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Short Report: Treatment

Mealtime fast-acting insulin aspart versus insulin aspart for controlling postprandial hyperglycaemia in people with insulin-resistant Type 2 diabetes

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Abstract

Aim This *post hoc* analysis explored whether mealtime fast-acting insulin aspart treatment provided an advantage in postprandial plasma glucose (PPG) control vs. insulin aspart in people with Type 2 diabetes receiving high doses of bolus insulin.

Methods A *post hoc*, post-randomization, subgroup analysis of a 26-week, randomized, double-blind, treat-to-target trial (onset 2) that compared mealtime fast-acting insulin aspart vs. mealtime insulin aspart, both in a basal–bolus regimen, in people with Type 2 diabetes uncontrolled on basal insulin therapy and metformin. At the end of trial, the impact of fast-acting insulin aspart and insulin aspart on PPG control was assessed with a standard liquid meal test and participants were grouped into three post-randomization subgroups: meal test bolus insulin dose ≤ 10 units per dose (n = 171), > 10–20 units per dose (n = 289) and > 20 units per dose (n = 146).

Results A statistically significant treatment difference in favour of fast-acting insulin aspart vs. insulin aspart was observed for the change in PPG increment at all post-meal time points (from 1 to 4 h) for those in the > 20 units bolus insulin subgroup. There was no difference in the magnitude of change from baseline in HbA_{1c} level between fast-acting insulin aspart and insulin aspart in any of the bolus insulin dose subgroups (data herein).

Conclusion Fast-acting insulin aspart may hold promise as a more effective treatment compared with insulin aspart for controlling PPG in people with insulin-resistant Type 2 diabetes.

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Introduction

Excessive postprandial plasma glucose (PPG) excursions in people with Type 2 diabetes have been linked to increased mortality [1], poor glycaemic control [2] and, consequentially, an increased risk of developing micro- and macrovascular complications [3]. People with insulin-resistant Type 2 diabetes receiving basal insulin and oral anti-diabetes drug therapy often require treatment intensification with bolus insulin to improve glycaemic control [4]. However, PPG control frequently remains suboptimal, even in people receiving a high bolus insulin dose [5,6]. Further, conventional rapid-acting insulin analogues do not seem to offer a therapeutic advantage over regular human insulin in these people; this is concerning and highlights the need for more efficacious bolus insulins in this population.

Fast-acting insulin aspart (faster aspart) is a novel formulation of insulin aspart containing niacinamide and L-arginine, with an absorption profile that more closely approaches physiological early-phase insulin secretion than conventional rapid-acting insulin analogues. In people with Type 1 diabetes, mealtime faster aspart was shown to be non-inferior to mealtime insulin aspart in reducing HbA_{1c} [7,8]. Further, faster aspart demonstrated superior PPG control with statistically significant improvements in both 1-h PPG [7,8] and 2-h PPG increments [7], compared with mealtime insulin aspart in people with Type 1 diabetes. In

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The subject-level analysis data sets for the research presented in the publication are available from the corresponding author on reasonable request.

What's new?

- The results of this *post hoc* analysis indicate that fast-acting insulin aspart may provide an advantage over conventional rapid-acting insulin analogues in controlling postprandial hyperglycaemia in people with insulin-resistant Type 2 diabetes requiring basal–bolus therapy.

Type 2 diabetes, mealtime faster aspart was also demonstrated to be non-inferior to mealtime insulin aspart in terms of HbA_{1c}, with a statistically significant improvement in 1-h PPG increment in favour of faster aspart [9]. In both Type 1 and Type 2 diabetes, the overall rates of treatment-emergent hypoglycaemia and safety profiles were similar between the mealtime faster aspart and insulin aspart treatment arms [7–9].

This *post hoc* analysis of the onset 2 trial (ClinicalTrials.gov: NCT01819129) explored whether mealtime faster aspart provided advantages in PPG control over insulin aspart in people with Type 2 diabetes receiving different dose ranges of bolus insulin, including people on high doses.

Methods

This study was a *post hoc*, post-randomization, subgroup analysis of the onset 2 trial: a randomized, phase 3a, 26-week, double-blind, treat-to-target trial that compared mealtime faster aspart with mealtime insulin aspart, both in a basal–bolus regimen, in people with Type 2 diabetes uncontrolled on basal insulin therapy and metformin [9].

