Adding fast-acting insulin aspart to basal insulin significantly improved glycaemic control in patients with type 2 diabetes: a randomised, 18-week, open-label, phase 3 trial (onset 3)

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Abstract

Aim: To confirm glycaemic control superiority of mealtime fast-acting insulin aspart (faster aspart) in a basal–bolus (BB) regimen versus basal-only insulin.

Materials and methods: In this open-label, randomised, 18-week trial (51 sites; 6 countries) adults (n=236) with inadequately controlled type 2 diabetes (T2D; mean glycosylated haemoglobin [HbA_{1c}] ±SD: 7.9±0.7% [63.1± 7.5 mmol/mol) receiving basal insulin and oral antidiabetic drugs underwent 8-week optimisation of prior once-daily basal insulins followed by randomisation 1:1 to a BB regimen with faster aspart (n=116) or continuation of once-daily basal insulin (n=120), both with metformin. Primary endpoint was HbA_{1c} change from baseline after 18 weeks' treatment. Endpoints included: postprandial plasma glucose (PPG) change and overall PPG increment (all meals); weight; treatment-emergent adverse events; hypoglycaemic episodes.

Results: HbA_{1c} reduced from 7.9% (63.2 mmol/mol) to 6.8% (50.7 mmol/mol; BB group) and from 7.9% (63.1 mmol/mol) to 7.7% (60.7 mmol/mol; basal-only group); estimated treatment difference [95% CI]: –0.94% [–1.17; –0.72]; –10.3 mmol/mol [–12.8; –7.8]; *P*<0.0001. Reductions from baseline in overall mean 2-h PPG and overall PPG increment for all meals (self-measured plasma glucose profiles) were statistically significant in favour of BB treatment (*P*<0.0001). Severe/blood glucose confirmed hypoglycaemia rate (12.8 vs 2.0 episodes per patient–years of exposure), total daily insulin (1.2 vs 0.6 U/kg) and weight gain (1.8 vs 0.2 kg) were greater with BB than basal-only.

Conclusions: In T2D, faster aspart in a BB regimen provided superior glycaemic control versus basal-only insulin, but with an increase in the frequency of hypoglycaemia and modest weight gain.

Trial Registration: The trial (NN1218-4049) is registered at Clinicaltrials.gov (NCT01850615). Initiated: 23 September 2013; completed: 17 November 2014.

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Introduction

The progressive nature of type 2 diabetes (T2D)[1] means that many people initiated onto oral antidiabetic drugs (OADs) will require treatment intensification. Addition of basal insulin therapy as part of an individualised, patient-centred approach is recommended when OADs alone do not achieve or no longer maintain glycaemic control.[2] Further treatment intensification may be required when target glycosylated haemoglobin (HbA_{1c}) levels[3,4] are not reached after 3–6 months of basal titration.[5]

Postprandial plasma glucose (PPG) contributes substantially to glycaemic control[6,7] and, as HbA_{1c} levels approach 7.0%, it becomes the dominant contributor to HbA_{1c}.[8] Thus, optimal PPG control is an important component of achieving target HbA_{1c}.[9,10] In T2D, blunted and/or delayed postmeal insulin secretion is a major pathophysiological factor underlying postprandial hyperglycaemia.[11]

Current guidelines recommend a variety of injectable intensification therapies to reduce PPG excursions,[2,12] and addition of mealtime rapid-acting insulin analogues (RAIAs) to basal insulin is a common approach to intensify treatment.[13,14] However, approved RAIA formulations do not adequately fully approach the physiological mealtime insulin response. Additionally, evidence suggests some degree of clinical inertia with regard to intensifying therapy in people with T2D on basal insulin.[13]

Fast-acting insulin aspart (faster aspart) is an ultra-fast-acting mealtime insulin that is insulin aspart in a new formulation, containing two additional excipients, niacinamide and L-arginine. Non-clinical data show the addition of niacinamide promotes the formation of insulin aspart monomers after subcutaneous injection, facilitating a more rapid rate of insulin aspart absorption across the endothelium into the blood.[15] Faster aspart has a twice as fast onset of appearance (4 min versus 9 min), plus, within the first 30 min, two-fold higher insulin concentration and 74% greater insulin action, compared with conventional insulin aspart in people with type 1 diabetes (T1D).[16]

As part of a BB regimen (and with no overall increase in the rate of hypoglycaemia), mealtime faster aspart has shown superior PPG control and statistically significant HbA_{1c} reductions versus insulin aspart in T1D,[17] and effective lowering of HbA_{1c} with improved PPG control 1 h after a meal test in inadequately controlled T2D.[18]

Here, we report findings from the 18-week onset 3 trial, which evaluated the efficacy and safety of adding faster aspart to basal insulin therapy versus basal insulin alone, both in combination with metformin, in patients with T2D.

