48		–25.44 [–36.12; –14.76]†
				Postmeal faster aspart	0.69 [0.09; 1.28]‡
					12.38 [1.65; 23.11]‡
2-h PPG (meal test)					
mmol/L	–0.44	0.55	0.49	Mealtime faster aspart	–0.93 [–1.62; –0.23]‖
mg/dL	–7.94	9.87	8.78		–16.73 [–29.26; –4.20]‖
				Postmeal faster aspart	0.06 [–0.64; 0.76]
					1.08 [–11.49; 13.66]
Mean 7-9-7-point SMPG profiles					
mmol/L	–0.34	–0.44	–0.27	Mealtime faster aspart	–0.07 [–0.29; 0.15]
mg/dL	–6.16	–7.95	–4.94		–1.22 [–5.20; 2.76]
				Postmeal faster aspart	–0.17 [–0.39; 0.05]
					–3.01 [–6.97; 0.96]
2-h PPG (SMPG)					
mmol/L	–0.59	–0.51	–0.44	Mealtime faster aspart	–0.15 [–0.43; 0.12]
mg/dL	–10.67	–9.18	–7.89		–2.78 [–7.74; 2.19]
				Postmeal faster aspart	–0.07 [–0.35; 0.20]
					–1.29 [–6.24; 3.66]
2-h PPG increment (SMPG)					
mmol/L	–0.54	–0.30	–0.33	Mealtime faster aspart	–0.21 [–0.47; 0.05]
mg/dL	–9.65	–5.44	–5.86		–3.79 [–8.49; 0.91]

				Postmeal faster aspart	0.02 [–0.24; 0.28] 0.41 [–4.27; 5.10]
1,5-AG					
µg/mL	0.85	0.19	0.35	Mealtime faster aspart	0.50 [0.24; 0.76]**
				Postmeal faster aspart	–0.16 [–0.42; 0.10]
FPG					
mmol/L	–0.17	–0.15	0.08	Mealtime faster aspart	–0.25 [–0.68; 0.18];
mg/dL	–3.08	–2.69	1.43		–4.51 [–12.28; 3.26]
				Postmeal faster aspart	–0.23 [–0.66; 0.20];
					–4.12 [–11.83; 3.59]

*P=0.0405 in favor of mealtime faster aspart; **P=0.0205 in favor of insulin aspart; †P<0.0001 in favor of mealtime faster aspart; ‡P=0.0238 in favor of insulin aspart ‖P=0.0089 in favor of mealtime faster aspart; **P=0.0001 in favor of mealtime faster aspart 1,5-AG, 1,5-anhydroglucitol; CI, confidence interval; ETD, estimated treatment difference (faster aspart–insulin aspart); faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; OR, odds ratio (faster aspart/insulin aspart); PPG, postprandial plasma glucose.

SUPPLEMENTARY DATA

Supplementary Table 7. Daily bolus, basal and total insulin dose (actual) and basal/bolus ratio at Week 1 and after 26 weeks of treatment

Visit (Week)	Treatment	Insulin dose N	Mean	SD	Median	Min	Max
Bolus dose (all meals), U							
Week 1	Faster aspart (meal)	370	29.3	16.0	25.7	5	112
	Faster aspart (post)	361	30.6	16.5	27.3	5	135
	Insulin aspart (meal)	370	32.5	20.3	26.8	4	154
Week 26	Faster aspart (meal)	386	36.8	26.5	29.7	6	286
	Faster aspart (post)	377	36.6	23.9	31.0	6	215
	Insulin aspart (meal)	380	37.7	27.0	30.0	5	197
Basal dose, U							
Week 1	Faster aspart (meal)	380	35.8	21.9	32.0	4	240
	Faster aspart (post)	370	38.7	20.9	34.0	6	126
	Insulin aspart (meal)	379	38.0	20.0	32.0	7	138
Week 26	Faster aspart (meal)	386	36.1	24.8	30.0	4	300
	Faster aspart (post)	377	40.0	24.8	34.0	7	160
	Insulin aspart (meal)	380	38.5	22.2	32.0	7	137
Total insulin dose, U							
Week 1	Faster aspart (meal)	370	65.0	31.9	58.0	20	265
	Faster aspart (post)	361	69.4	31.7	63.3	13	206
	Insulin aspart (meal)	370	70.4	34.8	62.7	20	292
Week 26	Faster aspart (meal)	386	72.9	42.1	61.3	17	383
	Faster aspart (post)	377	76.6	40.6	66.3	21	261
	Insulin aspart (meal)	380	76.2	43.0	65.8	17	301
Bolus dose (all meals), U/kg							
Week 1	Faster aspart (meal)	370	0.370	0.175	0.334	0.09	1.09
	Faster aspart (post)	361	0.374	0.176	0.348	0.07	1.45
	Insulin aspart (meal)	370	0.397	0.209	0.360	0.05	1.50
Week 26	Faster aspart (meal)	386	0.460	0.295	0.387	0.09	2.11
	Faster aspart (post)	377	0.447	0.273	0.392	0.09	2.69
	Insulin aspart (meal)	380	0.454	0.272	0.379	0.09	1.93