After an 8-week run-in period to optimize basal insulin, participants were randomized (1:1) to mealtime faster aspart ($n = 345$) or insulin aspart ($n = 344$), titrated using a simple daily subject-driven algorithm, plus insulin glargine U100 and metformin. Faster aspart or insulin aspart was administered subcutaneously 0–2 min before a main meal. The effects of faster aspart and insulin aspart on PPG control were assessed using a standard liquid meal test (80 g carbohydrate) during the run-in period and after 26 weeks of randomized treatment. The bolus insulin dose used for the second meal test was individualized, calculated by dividing 80 by the product of 500 divided by the participant's total daily insulin dose. In the present *post hoc* analysis, participants were stratified into three post-randomization subgroups: meal test bolus insulin dose ≤ 10 units per dose ($n = 171$), > 10–20 units per dose ($n = 289$) or > 20 units per dose ($n = 146$), representing approximately 25%, 50% and 25% of the study population, respectively.

Statistical methods

All statistical analyses were based on the full analysis set. Estimated treatment difference for change from baseline in PPG increment (meal test) after 26 weeks of treatment was analysed by an analysis of variance (ANOVA) model, which included treatment by dose–group interaction, continuous glucose monitoring strata (a subgroup continuous glucose monitoring assessment was performed at selected sites at two periods during the trial) and region as factors, and the actual bolus dose and total daily dose (nested within dose group) at end of trial, as well as baseline PPG increment (meal test), as covariates. Because both basal and bolus insulin doses were included as covariates in the regression model, the treatment difference within each subgroup reflects the expected difference in PPG increment between a participant receiving faster aspart and a participant receiving insulin aspart who had the same basal and bolus insulin dose.

Results

In the overall onset 2 population, baseline characteristics were similar between those randomized to mealtime faster aspart and those randomized to mealtime insulin aspart [9]. For the current *post hoc* analysis, baseline characteristics across post-randomization subgroups (≤ 10, > 10–20 or > 20 units) were similar; the total daily actual basal insulin dose values were 40.7, 51.3 and 72.8 units for those in the ≤ 10, > 10–20 and > 20 units subgroups, respectively (Table 1). Insulin dosing characteristics and body weight for all subgroups at week 26 are shown in the Appendix (Table A1). The mean age of the > 20 units bolus insulin dose subgroup was 58 years; mean BMI was 33.1 kg/m^2; mean duration of diabetes was ~ 12 years; and the mean meal test bolus insulin dose at week 26 was 33.4 units.

In the > 20 units bolus insulin dose subgroup, a statistically significant treatment difference in favour of faster aspart vs. insulin aspart was observed for the change from baseline in PPG increment at all post-meal time points from 1–4 h (Fig. 1). There were no other significant treatment differences in favour of faster aspart in the ≤ 10 and > 10–20 units dose subgroups at any post-meal time point from 1–4 h (Fig. 1).

There were no statistically significant differences in the magnitude of change from baseline in HbA_{1c} and 1,5-anhydroglucitol levels at week 26 between faster aspart and insulin aspart in any of the bolus insulin dose subgroups (Table A2).

Discussion

This *post hoc* analysis explored whether mealtime faster aspart provides better PPG control than conventional insulin aspart in people with Type 2 diabetes according to their degree of insulin resistance as reflected in their titrated doses of bolus insulin.

Overall, in the onset 2 trial, mealtime faster aspart significantly improved PPG control at the 1-h time point only, compared with mealtime insulin aspart [estimated

Table 1 Baseline characteristics of all post-randomization subgroups based on meal-test bolus insulin dose