Methods & materials

Trial design

This was an 18-week, multicentre, randomised, open-label, parallel-group trial comparing faster aspart in a BB regimen to basal insulin therapy alone, both in combination with metformin, in adults with T2D. Prior to randomisation there was an 8-week run-in period. Participant follow-up occurred at 7 and 30 days from the end of trial (EOT).

The trial was conducted in accordance with the Declaration of Helsinki[19] and the International Conference on Harmonization Good Clinical Practice.[20] Prior to trial initiation, all documentation was reviewed and approved according to local regulations by appropriate health authorities, and by Institutional Review Boards. The trial protocol is available online [URL to be added].

Participants

Participants were ≥18 years old with a body mass index ≤40.0 kg/m^2, diagnosed with T2D ≥6 months and treated for ≥3 months prior to screening with basal insulin (once-daily insulin detemir, insulin glargine U100, or neutral protamine Hagedorn [NPH]) and metformin ≥1000 mg with or without other OADs (please refer to Supplementary Appendix for additional detail). Participants had laboratory-measured HbA_{1c} of 7.5–9.5% (58.5–80.3 mmol/mol) if taking metformin, or 7.5–9.0% (58.5–74.9 mmol/mol) if

taking metformin plus another OAD at the screening visit (Appendix Table 1). Participants were requested to eat ≥3 main meals every day during the trial. Exclusion criteria included any use of bolus insulin, except short-term use due to intermittent illness (≤14 days consecutive treatment and not within 3 months prior to the screening visit); glucagon-like peptide 1 agonists and/or thiazolidinediones within 3 months prior to screening (please refer to the Supplementary Appendix for additional detail).

Interventions

Basal titration

At the start of the 8-week run-in, participants continued their once-daily basal insulin and metformin at pre-trial doses; all other OADs were discontinued. During run-in, basal insulin dose was optimised using a treat-to-target approach, with weekly adjustments to a pre-breakfast target self-measured plasma glucose (SMPG) of 4.0–6.0 mmol/L (71–108 mg/dL; Appendix Table 2). After run-in, the basal insulin dose was adjusted at the investigator's discretion. Basal insulin (100 U/mL) was injected once-daily subcutaneously (insulin detemir and NPH using a 3 mL FlexPen®; insulin glargine U100 using a 3 mL SoloStar® pen), at approximately the same time every evening.

Bolus titration

Participants requiring further intensification (i.e. meeting the randomisation criterion of HbA_{1c} 7.0–9.0% [53.0–74.9 mmol/mol], following optimisation of basal insulin during the run-in period) were randomised (baseline; Week 0 [Visit 10]) 1:1 to receive a BB regimen with mealtime faster aspart or to continue once-daily basal insulin, both in combination with metformin (pre-screening dose). Randomisation

was stratified based on the type of basal insulin used. All participants randomised to the BB group commenced 4 U of faster aspart before each meal, which was self-adjusted daily by 1 U increments (a '+1/0/–1' titration algorithm, with no specified maximum value) aiming for a pre-prandial or bedtime target of 4.0–6.0 mmol/L (71–108 mg/dL; Appendix Table 3). Faster aspart (100 U/mL; 3 mL PDS290 pen-injector prefilled pen) was injected subcutaneously into the abdomen 0–2 min before each main meal.

SMPG

At the run-in visit, participants were given blood glucose (BG) meters (Abbott Freestyle Lite® or Optium®; calibrated to display plasma glucose [PG] values) and instructed to perform 7-point profiles (PG values taken before and 2 h after each main meal, and at bedtime) on three consecutive days before their scheduled visit (Weeks 0, 6, 12 and 18). For titration, participants randomised to receive faster aspart + basal insulin recorded daily 4-point profiles (pre-prandial and at bedtime), while PG monitoring recommendations provided to participants randomised to receive basal insulin only were at the investigator's discretion.

Data conversions

The HbA_{1c} values were transformed from % to mmol/mol by multiplying by 10.929 and subtracting 23.49735. The conversion factor used for glucose between mmol/L and mg/dL was 0.0555.

Assessments

Primary endpoint

The primary endpoint was change in HbA_{1c} from baseline (Week 0; Visit 10) after 18 weeks' randomised treatment.

Supportive secondary efficacy endpoints

Secondary efficacy endpoints after 18 weeks included participants achieving HbA_{1c} targets of <7.0% (53.0 mmol/mol; American Diabetes Association [ADA])[3] and ≤6.5% (47.5 mmol/mol; International Diabetes Federation)[4], with or without severe hypoglycaemia.

Supportive efficacy endpoints derived from SMPG values included overall mean 2-h PPG (for all meals), overall PPG increment (for all meals), and mean 8-point SMPG profiles (from the second 7-point SMPG profile and the before breakfast measurement from the following day). Other endpoints included the proportion of participants achieving an overall 2-h PPG target ≤7.8 mmol/L [140 mg/dL] and the same targets without severe hypoglycaemia,[21] daily insulin dose, and change from baseline to Week 18 in fasting plasma glucose (FPG), 1,5-anhydroglucitol (1,5-AG; a marker for postprandial hyperglycaemia),[22] and body weight.

