Addition of fast-acting insulin aspart to basal insulin significantly improves glycaemic control in adults with type 2 diabetes: the onset 3 trial

1. Helena W. Rodbard
Endocrine and Metabolic Consultants, Rockville, MD, USA

2. Devjit Tripathy
Division of Diabetes, University of Texas Health Science Center, San Antonio, TX, USA

3. Maricela Vidrio Velázquez
Endocrinology, Metabolism and Nutrition, Hospital General Regional 110, Guadalajara, Mexico

4. Marek Demissie
Novo Nordisk A/S, Søborg, Denmark

5. Søren Can Tamer
Novo Nordisk A/S, Søborg, Denmark

6. Milivoj Piletič
General Hospital, Novo Mesto, Slovenia

Introduction

- Due to the progressive nature of type 2 diabetes (T2D),[1] further treatment intensification may be required when target glycosylated haemoglobin (HbA_{1c}) levels <7.0% [53 mmol/mol][2] or ≤6.5% [48 mmol/mol][3] (or other individual HbA_{1c} target level) have not been achieved after 3–6 months of basal insulin titration.[4]
- As HbA_{1c} levels approach 7.0% (53 mmol/mol), the dominant contributor to glycaemic control becomes postprandial plasma glucose (PPG).[5]
- Recent studies have shown that the addition of a mealtime rapid-acting insulin analogue (RAIA) to basal insulin therapy is the approach used by a majority of clinicians to intensify treatment;[6,7] however, currently available mealtime insulin formulations do not adequately approach the physiological endogenous insulin response,[8] and the optimal timing for initiation and intensification is not always clear.[9]
- Recognising this unmet need for a mealtime insulin for T2D, with an even faster onset of action than RAIAs, fast-acting insulin aspart (faster aspart: conventional insulin aspart [IAsp] in a new formulation) was developed.
- Faster aspart has a twice as fast onset of appearance in the bloodstream (4 vs 9 min), plus, within the first 30 min, a twofold higher insulin concentration and 74% greater insulin action, compared with conventional IAsp, in people with type 1 diabetes.[10]
- The onset 3 trial is part of an extensive clinical development programme with faster aspart that has included phase 3a trials in adults with diabetes.

Aims

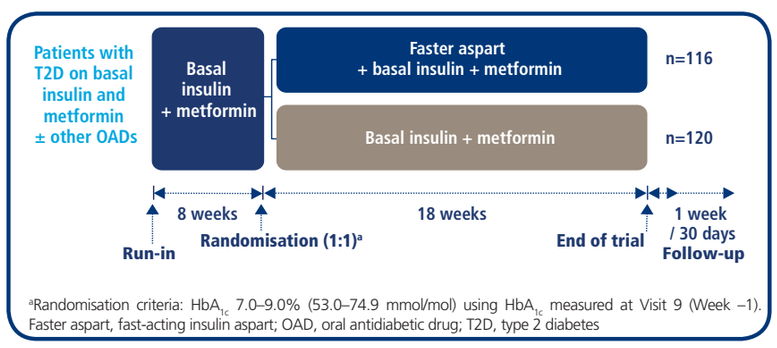
- The aim was to demonstrate the superiority of faster aspart in a full basal–bolus regimen vs basal insulin only, in terms of glycaemic control.

Methods

Design

- This was an 18-week, multicentre, open-label, parallel-group, randomised trial (Figure 1).
- Inclusion criteria:
  - Adults aged ≥18 years
  - T2D of ≥6 months' duration
  - Treated for ≥3 months with basal insulin (once-daily insulin detemir, insulin glargine U100, or neutral protamine Hagedorn) and metformin (≥1000 mg) ± other oral antidiabetic drugs (OADs)
  - Body mass index ≤40 kg/m²
  - HbA_{1c} 7.5–9.5% (58–80 mmol/mol; metformin only) or 7.5–9.0% (58–75 mmol/mol; metformin + another OAD).
- During the run-in period, basal insulin dose was optimised using a treat-to-target approach; following run-in, subjects were randomised 1:1 to continue their once-daily basal insulin regimen, or switched to a basal–bolus regimen with faster aspart at each main meal using a daily patient-driven bolus algorithm, both continuing with metformin (Figure 2).
- Subjects randomised to a basal–bolus regimen commenced with 4 U of faster aspart, and subjects self-adjusted daily by means of a '1-0-1' titration algorithm (Figure 2) based on self-measured plasma glucose (SMPG) values from the previous day.
- During the run-in period, all subjects performed pre-breakfast SMPG on 3 consecutive days prior to each site visit for basal insulin titration purposes.