	Bolus insulin								
	≤ 10 units			> 10–20 units			> 20 units		
Baseline characteristics	Faster aspart	Insulin aspart	Total	Faster aspart	Insulin aspart	Total	Faster aspart	Insulin aspart	Total
n	85	86	171	145	144	289	71	75	146
Sex, % male	45.0	48.8	46.9	48.3	50.0	49.1	49.3	53.3	51.4
Age, years (SD)	61.4 (9.7)	60.6 (10.7)	61.0 (10.2)	59.4 (8.7)	58.5 (8.5)	59.0 (8.6)	56.7 (9.2)	59.2 (9.4)	58.0 (9.3)
Duration of diabetes, years (SD)	13.6 (6.7)	13.7 (6.7)	13.7 (6.7)	13.1 (7.0)	11.6 (5.8)	12.4 (6.5)	12.6 (6.3)	11.2 (6.1)	11.9 (6.2)
Body weight, kg (SD)	82.8 (15.4)	84.3 (15.8)	83.5 (15.6)	90.7 (16.0)	88.3 (15.5)	89.5 (15.8)	97.0 (17.5)	95.0 (18.4)	96.0 (18.0)
BMI, kg/m^2 (SD)	29.9 (4.5)	29.7 (4.3)	29.8 (4.4)	31.9 (4.4)	31.2 (4.4)	31.6 (4.4)	33.4 (4.9)	32.8 (4.1)	33.1 (4.5)
HbA_{1c}, mmol/mol (SD)	61.2 (7.0)	61.6 (7.4)	61.4 (7.2)	64.4 (7.3)	63.2 (7.8)	63.8 (7.5)	64.7 (7.1)	63.3 (7.3)	64.0 (7.2)
HbA_{1c}, % (SD)	7.8 (0.7)	7.8 (0.7)	7.8 (0.7)	8.0 (0.7)	7.9 (0.7)	8.0 (0.7)	8.1 (0.7)	7.9 (0.7)	8.0 (0.7)
Baseline total daily actual basal insulin dose, units (SD)	41.1 (21.9)	40.2 (20.1)	40.7 (21.0)	53.6 (16.2)	49.0 (21.3)	51.3 (19.0)	73.6 (29.9)	72.0 (36.5)	72.8 (33.4)

Faster aspart, fast-acting insulin aspart.