Supportive secondary safety endpoints

Supportive secondary safety endpoints included the number of treatment-emergent adverse events (TEAEs), hypoglycaemic episodes, and injection-site and allergic reactions related to insulin. An adverse event (AE) was defined as treatment-emergent if the event onset occurred on or after the first day of exposure to and no later than 7 days after the last day of randomised treatment. Hypoglycaemia was categorised as 'severe' according to the ADA classification as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions,[21] or as BG confirmed by a PG value <3.1 mmol/L (56

mg/dL) with or without symptoms (an additional cut-off point, below which normal physiological symptoms of hypoglycaemia occur). A hypoglycaemic event was categorised as treatment-emergent if onset occurred on or after the first day of exposure to, and no later than, 1 day after the last day of randomised treatment. Information on cardiovascular (CV) events and deaths occurring after randomisation (baseline) were sent for evaluation by an external adjudication committee.

Statistical methods

Analyses of all efficacy endpoints were based on the full analysis set (FAS; all randomised participants). Safety endpoints were summarised based on the safety analysis set and statistical analyses for hypoglycaemic episodes were based on the FAS.

The primary endpoint was analysed using a mixed-effect model for repeated measurements (MMRM). All calculated changes in HbA_{1c} from baseline at Visits 16, 22, and 28 were included in the analysis (please refer to the Supplementary Appendix for additional detail).

Several sensitivity analyses of the primary endpoint were performed (please refer to the Supplementary Appendix).

For the supportive secondary efficacy endpoints, HbA_{1c} and PPG target endpoints were analysed separately based on a logistic regression model using treatment, strata, and region as factors, and baseline HbA_{1c} or baseline mean 2-h PPG as covariate. The mean of the 8-point profile (SMPG) was defined as the area under the profile divided by the measurement time and was calculated using the trapezoidal method. The overall mean 2-h PPG and PPG increments for all meals were derived from the individual mealtime mean 2-h PPG and PPG increment values. The change

from baseline in overall mean 2-h PPG (for all meals), overall PPG increment (for all meals), mean 8-point SMPG profiles, body weight, FPG, and 1,5-AG after 18 weeks' randomised treatment were analysed using a MMRM similar to that used for analysis of the primary endpoint and the corresponding baseline value as covariate. Insulin doses were summarised descriptively in units or units/kg.

Safety endpoints, including TEAEs, injection-site and allergic reactions, and major adverse CV events (MACE) were summarised descriptively. The number of treatment-emergent severe or BG confirmed hypoglycaemic episodes was analysed using a negative binomial regression model (please refer to the Supplementary Appendix for additional detail).

Role of the funding source

The sponsor of the trial was Novo Nordisk A/S (Bagsvård, Denmark). All authors had access to the study data and take responsibility for the accuracy of the analysis, and had authority in the decision to submit the manuscript for publication, in collaboration with Novo Nordisk A/S.

Results

Baseline characteristics

In total, 236 participants were randomised to receive faster aspart + basal (n=116) or basal insulin (n=120) and 94.1% completed the trial (Figure 1). Baseline characteristics were similar between treatment groups (Table 1).

Efficacy

Glycaemic control

Following run-in, mean HbA_{1c} decreased further in both treatment groups from baseline to Week 18 (Figure 2A). 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% confidence interval; CI]: –0.94% [–1.17; –0.72]; –10.3 mmol/mol [–12.8; –7.8]; *P*<0.0001), confirming the superiority of mealtime faster aspart in a full BB regimen versus basal insulin therapy.

A greater number of participants in the faster aspart + basal group than the basal group achieved HbA_{1c} <7.0% (53.0 mmol/mol), HbA_{1c} <7.0% (53.0 mmol/mol) without severe hypoglycaemia, ≤6.5% (47.5 mmol/mol), or ≤6.5% (47.5 mmol/mol) without severe hypoglycaemia (Figure 2B).

At EOT, observed overall mean 2-h PPG for all meals decreased from 10.0 mmol/L (180 mg/dL) at baseline to 7.2 mmol/L (130 mg/dL) in the faster aspart + basal group, and from 10.3 mmol/L (186 mg/dL) to 9.6 mmol/L (173 mg/dL) in the basal group; the estimated reduction from baseline in overall mean 2-h PPG for all meals between treatments was statistically significant in favour of faster aspart + basal (ETD [95% CI]: –2.48 mmol/L [–2.92; –2.03]; –44.6 mg/dL [–52.7; –36.6]; *P*<0.0001). Overall mean PPG increment (for all meals) in the faster aspart + basal group decreased from 2.4 mmol/L (43 mg/dL) at baseline to 0.9 mmol/L (17 mg/dL) at EOT, whereas in the basal group it decreased from 2.5 mmol/L (46 mg/dL) to 2.0 mmol/L (37 mg/dL); the estimated reduction from baseline in overall PPG increment was statistically significant in favour of faster aspart + basal insulin (ETD [95% CI]: –1.14 mmol/L [–1.50; –0.77]; –20.5 mg/dL [–27.1; –13.8]; *P*<0.0001).