Figure 1. Trial design.



[a]Randomisation criteria: HbA_{1c} 7.0–9.0% (53.0–74.9 mmol/mol) using HbA_{1c} measured at Visit 9 (Week –1). Faster aspart, fast-acting insulin aspart; OAD, oral antidiabetic drug; T2D, type 2 diabetes

- At randomisation, only subjects in the basal only group continued with pre-breakfast SMPG whereas subjects in the faster aspart + basal group recorded daily 4-point profiles (pre-prandial and at bedtime) for titration purposes.
- During the 18-week trial period, all subjects were instructed to record the date, time, and value of all SMPG measurements from 7-8-7-point profiles on 3 consecutive days before the scheduled visit during Weeks 0, 6, 12 and 18.
- Subjects were instructed to record any hypoglycaemic episodes that occurred; events were categorised according to American Diabetes Association (ADA) definitions[11] and an additional definition (blood glucose [BG] confirmed by plasma glucose [PG] value <3.1 mmol/L [56 mg/dL] with or without symptoms consistent with hypoglycaemia).

Figure 2. Titration algorithms.

Basal insulin algorithm
- **FPG target:** 4.0–6.0 mmol/L (71–108 mg/dL)
- **Adjustment:**
  - Run-in: weekly
  - Increase based on the mean of three pre-breakfast SMPG values
  - Decrease based on the lowest of three pre-breakfast SMPG values

Patient-driven bolus insulin algorithm[a]
- **Self-adjustment:** daily to reach pre-prandial/bedtime SMPG target 4.0–6.0 mmol/L (71–108 mg/dL)

mmol/L	mg/dL	Dose adjustment (U)
<4.0	<71	–1
4.0–6.0	71–108	No adjustment
>6.0	>108	+1

- **Adjustment:**
  - Pre-breakfast bolus insulin adjusted according to the previous day's pre-lunch SMPG
  - Pre-lunch bolus insulin adjusted according to the previous day's pre-dinner SMPG
  - Pre-dinner bolus insulin adjusted according to the previous day's bedtime SMPG

[a]Bolus insulin (faster aspart) was injected 0–2 min before each main meal. FPG, fasting plasma glucose; SMPG, self-measured plasma glucose

- Key endpoints:
  - Change from baseline in HbA_{1c} (primary endpoint)
  - SMPG: mean 8-point SMPG profiles and overall PPG increment (for all meals)
  - Proportion of participants achieving an overall 2-h PPG target ≤7.8 mmol/L [140 mg/dL] with or without severe hypoglycaemia
  - Number of treatment-emergent adverse events (TEAEs)
  - Number of treatment-emergent hypoglycaemic episodes.

Statistical analyses

- The primary endpoint was analysed using a mixed-effect model for repeated measurements (MMRM) where all calculated changes in HbA_{1c} from baseline at Weeks 6, 12 and 18 were included in the analysis. Superiority was considered confirmed if the upper bound of the 2-sided 95% confidence interval (CI) for the estimated treatment difference (faster aspart + basal – basal only) was <0%.
- HbA_{1c} target endpoints were analysed separately based on a logistic regression model.
- Other supportive secondary efficacy endpoints (mean of the 8-point profile [obtained from the second 7-point SMPG profile and the pre-breakfast measurement from the following day, and defined as area under the profile divided by the measurement time], and the overall PPG increment for all meals, fasting plasma glucose [FPG] and body weight) were analysed using an MMRM similar to the model used for analysis of the primary endpoint.
- The number of treatment-emergent severe or BG confirmed hypoglycaemic episodes 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.
- Safety endpoints, including TEAEs, injection-site reactions and major adverse cardiac events (MACE) were summarised descriptively.

Results

Trial subjects

- In total, 236 subjects were randomised to treatment with faster aspart + basal (n=116) or basal only (n=120; both with metformin). Baseline characteristics were similar between groups (Table 1); 94.1% of subjects completed the trial.

Table 1. Baseline characteristics.