Basal dose, U/kg							
Week 1	Faster aspart (meal)	380	0.451	0.247	0.405	0.05	2.62
	Faster aspart (post)	370	0.472	0.225	0.433	0.09	1.43
	Insulin aspart (meal)	370	0.467	0.219	0.432	0.09	1.64
Week 26	Faster aspart (meal)	386	0.449	0.270	0.388	0.05	3.22
	Faster aspart (post)	377	0.493	0.262	0.417	0.09	1.57
	Insulin aspart (meal)	380	0.467	0.232	0.425	0.08	1.59
Total insulin dose, U/kg							
Week 1	Faster aspart (meal)	370	0.819	0.339	0.752	0.30	2.89
	Faster aspart (post)	361	0.847	0.316	0.789	0.25	2.31
	Insulin aspart (meal)	370	0.864	0.349	0.784	0.29	2.95
Week 26	Faster aspart (meal)	386	0.909	0.447	0.801	0.25	3.79
	Faster aspart (post)	377	0.929	0.424	0.842	0.34	3.27
	Insulin aspart (meal)	380	0.922	0.421	0.833	0.33	3.29

Basal/bolus ratio	**Faster aspart (mealtime)**	**Faster aspart (postmeal)**	**Insulin aspart (mealtime)**
Week 1	55/45	56/44	54/46
Week 26	49/51	52/48	51/49

Safety analysis set. End of trial contains last available measurement. Faster aspart, fast-acting insulin aspart; meal, mealtime; N, number of subjects; post, postmeal; SD, standard deviation.

SUPPLEMENTARY DATA

Supplementary Table 8. TEAEs

	Faster aspart(mealtime)				Faster aspart(postmeal)				Insulin aspart(mealtime)			
	N	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**	**N**	**(%)**	**E**	**R**
Treatment-emergent AEs	284	(74)	892	4.79	264	(70)	807	4.41	285	(75)	866	4.58
SAEs	19	(5)	25	0.13	28	(7)	36	0.20	22	(6)	24	0.13
Injection-site reactions	7	(1.8)	9	0.05	9	(2.4)	10	0.06	3	(0.8)	3	0.02
Allergic reactions	38	(9.8)	42	0.23	31	(8.2)	36	0.20	38	(10.0)	45	0.24
Cough	10	(2.6)	11	0.06	12	(3.2)	13	0.07	12	(3.2)	12	0.06
Rash	6	(1.6)	6	0.03	3	(0.8)	3	0.02	2	(0.5)	2	0.01
Seasonal allergy	5	(1.3)	5	0.03	3	(0.8)	3	0.02	6	(1.6)	7	0.04

Treatment emergent: events occur after trial product administration after randomization and no later than 7 days after last trial product administration. A SAE was defined as any of the following: suspicion of infectious agents; death; life-threatening experience; in-patient 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 subject and require medical or surgical intervention to prevent one of the outcomes listed in this definition. All reported injection-site reactions (>1% subjects) include: injection-site reaction, injection-site bruising, injection-site hypertrophy, injection-site erythema, injection-site hematoma and injection-site irritation. In total, 11 injection-site reactions were judged as possibly/probably related to either bolus insulin (n=5) or to both basal and bolus insulin (n=6): of these, 10 were observed in the faster aspart groups (six in the postmeal group and four in the mealtime group) and one was seen in the insulin aspart group. %, percentage of subjects; AE, adverse event; E, events; faster aspart, fast-acting insulin aspart; N, number; R, rate; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

SUPPLEMENTARY DATA

Supplementary Table 9. Adjudicated cardiovascular events.