A statistically significant difference in favour of faster aspart + basal versus basal only was observed in the decrease from baseline in mean 8-point SMPG profile. Mean 8-point SMPG profile decreased from 8.7 mmol/L (157 mg/dL) at baseline to 6.7 mmol/L (121 mg/dL) at EOT in the faster aspart + basal group and from 8.9 mmol/L (161 mg/dL) to 8.4 mmol/L (152 mg/dL) in the basal only group (ETD [95% CI]: –1.88 mmol/L [–2.21; –1.54]; –33.8 mg/dL [–39.9; –27.8]; *P*<0.0001). The 8-point SMPG profiles averaged for each time point at Week 18 are shown in Figure 3.

At baseline, comparable numbers of participants in both groups achieved overall mean 2-h PPG values ≤7.8 mmol/L (140 mg/dL; 22.3% in the faster aspart + basal group versus 16.0% for the basal group). After 18 weeks' randomised treatment, approximately four times as many participants in the faster aspart + basal versus the basal group reached overall mean 2-h PPG values ≤7.8 mmol/L (140 mg/dL) or 2-h PPG ≤7.8 mmol/L (140 mg/dL) without severe hypoglycaemia (Figure 2C).

The estimated reductions from baseline to EOT in FPG were small and comparable in both groups (Appendix Table 4). Estimated change from baseline in 1,5-AG was greater in the faster aspart + basal group versus the basal group (ETD [95% CI]: 4.24 µg/mL [3.04; 5.44]; *P*<0.0001; Appendix Table 4).

Mean body weight increased from baseline to EOT in the faster aspart + basal group. The ETD (faster aspart + basal – basal only) for change from baseline in body weight was 1.66 kg (95% CI: 0.89; 2.43), which was statistically significant (*P*<0.0001; Appendix Table 4).

Daily insulin dosing

Total daily insulin dose increased in the faster aspart + basal group from baseline to Week 18 due to the bolus intensification, and mean total insulin doses at EOT were

1.2 U/kg and 0.6 U/kg (faster aspart + basal versus basal only; Appendix Table 5). The proportion of total daily insulin delivered as a bolus, relative to basal insulin, was approximately 55% after 18 weeks' randomised treatment.

Safety endpoints

Overall, TEAEs were reported in 40.9% of participants (n=47) in the faster aspart + basal group and 51.7% of participants (n=62) in the basal-only group (Appendix Table 6). Most TEAEs in both groups were mild or moderate. Four injection-site reactions were observed (1, faster aspart + basal; 3, basal). The most common allergic reaction was cough (4 [3.5%], faster aspart + basal; 1 [0.8%] basal).

Information on two non-treatment-emergent CV events were sent for adjudication (one in the run-in period, which was fatal, and one in the follow-up period in faster aspart + basal); there were no MACE in this trial, and no deaths during the treatment period.

Overall severe or BG confirmed hypoglycaemia was more frequent with faster aspart + basal (n=67 [58.3%]) than basal (n=30 [25.0%]; overall hypoglycaemia rates 12.8 versus 2.0 episodes per patient–years of exposure; treatment rate ratio [95% CI]: 8.24 [4.93; 13.76]; P<0.0001; Appendix Table 7). Severe hypoglycaemia was also more frequent in the faster aspart + basal group than in the basal group (0.18 versus 0.02 episodes per patient–years of exposure; treatment rate ratio [95% CI: 8.89 [0.27; 292.97]; P=0.22; Appendix Table 7).

Discussion

In this trial, addition and titration of mealtime faster aspart to basal insulin + metformin effectively improved glycaemic control in people with T2D, demonstrating

the expected superiority to basal insulin + metformin alone for HbA_{1c} and postprandial glycaemic control. There were no unexpected adverse events, and treatments were well tolerated. As anticipated, hypoglycaemia rates, weight gain and daily insulin dose were higher in the BB group compared with the basal-only group.

Participants had similar HbA_{1c} at baseline and, importantly, similar FPG and pre-breakfast SMPG levels at EOT; therefore, the PPG improvements may explain the improvement in HbA_{1c}. The importance of targeting both FPG and PPG was highlighted in the GINGER and PREFER studies, which demonstrated statistically significant improvements in glycaemic control, both in terms of HbA_{1c} reduction and PPG control, following administration of a BB regimen, compared with twice-daily premixed insulin in participants with T2D.[23,24]

The averaged 8-point SMPG profiles after 18 weeks' randomised treatment illustrate rising prandial PG and 2-h PPG levels in the basal-only group (which appeared to accumulate) over a 24-h period, emphasising the need for prandial glycaemic control in this population. The substantial improvements in PG increments with the addition of a mealtime insulin were mirrored by the 1,5-AG results.