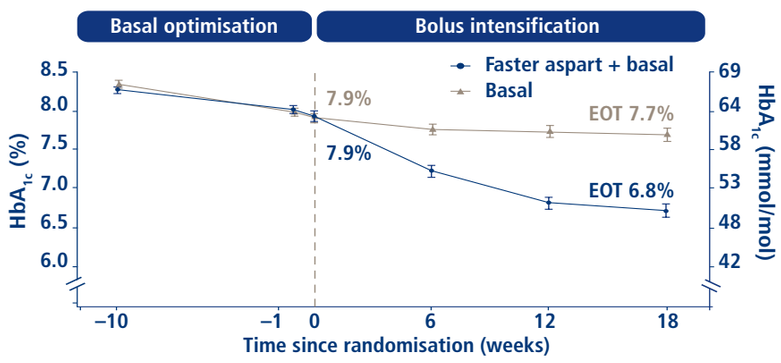
	Faster aspart + basal n=116	Basal n=120
Age, years	57.5 (9.9)	57.4 (8.5)
Males, n (%)	55 (47.4)	59 (49.2)
BMI, kg/m²	30.4 (5.0)	31.1 (4.7)
Body weight		
kg	82.2 (16.2)	85.1 (17.3)
lb	181.1 (35.8)	187.7 (38.2)
Duration of diabetes, years	10.9 (6.1)[a]	11.8 (7.4)
HbA_{1c}		
%	7.9 (0.7)	7.9 (0.7)
mmol/mol	63.2 (7.6)	63.1 (7.4)
FPG		
mmol/L	7.4 (2.4)	7.7 (2.9)[b]
mg/dL	132.5 (43.5)	138.9 (51.4)[b]

[a](n=115), [b](n=119). Data are mean (SD) unless otherwise stated. BMI, body mass index; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; SD, standard deviation

Glycaemic control

- Observed mean HbA_{1c} decreased in both treatment groups from baseline to Week 18 (Figure 3).
- The estimated change from baseline in HbA_{1c} was –1.2% (–12.7 mmol/mol) in the faster aspart + basal group and –0.2% (–2.4 mmol/mol) in the basal group (estimated treatment difference [ETD; 95% CI]; –0.94% [–1.17; –0.72]; –10.29 mmol/mol [–12.75; –7.82]; *P*<0.0001), confirming the superiority of faster aspart + basal vs basal only.

Figure 3. Mean HbA_{1c} over time.



Error bars: ± standard error (mean). *P*<0.0001 for ETD [95% CI]: –0.94% [–1.17; –0.72]; –10.3 mmol/mol [–12.8; –7.8]. Baseline=Week 0. CI, confidence interval; EOT, end of trial; ETD, estimated treatment difference; faster aspart, fast-acting insulin aspart; HbA_{1c}, glycosylated haemoglobin

Supportive secondary effi acy endpoints

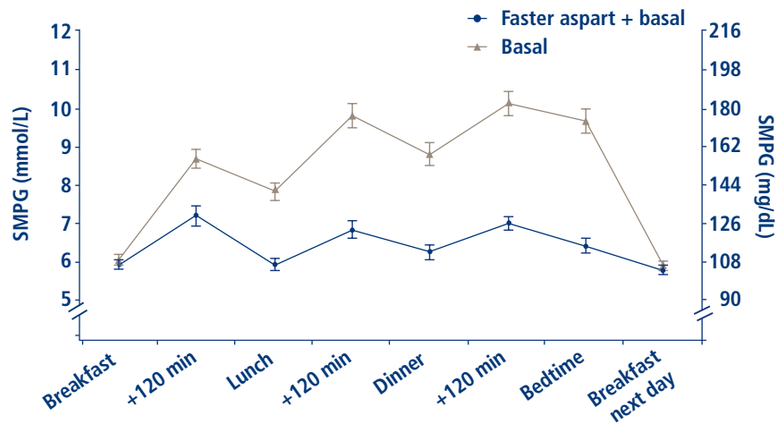
- More subjects achieved HbA_{1c} <7.0% (53 mmol/mol) or ≤6.5% (48 mmol/mol) in the faster aspart + basal group than in the basal only group. Similar findings were observed for both targets without severe hypoglycaemia (Figure 4).
- A statistically significant decrease was observed in the mean 8-point SMPG profile from 8.7 mmol/L (157 mg/dL) at baseline to 6.7 mmol/L (121 mg/dL) at end of trial (EOT) and from 8.9 mmol/L (161 mg/dL) to 8.4 mmol/L (152 mg/dL) for the faster aspart + basal and basal only groups, respectively (ETD [95% CI]: –1.88 mmol/L [–2.21; –1.54]; –33.84 mg/dL [–39.91; –27.78]; *P*<0.0001). The 8-point SMPG profiles averaged for each timepoint at Week 18 are shown in Figure 5.