	Faster aspart (mealtime)	Faster aspart (postmeal)	Insulin aspart (mealtime)
Events sent for adjudication	3	6	1
Events positively adjudicated	2	3	1
MACE	0	2	1
NSTEMI	0	1	0
Stroke	0	0	1
Cardiovascular death	0	1	0
Not categorized as MACE	2	1	0

Faster aspart, fast-acting insulin aspart; MACE, major adverse cardiovascular event; NSTEMI: non-ST-elevation myocardial infarction.

SUPPLEMENTARY DATA

Deaths during the trial

A 55-year-old male subject (not randomized) died during the run-in period due to a self-inflicted gun-shot wound (PT: self-injurious behavior). The most recent hypoglycemic episode reported was 3 days prior to the event. The event was judged by the investigator to be unlikely related to run-in trial product.

A 39-year-old male (treated with postmeal faster aspart) died on Day 96 of the trial. After autopsy, death was attributed to coronary atherosclerotic disease; the investigator and the sponsor judged the fatal event unlikely to be related to trial product and the death was later adjudicated and classified as a cardiovascular death. His medical history included type 1 diabetes (since 1991) and diabetic neuropathy (since 2000), and he was reported by the trial investigator as having coronary atherosclerotic disease.

Supplementary Appendix

Trial inclusion criteria

1. Informed consent obtained before any trial-related activities
2. Female or male, age ≥18 years at the time of screening (Visit 1)
3. Type 1 diabetes (diagnosed clinically) ≥12 months at the time of screening
4. Currently treated with a basal–bolus insulin regimen for ≥12 months prior to screening
5. Currently treated with a basal insulin analog (any regimen of insulin detemir or insulin glargine) for ≥4 months prior to screening
6. Glycosylated hemoglobin (HbA_{1c}) 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 performance of self-monitored plasma glucose (SMPG) profiles
9. Ability and willingness to eat ≥3 meals (breakfast, lunch and dinner) every day during the trial
10. Not currently using real-time continuous glucose monitoring (CGM) system and/or willing not to use a real-time CGM system during the trial other than the blinded one handed out in the trial if selected to the CGM subgroup

SUPPLEMENTARY DATA

Trial exclusion criteria

1. Use of any antidiabetic drug other than insulin within the last 3 months prior to screening
2. Anticipated change in concomitant medication known to interfere significantly with glucose metabolism, such as systemic corticosteroids, beta-blockers, monoamine oxidase inhibitors, or anti-obesity medications
3. Cardiovascular disease within the last 6 months prior to screening, defined as: stroke, decompensated heart failure New York Heart Association class III or IV, myocardial infarction, unstable angina pectoris, or coronary arterial bypass graft or angioplasty
4. Resting systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥100 mmHg
5. Impaired liver function, defined as ALAT/SGPT ≥2.5 times upper limit of normal, according to central laboratory reference ranges
6. Impaired renal function defined as serum creatinine ≥180 µmol/L (≥2.0 mg/dL) as assessed by central laboratory
7. Recurrent severe hypoglycemia (>1 severe hypoglycemic event during the last 12 months) or hypoglycemic unawareness as judged by the investigator, or hospitalization for diabetic ketoacidosis during the previous 6 months prior to screening
8. Proliferative retinopathy or maculopathy requiring treatment according to the investigator's judgement
9. Female of childbearing potential who is pregnant, breastfeeding or intending to become pregnant, or is not using adequate contraceptive methods (as required by local law or practice)
10. Any clinically significant disease or disorder, except for conditions associated with type 1 diabetes, which, in the opinion of the investigator, might jeopardize the subject's safety or compliance with the protocol
11. Any condition that the investigator judges would interfere with evaluation of the results
12. A life-threatening disease, including malignant neoplasms and medical history of malignant neoplasms, within the last 5 years (except basal and squamous cell skin cancer) prior to screening
13. Mental incapacity, psychiatric disorder, unwillingness, or language barriers precluding adequate understanding or co-operation as judged by the investigator, including subjects unable to read or write
14. Previous participation in this trial. Participation is defined as inclusion in the run-in period (Visit 2)
15. Known or suspected hypersensitivity to any of the trial products or related products
16. The receipt of any investigational product within 1 month prior to screening
17. Donation of blood within 1 month prior to screening
18. Known or suspected abuse of alcohol, narcotics, or illicit drugs