BB regimens are known to increase the risk of weight gain compared with basal insulin.[25,26] The expected increase in body weight in the BB group is modest and in line with weight gain following bolus intensification observed previously.[23–27]

As anticipated in the context of a BB regimen and lower mean HbA_{1c} levels achieved, there were more severe or BG confirmed hypoglycaemic episodes in the faster aspart + basal than basal-only group. However, hypoglycaemia rates were in line with those observed in other trials when initiating a full BB regimen in T2D. Indeed, in a recent meta-analysis of randomised controlled trials in T2D in which

insulin therapy was intensified to a BB regimen, the event rate for overall hypoglycaemia averaged 12.1 episodes per patient–year.[28] Nevertheless, in the current study, a large proportion of participants achieved the more ambitious HbA_{1c} target of ≤6.5% without experiencing severe hypoglycaemia, highlighting the feasibility of targeting PPG control to achieve glycaemic targets without severe hypoglycaemia, even for participants close to recommended targets.[29] Participants were recommended to achieve uniform, and near-normal levels of fasting and postprandial glucose, whereas in clinical practice target levels would be adjusted for each individual. The tight titration targets and frequent SMPG measurements probably contributed to the rate of hypoglycaemia seen in the BB arm of this trial.

No conclusion can be drawn from this study regarding the benefit of faster aspart over other mealtime insulins; other trials have demonstrated non-inferiority of faster aspart to insulin aspart in terms of HbA_{1c} control, and superiority in terms of PPG control in people with T1D or T2D.[17,18] The current study shows that faster aspart can be added to a basal regimen using a simple patient-driven titration algorithm and quantifies the benefit:risk assessment in terms of PPG and HbA_{1c} improvements versus increased hypoglycaemia risk and weight gain. This is valuable information to physicians considering different intensification options, including addition of a mealtime insulin, especially given the scarcity of trials wherein addition of bolus insulin is being compared with basal insulin + metformin. Although it is well-known that addition of bolus insulin to patients with T2D inadequately controlled on basal insulin improves glycaemic control, in real-world clinical practice there seems to be clinical inertia with regard to intensifying therapy, owing to several physician and patient barriers. As a result, patients eligible for intensification may remain on basal insulin-only for too long. A recently published retrospective cohort study involving

11,696 patients with T2D and investigating clinical inertia identified a failure to intensify treatment regimens when required in patients on basal insulin.[13] Indeed, only 30.9% of patients clinically eligible for intensification (HbA_{1c} ≥7.5%) actually had their treatment regimen intensified. Moreover, the median time to intensification with bolus or premix insulin or glucagon-like peptide-1 analogue after the first recording of HbA_{1c} ≥7.5% (58 mmol/mol) was 3.7 years. The reasons for not intensifying may be multiple and complex. In the current study, we demonstrate a simple method of treatment intensification, which could be applied by clinicians in routine practice.

The open-label design of the trial may be a limitation; however, masking would have required a large number of placebo injections and may have led to unmasking due to the lack of effect of placebo on PPG levels. The protocol specified a full BB regimen for intensification rather than the step-wise approach often used in clinical practice;[12,25,30] implementation of a step-wise approach may have reduced hypoglycaemia rates. However, this trial was designed to show the maximum benefit of the addition and titration of a mealtime insulin. Additionally, ~70% of people with T2D who are initiated onto a basal + one bolus insulin injection will require a full BB regimen within 1 year.[12,25,26] The trial was of relatively short duration (18 weeks). Initiating a new insulin treatment requires a period of dose adjustment characterised by successive titrations until PG levels and insulin dose stabilise. The use of a run-in period ensured optimisation of the basal insulin regimen in both groups prior to randomisation, and the daily algorithm used to calculate bolus insulin doses mirrors popular clinical approaches.

A BB strategy remains an effective option to intensify glycaemic control following a basal + OAD regimen. The EOT HbA_{1c} of 6.8% (50.7 mmol/mol) observed in the current study indicates the potential clinical benefit of this approach with faster aspart

as part of a BB regimen in T2D. The superior overall and PPG control observed following the addition and titration of mealtime faster aspart to basal insulin + metformin compared with basal insulin + metformin alone was accompanied by an expected increased rate of hypoglycaemia. Addition of bolus insulin is a valuable intensification approach in people with T2D inadequately controlled on basal insulin.