Figure 4. Subjects achieving HbA_{1c} targets at Week 18.

P<0.0001 for all comparisons. CI, confidence interval; faster aspart, fast-acting insulin aspart; HbA_{1c}, glycosylated haemoglobin; OR, odds ratio

- After 18 weeks, approximately four times as many participants in the faster aspart + basal vs basal only group reached overall mean 2-h PPG values ≤7.8 mmol/L (140 mg/dL; 81.3 vs 21.8%) or 2-h PPG ≤7.8 mmol/L (140 mg/dL) without severe hypoglycaemia (79.5 vs 21.0%).
- The overall change from baseline in PPG increment (for all meals) was statistically significantly different between groups (ETD [95% CI]: –1.14 mmol/L [–1.50; –0.77]; –20.45 mg/dL [–27.07; –13.84]; *P*<0.0001).
- Estimated reductions in mean FPG at EOT were small and comparable between groups (ETD [95% CI]: –0.12 mmol/L [–0.66; 0.42]; –2.19 mg/dL [–11.88; 7.51]).
- Mean body weight increased from baseline to EOT in the faster aspart + basal group. The ETD (95% CI; faster aspart + basal – basal only) for change from baseline in body weight was 1.66 kg [0.89; 2.43]; 3.66 lb [1.95; 5.36]; *P*<0.0001.
- Mean total daily insulin dose at EOT was 1.2 U/kg and 0.6 U/kg for faster aspart + basal and basal only, respectively. The proportion of total daily insulin delivered as a bolus, relative to basal insulin, was approximately 55%.

Figure 5. 8-point SMPG profiles at Week 18.



Values are averaged for each timepoint ± standard error of the mean. Observed data. Faster aspart, fast-acting insulin aspart; SMPG, self-measured plasma glucose

Safety

- Treatments in both groups were well tolerated, and no new safety issues or MACE were identified during the trial.
- The majority of TEAEs were of mild or moderate severity; one injection-site reaction was reported in the faster aspart + basal group, and three in the basal only group.
- The number of treatment-emergent severe or BG confirmed hypoglycaemic episodes were more frequent in the faster aspart + basal group than in the basal only group (estimated treatment ratio [faster aspart + basal/basal only; 95% CI]: 8.24 [4.93; 13.76]; *P*<0.0001; Table 2).

Table 2. Treatment-emergent hypoglycaemia.

	Faster aspart + basal				Basal			
	N	(%)	E	R	N	(%)	E	R
Severe or BG confirmed[a]	67	(58.3)	493	12.8	30	(25.0)	80	2.0

[a]BG confirmed: plasma glucose <3.1 mmol/L (56 mg/dL). Treatment-emergent hypoglycaemia was defined as episodes occurring after the randomisation and no later than 1 day after the last dose of the trial product. N, number of subjects with at least one event; %, percentage of subjects; E, number of hyperglycaemic episodes; R, event rate per patient–year of exposure; BG, blood glucose; faster aspart, fast-acting insulin aspart

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Conclusions

- Compared with basal insulin only, basal–bolus treatment with faster aspart in T2D demonstrated superior efficacy in reducing HbA_{1c} with improvements in postprandial glycaemic control, with a simple, daily, patient-driven bolus algorithm.
- The addition of bolus insulin in subjects not achieving target HbA_{1c} levels with basal insulin can be highly effective in improving overall glycaemic control; this effect appears to be primarily due to the greater reduction in PPG.
- The odds of achieving HbA_{1c} targets were in favour of those in the faster aspart + basal group, compared with the basal only group.
- Statistically significantly higher rates of severe or BG confirmed hypoglycaemia were seen in the faster aspart + basal group, as expected with a basal–bolus regimen.
- No new safety issues emerged during this trial; adverse event rates were similar to those in trials of currently available mealtime insulins used in a basal–bolus regimen in subjects with T2D.[12,13]
- The self-titration algorithm used by subjects in this trial was simple to use and the associated improvement in glycaemic control suggests this may be a useful approach for treatment intensification in this patient population.

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