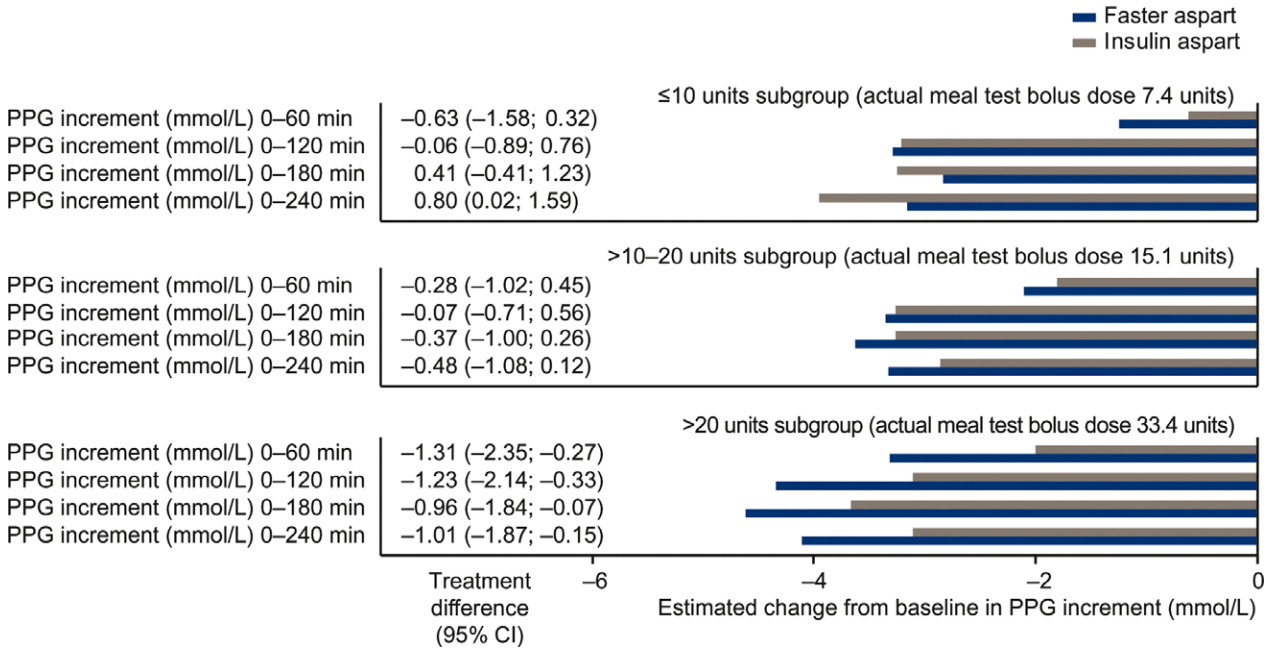

FIGURE 1 Change from baseline in postprandial plasma glucose (PPG) increment adjusted for insulin dose after 26 weeks of treatment with fast-acting insulin aspart in Type 2 diabetes stratified by bolus insulin dose subgroup. Actual meal test bolus doses reported for each subgroup are mean values. Change from baseline in PPG increment (meal test) over time (0–60 min; 0–120 min; 0–180 min; 0–240 min) was analysed using an ANOVA.

treatment difference (95% confidence interval) −0.59 mmol/l (−1.09; −0.09)] [9]. However, this *post hoc* analysis based on subgroup-defined post randomization demonstrated that, in the subgroup of participants receiving > 20 units of mealtime insulin, the relative improvement with faster aspart could be observed not only at 1 h after the meal, but also across all post-meal time points (0–60, 0–120, 0–180 and 0–240 min). Overall, people receiving > 20 units of mealtime

insulin (both faster aspart and insulin aspart) had a mean body weight of 100.1 kg and were receiving, on average, 128.5 and 206.3 units of total daily bolus insulin and total daily insulin, respectively, at 26 weeks (Table A1). There was, however, no difference in the magnitude of change in HbA_{1c} or 1,5-anhydroglucitol levels between faster aspart and insulin aspart, in this or any other subgroup after 26 weeks of treatment, a finding consistent with the primary analysis. A plausible reason why the PPG advantage of faster aspart in the high-dose group may not translate into an advantage in HbA_{1c} or 1,5-anhydroglucitol levels could be that a mealtime bolus dose calibration (up to 1-unit dose increase or decrease) in this trial was based on the prior day's total daily insulin usage rather than a value that is prospectively computed from the actual carbohydrate content of a meal about to be consumed and the carbohydrate–insulin ratio estimate (e.g. one derived from '500' formula). It should be noted that the *post hoc* analysis did not explore the rates of overall or meal-related hypoglycaemia with faster aspart vs. insulin aspart by bolus insulin subgroup.

The PPG advantage of faster aspart may have been most evident in those receiving > 20 units of bolus insulin because these people had a higher observed BMI than those receiving lower doses. The absorption of rapid-acting insulin analogues is delayed in people with obesity, and the glucose-lowering action is further delayed as the dose of the insulin is increased [5]. This effect has been attributed to reduced subcutaneous blood flow associated with increased adiposity [10]. It is possible that the formulation of faster aspart overcomes, to some degree, the barrier to early absorption in more insulin-resistant people with obesity, particularly when delivered as a larger dose (with a proportional delivery of a larger dose of niacinamide) within the subcutaneous depot. With greater early insulin absorption and action, a significant impact on postprandial control would be anticipated [11–13]. The improvement in PPG control observed with faster aspart compared with insulin aspart might also be brought about by greater early suppression of endogenous glucose production [14]. Although these results are intriguing, analyses of subgroups defined post randomization are susceptible to inherent bias, and causality assessments should be interpreted cautiously. With this caveat, this *post hoc* analysis of the onset 2 study [9] suggests that improvements in PPG control in Type 2 diabetes with faster aspart were more pronounced in those receiving the highest bolus insulin doses, indicating that faster aspart holds promise as a more effective treatment than insulin aspart for controlling PPG in people with insulin-resistant Type 2 diabetes. However, this potential benefit requires further confirmation in clinical practice.

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Competing interests

KB has participated in advisory panels for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Merck, Novo Nordisk, Sanofi, Johnson & Johnson; and speakers' bureaus for Novo Nordisk and Sanofi. JH has participated in advisory boards and received research support from Novo Nordisk. JK and JS are employees and hold stock in Novo Nordisk. BB has participated in advisory panels for Novo Nordisk, Sanofi and Adocia; has been a consultant for Medtronic, Sanofi and Novo Nordisk; received research support from Abbott, Boehringer Ingelheim/Lilly, BD, DexCom, Janssen, Lexicon, Medtronic, Novo Nordisk, Sanofi and Sensonics; participated in speakers' bureaus for AstraZeneca, Insulet, Janssen, Medtronic, Novo Nordisk and Sanofi; and holds stock in Glytec.