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Disclosures

H.W.R. was the principal investigator of this study, the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.D. was the responsible medical officer. S.C.T. was the responsible statistician. All authors had access to the study data, take responsibility for the accuracy of the analysis, and had authority in the decision to submit the manuscript for publication, in collaboration with Novo Nordisk. All authors meet the ICMJE criteria for authorship of this manuscript and approve the manuscript for publication. All contributors received compensation from, and the study was funded by, Novo Nordisk A/S. Novo Nordisk A/S provided the non-investigational medicinal products used in this trial; metformin was not considered a trial product and was not supplied by Novo Nordisk A/S.

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Figure 1. Participant disposition

A total of 323 participants entered the run-in period of the trial; the most common reason for failure during the run-in period was failure to meet the randomisation criteria (HbA_{1c} 7.0–9.0% [53–75 mmol/mol]) at Visit 9 (Week –1). The pattern of withdrawal was low and comparable between both groups, with 94.1% of the participants completing the trial. HbA_{1c}, glycosylated haemoglobin.

Figure 2 Observed mean HbA_{1c} change from baseline to Week 18 (A). Participants who achieved target HbA_{1c} (B) and PPG levels (C) at Week 18.

**P*<0.0001. Error bars: ± standard error of the mean. HbA_{1c} targets: <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) and <7.0% (53.0 mmol/mol) and ≤6.5% (47.5 mmol/mol) without SH. PPG (based on SMPG) target: 2-h PPG ≤7.8 mmol/L (140

mg/dL) and 2-h PPG ≤7.8 mmol/L (140 mg/dL) without SH. Basal insulin: insulin detemir, insulin glargine U100 or NPH insulin. CI, confidence interval; faster aspart; fast-acting insulin aspart; HbA_{1c}, glycosylated haemoglobin; OR, estimated odds ratio; PPG, postprandial plasma glucose; SH, severe hypoglycaemia during treatment period; SMPG, self-measured plasma glucose. The conversion factor used for glucose between mmol/L and mg/dL was 0.0555.

Figure 3. 8-point SMPG profiles at baseline (A) and Week 18 (B)

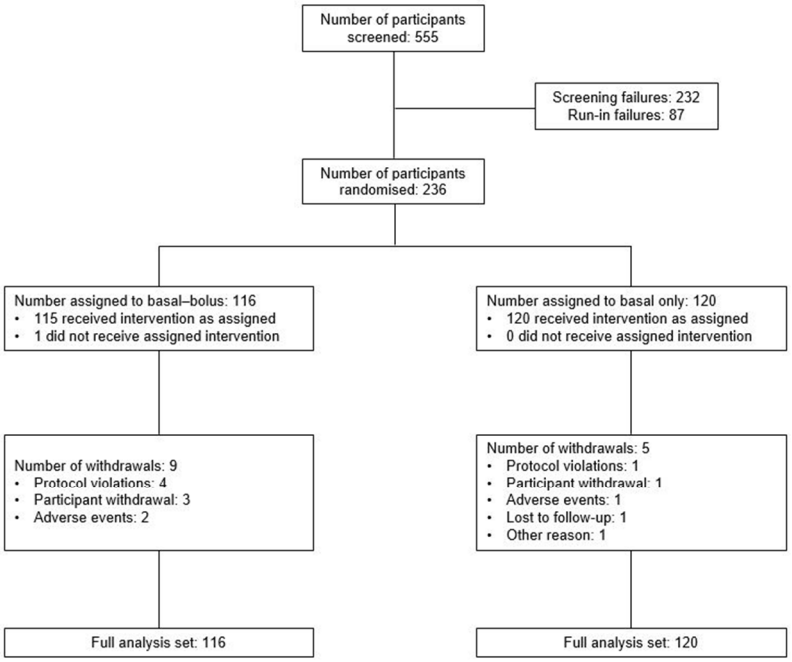
Values are based on the full analysis set and averaged for each time point ± standard error of the mean. Basal insulin: insulin detemir, insulin glargine U100 or NPH insulin. Breakf, breakfast; faster aspart, fast-acting insulin aspart; NPH, neutral protamine Hagedorn; SMPG, self-measured plasma glucose. The conversion factor used for glucose between mmol/L and mg/dL was 0.0555.

Table 1. Baseline characteristics at randomisation

Characteristic	Faster aspart + basal (n=116)	Basal (n=120)	Total (N=236)
N, FAS			
Age, years (SD)	57.5 (9.9)	57.4 (8.5)	57.4 (9.2)
Gender, n (%)			
Male	55 (47.4)	59 (49.2)	114 (48.3)

Female	61 (52.6)	61 (50.8)	122 (51.7)
BMI, kg/m^2 (SD)	30.4 (5.0)	31.1 (4.7)	30.8 (4.8)
Body weight, kg (SD)	82.2 (16.2)	85.1 (17.3)	83.7 (16.8)
Duration of diabetes, years (SD)	10.9* (6.1)	11.8 (7.4)	11.3 (6.3)
HbA_{1c}			
% (SD)	7.9 (0.7)	7.9 (0.7)	7.9 (0.7)
mmol/mol (SD)	63.2 (7.6)	63.1 (7.4)	63.1 (7.5)
FPG			
mmol/L (SD)	7.4 (2.4)	7.7† (2.9)	7.5 (2.6)
mg/dL (SD)	132.5 (43.5)	138.9 (51.4)	135.7 (47.7)
Basal insulin at baseline	n (%)	n (%)	N (%)
Insulin glargine	76 (65.5)	77 (64.2)	153 (64.8)
Insulin detemir	16 (13.8)	17 (14.2)	33 (14.0)
NPH	24 (20.7)	26 (21.7)	50 (21.2)