SUPPLEMENTARY DATA

Statistical appendix

Sample size calculations

The sample size was determined to ensure sufficient power in the first three steps in the hierarchical testing procedure. The calculation is based on the assumption that all withdrawn subjects, as anticipated, will have a measurement for the end-of-trial meal test. Furthermore 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)	1.15	0.0
Step 2	Two-sided 5.0%	NA	3.80	1.0
Step 3	One-sided 2.5%	0.4% (absolute)	1.15	0.1

NA, not applicable; SD, standard deviation.

With more than 365 subjects in each treatment arm there will be more than 90% power to reject the null hypothesis in the third step, i.e. a total of 1,095 subjects is required. With this given sample size there will also be more than 90% power to reject the null hypothesis under the given assumptions (Table) for the previous two tests.

Confirmatory analyses

The primary analysis included treatment, region, and stratification (including eight strata) based on the combination of method of insulin dose adjustment from randomization and onwards (principles of flexible dosing based on the carbohydrate content of the meal or using bolus dosing algorithms), CGM and frequently sampled meal test subgroup inclusion (yes or no) and basal dosing regimen (once or twice daily dosing) as fixed effects, subject as a random effect, HbA_{1c} at baseline as covariate and interactions between all fixed effects and visit and between the covariate and visit. An unstructured covariance matrix was used to describe the variability for the repeated measurements for a subject. From this model, contrasts would be set up to estimate the treatment difference after 26 weeks together with a 95% CI and associated p-value. Non-inferiority was considered confirmed if the upper boundary of the two-sided 95% confidence interval is below or equal to 0.4% or equivalent if the p-value for the one-sided test of
H_0: $D > 0.4\%$ against H_A: $D \leq 0.4\%$,
is less than or equal to 2.5%, where D is the mean treatment difference

The second confirmatory endpoint in the hierarchical testing procedure, the 2-h PPG increment, was analyzed using an analysis of variance (ANOVA) model including treatment, stratification and region as factors, and with the 2-h PPG increment at baseline as a covariate.

SUPPLEMENTARY DATA

The third step in the hierarchical testing procedure investigated the hypothesis of non-inferiority of post-meal administration of faster aspart versus insulin aspart in change from baseline in HbA_{1c} after 26 weeks of randomized treatment. This was done using a non-inferiority margin of 0.4%; the estimate and corresponding CIs were obtained from the same model as the primary statistical analysis model described above.

The fourth confirmatory endpoint was the number of treatment-emergent severe or BG confirmed hypoglycemic events from baseline until Week 26. This endpoint was analyzed using a negative binomial regression model with a log-link function, and the logarithm of the time period in which a hypoglycemic episode was considered treatment-emergent as offset; the model included treatment, stratification and region as factors.
The remaining confirmatory hypothesis and endpoints were analysed using similar methods to the above mentioned models.

Supportive secondary efficacy endpoints

Subjects who achieved the HbA_{1c} and PPG responder endpoints were analyzed separately based on a logistic regression model using treatment, stratification, and region as factors, and baseline HbA_{1c} and mean 2-h PPG as covariate, respectively.

The mean of the 7-9-7-point SMPG profile is defined as the area under the profile divided by the measurement time, and is calculated using the trapezoidal method. The endpoint is analyzed based on all planned post-baseline measurements until Week 26 using a MMRM similar to the model used for analysis of the primary endpoint and the corresponding baseline value as covariate.

Change from baseline after 26 weeks of treatment in PPG and PPG increment endpoints were analyzed separately using an ANOVA model including treatment, stratification, and region as factors and the corresponding baseline PPG or PPG increment as covariate.

Change from baseline in FPG and 1,5-AG at Week 26 was analyzed separately using all planned post-baseline measurements until Week 26, with an MMRM model similar to that used for analysis of the primary endpoint, except with the corresponding baseline value as covariate.

Supportive secondary safety endpoints

Treatment emergent adverse endpoints, MACE, physical examination, vital signs, fundoscopy, electrocardiograms and other laboratory assessments were subject to descriptive statistics using the SAS.