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Appendix

Table A1 Insulin dosing characteristics and body weight at week 26 for all post-randomization subgroups based on the meal-test bolus insulin dose.

	Bolus insulin								
	≤ 10 units			> 10–20 units			> 20 units		
Parameter	Faster aspart	Insulin aspart	Total	Faster aspart	Insulin aspart	Total	Faster aspart	Insulin aspart	Total
Meal test planned bolus dose									
Units	8.9 (4.9)	9.2 (4.1)	9.1 (4.5)	15.8 (3.3)	15.6 (7.2)	15.7 (5.6)	34.3 (15.3)	31.8 (12.4)	33.0 (13.9)
Units/kg	0.1 (0.1)	0.1 (0.0)	0.1 (0.1)	0.2 (0.0)	0.2 (0.1)	0.2 (0.1)	0.4 (0.2)	0.3 (0.1)	0.3 (0.2)
Meal test actual bolus dose									
Units	7.3 (2.1)	7.6 (2.1)	7.4 (2.1)	15.4 (2.8)	14.8 (3.0)	15.1 (2.9)	34.6 (15.3)	32.3 (12.3)	33.4 (13.9)
Units/kg	0.1 (0.0)	0.1 (0.0)	0.1 (0.0)	0.2 (0.0)	0.2 (0.0)	0.2 (0.0)	0.4 (0.2)	0.3 (0.1)	0.3 (0.2)
Total daily actual bolus dose									
Units	27.1 (21.2)	26.4 (14.9)	26.8 (18.2)	48.2 (18.1)	51.1 (32.7)	49.7 (26.4)	136.1 (73.4)	121.5 (64.8)	128.5 (69.2)
Units/kg	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.5 (0.2)	0.6 (0.3)	0.6 (0.3)	1.4 (0.9)	1.3 (0.7)	1.3 (0.8)
Total daily actual insulin dose									
Units	55.7 (30.0)	57.7 (25.6)	56.7 (27.8)	99.1 (20.7)	97.5 (45.4)	98.3 (35.3)	214.2 (95.2)	199.1 (77.7)	206.3 (86.5)
Units/kg	0.7 (0.3)	0.7 (0.3)	0.7 (0.3)	1.1 (0.3)	1.1 (0.4)	1.1 (0.4)	2.2(1.0)	2.0 (0.8)	2.1 (0.9)
Body weight, kg	81.2 (16.3)	83.0 (15.4)	82.1 (15.8)	93.9 (17.0)	90.8 (16.4)	92.4 (16.7)	101.1 (19.3)	99.1 (19.5)	100.1 (19.1)

Values for insulin dosing parameters and body weight at week 26 are arithmetic means (SD) of observed values (participants with available values change slightly between the units and units/kg, as not all participants were weighed at week 26). Faster aspart, fast-acting insulin aspart.

Table A2 Change from baseline in HbA_{1c} and 1,5-anhydroglucitol after 26 weeks of treatment with faster aspart in Type 2 diabetes stratified by bolus insulin dose subgroup.

	Estimated treatment difference (faster aspart – insulin aspart)	95% confidence intervals
HbA_{1c}, mmol/mol		
Bolus dose ≤ 10 units	−1.04	−3.49; 1.41
Bolus dose > 10–20 units	−0.36	−2.30; 1.58
Bolus dose > 20 units	0.29	−2.45; 3.03
HbA_{1c}, %		
Bolus dose ≤ 10 units	−0.09	−0.32; 0.13
Bolus dose > 10–20 units	−0.03	−0.21; 0.14
Bolus dose > 20 units	0.03	−0.22; 0.28
1,5-anhydroglucitol, µmol/l		
Bolus dose ≤ 10 units	−0.81	−2.38; 0.75
Bolus dose > 10–20 units	−0.45	−1.69; 0.79
Bolus dose > 20 units	0.46	−1.29; 2.21

Estimated treatment difference for change from baseline in HbA_{1c} and 1,5-anhydroglucitol was based on the full analysis set and analysed using an ANOVA model, which included treatment by dose–group interaction, continuous glucose monitoring strata and region as factors, and baseline HbA_{1c} and 1,5-anhydroglucitol at baseline as covariates, respectively.