*n=115; †n=119.Values for baseline characteristics are arithmetic means, unless stated otherwise. BMI, body mass index; FAS, full analysis set; faster aspart, fast-acting insulin aspart; FPG, fasting plasma glucose; HbA_{1c}, glycosylated haemoglobin; NPH, neutral protamine Hagedorn. The conversion factor used for glucose between mmol/L and mg/dL was 0.0555.



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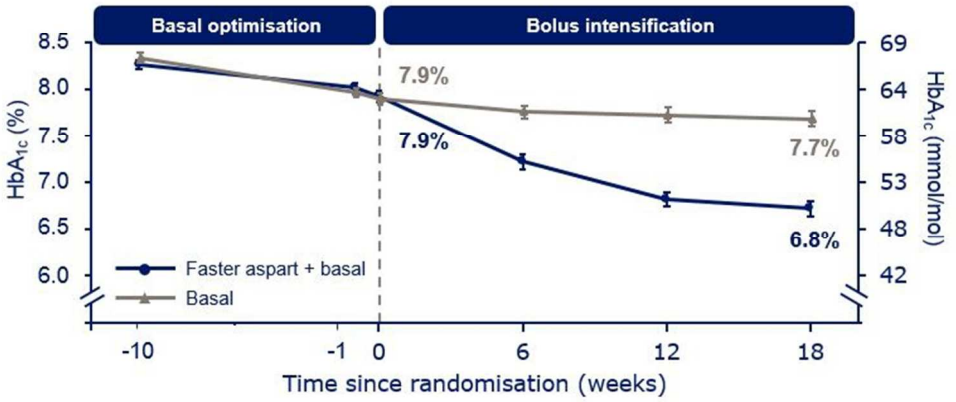

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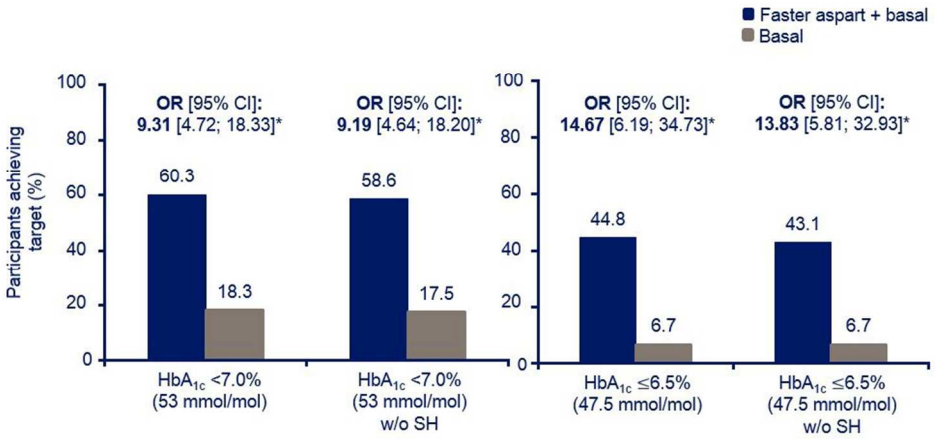

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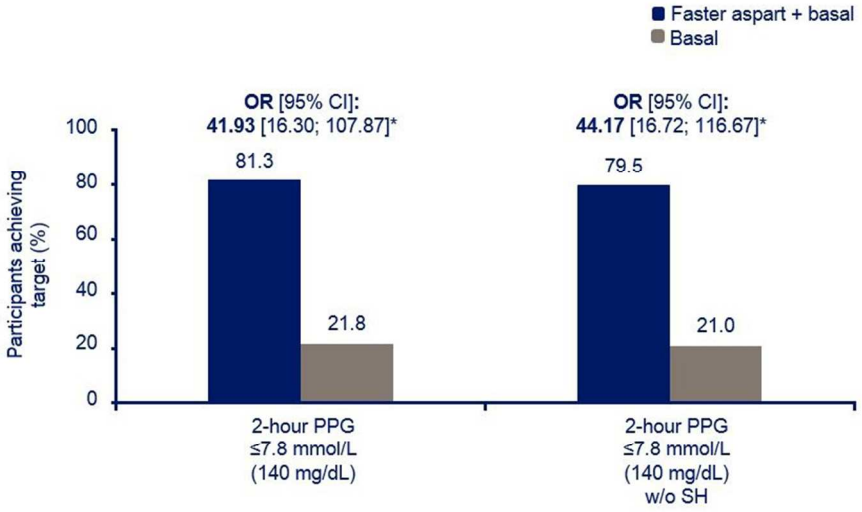