Treatment-emergent severe or BG confirmed hypoglycemic episodes were categorized in relation to time since start of meal, and recorded as occurring during 1 and 2 h after the meal. These were analyzed in the same way as overall treatment-emergent severe or BG confirmed hypoglycemic episodes.

SUPPLEMENTARY DATA

List of participating investigators

Belgium: Laurent Crenier, Christophe De Block, Chantal Mathieu, Guy T'Sjoen, Chris Vercammen; **Canada**: Keith C. Bowering, Martin D'Amours, Irving Gottesman, Stewart B. Harris, Irene Mary Hramiak, David Bruce Miller, Bruce A. Perkins, Zubin Punthakee, Remi Rabasa-Lhoret, Peter A. Senior, Bruno St-Pierre, Vincent C. Woo; **Czech Republic**: Jindřich Olšovský, Terezie Pelikánová, Martin Prázný, Jana Psottová, Alena Šmahelová; **Finland**: Päivi Kokkila, Jorma Lahtela, Merja Laine, Helena Likitalo, Jüri Linros, Lorenzo Sandini, Atte Vaden; **Germany**: Stephan Arndt, Thomas Behnke, Andreas Hagenow, Elena Henkel, Hans-Peter Kempe, Jost Hilgenberg, Jörg Lüdemann, Karsten Milek, Andrea Mölle, Joachim Müller, Peter Nitsche, Rainer Paulus, Ludger Rose, Armin Sammler, Joachim Sauter, Thomas Schaum, Toralf Schwarz, Alexander Segner, Jörg Simon, Andreas Staudenmeyer, Uta Dorothea Stephan, Simon Vidal, Ulrich Wendisch, Veronika Wenzl-Bauer, Hubert Wübbolding; **Hungary**: Marietta Baranyai, László Deák, Győző Kocsis, Gizella Petró, Robert Takács, Krisztina Wudi; **Poland**: Malgorzata Arciszewska, Irena Babol, Edward Franek, Jaroslaw Ogonowski, Ewa Skokowska, Andrzej Stankiewicz; **United Kingdom**: Michael Cummings, Andrew Gough, Simon Heller, Robert Lindsay, Sandra MacRury, Gerry Rayman, Peter Mansell, Antony Robinson, David Russell-Jones; **USA**: Andrew Ahmann, Amer Al-Karadsheh, Vanita Aroda, Stephen Aronoff, Timothy Bailey, Claire Baker, Richard Bergenstal, Subodh Bhuchar, William Biggs, Bruce Bode, Guenther Boden, Ronald Brazg, Peter Bressler, John Buse, Edward Busick, Luis Casaubon, Kristin Castorino, Harold Cathcart, Anna Chang, Deanna Cheung, Ronald Chochinov, Mark Christiansen, Elena Christofides, Jonathan Condit, Michael Dempsey, Gautam Desai, Thomas Donner, Steven Duckor, Ramanath Dukkipati, William Ervin, John Evans, Robert Ferraro, Raymond Fink, David Fitz-Patrick, Zachary Freedman, Bernard Garcia, Gregg Gerety, John Gilbert, Janice Gilden, Michael J. Gonzalez-Campoy, Craig Greenberg, Priscilla Hollander, Robert Hood, David Huffman, Patricia Kapsner, Dennis Karounos, Ahsan Kazmi, Eric Klein, James Lenhard, Sam Lerman, David Levenson, Philip Levin, Carol Levy, William Litchfield, Kathryn Lucas, Michael MacAdams, Stephen Maddock, Hiralal Maheshwari, Louis Maletz, Samir Malkani, Frank Mikell, Alan Miller, Bresta Miranda-Palma, Lyle Myers, Samer Nakhle, Joshua Neumiller, Paul Norwood, Adeniyi Odugbesan, Guido Perez, Athena Philis-Tsimikas, John Pullman, Philip Raskin, John Reed, Michael Robinson, Josette Romain, Julio Rosenstock, Jeffrey Rothman, Michael Shanik, Stephanie Shaw, Heidi Shea, John Shelmet, Robert Silver, Teresa Sligh, Christin Snyder, Stanley Stringam, Craig Stump, Danny Sugimoto, Martin Valdes, Carl Vance, Mark Warren, Sandra Weber, Daniel Weiss, Peter Weissman, Alan Wynne, Carol Wysham, Leonard Zemel.