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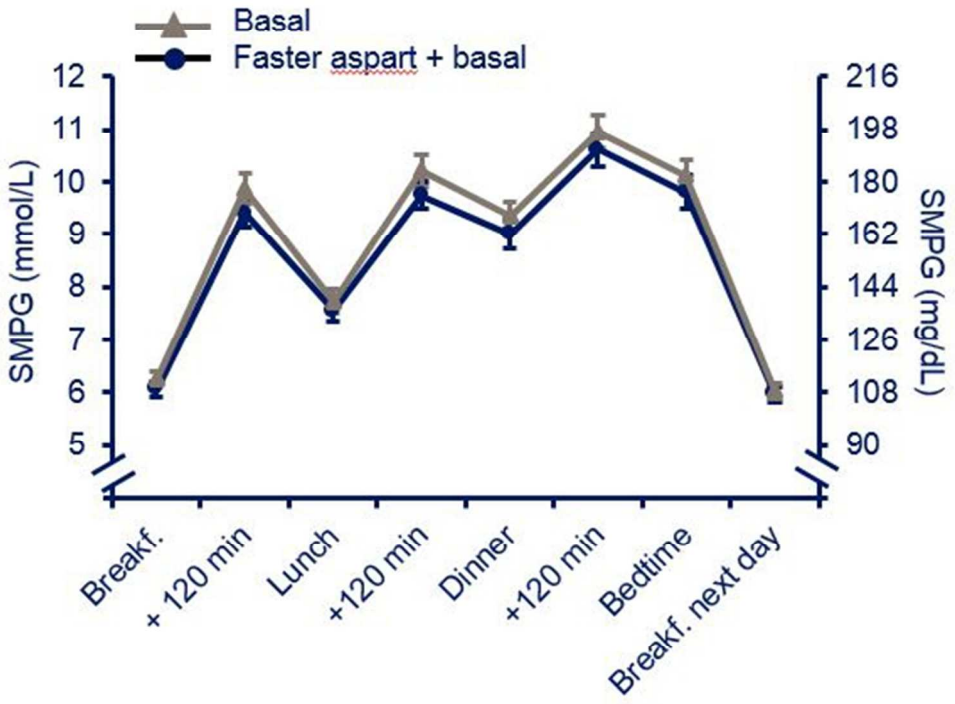

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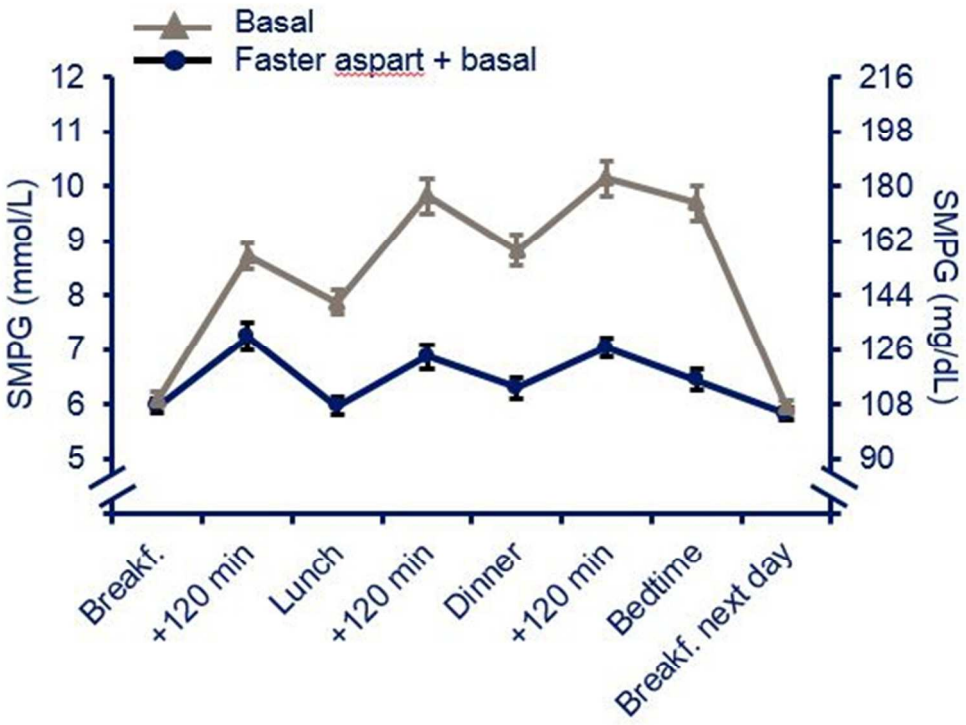

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